Pharyngeal and Laryngeal Lesions Presenting as "Hemoptysis" and Evaluated by Bronchoscopy — A Ten-Year Experience

Yong-Tze Chen, Chao-Chien Wu, Young-Fa Lai

Hemoptysis, an important and alarming symptom, often indicates serious disease. Whether the blood is expectorated from pulmonary or non-pulmonary source, the patients' description may be quite similar. Pseudohemoptysis can be distinguished from true hemoptysis by a history-taking, physical examination, and bronchoscopic evaluation. In this study, a total of 2017 patients who had undergone bronchoscopy for "hemoptysis" between 1992 and 2001 were retrospectively reviewed. We found 18 laryngeal and pharyngeal lesions (0.88%), of which 10 cases (0.54%) showed active oozing (pseudohemoptysis) during the bronchoscopic examination. Fourteen pathologic conditions were diagnosed with a biopsy: 4 nasopharyngeal carcinomas (0.2%), 1 hypopharyngeal carcinoma (0.05%), 2 metastatic carcinomas of the hypopharynx (0.1%), 1 vocal cord dysplasia (0.05%), 1 interarytenoid leukoplakia (0.05%), 4 cases of lymphoid hyperplasia (0.2%; 1 in the epiglottis, 3 in the nasopharynx), and 1 pharyngitis (0.05%). The seven malignant cases and one dysplasia all showed active oozing during the bronchoscopic examination, but only one of the five benign lesions did so. Thus, we consider malignancy to be the most common cause of pseudohemoptysis, due to the pharyngeal and laryngeal lesions. In addition, a subgroup of 831 patients (41.19%) with negative findings in the initial bronchoscopy, and without a past history of upper airway malignancy, was identified, of which 3 cases (0.36 %) turned out to have a diagnosis of upper airway malignancy during the follow-up period; all of them were nasopharyngeal carcinomas. Therefore, we conclude that an early diagnosis of pharyngeal and laryngeal malignancy can be made with a careful evaluation and multiple punch biopsies via the bronchoscopy. Those patients presenting with a long history of "hemoptysis", but with a negative bronchoscopy study, should be referred to the otorhinolaryngeal department for further evaluation. ***(Thorac Med 2002; 17: 309-316)***

Key words: hemoptysis, pseudohemoptysis, bronchoscopy, pharyngeal lesions, laryngeal lesions

Introduction

Hemoptysis is defined as the expectoration of blood that originates from the tracheobronchial trees or the pulmonary parenchyma, whereas pseudohemoptysis denotes the expectoration of blood which is derived from the alimentary tract, nose, oral cavity, pharynx, or larynx [1].

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Hematemesis is usually related to a long history of esophagogastric symptoms or alcoholism, and is often characterized by a dark color or a consistency of food particles [2]. In contrast, bleeding from the pharynx or larynx may be easily confused with true hemoptysis because of the lack of distinguishing features. An anxious and frightened patient may not be certain whether the blood was coughed up, aspirated, or swallowed and subsequently spit up.

DiLeo et al [3] reported that among all 471 patients presenting with hemoptysis, upper aero-digestive tract (UAT) diagnoses responsible for the expectoration of blood were found in 47 patients (10%), and UAT malignancies were found in 10 patients (2.1%).

The diagnostic evaluation for hemoptysis consists of a medical history, physical examination, a plain chest radiography, a computerized tomography (CT) of the chest, a fiberoptic bronchoscopy, and coagulation studies [4]. Bronchoscopy can be helpful in confirming the diagnosis, localizing the bleeder, and identifying the cause. However, the source of the bleeding may be above the vocal cord, and definitive diagnosis requires pathological yields. Moreover, a negative finding at the time of bronchoscopy is not uncommon, and does not refute the previous bleeding episode emanating from any point of the whole airway.

Past medical histories that may indicate a possible etiology of the bleeding include chronic bronchitis, bronchiectasis, pulmonary tuberculosis, lung cancer, congestive heart failure, trauma, blood dyscrasia, rhinitis, sinusitis, upper airway malignancy, and others. However, the presence of underlying pulmonary disease does not refute the possibility of pseudohemoptysis. In patients with mild hemoptysis, the best predictor of a specific bronchoscopic diagnosis was an abnormal finding on chest X-ray [5]. Nevertheless, abnormal findings on chest X-ray do not exclude pseudo-hemoptysis.

In this report, we gathered data from 14 patients with pharyngeal or laryngeal lesions, who had been determined by the evaluating physician as having "hemoptysis", and in whom histologic yields were obtained by bronchoscopy or laryngoscopy- guided biopsy. The frequency and various causes of pseudohemoptysis due to pharyngeal and laryngeal lesions are determined, and their clinical features and outcomes are described. We also identified 3 cases of newly detected NPC (0.36 %) in which the initial bronchoscopic examination for "hemoptysis" showed a negative finding, and the past history was negative for any upper airway malignancy.

Methods

Reports of bronchoscopies performed at Kaohsiung Chang Gung Memorial Hospital from 1992 through 2001 were retrospectively reviewed to determine the patients with pharyngeal or laryngeal lesions presenting as "hemoptysis". The medical records of these patients were subsequently reviewed for the following information: age, gender, medical history, the duration and amount of bleeding, chest X-ray findings, and histological diagnoses. Laboratory evidence of coagulopathy or a bleeding tendency was also sought from the chart review.

In addition, a subgroup of patients without a past history of any upper airway malignancy, and whose initial bronchoscopic examination showed a negative finding, was identified. Then, a retrospective computer search of medical diagnoses was performed to determine those patients who turned out to have malignancy of the upper airway above the vocal cord.

Aside from the patients who were intubated or on tracheostomy, all flexible fiberoptic bronchoscopes were operated via the transnasal route, using either the right or left side, and passed through the vocal cord to a level of the subsegmental bronchi. Pre-medication consisted of an intra-muscular injection of 0.4 mg atropine, and about 200 mg of 2% lidocaine by nasal spray. A local spray of 2% lidocaine was used as needed during the examination to reduce the cough reflex. Either a pulmonary staff physician or a fellow

under the supervision of a staff physician operated all the flexible fiberoptic bronchoscopes.

Pseudohemoptysis was defined as active oozing originating from the pharynx or larynx, rather than from the tracheobronchial trees, while the bronchoscopy was being performed. Chest X-rays were defined as normal in the absence of a mass, cavity, infiltrate, full hilum, localized fibrotic change, scarring, or pleural reaction. The bronchoscopy was defined as a negative finding if no abnormal lesions were seen in the upper airway, and none of the conditions below was not found in the tracheobronchial trees: (1) mucosal or submucosal infiltration, (2) mucosal ulceration, (3) endobronchial polyps, nodules, or mass, (4) fresh or dark blood, (5) hypertrophied and prominent submucosal capillaries, (6) purulent secretion, (7) fistula, and (8) foreign body.

Results

A total of 2017 patients presenting with "hemoptysis" were identified and evaluated by bronchoscopy. Pharyngeal and laryngeal lesions were found in 18 (0.88%) patients, of whom 10 (0.54%) had active oozing of the lesion (pseudohemoptysis) during the bronchoscopic examination. Fourteen of these 18 patients had histological diagnoses with a bronchoscopy or laryngoscopy-guided biopsy from multiple sites.

The other 4 patients did not undergo biopsy, and experienced a remission of the bleeding episode: one had a nasopharyngeal ulcer with active oozing, which subsided without further intervention; one a laryngeal granulation tissue, which did not show clinical progression despite the lack of treatment; one an epiglottic bulging mucosa, which was combined with thrombocytopenia (88000/cmm) at that time; and one a small hematoma over the right vocal cord, which was documented by the follow-up laryngoscopy, and thought to be leukoplakia in nature by the otorhinolaryngologist.

There was no endobronchial or tracheal abnormality demonstrated in these 18 patients, except in one (No.3) who also had purulent secretion in the right middle lobe bronchus, and was confirmed to have pulmonary tuberculosis by bronchial washing and chest X-ray finding.

Table 1 outlines the histological yields,

Table 1. The 14 newly detected pathological conditions in the pharyngeal and laryngeal regions.

Case No.	Histological diagnosis	Duration of the bleeding	Associated symptoms	Past medical history	Chest x-ray findings
1	NPC	1 month	Fever	DM, anemia	Non-localized
2	Lymphoid hyperplasia	10 days	Epistaxis, tinnitus	(-)	Localized infiltration
3	NPC	1 month	(-)	(-)	Localized infiltration
4	Lymphoid hyperplasia	3 months	Chest tightness	Chronic rhinitis	Normal
5	Pharyngitis	3 days	Dyspnea, chest tightness	(-)	Normal
6	Lymphoid hyperplasia	2 weeks	Body weight loss	(-)	Normal
7	Metastatic carcinoma	1 month	Dyspnea, tinnitus, Sore throat	(-)	Normal
8	Metastatic carcinoma	1 week	Cough	Tongue cancer	Normal
9	Lymphoid hyperplasia	2 days	Chest pain	Chronic B hepatitis	Localized Infiltration
10	Dysplasia	2 weeks	(-)	DM	Normal
11	Leukoplakia	3 days	Chest pain	H/T	Normal
12	NPC	3 months	(-)	(-)	Localized Infiltration
13	Hypopharyngeal carcinoma	3 days	Otorrhea, otalgia, hoarseness	COPD	Non-localized
14	NPC	9 months	Dyspnea	COPD	Non-localized

No.= number; NPC = nasopharyngeal carcinoma; DM = diabetes mellitus; H/T = hypertension; COPD = chronic obstructive pulmonary disease

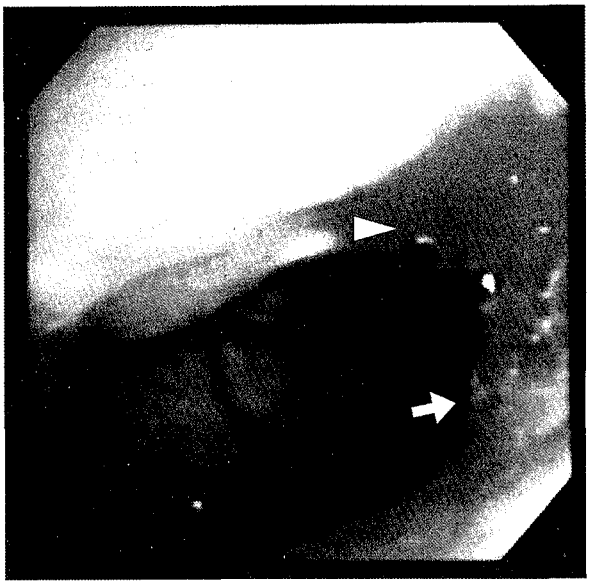

Fig.1. Nasopharyngeal carcinoma (arrow) with active oozing (arrowhead) in the right lateral wall of the nasopharynx.

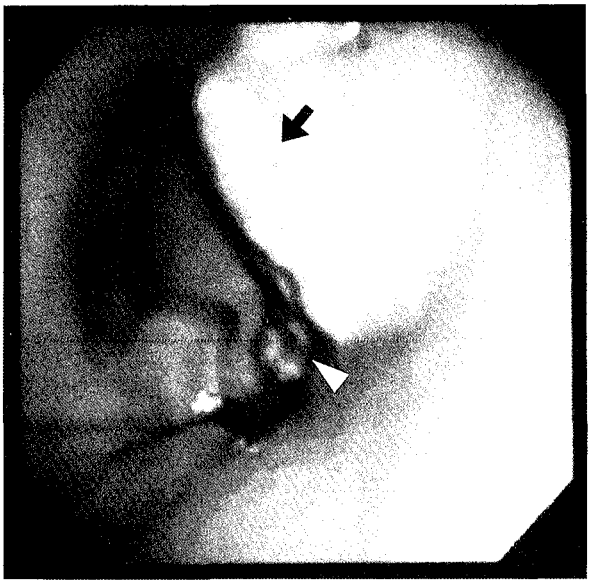

Fig.2. Hypopharyngeal carcinoma (arrow) with active oozing (arrowhead) on the right side.

duration of blood-tinged secretion, associated symptoms, past history, and chest X-ray findings, with regard to the 14 pathological conditions. All of these diseases were diagnosed after the episode of blood-tinged secretion, except one (No.8), which was a case of recurrent tongue cancer that was resected 7 years prior to this bronchoscopic examination. There were 11 males and 3 females. Ages ranged from 30 to 68 years, with a mean of 48.71.

Four nasopharyngeal carcinomas (0.2%) and one hypopharyngeal carcinoma (0.05%) were found, all of which showed active oozing during the bronchoscopic examination, and were treated with irradiation or concurrent chemoradiotherapy (CCRT). Two of these 5 patients died during the follow-up period (Figure 1-2).

Two tongue cancers (0.1%) with hypopharyngeal involvement were found: one was treated with CCRT, but the patient died of sepsis; the other was a recurrent case, and was treated again with a total resection of the tumor, followed by irradiation. Both of these 2 cases showed an active oozing of the lesions during the bronchoscopic examination.

One vocal cord dysplasia (0.05%) was found and also showed active oozing during the bronchoscopic examination, but was suspected to be malignant in the follow-up examination using laryngoscopy (Figure 3). One laryngeal leukoplakia (0.05%) was found, and treated with excision by laryngomicrosurgery and laser.

Five benign lesions were diagnosed: four cases of lymphoid hyperplasia (0.2%), and one

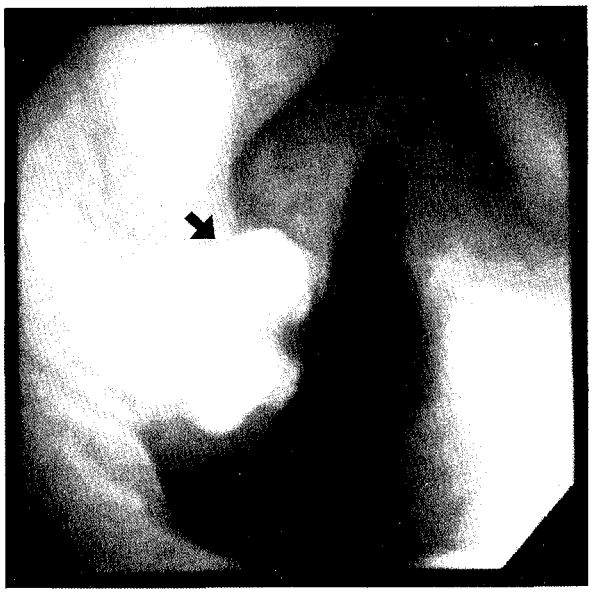

Fig.3. Left vocal cord nodules (arrow) with dysplasia.

chronic pharyngitis (0.05%). One (No.2) of the former was treated with an excision of the cystic epiglottic mass by laryngomicrosurgery and laser. None of these 5 cases showed active oozing during the bronchoscopic examination except one case of lymphoid hyperplasia, which had an appearance of multiple ulcerated nodules.

The duration of blood-tinged secretion varied from 2 days to 9 months, with a median value of 2 weeks. The amount of bleeding was trivial (drops of blood, or a bloody secretion) in the majority of these 14 patients, and moderate (1 to 2 cups, or less than 500 cc/day) in others. Three patients had otorhinolaryngeal complaints, including epistaxis, tinnitus, sore throat, otorrhea, otalgia, and hoarseness. Two of these 3 patients proved to have malignancy (No.7 and No.13), and the other had lymphoid hyperplasia (No.2). The 2 patients with a history of chronic obstructive pulmonary disease (No.13 and No.14) proved to have pseudohemoptysis originating from pharyngeal malignancy, and the patient with a tongue cancer history proved to have pseudohemoptysis due to a metastatic lesion. Ten patients had a normal or non-localizing chest X-ray, and three of them proved to have malignancy, whereas two of the four patients with a focally abnormal chest X-ray had malignancy. There was no coagulopathy or bleeding tendency documented in these 14 patients.

In addition, of the 2017 patients presenting as "hemoptysis", a subgroup of 831 patients (41.49 %) with negative findings in the initial bronchoscopic examination, and without a past history of upper airway malignancy, was identified. Three patients (0.36%) turned out to have NPC, which was diagnosed by the follow-up rhinoscopy or laryngoscopy-guided biopsy.

The first patient presented with 3 months of "hemoptysis" associated with dyspnea. The only past history was a blunt trauma 30 years ago, and the chest X-ray was normal. He visit an otorhinolaryngologist one month after the bronchoscopic examination because of bloody salivation and a newly found neck mass. Tumors on the right Rosenmuller's fossa and roof of the nasopharynx were found, and proved to be poorly differentiated squamous cell carcinoma. This was treated with radiotherapy and showed regression. The second patient presented with 7 months of "hemoptysis" associated with post-nasal dripping. No past history was contributory, and the chest X-ray was normal. He was referred to the oto-rhinolaryngology department. Tinnitus, left otorrhea, left hearing impairment, and a blood–stained nasal discharge developed later. A left nasopharyngeal tumor was found, and proved to be squamous cell carcinoma. It was also treated with radiotherapy, and showed regressive change. The third patient was one of the 14 patients described above (No.14). He had undergone the first bronchoscopic examination 6 months before the second one, which was arranged because of intermittent blood-tinged sputum.

Discussion

The pharynx is defined as that part of the throat located dorsal to the larynx, nasal, and oral cavities, extending from the roof of the pharynx to the beginning of the esophagus. The larynx begins at the opening and is bounded anteriorly by the free border of the epiglottis, laterally by the aryepiglottic folds, and posteriorly by the corniculate tubercles of the arytenoids cartilage.

Laryngeal examination is an essential aspect of bronchoscopy, and any unexpected finding may provide diagnostic clues to the underlying respiratory symptoms. This study showed that a small percentage of patients presenting with "hemoptysis" had pharyngeal or laryngeal lesions, most of which were responsible for the bleeding episode. Compared to the 10% incidence of pseudohemoptysis reported by DiLeo et al [3], the low percentage (0.54%) in our study can be attributed to: (1) the confinement of the pseudo-hemoptysis to the pharyngeal and laryngeal lesions only, (2) the possibility of overlooking the upper airway lesions, and (3) the associated symptoms not referable to pulmonary disease,

and leading to other examinations rather than bronchoscopy. In addition, there were 2 cases of epistaxis, which had been regarded as hemoptysis initially.

In another study, Watanabe et al [6] found 15 pathological conditions in the throat (0.92%), out of a total of 1632 patients who underwent upper gastrointestinal endoscopy for GI disease. This percentage was similar to that of the pharyngeal and laryngeal lesions (1.04%) in our study, but no pseudohemoptysis was determined in their study.

The common etiologies of laryngeal and pharyngeal bleeding include pharyngitis, epiglottic ulcer, pharyngeal carcinoma, angiofibroma, metastatic carcinoma, intubation injury, and blunt trauma [3]. Among the 14 pathological conditions in this study, malignancy or premalignancy was responsible for more than half (64.28%) of the cases which proved to be pseudohemoptysis, but only one benign lesion (lymphoid hyperplasia) was documented to be the source of bleeding (No.2). This may be due to the hypervascularity of the malignant tumor, and indicate that the possibility of malignancy is far higher if active oozing of the lesion is seen. Definitive diagnosis usually requires further surveys, such as biopsy and a CT scan of the head and neck.

In this study, nasopharyngeal carcinoma (NPC) was the most common cause of pseudohemoptysis, and had the highest mortality rate. Skinner et al [7] stated that the reasons for the late presentation of NPC included a delay in seeking medical advice, the confusing nature of the symptoms, the difficulty in clinical examination, and the spread of a silent submucosal lesion with a normal appearance.

Otorhinolaryngeal symptoms were recorded in only 3 patients with pseudohemoptysis. There was a possibility of overlooking subtle symptoms, such as hoarseness, epistaxis, and tinnitus. Therefore, it is important to inquire about pertinent medical history to avoid missing NPC in an early stage. In addition, NPC commonly involves both sides of the nasopharynx, and often has a submucosal sprea [8].Thus, it is prudent to take multiple punch biopsies from various regions to reach a definitive diagnosis [9].

Lymphoid hyperplasia or patches are localized solitary or multiple lymph follicles occuring in the oropharynx, posterior pharyngeal wall, and oral cavity. They are regarded as physiologic rather than pathologic, and appear as slightly elevated projections of the mucosa, with a yellowish or grayish color and with a size varying from a few mm to 1 cm. The diagnosis usually is based on clinical judgment. Furthermore, they are usually asymptomatic and require no treatment [10].

Leukoplakia applies to those lesions that cannot be scraped off or recognized as any other disease process. Approximately 80% of these lesions show a benign histology, and the remaining 20% represent premalignant epithelial dysplasia, carcinoma in situ, or frank invasive squamous cell carcinoma [10].

In this study, one leukoplakia and one dysplasia were demonstrated, and required further survey with a repeat biopsy via laryngoscopy to exclude malignancy. Four lymphoid hyperplasias looked like tumors grossly, but proved to be benign later.

The remaining 4 patients who did not undergo biopsy require further follow-up.

One nasopharyngeal ulceration with transient bleeding episodes may have been due to acute pharyngitis. One case with laryngeal granulation tissue may have been due to previous trauma, tuberculosis, or fungus infection. One epiglottic bulging mucosa may be due to submucosal hematoma associated with transient thrombocytopenia. Finally, one vocal cord hematoma and leukoplakia required further follow-up to exclude possible malignant change.

The low percentage (0.36%) of newly diagnosed upper airway malignancies in the subgroup with negative findings in the initial bronchoscopy indicates that bronchoscopy has a high negative predictive value (99.64 %) in the diagnosis of pharyngeal and laryngeal cancer presenting as pseudohemoptysis. The consistent

feature of the three newly detected NPC cases was the long duration of the "hemoptysis".

In conclusion, pseudohemoptysis accounts for a minority of all patients expectorating blood but poses a challenge for the early diagnosis. It can be caused by malignant or benign lesions. Bronchoscopy plays an important and effective role in distinguishing them, and allows tissue diagnosis. In this study, malignancy was the most common etiology of pseudohemoptysis due to pharyngeal and laryngeal lesions.

Certain subtle symptoms, such as epistaxis, tinnitus, and hoarseness, may indicate the presence of pseudohemoptysis. Abnormal chest X-ray findings or a positive past history of pulmonary disease cannot exclude pseudo-hemoptysis. Furthermore, it is prudent to take multiple punch biopsies if any abnormal pharyngeal or laryngeal lesion is found during bronchoscopic examination. Those patients presenting as long-term "hemoptysis", but having a negative bronchoscopic study, should be referred to the otorhinolaryngeal department for further evaluation.

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由支氣管鏡評估以"咳血"來表現的咽喉病灶 —十年的經驗

陳永哲 吳沼漪 賴永發

咳血是重要而且駭人的症狀， 它常暗示嚴重的疾病。無論血是從肺部或肺部以外的構造產生的， 病人的描述可能都類似。假性咳血可以藉由病史， 理學檢查，及支氣管鏡檢查來跟眞性咳血區別。 在本研究中，回顧了從 1992 到 2001 因為"咳血" 而接受支氣管鏡檢查的 2017 位病人。我們發現了 18 個(0.88 %)咽喉病灶 ，其中 10 個(0.54 %) 在支氣管鏡檢查時顯示活動性的血液滲出(假性咳血)。有 14 例經由切片證實的病理診斷：4 個鼻咽癌(0.2%)，1 個下咽癌(0.05%)，2 個下咽轉移癌 (0.1%)，1 個聲帶異生(0.05%)，1 個杓狀軟骨間白斑(0.05%)，4 個類淋巴增生(0.2%; 1 個在上會厭，3 個在鼻咽)，及 1 個咽炎(0.05%)。前面 7 例惡性腫瘤及 1 例異生在支氣管鏡檢查時都顯示活動性血液滲出，而後 5 例良性病灶中只有 1 例如此。因此，我們認為惡性腫瘤是咽喉病灶造成假性咳血最常見的原因。此外，我們還找出了一個包含 831 人(41.19 %)的次母群體，他們最初的支氣管鏡檢查都沒有任何發現，而且沒有上呼吸道癌症的過去病史; 其中有 3 例(0.36 %)在後續追蹤調查期間新診斷出上呼吸道癌症(皆為鼻咽癌)。所以，我們的結論是：經由支氣管鏡詳細的視察及多次切片可以早期診斷出咽喉的惡性腫瘤; 另外，長期咳血的病人若其支氣管鏡檢查為正常者，應轉診耳鼻喉科做進一步的檢查。 ***(胸腔醫學 2002; 17: 309-316)***

關鍵詞：咳血，假性咳血，支氣管鏡，咽喉病灶

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Radiographic Manifestation of Pneumocystis carinii Pneumonia (PCP)—A 5-Year Experience at Veterans General Hospital-Taipei (VGHTPE) (1996-2001)

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Pneumocystis carinii pneumonia (PCP) is a central and serious opportunistic infection in the immunocompromised host. We reviewed the initial chest roentgenograms of 36 patients whose PCP was diagnosed by etiology or by treatment response to Bactrim between 1986 and 2001, at Veterans General Hospital-Taipei, to detect the relative frequencies of its various roentgenographic patterns. PCP is estimated to occur in approximately 60 percent of patients with AIDS. Among the 36 patients reviewed, 26 had AIDS, and 4 had undergone a renal transplantation. The sex distribution was 32 males and 4 females. The most common radiographic pattern was a diffuse perihilar interstitial infiltration in twenty-two of the 36 patients (61.1 percent). Other radiographic manifestations consisted of alveolar patterns, ground glass patterns, cystic lesions, and pleural effusion. Eighteen of the 36 patients had accepted a chest CT examination, and we also reviewed the most frequent patterns. Early diagnosis and rapid treatment are relatively important with this disease. The radiographic manifestations may aid in the diagnosis of this disease, though there is no pathognomonic radiographic pattern for PCP. ***(Thorac Med 2002; 17: 317-323)***

Key words: pneumocystis carinii pneumonia, diffuse perihilar interstitial infiltration, radiographic manifestation.

Introduction

Pneumocystis carinii pneumonia (PCP) is the most common opportunistic pulmonary infection in the immunocompromised host [1,11]. The radiographic manifestations of PCP in both acquired immunodeficiency syndrome (AIDS) and non-AIDS patients are most commonly described as a bilateral interstitial or alveolar pattern. PCP frequently evolves from a primarily perihilar location into a more extensive and diffuse process. Other variable manifestations, such as alveolar patterns, ground glass patterns, cystic lesions, pneumomediastinum, and pleural effusion, have been observed, and may be related to the patient's underlying or accompanying disease, the state of immunosuppression, the duration of infection, concurrent infection with other organisms, or previous radiation therapy. The patient with recurrent pneumocystis infection may manifest chronic interstitial lesions, small cysts, or a honeycombing appearance on chest radiography [1].

The radiologically variable manifestations of PCP prompted us to characterize these

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Table 1. Patient Characteristics

Characteristics	No. (%)
Sex distribution:	
Male/female	32/4
Underlying disease	
AIDS	25 (72.3%)
Renal transplantation	4 (11.1%)
CML	1 (2.77%)
MDS	1 (2.77%)
Lymphoma	1 (2.77%)
Ovarian cancer	1 (2.77%)
ALL	1 (2.77%)

Table 2. Radiologic Manifestations of PCP

Patterns	No.(%)
chest film pattern	
Interstitial pattern	22 (61.11%)
Alveolar pattern	6 (16.66%)
Combined interstitial/alveolar pattern	8 (22.22%)
Cyst lesion	7 (19.44%)
Lymphadenopathy	1 (2.77%)
Pleural effusion	5 (13.88%)
Pneumomediastinum/pneumothorax	1 (2.77%)
chest CT manifestation	
ground-glass pattern	17 (94.44%)
interstitial pattern	1 (5.55%)

manifestations in the lung. We reviewed all the chest films and chest CT scans of PCP patients, including those with underlying AIDS and non-AIDS patients, treated from 1996 to 2001 at VGHTPE.

Methods

We reviewed 36 cases of PCP documented between 1996 and 2001 at VGHTPE, The underlying diseases included 26 AIDS, 4 renal transplantations, 1 lymphoma, 1 chronic myelocytic leukemia, 1 acute lymphocytic leukemia, 1 myelodysplasia syndrome, and 1 ovary cancer (Table 1). The sex distribution was 32 males and 4 females. The diagnosis of all the PCP patients was confirmed either by etiology, or was based on treatment response to Bactrim. The evidence of a definite diagnosis of Pneumocystis carinii infection was based on the results of fibrobronchoscopic bronchoalveolar lavage, and special stains with Papanicollou's stain and Gomori methenamine silver nitrate stain for the lavage fluid. The chest radiographs of the 36 cases were those obtained during the acute illness, and chest high-resolution CT scans were available in 18 out of 36 cases. They were analyzed by a radiologist and the authors. Three categories of radiographic abnormality were defined as well as some associated abnormalities. The interstitial pattern was recognized as one with a granular, nodular, reticular, or reticulonodular appearance. The alveolar pattern was characterized by air-space filling, the presence of air bronchograms, or confluent acinar infiltrates. The combined interstitial-alveolar patterns included characteristics of both interstitial and alveolar categories.

Results

The abnormal findings on the chest radiographs and chest CTs are shown in Table 2. An interstitial pattern (Figure 1) was observed in 22 patients (61.11 percent), an alveolar pattern (Figure 2) in 6 (16.66 percent), and a combined interstitial-alveolar pattern in 8 patients (22.22 percent). In addition to these findings, seven patients had small air cysts (Figure 3), five patients had pleural effusion, one patient had lymphadenopathy, and one patient had pneumomediastinum and pneumothorax (Figures 4-1 and 4-2).

The radiographic infiltration involved a distribution to both lungs in 32 patients (89 percent) and to the right lung only in 4 patients (11 percent). The anatomic distribution of the pulmonary infiltration is shown in Table 3, revealing a diffuse type in 19 cases (50.27 percent), perihilar distribution is 4 (11.11 percent), and lower lung field distribution in 7 cases (19.44 percent).

Most of the chest high-resolution CT manifestations (17 cases, 94.4%) were ground-glass patterns (Figure 5), and only one was an

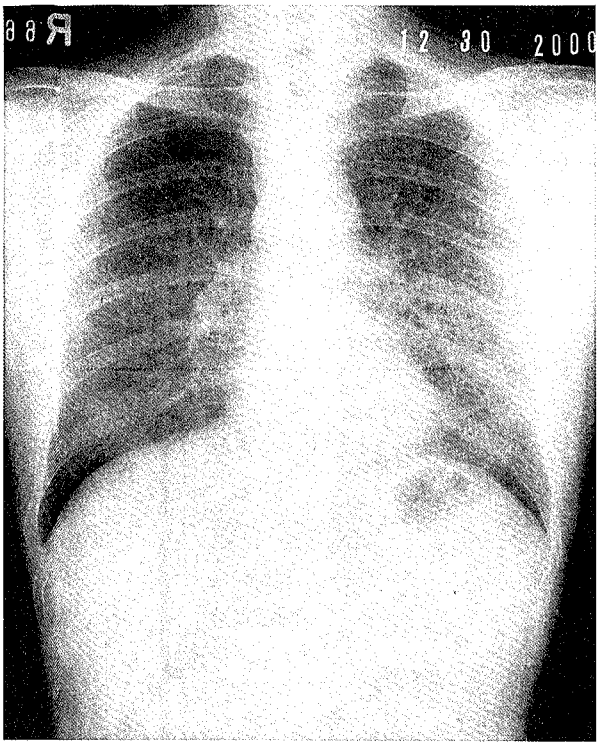

Fig. 1. Diffuse perihilar interstitial pattern.

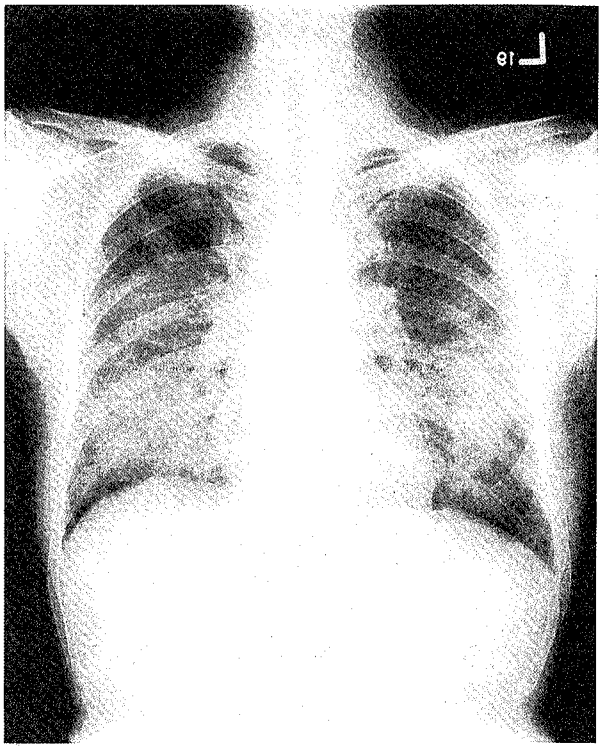

Fig. 2. Diffuse alveolar pattern.

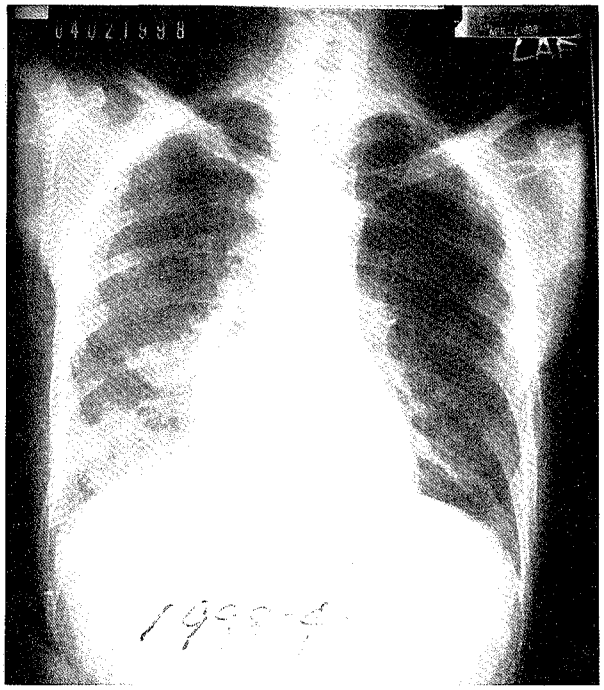

Fig. 3. Cystic lesion, RUL.

interstitial pattern (5.55 percent).

Discussion

PCP is the most common and serious opportunistic pulmonary infection in immunocompromised patients, and contributes significantly to the overall morbidity and mortality of these patients [1]. A recognition of the variety of radiographic patterns may be helpful in the early diagnosis and appropriate management of these patients. In order to gain an insight into the range of these patterns, we reviewed the chest radiograph and CT manifestations of the PCP patients treated in our hospital from 1996 to 2001. David et al [8] has reviewed a wide variety of radiographic manifestations of PCP found in patients. Typically, PCP caused bilateral perihilar, basilar reticular, or reticulonodular infiltrates which rapidly progressed within three to five days, becoming a diffuse air-space consolidation involving almost the entire lung. Our results found a diffuse bilateral interstitial infiltration beginning in the perihilar regions to be the most common (61.38 percent) radiographic manifestation of PCP, and a ground-glass pattern appeared in the chest CT of almost all patients

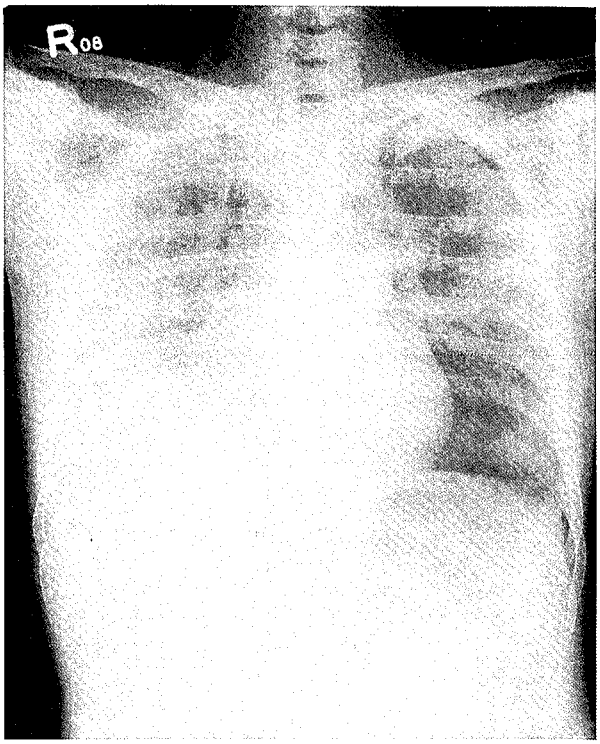

Fig. 4-1. Pneumomediastinum--CXR.

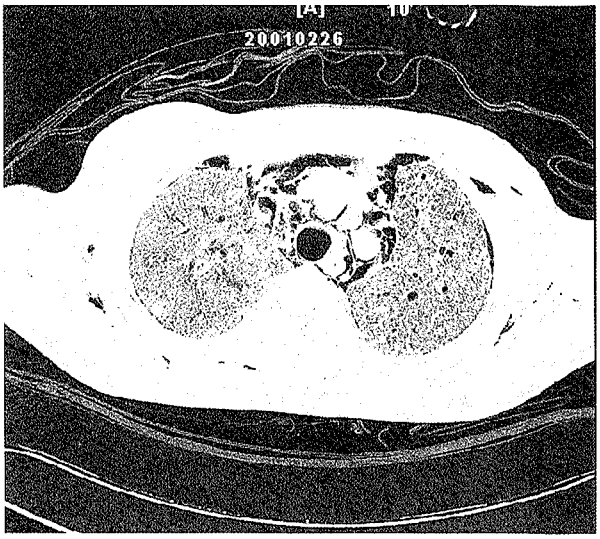

Fig. 4-2. Pneumomediastinum--Chest CT.

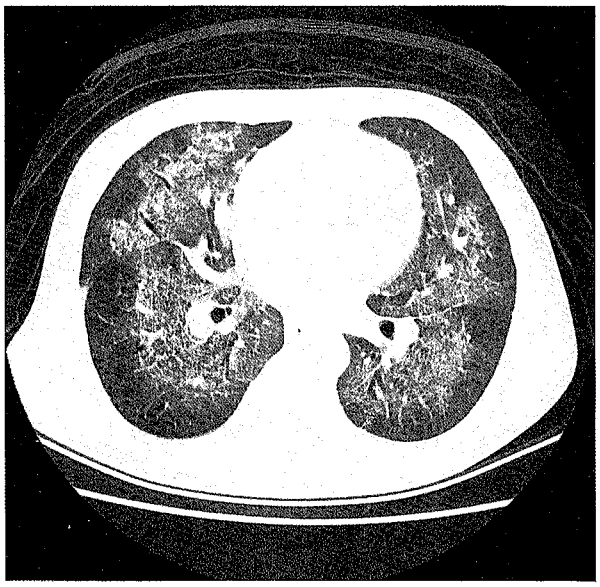

Fig. 5. Chest CT: ground-glass pattern.

Table 3. Disease Distribution and Patterns

Disease characteristics	No. (%)
Disease distribution	
bilateral	32 (89%)
right lung	4 (11%)
left lung	0
Distribution patterns	
diffuse	19 (50.27%)
perihilar	4 (11.11%)
upper and middle lung	2 (5.55%)
middle and lower lung	2 (5.55%)
upper lung	2 (5.55%)
lower lung	7 (19.44%)

(94.44 percent). Other less common radiographic patterns included cystic lesions, pleural effusion, hilar adenopathy, and pneumomediastinum. Sandhu et al identified radiographic findings associated with PCP in AIDS patients, the pulmonary cysts are found about 10% [2]. They was no predilection for a particular area in the lung field or in the clinical course of manifestation. An analysis of the available radiographs indicated a resolution of the pulmonary cysts within 7 months in a majority of cases. The mechanism of these cysts is unknown, but possible mechanisms are check-valve obstruction or parenchymal necrosis. A rupture of these cysts may lead to spontaneous pneumothorax. With the growing use of CT in the evaluation of immunocompromised patients with unknown sources of fever or unexplained pulmonary symptoms, an awareness of the spectrum of CT findings in PCP becomes

increasingly important. Janet et al collected the chest CT scans of 39 PCP patients, and found a ground-glass pattern in 10 of 39 (26%), a patchywork pattern in 22 of 39 (56%), and an interstitial pattern in 7 of 39 patients (18%) [4]. All 39 cases had bilateral parenchymal infiltrates. In David's report, a radiographic resolution of the PCP could usually be demonstrated 2 weeks following the initiation of therapy [8]. Bernard et al reviewed 59 cases of PCP, and 4 normal lungs were noted. A diffuse interstitial pattern was seen in 30 out of 59 patients [9]. Lawrence et al reported that the most common chest film pattern was diffuse interstitial infiltrates, which were seen in 99 out of 104 cases [1]. The others were a unilateral infiltration in 5 patients, the entire lung field involved in 50 patients, localized infiltration involving the lower lungs in 35 patients, the upper lung fields in 6 patients, the middle lung fields in 6 patients, and both middle and lower lung fields in 7 patients [1].

High-resolution computed tomography (HRCT) may allow the exclusion of PCP in patients with findings that are normal, equivocal, or nonspecific on chest radiographs. HRCT has 100% sensitivity, 89% specificity, and 90% accuracy for the diagnosis of Pneumocystis carinii pneumonia [12]. In summary, only a high index of suspicion can lead to an early diagnosis of PCP. We should keep the disease in mind and make a decision based on history, physical examination, and radiographic manifestations of PCP.

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卡氏肺囊蟲肺炎的胸部放射學表現—台北榮總5年(1996～2001)經驗

蔡清和　賴信良

卡氏肺囊蟲肺炎是免疫不全的人最常見且嚴重的伺機性感染，我們回顧台北榮總最近5年(1996～2001)36位卡氏肺囊蟲肺炎病人患病早期的胸部X光片，來分析各種胸部放射學類型出現的相對機率，這些病人是經由病因診斷或對 bactrium 治療有進步。成人免疫不全症候群大約有百分之陸拾的機率會發生卡氏肺囊蟲肺炎。36位病人中有26位是成人免疫不全症候群病人，4位是腎臟移植病人; 其中有32位是男性，4位是女性。

最常見的胸部放射學表現為兩側肺門旁瀰漫性間質型浸潤，佔百分之六十一點一。其他不同的表現有肺泡型、毛玻璃狀型，且亦可能以囊狀病灶及肋膜積水表現。在36位病人中有18位接受電腦斷層掃描，我們亦回顧其片子，找出最常見的類型為毛玻璃狀型(佔百分之九十四點四)。

在這疾病早期診斷、快速治療，是相對的重要。雖然沒有一種胸部放射學的表現能像病理提供那麼確定的診斷，但其可給予最早的警訊。 ***(胸腔醫學2002; 17: 317-323)***

關鍵詞：卡氏肺囊蟲肺炎、肺門旁瀰漫性間質型浸潤、放射學表現

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Clinical Experience with Surgical Lung Biopsy for Diffuse Pulmonary Lesions

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Hung-Chang Liu*, Yu-Jan Chen**

Background: Diffuse pulmonary lesions include a large group of pulmonary disorders associated with inflammatory-fibrotic changes. History, physical examination, imaging studies, sputum analysis, serology, and pulmonary function tests may all contribute to a diagnosis. However, surgical lung biopsy is still required in some patients in order to reach a definitive diagnosis.

Materials and Methods: We retrospectively reviewed the charts of 40 patients who had undergone surgical lung biopsy from April 1991 to November 2001. Patients were excluded from the study if their final diagnosis was lung cancer, empyema, or tuberculomas. In the end, we enrolled 22 patients into our study with diffuse pulmonary interstitial infiltrates on radiographic examinations into our study. Ten had had pulmonary function tests which were performed before the surgery.

Results: Four of 10 (40%) had a mild to moderate restrictive lung defect and 2 had an obstructive lung defect found on the pre-biopsy pulmonary function tests. Three patients had diminished diffusing capacity. A definitive pathological diagnosis based on the biopsy specimen was made in all 22 patients. The average duration of chest tube placement after open-lung biopsy was 8.9 ± 4.6 days. The average hospitalization was 22.0 ± 9.3 days. The major complication after surgical lung biopsy was infection (13.6%) and persistent air leakage (9.1%). Nine patients died,_8 of them due to their underlying diseases. ***(Thorac Med 2002; 17: 324-330)***

Key words: diffuse lung disease, surgical lung biopsy

Introduction

"Diffuse pulmonary lesions" is a term denoting a large group of pulmonary disorders associated with pulmonary interstitial or alveolar inflammatory and fibrotic changes. The etiologies may include idiopathic pulmonary fibrosis, collagen vascular disease, metastasis, occupational and environment-related disorders, infectious diseases, familial or congenital disorders, and radiation lung disease. The most common group of diffuse lung lesions is interstitial lung diseases (ILDs), disorders which result in disruption of the distal lung parenchyma and progressive impairment of ventilation. Many of these disorders have common clinical, radiographic, and physiologic consequences. Progressive dyspnea, initially with

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exercise and then at rest, and sometimes cough and fatigue, are the most common complaints.

The roentgenographic features include both alveolar and interstitial infiltrates, and may have 'air bronchogram', diffuse consolidation, or miliary, reticular patterns [1]. The diagnostic approach to these lesions begins with a careful history and physical examination, lung imaging studies, sputum examination, blood serology, and pulmonary function tests. Although some investigators have used bronchoalveolar lavage (BAL) or transbronchial lung biopsy as a diagnostic tool for ILDs, low tissue yield and significant complications limit their usefulness [2-3]. Surgical lung biopsy (SLB) procures larger tissue specimens and is generally considered the most reliable diagnostic method. It may be required for a specific diagnosis in one-third of the patients with diffuse lung diseases [2,13]. However, as an invasive procedure with significant morbidity and mortality, it is not considered a routine diagnostic procedure.

In this study, we reviewed the diagnostic yield and outcome of our patients with diffuse pulmonary lesions who underwent SLB.

Materials and Methods

From April 1991 to November 2001, 40 patients underwent SLB at Mackay Memorial Hospital. Of these 40, 18 had either lung cancer, empyema, or tuberculomas and were excluded from the study.

The records of the remaining 22 patients were retrospectively reviewed. Diffuse pulmonary diseases were suspected in all 22, based on either chest plain films or high resolution computerized tomography, but no definitive diagnosis could be made clinically. Ten patients had had pulmonary function tests (PFT) before open lung biopsy. Of the other 12 patients, 10 could not complete the PFT because of severe dyspnea, and 2 patients were bed-ridden. Biopsies were performed using video-assisted thoracoscopic surgery (VATS) in 14 patients and thoracotomy with a wedge resection (OLB) in 8, with tissue obtained from the lobes most involved radiologically. The method we chose for biopsy usually depended on the medical condition of the patient, an evaluation of the preoperative PFT, the distribution of infiltration in the radiographic findings, technique difficulties in patients as judged by the surgeon, and the risks of thoracotomy. If the medical condition was very complicated and the patient had developed respiratory failure, VATS would be suggested. A chest tube was inserted following each operation, and was removed as soon as no air leak or bleeding was present.

Results

The study group included 8 males (36.4%) and 14 females (63.6%), with an average age of 50.0 ± 15.3 years (range: 18 to 74). The PFT for those tested revealed a mild to moderate restrictive lung defect in 4/10 and impaired diffusing capacity in 5/10. A combined restrictive defect and decreased diffusing capacity was present in 3, and a combined mild obstructive lung defect and decreased diffusing capacity was found in 2. Nine patients were considered immunocompromised (2 with AIDS, 2 with dermatomyositis, 1 with polymyositis, and 4 with malignancy), while the remaining 13 were immunocompetent. The clinical diagnoses included dermatomyositis in 2, polymyositis in 1, recurrent pneumothorax in 2, tuberculosis in 2, lung metastasis in 7, atypical pneumonia in 2, idiopathic pulmonary fibrosis (IPF) in 2, systemic amyloidosis in 1, chronic obstructive lung disease in 1, lymphangioleiomyomatosis (LAM) in 1, and pulmonary alveolar proteinosis (PAP) in 1 (Table 1).

The final diagnoses based on the biopsy included diffuse alveolar damage (DAD) in 3, LAM in 3, histiocytosis X in 2, PAP in 1, bronchiolitis obliterans with organizing pneumonia in 1, *Pneumocystis carinii* pneumonia in 2, usual interstitial pneumonia in 2, non-specific interstitial pneumonia in 2, lymphocytic interstitial pneumonia

Table 1. Patients Demographics, Diagnoses, and Complications (n=19)

Case	Age	Gender	Pre-biopsy Diagnosis	Biopsy Technique	Pathologic Diagnosis	Complication	Outcome (death)
1	45	F	D/M	OLB	DAD	Pneumonia	Yes
2	18	M	Bilateral Pneumothorax	VATS	Histiocytosis X	Persistent air-leak	No
3	38	F	Recurrent Pneumothorax	VATS	LAM	-	No
4	38	F	Tuberculosis	OLB	LAM	-	No
5	36	M	PAP	OLB	PAP	-	No
6	61	M	Metastatic Lung Tumors	VATS	BOOP	-	No
7	46	F	IPF	VATS	NSIP	-	No
8	55	M	Pneumonia	VATS	PCP	Fungal infection	Yes
9	53	F	D/M	OLB	DAD	-	Yes
10	55	F	PM	VATS	DAD	-	Yes
11	74	F	IPF	VATS	UIP	-	No
12	69	F	Amyloidosis	VATS	Amyloidosis+LIP	-	No
13	63	M	Lymphangitic carcinomatosis	VATS	UIP	-	No
14	71	F	COPD	OLB	NSIP	-	Yes
15	56	F	Cx Ca with metastasis	OLB	Organizing pneumonia	Pneumothorax	Yes
16	23	M	TB	VATS	Histiocytosis X	-	No
17	40	F	LAM	VATS	LAM	-	No
18	39	M	Atypical Pneumonia	OLB	PCP+CMV	-	Yes
19	41	F	Lymphangitic carcinomatosis	VATS	Metastasis	Pneumonia	Yes
20	50	F	Lymphangitis carcinomatosis	VATS	Metastasis	-	Yes
21	48	F	Lymphangitis carcinomatosis	VATS	Metastasis	-	No
22	74	M	Metastasis	OLB	Pneumoconiosis	-	No

*D/M: dermatomyositis; PM: polymyositis; IPF: idiopathic pulmonary fibrosis; Cx Ca: cervical cancer

*OLB: open lung biopsy; VATS: video-assisted thoracoscopic surgery

*DAD: diffuse alveolar damage; LAM: lymphangioleiomyomatosis; PAP: pulmonary alveolar proteinosis;

*BOOP: bronchiolitis obliterans obstructive pneumonia; NSIP: non-specific interstitial pneumonitis; UIP: usual interstitial pneumonitis, LIP: lymphocytic interstitial pneumonitisPCP: pneumocystic carinii; CMV: cytomegalovirus

in 1, bleomycin-induced organizing pneumonia in 1, metastasis in 3, and pneumoconiosis in 1 (Table 1). The lung biopsy thus confirmed the pre-biopsy diagnosis in 14/22 (63.6%).

The average duration for a required chest tube insertion after operation was 8.9 ± 4.6 days (range: 3 to 17 days). Excluding the 4 patients who developed acute respiratory failure and died in the ICU, the mean length of ICU stay after lung biopsy was 2.1 ± 1.5 days. The average

Table 2. Characteristics of 19 Patients Undergoing Open Lung Biopsy, Apr. 1991 to Dec. 2001.

	Range/Number	Mean ±SD
Age, yrs	18~74	50.0±15.3
Sex		
male	8	
female	14	
ICU stay, d	0~6	2.1 ±1.5
Chest tube, d	3~17	8.9 ±4.6
Hospitalization, d	7~47	22.0 ±9.3
Method of surgery		
VATS	14	
OLB	8	
Immunocompromised	9	
Change in diagnosis	8	
Change in therapy	7	
Complications	5	
Death	9	
PFT	10	
Restrictive (TLC, %)	2	62.5 ±6.4
(FVC, %)	4	56.8 ±19.6
Obstructive (FEV1, %)	2	63.5 ±19.1
Decrease (DLCO, %)	5	57.2 ±10.8

hospital stay was 22.0 ± 9.3 days, excluding 1 patient with histiocytosis X with persistent air-leak, and 1 who underwent bronchoalveolar lavage twice for alveolar proteinosis. Complications after SLB included pneumonia (3 cases, 13.6 %), persistent air leak (1, 4.5%), and recurrent pneumothorax (1,4.5%), for an overall complication rate of 22.7% (Table 2). Nine of the 22 patients (40.9%) died, 8 due to their underlying diseases and 1 with nonspecific interstitial pneumonitis who developed progressive lung fibrosis and acute respiratory failure. The remaining 13 patients have been followed as outpatients for several years. The complications and mortality differed significantly between the immunocompromised and immunocompetent patients, with more complications (4/9, 44.4% vs 1/13, 7.7%) and higher mortality (8/9, 88.9% vs 1/13, 7.7%) among the immunocompromised patients.

Discussion

Making an accurate diagnosis of diffuse pulmonary lesions is very difficult. A complete history, physical examination, chest radiography, and sputum examination yield a reliable diagnosis in less than 30% of patients [4-5]. Even bronchoscopic biopsy is not totally reliable, providing a definitive diagnosis in from 38% to 85% of patients only. In comparison, the reported diagnostic yield of OLB ranges from 80% to 100% [6]. Gary *et al* performed a prospective, blinded study using OLB in patients with suspected pulmonary fibrosis. The sensitivity, specificity, and accuracy were 87%, 95%, and 90%. The investigators suggest that lung biopsy may be required for diagnosis when clinicians have limited experience, when the diagnosis is uncertain, and when the clinical diagnosis is not IPF [7]. Danis *et al* retrospectively reviewed 43 patients referred for diagnostic lung biopsy: 22 had had VATS and 21 OLB. They found the two methods to be comparable, with the diagnostic accuracy 95% and 100%, respectively [8]. In recent studies, VATS seems to be the preferred method for obtaining adequate multiple lung tissue samples because of the lower rate of associated morbidity, although the magnitude of this differences between VATS and OLB has been questioned. However, open thoracotomy is occasionally required because of severe pleural disease or the need for more definitive control of bleeding. In consideration of the risk of surgery, pulmonary function test results, and the patient's medical cormorbidity in our study, 14 cases had VATS and 8 had OLB. In our investigation, VATS and OLB allowed a definitive tissue diagnosis in all 22 patients.

Abnormal PFT results were present in 5/10 patients in our study. A restrictive ventilatory defect is typical. In a study of 56 patients with IPF reported by Jezek *et al*, reduced FVC and DLCO were associated with reduced survival, particularly in patients with an initial FVC less than 60% predicted, a DLCO less than 40%

predicted, or an age at symptom onset of over 40 years [9]. A combined reduction in VC and TLC was reported to be associated with a 46% reduction in 5-year survival rates [10]. Although the results vary somewhat, the available studies generally suggest a poorer prognosis in patients with decreased FVC, TLC, and DLCO. Nevertheless, normal pulmonary function tests cannot be assumed to exclude pulmonary fibrosis in the presence of suggestive clinical or radiographic abnormalities [11]. Thus far, none of our patients with abnormal PFT results have died.

Some investigators have reported a shorter period of pleural drainage and a shorter hospital stay. In the studies of Boutin *et al* [19] and Dijkman *et al* [22], the need for pleural drainage was 3.4 days and 4.5 days respectively. Arthas *et al* also revealed that the average hospital stay after biopsy was within 8 days, but the total hospital stay was longer than 20 days [6]. In the study of Denis *et al*, 2 patients with complications were excluded because of a refractory air leak and postoperative bleeding, both leading to respiratory failure. These complications resulted in a prolonged pleural drainage (23.1 vs 18.5 days) and hospital stay (41.1 vs 25.1 days) [8]. In our study, the average time of chest tube drainage and the average hospital stay were 8.9 ± 4.6 days and 22.0 ± 9.3 days, including the complicated cases and the terminal patients. Clearly, the time required for pleural drainage following lung biopsy and the length of hospital stay are always dependent on a number of confounding variables, especially in an immunocompromised group.

We had a low complication rate (5/22, 22.7 %), but 9 patients died, 8 mainly due to the progression of the underlying primary disease. Arthas reported postoperative complications in 17% of patients and an operative mortality of 8.4% [6]. Bove had a complication rate in 12% (9/73) after OLB [12]. The most common complication reported was persistent air leak [20]. Others included recurrent pneumothorax, pneumonia, and bronchopleural fistula [12]. The pathologic findings on OLB have been reported to lead to a change of therapy in 51% [13] to 87% [14] of cases. We changed treatment in 7/22 cases based on the SLB results.

Immunocompromised patients undergoing SLB have high mortality. Chen and co-workers evaluated 37 immunocompromised and immunocompetent patients undergoing SLB, comparing diagnostic yield, change in therapy, complications, and mortality. They found that the immunocompetent group was better in all categories [13,18]. Our results support this finding, with 8/9 immunocompromised patients dying. The only immunocompetent patient who died had progressive lung fibrosis. Patients with collagen vascular diseases have been reported to develop DAD [15], which progresses rapidly to mortality [16-17]. In our study, three patients with polymyositis-dermatomyositis rapidly developed acute respiratory failure, and died of hypoxemia. All were shown pathologically to have had DAD.

In conclusion, while SLB is an invasive method, it produces sufficient tissue for a reliable histologic study, especially in diffuse pulmonary diseases [19]. Careful consideration must be given to patient selection, including the patient's immune status [21]. The procedure has a high diagnostic yield for diffuse pulmonary lesions with a relatively low complication rate, especially in immunocompetent patients.

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以外科手術肺切片診斷瀰漫性肺疾病的臨床經驗

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前言：瀰漫性肺疾病乃是一群肺部的急慢性發炎與纖維化病變，通常需藉助病史、理學檢查、影像學檢查、痰液分析、血清檢驗、肺功能測驗、乃至組織學來得到正確的診斷。而外科手術肺切片是最終也是準確性最高的診斷工具。

材料與方法：在 1991 年 4 月到 2001 年 12 月期間，我們總共篩選了 40 位無確切診斷，且已接受開胸肺切片之患者來進行分析。最後有 22 位患者進入本研究之中，其中男性 8 位，女性 14 位，平均年齡 50.0 歲。所有患者均做過放射線學的檢查，其中也包括了肺功能的檢查。

結果：10 位接受術前肺功能測驗的患者當中，40% 顯示侷限型肺功能障礙。胸管引流時間，平均為 8.9±4.6 天；住院日數，平均為 22.0±9.3 天。主要的術後併發症為感染症與持續性氣漏。在我們的研究中，病理的診斷率達 100%。手術後其中有 9 個人死亡，其餘繼續在門診追綜當中。

結論：在瀰漫性肺疾病當中，開胸肺切片有著極高的診斷率，與較低的併發症發生率 (諸如持續性氣漏、術後感染症等)。在免疫功能正常的患者身上施行此術，可得到極高的診斷率與良好的治療方針；但在面對免疫功能不良的患者時，仍應謹慎為之。 ***(胸腔醫學 2002; 17: 324-330)***

關鍵詞：瀰漫性肺疾病，外科手術肺切片

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Respiratory Effort and Ventilatory Drive in Obstructive Sleep Apnea

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Obstructive sleep apnea syndrome (OSAS) is a disorder characterized by the collapse of the pharyngeal airway during sleep, leading to the physiological dysfunction of OSAS. The aim of this study is to investigate the respiratory effort and ventilatory drive in patients with OSAS. We enrolled 32 adults with an AHI higher than 10, and 24 adults with an AHI less than 10, for a respiratory drive study. The OSAS patients had a higher mean AHI (28.39 ± 3.25, n=32 vs 3.45 ± 0.53, n=24, P<0.0001), a higher mean BMI (26.67 ± 0.92 vs 22.99 ± 0.85, P<0.01), and a higher mean neck circumference (NC) (40.48 ± 0.74 cm vs 37.03 ± 0.75 cm, P<0.005) than the control group. In addition, the AHI was significantly correlated with BMI (r=0.49, p=0.004, n=32) and NC (r=0.55, p=0.002, n=32) in the OSAS group. The PEMax was significantly higher in patients with OSAS (85.07 ± 4.78 %, n=32, p< 0.05) compared with that in the control group (68.90 ± 5.09 %, n=24). However, the baseline $P_{0.1}$, $\Delta P_{0.1}/\Delta PetCO_2$, $\Delta MV/\Delta PetCO_2$, and PIMax did not show a significant difference between the two groups. We conclude that a higher BMI and neck mass loading cause more severe OSAS and a higher respiratory effort. It seems that the central respiratory drive does not intervene in OSAS. ***(Thorac Med 2002; 17: 331-339)***

Key words: obstructive sleep apnea syndrome, respiratory effort, ventilatory drive

Introduction

The sleep apnea/hypopnea syndrome (SAHS), divided into obstructive and central types, is probably the most common medical disorder to be described in the second half of the twentieth century [1-2]. Obstructive sleep apnea syndrome (OSAS) is a disorder characterized by a collapse of the pharyngeal airway during sleep, accompanied by arousal from sleep. OSAS occurs in 2-6% of middle-aged men and in 1-2% of middle-aged women, and poses a major health problem to the public [3-6]. The minor symptoms are unrefreshing nocturnal sleep, excessive daytime sleepiness, poor concentration, snoring, nocturia, morning lethargy, difficulty driving long distances, decreased sex drive, and mental retardation [7]. Its major sequels include systemic or pulmonary hypertension, life-threatening arrhythmia, myocardial infarction, cor pulmonale, chronic respiratory failure, and cerebrovascular disease. OSAS has a significant impact on quality of life, and also carries a high cardiovascular and cerebrovascular morbidity and mortality [8-9]. Nevertheless, only a small proportion of OSAS subjects is properly diagnosed, contributing to a lack of awareness of OSAS among the public and

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physicians [10].

Obstructive sleep apnea (OSA) is also defined by the persistence of respiratory effort during the interruption of airflow. Several reports have shown that respiratory effort increases throughout the apneas [11-13]. However, these studies involved small numbers of patients and could therefore not investigate the factors of the between-patient variability in the magnitude of respiratory effort. Given the suggested role of respiratory effort in the consequences of sleep apneas, including arousal [14] and hemodynamic [15] or endocrine [16] consequences, it seemed of interest to analyze the factors predicting the magnitude of respiratory effort.

Disorders in the control of ventilation may have an important role in sleep apnea syndrome (SAS). Some evidence suggests that patients with obesity hypoventilation syndrome (OHS) may have a measurable premorbid impairment of ventilatory chemoresponsiveness [17]. Such an impairment of ventilatory chemoresponsiveness in OHS, however, may be an acquired and reversible consequence of severe obstructive sleep apnea (OSA). Ventilation is constantly monitored and adjusted to maintain appropriate arterial pH (pHa) and PaO_2 [18]. This homeostatic control system requires a system of sensors, a central controlling mechanism, and an effector system to carry out its commands. Its response to changes in blood chemistry, mechanical load, metabolic rate, and respiratory neural receptors enables the respiratory system to adapt to special physiologic circumstances such as sleep, exercise, and altitude, as well as to compensate for pathologic disorders such as asthma, COPD, drug use, Cheyne-Stokes respiration (CSR), and neurologic disease [19]. It is well known that the transient withdrawal of the central respiratory drive to respiratory muscles results in central sleep apnea (CSA). However, there has been little study of the effect of obstructive sleep apnea on the ventilatory drive.

Therefore, this study was designed to investigate the respiratory effort and ventilatory drive in patients with obstructive sleep apnea syndrome.

Materials and Methods

Patients and study design

Fifty-six adult patients were enrolled from July 2001 to February 2002, at Chang Gung Memorial Hospital, for an evaluation of their sleep-disordered breathing. They were all either Taiwanese or Hakka. They were divided into OSAS and non-OSAS groups, according to their polysomnography results. There were thirty-two patients in the OSAS group, aged from 26 to 82 years old, with a mean apnea-hypopnea index (AHI) of 28.39; and there were twenty-four patients in the control group, aged from the 25 to 83, with a mean AHI of 3.45 (Table 1). All of the two groups of patients underwent a respiratory effort and ventilatory drive study. Subjects were asked to refrain from caffeine and tobacco consumption on the day of the study until after completion of the lung function tests, ventilatory response measurements, and arterial blood gas sampling. The study protocol was approved by the local Ethics Committee and all patients gave informed consent.

Table 1 Subject demographics

Measurement	OSAS(AHI>10)(n=32)		CONTROL(AHI<10)(n=24)		P Value
	Mean	SEM	Mean	SEM	
AHI, events per hour	28.39	3.25	3.45	0.53	<0.0001
Age, yr	60.84	2.84	62.04	3.15	0.78
BMI, kg/m^2	26.67	0.92	22.99	0.85	0.0061
Neck circumference, cm	40.48	0.74	37.03	0.75	0.003

Definition of abbreviations: AHI = apnea-hypopnea index; BMI = body mass index; OSAS = obstructive sleep apnea syndrome.

Clinical evaluation

Each patient's age, gender, weight, and height were recorded. Body mass index (BMI) was calculated based on the patient's height and weight in standard units of kilograms-per-meter squared (Table 1). Neck circumference (NC) was measured at the level of the thyroid cartilage. A single physician performed all measurements [20].

Polysomnographic study

A one-night polysomnography (Embla, Flaga hf, Iceland) was performed with all patients. During the polygraphic recording, the monitored variables included central, occipital, and frontal electroencephalograms, electro-oculograms, chin electromyogram, electrocardiogram, and chest and abdominal wall motion tests. Airflow was measured by thermistor, and oxygen saturation by pulse oximeter. Snoring was measured with a microphone attached to the lateral surface of the thyroid cartilage. Sleep was scored using the criteria of Rechtschaffen and Kales [21] for 30 s epochs, and respiratory events were scored using standard criteria. Diagnostic definitions were: (1) apnea, a cessation of airflow for at least 10 s; and (2) hypopnea, a greater than 50% reduction in airflow for at least 10 s, associated with a more than 4% fall in oxygen saturation. Only those patients who had more than 10 episodes of apnea/hypopnea per hour, with at least 80% of the episodes of an obstructive or mixed type, were considered for enrollment in the OSAS group.

Respiratory effort study

Measurement of PEMax and PIMax

The mouth occlusion pressure at maximum expiration (PEMax) and inspiration (PIMax) was measured while the patient performed maximal expiratory and inspiratory efforts. As soon as the patient started to exhale or inhale, the shutter closed and measured pressure automatically. Ma-neuvers were repeated until three measurements with less than 5% variability were recorded. The highest value obtained was utilized for analysis.

Arterial blood gas was drawn, and arterial pH, PaO_2 (arterial partial pressure of oxygen) and $PaCO_2$ (arterial partial pressure of carbon dioxide) were analyzed with a Corning 288 Gas analyzer.

Ventilatory drive study

A) Measurement of $P_{0.1}$

The patients were comfortably seated wearing a nose clip. The mouthpiece was connected to a pneumotach apparatus, using a shutter valve (Erich Jaeger, Hoechberg, Germany), which consisted of an electronically-controlled magnetic valve. The shutter was activated at end-expiration in irregular intervals during measurement. At the end of expiration, the shutter was set automatically. After 0.1 seconds the inspiratory mouth pressure ($P_{0.1}$) was measured while the patient attempted to inhale. One trial could be ended after the shutter had been set for about 10-15 times. The mouth occlusion pressure was expressed as absolute value (cmH_2O). The pneumotach apparatus also measured the minute ventilation (MV). The $P_{0.1}$ and MV data were obtained from the mean calculated value of the last 10 breaths.

B) CO_2 challenge test

The measurement of mouth occlusion pressure after the CO_2 challenge ($P_{0.1}CO_2$) was performed while the patient inhaled a 6% CO_2 gas mixture. The gas mixture (6% CO_2 and 94% room air) cylinder was connected to a 25-liter gas bag, which was connected to a Y-valve (Erich Jaeger, Hoechberg, Germany) with the shutter. The patient was asked to approach the mouthpiece and breathe quite normally from the gas bag for 1-3 minutes, allowing the subject to equilibrate with the circuit as shown by the plateau on the end-expired CO_2 ($PetCO_2$) record. The $P_{0.1}CO_2$ was measured when the $PetCO_2$ was raised 10 mmHg above the base data. We calculated the slope using $P_{0.1}CO_2$ minus $P_{0.1}$, divided by the raised value of $PetCO_2$ (about 10 mmHg), expressed as $\triangle P_{0.1}/\Delta PetCO_2$. Expired CO_2 ($PetCO_2$) was measured contin- uously at the mouth by an infra-red CO_2 Meter-Capnometer

8200 (BCI International Co., Wisconsin, USA). Oxygen saturation was continuously monitored by a Pulse Oximeter 3301 (BCI International Co, Wisconsin, USA). The periods of the two measurements (one inhaling room air, the other inhaling oxygen) were 10 min in duration each, separated by 2 hours as a washout phase.

Statistical Analysis

All the numeric data were presented as means and standard error of means. The unpaired T test was used for comparison between the OSAS group and the control group. A statistically significant difference was considered when the P value was smaller than 0.05. Pearson's correlation coefficient was used to evaluate the relationship between those variables with a significant difference and the AHI score. Prism software, version 3.0, was used for all statistical analysis.

Results

Baseline characteristics

The anthropometric variables of the OSAS and control groups are presented in Table 1. The OSAS group had a higher mean AHI (28.39 ± 3.25, n=32 vs 3.45 ± 0.53, n=24, P<0.0001), a higher mean BMI (26.67 ± 0.92 vs 22.99 ± 0.85, P<0.01), and a higher mean neck circumference (NC) (40.48 ± 0.74 cm vs 37.03 ± 0.75 cm, P<0.005) than the control group, respectively, whereas these two groups had a comparable age. In the OSAS group, the AHI was significantly correlated with BMI (r=0.49, p=0.004, n=32) and NC (r=0.55, p=0.002, n=32) (Fig. 1 and 2).

Respiratory effort and arterial blood gas analysis in OSA

The PEMax was significantly higher in patients with OSA (85.07 ± 4.78 %, n=32, p< 0.05), compared with that in the control group (68.90 ± 5.09 %, n=24). However, the PIMax did not show a significant difference between the two groups (52.05 ± 3.53 %, n=32 vs 48.12 ± 4.64 %, n=24, p>0.05)

Based on the increase in breathing effort, the $PaCO_2$ in room air was lower in the OSAS group compared with the control group (38.18 ± 1.14 mmHg vs 41.94 ± 1.33 mmHg, P<0.05). By contrast, the PaO_2 in room air was higher in the OSAS group compared with the control group (78.78 ± 3.24 mmHg vs 69.22 ± 2.50 mmHg, P<0.05).

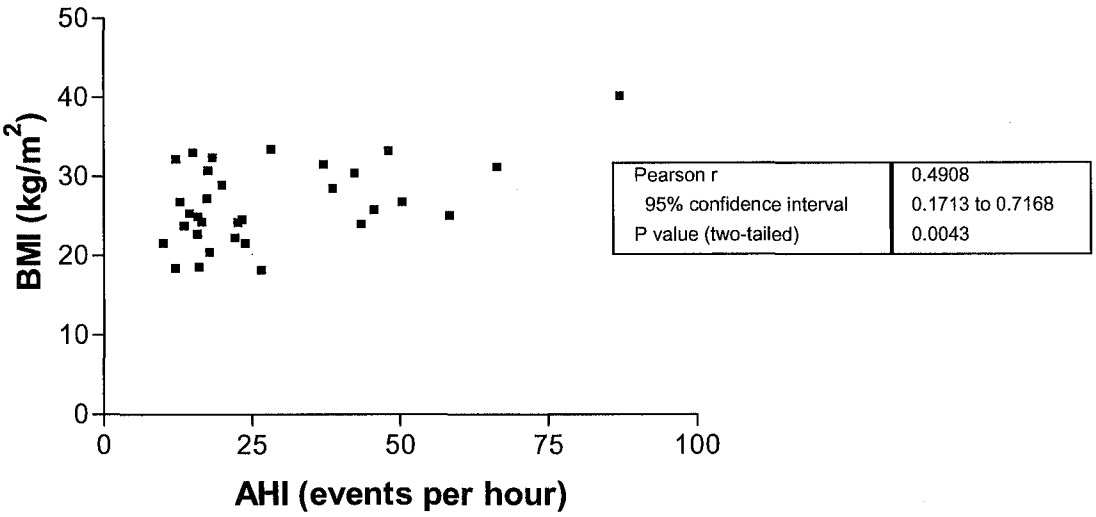

Fig. 1. The correlation between AHI and BMI in patients with OSAS.

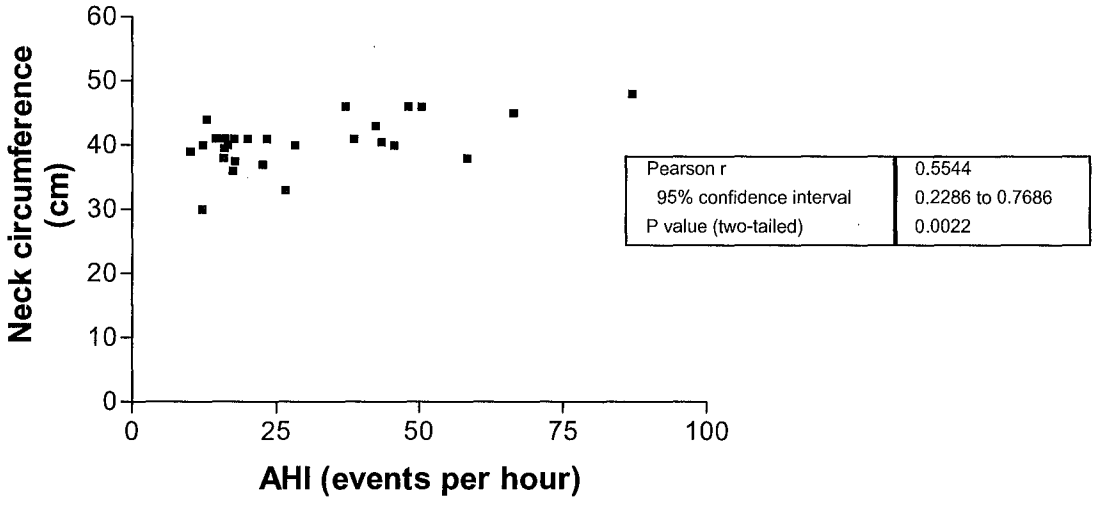

Fig. 2. The correlation between AHI and neck circumference in patients with OSAS.

Ventilatory drive in OSA

The baseline $P_{0.1}$, $\Delta P_{0.1}/\Delta PetCO_2$, $\Delta MV/\Delta PetCO_2$, and $P_{0.1}/PIMax$ did not show a significant difference between the two groups (Table 2). Similarly, there was no significant correlation between AHI and baseline $P_{0.1}$, $\Delta P_{0.1}/\Delta PetCO_2$, $\Delta MV/\Delta PetCO_2$, $P_{0.1}/PIMax$, $PaCO_2$, and PaO_2, in the two groups.

Discussion

Our results showed that there were significant differences in body mass index and neck circumference between the OSAS and control groups. The level of AHI in patients with OSAS was highly correlated to BMI and neck circumference. We also found that the expiratory effort, but not the inspiratory effort, was signify-cantly increased in patients with OSA, thus leading to greater effort in breathing. However, the ventilatory drive in OSAS patients, including $P_{0.1}$, $\Delta P_{0.1}/\Delta PetCO_2$, and $\Delta MV/\Delta PetCO_2$, was not significantly different from that of the control group, adjusted for age and lung function.

OSAS results from recurrent narrowing of the supraglottic airway during sleep. The site of airway narrowing during sleep is usually at the retropalatal or retroglossal level [22-23]. There is considerable evidence indicating that anatomical factors contribute to this upper airway narrowing. Patients with OSAS have an increased deposition of adipose tissue around the upper airway, particularly lateral to the pharynx [24-25]. The anteroposterior shortening of the face produces a narrowing of the upper airway [26-28]. Many studies have shown that the upper airway in patients with OSAS is more liable to collapse during both wakefulness and sleep [29-31]. Anatomic factors, such as neck soft tissue mass, parapharyngeal fat, and craniofacial bony structure, are likely to be important determinants in OSAS. It is reasonable to assume that particular features of the craniofacial bony and soft tissue structure might increase pharyngeal collapsibility, and that these differences are significant between OSAS and control groups. Our data demonstrated that body mass index and neck circumference not only showed a significant difference between the OSAS and control groups, but also highly correlated to the AHI, suggesting that those who had a higher BMI and neck mass loading might have more severe OSAS. These results are similar to previous observations [32]. In another study, neck circumference was thought to be a more useful predictor than general obesity [33].

In normal subjects, this narrowing of the airways, caused by a higher BMI and neck mass loading, results in increased airflow resistance

Table 2 Clinical and respiratory drive data of OSAS and control patients

Measurement	OSAS(AHI>10)(n=32)		CONTROL(AHI<10)(n=24)		P Value
	Mean	SEM	Mean	SEM	
$P_{0.1}$, cmH_2O	0.41	0.05	0.42	0.04	NS
$P_{0.1}$, %	214	25.59	256	28.64	NS
$P_{0.1}$ CO_2, cmH_2O	0.7	0.07	0.8	0.08	NS
Δ $P_{0.1}/\Delta$ $PetCO_2$	0.22	0.04	0.31	0.05	NS
Δ MV/Δ $PetCO_2$	0.49	0.08	0.51	0.08	NS
$P_{0.1}$/PIMax	8.78	1.21	11.1	1.94	NS
PIMax, %	52.05	3.53	48.12	4.64	NS
PEMax, %	85.07	4.78	68.9	5.09	0.028*
$PaCO_2$, mmHg	38.18	1.14	41.94	1.33	0.036*
PaO_2, mmHg	78.78	3.24	69.22	2.5	0.032*

Definition of abbreviations: OSAS = obstructive sleep apnea syndrome; AHI = apnea-hyponea index;
$P_{0.1}$ = mouth occlusion pressure; $P_{0.1}$, % = percentage of predicted $P_{0.1}$ value
$P_{0.1}CO_2$ = mouth occlusion pressure after carbon dioxide challenge
Δ $P_{0.1}$ = $P_{0.1}CO_2$ - $P_{0.1}$; Δ MV = change of minute ventilation after CO_2 challenge
Δ $PetCO_2$ = change of end-tidal carbon dioxide pressure after carbon dioxide challenge
PIMax, % = percentage of predicted maximum inspiratory pressure
PEMax, % = percentage of predicted maximum expiratory pressure
$PaCO_2$ = arterial partial pressure of carbon dioxide
PaO_2 = arterial partial pressure of oxygen
NS= not significant
* Significant difference between OSAS patients and control subjects

that is usually of no major significance [22]. However, in about 50% of middle-age men and 30% of middle-age women, this upper airway narrowing is sufficient to cause marked turbulent flow with the associated vibration of snoring. This observation may also be related to the shallow breathing pattern observed after upper airway occlusion in normal subjects [34], suggesting that the respiratory effort will increase in association with a higher resistance of the upper airway. Therefore, it is reasonable that our data showed an increase in the respiratory effort in patients with OSAS, thus leading to a rapid and shallow breathing pattern.

Studies that have evaluated the relationship between ventilatory responsiveness to hypercapnia and OSAS have shown inconsistent results. Verbraecken et al [35], for instance, observed an increase in response to hypercapnia in 14 normocapnic OSAS patients. Garay et al [36], in contrast, showed normal responses to hypercapnic stimulation in six eucapnic OSAS patients. In both studies, hypercapnic OSAS patients demonstrated a blunted response to hypercapnia. Lopata and Onal [37] reported a diminished response to hypercapnia in 15 OSAS patients, half of whom were normocapnic. Inadequate control of confounding variables, such as obesity, age, gender, and presence of comorbid conditions make interpretation of these studies difficult. Moreover, these studies enrolled relatively few patients, resulting in diminished statistical power. Therefore, we studied a larger group of patients with and without OSAS, to ascertain the independent effects

of OSAS on hypercapnic ventilatory response using a CO_2 challenge test, and to identify important determinants of hypercapnic ventilatory response. According to our data, it seems that the central respiratory drive, even with the stimulation of CO_2, does not intervene in sleep apnea syndrome, obstructive type. This result was consistent with the report of De Luca et al [38], who showed that there was no difference in ventilatory drive, $P_{0.1}$, between OSAS patients and a control group. Thus, pharmacological therapy, including central respiratory stimulants, is not useful in the management of OSAS.

We also found that there was a significant difference in $PaCO_2$ between these two groups. The patients with OSAS had a lower level of $PaCO_2$ than the control subjects. However, there was no significant difference in baseline $P_{0.1}$, $\Delta P_{0.1}/\Delta PetCO_2$, $\Delta MV/\Delta PetCO_2$, PIMax, and $P_{0.1}$/PIMax between the OSAS and control groups. In addition, in both groups, there was no significant correlation between AHI and baseline $P_{0.1}$, $\Delta P_{0.1}/\Delta PetCO_2$, $\Delta MV/\Delta PetCO_2$, PIMax, and $P_{0.1}$/PIMax. This implies that the difference in $PaCO_2$ might be due to the change in respiratory effort, and not the ventilatory drive.

We conclude that the severity of OSAS was highly correlated to BMI and neck circumference, resulting in the increase of respiratory effort in patients with OSAS. Moreover, it seems that the central respiratory drive does not intervene in OSAS.

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阻塞性睡眠窒息症候群(OSAS)之呼吸使力(Respiratory Effort)及通氣驅動力(Ventilatory Drive)

蘇榮璋 羅友倫 林孟賢 沈資益 鄭志賢 林鴻銓 郭漢彬 陳豪成

阻塞性睡眠窒息症候群(OSAS)肇因於睡眠時咽部呼吸道之重複塌陷，導致生理功能之失調。為了正確了解阻塞性睡眠窒息症候群(OSAS)病人呼吸使力(respiratoy effort)及通氣驅動力(ventilatory drive)的差異，本研究比較三十二個阻塞性睡眠窒息症候群(OSAS)病人及二十四個對照組病人有關呼吸使力及通氣驅動力的差異。研究結果顯示二組病人間身體質量指數(BMI)、頸圍、及最大吐氣壓力(PEMax)有明顯差異；但有關每百毫秒口腔阻壓力($P_{0.1}$)、每分鐘通氣量的改變($\Delta MV/\Delta PetCO_2$)、及最大吸氣壓力(PIMax)，則二組病人之間並無明顯差異。研究結果認為較大的身體質量指數(BMI)及頸圍，易導致較嚴重之阻塞性睡眠窒息症候群(OSAS)及較高之呼吸使力，但中樞之通氣驅動力似乎無明顯差異。 ***(胸腔醫學2002; 17: 331-339)***

關鍵詞：阻塞性睡眠窒息症候群(OSAS)，呼吸使力，通氣驅動力

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Eventration of the Diaphragm in Adults—Experience at Taipei-VGH

Chih-Ming Lin, Yu-Chung Wu, Wen-Hu Hsu, Ming-Hsiung Huang, Liang-Shun Wang

Diaphragmatic eventration is a condition with all or a portion of the hemidiaphragm elevated permanently, yet retaining its continuity and normal attachments to the costal margins. This diaphragmatic disease is rare and the cause is yet to be understood. In newborns, eventration with respiratory failure may require intubation and immediate surgical attention. For adults, indications for surgery are uncommon, and one must be very careful before recommending plication for respiratory or digestive symptoms. From 1978 to 2001, eleven adults were treated for diaphragmatic eventration, and their data were reviewed for this study. Their ages at diagnosis ranged from 34 to 82 years, with a mean of 55.3 years. Male and female were almost equally affected (6 men, 5 women). The left diaphragm was more frequently involved (9 left, 2 right). Ten symptomatic patients underwent exploratory thoracotomy, and one asymptomatic patient underwent thoracoscopy to confirm the diagnosis. Nine cases were classified as complete types, and the other two as partial types. Two of the 11 patients obtained a definitive diagnosis only after surgical intervention under the impression of diaphragmatic neoplasms. Diaphragmatic plications were performed for all ten symptomatic patients. The asymptomatic patient didn't undergo management after the diagnosis was confirmed via thoracoscopy. No surgical complication or mortality was encountered in our series. All ten symptomatic patients showed both subjective and objective improvement after operation. Based on our experience, diaphragmatic plication is a safe and effective procedure in the management of patients with symptomatic eventration.
(Thorac Med 2002; 17: 340-345)

Key words: diaphragmatic eventration, plication

Introduction

Eventration of the diaphragm is a rare disease entity and its cause is not well known [1-2]. True eventrations are always derived from a congenital developmental defect in the musculature of one portion or of the entire central part of the diaphragm, but the weakened diaphragm retains its continuity and normal attachments to costal margins. It is differentiated from a hernia by the unbroken continuity of the diaphragm. In general, congenital eventration of the diaphragm is probably a true congenital defect acquired during fetal development. Phrenic interruption after birth may result in diaphragmatic paralysis, gradual atrophy, and the ultimate disappearance of the diaphragmatic muscle. A large diaphragmatic

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eventration in the newborn or neonate may be associated with secondary hypoplasia of the lung on the involved side, and lead to severe cardiopulmonary embarrassment [3]. In adults, complete eventration is more often found on the left side, and the elevated diaphragm is routinely found on chest radiographs. Partial eventration is more frequently observed on the right side and the anterior. The clinical features consist of dyspnea on exertion, shortness of breath, recurrent pneumonia, chronic bronchitis, chest pain, cardiac arrhythmia, or functional disorders of the stomach. The intraabdominal organs may be upwardly displaced, and cause organo-axial volvulus with subsequent alimentary symptoms [4-5]. Patients with impaired respiratory and alimentary functions caused by diaphragmatic elevation generally require surgical correction. A variety of surgical treatments have been developed. However, on account of the low incidence of the disease, the available literature does not provide adequate information about the differential diagnosis, indications and modes of surgical treatment, and the long-term functional results after management. Herein, we report our experience in the diagnosis and treatment of 11 patients with diaphragmatic eventration, as well as the long-term results after surgical correction. Then, diagnostic approaches, therapeutic indications, and modes will be further discussed.

Material and Methods

The data of eleven patients with diaphragmatic eventration treated between 1978 and 2001 at Taipei-Veterans General Hospital were retrospectively reviewed. The information obtained from the medical records is summarized in Table 1. There were 6 males and 5 females, and their mean age at diagnosis was 55.3 years old, ranging from 34 years to 82 years. All patients were referred from other hospitals under the suspicion of diaphragmatic abnormalities, or tumors. No patients had a history of thoraco-abdominal injury. After admission, the preoperative work-up consisted of blood cell counts, biochemistry studies, chest radiography, pulmonary functional tests, and fluoroscopy. An upper gastrointestinal (UGI) series and computed tomography of the chest and/or upper abdomen were also done if needed. In addition, a video-assisted thoracoscopy would be performed if a diaphragmatic tumor was highly suspected. All symptomatic patients were managed surgically. After discharge from the hospital, the patients were regularly followed up at the out-patient clinic. The respiratory and alimentary symptoms were carefully evaluated, but only two patients received a postoperative pulmonary function test (3 months after surgery) for comparison.

Results

Ten (91%) of the 11 patients had developed clinical symptoms of various duration (two to six months) before admission to the hospital. As shown in Table 1, most of the symptoms were related to respiratory problems, including dyspnea (82%) and cough (11%). Only one patient, who had a partial eventration of the diaphragm (case 7), was asymptomatic. After admission, nine patients were found to have an elevated diaphragm, as evidenced on the chest radiograph (Figure 1), and the diagnosis of diaphragmatic eventration or paralysis was recommended by the radiologists. Furthermore, only two of these 9 patients showed an obviously abnormal motion of the diaphragm on fluoroscopic studies. Unfortunately, the other two patients (cases 3 and 7) were given a definitive diagnosis only after surgical intervention due to the initial suspicion of diaphragmatic neoplasms. These two patients were found to have the partial type of diaphragmatic eventration. Thus, the rate of misdiagnosis before surgery was 18.2%. The distribution of diaphragmatic eventration consisted of 9 left-side diaphragms (8 complete types and one partial type) and 2 right-side diaphragms (one complete and one partial) (Table 1). The modes of surgical approach included 10 limited

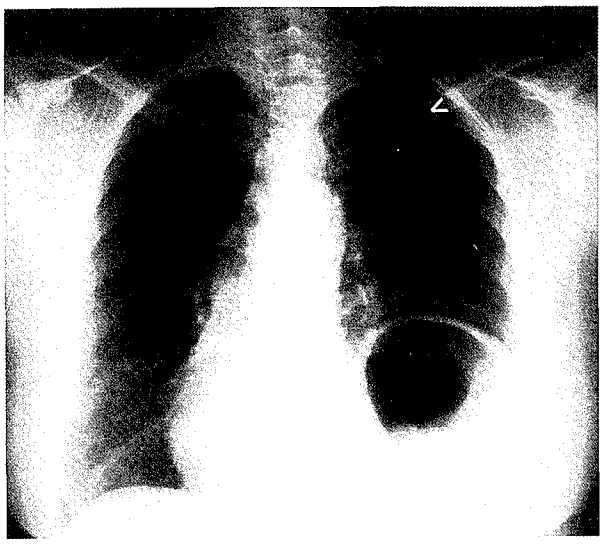

Fig. 1. Left complete eventration before operation. The patient had cough and dyspnea on exertion.

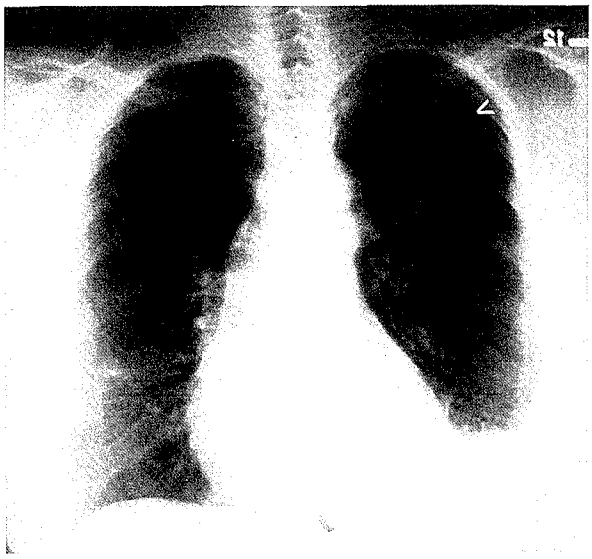

Fig. 2. After diaphragmatic plication. The diaphragm is restored to its normal position.

thoracotomies with diaphragmatic plication (Figrue 2). and one video-assisted thoracic surgery (VATS) for diagnosis of a partial eventration of the diaphragm. No surgical complication or mortality developed in this series, and all patients were discharged uneventfully. Clinically, all symptomatic patients undergoing diaphragmatic plication experienced an improvement of symptoms, especially respiratory distress. Compared with the results of the preoperative pulmonary function tests, two patients showed an obvious increase in postoperative pulmonary function. (Table 2).

Discussion

Eventration was first recognized and described by Petit in the 18th century, and the first report of a successful repair was made by Morrison in 1923 [6]. Most eventrations reported in the literature were left-sided, with a male predominance. Complete eventration is more common on the left side, but the partial type is more usually on the right side and anterior. In our series, complete eventration of the left hemidiaphragm was predominant, but nearly equal in sex distribution. Diaphragmatic or hepatic tumors should be differentiated before operation, particularly for the smaller partial eventration. Grossly, the eventrated diaphragm is thin with a membranous appearance, whereas the more peripheral portion is still muscular with normal attachments to the sternum, ribs, and dorsolumbar spine. Microscopically, the abnormal area of diaphragm always contains some muscular fibers, although these are lower in number and dispersed in every direction. Spirometry is usually used for the diagnostic evaluation of the disease, but the clinical course does not seem to be absolutely correlated to the extent of involvement [5]. Patients with small unilateral lesions may be asymptomatic, or only mildly symptomatic. On the other hand, patients may also be asymptomatic even in the presence of a large or bilateral eventration of the diaphragm. These asymptomatic patients generally do not require treatment [3]. Unfortunately, almost all the patients with a complete type of diaphragmatic eventration in our series were associated with respiratory or alimentary symptoms. Occasionally, congenital eventrations have been reported to be associated with other developmental defects such as hypoplastic aorta, cleft palate, transposition of the abdominal organs, or undescended testicle [7].

Acute respiratory failure is the most pronounced feature of the large eventration in the

Table 1 Summary of patient data

Case No.	Sex/Age		Symptoms & Signs	Extent and side	Operation	Clinical result
1	F	58	Cough, DOE	LT, complete	Plication	Improved
2	F	50	DOE	LT, complete	Plication	Improved
3	M	65	DOE, SOB	RT, partial	Plication	Improved
4	M	44	SOB	LT, complete	Plication	Improved
5	M	55	SOB	LT, complete	Plication	Improved
6	M	34	DOE	LT, complete	Plication	Improved
7	F	58	--	LT, partial	Thoracoscopy	--
8	M	39	DOE	RT, complete	Plication	Improved
9	F	55	Cough, DOE	LT, complete	Plication	Improved
10	M	68	Bloating	LT, complete	Plication	Improved
11	F	82	SOB	LT, complete	Plication	Improved

DOE: dyspnea on exertion; SOB: shortness of breath.

Table 2. Pulmonary Function Evaluation

Case	Pre-OP		Post-OP	
No.	FEV1	FVC	FEV1	FVC
9	1.37(65%)	1.74(67%)	1.62(82%)	2.20(90%)
10	1.74(76%)	2.16(69%)	1.82(79%)	2.38(76%)

FEV1: forced expiratory volume in 1 second

FVC: forced vital capacity; (%) predictive percentage

newborn, and it is important to differentiate eventration from a congenital diaphragmatic hernia [3-4]. In children with eventration, diaphragmatic plication remains controversial for those who are asymptomatic. However, when one considers that the lung continues to grow until the age of 10 years, it seems reasonable to provide space for future pulmonary development [8]. In adults, the diagnosis of eventration can be made on standard posteroanterior and lateral chest films. With fluoroscopy, paradoxical respiration is not seen in true eventration. In acquired paralysis, the entire diaphragm is immobile and there is a true paradoxical motion. Diagnostic pneumoperitoneum, a technique described by Zeitlin in 1930 might be useful [9]. A CT scan or ultrasonography is not very useful in the diagnostic differentiation of eventration and herniation of the diaphragm. The definite diagnosis may only be made at surgery when the classical appearance of the normal peripheral muscles and the atrophic eventrated portion are seen. There is little difficulty at thoracotomy in distinguishing eventration with its membranous appearance from diaphragmatic paralysis, in which the diaphragm, even if somewhat atrophic, is still fully muscular. In our series, the mis-diagnostic rate before surgery was rather high.

Most patients with diaphragmatic eventration should be treated conservatively unless significant dyspnea develops and compromises their daily activities, or alimentary symptoms are clearly related to the high position of the diaphragm. For symptomatic patients, diaphragmatic plication may be indicated in order to improve the pulmonary parenchymal volume by restoring the diaphragm to its normal position [5,10]. Diaphragmatic plication is performed generally via a limited thoracotomy. Entry into the pleural space is made through the bed of the 8th rib or the 8th intercostal space [2]. The thinned-out diaphragmatic leaf is repaired by plication after the adhesion is freed. In addition to plication, the leaf can be incised and then carried out by imbricating one layer over the other with interrupted sutures of nonabsorbable suture material. Recently, the repair of diaphragmatic eventration has also been performed by video-assisted thoracic surgery (VATS), rather than the standard thoracotomy [10-12]. With this technique, the eventrated diaphragm is pushed down by endoscopic clamps and then plicated using two superimposed transverse continuous sutures. The

advantage of VATS is its minimal invasiveness and shortening of the hospital stay. However, the thoracoscopic surgery may be limited by pleuropulmonary adhesions. The rate of surgical morbidity and mortality is quite low. All of the ten symptomatic patients obtained both subjective and objective improvement in respiratory and alimentary symptoms, and no surgical complication occurred after operation.

Conclusion

Eventration is a rare anomaly in adults and is always with or without nonspecific symptoms. Surgical intervention is suggested only for symptomatic patients, and is not necessary for asymptomatic ones. Either thoracotomy or VATS can be used to relocate the elevated diaphragm to its normal position. Nearly all symptomatic patients can improve clinically, even if pulmonary function doesn't increase. Although diaphragmatic plication is a safe procedure, one has to be even more careful in recommending surgery before an appropriate period of observation and medical treatment.

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成年人之橫膈上提—台北榮總之經驗

林志銘　吳玉琮　許文虎　黃敏雄　王良順

橫膈上提(diaphragmatic eventration)為一種少見且原因不明之疾病，病患之橫膈膜有部份或全部上提之情形，但其與肋骨之接合處為完整的。就新生兒患者而言，若有呼吸障礙之情形，往往需要立即施予氣管內插管及手術矯正；就成人而言，手術治療僅建議於有呼吸或腸道症狀之患者來施行。從 1978 年至 2001 年，本科共有 11 位橫膈上提之患者接受治療，其年齡分佈從 34 至 82 歲，平均年齡為 55.3 歲。男性患者 6 位，女性患者 5 位；左側橫膈上提者 9 位，右側 2 位；完全型橫膈上提者 9 位，部份上提者 2 位。共有 10 位患者因具症狀而接受手術治療(包括 9 位手術前診斷為橫膈上提及一位疑為橫膈腫瘤)，另一位無症狀患者，僅接受胸腔鏡檢查而確定診斷，並未接受進一步治療。因此，術前之誤診率可高達 18.2%。前述接受手術治療之 10 位病患，並無併發症或死亡之發生，術後無論是客觀或主觀評估，症狀均獲得改善。依據吾等之經驗，橫膈摺疊術對有症狀之橫膈上提患者而言，為一種既安全又有效之治療方式。 ***(胸腔醫學 2002; 17: 340-345)***

關鍵詞：橫膈上提，橫膈摺疊術

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Clinical Experience with Embolotherapy of Pulmonary Arteriovenous Malformations— Results and Follow-up in Six Patients

Chang-Sang Mai*, Pei-Jan Chen, Hsu-Tah Kuo

Pulmonary arteriovenous malformations (PAVM) are direct communications between branches of the pulmonary artery and pulmonary vein, without an intervening capillary network. The clinical manifestations include dyspnea, fatigue, cyanosis, transient ischemic attacks, brain abscess, and hemothorax. Pulmonary angiography remains the diagnostic gold standard for PAVM. Treatment options include occlusion by embolotherapy or surgical excision. We report our experience with 9 patients with PAVM, 6 of whom were treated with embolotherapy. All 6 had improvement of symptoms and arterial oxygenation, and there were no complications. The safety of embolotherapy makes this procedure the treatment of choice in PAVM. ***(Thorac Med 2002; 17: 346-353)***

Key words: pulmonary arteriovenous malformation (PAVM), embolotherapy.

Introduction

Pulmonary arteriovenous malformation (PAVM) was first described relatively recently in medical history, when Churton, in 1897, reported the autopsy findings in a young boy with cyanosis [1]. PAVM was first diagnosed in a living patient in 1939 [2]. PAVM consists of direct connections between a branch of a pulmonary artery and a pulmonary vein through a thin-walled aneurysm. The clinical presentation ranges from incidental findings on a chest radiograph in an asymptomatic patient to dyspnea on exertion, orthodeoxia, hemoptysis, fatigue, epistaxis, chest pain, clubbing, stroke or transient ischemic attack, or brain abscess [3]. Sometimes the clinical features are ignored, delaying the diagnosis. Noninvasive procedures for evaluating patients with suspected PAVM include chest radiographs, spiral dynamic computed tomography, contrast echocardiography, color Doppler ultrasound, radionuclide angiography, perfusion lung scan, fluoroscopy, and magnetic resonance imaging [4-5]. These are used to confirm or reject a clinical diagnosis. Pulmonary angiography, however, remains the diagnostic gold standard for PAVM.

The natural history of this disease is still incompletely understood, owing to the paucity of cases, although recent studies suggest it is far from benign. Treatment options for PAVM include occlusion by less-invasive therapy (embolotherapy) and surgical excision.

We hevein review our clinical experience with 9 patients with PAVM seen at Mackay Memorial Hospital from 1990 to 2001.

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Table 1. Clinical data of patients with PAVM

Case No	Gender	Age (years)	No. of PAVMs	PAVM size (cm^2)	PAVM location
1	M	26	1	1.3×1.2	LLL
2	F	17	1	1.8×1.4	RUL
3	F	33	2	1.8×1.2	RLL
				1.4×1.2	RLL
4	F	45	1	2.0×1.4.	RUL
5	F	29	1	1.5×1.2	RLL
6	F	33	1	2.5×2.0	LLL
				1.4×1.1	LLL
7	F	52	3	1.2×1.0	LLL
				1.0×0.8	RML
				2.0×1.5	LLL
8	M	40	3	1.6×1.2	RML
				1.2×0.8	LLL
9	F	11	Multiple	<1.0×0.6	Bilateral

(F: female, M: male,PAVM: pulmonary arteriovenous malformation, LLL: left lower lobe, RUL: right upper lobe,RLL: right lower lobe, RML: right middle lobe)

Materials and Methods

We retrospectively reviewed the charts of 9 patients with documented PAVM seen at Mackay Memorial Hospital from 1990 to 2001. In all patients, the diagnosis was confirmed by pulmonary angiography. Data recorded included the complete history, physical examination, chest radiographic findings, and arterial blood gas (ABG) measurement with room air. The number, size, and location of the PAVMs were recorded from the angiography report. Therapy was also analyzed.

Table 2. Clinical presentation

Case No	Symptoms & Signs
1	Dyspnea
2	Dyspnea, dizziness, cough
3	Chest pain, cough, dyspnea
4	Dyspnea on exertion, cough, finger clubbing , central cyanosis
5	Epistaxis
6	Epistaxis
7	Epistaxis, dyspnea
8	No symptoms
9	Lip cyanosis, finger clubbing , dyspnea, polycythemia

Results

The patient cohort included 2 males and 7 females who ranged in age from 11 to 52 years (mean 31.8 years). Five patients had a single PAVM, while 4 had more than 2 lesions. The clinical presentations and locations of the PAVMs are listed in Tables 1 and 2. Three patients (7, 8, 9) were diagnosed with Osler-Weber-Rendu syndrome. Six patients underwent a coil occlusion of the PAVM, with one requiring the multiple embolization of two PAVMs. After embolization, their symptoms and arterial blood gas measurements improved (Table 3). Two patients (cases 7, 8) refused any further intervention because of age (patient 7) or lack of symptoms (patient 8). One patient (9) had multiple bilateral PAVMs, and was in poor condition clinically, so the decision was made to perform lung transplantation. The 6 patients who underwent lung embolization were followed in our OPD. None had recanalization, nor were there any complications post-embolotherapy The average follow-up was 1.5 years (0.6-7 years) The chest

Table 3. Pre- and post-embolotherapy PaO_2 on room air*

Case No:	pre-embolization PaO_2 mmHg	post-embolization PaO_2 mmHg
1	82.5	97.7
2	84.2	98.3
3	83.5	94.6
4	52.3	84.7
5	85.6	94.7
6	73.4	126.4*

(*Average $PaCO_2$ before therapy: 25.6 mmHg)

(All data under spine position check up)

radiographic findings of a patient pre- and post-embolization are shown in Figures 1, 2, and 3.

Discussion

PAVM results in a direct right-to-left shunt. Multiple lesions may produce profound dyspnea, cyanosis, or polycythemia. PAVM predominantly affects the lower lobe [6]. In our series, 7 patients had lower lobe involvement, 5 had a solitary PAVM, and 4 had multiple PAVMs (>2). One of the latter had more than 10 PAVMs bilaterally.

In previous reports, approximately 30-50% [7] of patients with PAVM have had Osler-Weber-Rendu disease (OWRD), in which condition the PAVMs are more likely to be multiple [8]. In our series, 3 patients had this syndrome, and all had multiple PAVMs.

When left untreated, a percentage of patients with PAVM sustain significant morbidity and mortality from brain abscess, stroke, hemoptysis, and hemothorax [6]. The goals of therapy are therefore twofold: to reduce or eliminate the pulmonary shunt and to prevent the devastating neurological consequences of paradoxical embolism.

Previously, the treatment for PAVM consisted of thoracotomy and resection. The first successful surgical approach was pneumonectomy, reported in 1942 [9]. This treatment resulted in the disappearance of polycythemia. As thoracic surgery improved, the use of extensive surgery diminished. By 1959, local excision was the procedure of choice [10-11]. Even so, the surgical removal of a PAVM inevitably resulted in the loss of viable lung tissue. Although surgical mortality could be very low (9), general anesthesia, the morbidity of a thoracotomy, and the loss of visible lung tissue made a new approach desirable.

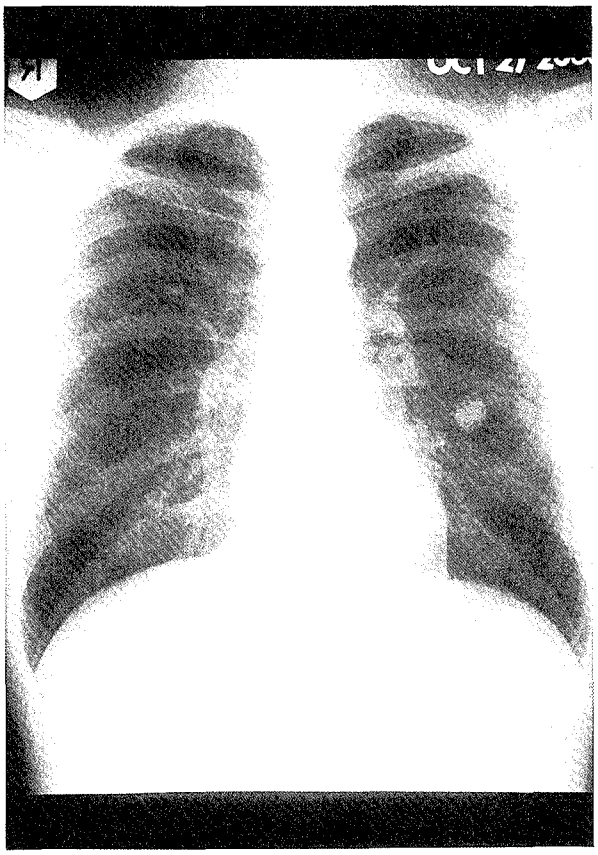
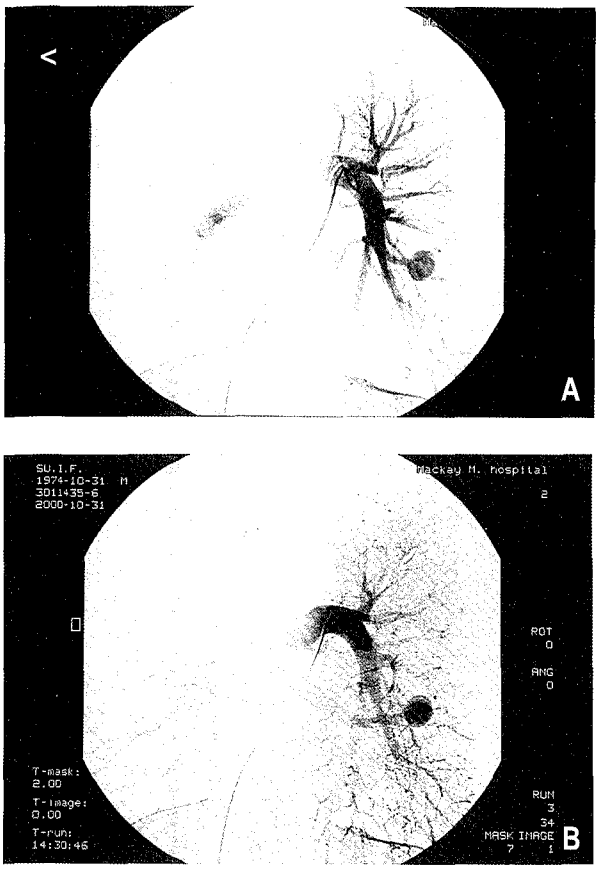


Fig. 1. Chest PA: a well-defined nodular lesion over the left middle lung field. The feeding vessel radiating from the hilus is also visible.

Taylor and associates pioneered the technique of the therapeutic embolization of the pulmonary



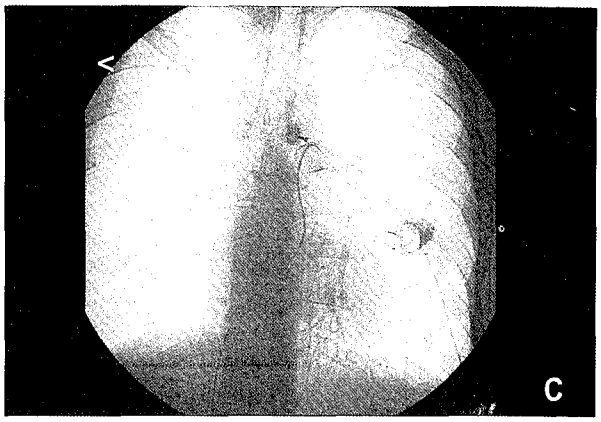


Fig. 2. Pulmonary angiography: (A)Arterial phase:showing the feeding artery .(B)Venous phase. (C)Placement of steel coils at the proximal end of the feeding artery.

artery using steel coils [12]. Terry and colleagues in 1980 and Hatfield and Fried in 1981 reported the successful balloon embolotherapy of PAVM [13]. They felt that balloon occlusion would be less hazardous than using steel coils because of the lower possibility of the systemic embolization and occlusion of arterial branches supplying viable lung tissue.

White and co-workers evaluated PAVM using superselective angiography and stressed the importance of the angioarchitecture of the malformation [14]. A simple PAVM has a single feeding vessel and a nonseptated aneurysmal sac, whereas a complex PAVM has multiple feeding arteries and a septated arteriovenous connection. Arterial occlusion of the simple type is easier, but the risk of paradoxical embolism is greater [14].

In multiple PAVMs, some authors recommend stepwise embolization due to limited patient tolerance of the procedure and the need for a large amount of contrast material [15]. A recent study documented substantial improvement in SaO_2 without evidence of a loss of lung function [16]. The residual right-to-left shunt following embolization in some patients may reflect the presence of numerous microscopic PAVMs [17].

White et al, in a series of 276 patients who underwent long-term follow up, showed minimal morbidity and no mortality in patients treated with balloon embolotherapy [10]. They concluded that all PAVMs with arteries exceeding 3 mm in diameter should be occluded by means of embolotherapy [17-18]. In our series, all the patients treated with embolization had feeding arteries exceeding 4-5 mm in diameter

The traditional indications for treatment have been progressive PAVM enlargement, paradoxical embolization, and symptomatic hypoxemia [19]. Recently, PAVMs less than 2 cm in diameter, with afferent arteries more than or equal to 1 mm in diameter, have been documented to cause transient ischemia attacks, stroke, or brain abscess [20-22]. Based on such findings, White and coworkers [17-18] have recommended the treatment of all PAVM with feeding vessels 1 mm or larger. Recent reports have shown that patients with contrast medium allergy or pulmonary hypertension [23] should not receive embolization. The reported reasons

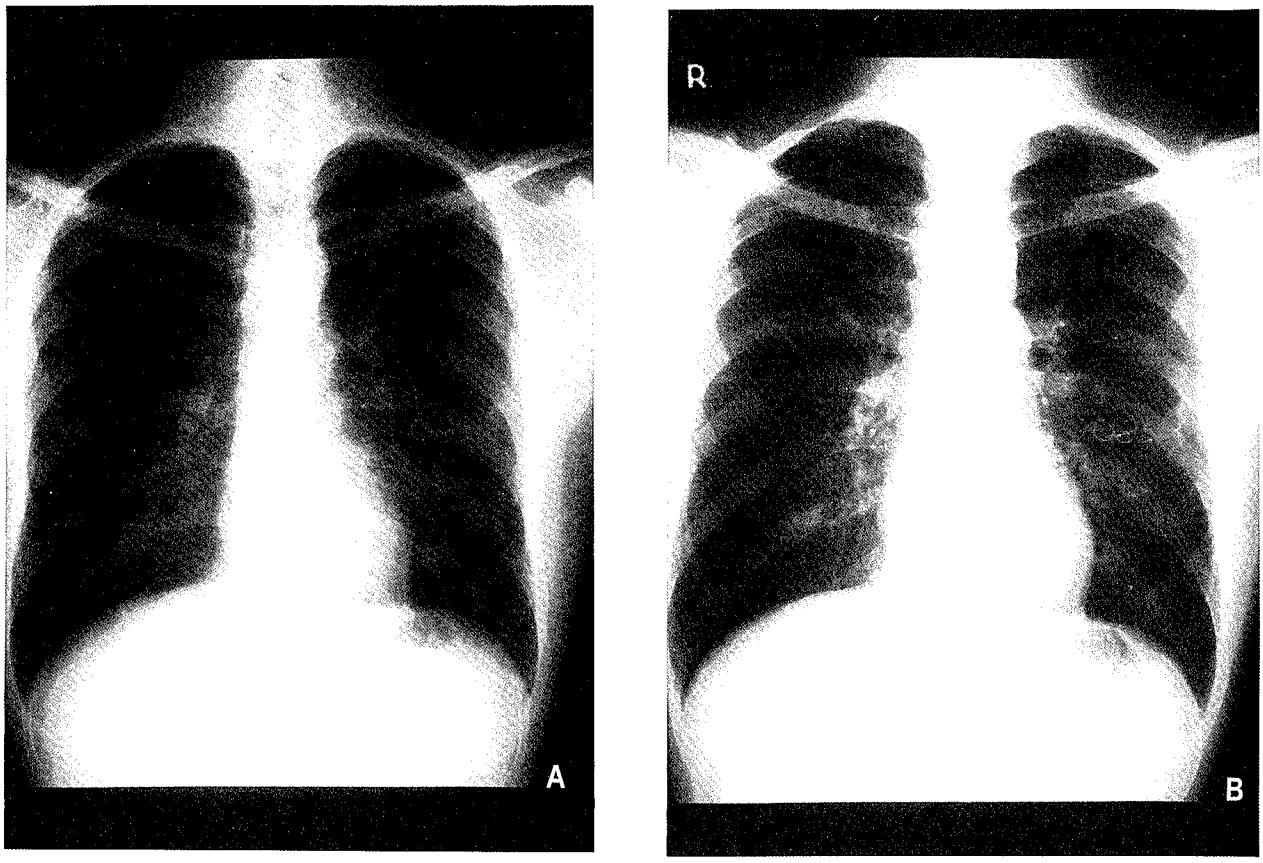


Fig. 3. (A) After embolotherapy. (B) Follow up 15 months later. The steel coils were still in place and the nodular lesion had disappeared.

for embolization failure include (1) failure to achieve selective catheterization,(2) unstable catheter position,(3) insufficient number of coils deposited, and (4) elongated coils[24]. In our series, no embolization failures occurred.

The technique of coil embolotherapy involves the localization of the PAVM by angiography followed by the selective catheterization of the feeding artery [25]. The catheter tip is advanced past the point of any proximal vessels that would supply the normal lung parenchyma, and positioned as close to the neck of the PAVM as possible. A coil is advanced through the catheter and released at this point, angiography is repeated, and additional coils are positioned if needed until blood flow to the PAVM has ceased .In a previous report, up to 10 coils were used on a single PAVM [26]. In our series, each PAVM require 2-6 coils. The mean procedure time was about 30 minutes.

Serious complications with embolotherapy are rare. Air embolism is one potential problem, occurring in less than 5% of patients [10]. Paradoxical embolization has been reported, but without serious sequelae to date.

The most common post-embolotherapy symptom is pleurisy, reported in 10% of patients [10]. The onset may be delayed for up to 9 days and may range in severity from mild pain to a level of discomfort requiring hospitalization. These episodes are sometimes accompanied by a large pleural effusion. The effusions and resultant hypoxemia always resolve within several weeks [17]. In our series, the patients remained hospitalized post-embolotherapy for 2-3 days, and none developed pleurisy.

In summary, patients with PAVM can be successfully treated by embolotherapy with a resolution of essentially all symptoms and a substantial reduction in the risk of complications. It is now the procedure of choice, with a negligible

mortality, few or no serious complications, no loss of pulmonary parenchyma, and no exposure to anesthesia or thoracotomy.

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六肺動靜脈瘤管病例之栓塞治療臨床經驗報告

麥昌盛* 陳培然 郭許達

肺動靜脈瘤管為一種近代醫學才開使描述的疾病。肺動靜脈瘤管為肺動脈與肺靜脈之異常交通，導致右至左分流及動脈低血氧症。臨床上可發生於無主訴之病患身上以至於有呼吸急促、直立性血氧過低、咳血、流鼻血、胸痛、杵狀指的病人都可能在其胸部 X 光發現有肺動靜脈瘤管。而肺動脈血管攝影檢查仍是目前唯一能確定診斷肺動靜脈瘤管的工具。

現今治療肺動靜脈瘤管的方式有手術切除及栓塞治療。此次收集九位肺動靜脈瘤管之病患，其中六位接受穿皮經動脈導管栓塞術治療後，評估病患之臨床症狀及動脈血氧值均有明顯改善，並追蹤其胸部 X 光之影像顯示栓塞治療的金屬線圈仍在原位，而原先之肺動靜脈瘤管陰影幾乎看不見。

對於肺動靜脈瘤管病患接受穿皮經動脈導管栓塞術治療的安全性與有效性已頗受贊同，即使於多發性肺動靜脈瘤管病患，亦能以個別栓塞而不傷及正常肺功能，因此穿皮經動脈導管栓塞術治療已成為肺動靜脈瘤管病患之優先選擇治療方式。 ***(胸腔醫學2002; 17: 346-353)***

關鍵詞：肺動靜脈瘤管、穿皮經動脈導管栓塞術

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Augmented Effect of Hyperoxia and Tumour Necrosis Factor- α on Leukosequestration and Pro-inflammatory Cytokines Release in Rat Airways

Chih-Teng Yu, Chia-Chun Tang, Kuo-Hsiung Huang, Chun-Hua Wang, Chien-Ying Liu, Han-Pin Kuo, Horng-Chyuan Lin

Background: Although oxygen is an important adjunct to therapy in hypoxemic respiratory failure from diverse causes, exposure to high oxygen tension may contribute to exacerbate acute lung injury as a result of increased production of reactive oxygen metabolites. Moreover, tumour necrosis factor-α (TNF-α) is though to be implicated in the many pulmonary and airway diseases, especially in neutrophil mediated lung injury.

Objective: To investigate the augmented effects of hyperoxia on TNF-α - induced leukosequestration and pro-inflammatory cytokines release in rat airways. A prospective, randomized, controlled animal study was conducted.

Methods: Male Sprague-Dawley rats weighing 350-500 g. were pretreated with intratracheal administration of saline, TNF-α or 95% O2, or both. Bronchoalveolar lavage fluid was recovered from the airway of S-D rats after exposure to 95% O2 and TNF-α for 6 hours under ventilator support. Cells in lavage fluid were isolated and examined for total and differential counts by haematocytometer. TNF-α and IL-1β in lavage fluid were measured by ELISA.

Results: The percentage of neutrophils in BAL fluid was significantly higher in rats exposure to hyperoxia+ TNF-α (29.7±12.5%) compared with rats with hyperoxia (16.3±1.2%), TNF-α (4.2±1.1%) or room air (5.0±1.8%) alone ($p<0.05$, respectively). Rats exposure to hyperoxia+ TNF-α significantly produced higher level of TNF-α and IL-1β, compared with rats with TNF-α, hyperoxia or room air alone. There was a significant correlation between TNF-α and IL-1β ($p<0.05$, $rs=0.62$, $n=20$). The total cells and the percentage of neutrophils were also significantly correlated with TNF-α and IL-1β respectively.

Conclusions: The combined exposure to hyperoxia and TNF-α contributes to leukocyte recruitment and subsequently TNF-α and IL-1β release. ***(Thorac Med 2002; 17: 354-363)***

Key words: hyperoxia, tumor necrosis factor-α, interleukin-1β, neutrophils

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Introduction

Tumour necrosis factor-α (TNF-α) is a 17.5 kDa cytokine that is implicated in the many pulmonary and airway diseases, especially in neutrophil mediated lung injury [1]. Chronic inflammatory lung diseases, such as asthma, chronic bronchitis and adult respiratory distress syndrome, are associated with elevated levels of TNF-α in lung fluids [2]. Such patients often require supraphysiological concentrations of O2 (>21%) to maintain organ viability and homeostasis [3]. Clinically, hyperoxia therapy is frequently used in the care and management of mechanically ventilated, critically ill patients with acute respiratory distress syndrome (ARDS). Although oxygen is an important adjunct to therapy in hypoxemic respiratory failure from diverse causes, exposure to high oxygen tension may contribute to acute lung injury as a result of increased production of reactive oxygen metabolites [4-6]. In a broad sense, hyperoxia superimposed on lung injuries involves an imbalance between oxidants and endogenous anti-oxidant, anti-inflammatory systems. There is much interest in the novel therapies to protect the injured lung against further oxygen toxicity. However, the combined effect of hyperoxia and acute lung injury on pro-inflammatory cytokines production is controversial and depends on the experimental condition.

Polymorphonuclear neutrophils are critical to host defense against bacterial infection after injury, but pathologic PMN hyperactivity is also implicated in ARDS and multiple organ failure [7-10]. Further damage of airway epithelial cells and alteration of inflammatory cytokines production is a cause of subsequent leukocyte adhesion [11]. In response to oxidant injury by hyperoxia and TNF-α, it is likely that the increase in the leukocyte sequestration with altered early response cytokines, such as interleukin-1β (IL-β) and TNF-α, may contribute to the aggravation of lung damage. In the present study, we explored this hypothesis by intratracheal administration of TNF-α and 95% O_2 into rats to induce leukosequestration and IL-β, TNF-α release.

Materials and Methods

Animal preparation

Male Sprague-Dawley rats weighing 350-500 g were obtained in pathogen-free containers and were maintained in closed-circulation cubicles. After the animals were anaesthetized with urethane (8 mg kg^{-1} body weight) intraperitoneally, the trachea and left external jugular artery were cannulated. The animals were ventilated with a small animal constant volume respiratory pump (Harvard Apparatus, Ltd., Edenbridge, U.K.) operating at 60 strokes min^{-1} of 1 ml of laboratory air per 100 g body weight. A total volume of 0.5 ml TNF-α (10^3 U) or sterile 0.9% saline was injected via a 25-gauge needle into the trachea. The animals were then exposed to normoxia or hyperoxia (> 95% O_2, initially 30 minutes) for 6 hours via the respiratory pump. The overflow pressure was measured with a differential pressure transducer (Farnell Electronic Components Ltd., Leeds) after a stable state was reached. Drugs were injected via the jugular veins. Blood pressure was monitored continuously via an indwelling cannula filled with heparin-saline (10 μ ml^{-1}) in the left carotid artery.

Bronchoalveolar lavage (BAL)

BAL was performed with a total volume of 50 ml of pre-warmed (37°C) sterile 0.9% saline via the tracheal cannula. The fluid was recovered manually through gentle aspiration with a disposable pyrogen-free syringe. The lavage fluid was immediately centrifuged (10 min, 4 °C, 2000 r.p.m.). The supernatant of BAL was stored at -80 °C until analysis of the IL-β and TNF-α content. The cell pellet was washed with phosphate buffered saline (PBS) twice and resuspended for polymorphonuclear neutrophil (PMN) isolation. The absolute cell number was enumerated with a haematocytometer counting chamber. Cyto-centrifuged preparations (Shandon, Runcorn,

U.K.) were stained with modified Wright-Giemsa stain and a differential cell count, based on morphologic criteria, was made on 200 cells. The PMN numbers recovery in BAL were calculated by multiplying the ratio of PMNs.

Rat TNF-α and IL-1β assay

Supernatant of BAL was sampled at various time points and freez-dried at -76°C under -3.0 ATM for 24 h. The samples were then resuspended in one tenth of original volume of PBS and stored at -80°C for later measurement of TNF-α and IL-1β concentration. The concentrations of TNF-α and IL-1β were measured by use of specific ELISA kits (Cyto*screen*™ Immunoassay kit, raTNF-α and raIL-1β kit, BioSource International, Inc. Camarillo, California, USA), which employed the in vitro quantitative determination of TNF-α and IL-1β in rat serum, buffered solution, or cell culture medium. Antibodies specific for raTNF-α and raIL-1β had been coated onto the wells of the microtiter strips provided. Samples containing standard amounts of raTNF-α and raIL-1β as well as study samples were added to individual wells where any TNF-α or IL-1β present would bind to the immobilized antibody. After 4 washes, which removed any unbound protein, a biotinylated antibody specific for raTNF-α or raIL-1β was added to the wells. After removal of excess antibody, Streptavidin-Peroxidase was added to bind to the biotinylated antibody to complete the four-member sandwich. After another four washes, a substrate solution (Stabilized Chromogen) was added and a colour developed in proportion to the amount of raTNF-α or raIL-1β present. After a Stop Solution was added, the degree of colour generated was determined by measuring the optical density at 450 nm in a spectrophotometric microtitre plate reader. The standard curve was linearized by means of log/log scale and subjected to regression analysis. The TNF-α or IL-1β concentration of unknown samples was determined by use of the regression equation generated by the standard curve run concurrently with the samples. The limits of detection of raTNF-α and raIL-1β were 6 pg/ml and 7 pg/ml respectively. In this study, the results are presented as pg of TNF-α or IL-1β per ml of BAL fluid.

Statistics

Standard formulae were used for the analysis. Data did not approximate a Gaussian distribution, whereby the mean value did not approximate the median value. Nonparametric statistical analyses were therefore employed, and the probability of the differences between groups was initially assessed by Kruskal-Wallace analysis. One-way analysis of variance (ANOVA) for mixed design is used to compare values of more than two different experimental groups. If variance among groups is noted, a Bonferroni test is used to determine significant differences between specific points within groups. The number of animals in a group was too small to allow for a strict median test between groups, and subsequent analysis was performed by the Mann-Whitney U test (two-tailed to assess the significance of differences between groups. To minimize the possibility of obtaining chance significance as a result of multiple comparisons, preplanned comparisons between specific groups were made and the significant values confirmed with Newman-Keuls analysis. Spearman rank correlation (rs) was used to assess the relationship between neutrophils and cytokine level. Data are presented as mean±SE. The null hypothesis was rejected at $P<0.05$.

Results

Hyperoxia and TNF-α -induced leukosequestration

Intratracheal administration of Hyperoxia and TNF-α induced an increase in the BAL cells and most prominently neutrophils in the airways. Hyperoxia+ TNF-α significantly increased the total cell count (TCC) in the airways ($8.8\pm0.7 \times 10^6$ cells) compared with saline control ($2.0\pm0.2 \times$

Table 1. The effect of Hyperoxia+ TNF-α on the total cell count (TCC) and the percentage of neutrophils retrieved in BAL fluid

	Control	TNF-α	95% O2	TNF-α + 95% O2
BAL				
TCC (10^5)	20.24 ±1.64	37.58 ± 8.79	41.68 ± 7.14	87.68 ± 7.31 *#ψ
Differential counts (%)				
Neutrophil	4.96 ± 1.82	4.25 ± 1.07	16.33 ± 1.52 *#	29.73 ± 3.99 *#ψ
Lymphocyte	4.32 ± 1.24	4.26 ± 1.28	7.39 ± 5.03	6.65 ± 4.15
Monocyte	90.70 ± 1.85	91.29 ± 2.29	76.28 ± 5.49	63.64 ± 4.44

Abbriviation: BAL: Bronchoalveolar lavage.

* p<0.05 compared with Control; # p<0.05 compared with TNF-a; ψ p<0.05 compared with 95% O2

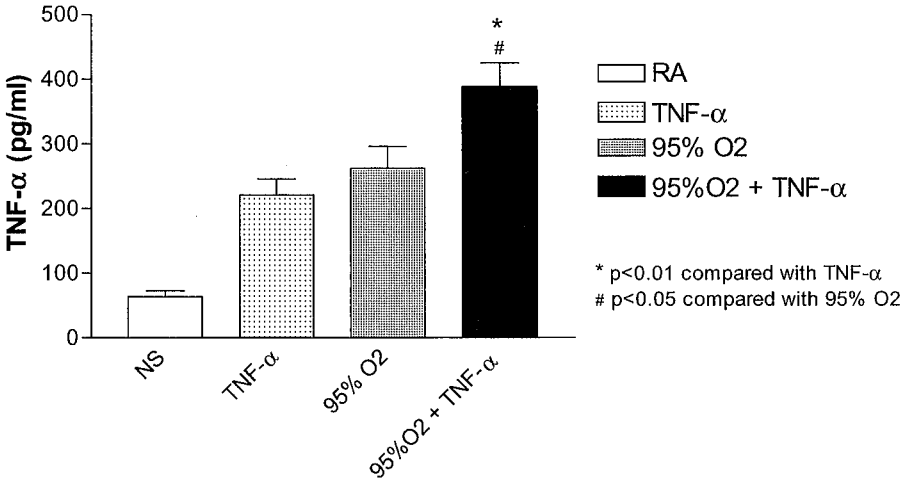

Fig. 1. Hyperoxia+ TNF-α significantly produced a level of TNF-α in BAL fluid, compared with those in saline control group, TNF-α alone group, and hyperoxia alone group.

10^6 cells), TNF-α (3.8±0.9 × 10^6 cells), or hyperoxia alone (4.2±0.7 × 10^6 cells)(n=5, p<0.05; respectively) (Table 1). Hyperoxia+ TNF-α also increased the percentage of neutrophils retrieved in BAL fluid to 29.7±12.5% (n=5) which was significantly higher than those in rats exposed to saline control (5.0±1.8%, n=5, p<0.05), TNF-α (4.2±1.1%, n=5, p<0.05), and hyperoxia alone (16.3±1.2%, n=5, p<0.05) (Table 1).

Hyperoxia and TNF-α -induced TNF-α and IL-1β release

Rats exposed to hyperoxia+ TNF-α produced a significantly elevated level of TNF-α in BAL fluid to 389.2±88.7 pg/ml (n=5) which was significantly higher than those in saline control group (64.1±9.1 pg/ml, n=5, p<0.01), TNF-α alone group (226.0±82.6 pg/ml, n=5, p<0.01), and hyperoxia alone group (262.7±33.9 pg/ml, n=5, p<0.05) (Figure 1). Hyperoxia+ TNF-α also caused a significantly higher level of IL-1β in BAL fluid (182.5±30.3 pg/ml, n=5), compared those in saline control group (66.1±19.1 pg/ml, n=5, p<0.05), TNF-α alone group (80.4±8.9 pg/ml, n=5, p<0.05), and hyperoxia alone group (106.7±13.2 pg/ml, n=5, p<0.05) (Figure 2).

The correlation between leukocyte recruitment and TNF-α & IL-1β release

The level of TNF-α was also significantly correlated to the IL-1β in BAL fluid (rs=0.62, p<0.005) (Figure 3). The total cells in BAL fluid was highly correlated to the production of TNF-α (Figure 4A) and IL-1β in BAL fluid (Figure 4B).

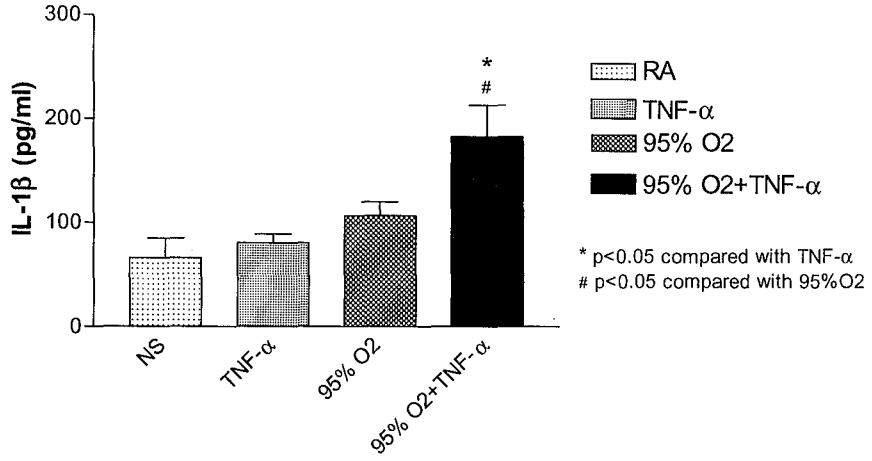

Fig.2. Hyperoxia+ TNF-α significantly produced a level of IL-1β in BAL fluid, compared with those in saline control group, TNF-α alone group, and hyperoxia alone group.

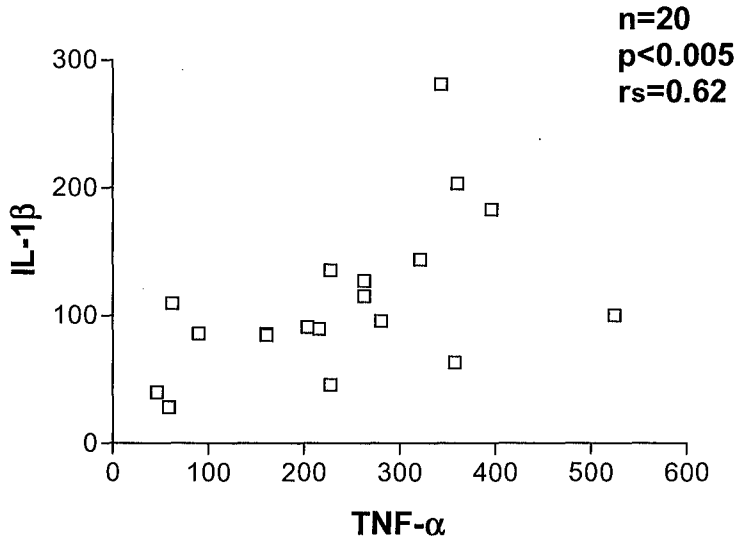

Fig.3. The relationship between the magnitude of TNF-α and IL-1βin BAL fluid. The significance is indicated.

The percentage of neutrophil in BAL fluid was also significantly correlated to the production of TNF-α (Figure 5A) and IL-1β in BAL fluid (Figure 5B).

Discussion

Pulmonary oxygen toxicity is though to be related to neutrophil-mediated injury. Our present study provides evidence showing that intratracheal administration of hyperoxia+TNF-α induced an increase in neutrophil accumulation as well as TNF-α, and IL-1β retrieved in BAL fluid. The percentage of neutrophils in BAL fluid was significantly correlated to the production of TNF-α and IL-1β in BAL fluid. These findings support our hypothesis that the augmented effect of oxidant injury by hyperoxia and TNF-α on the leukocyte sequestration, with altered early response cytokines, such as interleukin-1β (IL-β) and TNF-α, may contribute to the aggravation of acute lung damage.

TNF-α has been implicated in the pathogenesis of many inflammatory airway and pulmonary diseases [12-14]. Many experiments on airway or lung injury have also indicated that

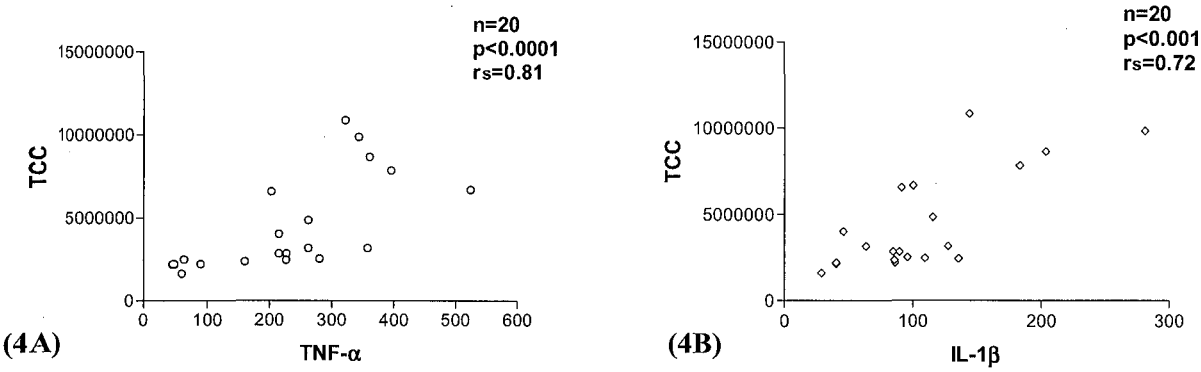

Fig. 4. *4A:* The relationship between the magnitude of total cell counts and TNF-α in BAL fluid. *4B:* The relationship between the magnitude of total cell counts and IL-1βin BAL fluid. The significance is indicated.

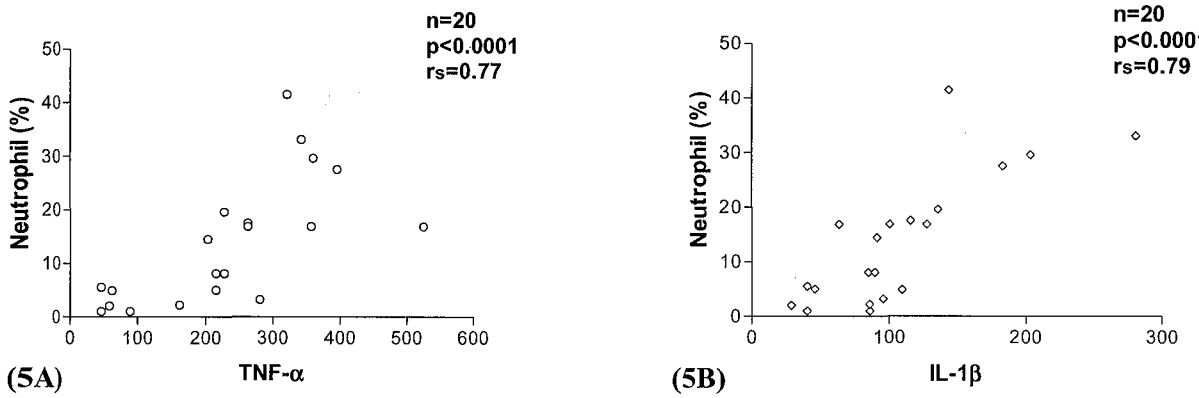

Fig.5. *5A:* The relationship between the percentage of neutrophils and TNF-α in BAL fluid. *5B:* The relationship between the percentage of neutrophils and IL-1βin BAL fluid. The significance is indicated.

proinflammatory signals, especially TNF-α, initiate an inflammatory cascade, thus leading to diffuse alveolar damage [15-16]. In the meanwhile, hyperoxic gas mixtures are frequently administered to those patients with severe airway dysfunction or acute lung injury to increase oxygen tension in arterial blood and tissues. Although previous studies have demonstrated that prolonged inhalation of hyperoxic air can cause serious airway damage [17-18], little is focused on the synergistic effect of hyperoxia superimposed on TNF-α-induced airway or lung injury. In the present study, the concomitant exposure of rat airway to TNF-α and 95% concentration of O2 was designed to mimic critically ill patients who suffered from severe airway or pulmonary inflammatory diseases requiring mechanical ventilation as well as high concentration of O_2 therapy to maintain organ viability and hemeostasis.

There is an increase in the level of TNF-α and IL-1β in the lungs in the course of hyperoxia, even before histological changes are seen [19-22]. Previous studies have reported that transcriptional mechanisms associated with NF-κB are possible candidates for these effects, since NF-κB is responsible for TNF-α and IL-1β transcription and NF-κB is activated by hyperoxia [20, 23]. Thus, the synergistic effect of TNF-α and 95% concentration of O2 on TNF-α and IL-1β production may be at the level of NF-κB mediated transcription level.

Among many chemoattractants, IL-8 and CINCs/GRO are known to have a potent

chemotactic activity *in vitro* [24] and act as a functional chemoattractant for neutrophils *in vivo* [25]. To date, the rat counterpart of human IL-8 has not been identified, and CINCs/GRO are thought to be the predominant chemokines in rats [26]. CINCs are the rat equivalent of human growth-regulated gene products, and include CINC-1, CINC-2α, CINC-2 β, and CINC-3. Although our previous study [27] indicated that the human IL-8 equivalent was responsible for the TNF-α-induced leukosequestration, chemotactic factor, such as GRO/CINC-1, related to neutrophil infiltration after hyperoxia+ TNF-α exposure remains unclear. Therefore, it needs further study to examine the effect of hyperoxia+TNF-α on the production of GRO/CINC-1 or IL-8 if available.

Our previous study [28] showed that endogenous NO inhibits neutrophil adherence to lung epithelial cells to modulate proinflammatory cytokines release. Previous reports [29] also suggested that TNF-α induced an increase in airway neutrophils adherence to epithelial cells and subsequent release of IL-8 from neutrophils, endothelial and epithelial cells [30, 31], leading to a self-perturbation of neutrophil recruitment. Therefore, further study may be needed to examine whether the synergistic effect of TNF-α and 95% O2 on the airway leukosequestration is through an action on the neutrophil adherence and interaction with airway epithelial cell, or an inhibitory effect on endogenous NO.

Kuo and colleagues [29] reported that intratracheal TNF-α stimulation caused leukosequestration and IL-8 release in airways mediated via an increase in intracellular oxidant stress. Hyperoxia alone can cause profound cellular injury by the generation of oxygen radicals, such as hydrogen peroxide (H_2O_2), superoxide anion and hydroxyl radical [32-34]. Therefore, in the present study, hyperoxia may further aggravate TNF-α increased intracellular oxidative stress leading to synthesis of pro-inflammatory cytokines and chemokines.

It is not clearly elucidated in the present study about whether the modulatory effects of hyperoxia+TNF-α-induced leukosequestration as well as TNF-α and IL-1β release are through an action on neutrophil adherence. The adhesion molecules especially β2 integrins, CD11b/CD18, mediate neutrophil-endothelial cell adherence and TNF-α-induced neutrophil transmigration across epithelial cells [35]. Oxidants was found to enhance neutrophil adherence to endothelium by upregulation of CD11b/CD18 expression or by increasing ability of constitutively expressed CD11/CD18 to form an adhesive bond with the endothelial cell surface [36]. Moreover, Superoxide production via NADPH oxidase [37] will increase intracellular oxidative metabolism [38], which is essential in mediating neutrophil adherence by upregulation of surface adhesion molecules and production of pro-inflammatory cytokines. It needs further study to investigate the changes in CD11b/CD18 expression and intracellular oxidants production by hyperoxia+ TNF-α, which may explain, in part, the enhanced leukosequestration and subsequently cytokine release in response to hyperoxia+TNF-α.

In conclusion, the results of this study indicate that combined exposure to hyperoxia and TNF-α is an important factor contributory to leukocyte recruitment and subsequently TNF-α and IL-1β release. Thus, through an approach by a view on cell biology, our data further confirm the concept that prevention of prolonged exposure to high concentration O2 in critically ill patients with acute airway or pulmonary injury may play a protective role in self-limiting the magnitude of airway or pulmonary inflammatory responses.

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合併暴露於高氧與腫瘤壞死因子對嗜中性白血球之聚集與腫瘤壞死因子和介白質-1β釋放的影響

余志騰　唐家駿　黃國雄　王圳華　劉劍英　郭漢彬　林鴻銓

背景：儘管氧氣對於血氧過低所導致的呼吸衰竭是一項重要的輔助療法，暴露在高氧氣壓力下可能增加氧氣代謝物的的產生、使肺臟傷害惡化。此外、腫瘤壞死因子 (TNF-α) 也認為與許多肺部和呼吸道的疾病有關，尤其在嗜中性白血球 所導致的肺臟傷害。

目的：本研究則是使用動物實驗來探討合併高氧 (hyperoxia) 與腫瘤壞死因子對嗜中性白血球之聚集 (leukosequestration) 和前發炎細胞激素 (pro-inflammatory cytokines)的加強的影響。

方法：實驗採用重量 350-500 公克的雄性 Sprague – Dawley 老鼠。以生理食鹽水、腫瘤壞死因子注射入氣管內，或者給予 95%氧氣，或者合併給予 95% 氧氣和腫瘤壞死因子。在呼吸器支持 6 小時後，實施氣管肺泡灌洗術得到氣管肺泡灌洗液。由 haematocytomete 計數氣管肺泡灌洗液之細胞總量及其分類。ELISA 測驗測量氣管肺泡灌洗液中的腫瘤壞死因子和介白質-1β (IL-1β)的高低。

結果：在氣管肺泡灌洗液中，neutrophils 的百分比在暴露於 hyperoxia+ TNF-α 下，比單獨接受生理食鹽水、腫瘤壞死因子、或者高氧之老鼠，很明顯且有意義的增加 ($p<0.05$) 。 另外、老鼠在露於 hyperoxia+ TNF-α 下，也明顯且有意義的增加腫瘤壞死因子和介白質-1β的釋放。而腫瘤壞死因子和介白質-1β的增加，有明顯的相關。另外、neutrophils 的百分比，也和腫瘤壞死因子和介白質-1β的增加，呈現明顯的相關性。

結論：合併暴露於高氧與腫瘤壞死因子，對嗜中性白血球之聚集與，腫瘤壞死因子和介白質-1β 的釋放，有明顯加強性的影響。 ***(胸腔醫學 2002; 17: 354-363)***

關鍵詞：高氧，腫瘤壞死因子，介白質-1β，嗜中性白血球

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Treatment of Small Cell Lung Cancer – Ten Years' Experience at Taipei Veterans General Hospital

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The purpose of this study was to evaluate the outcome of patients with small cell lung cancer (SCLC) treated at VGH-Taipei between July 1991 and December 2000, when cisplatin-based regimens were used.

We retrospectively analyzed a series of 211 consecutive SCLC patients treated with standard chemotherapy using an etoposide/cisplatin (PVP) regimen combined with or without radiotherapy at a single institution during a 10-year period. Patients had a minimal follow-up of 1.2 years. Several pretreatment variables assessable in routine practice were analyzed for the treatment outcome comparison.

The overall response rate was 63%, including a complete response in 15.6% of patients, a partial response in 47.4%, stationary disease in 12.8%, and progressive disease in 24.2% of patients. The significant favorable response factors were disease extent, performance status, and smoking status. The overall median survival time was 9.8 months, of which, survival was 12.9 months in limited stage patients and 7.4 months in extensive stage patients, respectively. The significant favorable survival factors included disease extent, treatment response, performance status, and smoking status.

Patients with limited stage SCLC given an etoposide/cisplatin regimen plus chest radiotherapy were significantly associated with prolonged survival. Disease extent, performance status, and smoking history had a significant influence on disease outcome. ***(Thorac Med 2002; 17: 364-371)***

Key words: small cell lung cancer, chemotherapy, survival time, response

Introduction

Lung cancer is the leading cause of cancer death in Taiwan [1]. Small cell lung cancer (SCLC) accounts for approximately 10 to 15% of all lung cancer cases in Taiwan [2] and about 20% of all lung cancers in other countries [3]. It is characterized by early tumor dissemination, rapid growth, and high response to chemotherapy and radiotherapy. Early attempts at surgical resection were abandoned in the 1960s and 1970s in favor of single-agent chemotherapy or chest radiotherapy with or without chemotherapy [4]. Subsequent clinical research reported in the 1970s showed that the administration of combination chemotherapy prolonged median survival four- to fivefold in comparison with those treated with surgical resection or chest radiotherapy alone [5]. Therefore, combination chemotherapy was adapted as the standard treatment in patients with SCLC in the 1970s. To

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improve response rate and prolong survival duration, various therapeutic strategies, including dose-intense chemotherapy, alternating chemotherapeutic regimens, weekly chemotherapy, highdose chemotherapy with hematopoietic stem cell support, and combined chemotherapy and chest radiotherapy, have been tested [6]. Among these, the combination of etoposide-cisplatin has became the most common first-line combined therapy for patients with SCLC, on the basis of at least equivalent efficacy and less hematologic toxicity in comparison with cyclophosphamide- based regimens [7-8]. The addition of chest radiotherapy to combination chemotherapy has been shown to prolong survival in randomized studies of patients with limited-staged disease [9-10]. At our hospital, the combination of etoposide/cisplatin (PVP) regimens has been the first-line chemotherapy for patients with SCLC throughout the 1990s. The purpose of the current report is to analyze the data of patients with SCLC treated with PVP regimens at our hospital in the past 10 years, to identify pretherapeutic factors predicting a prognosis for response to chemotherapy and overall survival.

Material and Methods

Patient eligibility

Patients with histologically or cytologically proven SCLC, without prior therapy between July 1991 and December 1999, were enrolled. All patients had measurable or evaluable disease. The initial work-up consisted of a complete history and physical examination, chest radiography and computerized tomography (CT), including the liver and bilateral adrenal glands, and a whole body bone scan. Limited disease (LD) was defined as disease confined to one hemithorax, the mediastinum, or bilateral supraclavicular nodes. Extensive disease (ED) was defined as disease extending to the contralateral hilum, pleura, or other distant sites. The performance status was based on the Karnofsky performance scale (K.P.S.). The last date of follow up was February 2001.

Treatment protocol

All eligible patients were treated with PVP regimens (cisplatin 80mg/M^2 on day 1 and etoposide 80mg/M^2 on days 1-3). Treatment was repeated every four weeks. Four weeks after completing the third cycle of chemotherapy, all patients were evaluated for response.

Statistical analysis

The actuarial duration of survival was calculated from the diagnosis day until death or the last patient contact. Survival curves were estimated using the Kaplan-Meier method. Differences in the survival time of the subgroups were compared using the log-rank test. The comparisons of treatment outcome with regard to categorical variables were analyzed using the Chi-square test. A p-value of less than 0.05 was considered significant.

Results

A total of 211 patients were registered between July 1991 and December 1999. The characteristics of the entire population of patients with SCLC at the initiation of treatment are summarized in Table 1. Patients were predominantly male, with a mean age of 70 (range, 45-86 years). One hundred and twenty-eight (60.7%) patients were older than 70 years old; 83 (39.3%) had a K.P.S. less than 70; 55 (26.1%) had no smoking history; 124 (58.8%) had LD; and 87 (41.2%) patients had ED. The most common tumor location was the right upper lobe (35.1%), followed by the left upper lobe (23.0%). The common metastatic sites were the liver (18.0%) and bone (13.7%). Twenty patients developed pleural effusion. Superior vena caval syndrome was found in 12 patients.

One hundred and fifty-six (74%) patients underwent at least four cycles of chemotherapy. (Table 2) The most frequently reported toxicities are listed in Table 3; alopecia was the most

Table 1. Population characteristics

Variable	No. of patients (%)
Gender	
Male	198 (93.8%)
Female	13 (6.2%)
Age (yrs)	
<70	83 (39.3%)
≥70	128 (60.7%)
Performance status	
<70	83 (39.3%)
≥70	128 (60.7%)
Smoking history	
Nil	55 (26.1%)
Yes	156 (73.9%)
Tumor location	
RUL	74 (35.1%)
RML	5 (2.4%)
RLL	45 (21.3%)
LUL	48 (23.0%)
LLL	29 (13.9%)
Others	10 (4.7%)
Disease extent	
Limited	124 (58.8%)
Extensive	87 (41.2%)
Metastatic site	
Bone	29 (13.7%)
Brain	6 (2.8%)
Liver	38 (18.0%)
Adrenal gland	11 (5.2%)
Lung	2 (0.9%)
Pleural effusion	20 (9.5%)
SVC	12 (5.7%)

Table 2. Treatments modality of patients

Variable	No of patients (%)
Cycles of PVP	
1	9 (4.3%)
2	15 (7.1%)
3	29 (13.7%)
4	45 (21.3%)
5	28 (13.3%)
6	73 (34.6%)
7	5 (2.4%)
8	5 (2.4%)
Radiotherapy	
Nil	145 (68.7%)
Yes	66 (31.3%)

Table 3. Side effects of chemotherapy (WHO grade 3 or 4 toxicity)

Variable	No of patients (%)
Alopecia	126 (59.7%)
Nausea	95 (45.0%)
Vomiting	39 (18.5%)
Leukopenia	27 (12.8%)
Esophagitis	9 (4.3%)
Peripheral neuropathy	3 (1.4%)

Table 4. Response of treatment to chemotherapy

Category	Best response (Number)	Rate (%)
Complete response	33	15.6%
Partial response	100	47.4%
Stable disease	27	12.8%
Failure	51	24.2%

common toxicity. Twenty-seven (12.8%) patients experienced leukopenia, which may be life-threatening. Radiotherapy was administered 66 (31.3%) patients as adjuvant or palliative therapy

Table 4 provides the distribution of the best responses to chemotherapy. The overall (complete response plus partial response) tumor response was 63% (15.6% CR plus 47.4% PR, respectively). In univariate analysis, several variables which are associated with a higher objective response rate ($p<0.05$) were limited disease (75% vs. 46%, $p<0.001$), a Karnofsky performance status ≥70 (78% vs. 40%, $p<0.001$), and no smoking history (78% vs. 58%, $p=0.011$). (Table 5)

The overall estimated median survival time was 9.8 months (95% C.I., 8.7-10.9): 12.9 months in limited disease patients and 7.4 months in extensive disease patients, respectively. Table 6 gives the detailed results of the univariate analysis. The following factors were identified as favorable prognostic indicators: limited disease ($p<0.001$), no smoking history ($p=0.0016$), a Karnofsky performance status ≥70 ($p<0.001$), and

Table 5. Univariable Chi-square analysis of response

Variable	Response rate	Odds ratio (95% C.I.)	p value
Disease extent			
Limited	75%	0.26 (0.16-0.51)	p<0.001
Extensive	46%		
Smoking history			
Nil	78%	0.38 (0.17-0.78)	p=0.011
Yes	58%		
Performance			
<70	40%	5.41 (12.94-9.93)	p<0.001
≥70	78%		

Table 6. Univariate Survival Analysis

Variabe	MST (months)	95% C.I.	p value
Gender			
Male	9.8	8.7-10.9	p=0.248
Female	12.4	0.3-24.5	
Disease extent			
Limited	12.9	11.2-14.6	p<0.001
Extensive	7.4	6.2-8.6	
Smoking history			
Nil	13.2	11.3-15.1	p=0.0016
Yes	8.9	7.9-9.9	
Performance			
<70	7.2	6.4-8.0	p<0.001
≥70	12.9	11.1-14.7	
Response			
Complete	21.1	13.8-28.4	p<0.001
Partial	11.8	10.2-13.4	
Stable	6.9	5.5-8.3	
Failure	5.6	3.8-7.4	

a good treatment response (p<0.001). The graphic representation of the Kaplan-Meier estimate categorized by treatment response is shown in Figure 1.

Discussion

Small cell lung cancer (SCLC) is one of the most aggressive and lethal cancers in man. Without treatment, the median length of survival after diagnosis is 1-3 months. It is, however, responsive to both chemotherapy and radiotherapy. Combination chemotherapy is the cornerstone of treatment for these patients, yielding high initial rates of 65% to 85% [5]. Patients with limited disease (LD) have achieved a median survival of 14-16 months, and those with extensive disease (ED) a median survival of 8-11 months [11]. Many studies have attempted to identify the predictive factors of response and toxicity to treatment.

Clinical stage at initial presentation is one the most powerful prognostic factors identified in most studies [12]. Although the number of patients in our report with a limited stage were greater than those in another report [6], our

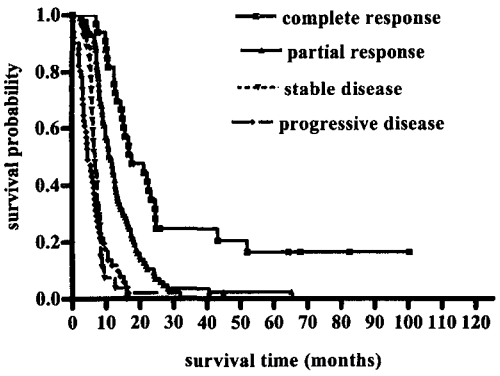

Fig. 1. Kaplan-Meier estimates for the survival distribution of the patients categorized by treatment response

results revealed that the estimated median survival was shorter than that of other reports (12.9 months in limited disease patients and 7.4 months in extensive disease patients). The reason is that many studies reporting clinical trials have excluded those patients ineligible for the study design, so, their patient population cannot be constructed as an overall patient population. Alhde found that liver or cerebral metastases conferred a significantly shorter survival compared to bone, soft tissue, or marrow involvement [13]. Shepherd defined a subgroup of patients with LD, without mediastinal node involvement, that had a better median survival [14]. Superior vena caval obstruction in limited disease patients has not been found to be an adverse prognostic factor [15]. Poor performance status usually confers a poor prognosis [12]. Our study also provided information about the impact of performance status on treatment response and survival. However, performance status is a subjective factor that can be affected by acute self-limiting events.

Some retrospective studies have found that increasing age is an independent adverse prognostic factor in SCLC [16-17]. However, elderly patients experience a larger number of dosage reductions or omissions and suboptimal treatment with chemotherapy due to toxicities. A review of patients treated with concurrent thoracic irradiation has found that age did not appear to impact on the delivery of, tolerance to, or efficacy of radiotherapy in combined modality therapy [18]. Our study also found that elderly patients' response rates and survivals are not inferior to those of a younger population. Many studies have suggested that female gender confers an independent survival benefit and higher response rate to treatment [19]. Wolf found that this advantage was restricted to woman aged less than 60 years old [20]. Although only 13 (6.2%) female patients were included in our study, we found that female gender was not an independent favorable prognostic characteristic. To our knowledge, the role of smoking history in relation to response rate and survival has never been analyzed. We found, however, that those with a smoking history had a poor treatment response (58% vs. 78%) and a shorter median survival time (8.9 months vs. 13.2 months). This impact of a smoking history both on response rate and on survival is noteworthy.

Although combination chemotherapy has produced high response rates, long term survival is rare, with only about 4% alive at 5 years [11]. A randomized study in 105 LD patients has suggested that moderately higher initial doses of chemotherapy can improve disease-free and overall survival [21]. However, an MRC randomized trial found that some patients may not necessarily benefit from more intensive treatment. This study randomized 310 poor-prognosis SCLC patients between a four-drug regimen and a less intensive two-drug regimen. No difference was seen in response or survival, but the four-drug regimen was associated with higher toxicity as well as early death [22]. Relative dose intensity can be increased by reducing the interval between treatments, leading to the so-called dose density. Sculier compared combination chemotherapy with dose-dense weekly regimens to conventional 3-weekly regimens. No benefit for weekly therapy was found [23]. The alternating chemotherapy based on the hypothesis that more active chem-

otherapeutic agents will achieve better treatment response had failed to demonstrate any consistent, clinically significant improvement in survival or response rate [7,24]. Our previous study also found that alternating chemotherapy provided no therapeutic advantage compared with four-agent combination chemotherapy, in terms of tumor response, median survival, and 2-year survival rate for SCLC patients [25]. The addition of chest radiotherapy to combination chemotherapy has been shown to prolong survival in several randomized studies of patients with limited-stage SCLC [10,26]. Chute reviewed all the SCLC patients treated at the US National Cancer Institute from 1973 to 1993. No significant change was found in the pretreatment factors and no significant difference was found in the survival of the patients, despite the change in treatment regimen [6].

Despite the use of more active drugs and more intensive regimens, chemotherapy response rates and median survival do not seem to have improved significantly overall in the past two decades. Performance status and disease extent are almost uniformly found to be the most important clinical factors. We found that smoking history is another possible prognostic factor. There is general agreement that the goals of therapy are different in good and bad prognosis patient groups. The aim is to produce a proportion of long-term survivors among good prognosis patients, whilst ensuring maximal palliation with minimal toxicity in poor prognosis patients.

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小細胞肺癌的治療—台北榮總十年經驗

黃國良　賴信良　彭瑞鵬

肺癌高居國人癌症死因的第一位，其中小細胞型肺癌約佔肺癌病例的 10-15%。小細胞型肺癌具有快速生長及早期轉移的特性。雖然對化學治療反應良好，但病患的中位數存活期卻比非小細胞肺癌差。本文統計了十年間在本院接受相同化學治療的小細胞型肺癌治療的結果，並探討影響結果的各項因素。

在研究期間，總共有 211 例(198 例男性, 13 例女性)經細胞學或病理切片診斷為小細胞型肺癌的病患，接受 cisplatin+VP-16 (PVP)的化學治療，視病情需要決定是否加作放射治療，病患生存時間以診斷為小細胞型肺癌至死亡或最後追蹤日期為止。

有 33 例(15.6%)達到 complete response，100 例(47.4%)達到 partial response，27 例(12.8%)為 stable disease，51 例(24.2%)為 failure。病患的中位數生存期為 9.8 個月，其中擴散期病患為 7.4 個月，侷限期病患為 12.9 個月。影響患者預後的因素包括疾病分期、患者活動力狀態及抽菸史。

回顧文獻，過去二十多年來雖然許多學者嘗試了各種化學治療方式，但病患整體的治療反應率及中位數存活期並沒有明顯的增加。以 PVP 為第一線的化學治療輔以放射治療，目前仍然是小細胞型肺癌的標準治療。如何增加反應率、延長存活期及減低治療的副作用仍需進一步研究。 ***(胸腔醫學 2002; 17: 364-371)***

關鍵詞：小細胞型肺癌，化學治療，存活期，療效

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The Incidence of Ventilator-Associated Pneumonia in Weekly and Bi-Weekly Ventilator Circuit Changes

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Background: Patients undergoing mechanical ventilation are exposed to the risk of ventilator-associated pneumonia (VAP). Frequent ventilator circuit changes are expensive and unnecessary. We investigated whether extending ventilator circuit intervals from twice weekly to once weekly would impact VAP rates at our hospital.

Methods: Prospective 2-year review of mechanically ventilated adult patients in the medical ICU, respiratory ICU, and general ward at Changhua Christian Hospital. The patients whose ventilator circuits were changed twice a week (at 3- or 4-days intervals) from January 1999 to June 1999 comprised the control group; those whose ventilator circuits were changed once a week from January 2000 to June 2000 formed the study group. There were 210 patients in the control group and 340 patients in the study group receiving mechanical ventilation. Ventilator-related pneumonia was diagnosed based on the criteria of the United States Centers for Disease Control (CDC). The incidence of VAP was determined in both groups.

Results: In the control group, 20 patients developed VAP within 3,372 ventilator days, resulting in a rate of 5.93 per 1000 ventilator days. In the study group, 20 cases of VAP in 5,035 ventilator days resulted in a pneumonia rate of 3.97 per 1000 ventilator days. The difference between the groups was not statistically significant (relative risk 1.51; 95% confidence interval 0.81-2.80; p=0.196).

Conclusions: Extending the intervals between ventilator circuit changes from twice a week to once a week does not increase the risk for VAP. ***(Thorac Med 2002; 17: 372-379)***

Key words: mechanical ventilation, ventilator-associated pneumonia, ventilator circuit change, pneumonia

Introduction

Ventilator-associated pneumonia (VAP) is a nosocomial bacterial pneumonia that develops in patients with respiratory failure who are on mechanical ventilator. VAP is commonly associated with increased mortality, an extended length of hospital stay and concomitant increases in hospital costs [1]. While the aspiration of contaminated secretions from the oropharynx and stomach have been identified as a cause, the ventilator circuit, humidifier, and tubing may also be involved in the development of VAP. This

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hypothesis is based on the increased rate of nosocomial pneumonia as a result of the increased manipulation of the patient, endotracheal tube, or ventilator tubing, which may lead to flushing contaminated tubing condensate into the patient's lungs, or increasing the leakage of bacteria around the endotracheal tube into the trachea.

In 1994, revised Centers for Disease Control (CDC) guidelines recommended that the ventilator circuit change interval be no less than 48 hours, but offered no guidance on how long the change interval may be safely extended [2]. Several studies have reported that extending the circuit change interval beyond 2 days does not increase the risk of VAP [3-5]. The purpose of this investigation was to determine the incidence and mortality of VAP in patients on mechanically ventilation support, with circuit changes twice weekly in one group, and once weekly in another.

Materials and Methods

Study Design

The design was based on a prospective 2-year review of mechanically ventilated patients. All patients undergoing invasive mechanical ventilation at the Medical ICU (18 beds), Respiratory ICU (12 beds), and General Medical Ward in Changhua Christian Hospital were enrolled. Those patients whose data were collected for analysis must have received mechanical ventilation at the unit or ward for more than 48 hours. To avoid the possible effects of seasonal variation in the two groups, the incidence of VAP was calculated for patients ventilated during the same seasonal time frame. The ventilator circuits were exchanged twice a week (at 3- or 4-day intervals) during the 6-month period from January 1999 to June 1999 in the control group, and exchanged once a week during the 6-month interval from January 2000 to June 2000 in the study group. The study protocol was approved by the Infection Control Committee of our hospital.

Equipment Used

The ventilators used for this study were the following: Siemens Servo 900C and 300, Puritan-Bennett 7200AE and 740, and LifecarePLV-102. All mechanical ventilators were equipped with humidifiers (Fisher-Paykel MR410 and MR730) and water reservoirs (Fisher-Paykel 370) filled with sterile distilled water and heated (or unheated) reusable ventilator circuits. Ventilator circuits consisted of a swivel adapter, Y-connector, inspiratory and expiratory tubing and traps, and humidifier sterile water reservoir (Fisher-Paykel MR370). All components were reused after autoclaving.

Diagnosis of Ventilated-Associated Pneumonia

The diagnostic criteria for ventilated-associated pneumonia were based on the United States Centers for Disease Control (CDC) standard [6]. The diagnosis of nosocomial pneumonia included combinations of clinical, radiographic, and laboratory evidence of infection. The diagnosis must have met these two conditions:

(1) Radiographic evidence of new persistent or progressive infiltrates. (Persistence was defined as the presence of infiltrates on the roentgenogram for at least 72 hours) (2) Consolidation, cavitation, or pleural effusion on chest roentgenography, an organism isolated from the blood culture, the isolation of a pathogen from a specimen obtained by transtracheal aspirate, bronchial brushing or biopsy, or histopathologic evidence of pneumonia. Nosocomial pneumonia was considered to be ventilator-associated pneumonia (VAP) if the pneumonia occurred between 48 hours after the initiation of mechanical ventilation and 48 hours after weaning in a mechanically ventilated patient without clinical evidence of pneumonia prior to intubation. VAP occurring within 48 hours after the patient was transferred from one unit to another would count as an incidence of VAP in the former unit.

Definition

Hospital mortality or total mortality was defined as those patients whose death occurred in the hospital admission during which the patients were studied. VAP- related mortality was determined when a patient died of VAP and death could not be directly attributed to any other cause. VAP fatalities were defined as those patients who had acquired VAP and died of it in the hospital admission during which they were studied.

Data Collection

For all study patients, the following data were recorded: age, sex, diagnosis at admission, PaO2/FIO2, place of care, ventilated days and onset of VAP days in each hospital unit, total ventilator days, length of hospitalization, hospital mortality, and mortality related to VAP in each hospital unit.

Statistical Analysis

The comparison of continuous variables between the once-a-week and twice-a- week circuit change groups was done with the Student's t test, and the Chi-Square test or Fisher's exact test was used for categorical data comparison, when appropriate. The duration of ventilator use or time to the onset of VAP, whichever occurred first, was summed up as the denominator of the incidence rate of VAP. Poisson regression analysis was performed to calculate relative risk and 95% confidence interval for the incidence rate of the twice-a-week circuit change over the once-a-week change in each hospital unit (MICU or RICU or general ward). The mortality rates of VAP-related and overall causes were compared using the Fisher's exact test with the once-and twice-a-week circuit change patient groups. The Cochran-Mantel -Haenszel Chi-Square test was performed to examine the general association between death and frequency of circuit change. All statistical analyses were performed using computer software (SAS version v.6.12), and a p-value less than 0.05 was considered to be significant.

Results

During the 2- year study period, 550 patients in different hospital units were included. Table 1 presents the demographic characteristics of all the patients. Among 550 patients, 210 patients received a twice-a-week circuit change (control group), and 340 patients underwent once-a-week circuit change (study group). There was no statistical difference in the demographic characteristics of the two groups.

VAP occurred at a mean of 10.2 days after the initiation of ventilation in the control group, and 10.0 days after the initiation of ventilation in the study group However, the difference was not statistically significant (p=0.931). Since the APACHE II score (Acute Physiology, Age, and Chronic Health Evaluation) was not routinely recorded in some areas, it was not included in this study.

In the control group, the 210 patients undergoing a circuit change twice a week accounted for 3372 days of mechanical ventilation. In the study group, 340 patients received a circuit change once a week and accounted for 5035 days of mechanical ventilation. In the control group, 20 patients acquired VAP, with an incidence of 5.93/1000 ventilator days. When compared with the control group, the study group had a lower rate of VAP (3.97/1000 ventilator days), but with no statistical significance (p=0.196) (Table 2). In the study group, seven patients out of the 20 who acquired VAP died of VAP, and in the control group,13 patients out of the 20 who acquired VAP died of VAP. VAP fatality appeared to be high in both groups, but there was no statistically significant difference. (65% in the twice-a-week group compared with 35% in the once-a-week group (P=0.113). The VAP-related mortality rate of ventilated patients in the study group was 2.1%, and the VAP-related mortality rate of ventilated patients in the control group was 6.2%. The mechanically ventilated patients with a circuit change once a week had a statistically significant lower VAP-related mortality than patients with a

Table 1. Demographic data for all patient times

	Circuit change	1/w		2/w		
		N	%	N	%	p-value
Total		340	100	210	100	
Age	Mean ± SD	71.6 ± 14.8		73.8 ± 13.3		0.073
	Median (Range)	75 (26-109)		75 (10-95)		
Sex	Male	192	56.5	125	59.5	0.481
	Female	148	43.5	85	40.5	
Diagnosis on admission	Chronic lung	99	29.1	70	33.3	0.081
	Acute lung	79	23.2	39	18.6	
	Cartdiac	47	13.8	16	7.6	
	Neurologic	45	13.2	31	14.8	
	Postoperative	2	0.6	4	1.9	
	Other	68	20.0	50	23.8	
Unit	MICU	148	43.5	100	47.6	0.241
	RICU	93	27.4	44	21.0	
	G ward	99	29.1	66	31.4	
PaO2/FiO2	Mean ± SD	266.8±124.0		282.1±124.4		0.205
	Range	30-607.5		74-624		

p-value by Chi-square test or Fisher's exact test for categorical data, when appropriate; by Student's t-test for continuous variables.

1/w: circuit change once weekly

2/w: circuit change twice weekly

Table 2. VAP incidence by circuit change

	CIRCUIT CHANGE						Relative	95%	
	1/w			2/w			Risk	Confidence	
Unit	Vent. day	VAP	/1000	Vent. day	VAP	/1000	(RR)	Interval	p-value
MICU	2060	9	4.37	1325	11	8.30	1.90	0.79-4.59	0.153
RICU		1304	6	4.60	887	6	6.76	1.47	0.47-4.56
0.541									
G ward	1671	5	2.99	1160	3	2.59	0.86	0.21-3.62	0.842
Total	5035	20	3.97	3372	20	5.93	1.49	0.80-2.78	0.205
Unit adjusted RR							1.51	0.81-2.80	0.196

1/w: circuit change once weekly

2/w: circuit change twice weekly

Table 3 Association between VAP and mortality

	VAP						Fisher's exact test
	NO			Yes			
Unit	N	Death	%	N	Death	%	p-value
Circuit change							
1/w	320	138	43.1	20	10	50.0	0.644
2/w	190	88	46.3	20	14	70.0	0.059
Overall	510	226	44.3	40	24	60.0	0.512

1/w: circuit change once weekly
2/w: circuit change twice weekly

circuit change twice a week (p=0.017). The overall hospital mortality was 42.6% in the once- weekly group and 48.1% in the twice- weekly group (p=0.212). There was no association between VAP- related mortality and overall mortality (p=0.512) (Table 3).

Discussion

Patients on mechanical ventilator support are exposed to the risk of ventilator-associated pneumonia. Many studies have addressed pharmacologic and non-pharmacologic interventions to reduce the incidence of VAP. The frequency of the ventilator circuit changes and its relation to VAP has been one of the topics that investigators have focused on in the past 2 decades. In 1978, Lareau et al [7] showed that the incidence of VAP was the same whether the circuits were changed every 8 or 24 hours. Craven et al [8] showed that there had been a twofold increase in the risk of VAP, with 24-hour circuit change intervals, when compared with the 48-hour interval. Craven et al also identified a twofold increase in the risk of VAP during the fall and winter seasons [9]. Several years later, Dryfuss et al [10] randomized 63 patients into a 2-day circuit change group and a no-circuit-change group under the diagnostic procedure of a lower respiratory tract sampling with quantitative cultures, and showed no difference in the incidence of VAP. Hess et al [11] in a large sequential study of 3,423 patients with nearly 20,000 ventilator days, and extending the circuit change interval from 2 days to 7 days, showed no difference in the rate of VAP with the less frequent circuit change. Fink et al [12] demonstrated that the incidence of VAP was statistically significantlt lower with circuit change intervals of either 7 days (3.3 per 1,000 ventilator days) or 30 days (6.3 per 1,000 ventilator days), compared to 2 days (11.9 per 1,000 ventilator days) (p=0.0004).

Our study suggests that the incidence of VAP did not increase by extending the ventilator circuit change interval from twice weekly to once weekly. Moreover, the group with a once-weekly circuit change tended toward a non-significantly lower VAP rate. It is important to note that the design of this study has several limitations. First, many factors may influence the risk of VAP. We could not evaluate the disease severity of patients ventilated on the general ward because the APACHE II score of those patients was not recorded. The disease severity between the two groups was not evaluated. The reasons for mechanical ventilation, the use of antibiotics prior to the diagnosis of VAP, or the prophylaxis of a stress ulcer may also influence the risk of VAP. Second, the clinical diagnosis of VAP is less specific. In our study, VAP was diagnosed according to CDC criteria, but did not rely on semi-quantitative lower airway cultures. The clinical method of establishing the diagnosis of VAP is controversial due to the lack of specificity. However, the use of clinical criteria has an

Table 4 Comparison of VAP rates of extended ventilator circuit change intervals

Study,Year	No. of Patients	Study Design	Change Interval Days	Ventilator Days Vent. Days	VAP/1,000	Result
Dreyfuss, 1991 [10]	35	Randomized	2	448	24	No Difference
	28		No Change	280	28.6	
Hess, 1995 [11]	1,708	Sequential	2	9,858	9.6	No Difference
	1,715		7	9,160	8.6	
Kollef, 1995 [5]	147	Randomized	7	2,190	16.4	No Difference
	153		No Change	2,524	17.4	
Fink, 1998 [12]	403	Sequential	2	4,030	11.3	Less VAP with
	164		7	1,553	3.2	7 d and 30 d
	181		30	2,172	6.6	
Han, 2001[15]	413	Sequential	2	2,277	16.7	Less VAP with
	231		7	972	8.2	7 d
Lien, 2000[16]	6213	Sequential	2	65,467	2.66	No Difference
	7068		7	87,338	2.58	
Present Study	210	Sequential	3	3,372	5.93	No Difference
	340		7	5,035	3.97	

outcome incidence similar to semi-quantitative cultures for the diagnosis of VAP [13-14]. Third, a sequential design was used which did not adequately control for the ongoing changes in medical practice at the study facility. Patients using either heated or unheated wire circuits were not randomized into two groups. The use of heated wire circuits may decrease the VAP by reducing the accumulation of contaminated tubing condensate. However, there was no difference in the strategy for mechanical ventilation and the infection control policies for mechanical ventilation in both the study group and the control group.

The incidence rate of VAP in our study seems to be lower than the rate of previous studies (Table 4). The risk for pneumonia from January through June (spring and summer in Taiwan) may be lower than during fall and winter. Different proportions of patient populations or differences in the facility, infection control practices, or tube change practices might account for the different rates of VAP. However, we do not consider these factors as having a significant influence on the study result, since there was no change in other relevant factors for either group. Our overall mortality rates were higher than those of previous studies. The difference in patient population (almost all our patients were elderly medical patients), or the disease entity, would account for the higher mortality rates. Although there was no significant association between VAP-related mortality and overall mortality in either the once-weekly change group or the twice-weekly group, VAP-related mortality was higher in the twice-weekly group ($p=0.017$). However, we did not evaluate disease severity (APACHE II score) or all the potential confounding variables that could influence the occurrence of VAP and its related mortality in either group. Potential confounding variables included 1) previous antibiotic exposure in mechanically- ventilated patients before VAP occurred, and 2) medical care quality changes for those patients who were transferred from the ICU to the general ward. Despite the limitation of this study, we found it promising that the study group had a lower VAP- related mortality. The clinical significance of this study result should be further investigated.

Although we did not calculate the annual supply and labor cost associated with ventilator circuit changes, the cost saving would be substantial with once-weekly circuit changes. We conclude that extending ventilator circuit changes from 3- or 4- day intervals to a 7-day interval does not increase the incidence of VAP.

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呼吸器換管頻率與呼吸器相關性肺炎發生率之研究

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背景：接受呼吸器治療的患者會併發呼吸器相關肺炎的可能，國內外醫院研究發現過度頻繁的呼吸器管路更換甚至可能增加肺炎的發生率，本研究目的探討呼吸器管路每週二次延長為每週一次對於肺炎發生率的影響。

方法：本院內科加護病房、呼吸加護病房及普通病房接受呼吸器的成人患者（十五歲以上），依兩年的追蹤比照研究，研究組 340 位患者在 2000 年一月至六月間接受呼吸器管路每週一換；對照組內 210 個患者在 1999 年一月至六月間接受呼吸器管路每週兩換。計算兩組呼吸器相關性肺炎的發生率。肺炎診斷依據美國疾病管制中心所建議的條件。

結果：對照組總計在 3,372 呼吸器使用日中有 20 次肺炎發生，發生率每千人日 5.93 次。研究組在 5,035 呼吸器使用日中有 20 次肺炎發生發生率為每千人日 3.97 次。兩組肺炎發生率統計上並無顯著差別。

結論：延長呼吸器換管頻率從每週二次至每週一次並不影響肺炎發生率。***(胸腔醫學 2002; 17: 372-379)***

關鍵詞：呼吸器，呼吸器相關性肺炎，呼吸器管路更換，肺炎

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Tracheal Stenosis Demonstrated by Computerized Tomography with 2-Dimensional and 3-Dimensional Reconstruction—A Case Report

Chien-Ming Liu, Liang-Wen Hang, Te-Chun Hsia,
Wu-Huei Hsu

Tracheal stenosis is occasionally encountered by chest physicians. We report a patient with tracheal stenosis which developed after endotracheal intubation three months previous. Routine chest roentgenography was not able to show the stenosis (apparently) and bronchoscopy could not pass through the narrowed lumen to yield a careful assessment. Nevertheless, computerized tomography with 2-dimensional and 3-dimensional reconstruction easily demonstrated the tracheal stenosis, with an assessment of the entire anatomy and surrounding tissue, as well as of the severity and length of the stenosis. After laser therapy and permanent stent implantation, the patient was discharged in stable condition, and was followed-up at the outpatient department. ***(Thorac Med 2002; 17: 380-386)***

Key words: 2-dimensional and 3-dimensional reconstruction, bronchoscopy, computerized tomography, tracheal stenosis

Introduction

Tracheal stenosis post-intubation is usually due to prolonged intubation, although the incidence after intubation has shown a decrease with the use of the low-pressure large-volume cuff endotracheal tube [1]. Once the diagnosis of tracheal stenosis is confirmed, general management may consist of surgery, bronchoscopic tracheal dilatation, laser therapy, and tracheal stent implantation. Previously, the diagnosis of tracheal stenosis was often made by chest roentgenography (CXR) and bronchoscopy, but the entire anatomy, severity, and lesion length of the stenosis could not be assessed in detail with these techniques. With improvements in the imaging modality and computerized function, computerized tomography (CT) with two- dimensional (2-D) and three-dimensional (3-D) reconstruction can easily demonstrate the lesion, with a confident assessment of the location, anatomy and severity [2,3]. Herein, we present a patient with tracheal stenosis which could not be evaluated by fiber optic bronchography, but was easily illustrated by chest CT with 2D and 3D reconstruction.

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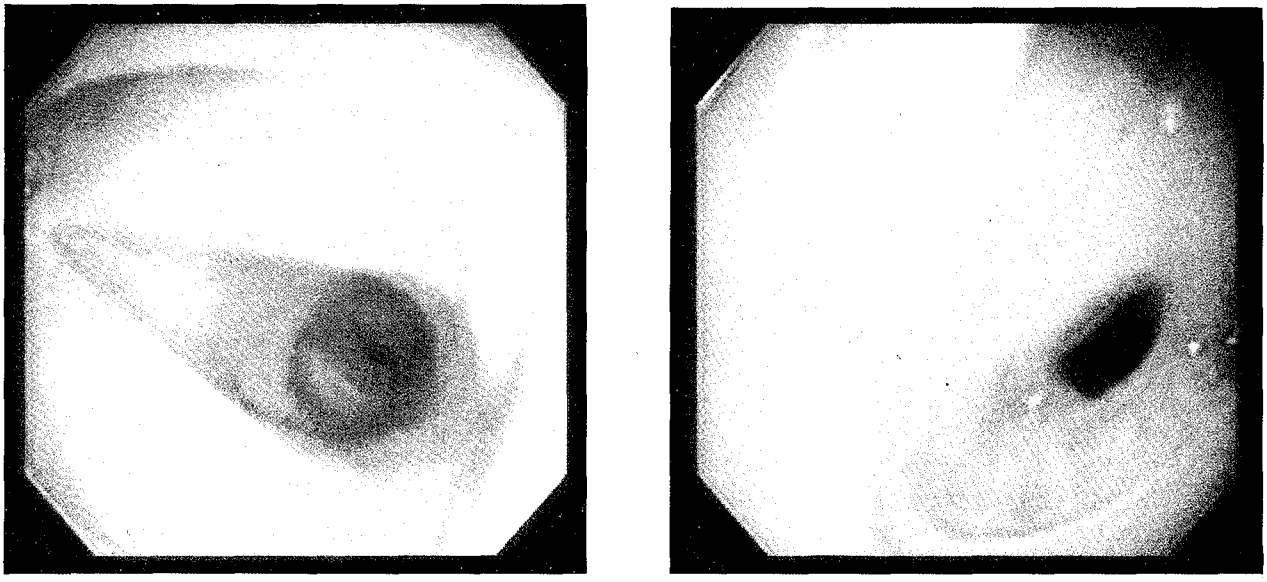
Case Report

An 82-year-old female, with a history of diabetes mellitus, hypertension, and sick sinus syndrome with permanent pacemaker implantation, visited a local clinical physician for a progressively worsening dyspnea of one week's duration. There was no cough, purulent sputum production, fever, or chills. She was initially diagnosed and treated as chronic obstructive pulmonary disease (COPD) with acute exacerbation, but the symptom of dyspnea persisted. Therefore, she was transferred to our hospital for further evaluation and management. Tracing her past medical history, she had been admitted to a medical center due to a fever of unknown origin complicated with respiratory failure, about three months ago. At that admission, she underwent endotracheal intubation with ventilator support for about one month, and was then successfully weaned from the ventilator and endotracheal tube.

On admission to our hospital, she had clear consciousness and acceptable vital signs: blood pressure 112/68 mmHg, regular pulse rate 87 per min, and body temperature 36.8 C. However, she was noted to have respiratory distress and inspiratory and expiratory wheezing accompanied with the use of the accessory respiratory muscle in breathing, tachypnea up to 22/min, and chiefly inspiratory wheezing. Another respiratory symptom was a cough with scanty whitish sputum. The remaining admission examination results, including the blood test, arterial blood gas analysis, and urine and stool tests, were all within normal limits, except for the premature ventricular contractions found in the eletrocardiography. The CXR revealed cardiomegaly and a pacemaker implantation. Bronchodilator agents, and steroid and oxygen therapy were given first, but the symptoms showed mild relief only. Under the suspicion of tracheal stenosis instead of the previously diagnosed COPD with acute exacerbation, bronchoscopy was performed and a tracheal stenosis 2-3 cm below the vocal cord was found (Figs. 1A, 1B). Nevertheless, the bronchoscopy could not pass through the narrowed tracheal lumen, so the airway condition could not be evaluated by bronchoscopy alone. Therefore, a chest CT with 2-D and 3-D reconstruction was arranged (Picker5000 spiral CT scan, with 10 mm



(A) (B)

Fig. 1. (A) Severe tracheal stenosis is seen during bronchoscopy from the vocal cord area (left). (B) Subglottic stenosis with a difficulty passing through is noted during bronchoscopy (right).

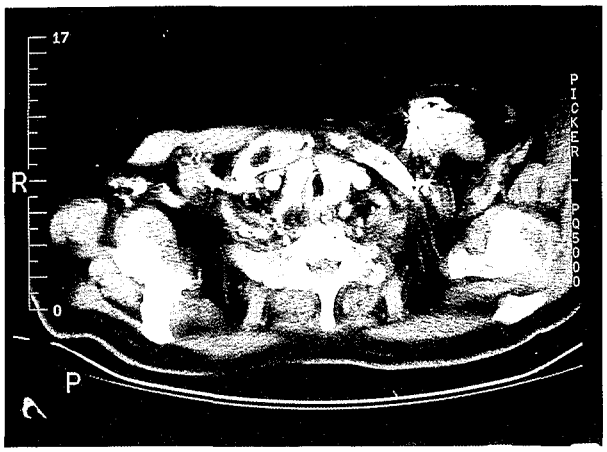


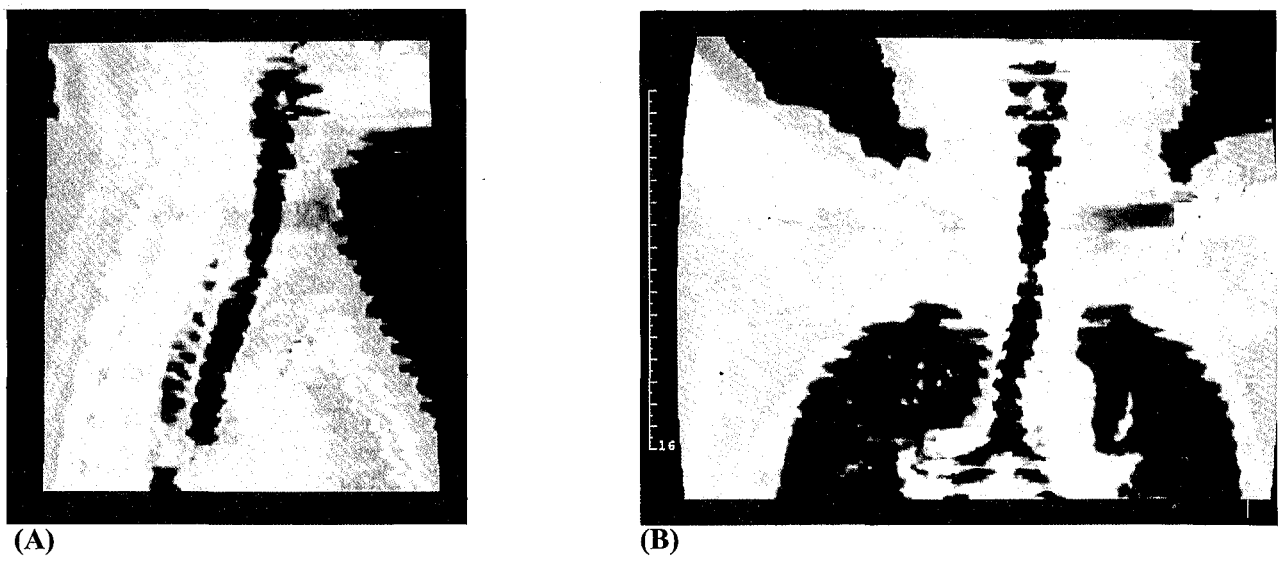
Fig. 2. Chest computerized tomography shows tracheal narrowing predominantly in the coronal plane just below the thyroid level (the coronal and anteroposterior diameters are separately measured at 8.5 mm and 17.0 mm in width).

collimation and 10 mm intervals; multiplanar reformations, 4-dimensional reconstruction, and virtual bronchoscopy images were produced by Voxel Q software in a Marconi workstation), and was able to show the whole anatomy, and severity and length of tracheal stenosis, in detail: the stenosis was predominantly in the coronal plane (the coronal and anteroposterior diameters were separately measured as 8.5 mm and 17.0 mm in width), just below the thyroid level about 2 cm in length (Figs. 2, 3A, 3B, 4, 5A, and 5B). The remaining airway was patent. The pulmonary function test at this time revealed fixed upper airway obstruction, compatible with the clinical condition, and the bronchoscopy and CT findings.

In spite of medical treatment (including steroid and bronchodilator agents), the patient's condition had not much improved. Thus, laser therapy was performed to remove the granulation tissue, and the patient's symptom of dyspnea was relieved rapidly. However, tracheal stenosis developed again one month after laser therapy, and a permanent tracheal stent was implanted after a survey. Thereafter, the patient was discharged in stable condition, and has been followed-up at the outpatient department up to this writing, five months later.

Discussion

Tracheal stenosis may be due to infection, a trauma, a tumor, a congenital condition, or external compression. Causes including amyloidosis, polychondritis, tracheobronchitis, complete cartilage ring damage, sclerodema, sacroidosis, Wegener's granulomatosis, tracheomalasia, bronchomalasia, trauma, infection disorder, and foreign



(A) (B)

Fig. 3. (A) Computerized tomography multiplanar reformation in the coronal plane demonstrates a 2-cm in length tracheal stenosis just below the thyroid level (left). (B) The same lesion demonstrates by sagittal multiplanar reformatted image (right).

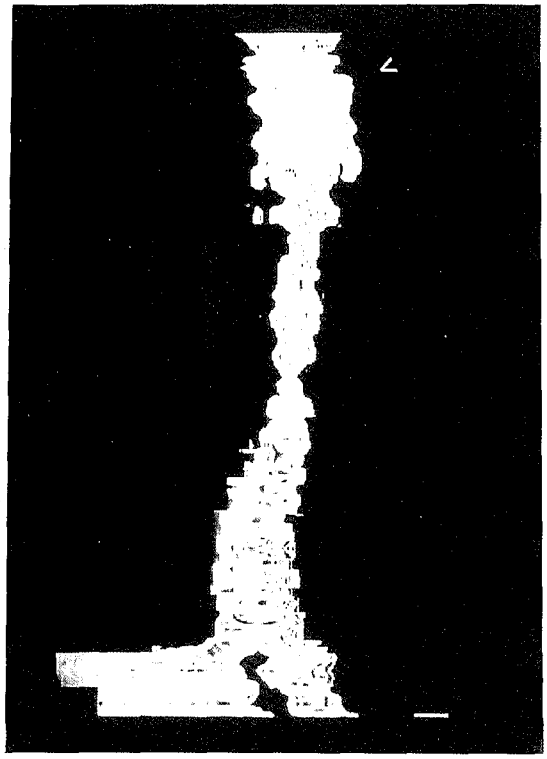
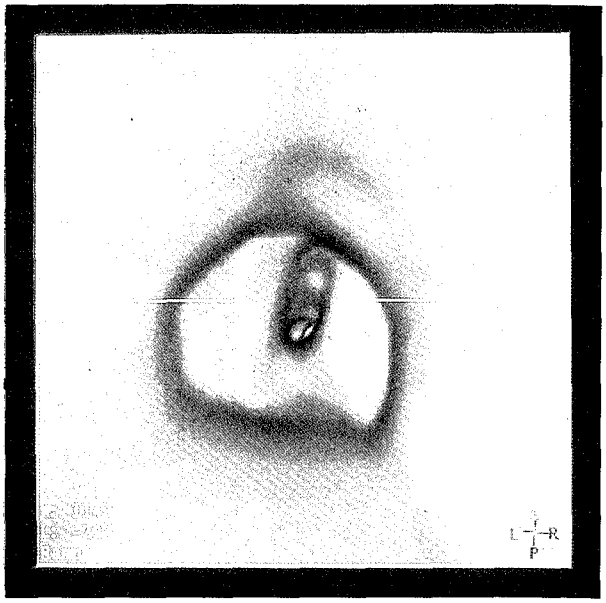


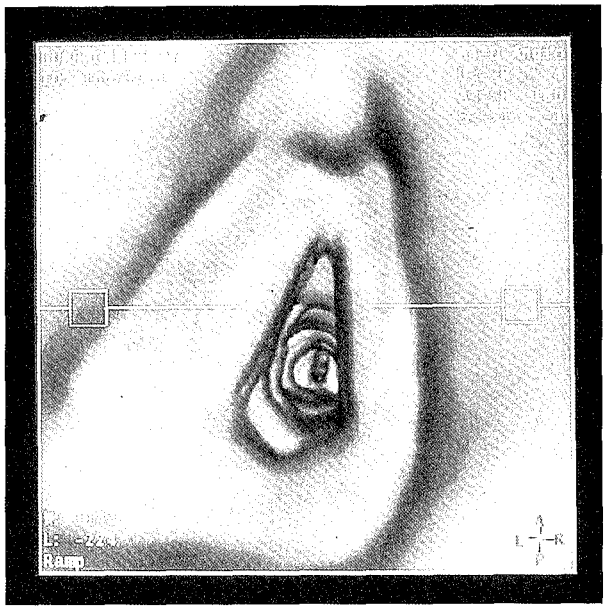
Fig. 4. Computerized tomography 3-D reconstruction (surface-shaded display model) demonstrates the structure of the trachea and stenosis site.

body aspiration-induced chronic lesions, have been found in the literature [4]. Post-intubation- induced tracheal stenosis has recently been encountered less frequently, due to the popularity of the use of the large-volume low-pressure cuff endotracheal tube, but clinically it is still the major reason for tracheal stenosis. As reported from a 3,500-bed tertiary referral teaching hospital, the incidence of symptomatic tracheal stenosis is often less than one per thousand intubated patients [5], and the cause of this condition in most patients can be traced to prolonged intubation.

Post-intubation complications may be due to both tube- and cuff-induced damage to the hypopharynx, larynx, and trachea. Generally speaking, laryngeal damage usually occurs within 72 hrs and often reaches spontaneous resolution without any complication [6]. Virtually all patients undergo intubation for 2 to 6 days, then laryngeal edema, ulceration, and hemorrhage may occur. If cuff pressure is over 30 mmHg, the



(A)



(B)

Fig. 5. (A) Severe tracheal stenosis is seen from the vocal cord area with 3-D reconstruction, surface-shaded display model (virtual bronchoscopy) (left). (B) Another view just above stenosis site using virtual bronchoscopy (right).

mucosal capillary pressure flow will decrease [7]. This causes mucosal ischemia and leads to the ulceration and chondritis of the cartilage rings. Later, fibrotic change and tracheal necrosis may develope and possibly progress to tracheal

stenosis. Clinically, the large-volume and low-pressure (20-30 mmHg) cuff can decrease the incidence of tracheal stenosis, and is now standard practice in modern ICU care [1,5,8]. Even so, tracheal stenosis can still occur, commonly at the tip and cuff area in the lower third of the trachea, and stenosis in the subglottic area is also often seen. However, the relationship between the duration of previous tracheal intubation and tracheostomy timing is not well known [6-7].

Clinically, tracheal stenosis may present progressive dyspnea on exertion, a chronic cough, an inability to clear secretions, and a lack of response to bronchodilator agent treatment. Especially, wheezing in the inspiratory phase or stridor is also often seen, and may mimic bronchial asthma with acute bronchospasm, making the diagnosis incorrect and delayed. In our case, the predominant inspiratory wheezing and poor response to bronchodilator agents alerted us to an early diagnosis of tracheal stenosis. Reviewing the literature, these symptoms of tracheal stenosis usually occur when the stenosis area is up to 30%. The initial correct diagnosis is less than 56% [5], and most cases are initially misdiagnosed as bronchial asthma. Thus, the clinical physician should note in the history-taking, especially in patients with atypical respiratory symptoms, any previous intubation history, and poor response to bronchodilator agent treatment. This evidence and the clinical presentations are important clues in the diagnosis of tracheal stenosis. The timing of the onset of post-intubation tracheal stenosis is another problem. Most cases occur within two months after extubation, but some may appear very late, even after 20 years [9]. As in our patient, tracheal stenosis developing three months post-extubation is relatively rare, and is a warning that tracheal stenosis should be kept in mind in patients with the symptoms of respiratory wheezing and dyspnea, and a history of endotracheal tube intubation.

The diagnosis of tracheal stenosis is usually made by CXR, bronchoscopy, and CT. CXR is the most convenient image examination but can't accurately assess the lesion and the adjacent structure. Fiber optic bronchoscopy is a useful technique for initially examining the nature and extent of the endobronchial lesion, and can further provide management planning. Nevertheless, fiber optic bronchoscopy still has its limitations, such as in the examining of the adjacent anatomy and structure of an area of severe stenosis, and in the limited access of the bronchoscope. In addition, bronchoscopy is an invasive procedure and not suitable for every patient. With current improvements in the imaging modality and computerized function, modern chest CT can produce high resolution images and assess the entire lesion anatomy, length of the stenosis, and related adjacent tissues and pulmonary lesions in detail. Moreover, an evaluation of airway abnormalities may gain an advantage from multiplanar reformations and 3-D reconstructions, by nature of the volumetric acquisition enabling truly contiguous scanning, which generates high-quality multiplanar and 3-D images. Advances in computer technique allow the creation of virtual endoscopy from spiral CT. The virtual bronchoscopy technique gives the bronchoscopist a view of the inner surface of the major bronchi. It may assist in planning for bronchoscopy and surgery, and provide familiar images for the bronchoscopist, and a non-invasive study of endobroncial lesions post-tracheal stenosis, which the bronchoscope can't pass through [2-3,10-11]. As in our case, chest CT with 2-D and 3-D reconstructed images, including virtual bronchoscopy, allowed for an easier and more confident diagnosis, evaluation, and treatment planning. However, the patient with persistent stridor is not able to hold a single breath during the CT examination. We could not get good quality images during a single breath-holding after hyperventilation. The pulmonary function test is not a specific and reliable diagnostic tool for tracheal stenosis because it may show the combined characteristics of airway and pulmonary

diseases.

The classical treatment of choice for complex stenosis is still tracheal sleeve resection, though successful treatment for early extubation tracheal stenosis using steroids has been reported [12-13]. Nd-Yag laser resection or stent implantation can also be considered [14], especially in patients with clinical conditions not suitable for operation. Rigid bronchoscopy and tracheal dilatation with a cone-shaped scope are occasionally helpful.

In conclusion, the early diagnosis of tracheal stenosis depends on the clinical symptoms and an initial complete history-taking. Imaging modalities, especially chest CT with 2-D and 3-D reconstruction, can help reach a diagnosis and assessment of the tracheal stenosis with ease, convenience, and confidence. In any patient with a post-intubation history and a presentation of respiratory distress and related symptoms, tracheal stenosis should be considered in the differential diagnosis.

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胸部電腦斷層及 2-D,3-D 影像重組技術診斷氣管狹窄—病例報告

劉建明　杭良文　夏德椿　徐武輝

胸腔科醫師偶而會遇到氣管狹窄的問題，原因包括感染，創傷，氣管插管後併發症，先天性以及外圍組織壓迫所造成。相對而言，最常發生氣管狹窄的原因仍然是氣管插管及氣切管插管所造成。在此，我們陳述一位 82 歲因為前三個月接受過氣管插管而造成氣管狹窄的女性病人，傳統胸部 X 光並無法顯示狹窄的位置及範圍；雖然軟式支氣管鏡檢查發現在聲帶 3 公分以下，氣管明顯狹窄但卻無法再深入檢查。在這種情況下，利用胸部電腦斷層及 2-D，3-D 重組影像來估計氣管狹窄的大小。影響的範圍及週邊的組織，有助於進一步的診斷。經一系列評估完後，病人接受雷射及安置永久性支架治療，病情迅速改善，現在持續穩定門診追蹤中。
(胸腔醫學 2002; 17: 380-386)

關鍵詞：2-D, 3-D 影像重組, 支氣管鏡檢查, 電腦斷層, 氣管狹窄

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Detection of Upper Airway Obstruction Using the Forced Oscillation Technique

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It is important to make an early diagnosis of upper airway obstruction (UAO), because it may lead to severe respiratory problems or respiratory failure. UAO is often diagnosed by bronchoscopy when the obstruction is severe enough to be symptomatic. Traditionally, UAO can be suspected with the flattening of the flow-volume loop or by positive findings on the so-called UAO indices.

The forced oscillation technique (FOT) is a new technology, which was proposed in the 1950s but was not used clinically until recently. It requires only the minimal cooperation of the patient, and has the advantages of separating central and peripheral airway resistance. In order to determine whether or not the FOT is a more sensitive method for detecting UAO than the UAO indices, we designed this study to compare the parameters of airway resistance in the FOT with the parameters in the UAO indices in the detection of artificial UAO. This study demonstrates that the FOT is a more sensitive tool in detecting UAO than the UAO indices. Most of these parameters are significant when the obstructive level is up to 8 mm. ***(Thorac Med 2002; 17: 387-394)***

Key words: upper airway obstruction, upper airway obstruction indices, forced oscillation technique

Introduction

It is important to make an early diagnosis of upper airway obstruction, because it may lead to severe respiratory problems or respiratory failure. Frequently, neither the nature nor the severity of the lesion is realized clinically until an endoscopy is performed. Upper airway obstruction can be detected conventionally by the forced flow-volume loop (FVL) as reflected in a flattened FVL contour, and the reduced effort-dependent inspiratory and expiratory flow rates [1-2]. Abnormal values of the so-called UAO indices, such as the forced expiratory volume in one second/forced expiratory volume in 0.5 second (FEV1/FEV0.5) ratio, the FEV1/peak expiratory flow rate ratio (FEV1/PEFR), the forced expiratory flow measured at 50% of expiratory vital capacity/forced inspiratory flow measured at 50% of inspiratory vital capacity (FEF50%/ FIF50%) ratio, and the PEFR/peak inspiratory

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flow rate ratio (PEFR/PIFR), have also been reported [3-5]. Among these parameters, the FEV1/PEFR ratio is more sensitive and can be useful in assessing UAO [3-4]. A previous study of normal subjects by Empey et al, simulating UAO with a small orifice inserted in the mouthpiece of normal subjects, showed an increased FEV1/PEFR ratio above 10 once the orifice was 6 mm or less [4]. The accuracy of the test however depends to some extent on the cooperation and effort of the patient.

The forced oscillation technique (FOT) is a relatively new method used to assess airway resistance. The potential advantages of the FOT, as reviewed by Johnson, include 1) a quiet breathing maneuver that is simple to perform, 2) separate values for large and peripheral airway resistance [6-7], 3) no deep inspiration required, and avoidance of airway collapse and avoidance of flow limitation, 4) usefulness in challenge studies, 5) possible usefulness in monitoring situations, and 6) use in younger patients compared with spirometry [8]. There is also a strong correlation (r=0.81 to 0.83) between the measurement of respiratory system resistance by FOT at 6 to 8 Hz and airway resistance measured by a whole body plethysmography [9-11]. The airway resistance measured by FOT is reported to be as sensitive as FEV1, FVC, and midexpiratory flow rate in detecting airway obstruction [12-14]. In reviewing the literature, the critical severity of UAO that can be detected by the FOT has not been determined. Thus, we designed this study to determine if the FOT is more sensitive than the flow-volume loop in detecting the presence of UAO.

Materials and Methods

Fifteen normal subjects, including two female and thirteen male adults, aged 19-40 years old, all healthy and without a history of smoking and respiratory disease, were included in this study.

All testing was performed in a standing position using a nasal clip. Both the forced flow volume loop and the FOT were performed with the Masterscreen IOS (Jager-breathing unit, Hoechberg, Germany).

After obtaining the baseline forced expiratory flow volume loop, a simulated artificial UAO was made using mouthpieces fitted with orifices 16, 12, 8, and 4 mm in diameter. The test began without occlusion in the tubing, then the level of occlusion increased. Each subject underwent testing of the following 6 items: (1) baseline, not obstructed by the mouthpiece, the diameter of test tube was 26 mm, (2) obstructed with a mouthpiece orifice 16 mm in diameter, (3) 12 mm in diameter, (4) 8 mm in diameter, (5) 4 mm in diameter, and (6) return to baseline. The best recording of each item was taken and expressed in B.T.P.S. The measurement of R5, R20, Rc, Rp, and all the UAO indices including FEF50%/FIF50%, FEV1/PEFR, and FIF50%, were recorded and expressed as mean ± SD. A comparison of each group was made with an unpaired *t* test. A p-value of less than 0.05 was considered significant.

Results

The data of each parameter (R5, R20, Rc, FEV1/PEFR, and FEF50%/FIF50%) is expressed as mean ± SD (Figure 1-5). A comparison of each group was made and is shown in Table 1. The p-value is expressed in *italics* if $p < 0.05$.

In R5, R20, and Rc, the p-value was less than 0.05 in relation to the baseline and 16-mm diameter groups. Among all the UAO indices, FEV1/PEFR was the most sensitive, and the p-value is less than 0.05 in the 16-mm diameter and 12-mm diameter groups. The p-value was not so predictable and fluctuated in FEF50/FIF50 and Rp. These findings suggest that parameters obtained by the FOT can detect UAO at minimal obstruction (16-mm diameter), as reflected by the significant increase of R5, R20, and Rc.

All the p-values of the 12-mm diameter and 8-mm diameter groups were less than 10^{-4} (except

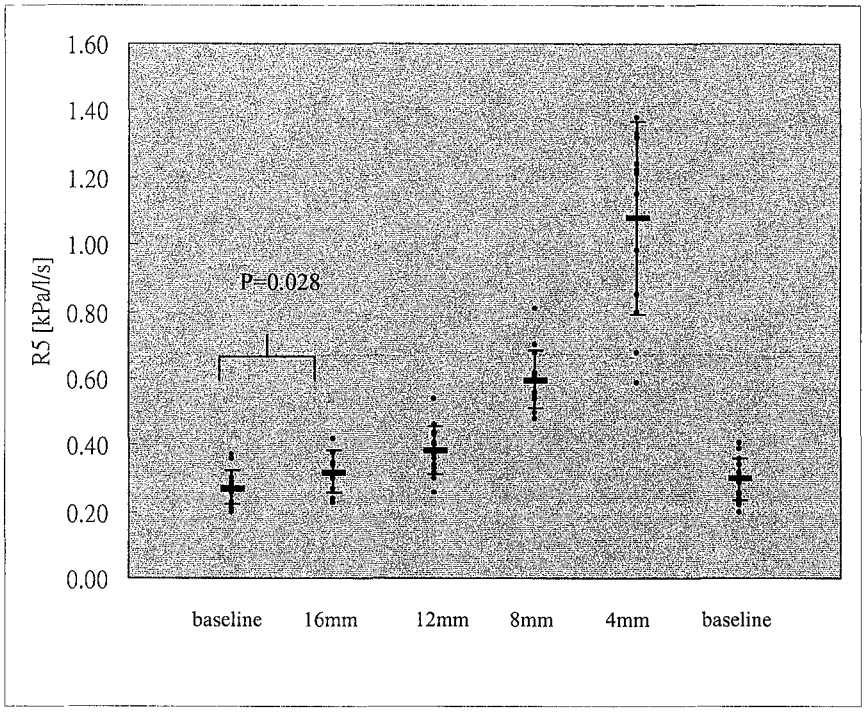

Fig. 1. Airway resistance measured by the FOT at 5 Hz (R5) ± SD, obtained at baseline, orifice at 16-mm diameter, 12-mm diameter, 8-mm diameter, 4-mm diameter, and repeated baseline. The p-value of the baseline and 16-mm diameter groups is less than 0.05.

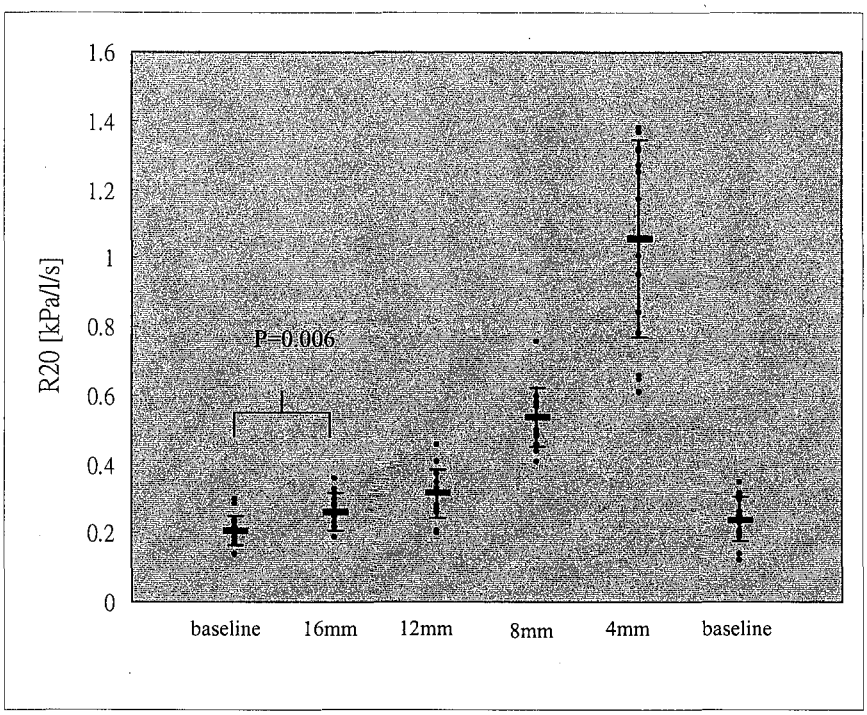

Fig. 2. Airway resistance measured by the FOT at 20 Hz (R20) ± SD. The p-value of the baseline and 16-mm diameter groups is less than 0.05.

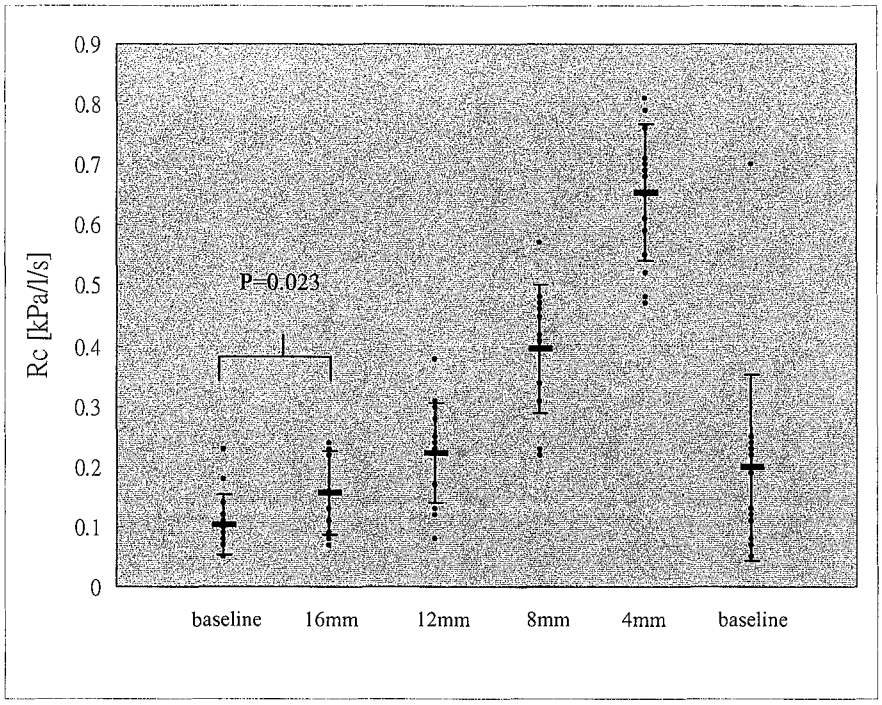

Fig. 3. Central resistance (Rc) ± SD, obtained with baseline, orifice at 16-mm diameter, 12-mm diameter, 8-mm diameter, 4-mm diameter, and repeated baseline groups. The p-value of the baseline and 16-mm diameter groups is less than 0.05.

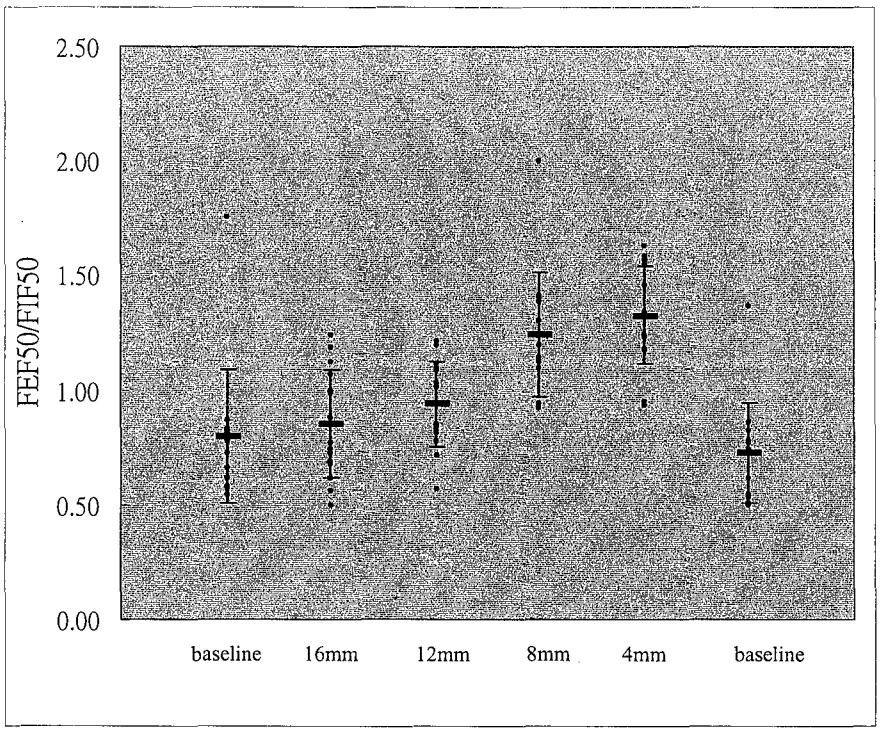

Fig. 4. The FEF50%/FIF50 ratio ± SD. The p-value is not so predictable and fluctuates between the groups.

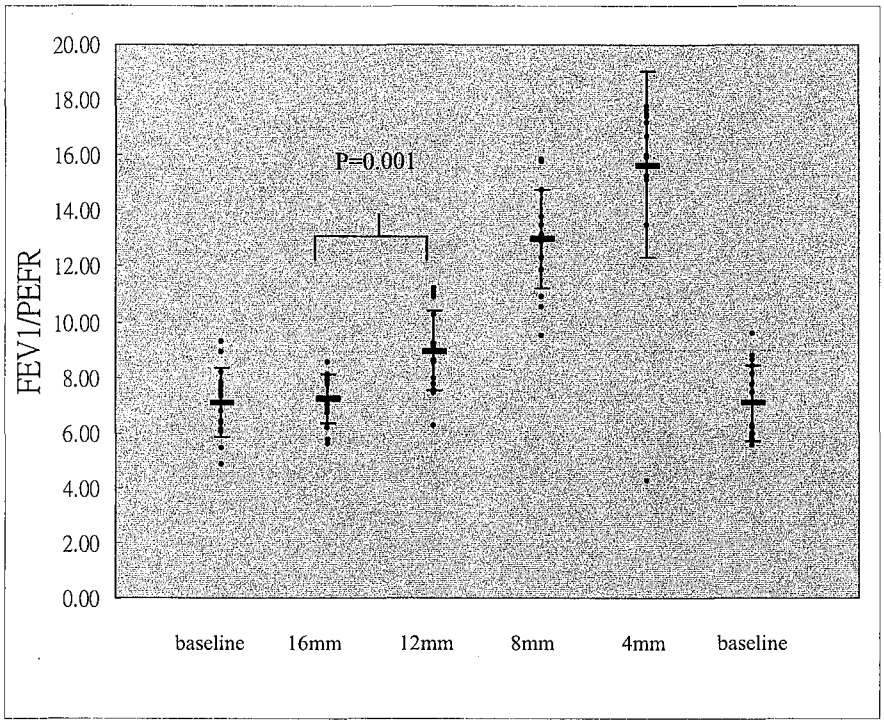

Fig. 5. The FEV1/PEFR ratio ± SD. The p-value of the 16-mm diameter and 12-mm diameter groups is less than 0.05.

Table 1. The p-value analysis of the groups

Parameters / Groups	FEV1/PEFR	FEF50/FFI50	FIF50	R5	R20	Rc	Rp
Baseline and 16-mm diameter	0.669	0.601	0.415	***0.028***	***0.006***	***0.023***	0.619
16-mm diameter and 12-mm diameter	***0.001***	0.264	0.127	***0.014***	***0.034***	***0.027***	0.077
12-mm diameter and 8-mm diameter	$2.78x10^{-7}$	***0.002***	$6.02\,x10^{-7}$	$7.36x\,x10^{-8}$	$1.59\,x10^{-8}$	$3.03\,x10^{-5}$	0.061
8-mm diameter and 4-mm diameter	***0.012***	0.336	$1.45\,x10^{-10}$	$1.04\,x10^{-5}$	$4.17\,x10^{-6}$	$5.44\,x10^{-7}$	***0.038***
4-mm diameter and Baseline	$2.38\,x10^{-8}$	$2.61\,x10^{-8}$	$8.42\,x10^{-10}$	$2.68\,x10^{-8}$	$1.44\,x10^{-8}$	$1.31\,x10^{-9}$	***0.006***
Baseline and Repeated baseline	0.987	0.421	0.601	0.249	0.132	***0.037***	0.362

*P-value <0.05 is considered significant and is expressed in italics.

for FEF50/FIF50 and Rp). This means that the data in the 8-mm diameter group is very different from that of 12-mm diameter group. The least level of obstruction that could be detected by these parameters in this study was an 8-mm diameter.

Discussion

In 1968, Jordanoglou and Pride introduced the maximal flow-volume curve to diagnose large airway obstruction, and they proposed the

midexpiratory to midinspiratory ratio as being very helpful [15]. In 1972, Empey introduced the ratio of FEV1/PEFR as being helpful in the diagnosis, and concluded that a value for this ratio more than 10 when upper airway obstruction is suspected indicates that significant obstruction may be present. An upper airway obstruction must narrow the lumen of the airway to less than 6 mm in diameter to produce abnormalities on the flow-volume curve [4]. In 1975, Rotman compared four parameters and concluded that the most useful measurements are the midflow ratio, FEF50%/FIF50%, and the FEV1/PEFR [3]. Our study demonstrates that FEV1/PEFR is the most sensitive parameter among the UAO indices since it could tell the difference between the 16-mm diameter and 12-mm diameter groups. This is compatible with the findings of Rotman and Empey.

The oscillometry allows a functional differentiation into the proximal (stiff) and distal (dispensable) airways. Low frequencies (5 HZ) pass through the whole lung. Therefore the parameter R5 (total respiratory resistance) includes the extrathoracic, central, and peripheral airways. Tissue and thoracic resistance is rather low and can be neglected. Higher frequencies (20 HZ) are stunted in the central airway. Therefore the parameter R20 (distal respiratory resistance) covers only the extrathoracic and central airways. On the other hand, Rc (central resistance) and Rp (peripheral resistance) are structural data using the 7-element Mead model. Rc and Rp are interpreted parameters whereas R5 and R20 are measured. We demonstrated that R5, R20, and Rc are all sensitive parameters in detecting UAO. They could differentiate the difference between the baseline and 16-mm diameter groups with a p value < 0.05. Rp is less sensitive and could not differentiate until reaching the 8-mm diameter and 4-mm diameter groups. FEV1/PEFR could differentiate the 16-mm diameter group from the 12-mm diameter group with a p value <0.05. We demonstrated that R5, R20, and Rc are more sensitive than FEV1/PEFR in detecting the presence of UAO.

The least level of obstruction that could be detected in Empey's study was 6 mm. Our study revealed that 8 mm was sufficient to detect UAO. All of the parameters, including FEV1/PEFR, R5, R20, and Rc, increased significantly when obstructed by an 8-mm orifice, and 8 mm was the critical point of obstruction that could be detected clinically in this study. However, the UAO in this study was simulated with a small orifice, so further clinical study of UAO patients is mandatory.

Many investigators have reported the wide range of normal values and low reproducibility of the FOT as compared to spirometry. Timonen reported the variation in Rrs, FOT (resistance of respiratory system using the FOT method) values was larger than that of most spirometric indices [16]. Cuijpers reported that the diagnostic value of the impedance parameters appeared to be low, as no cut-off points were found to discriminate clearly between symptomatic and symptom-free children [17]. Our study did not measure the reproducibility directly, however FEV1/PEFR seems to have a higher reproducibility (p-value is 0.987) when comparing the baseline group with the repeated baseline group. The relatively low repeatability of the oscillometry parameters requires more clinical studies for clarification.

Conclusion

Using the FOT to obtain measurements is non-invasive, independent of effort, and requires little or no co-operation from the subject. The FOT can also separate values for large airway and peripheral airway resistance. We have demonstrated that R5, R20, and Rc are so much more sensitive than the UAO indices in detecting simulated UAO that FOT may be a suitable tool for the detection of UAO. The ratio of FEV1/PEFR is still the most sensitive parameter among the UAO indices. When the orifice of artificial UAO is decreased to 8mm, most parameters will show the difference. The cut-off point, sensitivity, and

reproducibility of the resistance values of the FOT need to be further studied.

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以強迫振盪技術偵測上呼吸道阻塞

陳威男 蔣士仁* 黃曉蕙 陳重華

診斷上呼吸道阻塞就臨床而言非常重要，但病人常因阻塞程度非常嚴重才經由內視鏡檢查而得到診斷。傳統肺功能檢查主要靠流速容積圖（flow volume loop）、及所謂的上呼吸道阻塞指數(Upper airway obstruction indices-UAO Indices) 如 FEV1/PEFR、FEF50%/FIF50%等數值得到結果。其敏感性及特異性以往研究多所描述。強迫振盪技術 (forced oscillation technique)乃基於肺生理學及電學原理將肺功能各項參數加以測量，其有較不需依賴病人合作及可分出中心氣道及週邊氣道阻力之優點。本研究以人為氣道阻塞模擬上呼吸道阻塞疾病，並以強迫振盪技術所測量之參數包括中心氣道阻力 (Rc)、週邊氣道阻力 (Rp)、5Hz 氣道阻力 (R5)及 20Hz 氣道阻力 (R20)與上呼吸道阻塞指數(UAO indices)做一比較。本研究發現對於發現上呼吸道阻塞而言，強迫振盪技術較上呼吸道阻塞指數靈敏，且當阻塞程度達 8 mm 時多數參數皆可偵測。***(胸腔醫學 2002; 17: 387-394)***

關鍵詞：上呼吸道阻塞、上呼吸道阻塞指數、強迫振盪技術

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Bronchiolitis Obliterans and Post-Transplantation Lymphoproliferative Disorder in a Patient with Bilateral Lung Transplantation—A Case Report

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Hon-Ki Hsu*, Hung-Chou Chang*, Ming-Ting Wu**,
Hui-Hua Tseng***, Jyh-Seng Wang***

For patients with severe functional impairment of the lung and limited life expectancy, lung transplantation offers the possibility of a markedly improved quality of life and longer survival. Nonetheless, post-operation complications are frequent and result in constraints on the long term preservation of the graft function and patient survival. We present a case of a 53-year-old female who presented with progressive dyspnea and was diagnosed as bronchiolitis obliterans associated with consumption of Sauropus androgynus. The patient underwent a left and right lung transplantation, separately. However, bronchiolitis obliterans and lymphoma developed in the bilateral lungs about two years after transplantation. A progressive decline of the lung function and characteristic findings of HRCT were clues to the clinical diagnosis of identify BO. In addition, with a new and persistent patchy or mass lesion in the chest roentgenogram in transplant recipients, post-transplantation lymphoproliferative disorder (PTLD) should be on the list of differential diagnoses. ***(Thorac Med 2002; 17: 395-401)***

Key words: bronchiolitis obliterans, lung transplantation, post-transplantation lymphoproliferative disorder

Introduction

As a result of improvements in surgical techniques, immunosuppression, and postoperative management, the current 1-year survival rate following lung transplantation is 71%, and 46% of transplant recipients will survive at least 5 years. Although infection and malignancy remain important complications, prolonged survival is limited predominantly by bronchiolitis obliterans (BO) [1-3]. The complication may lead to substantial disability and mortality secondary to augmented immunosuppression in attempts to halt progression.

An increased risk of certain malignancy is a well-recognized complication in organ transplant recipients. Kidney and heart transplant recipients have an increased incidence of cancer, amounting to approximately 6%. Because of the relatively

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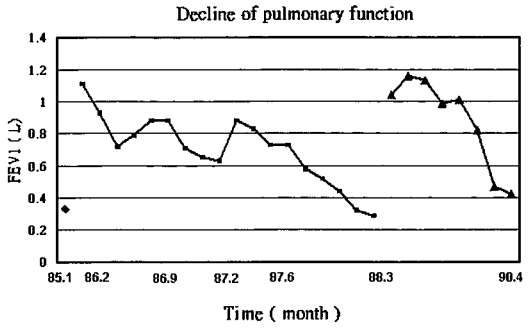


Fig. 1. The pulmonary function declined gradually after lung transplantation.

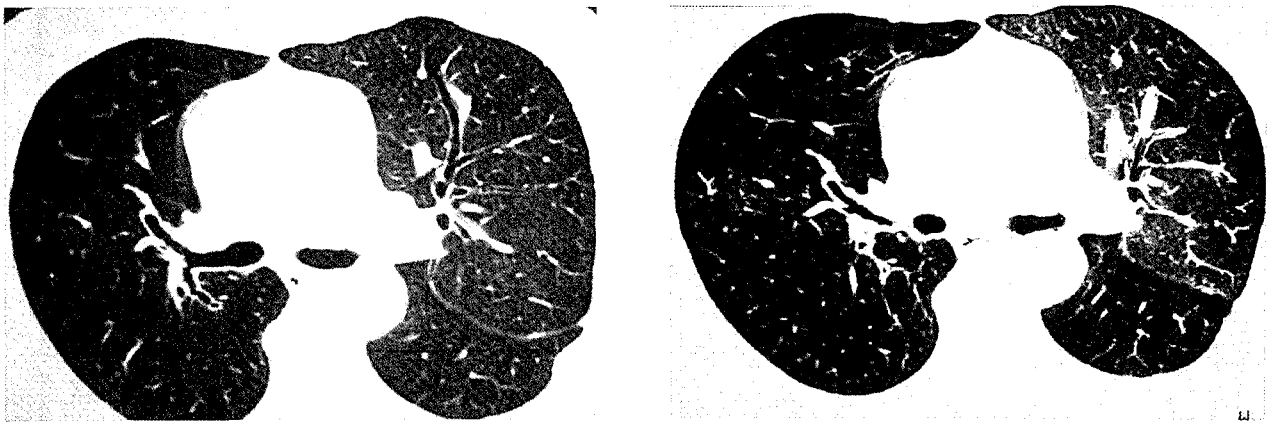
short follow-up period, the prevalence of malignancy after lung transplantation is uncertain. The neoplasms that are frequently observed in the general population (carcinomas of the lung, breast, prostate, colon, and invasive uterine cervical carcinomas) are not more prevalent in the recipients. The predominant malignancies in transplant patients have been lymphoma, skin cancer, kidney cancer , Kaposi's sarcoma, etc [4].

We present a case with identify BO (Sauropus androgynus-associated), who had received a left and right single lung transplantation, separately, and who developed BO and lymphoma about two years thereafter.

Case Report

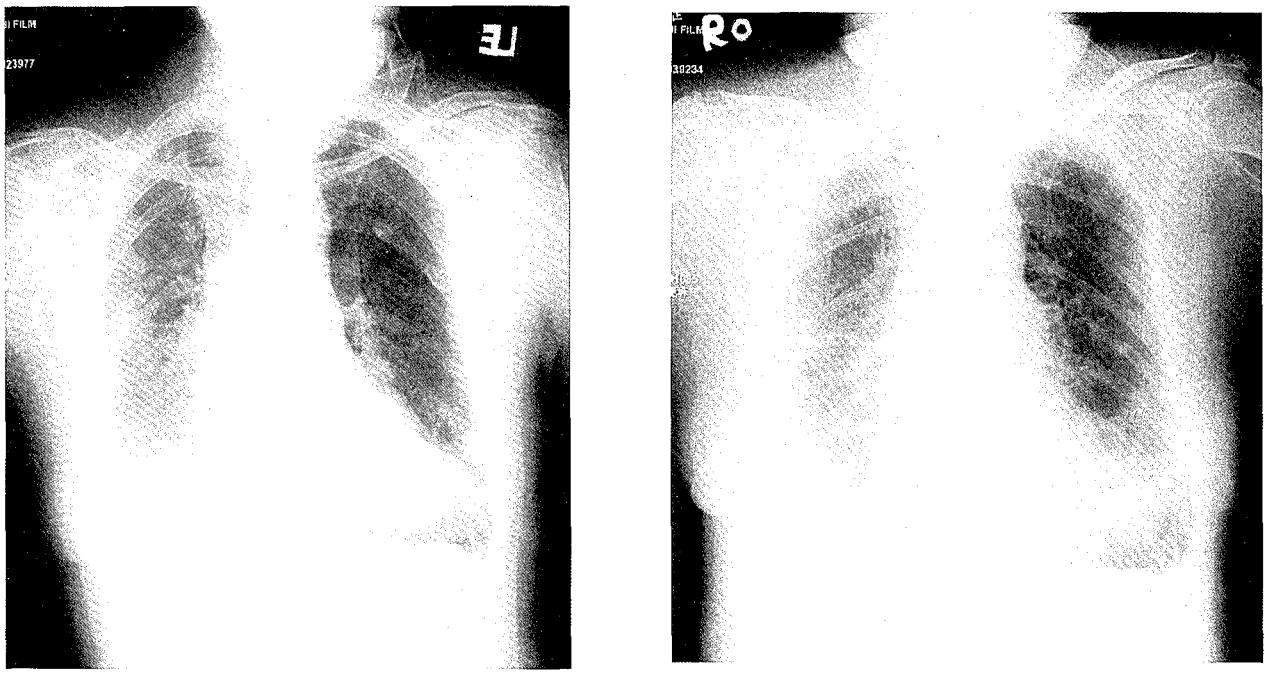
A 53-year-old female patient suffered from progressive dyspnea and persistent cough for months in 1995. The pulmonary function test revealed severe airflow obstruction with FEV1 0.33 L (26% predicted). There was no bronchodilator response. Chest roentgenograms were essentially normal and high-resolution computed tomography (HRCT) of the thorax showed a patchy low attenuation of the lung parenchyma with mosaic perfusion, which was compatible with small airway disease. The immunologic studies, which included ANA, anti-ds DNA, rheumatoid factor, C3, and C4 were within the normal range. The diagnosis was bronchiolitis obliterans associated with consumption of Sauropus androgynus, proven by open lung biopsies. The lung condition became progressively deteriorated in spite of various treatments, such as immunosuppressants (two courses of pulse therapy with methylprednisolone 500 mg for 3 days), bronchodilators, Chinese medication, etc. The patient underwent a left single lung transplantation in Sep. 1997. The operation was successful, with only minimal acute rejection noted. The lung function dramatically improved post-transplantation. She was followed up at the outpatient department with oral acyclovir, trimethoprim-sulfamethoxazole, and bronchodilator inhalations, and was placed on standard immunosuppressive therapy with cyclosporine, azathioprine, and prednisolone. Her clinical condition was relatively stable for another year.

However, the patient still suffered from dyspnea on exertion, and increasingly limited daily activities month by month after lung transplantation. The lung function declined gradually to a pre-operation level, with FEV1 0.29 L (23% predicted) in March 1999 (Figure 1). A right single lung transplantation was decided on and performed in April 1999. The pathologic report revealed diffuse BO changes in the right lung specimen. After operation, the lung function improved temporarily. The patient continued to take anti-viral, and anti-pneumocystis carinii pneumonia medication and immunosuppressive therapy (tacrolimus, azathioprine, and prednisolone). However, the gradually declining pulmonary function was inevitable. A HRCT series showed progressive changes in discrepant vessel caliber and patches of low attenuation with mosaic perfusion in the bilateral lung field, which were compatible with BO formation (Figure 2). She called on the emergency department due to exacerbated dyspnea in April 6, 2001. A series of chest roentgenograms showed a progressively change of one patchy lesion in the left lower lung field (Figure 3). Respiratory failure and septic shock developed in spite of treatment, and the patient died on May 5, 2001. At autopsy, the histopathological findings revealed an organizing inflammatory response centered on respiratory



(A) (B)

Fig. 2. (A) Inspiration (B) Expiration Discrepant vessel caliber, mosaic perfusion and air trapping.



(A) (B)

Fig. 3. (A) At the initial admission, a patchy lesion involving the left lower lung. (B) The lesion worsened.

and terminal bronchioles in the bilateral lungs. The mature collagen filled the lumen of the bronchioles and the subepithelial location. These findings were compatible with BO (Figure 4). In addition, multiple nodules were noted in the bilateral lungs which were proved to be large cell lymphoma (Figure 5).

Discussion

Bronchiolits obliterans is a term restricted to the membranous and respiratory bronchioles, and refers to dense eosinophilic hyaline fibrous plaques in the submucosa of the small airways, which may be concentric or eccentric and result

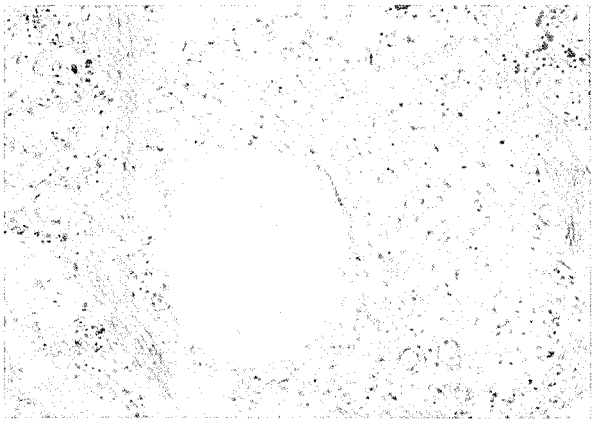
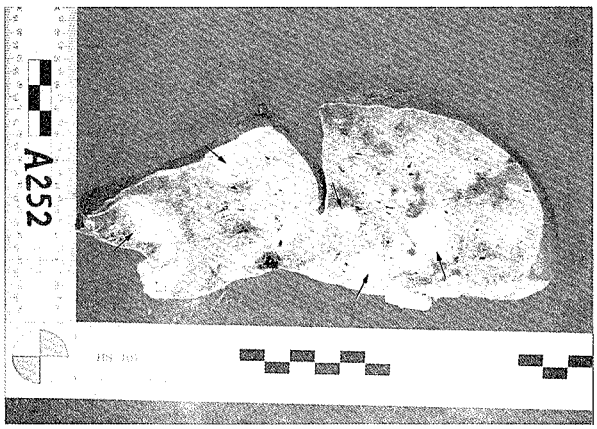


Fig. 4. Constrictive bronchiolitis obliterans, fibrous obliteration of the bronchiole. (H&E, x 100)

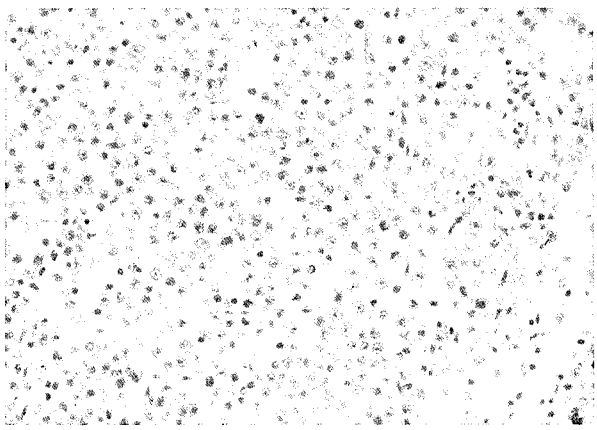
in partial or complete occlusion of the lumen. The scar tissue may be associated with the fragmentation and destruction of the smooth muscle wall, and may extend into the peribronchiolar interstitium [5]. The common etiologies of BO include viral infection, organ transplantation (bone marrow, heart-lung), autoimmune disease (rheumatoid arthritis), and drugs (d-penicillamine) etc. The association of BO with some vegetable consumption was described in Taiwan in 1996 [6]. The patient presented in this case report was one of the BO victims treated in Kaohsiung Veterans General Hospital. She had received a left and right lung transplantation, separately. BO and lymphoma developed in the bilateral lungs in two year later.

The prevalence of clinically or histologically diagnosed BO in lung transplant recipients within the first year after transplantation was 28%, and the actuarial freedom from BO was 67, 47, 42, and 15% at 1, 2, 3, and 5 years after lung transplantation. Long-term data indicate that the cumulative risk of BO may reach 60 to 80%, 5 to 10 years after transplantation [7,8]. Two working hypotheses have evolved to explain the etiology of chronic rejection. In the first, the processes are thought to be primarily an antigen-dependent phenomenon influenced by early immunologic injury such as acute rejection and continuing host alloresponsiveness. The second hypothesis is that alloantigen-independent factors such as prolonged ischemia, surgical manipulation, reperfusion injury, recurrent infection, and aspiration may lead to progressive changes [9].

The diagnosis of BO usually requires tissue obtained from open lung biopsies. However, severe obstructive pulmonary dysfunction in transplant recipients with BO may increase the risk of open lung biopsy. Therefore, a clinical diagnosis of BO can be made without histologic confirmation in patients with typical clinical presentations, and pulmonary function and radiological manifestations. Progressive irreversible airflow obstruction in transplant patients has proved to be almost always a consequence of BO. The FEV1 has been found to be a reliable and consistent indicator of graft function. The term



(A)



(B)

Fig. 5. (A) Multiple nodules were noted on the gross specimen, but were invisible in the CXR. (B) Large B-cell malignant lymphoma featuring a diffuse proliferation of monotonous large atypical lymphocytes. (H&E, x 400)

bronchiolitis obliterans syndrome (BOS) describes a deterioration of the graft function, which can not be explained by acute rejection, infection, or problems of the bronchial anastomosis, after lung transplantation. The BOS grading system has been used widely and commonly reported in clinical studies of chronic lung allograft rejection. In addition, the BO manifestation in the thorax using HRCT scanning, includes the low attenuation of the lung subserved by narrowed small airways failing to deflate on expiration, bronchodilatation, and air-trapping [10]. HRCT scanning also allows any bronchiectasis to be demonstrated, and can exclude interstitial lung disease. In the present case, the lung function showed a gradually declining FEV1, and HRCT revealed mosaic perfusion and air-trapping after the left single lung transplantation. BO was highly suspected clinically, and confirmed by pathological findings subsequently. Unlike acute rejection, chronic rejection is often refractory to treatment. Currently, the response of BO to immunosuppressive therapy is limited. Although retransplantation is a controversial option, the patient underwent a right single lung transplantation for severe irreversible allograft failure.

In this case, a patchy lesion in the left lower lung and multiple small nodules in the bilateral lung fields on the chest roentgenogram were proved to be large-cell lymphoma. Solid organ transplant recipients also have an increased incidence of malignancy. Cancer incidence in patients who undergo transplantation ranges from 4-18% (average 6%). Lymphomas are much more common in heart or heart and lung recipients. The diverse lymphoproliferative diseases (including lymphoma) that arise after transplantation are referred to collectively as PTLD. They comprise a morphologically and clonally heterogenous group that has been closely tied to Epstein-Barr virus (EBV) infection. The diagnosis of PTLD historically has been associated with a mortality rate of 50-80% in patients who have a monocolonal form of disorder. Recently described aggressive approaches to the diagnosis and treatment of PTLD have the potential to improve outcome [11-13].

In this case report, a progressive decline of the lung function and characteristic findings of HRCT were clues to the clinical diagnosis of BO. With new and persistent patchy or mass lesions on the chest roentgenogram in transplant recipients, PTLD should be on the list of differential diagnoses.

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肺移植後併發阻塞性細支氣管炎及淋巴增殖性疾病——一病例報告

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對於肺功能有嚴重障礙及可預期存活時間不長的病人，肺移植提供了顯著改善生活品質及延長生命的可能性。然而，術後常出現後遺症，且限制了移植肺的功能及病患長期的存活。我們在這裡提出一個病例報告，這是一位 53 歲女性，臨床上出現漸進性呼吸困難,經診斷為因食用守宮木(減肥菜)造成阻塞性細支氣管炎。此病患分別接受了左肺和右肺移植。然而，在肺移植的兩年後在肺部的兩側出現了阻塞性細支氣管炎及淋巴瘤。漸進性肺功能下降以及 HRCT 上的特殊表現是臨床上診斷阻塞性細支氣管炎的線索。除此之外，在受移植者 X 光片上若出現新的持續性斑點或腫塊性病灶，移植後淋巴增殖性疾病應列入鑑別診斷。 ***(胸腔醫學 2002; 17: 395-401)***

關鍵詞：阻塞性細支氣管炎，肺移植，移植後淋巴增殖性疾病

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Chest Wall Rhabdomyosarcoma—A Case Report

Kuang-Chao Chang, Ming-Jen Peng, Pei-Jan Chen, Hung-Chang Liu*, Chi-Yuan Tzan**

Chest wall tumors usually present as a slowly enlarging mass causing localized dull pain. Approximately 60% are malignant. Rhabdomyosarcomas are rare and highly malignant tumors sometimes found on the chest wall. They are relatively radioresistant; surgical resection should be combined with adjuvant chemotherapy to achieve the best survival.

We report a 56-year-old patient presenting with intermittent chest pain related to movement lasting for 20 days. The physical examination revealed an ill-defined protruding soft tissue mass located on the right anterior chest wall between the 6th and 7th intercostal space. Chest X-ray showed an oval-shaped calcification in the lower right chest wall.

Echo-guided needle aspiration was performed. The cytologic examination was highly suggestive of a malignant mesothelioma, and the pathologic examination revealed vimentin-positive sarcoma. After the surgical removal of the chest wall lesion, and a wedge resection of the lung, the final pathologic diagnosis was rhabdomyosarcoma.

Chest wall sarcomas, therefore, should be considered in those who suffer from intermittent chest pain, although they are uncommon. ***(Thorac Med 2002; 17: 402-407)***

Key words: chest wall tumor, rhabdomyosarcoma, chest pain

Introduction

Chest wall tumors are much less common than lung tumors. They usually present as a slowly growing mass with localized pain. Approximately 60% are malignant, and 40 to 50% are metastatic in origin. Primary malignant tumors include fibrosarcoma, chondrosarcoma, solitary plasmacytoma, Ewing's sarcoma, liposarcoma, osteogenic sarcoma, reticulum cell sarcoma, rhabdomyosarcoma, hemangiopericytoma, and melanoma.

Rhabdomyosarcomas are rare and highly malignant. The tumor spreads along fascial planes and metastasizes early by hematogenous spread. Antidesmin, muscle-specific actin, and MyoD are the most sensitive histochemical markers for rhabdomyosarcoma. Staining for vimentin, myoglobin, cytokeratin, creatine kinase M, S100, and neuron-specific enolase, have been reported [1].

Frequent and diverse p53 mutations have been reported in both alveolar and embryonal tumors [2].

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Tumors with an alveolar histology often have a characteristic translocation involving chromosomes 2 and 13 – t(2;13)(q35:q14) [3].

The differential diagnosis of extremity and truncal lesions includes other soft tissue sarcomas, bone tumors such as Ewing's sarcoma and osteogenic sarcoma, and neuroectodermal tumors.

Fever, anorexia, weight loss, and pain suggest widespread disease[4]. Tumors of the trunk are more likely to be alveolar in type and to be large lesions; they tend to recur locally after resection and to spread distantly. Metastatic tumors most commonly involves the lung, bone, bone marrow, and regional or distant lymph nodes. Metabolic disturbances (hypocalcemia or hypercalcemia) may be seen at presentation, and DIC may complicate the clinical picture in advanced disease. With the introduction of multi-agent chemotherapeutic regimens, 5-year survival as high as 70% has been observed, compared with 25% in 1970 [5].

Case Report

A 56-year-old patient was hospitalized with the chief complaint of intermittent chest pain with movement lasting for 20 days. He was quite well until 20 days before admission, when he noted a sudden onset of severe chest pain in the right chest. Subsequently, he noted a palpable chest wall mass. He denied cough, fever, or weight loss.

He had smoked 1 pack of cigarettes per day for over 30 years. The physical examination revealed an ill-defined, elevated mass located between the 6th and 7th intercostal spaces of the anterior aspect of the right chest wall. Serum laboratory data was within normal limits, except a mild hyperglycemia. The pulmonary function test was normal.

On the chest radiograph, there was an oval-shaped calcification in the lower right lung field (Figure 1). A hypodense mass with marginal calcification was seen in the right lower thorax on the chest CT. (Figure 2) A Tc-99m MDP bone scan showed a focally increased uptake of radioactivity in the anterolateral aspect of the right 6th and 7th ribs, and the posterolateral aspect of the left 5th rib.

Chest ultrasonography revealed a hypoechoic lesion on the lateral aspect of the right chest wall (Figure 3), and echo-guided needle aspiration was performed. The cytology revealed hyperchromatic malignant cells which were positive for vimentin and negative for cytokeratin and mucin, which was highly suggestive of malignant mesothelioma.

One week later, the patient underwent a surgical resection.A huge (16 cm x 10 cm x 5 cm) mass was found in the lower right chest wall. The mass adhered tightly to the pleura, which was

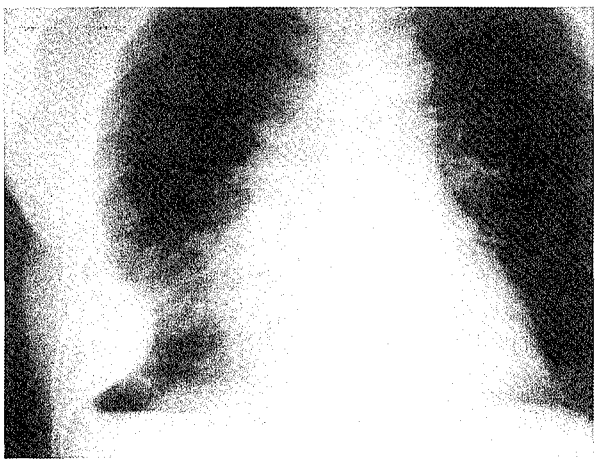

Fig. 1. An oval-shaped calcification in the lower right lung field on plain chest film.

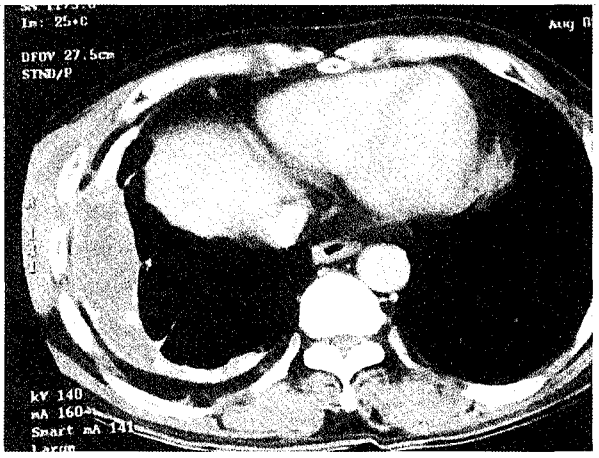

Fig. 2. A hypodense mass lesion with marginal calcification in the lower right lung on chest CT.

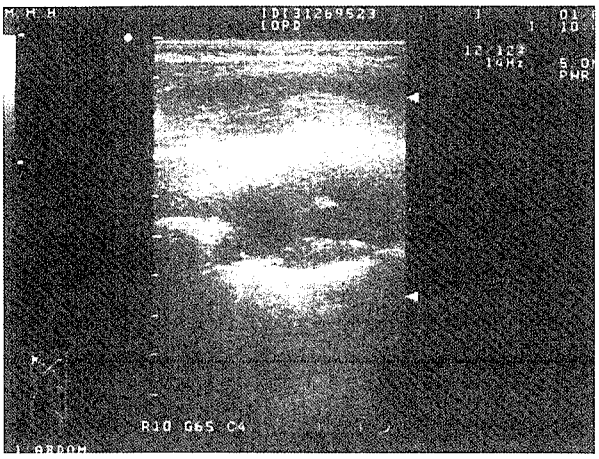

Fig. 3. Chest ultrasonography reveals a hypoechoic mass on the lateral aspect of the right chest wall.

thickened and calcified. An en bloc resection of the tumor was performed, with a 2 cm margin around the tumor.

The pathologist reported large polygonal to round cells growing in nests, sheets, or alveolar structures (Figure 4). MyoD was positive (Figure 5) and myoglobin was weakly positive. The diagnosis was alveolar rhabdomyosarcoma.

After surgical excision, the patient received radiotherapy (total dose 50.4 Gy at 180 cGy per day for 28 days), and has been followed in the OPD.

Discussion

Rhabdomyosarcoma was first described by Weber in 1854 as a tumor of the tongue in a 21-year-old patient. In 1958, Horn and Enterline proposed a classification of rhabdomyosarcomas into four distinct subgroups: embryonal, alveolar, botryoid, and pleomorphic[6].

The site of the primary tumor is an important determinant of prognosis. Rhabdomyosarcomas arising in the genitourinary tract and orbit generally have the best prognosis, whereas parameningeal, retroperitoneal, and truncal tumors carry the worst prognosis.

These tumors arise from primitive mesenchymal cells and spread locally to invade adjacent structures. They may also metastasize distantly

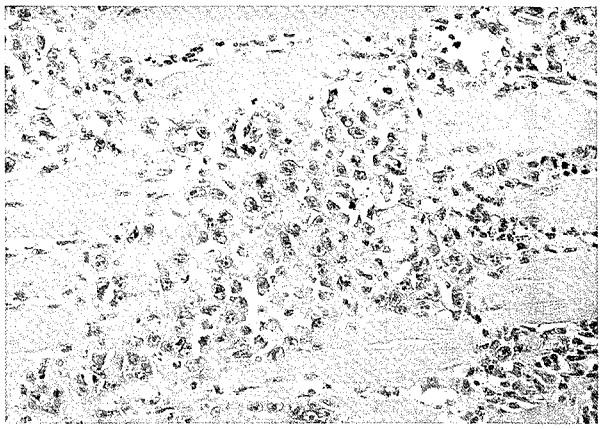

Fig. 4. Most tumor cells have vesicular nuclei and prominent nucleoli, many with eosinoplilic cytoplasm. The pathologist reported viable tumor tissue consisting of large polygonal to rounded cells growing in nests, sheets, or alveolar structures. (H & E. 400 x)

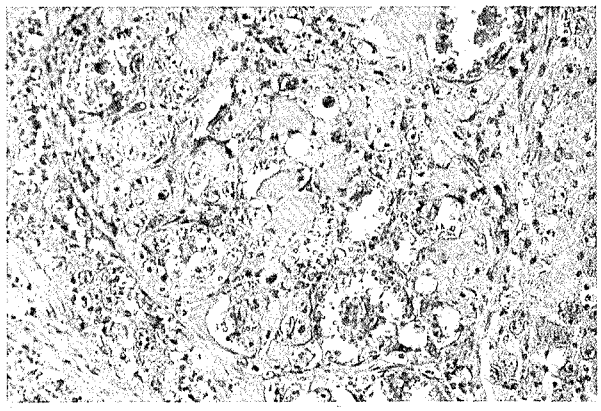

Fig. 5. The immunostain reveals MyoD positive; alveolar rhabdomyosarcoma is most likely.

via both lymphatic and hematogenous routes. Fortunately, our patient had a calcified, thickened pleura, which protected the lung from tumor invasion.

The most common type of rhabdomyosarcoma is the embryonal type, with the head, neck, and urogenital organs being the most commonly involved sites. Histologically, the tumor consists of a mixture of undifferentiated round cells and immature striated muscle-like cells with abundant eosinophilic cytoplasm.

The botryoid type is a morphologic variant of the embryonal rhabdomyosarcoma, and often presents in the urogenital tract, head, neck, or gastrointestinal tract as a polypoid mass. The

prognosis is excellent. Histologically, the tumor consists of undifferentiated rounded and spindle-shaped cells admixed with more differentiated, elongated rhabdomyoblasts.

The pleomorphic or adult form of rhabdomyosarcoma is extremely rare in children. The majority of cases show mixed morphologic features, with areas of embryonal or alveolar components. The tumor occurs more often in the extremities and trunk, and is characterized by the presence of large, pleomorphic cells, large round cells, and multinucleated giant cells [7].

The alveolar type is second to the embryonal in frequency, and occurs more commonly in the extremities, trunk, and perianal area. There appears to be no age predilection. This tumor type has the poorest prognosis. Light microscopy shows this tumor to have rhabdomyoblasts mixed with large round cells with prominent eosinophilic cytoplasm.

On light microscopy, our patient's tumor had rhabdomyoblasts mixed with large round cells with prominent eosinophilic cytoplasm, and was MyoD positive, which is compatible with the diagnosis of an alveolar rhabdomyosarcoma.

Rhabdomyosarcomas and mesotheliomas are easily confused due to the following: the alveolar rhabdomyosarcoma cells are mononucleated granular epitheloid cells with round nuclei and prominent nucleoli with eosinophilic granular cytoplasma; the mesothelioma cells are enlarged, the nuclei tend to be round with acidophilic stainable cytoplasma, and the nucleoli are also prominent. Both of them yield a PAS-positive stain. Antidesmin, muscle-specific actin, and MyoD are the most sensitive histochemical markers for rhabdomyosarcoma in the differential diagnosis.

The successful treatment of rhabdomyosarcoma requires a coordinated, multidisciplinary approach that should include surgery, radiotherapy, and chemotherapy [8].

The aim of surgery and radiotherapy is the eradication of the tumor, while chemotherapy acts locally and systemically to prevent the emergence of metastatic disease.

En bloc resection with adequate margins is required for eradication. Tumors with a regional extension are traditionally treated with chemo- and radiotherapy.

Although a strict dose-response curve has never been established, radiation doses in the range of 40 to 60 Gy are most commonly administered. The response rates are 90% in patients with microscopic, and 70 to 80% in patients with gross residual or nonresectable disease, respectively [9].

All patients with rhabdomyosarcoma should undergo combination therapy because it significantly improves survival. The most frequently used combinations are VAC (vincristine, actinomycin D, and cyclophosphamide) or IVA (ifosfamide, vincristine, and actinomycin D) [3].

The successful treatment of primary chest wall tumors requires an early diagnosis and aggressive surgical resection. Advances in chemotherapy, surgery, and radiotherapy are all helping to improve local control and survival.

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胸壁橫紋肌瘤——病例報告

張光照　彭明仁　陳培然　劉洪彰* 曾歧元**

胸壁腫瘤常常以緩慢增大的腫塊表現，造成胸部局部疼痛。將近有六成的胸壁腫瘤是惡性的。

橫紋肌瘤是罕見且高度惡性的腫瘤，經常對放射治療產生耐受性，外科切除合併化學治療可以產生最佳的效果。

我們報告一位 56 歲的男性，主訴有 20 天的漸歇性胸痛， 疼痛會伴隨著身體的運動而加劇。 理學檢查發現，在右前胸第六及第七肋間，有輪廓不清的突出腫塊。 血液學檢查及肺功能都在正常範圍。X 光顯示右下胸壁有橢圓形鈣化。 藉由超音波導引的經皮穿刺抽取細胞檢查，高度懷疑是惡性間皮瘤。 在進行外科切除胸壁病灶及肺部楔形切除後， 病理切片及特殊染色報告顯示，此腫瘤為橫紋肌瘤。***(胸腔醫學 2002; 17: 402-407)***

關鍵詞：胸壁腫瘤，橫紋肌瘤，胸痛

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Solitary Fibrous Tumor Associated with Hypoglycemia —A Case Report of the Doege-Potter Syndrome

Chao-Hung Chen, Chang-Jer Huang, Hung-Chang Liu, Be-Fong Chen*, Chin-Yin Sheu**

Solitary fibrous tumors (SFTs) of the pleura are uncommon, slow-growing neoplasms, which originate from submesothelial mesenchymal cells. Unlike the ominous prognosis of malignant mesothelioma, SFTs of the pleura are typically benign and not related to asbestos. An immunohistochemical study is very helpful in the differential diagnosis. Doege-Potter Syndrome is a rare phenomenon that is presented with a solitary fibrous tumor associated with hypoglycemia. The overproduction of insulin-like growth factor II (IGF-II) by SFTs increases glucose utilization and gives rise to hypoglycemia. Surgical resection is the usual approach adopted for treatment.

We report a 49-year-old female with Doege-Potter syndrome, whose initial presentation was a progressive shortness of breath for one month. Severe hypoglycemia was found in the blood sampling. The chest film showed a huge mass occupying the whole right lung field. The computed tomogram of the chest revealed a lobulated mass with heterogeneous density and calcification. A right thoracotomy with tumor resection and bilobectomy was performed. The hisstological examination proved the specimen to be a solitary fibrous tumor. After twenty-five months of follow-up, the patient was free from the tumor and episodes of hypoglycemia. ***(Thorac Med 2002; 17: 408-414)***

Key words: Doege-Potter syndrome, solitary fibrous tumors of the pleura, hypoglycemia

Introduction

Primary tumors of the pleura are of two types: diffuse and localized. The diffuse type is well-known as an asbestos-inducted entity with a dramatically gross appearance and a rapidly fatal course. The localized type, however, is more perplexing because of its variety of names, including fibrous mesothelioma, benign mesothelioma, subpleural fibroma, solitary fibrous tumor (SFT), and localized fibrous tumor of the pleura. Together, these reflect the range of clinical and pathologic characteristics as well as competing theories of histogenesis.

Two-thirds to 80% of the solitary fibrous tumors of the pleura are originally from the visceral pleura, often with a pedicle [1-2]. The others arise from the parietal pleura of the chest wall, diaphragm, or mediastinum. Neoplasms in

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these atypical sites, together with fissural lesions and lung-invaded lesions, are more often malignant. They account for approximately 12% of all SFTs of the pleura. Malignant SFTs include any one of the following histological features: (1) high cellularity with crowding and overlapping of nuclei; (2) high mitotic activity [more than four mitotic figures (mf) per 10 high-power fields (hpf)]; and (3) pleomorphism judged as mild, moderate, or marked, based on nuclear size, irregularity, and nucleolar prominence [1,3].

Hypoglycemia with clinical symptoms has been reported in approximately 4% of SFTs [2]. A SFT with hypoglycemia was first reported by Doege and Potter in 1930, when the name of Doege-Potter syndrome was specified [4-5]. Of the numerous hypotheses explaining this phenomenon, the most plausible one is that the tumor secretes substances with insulin-like activity.

A case of Doege-Potter syndrome is herein presented. Further clinical manifestations, the diagnosis and immunohistochemical evaluation, as well as the mechanism of the associated hypoglycemia of SFTs will be discussed.

Case Report

A 49-year-old female patient was sent to our emergency room with a presentation of progressive shortness of breath for one month. Tracing her history, a right lung mass had been found on a radiological examination four years ago, but further evaluation and treatment were refused. The initial evaluation on this visit revealed tachycardia, tachypnea, and consciousness disturbance. In the physical examination, the patient's breathing sounds were diminished in the right lung field. An endotracheal tube was inserted immediately. The hemogram and biochemical findings were within normal limits, except a severe hypoglycemia (37 mg/dl). The chest radiograph showed a huge mass occupying almost the entire right lung field (Figure 1). The computed tomogram of the chest revealed a 15 x 30 x 15 cm lobulated mass with heterogeneous density and calcification (Figure 2). The percutaneous aspiration report and biopsy led to a suspicion of mesothelioma. Intermittent hypoglycemic episodes were evidenced during the period of hospitalization. Progressive dyspnea, which resulted in respiratory failure and ventilator dependency, was noted.

Fig. 1. Chest X-ray film taken at the time of hospital admission, showing a large intrathoracic tumor in the right hemithorax

After a complete study, a right posterolateral thoracotomy was performed for the resection of the tumor. The tumor was encapsulated with a peel and severely adhered to the right middle and lower lobes of the lung. Tumor resection accompanied with a bilobectomy of the right middle and lower lobes was performed.

The pathological report confirmed the diagnosis of a solitary fibrous tumor. Grossly, it revealed a firm, grayish, and whorled mass with multiple foci of hemorrhage. Histologically, the mass lesion was composed of short spindle cells arranged in a variety of architectural patterns. Strands of collagen in a wire-like or plexiform

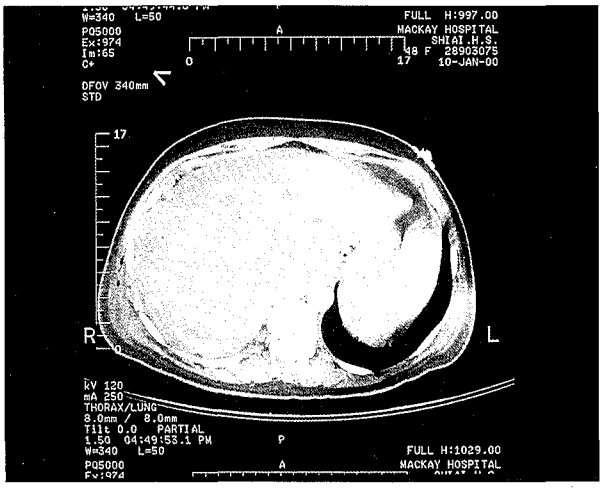

Fig. 2. CT scan showing a lobulated mass with heterogeneous density and an area of calcification

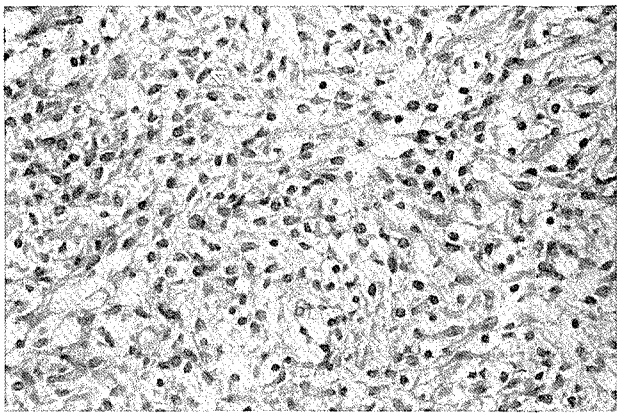

Fig. 3. Tumor histology demonstrating the typical "patternless pattern": a disorderly arrangement of fibroblast-like spindle cells with abundant intercellular collagen

pattern were scattered throughout the lesion (Figure 3). Mitoses were scanty, but the lung parenchyma had been directly invaded. The immunohistochemical study showed a positive vimentin stain, but negative stain for cytokeratins, actins, and desmin.

The post-operative course was uneventful. Throughout a twenty-five-month follow-up period, the patient was free from disease and had no further hypoglycemic episodes.

Discussion

The first report of a primary pleural tumor was that by Lieutaud in 1767 [6]. Wagner was the first to report, in 1870, the detailed histological description of a tumor which had been derived from the mesothelium of the pleura. Klemperer and Rabin [7] in 1931 divided primary pleural neoplasms into two categories: diffuse and localized. The diffuse form, malignant mesothelioma, was assumed to derive from the mesothelial cells, whereas the localized tumor was derived from the submesothelial layer, according to its immunoprofile and ultrastructural features [8-9]. Malignant mesotheliomas represent 75-90% of primary pleural tumors, and usually behave aggressively. The presence of these tumors is closely related to a history of exposure to asbestos. The localized form, SFTs of the pleura, represent about 17% of all benign intrathoracic tumors [10]. SFTs are not associated with asbestos exposure and usually show a good prognosis.

SFTs of the pleura are rare, with an incidence of 2.8 cases per 100,000 tumor registrations at the Mayo Clinic [3]. The neoplasms arise at varying ages, and demonstrate no gender predilection. More than 50% of the cases present an asymptomatic mass discovered incidentally on chest radiographs. A large tumor tends to have local (e.g., chest pain, cough, dyspnea, and hemoptysis) or systemic symptoms (e.g., general weakness, nocturnal sweating, chills, body weight loss, digital clubbing, hypertrophic osteoarthropathy, and hypoglycemia) [2,11-12]. Hypertrophic osteoarthropathy affects 20 to 35% of the cases with SFTs [2,13]. It is related to the abnormal production of hyaluronic acid by tumor cells, which has an osteolytic effect. The initial presentation of our patient included dyspnea and tachypnea, which are favored to be caused by the compression effect of the huge mass. However, the consciousness disturbance of this patient was more likely due to severe hypoglycemia.

SFTs usually involve the pleura. In the most recent 10 years, extrathoracic SFTs have increasingly been diagnosed in a wide variety of

organs, such as the peritoneum, mesentery, liver, stomach, ovaries, kidney, pericardium, mediastinum, thyroid, breast, periosteum of the tibia, parapharyngeal space, salivary glands, meninges, paracranial areas, paranasal sinuses, orbits, lacrimal sacs, and any soft tissues [14-15]. Because of its histological variability, it is difficult to diagnose SFT out of the pleura.

The tumor usually appears as a sharply circumscribed, homogeneous mass ranging in size from 1 cm to 40 cm, as seen in chest roentgenographs [1-2]. Small lesions typically have tapering margins, and form obtuse angles. A pedunculated tumor may change position with respiration. Pleural effusion is rarely presented, and occurs more commonly in malignant tumors. The computed tomography of a small SFT usually shows a homogenous enhancement equal to or greater than that of muscle, while large tumors may have a heterogeneous enhancement, calcification, or areas of fluid attenuation within the mass.

Transthoracic needle biopsy dose not easily diagnose SFTs. However, with the development of immunohistochemical analysis, a proper and cost-effective preoperative diagnosis can be made [16].

Grossly, the size of the tumor varies in diameter. Most tumors are round or ovoid in appearance. The shape of large tumors, as in our case, is modified by the anatomy of the hemithorax. Frequently, it is encapsulated with a thin to thick membrane, which microscopically proves to be collagen, and is covered by normal mesothelial cells. Nearly half of the tumors are attached to the pleura via a single pedicle. Neoplasms with pedicles are usually benign, and most are attached to the visceral pleura. The tumors usually have a gray to white cut surface with a rubbery to firm consistency. Hemorrhage, edema, and necrosis may present in large, especially malignant, lesions [1,11].

Histologically, the so-called "patternless pattern" consists of disorderly arranged fibroblast-like spindle cells in varying proportions of collagenous stroma [11]. The tumors commonly manisfest narrow cords or interlacing fascicles of cells with interspersed thick bundles of collagen. Focal myxoid change or fibrous tissue hyalinization are often present, particularly in larger tumors. Blood vessels are prominent in some tumors. In most benign tumors, nuclear atypia and mitotic figures are sparse. Mitotic figures in malignant SFT, however, are more abundant (more than 4 mf per 10 hpf), and there is an appreciable degree of nuclear atypia [1,3]. In our case, the mitotic figures were less than four per 10 hpf. However, a direct invasion to the pulmonary parenchyma was found.

The immunohistochemical study of our patient revealed a positive vimentin stain, but a negative stain for cytokeratins, actins, and desmin. SFTs typically show a strong positive for CD34, CD99, and vimentin, and a negative for cytokeratin, S100, desmin, and CD31 [8,11,17]. CD34 is an antigen expressed on the surface of the endothelium and hematopoietic progenitor cells. It has been found to stain primitive mesenchymal stromal cells and several mesenchymal tumors. A positive CD34 may help to distinguish SFT from other tumors, but it is not an absolute indicator for SFT. Recently, the B-cell leukemia/lymphoma-2 (bcl-2) protein has been used together with CD34 in the diagnosis of SFT, to distinguish from other spindle cell neoplasms, such as neurofibroma, spindle cell lipoma, dermatofibrosarcoma protuberans, and hemangiopericytoma [17-18].

Doege and Potter in 1930 reported the first case of profound hypoglycemia in association with a tumor of mesenchymal origin. Briselli reviewed 368 cases of SFTs of the pleura, and found a 4% incidence of spontaneous hypoglycemia, which was more likely to occur with larger tumors and those with a high mitotic rate [2]. Numerous theories have been proposed to explain why non-islet cell tumors can produce hypoglycemia. These have included: (1) excessive utilization of glucose by the tumor; (2) production by the tumor of a substance that

stimulates insulin production by the pancreas; (3) production of substances that inhibit insulinase or compete with insulin for insulinase; and (4) production by the tumor of insulin or an insulin-like material [18]. Our case presented with an initital consciousness disturbance which was more likely due to severe hypoglycemia. Severe episodes of hypoglycemia also occurred before operation. With adequate surgical intervention, such as in our case, the hypoglycemia and be ended without any sequel [22-23].

Using a radioreceptor assay, Gorden et al. found that extrapancreatic tumors and hypoglycemia both involved elevated levels of insulin-like growth factor (IGF) [19]. Froesch et al. separate IGF into two components, IGF-I and IGF-II, with more refined radioimmunoassays [20]. With the help of positron emission tomography, Eastman et al. found that circular IGF-II-like proteins are partial insulin agonists, and that hypoglycemia in non-islet cell tumors with IGF-II production is predominantly due to glucose uptake by the skeletal muscles and the suppression of glucose production [21]. Messenger RNA for IGF-II has been found in tissue from soft tissue tumors associated with hypoglycemia, suggesting that IGF-II is secreted by the tumor [22]. The autonomous secretion of IGF-II by such tumors may lead to the suppression of plasma growth hormone concentrations and hence to low concentrations of IGF-I, the main binding protein, and to a low ratio of IGF- I to IGF-II [23].

The majority of SFTs have a benign clinical outcome, with a long-term disease-free survival in about 90% of cases [11-12]. The single best predictor of a benign course is complete surgical excision with microscopically free surgical margins [12]. Every patient who is diagnosed with or suspected of having SFT, should undergo an operation, and the intraoperative confirmation of free surgical margins is mandatory. A large resection of the lung parenchyma and the surrounding pleura is recommended if the tumors present a broad base or attach to the pleural surface. We performed a tumor resection and bilobectomy because of the severe compression of these two lobes, and the lack of a surgical plane between the tumor and the lobes. The pathology report found a direct invasion to the lung parenchyma. Postoperative adjuvant therapy with radiotherapy, chemotherapy, or both has been reported, but its effect is still controversial [11-12].

In conclusion, the solitary fibrous tumor is a rare neoplasm originating from the submesothelial mesenchymal cells. Over 80% of SFTs are clinically benign. Complete surgical resection with free margins is the single best predictor of outcome. The "patternless pattern" is the most common presentation of the histological findings. An immunohistochemical study, showing CD34, and vimentin positive, and cytokeratin, desmin, and S100 negative, is extremely useful in distinguishing SFT from other lesions. Doege-Potter syndrome is a SFT associated with hypoglycemia, and IGF-II-like protein is responsible for the occurrence of hypoglycemia. The surgical resection of the tumor results in an immediate cure.

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孤立性纖維腫瘤合併低血糖症—道奇波特症候群之病歷報告

陳兆弘 黃常哲 劉洪彰 陳碧芳* 許清寅**

肋膜孤立性纖維腫瘤是由間皮下層的間葉細胞所長出之不常見且生長慢速的腫瘤。與惡性間皮瘤之極差預後不同的是，肋膜孤立性纖維腫瘤通常是良性的，且與石綿暴露無關。免疫組織學檢查對於鑑別診斷非常有用。道奇波特症候群為一種極罕見的表現，為孤立性纖維腫瘤同時合併低血糖症。腫瘤過分製造第二型類胰島素生長因子會增加葡萄糖使用進而產生低血糖。手術切除是目前治療中最重要的方法。本文報告一名49歲女性，症狀為近一個月來漸進性的喘氣，抽血檢查發現嚴重的低血糖症，胸部X光呈現一個巨大腫瘤佔據大部分右側胸廓，電腦斷層掃描顯示出分葉狀、不均勻的腫塊，同時有局部鈣化。這病人接受右側開胸手術將腫瘤及右肺兩葉切除。組織學檢查確定是孤立性纖維腫瘤。術後追蹤了二十五個月，病人並沒有復發，且低血糖也不再出現。 ***(胸腔醫學2002; 17: 408-414)***

關鍵詞：道奇波特症候群，肋膜孤立性纖維腫瘤，低血糖症

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The Diagnosis and Treatment of Tracheal Adenoid Cystic Carcinoma Via the Aid of Virtual Bronchography —A Case Report and Review of the Literature

Chin-Ming Chen, Jiunn-Min Shieh, Yoau Fong*, Jinn-Ming Chang**, Chin-Nan Lin***

Owing to advances in computer technology, the three-dimensional (3-D) reconstruction technique can now display lesions of the upper and lower airways. Primary tracheal tumors are rare in the upper airway, as compared with those in the lungs, and are very difficult to diagnose early because of their nonspecific symptoms and slow growth. Adenoid cystic carcinomas which derive from the tracheobronchial mucous glands are the second commonest tracheal neoplasm. We report a precisely displayed and successfully treated primary tracheal adenoid cystic carcinoma that was presented with the help of virtual bronchography images. The patient, who subsequently received radiotherapy after segmental resection of the trachea, withstood the therapy well and undergoes regular follow-up. Surgical resection offers the best chance of cure. CT-simulated tracheobronchial trees can assist in the planning of therapeutic strategies before an operation. ***(Thorac Med 2002; 17: 415-419)***

Key words: computer simulation, tracheal tumor, adenoid cystic carcinoma

Introduction

Computed tomography virtual bronchography is a noninvasive radiological technique which reveals the lesions in the tracheobronchial trees by three-dimensional reconstructions from CT image data. With this new technology, three-dimensional anatomy can easily be appreciated without mentally reconstructed contiguous axial images. This technique is quite similar to the conventional double contrast bronchogram, but it is noninvasive and more acceptable. Tracheal tumors amount to only 2% of those in the respiratory tracts [1]. Adenoid cystic carcinomas are the second commonest tracheal cancer [2]. Early diagnosis seems challenging to clinical physicians because of the non-specific symptoms and slow growth of the tumor. We report a 43-year-old male who was diagnosed with a preoperative 3D virtual bronchography. The patient responded well to the segmental resection of the trachea and the subsequent radiotherapy.

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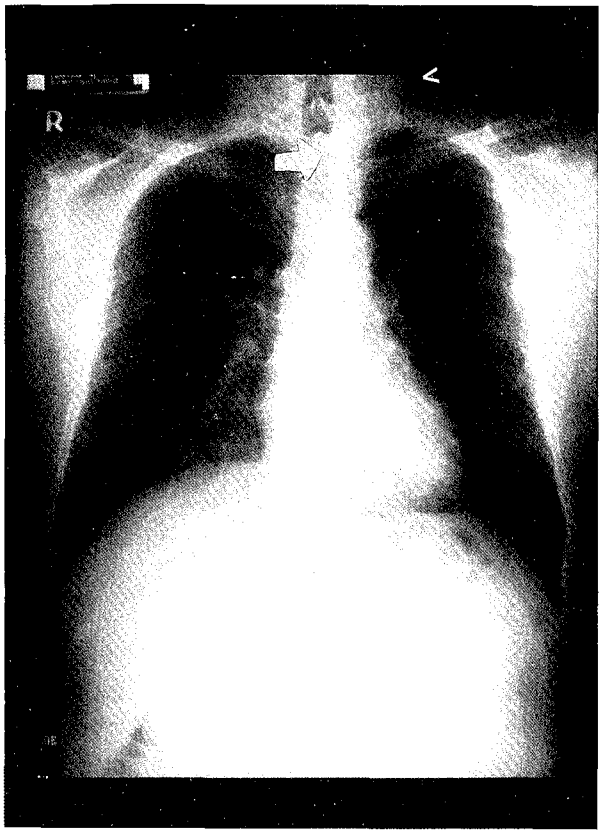
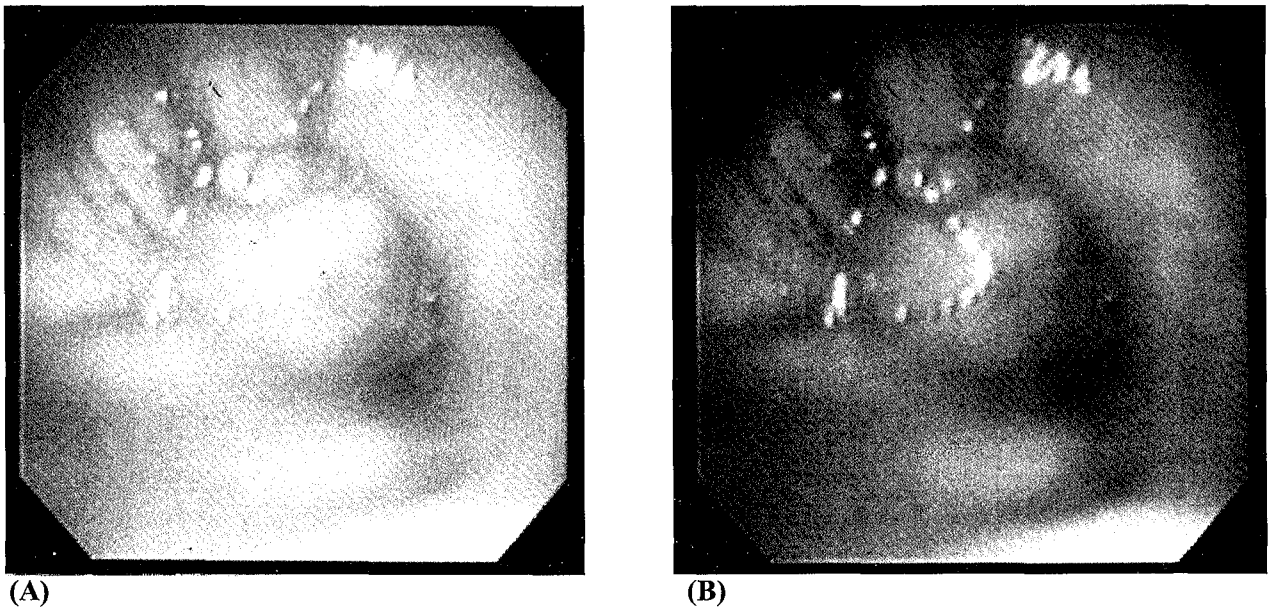


Fig. 1. Demonstrating a filling defect within the tracheal air column implicating a protruding tumor (see arrow)

Case Report

A 43-year-old male visited our hospital on December 17, 2001, due to the presence of progressive dyspnea on exertion and blood-tinged sputum in the most recent 2 months. He had suffered from occasional episodes of bloody sputum expectoration and fluctuating dyspnea without a definite diagnosis in the past year. This patient had a chronic ill-looking appearance with clear consciousness on admission. Vital signs showed a blood pressure of 114/66 mmHg, a body temperature of 37.1℃, pulse rates of 76 beats/min, and a respiratory rate of 20 breaths/min. The patient's supple neck was with no palpable lymph node. An inspiratory stridor could be heard in the upper neck area. The laboratory data disclosed a WBC count of 7700/uL with a normal differential count, and a Hb of 11.9 g/dL. The chest radiography showed a filling defect within the tracheal air column, implicating a protruding tumor (Figure 1). The bronchoscopy revealed a tumor growth from the middle left tracheal wall, causing nearly 80% obstruction of the lumen (Figure 2). The pathological findings of the bronchoscopic biopsy showed an adenoid cystic carcinoma (Figure 3).



(A) (B)

Fig.2. Demonstrating a tumor growth from the middle left tracheal wall, causing nearly 80% obstruction of the lumen

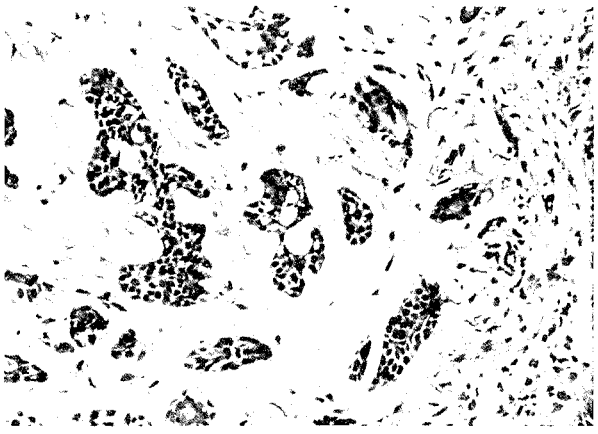


Fig.3. Tumor cells are arranged in a typical cribriform pattern in the bronchial submucosa region (H and E stain, 200X)

A 3-D chest CT image (virtual bronchography) was performed for the pre-operation evaluation, which evidenced a filling defect over the middle left third portion of the tracheal wall (Figures 4, 5). In the brain and bone scans, no distal metastasis was seen. The chest surgeon performed a segmental resection of the tracheal tumor, with an end-to-end anastomosis, on January 5, 2002. A thyroid invasion was also detected during the operation. The patient was discharged 2 weeks after operation. He withstood well the adjunctive radiotherapy at our OPD.

Discussion

In 1988, Zinreich et al stated the usefulness of 3-D display in the head and neck regions because of the clinician's easy appreciation of the 3-D anatomy rather than having to mentally reconstruct the contiguous axial images [3]. The 3-D reconstructions acquired from spiral CT data have several advantages: 1.) a non-invasive technique; 2.) an ability to view the lesions from any angle; and 3.) an objective documentation of the progression or response to therapy [4]. Nevertheless, this technique still has some drawbacks as there is no tissue obtained for diagnosis and a limited color resolution. The rapid progress in computer technology has allowed more excellent tissue visualization and a presentation of the fine details of the tracheobronchial trees. Some virtual endoscopy simulations can also accurately manifest intra-luminal lesions. Furthermore, from the practical point of view, we may be able to develop a portable computer workstation for the bronchoscopy suite to supply endobronchial

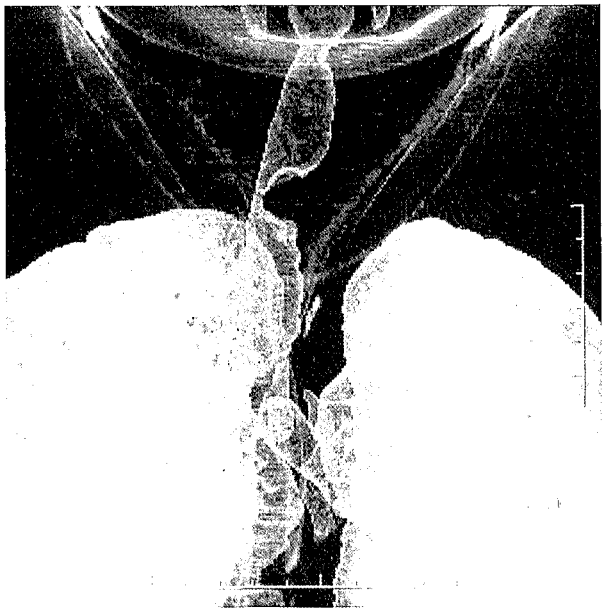


Fig. 4.

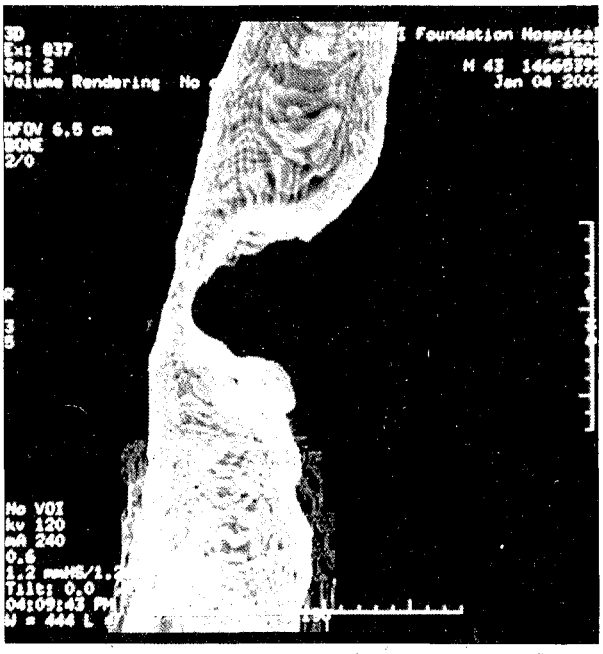


Fig. 5.

Fig.4, 5. Virtual bronchography revealing a filling defect in the middle left third portion of the tracheal wall

simulations [5], which might be beneficial in guiding the transbronchial needle aspiration, thereby potentially enhancing the yield of this non-surgical diagnostic and staging procedure.

Primary tracheal tumors have an incidence of 0.2 per 100,000 persons per year [6]. In adults, most of the tumors are malignant, and are predominantly squamous cell carcinoma [2]. According to Grillo's report, the primary tracheal tumors lie mostly in the lower trachea and bifurcation, with only 15~20% in the middle trachea [7]. Cough, dyspnea, hemoptysis, recurrent pneumonitis, wheezing, and stridor are the most frequent signs and symptoms. Many cases are often misdiagnosed, for long periods, as asthma or chronic bronchitis, due to their slowly progressive properties.

Adenoid cystic carcinomas (ACC) are the second commonest tracheal tumor, and have a lower-grade malignant tendency. The tumors originate from the tracheobronchial mucous glands. The etiology is unknown, but smoking does not cause these tumors. Two series of studies have revealed that the average ages of tumor manifestation are between 45 and 60 years old, without a sex predilection [6,7]. In contrast, 90% of squamous cell carcinomas(SCC) occur in males [2]. In Regnard's review of 208 cases, ACC had a longer delayed diagnosis than SCC after the symptoms had occurred (12 months versus 4 months) [2]. ACC is three times more likely than SCC to extend beyond the trachea to sites like the thyroid or larynx [8]. In our case, thyroid invasion was noted.

Surgical resection with reconstruction of the airway is the only potential curative treatment for ACC. Irradiation (either external beam or high-dose-rate brachytherapy) 3-6 weeks following surgery can improve local tumor control. Unresectable ACC shows a poor response to chemotherapy. In general, ACC has a more favorable long-term prognosis than other tracheal cancers, even with synchronous metastases. Perelman et al reported a 66% 5-year and a 55% 10-year survival in 56 resected patients [1]. However, distal metastasis once was found as late as 25 years after diagnosis [6]. A long-term follow-up is deemed essential for ACC.

In conclusion, primary tracheal adenoid cystic carcinomas are relatively rare. Surgical resection is the best prerequisite for tumor control. With the advent of the new era of 3-D virtual bronchography, surgeons can have a good simulation of the tracheal tumors preoperatively. This new technique may also play a role in prebronchoscopic planning and diagnostic assistance. Integrating the technique with all available technologies, such as stereotactic imaging systems, can provide a better therapeutic modality in the future.

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經虛擬支氣管攝影診治氣管囊腺癌—病例報告及文獻回顧

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由於電腦科技的進步，三度空間重組術能顯示上呼吸道及下呼吸道的病變。原發性氣管腫瘤是上呼吸道腫瘤，比肺部腫瘤更罕見，且由於非特異性的症狀及腫瘤緩慢生長的特性，要早期診斷是相當困難。囊腺癌是起源於氣管支氣管黏液腺，為第二常見的氣管腫瘤。我們現在報告利用這種虛擬支氣管攝影之助而精確地指出原發性氣管囊腺癌，並成功地治療。這病人在做完節段切除氣管後，接受後續放射線治療。此病人對治療的反應良好並規則追蹤中。外科切除提供對氣管腫瘤的最好治療。經由電腦斷層虛擬氣管支氣管，可以幫助我們在術前擬定治療的計劃。 ***(胸腔醫學2002; 17: 415-419)***

關鍵詞：電腦虛擬，氣管腫瘤，囊腺癌

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Intraatrial Recurrence of Small Cell Lung Cancer Mimicking Superior Vena Cava Syndrome —A Case Report

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We present herein a case of small cell lung cancer exhibiting intracardiac metastases with a clinical appearance of superior vena cava obstruction which occurred six months after complete chemotherapy. This condition was suspected with a computed tomography of the chest, and was then confirmed by subsequent magnetic resonance imaging of the thorax. After local radiotherapy, the patient's clinical symptoms improved, and a significant diminishing of intraatrial mass was demonstrated by follow-up computed tomography of the chest. Although superior vena cava syndrome is a common complication of small cell lung cancer, our case may have resulted from an intracardiac invasion, which is rarely seen clinically. Enhanced magnetic resonance imaging is an important non-invasive diagnostic tool used to differentiate between a thrombus and an intracardiac tumor. The radiotherapy which showed success in this case may be an effective alternative management for the intracardiac metastasis of small cell lung cancer. ***(Thorac Med 2002; 17: 420-424)***

Key words: atrial metastasis, magnetic resonance imaging, small cell lung cancer, superior vena cava syndrome, radiotherapy

Introduction

Lung cancer continues to be a major health problem in Taiwan, accounting for 38% of all male and 17% of all female cancer deaths [1]. In the Taiwan area, for the year 2000, lung cancer was the most common of the leading causes of death from cancer, and the number of deaths caused by lung cancer was 6,261[1].

Distant metastasis is the most common characteristic features of incurable lung cancer, but cardiac metastases from bronchogenic carcinoma are not commonly diagnosed prior to death, and most cardiac metastases are usually asymptomatic[2]. Clinical presentations of cardiac involvement are non-specific, including an enlarged heart on the chest X-ray, the development of congestive heart failure, or electrocardiographic changes. We report herein a case with recurrent small cell lung cancer (SCLC) presenting as superior vena cava (SVC) syndrome. Intracardiac invasion was disclosed by enhanced chest computed tomography (CT) and confirmed by magnetic resonance imaging (MRI). The symptoms were effectively controlled by radiotherapy.

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Case Report

This 66-year-old male patient, with a history of long-term cigarette smoking, complained of a right neck mass for 6 months, and had coughed on and off for 2 months. He called on this hospital in April, 1999, because of progressive exertional dyspnea and hoarseness in the previous weeks. At admission, his vital signs included a temperature of 36.7℃, pulse rate of 88/min, respiratory rate of 25/min, and a blood pressure of 160/73 mmHg. On physical examination, cardiac auscultation was normal and the breathing sound was clear. An enlarged lymph node on the right-side supraclavicular fossa, about 2×3 cm^2 in size, was palpable. The others were unremarkable. His white blood cell count was 5000/mm; hemoglobulin level 10.0 g/dL; platelet count 223×1000/mm^3; serum level of urea nitrogen 26mg/dL; creatinine 1.5mg/dL; lactate dehydrase (LDH) 200 IU/L. His chest radiography revealed a mass at the right hilum. The chest CT scan showed a right hilar mass and a moderate amount of pericardial effusion without cardiac tamponade. The pathological report of the biopsy from the right neck lymph node proved SCLC. Abdomen sonography revealed no abdomenal metastasis. Combination chemotherapy with cisplatin and etoposide was then started. After six courses of chemotherapy, the patient achieved a complete response, and was then regularly followed up at the clinic. In Aug, 2000, he called on the clinic due to a severe puffy face and upper limb swelling, similar to the features of SVC syndrome. A chest CT scan demonstrated an intracardiac mass. (Figure 1,left) The chest MRI revealed a soft tissue mass invading the right atrium and crossing into the left atrium. This mass showed a bright signal intensity on T2, which indicated tumor growth rather than thrombus. (Figure 2) This patient was scheduled to undergo palliative mediastinal radiotherapy, with a total dose of 5600 cGy within one month. After radiotherapy, the symptoms of face and upper limb swelling subsided. The follow-up chest CT revealed the disappearance of the intracardial tumor mass. (Figure 1, right) The patient refused subsequent chemotherapy. Brain metastasis occurred 6 months later, and he expired 9 months after the diagnosis of intracardiac metastasis.

Discussion

Metastatic tumors of the heart are uncommon, yet they are 20-40 times more common than primary cardiac tumors [3]. The commonest metastatic carcinomas originate from the lung and breast [4]. Strauss et al reported an incidence of 25% of secondary involvement of the heart in autopsied cases of lung cancer, and noted that cardiac metastases were more common in patients with both extensive disease and poor cell differentiation [2].

Cardiac metastases can occur by lymphatic

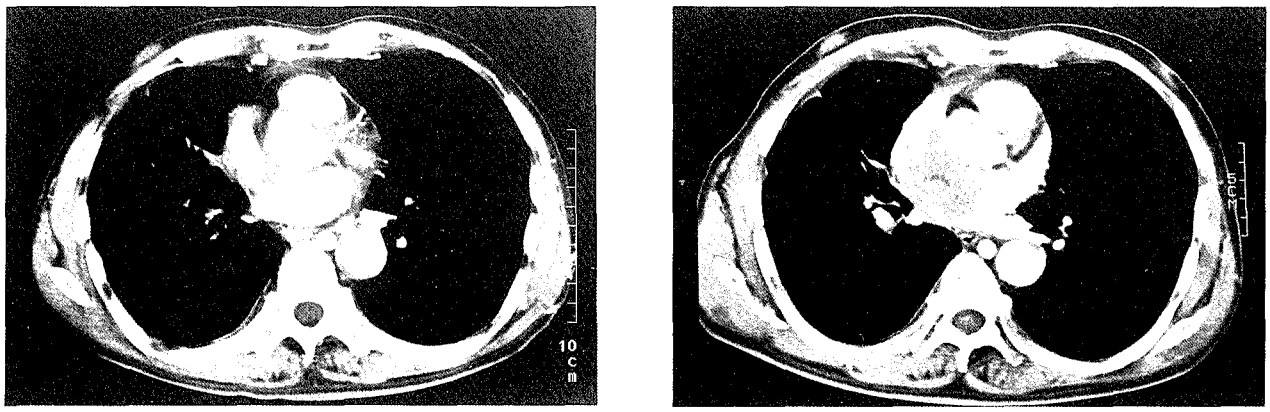

Fig. 1. (Left) Chest CT scan revealing a mass lesion in the right atrium (before radiotherapy)
(right) Follow-up Chest CT revealing the complete disappearance of the intraatrial mass (after radiotherapy)

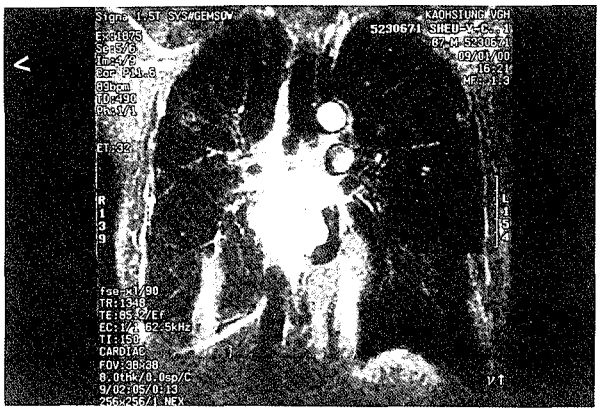

Fig. 2 Coronal image in the chest MRI showing a soft tissue mass in the right atrium, and crossing into the left atrium. The mass showed bright signal intensity on T2, which indicated tumor growth rather than thrombosis.

spread, the hematogenous route, or by the direct extension of the adjacent tumor [5-7]. No matter whether the spread is lymphatic metastases or a direct extension, it is difficult to differentiate in areas near the primary tumor. The major metastatic pathway from the lung to the heart was considered to be the lymphatic. [8] In a series of autopsied cases, lymphatic spread was noted in 78.3% of patients with cardiac involvement, and in most patients with pericardial effusion [8].

Most cardiac metastases are asymptomatic, with fewer than 10% being clinically manifested [2]. Because metastatic cardiac invasion is difficult to recognize clinically, new imaging techniques such as echocardiography (either transthoracic or transoesophagial echocardio-graphy, TEE), contrast enhanced CT scans, MRI, positron emission tomography (PET), or angiography have simplified the in vivo detection of intracardiac metastases. Two cases in two other reports were diagnosed by CT scan. One case was lung metastasis invading the left atrium [10] and the other was bronchogenic carcinoma metastatic to the left atrium [11]. The CT scan is still the usual image procedure in the evaluation of lung masses, either primary or secondary, for planning the appropriate therapy. A contrast medium can be used to assess whether juxtacardiac or hilar masses involve the heart. Nevertheless, MRI is another procedure of choice for evaluation of cardiac tumors and has become the gold standard for the analysis of cardiac structure and morphology. Importantly, thrombus, which may occur in any cardiac chamber, showed no increase in signal intensity after contrast administration. Thus, contrast enhancement in MRI plays an important role in the differential diagnosis between cardiac masses and thrombus [12].

As in our case, the symptomatic intracardiac recurrence of small cell carcinoma presents very rarely with head fullness, facial swelling, and upper limbs swelling, which is clinically a typical SVC syndrome. The chest CT found the intracardial mass and no external SVC compression. MRI confirmed the metastatic intracardial tumor in nature, and that it was not a thrombus, by increased T2 signal intensity. The effective differentiation of metastatic cardiac tumors from thrombus using MRI, was confirmed in our case as in the previous reported literature [13].

In the report of Cham and colleagues [14], after a radiation dose of at least 3000 rads within 4 weeks was given, 23 of 38 patients (61%) irradiated for cardiac metastases obtained clinical improvement, with a duration of 12 to 36 months. This favorable response to radiotherapy was consistent with the result with our patient. It would appear that using irradiation with cardiac metastases is worthwhile to relieve the distressing symptoms, and maybe prolong life.

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小細胞肺癌心房內復發疑上腔靜脈症候群—病例報告

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一位經化學治療反應良好的小細胞肺癌病人，在常規追蹤中臨床上表現出像臉脹、上肢腫等疑似上腔靜脈症候群，經電腦斷層發現是心房內腫塊，並經進一步的核磁共振證實是肺癌轉移至左右心房。病人經完整的高放射線劑量治療，除在臨床上表現改善外，經追蹤的電腦斷層檢查發現腫塊明顯的消失。雖上腔靜脈症候群是小細胞肺癌常見的併發症，但在我們的病例上，卻可能是罕見的左右心房轉移造成的臨床表現。對於心內腔室的腫瘤和血塊的鑑別診斷，加顯影的核磁共振是非侵犯性的重要診斷工具。此病例對放射線治療的良好反應，也許可作為轉移性心內腫瘤的另一選擇性治療。 ***(胸腔醫學2002; 17: 420-424)***

關鍵詞：心房轉移，核磁共振，小細胞肺癌，上腔靜脈症候群，放射線治療

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Disseminated Cryptococcosis with Acute Respiratory Distress Syndrome in A Patient with Newly Diagnosed Systemic Lupus Erythematosus—A Case Report

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Opportunistic cryptococcal infection has been noted to occur in patients with acquired immunodeficiency syndrome (AIDS), and may contribute to acute respiratory distress syndrome (ARDS) with a high mortality. But in human immunodeficiency virus (HIV)-negative patients, cryptococci rarely cause ARDS, and are often ignored in the beginning stages of the disease. We reported a 30-year-old pregnant female with diffuse pulmonary cryptococcosis. She developed acute respiratory failure due to diffuse alveolar hemorrhage from systemic lupus erythematosus (SLE). Methylprednisolone pulse therapy was given for the diffuse alveolar hemorrhage, and the chest roentgenogram showed initial improvement. Unfortunately, bilateral lung infiltrations became exacerbated again, and the patient later developed ARDS. Cryptococcal yeasts were identified promptly using India ink staining of the bronchoalveolar lavage fluid. Blood culture and cerebrospinal fluid studies also revealed cryptococcal infection. Disseminated cryptococcosis contributing to ARDS was finally diagnosed. A review of the literature showed that ARDS caused by disseminated cryptococcosis is rarely seen in HIV-negative patients. ***(Thorac Med 2002; 17: 425-429)***

Key words: disseminated cryptococcosis, acute respiratory distress syndrome, India ink stain, systemic lupus erythematosus

Introduction

Cryptococcosis is usually caused by *Cryptococcus neoformans*. The portal of entry is the lung. Cryptococcal infection ranges from harmless colonization in the airway to fatal disseminated disease, and presents with variable patterns in the chest roentgenogram [1, 2]. Opportunistic cryptococcal infection occurs in 2-30% of AIDS patients, and may result in ARDS with a high mortality [3, 4]. But in non-AIDS patients, *Cryptococcus neofromans* most often causes limited disease and contributes rarely to acute respiratory failure. We present a SLE patient with ARDS caused by disseminated cryptococcosis and discuss the role of India ink stain in the diagnosis.

Case Report

This 30-year-old female had been an expectant mother for 24 weeks. Two weeks before admission, she suffered from generalized ecchymosis, purpura, and gum bleeding. The hemogram showed anemia, thrombocytopenia, and a prolongation of the active partial thromboplastin time. She was admitted to the

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hematology ward on June 23, 2001, and the initial vital signs were blood pressure: 120/80mmHg; pulse rate: 100/min; respiratory rate: 20/min; and temperature: 38.5℃. The serum alanine aminotransferase (ALT), aspartate transaminase (AST), alkaline phosphatase, direct and indirect bilirubin, blood urea nitrogen (BUN), and creatinine were within normal limits. The routine urinalysis was: color: bloody; specific gravity: 1.015; pH: 6.5; leukocytes: trace; nitrite: negative; protein: 500 mg/dl; glucose: negative; urobilinogen: 0.1mg/dl; blood: 4 plus; red blood cells: numerous; white blood cells (WBCs): 8 WBCs per high-powered field; epithelial cells: negative. Bone marrow biopsy revealed megakaryocytic hypercellularity. Other studies included a positive direct Coombs test, antinuclear antibody, and anti-double-stranded DNA, and a decreased third component of complement (C3) and fourth component of complement (C4). SLE was diagnosed based on the above examinations.

On June 26, 2001, she developed hypoxemic respiratory failure and the chest roentgenogram showed diffuse infiltrations in both lung fields. The bronchoalveolar lavage (BAL) was positive for iron stain, with 66% siderophages. Bacterial culture, cytomegalovirus (CMV) shell vial culture, and acid-fast bacillus smear were all negative. Because she did not received any immunosuppressive therapy prior to admission, fungal infection was not considered in the beginning. Diffuse alveolar hemorrhage caused by SLE activity was suspected, and pulse therapy with methylprednisolone 500mg bid for 3 days, followed by methylprednosolone 40mg q6h, were given. The chest roentgenogram improved and she was extubated on June 29, 2001.

On July 2, 2001, the patient's condition deteriorated, and the follow-up chest roentgenogram showed diffuse bilateral infiltrations once again. Recurrent pulmonary hemorrhage was suspected, and pregnancy was terminated due to pulmonary hemorrhage and fetal growth retardation. Her clinical condition ameliorated, though the chest roentgenogram did not resolve completely, and she was extubated on July 5, 2001. However, ten days later, acute respiratory distress occurred again, and the chest roentgenogram showed more infiltrations with air bronchograms in the bilateral lung fields (Figure 1). Under mechanical ventilation with an 80% inspiratory oxygen concentration (FiO_2), the arterial blood gas analysis revealed a PaO_2 of 88 mmHg, and the PaO_2 /FiO_2 ratio was 110 mmHg. The repeated BAL studies revealed positive cryptococcal yeasts in India ink staining (Figure 2), but cultures for bacteria and *Pneumocystis carinii* were negative. The cell count of the BAL fluid this time consisted of 78% neutrophils but only 14% siderophages. Serum cryptococcal antigen was 1:1024, and CMV IgM and HIV antibodies were negative. Repeated serum BUN and creatinine were still within normal limits. Pulmonary catherization revealed pulmonary arterial pressure: 46/24mmHg; pulmonary capillary

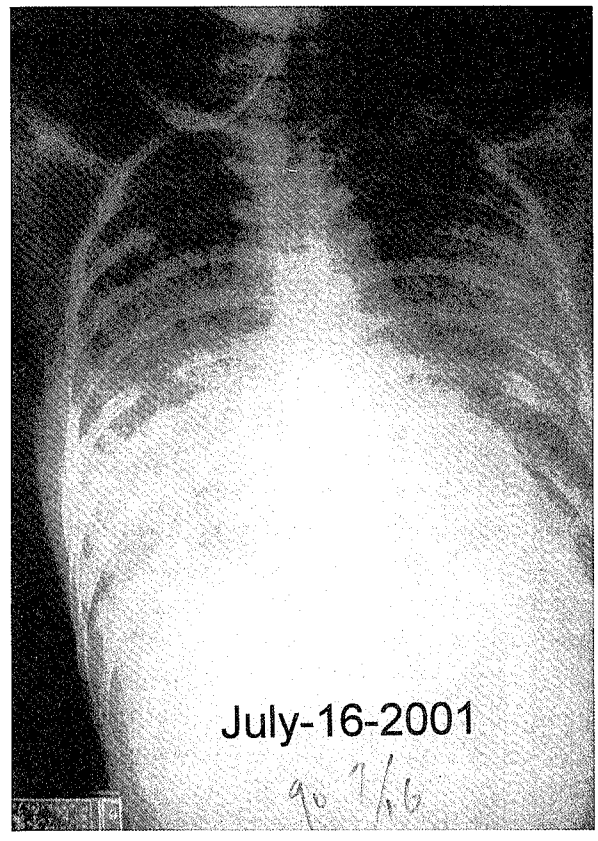

Fig. 1. The chest roentgenogram reveals diffuse bilateral infiltrations with air bronchograms in the secondary respiratory failure. Disseminated cryptococcosis with ARDS was finally diagnosed.

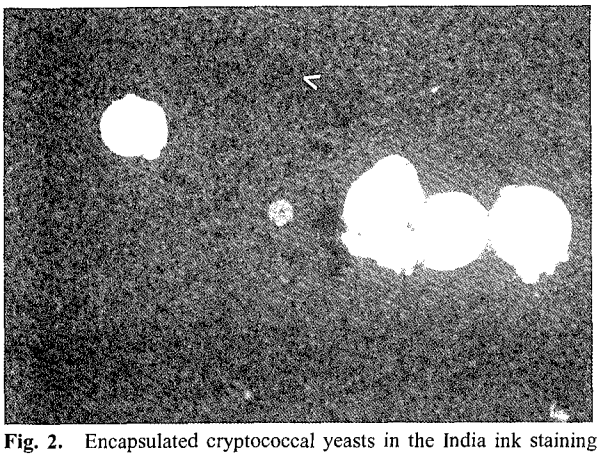

Fig. 2. Encapsulated cryptococcal yeasts in the India ink staining of the bronchoalveolar lavage fluid, x400.

wedge pressure (PCWP): 11 mmHg; systemic venous resistance index: 1530 dynes. sec.m^2/cm^5; and cardiac index: 4.97 L/min/m^2. *Cryptoccocus neoformans* was cultured from the blood and cerebrospinal fluid (CSF) several days later. Disseminated cryptococcosis with ARDS was finally diagnosed [5]. Amphotericin B combined with intravenous fluconazole was started and her clinical condition improved. Unfortunately, episodes of nosocomial *Escherichia coli* urosepsis and *Pseudomonas aeruginosa* pneumonia occurred, and she died on the 64th day after admission.

Discussion

Cryptococcus neoformans is a ubiquitous encapsulated fungus first described in 1894. The wide spectrum of host responses ranges from harmless colonization of the airway or asymptomatic infection, to meningitis and/or disseminated cryptococcosis [1]. The serious cryptococcal infections occur in individuals with defective cell-mediated immunity, such as those with HIV infection, corticosteroid treatment, reticuloendothelial malignancy, organ transplantation and sarcoidosis [1]. The lung, the portal of entry, is a common site of disease. Pulmonary cryptococcosis has variable chest radiographic patterns including nodules and masses, patchy consolidation, widespread small nodular or irregular shadows and pleural effusions. Cavitations and diffuse dissemination in the lung may occur in immunocompromised individuals, mostly in AIDS patients [2]. Meyohas and colleagues reviewed the records of 85 AIDS patients infected with *Cryptococcus neoformans*, and found that 27 had pulmonary cryptococcosis. The most common pattern was diffuse interstitial opacities (70.5%) [3]. On the other hand, pulmonary cryptococcosis presenting with bilateral pulmonary infiltrations has been noted rarely in non-AIDS patients. Roebuck and coworkers undertook a review of the medical charts and radiographs of 44 consecutive HIV negative patients with proven cryptococcosis, and discovered that the pattern of interstitial opacities was present in only three patients (7%). All three patients were possibly immunosuppressed [6].

Cryptococcosis occurs in 2-30% of patients with AIDS [3]. In a retrospective case-control study, among the AIDS patients, the incidence of acute respiratory failure associated with cryptococcosis was 13.8%, and contributed to 100% of in-hospital mortality [4]. But in non-AIDS patients, to our knowledge, cryptococcosis with ARDS is seen rarely and given little emphasis in the literature. Ronzenbaum and colleagues retrospectively studied 171 patients with cryptococcosis and found that only 5.9% of nonimmunosuppressed patients and 9.1 % of non-AIDS patients with other immunocompromised conditions or receiving immunosuppression drugs presented with interstitial infiltrates and interstitial infiltrates mixed with alveolar infiltrates [7]. But whether acute respiratory failure, or even ARDS, occurred or not was not mentioned in this series. Recently, Vilches and colleagues reported acute respiratory failure associated with pulmonary cryptococcosis in 11 of 33 non-AIDS patients. Among those, 7 of the 11 patients were solid-organ transplant recipients receiving long-term immunosuppressive therapy [8]. But none of those had a definitive diagnosis of ARDS. Our patient presented with diffuse pulmonary hemorrhage from SLE initially, and ARDS occurred afterward due to disseminated

cryptococcosis. The diagnosis of ARDS was based on bilateral pulmonary infiltrations on the chest radiograph; severe arterial hypoxemia with a PaO_2/FiO_2 ratio of less than 200 mmHg and normal PCWP (11mmHg) ruled out left ventricular failure and fluid overload [5]. This has never been reported before.

On the other hand, cryptococcal yeasts were identified promptly by India ink staining of the secondary BAL fluid in this patient. In the diagnosis of pulmonary cryptococcosis, India ink preparation is a convenient method and can detect cryptococcal yeasts immediately after BAL, more rapidly than culture, biopsy, and cryptococcal antigen titer. In using an India ink preparation, the necessary concentration to detect 1 organism per high power field is 100,000 organisms/ml, and centrifugation increases the sensitivity of the visual methods ten-fold, so that only 10,000 organisms/ml is needed [9]. In the literature, India ink stain applied in the diagnosis of cryptococcal meningitis had been well discussed, but there have been few studies reporting on the role of India ink stain in the diagnosis of pulmonary cryptococcosis.

In summary, *Cryptococcus neoformans* is a possible etiology of ARDS, not only in AIDS patients but also in HIV-negative immuno-compromised patients. India ink staining of the BAL fluid is a simple method to rapidly recognize cryptococcal yeasts, and should be performed in the initial studies for screening the etiologies of ARDS. With the finding of positive cryptococcal yeasts in India ink stain, pulmonary cryptococcosis can be treated immediately after BAL.

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系統性紅斑性狼瘡的患者發生瀰散性隱球菌症合併急性呼吸窘迫症—病例報告

林進國　蔡熒煌　黃崇旂

後天免疫不全的病人，容易得到隱球菌的感染且可能導致急性呼吸窘迫症，並造成很高的死亡率。但是在非後天免疫不全的病人，隱球菌很少引起急性呼吸窘迫症，而且常被忽略。我們報告一位三十歲懷孕女性因全身瘀青及紫癜而住院，之後發生急性呼吸衰竭，初步診斷為系統性紅斑性狼瘡合併瀰散性肺出血。以類固醇脈衝治療後，肺出血初步有改善，但隨後又發生急性呼吸窘迫症。用墨汁染法發現支氣管肺泡沖洗液存有隱球菌，血液及腦脊髓也都有隱球菌感染。最後診斷為瀰散性隱球菌症合併急性呼吸窘迫症。回顧過去的文獻，非後天免疫不全的病人發生瀰散性隱球菌症合併急性呼吸窘迫症相當罕見。 ***(胸腔醫學 2002; 17: 425-429)***

關鍵詞：瀰散性隱球菌症，急性呼吸窘迫症，墨汁染法，系統性紅斑性狼瘡

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Mucoepidermoid Carcinoma of the Lung Arising from the Segmental Bronchus—A Case Report

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Mucoepidermoid carcinoma of the lung is uncommon, and is characterized by a mixture of mucus-secreting and epidermoid cells. It is analogous to carcinomas of the salivary gland tissues. The tumors usually arise from the main and lobar bronchi or trachea. Herein, we report an unusual case of mucoepidermoid carcinoma originating from the left posterior basal bronchus (LB10) , which had caused recurrent pneumonia during the previous 8 years. The histology revealed a low grade malignancy. The patient's clinical course was uneventful, and there were no without any signs of recurrence 4 years after the surgical resection of the tumor. ***(Thorac Med 2002; 17: 430-435)***

Key words: mucoepidermoid carcinoma, lung, segmental bronchus

Introduction

Mucoepidermoid carcinomas can be found in the salivary glands, lungs, breasts, adnexa of the ovaries, pancreas, liver, esophagus, thymus, and thyroid glands, with the salivary gland having the of highest incidence. Mucoepidermoid carcinomas of the lung are rare, comprising only 0.1-0.2 % of primary lung cancers.

Mucoepidermoid tumors of the lung characteristically arise from the trachea or large bronchi [1-4]. A number of few cases with the tumor originating from the segmental bronchus have been reported previously. Herein, we report another rare case of mucoepidermoid carcinoma of lung arising from the segmental bronchus – the left posterior basal bronchus (LB10) and review the literature.

Case Report

A 24-year-old Chinese female who lived in Germany was admitted in December 1997 due to fever and productive cough for 2 months. She had experienced three episodes of pneumonia located in the left lower lobe (LLL) in the past 8 years. Two months before this admission, the patient began to experience fever and productive cough, and came back to Taiwan to treat the unresolved symptoms. At our outpatient clinic, the chest radiograph showed a solitary nodule located in the LLL (Figure1). The patient underwent a bronchoscopy, and a mass with a smooth surface in the orifice of the left posterior basal bronchus, with nearly total occlusion of the lumen, was found during the examination (Figure 2). She was then admitted for further evaluation , and

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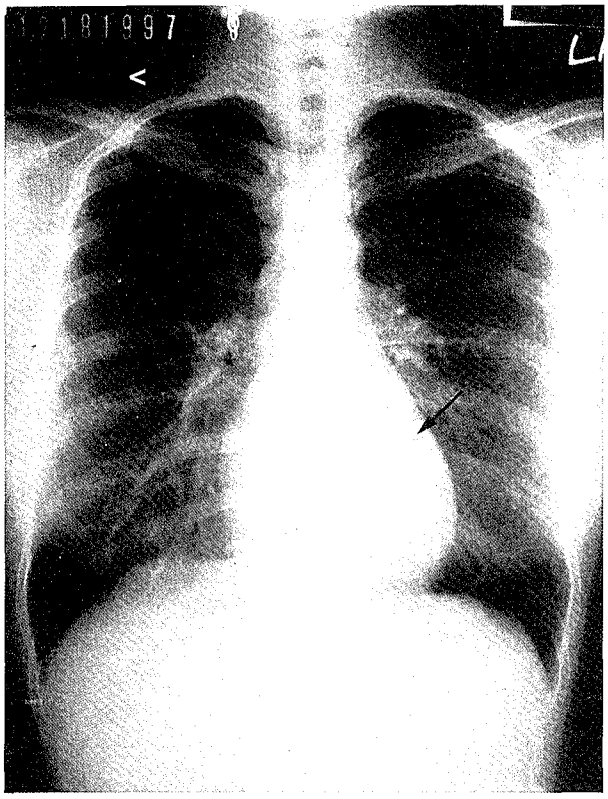

Fig. 1. Chest radiograph shows a solitary nodule (arrow), about 2 cm in diameter, in the left lower lobe.

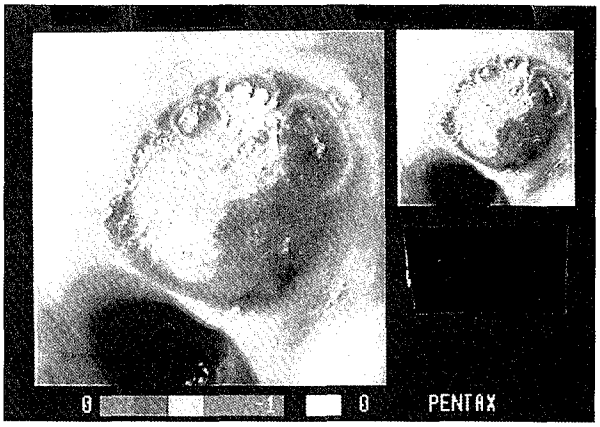

Fig. 2. Fibrobronchoscopy discloses a mass with a smooth surface in the orifice of the left common basal bronchus, causing a nearly total occlusion of the lumen

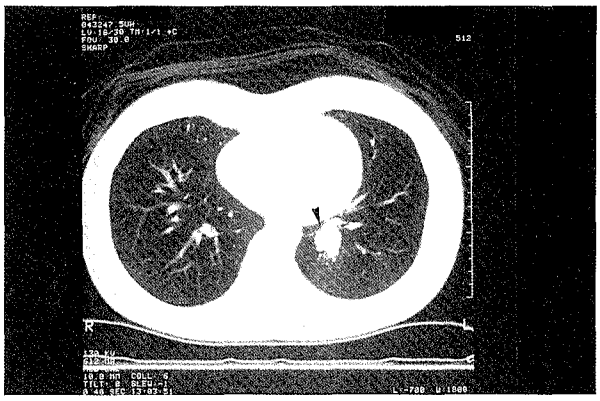

Fig. 3. Thoracic computed tomograph reveals a well-defined nodule (arrowhead), measuring 2 x 2 cm in size, without calcification and fat content, located in the left lower lobe.

management.

The physical examination on admission showed no remarkable finding except for rales heard in the left lower chest. The results of the routine blood, urine, and stool tests and blood biochemistries were within normal limits. Chest computed tomography was performed and revealed a well-defined nodule measuring 2.5 x1.5 x 3 cm in size in the left lower lobe of the lung, without evidence of calcification or fat content (Figure 3). There were no lymphadenopathies in the mediastinum and hilar regions.

A lobectomy of the left lower lobe, with a lymph node dissection, was performed under thoracoscopic assistance. A well- encapsulating tumor, measured 1.5 x 2.5 cm, was located in the LLL near the hilum with local adhesion. There were enlarged lymph nodes in the interlobar and hilar regions. The gross findings of the tumor showed an intrabronchial polypoid tumor, measuring 2.5 x 2 x 2 cm, with a wellcircumscribed, yellowish, soft appearance. Microscopic findings disclosed a picture of mucoepidermoid carcinoma of the lung, composed of clusters of neoplastic epidermoid cells arranged around multiple mucus-containing cysts and glands (Figure 4). There was no pathological finding in the interlobar and hilar lymph nodes. No pleural invasion was found. The post-operative course was uncomplicated and the patient was discharged 10 days later. No local or distant metastases had developed 4 years after the surgical resection of the tumor.

Discussion

Mucoepidermoid tumors of the lung are rare tracheobronchial neoplasms, composing 1-5% of primary bronchial neoplasms, and approximately

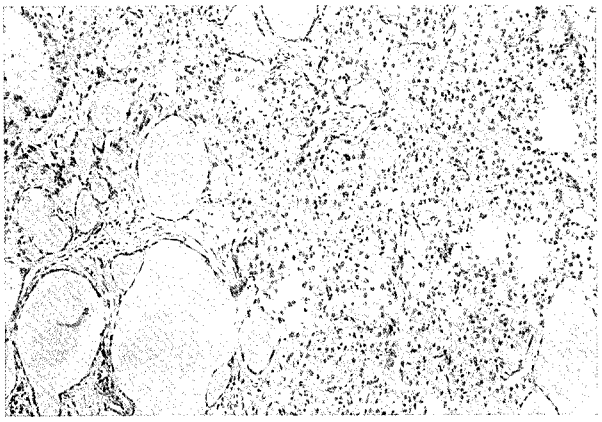

Fig. 4. Under microscopic examination, the tumor is composed of clusters of neoplastic epidermoid cells, arranged around multiple mucus-containing cysts and glands. (x100)

0.1- 0.2% of all lung tumors [5-8]. Mucoepidermoid tumors in the salivary glands were first described in 1945 by Stewart *et al.* [9-10], where they were presumed to arise from the excretory ducts. Mucoepidermoid tumors within the bronchi were first reported in 1952 by Smetana *et al.* They were characterized by the coexistence of epidermoid, mucus-secreting, and intermediate cells, and were believed to arise from the terminal ducts of the proximal tracheobronchial trees [11]. Patients vary in age, from 3 months to 78 years old , but nearly half are younger than 30 years old[12].

Mucoepidermoid tumors are composed of a mixture of well-differentiated mucus cells and sheets of squamous cells with keratinization and intercellular bridges. Histopathologically, mucoepidermoid tumors are divided into low-grade and high-grade tumors [1,15]. The histologic grade usually correlates with tumor behavior. Lowgrade mucoepidermoid tumors are wellcircumscribed and predominantly endobronchial polypoid lesions covered by mucosa. Hilar lymph node involvement and extrathoracic metastasis are rare. High-grade tumors are larger, with an obvious infiltration of the lung parenchyma. Lymphangitic and hematogenous spread has been shown to occur, and the common metastatic sites are the regional lymph nodes, lung, bone marrow, adrenal glands, brain, and skin. Although low-grade mucoepidermoid tumors have a relatively benign clinical course, cases of low-grade mucoepidermoid tumors that behaved aggressively have been reported [14-16]. Most investigators agree that the tumors have a favorable course, but others have reported cases in which apparently low-grade mucoepidermoid tumors were highly aggressive and associated with a poor prognosis [13, 17-19]. There have been documented cases of metastasis to the regional lymph nodes, skin, bone, brain, and liver [6, 20-21]. In children and adolescents, low-grade tumors are more common. Most of these tumors are located in the proximal airways and trachea, although subpleural mucoepidermoid tumors have been reported [10].

Mucoepidermoid carcinoma of bronchial gland origin is extremely rare. The tumor is occasionally found in the bronchial tree [22-27,10]. To our knowledge, the tumor has been reported in the segmental bronchus in only one case. Our case seems to be one of the rare reports of an mucoepidermoid tumor arising from the segmental bronchus.

The most common presenting symptoms are cough, fever, recurrent pneumonia, hemoptysis, wheezing, and dyspnea, caused by bronchial irritation and obstruction. Because of the predominately proximal location of the tumor, bronchoscopy and biopsy are helpful in the diagnosis of these patients, especially in the tumor grading.

The radiologic features of mucoepidermoid tumors are not specific and include normal, solitary mass or nodule, focal areas of pneumonic consolidation, partial or complete atelectasis, and peripheral subpleural tumors [28]. The thoracic computed tomographic (CT) findings of mucoepidermoid tumors of the lung have been described in one series [29]. On the chest CT, the tumors were all smoothly oval (n=6) or lobulated (n=6), in, adapting to the branching features of the airways. Punctate calcification within the tumor was seen in six patients.

In low-grade tumors, surgical resection is the treatment of choice, with an excellent long-

term prognosis. Lobectomy and bronchoplastic or sleeve resection with a sampling of the lymph nodes are recommended in patients with low-grade tumors. Postoperative radiation or chemotherapy is usually unnecessary. High-grade tumors carry a poor prognosis and should be treated with a more radical procedure such as lobectomy or pneumonectomy.

For a young female, repeated attacks of pneumonia in the same location should lead to the suspicion of bronchiectasis, or endobronchial lesion, or congenital problems such as pulmonary sequestration. Accordingly, bronchoscopy is mandatory for patients with repeated pneumonia in the same area, to rule out endobronchial lesions. For mucoepidermoid tumors, early diagnosis may lead a better prognosis since even low grade tumors may behave aggressively [13, 17-19].

Mucoepidermoid carcinoma is believed to develop from the terminal ducts of the proximal tracheobronchial tree. The tumor usually occurs in the trachea, or main or lobar bronchi appearing as an intraluminal polypoid mass causing bronchial, obstruction, recurrent pneumonia, cough, and/or hemoptysis clinically. In our case, the tumor was located in the segmental bronchus (LB10), but the clinical features were unusual. As with other patients whose tumors are located in the larger airways, the clinical course in our patient was uneventful; the tumor was completely resected and non-aggressive.

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粘液類上皮癌——一病例報告

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發生在肺部的粘液類上皮癌並不常見，其特徵是混和著粘膜分泌細胞和類上皮細胞，頗類似從唾液腺組織長出之腫瘤細胞。病患之年齡層分布極廣，從嬰兒至老年人，但幾乎一半病人之年齡小於 30 歲。腫瘤大部分長在氣管，主支氣管，或葉支氣管中，從肺節支氣管長出的病例較為罕見。在此提出一病例報告是一 24 歲女性，臨床表現為反覆性左肺下葉肺炎。支氣管鏡檢查發現腫瘤是從左肺後基底支氣管枝長出，經手術切除，組織病理學顯示低度惡性。病患在手術後 4 年的追蹤檢查並無復發跡象。 ***(胸腔醫學 2002; 17: 430-435)***

關鍵詞：粘液類上皮癌，肺，節支氣管

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Acrometastases from Bronchogenic Carcinom—A Short Report of Three Cases and Review of the Literature

Han-Yu Huang, Yuh-Min Chen, Ming-Fang Wu*, Yu-Chin Lee, Reury-Perng Perng

Acrometastases means metastases over distal part of limbs by the malignant tumors. They usually occur as rare, pre-terminal events, and often are part of a widespread dissemination of metastases. Failure to recognize these lesions when they do not fit that pattern has led to delayed diagnosis or inappropriate treatment. We describe 3 patients in whom phalangeal metastases were associated with inflammatory signs that mimicked acute infection. All these cases were diagnosed and treated initially as acute infection of the digits. Two cases were confirmed as carcinoma by fine needle aspiration cytology. The other was ascertained by incision biopsy. ***(Thorac Med 2002; 17: 436-439)***

Key words: acrometastases, bronchogenic carcinoma

Introduction

Osseous metastases develop in approximately 30% of all patients with cancer, but only 0.007 to 0.3% of such patients have acrometastases. Three cases of acrometastases from bronchogenic carcinoma have appeared at Veteran General Hospital – Taipei since 1984. All these cases were initially misdiagnosed as acute infection of the digits. Two cases were confirmed as carcinoma by fine needle aspiration cytology later. The other was ascertained by incision biopsy. The literature regarding acrometastases is also reviewed.

Case Reports

Case 1

A 60-year-old female was a patient with poorly differentiated carcinoma of the left lower lobe of the lung. The clinical stage was T4N3M0, stage IIIB. She underwent chemotherapy with paclitaxel and gemcitabine, followed by curative radiotherapy. Painful swelling of the left index finger was noted 2 months later (Figure 1). She visited our emergency room where bony destruction in the distal part of the finger was noted by X-ray (Figure 2). Cellulitis was suspected and she was admitted. Antibiotics were given, but in vain. Aspiration cytology showed metastatic carcinoma (Figure 3). An amputation of the left index finger was performed, and the pathology also showed metastatic carcinoma. She has survived 15 months up to this writing.

Case 2

A 45-year-old female was a victim of adenocarcinoma of the lung in the left hilar area. The clinical stage was T4N3M0, stage IIIB.

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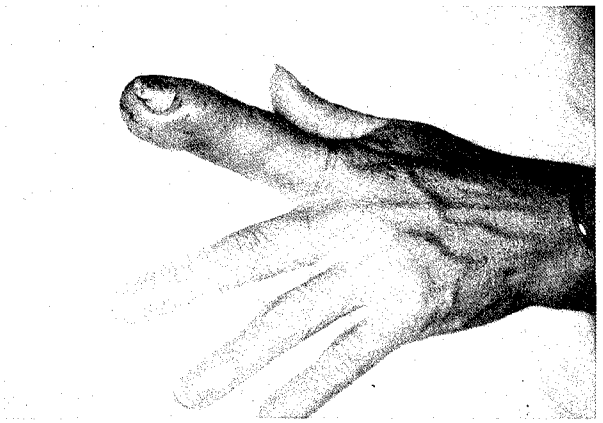

Fig. 1. Painful swelling and erythematous change in the patient's left index finger.

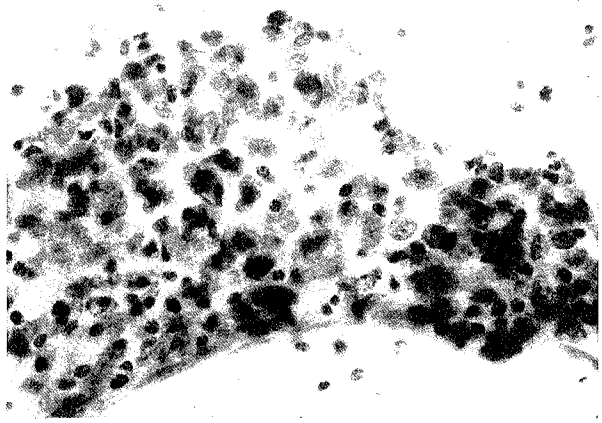

Fig. 3. Aspiration cytology from the patient's left index finger shows metastatic carcinoma (Papanicolaou stain 400x).

Radiotherapy only to the primary tumor was given, at the patient's request. Unfortunately, painful swelling of the distal phalanx of the right fifth finger was noted about 3 months later. Aspiration cytology revealed metastatic adenocarcinoma. She accepted local radiotherapy to the finger and died from obstructive pneumonitis 2 months later.

Case 3

A 74-year-old male suffered from squamous cell carcinoma of the right lower lobe of the lung. The clinical stage was T1N0M0, stage IA. Due to the patient's refusal of operation, no further treatment was given. Painful swelling in the right thumb was noted 2 months later. He visited our orthopaedic OPD. Incision biopsy revealed

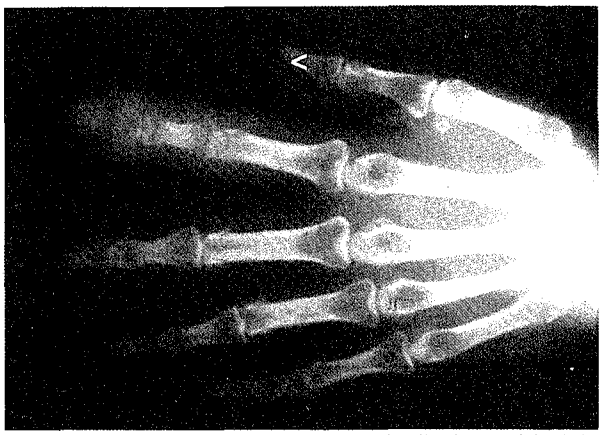

Fig. 2. X-ray reveals bony destruction in the distal part of the left index finger.

metastatic squamous cell carcinoma. He accepted amputation of the right thumb and radiotherapy to the primary tumor, but died of pneumonia 8 months later.

Discussion

Osseous metastases develop in approximately 30% of all cancer patients, but only 0.007 to 0.3% of bony metastatic patients have acrometastases [1]. The reason for the relative rarity of acrometastasis is not clear. Mulvey suggested that two different mechanisms of hematogenous spreading probably are involved in bony metastases [2]. The common mechanism involves communications within the vertebral venous plexus through which tumor emboli might be deposited in portions of the axial skeleton, but not in the peripheral bones. The other, more infrequent possibility is venous erosion by a pulmonary malignancy that allows tumor emboli to enter into the pulmonary vein and later into the systemic arterial circulation. The mechanism of acrometastasis is probably the later one. Investigators have also suggested that increased blood flow and trauma, or both, can be predisposing factors for acrometastasis [3]. The most commonly affected bones were the metacarpals, phalanges in the hand, metatarsals, and the calcaneus in the foot [3]. In addition, metastases to the dominant hand are twice as common as to the non-dominant

hand. This is probably due to higher blood flow to the dominant than non-dominant hand and, subsequently, more concomitant tumor emboli [4]. In our patient, the local infection over the left index finger initially may have increased blood flow and capillary permeability over the left index finger, and thus induced the metastasis.

Osseous metastases to the hand are most commonly caused by bronchogenic carcinomas, whereas foot metastases are more often seen with tumors originating in the gastrointestinal or genitourinary tracts [5]. The reason is unknown. The clinical findings of acrometastasis commonly include pain, swelling, and erythema [3]. The carcinomatous acrometastases are radiographically lytic without new bone formation, except in metastatic prostate carcinoma [3,6]. This lytic change is evident radiographically one to three months after the onset of pain [3].

Even after the radiographic abnormalities are identified, the metastatic carcinoma is easily misdiagnosed. The differential diagnosis includes soft tissue infection, inflammatory arthritis, osteomyelitis, gout, and non-pathologic fracture [5-6]. There was no statistically significant difference in the survival of patients based on the different sites of acrometastasis or the histological diagnosis [3]. The patient's age and the number of acrometastases were also not significantly correlated with the duration of survival [3].

The treatment is directed toward relief of symptoms and restoration of function [3,5]. Radiotherapy is used exclusively for patients with multiple or inoperable lesions. Amputation is also successful in relieving pain and restoring function in the operable lesions of patients with an estimated life expectancy exceeding a few months [3].

We report these cases to highlight that pain and swelling in a single finger simulating cellulitis or osteomyelitis may occasionally be due to metastasis from carcinoma, particularly from the lung. Every effort should be made to rule out the metastatic possibility when the patient does not respond to antibiotic treatment properly, especially those patients with a pre-existing malignancy.

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肺癌合併肢端轉移—三個病例報告及文獻回顧

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在所有癌症病患中，約有百分之三十的機率發生骨頭轉移；但是，只有小於千分之三的病人發生肢端轉移。自西元 1984 年至今，台北榮總共發現三個肺癌合併肢端轉移的個案。第一個個案是一位六十歲的女性，被發現左下肺葉有一分化不良型上皮細胞癌合併左側食指轉移。她接受化學治療及左側食指截肢術。至今已存活超過十五個月。第二個個案是一位四十五歲的女性，被發現有左側肺門肺腺癌合併右側尾指轉移。她只接受局部放射治療於右側尾指；不幸，二個月後死於阻塞性肺炎。第三個個案是一位七十四歲的男性，被診斷出右下肺葉鱗狀上皮細胞癌合併右側拇指轉移。他接受放射治療於肺腫瘤處及右側拇指切除；不幸，於八個月後死於肺炎。起初，這三個個案都被誤診為指端的急性感染。後來，二個個案靠細針抽取細胞獲得診斷；另一個個案靠切片病理診斷。關於肢端轉移的文獻，我們在文中有詳細回顧。*(胸腔醫學 2002; 17: 436-439)*

關鍵詞：肢端轉移，肺癌

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Pulmonary Edema Due to Inhalation of Nitric Acid Fumes —A Report of Three Cases

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This report presents the case histories of three men who developed fulminant non-cardiogenic pulmonary edema on the same occasion after an accidental inhalation of nitric acid fumes. The exposure time was 10 minutes. All of them required mechanical ventilation six hours after the exposure because of severe hypoxemia which was refractory to positive end-expiratory pressure, high concentration oxygen, and the administration of corticosteroids. The patients all died within 24 hours after the exposure. ***(Thorac Med 2002; 17: 440-444)***

Key words: nitric acid, acute respiratory distress syndrome, inhalational injury

Introduction

Nitric acid (HNO_3) is a potent oxidant used for metal refining and cleaning in various industries [1]. The exposure of nitric acid fumes to open air or organic materials rapidly generates oxides, including nitric oxide (NO) and nitrogen dioxide (NO_2) [2]; both can cause damage to the distal respiratory tracts [3]. At levels of 100-150 ppm, toxicity occurs within 30-60 min, and at levels of 200-700 ppm, fatalities result after short exposure [4]. The inhalation of nitric acid fumes therefore results in exposure to potential acidic injury by nitric acid and toxicity by the highly reactive NO and NO_2.

Inhalational injury due to nitric acid has been reported occasionally, and commonly features a period of relative well-being lasting a few hours, followed by rapidly progressive and often fatal non-cardiogenic pulmonary edema [2-5]. Although its pathogenesis is not fully understood, the edema has been shown to be a consequence of increased microvascular permeability, initiated by NO_2-mediated capillary injury [3,6]. Unfortunately, in severe exposure, progressive pulmonary edema develops instantaneously and the patients may not survive for more than 24 hours [7].

Case Reports

Three previously healthy men, aged 19, 23, and 40, respectively, were ordered to dispose of some barrels containing nitric acid that were located in a silo. They were accidentally exposed to fumes simultaneously because of leakage. The exposure duration was about 10 minutes. Only transient dizziness and mild respiratory tract irritation were noticed initially. However, they developed rapidly progressive shortness of breath

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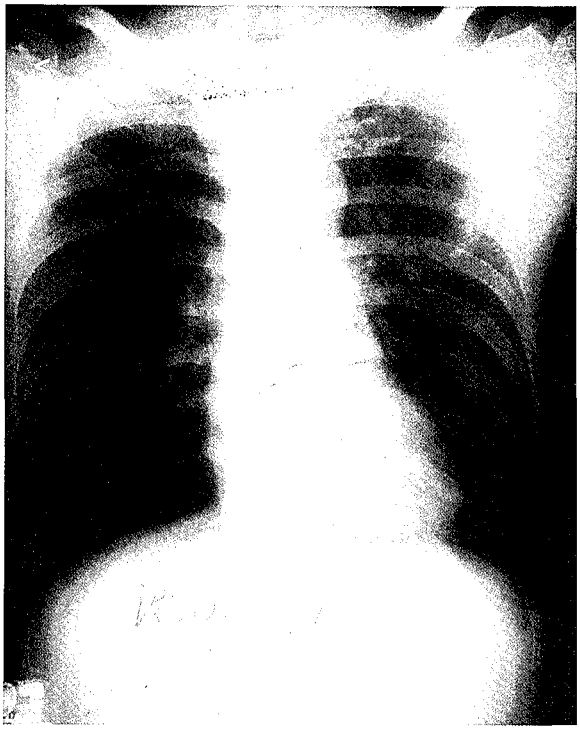

Fig. 1. Chest radiograph shows generalized mild ill-defined opaque patches in both lung fields.

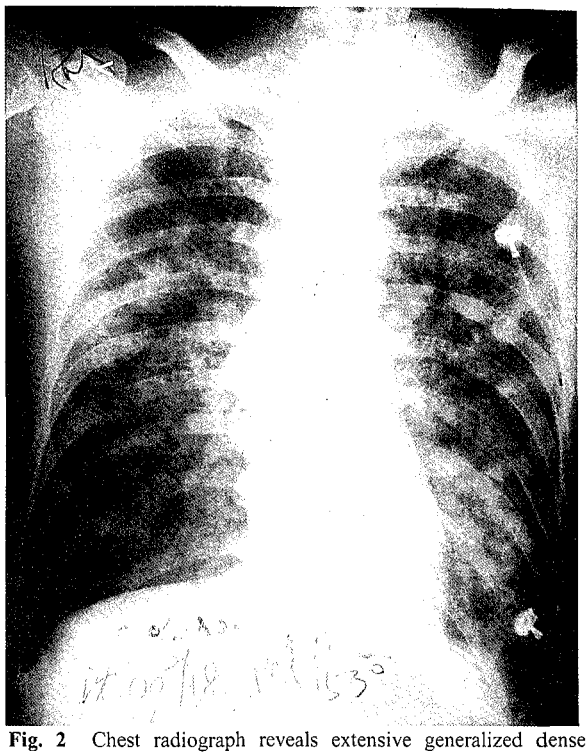

Fig. 2 Chest radiograph reveals extensive generalized dense alveolar opacities bilaterally.

and chest tightness two hours later and were sent to the emergency department.

The patients were soldiers and had had no previous experience dealing with nitric acid products. There was no history of systemic disease, and no respiratory symptoms were noticed before the exposure.

On arrival they had clear consciousness, but the patients manifested peripheral cyanosis and general paleness. There was no fever. The vital signs and laboratory data on arrival and the arterial blood gas analysis are summarized in Table 1. Auscultation of the chest revealed bilateral pulmonary crackles without wheezes. Chest radiographs of the three patients showed similar findings. The first chest X-ray showed generalized mild ill-defined opaque patches in both lung fields (Figure 1). Because of a definite exposure to nitric acid and the presence of symptoms and radiographic abnormality, intravenous methylprednisolone administration was started soon after arrival. However, their respiratory condition deteriorated within four hours. Severe hypoxemia was found and subsequent chest radiographs revealed frank bilateral confluent alveolar-interstitial densities compatible with pulmonary edema (Figure 2). The patients were intubated and admitted to the medical Intensive Care Unit (ICU) for mechanical ventilatory support. Foamy and plasma-like fluid and sputum was aspirated via the endotracheal tube. High positive end- expiratory pressure (PEEP), large amounts of intravenous methylprednisolone, and 100% oxygen were given but the hypoxemia became refractory to all measures. Two of the patients were discharged with dire hemodynamic conditions and severe hypoxemia against medical advice 3 hours after ICU admission; the other patient died 10 hours after ICU admission due to refractory hypoxemia. The salient features are summarized in Table 1.

Table 1. Clinical and laboratory data after admission to the hospital

Clinical and laboratory data	Patient 1	Patient 2	Patient 3
Age	23	19	40
Features at admission			
Respiratory rate	14	20	26
Blood pressure	135/80	139/62	103/60
Pulse	115	128	98
SpO2 (cannula 3L/min)	94%	98%	83%
Features at intubation			
PH	7.39	7.38	7.22
Pco2	37.9	39.1	41.3
PO2	74.8	84.6	104
HCO3	22.7	22.8	16.7
FiO2	100%	100%	100%
WBC	7500	7800	8300
Hemoglobin	15.1	12.4	15.8
Hematocrit	44.9	38.6	46.3
Time of death after intubation	9 hours (AAD)	9 hours (AAD)	16 hours (Expired)

Discussion

In this report, the three cases of nitric acid exposure are characterized by a common fulminant course of refractory hypoxemic respiratory failure, bilateral lung hazziness, and the presence of frothy and plasma-like secretion, compatible with non-cardiogenic pulmonary edema. The hypoxemia was refractory to treatment.

Nitric acid is the most prevalent acid air pollutant in the western United States, and has the potential to cause adverse respiratory effects through both acidification and oxidative reactions. Its oxides, NO and NO_2, are insoluble in water and therefore cause less irritation on the conjunctiva and oropharynx. Thus, victims such as the reported cases who are not familiar with nitric acid handling, may be unaware of their exposure to NO and NO_2 initially. After inhalation, structural lung injury becomes manifest mainly in the distal bronchioles and adjacent alveoli. The subsequent cellular damage is attributed to the formation of chemical-free radicals [8-9] and of nitric and nitrous acids from the hydration of NO_2. These time-dependent interactions account, in part, for the delayed manifestations of lung injury. The pulmonary edema correlates with the necrosis of the alveolar epithelium and/or endothelium [8-9]. Pathological findings reveal bronchiolar epithelial necrosis, marked capillary engorgement, and slight interstitial edema or alveoli. Notably, protein-rich edema fluid fills all the alveolar spaces, and is most marked in the peribronchiolar and, especially, the alveolar dust areas [7].

There is no doubt that nitric acid and probably most acidic pollutants are potent toxins to the lung in sufficient concentration. An animal study has demonstrated that progressively exacerbated breathing-pattern responses at high concentrations of acidic gas inhalation were associated with lung injuries and inflammation changes [10]. Human subjects with asthma and exerciseinduced bronchospasm had significant pulmonary function changes following short-term exposure to H_2SO_4 and SO_2, and also after exposure to a low concentration (0.05 ppm) of

nitric acid [11]. Exposure usually occurs to the mixture of nitrogen oxide fumes that evolve from industrial, manufacturing, or farm sources. Silos may contain nitrogen dioxide, nitric oxide, and carbon dioxide, as a result of plant decomposition in the presence of high nitrate levels. Occupational exposures usually result from the manufacture of dyes, fertilizers, celluloid, and lacquers, as well as from welding, glass blowing, and food bleaching. We should be very attentive to avoid any possible exposure to such irritable gases, and carry out preventive measures.

Previous reports have described the rapid progressive respiratory failure after nitric acid inhalation [7, 12]. As in our cases, the course of rapid and fulminant respiratory failure is manifest, and most patients die within 24 hours after exposure. Though supplementary surfactant and low-dose inhalation therapy with nitric oxide were prescribed, the patient in our report died on the 4th day [12]. For toxic fumes inhalation pulmonary edema due to increased microvascular permeability, the topical and systemic application of steroids has been recommended [13]. However, no satisfactory or promising therapy for nitric acid inhalational pulmonary edema is available. Experience with systemic corticosteroid treatment immediately after exposure has not been reported, probably because most patients have no respiratory distress shortly after exposure, and the effects of corticosteroid treatment may be limited with diffuse, frank alveolar epithelial/endothelial damage. Adjusted mechanical ventilator settings, additional nitric oxide inhalation, replacement of the surfactant, and extracorporeal membrane oxygenation (ECMO) as used in treating acute respiratory distress syndrome (ARDS), are the only practical treatments. Therefore, the avoidance of metric acid exposure should be the primary measure.

In summary, the course of respiratory disease following the inhalation of nitric acid fumes is characterized by the occurrence of pulmonary edema with rapid and fulminant respiratory failure. Treatment is usually ineffective if hypoxemia develops. The prevention of nitric acid exposure should be stressed, and novel therapy sought.

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吸入硝酸氣體引起肺水腫—三個病例報告

鄭世隆　鄭之勛　余忠仁

此病例敘述是由三個年輕男性在意外吸入硝酸氣體後產生急速惡化的非心因性肺水腫 (non-cardiogenic pulmonary edema)。暴露時間為十分鐘。在暴露硝酸 6 個小時以內，由於嚴重的缺氧，這三個人都需要機械性呼吸器而且對於吐氣末正壓 (positive end- expiratory pressure)，高濃度氧氣輔助，及類固醇使用均無效。這三個病人在暴露硝酸 24 個小時以內全都死亡。 ***(胸腔醫學 2002; 17: 440-444)***

關鍵詞：硝酸，急性呼吸窘迫症候群，吸入性損傷

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