Culture of Human Primary Airway Epithelial Cells

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Introduction

The airway epithelium is the first line of defence against airborne pathogens and inflammatory agents. This protective layer consists of several different cell types including columnar cells, ciliated cells, basal cells and secretory/goblet cells. It was originally believed that the primary function of the epithelium was to act purely as a physical barrier between the lumen and the submucosa. However, there is now increasing evidence that the epithelium actively participates in the inflammatory processes and thereby regulates many mediators of inflammation [1-4]. Moreover, the airway epithelium can behave as both a target cell for external stimuli and as an effector cell by releasing many inflammatory mediators including cytokines, chemokines, lipid and peptide mediators, reactive oxygen and nitrogen species, enzymes and inhibitors. Therefore, an appreciation of how the epithelium participates in the inflammatory response may be beneficial to understanding the underlying pathophysiology of inflammatory airway diseases such as asthma and chronic obstructive pulmonary disease (COPD). Attempts to address this question have led to the development of epithelial systems that enable the study of mechanisms relating to epithelial function in the regulation of airway inflammation.

The successful culture of human primary airway epithelial cells has been dependent upon the development of defined cell culture media, first described in the mid 1980s [5-6]. A rich basal media (e.g. Ham's F12) is required and, in contrast to the culture of epithelial cell lines, serum supplementation alone is not sufficient for the expansion and proliferation of primary cells. Hence, various growth supplements must be added to the media to ensure optimal growth of primary epithelial cells. These supplements include insulin, epidermal growth factor (EGF), transferrin and triiodothyronine (T_3) [5,7]. All these factors increase epithelial cell proliferation [8]. Two other additives commonly included in culture media are hydrocortisone and retinoic acid. Hydrocortisone is thought to suppress fibroblast growth [9] and promote epithelial differentiation [10]. Similarly, retinoic acid can also promote the differentiation of epithelial cells [11-12]. This is an important consideration since the differentiation status of epithelial cell *in vitro* can define the type of responses observed [13-14].

Using defined media systems it has been possible to culture cells from explant tracheal tissue [11, 15-16], both enzyme digests of trachea and bronchus taken from surgical and post-mortem tissue [17-18] and airway brushings of living donors [19-20]. Although, the specifics of handling tissues to obtain cells differ between systems, the principle of cell culture of human primary airway epithelial cells remains the same for each of these cell sources.

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Quick quides for culture of human airway epithelial cells

1. Culture systems

i) Media: The defined media in which cells are cultured is crucial for the successful culture of human primary epithelial cells. The system routinely used in the author's laboratory is essentially that of Dent *et al* [21]. The basal media used is Ham's F12 containing 5% (v/v) foetal calf serum (FCS) or NuSerum IV, 1 μ M hydrocortisone, 5 ng/ml EGF, 10 μ g/ml insulin, 10 nM retinoic acid, 0.5 μ g/ml transferrin, 2 μ g/ml T_3, 1.5 mg/ml NaHCO3, 100u/ml penicillin, 100 μ g/ml streptomycin and 0.25 μ g/ml amphotericin B. Although FCS has been reported to inhibit epithelial cell proliferation [7] its inclusion in culture media can stimulate the differentiation of epithelial cells [22].

ii) Culture surface: The attachment of cells to the culture surface, along with their growth and differentiation can be determined by the substrata on which they are cultured. In particular, differentiation of epithelial cells is enhanced when cultured on a collagen substratum [23]. Most commonly, plasticware is coated with a 1% (w/v) of collagen prior to use. The recent introduction of cell culture plastic specifically designed for the culture of primary cells (e.g. Primaria®, Falcon, Becton-Dickinson) has facilitated the culture of primary cells in the absence of collagen and is the system now used in this laboratory [24-25].

2. Source of epithelial cells

The limited availability of human tissue has restricted the culture of primary airway epithelial cells. Nevertheless, there are different strategies by which the limited amount of source material can be utilized.

i) Explant culture: Biopsy pieces taken from patients undergoing bronchoscopy are placed onto collagen coated, plastic culture dishes and are fed with a minimal volume of media to just cover the pieces of tissue. The tissue will attach to the cell culture dishes and epithelial cells will grow out from the explant to a radius of approximately 2-3 cm (Fig. 1a). Similarly, pieces of airway obtained from surgical specimens or post-mortem tissue can be carefully dissected. The pieces of airway can be cut carefully into small pieces (1-2 mm^3) and cultured in a similar manner to the biopsy pieces. In both cases, the cells will grow out from the airway segments and exhibit typical cuboidal, 'cobblestone' morphology. However, proliferation can be restricted further away from the original explant. This can be ameliorated by the removal of the explant tissue from the culture dish followed by addition of fresh media to the remaining cells to stimulate proliferation. The removed explant tissues can then be placed in new culture vessels and proliferation of epithelial cells will continue from the explant.

One advantage to this approach is that many cells can be cultured from a single piece of tissue. Furthermore, these cells have not been exposed to any proteolytic enzymes that could damage cell surface proteins. The main disadvantage of using this method to obtain cultures of epithelial cells is the possibility of contaminating cell types growing out from the explant. Fibroblasts are the major contaminating cell in this type of culture. They can be relatively easily identified in culture by their characteristic morphology. Fibroblasts appear as long, thin cells and tend to grow in parallel lines rather like 'tram-tracks' (Fig 1b). the inclusion of hydrocortisone and NuSerum IV in the cell culture media may help to suppress the growth of fibroblasts *in vitro*.

ii) Brushing cells: Viable epithelial cells can be obtained from brushing the airways of patients undergoing bronchoscopy [19]. The collection of viable cells is dependent on the technique used by the bronchoscopist. The number of cells collected is directly related to the number of brushings that can be performed on the airway, whereas viability is dependent upon the concentration of lidocaine that has to be applied to the vocal cords during

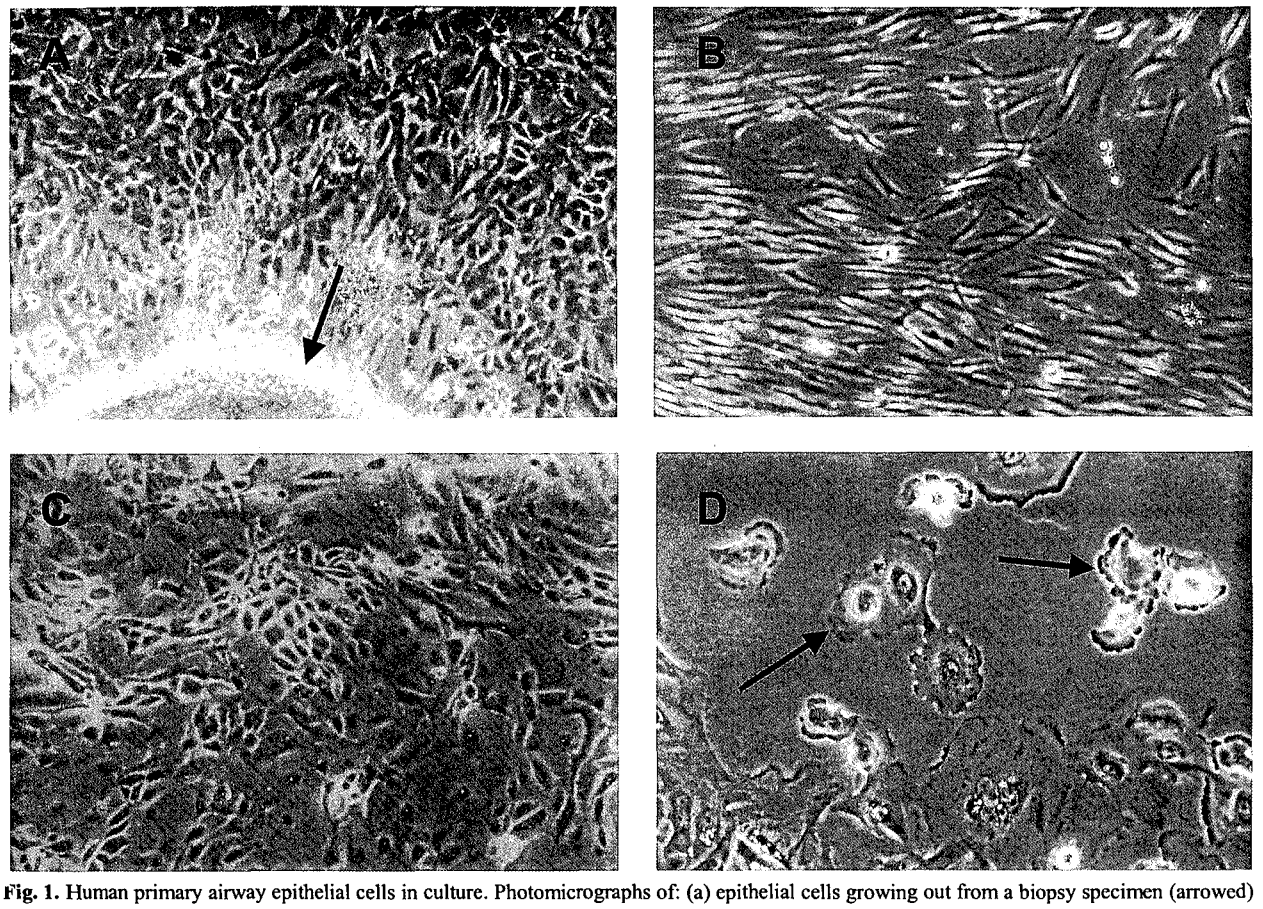

Fig. 1. Human primary airway epithelial cells in culture. Photomicrographs of: (a) epithelial cells growing out from a biopsy specimen (arrowed) exhibiting 'cobblestone' morphology, (b) contaminating fibroblasts with long, thin-spindle shaped morphology, (c) epithelial cells cultured from bronchial brushings, (d) passaged epithelial cells with ruffled cell membrane and enlarged cytoplasm showing 'fried-egg' morphology (arrowed).

the bronchoscopy. Concentrations of lidocaine above 2% (v/v) are cytotoxic [19]. Therefore, in this laboratory 2% lidocaine is applied routinely [25]. Epithelial cells can be washed off the cytology brush into cold media and maintained on ice for transport back to the tissue culture facility. The cells are then washed in Hanks' balanced salt solution (HBSS) before resuspending in cell culture media and seeding into cell culture plates. Microscopic examination of the cells at this time will reveal that many ciliated cells appear to be 'swimming' in the media. Although this demonstrates that the cells are viable, it can make attachment of these cells to the substrata difficult. In this laboratory, cells that have not attached to the surface of the culture dish after 5 days in culture are removed and reseeded into fresh culture vessels where they usually attach, proliferate and develop epithelial cell morphology (Fig 1c & Fig 1d). Similar techniques have also been used to obtain nasal epithelial cell cultures [20]. A major advantage of this approach is that the donors can be sampled repeatedly. Consequently, changes in development of the disease state, or treatment efficacy can be monitored. Another advantage of this technique is that the population of epithelial cells obtained contains a mixture of columnar, secretory and basal cells (Fig. 2), but does not contain proliferative contaminating non-epithelial cells. The main types of cells that contaminate the brushing samples are red blood cells and very occasionally alveolar macrophages; however, red blood cells and alveolar macrophages do not survive long-term culture. Finally, the epithelial cells are not subjected to enzymatic digestion and

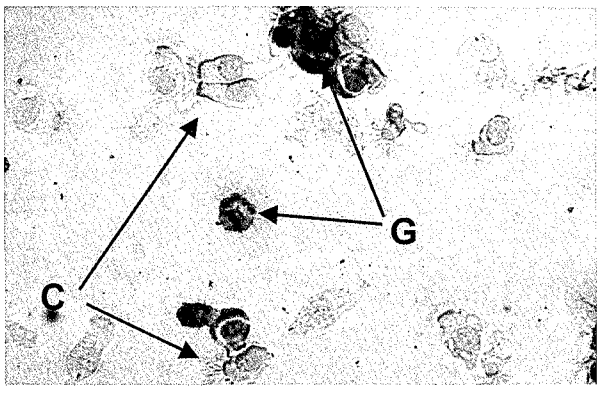

Fig. 2. Differential staining of epithelial cells obtained from bronchial brushings. Bronchial brushing cells were fixed onto poly-L-lysine coated slides and stained with Alcian blue and fuchsin red. Ciliated columnar cells (C) stain pink and secretory/goblet cells (G) stain blue.

exhibit all cell surface proteins. The major disadvantage of obtaining epithelial cells in this manner is that the number of cells obtained can be too few to perform complex experiments.

iii) Dissociated cells: In many animal studies, primary airway epithelial cells have been obtained following enzymatic digest of tracheal tissue [8, 26]. Similar protocols have been applied to human tissue [4, 17, 27]. Typically, tissue is digested overnight at 4 ℃ using solutions containing either collagenase or pronase [17, 27-29]. Digestion of the tissue is usually performed at 4℃ since prolonged digestion of the tissue at 37℃ can drastically reduce the number of viable epithelial cells. Following the digest, cells are harvested by centrifugation, resuspended in culture media and seeded into culture plates. The advantages of this technique are that large numbers of cells can be harvested from quite small pieces of tissue and the precise culture conditions can be completely controlled. There are disadvantages to this technique, the most obvious being that exposure to proteolytic enzymes can damage the cells by stripping any cell surface proteins. This may lead to changes in cell responses and morphological features. There is also a problem of contamination from other cell types, most notably fibroblasts.

3. Culture

Human primary airway epithelial cells can be successfully cultured in a variety of media as described above. However, other factors are also required for the culture of these cells.

i) Ensuring viable cultures: One of the major difficulties in the maintenance of primary cultures is contamination with bacteria or fungi. This can be a particular problem when samples have been obtained from patients with upper respiratory tract infections. The inclusion of antibiotics and antimycotics in the culture media (and washing solutions) is essential for successful cell culture. The time taken to obtain tissue from surgery or post-mortem may be critical in obtaining viable cultures. Gruenert *et al* [29] reported that a lag of more than 6h between the sample being obtained at surgery or post-mortem and cells being isolated using enzymatic digest can drastically reduce the number of viable cells available for culture. However, it is possible to obtain viable cells from explant cultures for up to 48h post removal of tissue at surgery or post-mortem [29-30]. In this case, it is beneficial for tissue to be stored in cell culture media at 4℃ before careful dissection and plating into cell culture dishes.

ii) Trysinisation (passaging): Fibroblasts are the major contaminating cell in cultures of primary airway epithelial cells. However, they are easily distinguished from epithelial cells in culture (see section 2.i). Fibroblasts can be selectively removed from the cultures using trypsinisation [29]. Cultures are exposed to a 0.02% (w/v) solution of trypsin and monitored microscopically. As soon as the fibroblasts change shape and 'round up' the cells can be detached using aspiration. The remaining, attached cells (epithelial cells) can then be replenished with fresh media and maintained in culture. This procedure can be repeated, if needed, to obtain pure cultures of epithelial cells.

The continued propagation of primary epithelial cells has met with limited success. Primary human airway epithelial cells can be

passaged using trypsin [27, 29] although the cells may undergo morphological changes and develop a 'fried-egg' shaped morphology [16] (Fig. 1d). Passaged cells may not only exhibit an altered morphology, they may also exhibit a reduced responsiveness to stimuli [30]. Primary cells appear to be more sensitive to trypsin when compared with established epithelial cell lines such as A549 and BEAS-2B. Consequently, Gruenert *et al* [29] include polyvinylpyrrolidine in the trypsinisation solution to protect the cells [29]. In Contrast, Robinson and Wu [27] reported that passage of cells cultured on collagen is not recommended. This is because trypsin-induced detachment of cells from collagen can be a lengthy process that can damage the cells irreparably. In the author's laboratory, use of a non-enzymatic cell dissociation solution (Sigma) has greatly facilitated the passage of primary cells.

(iii) Differentiation: The study of many functions of the epithelium including mucus production and cilia regulation requires the differentiation of cultured epithelial cells. Primary epithelial cells maintained in culture most resemble basal epithelial cells. It has been proposed that these cells are the epithelial stem cell in the human airway and together with parabasal cells contribute to the proliferative compartment of the airway epithelium [31-32]. Therefore, in order to study many of the functions of the epithelium, these cells have been manipulated *in vitro* to exhibit various phenotypes. Cultured airway epithelial cells retain the ability to differentiate into the different epithelial phenotypes since seeding of these cells onto denuded tracheal grafts can lead to repopulation of the epithelium [7].

Under the culture conditions described herein, epithelial cells tend to develop a more squamous morphology that can be monitored using the squamous cell marker α-cornifin. The addition of retinoic acid (vitamin A) to cell culture media has been used in many systems of epithelial cell differentiation [6, 28, 33]. Under

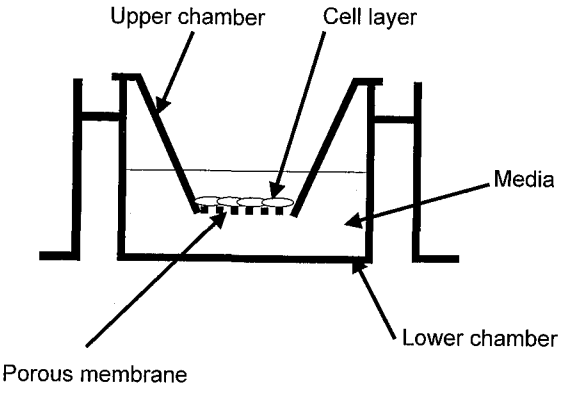

Fig. 3. Bi-phasic chamber for the culture of epithelial cells at an air/liquid interface. Cells are cultured on the porous membrane until confluent. Media is then removed from the upper chamber thus leaving cells at an air/liquid interface.

such conditions, epithelial cells will differentiate into mucus-producing cells and lose the ability to express α -cornifilim [28, 33]. Differentiation towards a mucus-producing phenotype can be optimized by culturing cells on a collagen gel in the presence of retinoic acid [28]. However, unlike hamster tracheal epithelial cells [34], human cells are unable to produce new cilia when cultured under these conditions [28].

In order to develop a ciliated phenotype, cells have to be cultured at an air/liquid interface. This has been made possible by the development of biphasic chamber systems, first described by Whitcutt *et al* [35]. These chamber systems are now available commercially (Falco, Nunc, CoStar) (Fig. 3). Different types of porous membrane are available including those pre-coated with extracelluar matrix proteins. Epithelial cells are seeded onto the membrane and both the upper and lower chambers filled with media until the cells reach confluence. The cells are then cultured at an air/liquid interface by removing the media from the upper chamber and feeding from below only. These systems allow the differentiation of cells into ciliated, columnar [35] and mucus-producing phenotypes [36]. Again, the inclusion of retinoic acid appears to be essential for the development of mucociliary differentiated epithelial cells [13, 36].

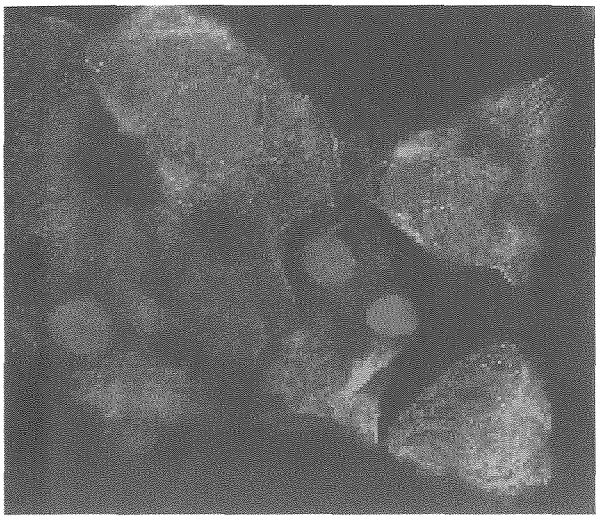

Fig. 4. Immunostaining of epithelial cells with anti-cytokeratin antibodies. Human airway epithelial cells were stained with anti-cytokeratin antibodies AE1/AE3 and detected using bodipy labeled goat anti-mouse IgG and the nuclei detected using DAPI. The slides were observed using the *uv* laser on a Leica confocal microscope. Cytokeratin within the cells can be observed as green staining and the nucleus as blue.

4. Identification of epithelial cells

The identification of different types of epithelial cells in the airway can be performed on 'smears' or cytospins of bronchial brushings. Cells can be stained with Alcian blue and basic fuchsin, which allows for the identification of columnar epithelial cells and secretory cells [30, 37]. To facilitate staining, cell smears are prepared on poly-L-lysine slides and fixed using 10% (v/v) formalin. The slides are then sequentially stained with 1% (w/v) Alcian blue in 3% (v/v) acetic acid and 0.4% (w/v) basic fuchsin. Using this method, cilia are clearly visible and secretory cells stain bright blue (Fig. 2). However, cultured epithelial cells do not exhibit such easily identifiable phenotypes. Most workers have chosen to identify epithelial cells in culture on the basis of morphology and the expression of cytokeratins.

Epithelial cells express cytokeratins which can be broadly separated into type I (acidic) and type II (basic) sub-families [38]. Epithelial cells express at least one of each of the cytokeratin sub-family. Consequently, the use of pan-cytokeratin antibodies has been useful in the identification of these cells since fibroblasts and smooth muscle cells do not express cytokeratins. Typically, the monoclonal anti-epithelial keratin (AE1/AE3) mixture (ICN Flow) is used to identify epithelial cells [29] (Fig. 4). Most bronchial epithelial cells express cytokeratin-7. However, this protein is not expressed by basal cells suggesting that cytokeratin expression may also reflect the differentiation status of epithelial cells [39]. Basal cells preferentially express cytokeratins 5 and 14 and the use of specific antibodies to these cytokeratins has enabled the identification of basal cells [32]. To further distinguish epithelial cells from fibroblasts and smooth muscle cells, the expression of cell specific markers such as vimentin (fibroblasts) and α -actin or myosin (smooth muscle) can also be determined [17].

Applications of human primary airway epithelial cells *in vitro*

Numerous studies of primary airway epithelial cells have contributed to understanding that epithelial cells not only act as a defence barrier in the lung, but can also regulate airway inflammation [1-2, 4]. Moreover, airway epithelial cells from cystic fibrosis patients demonstrate differences when compared with those from normal donors [29, 40]. Although epithelial cells are ideal for study of the role of the epithelium in the pathophysiology of airway inflammation, there are limitations to the use of such systems. Firstly, the cells used for many experiments are in a non-differentiated state. Despite many workers attempting to address this problem [34-36, 41], generation of a heterogeneous epithelium *in vitro* akin to that *in vivo* has not yet been developed. Other limitations for the use of primary epithelial cells include the availability of tissue and the limited life span of primary cells in culture. In order to address the latter problem, immortalized cell lines have been generated (e.g. BEAS-2B and 16 HBE-14o$^-$) [42-44]. Whilst these cell lines provide excellent systems for the study o

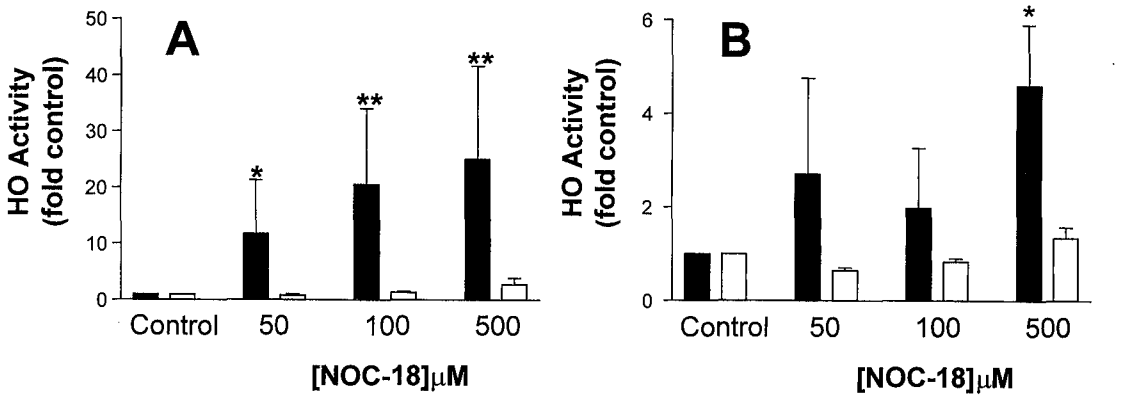

Fig. 5. Heme oxygenase (HO) activity and HO-1 expression in primary airway epithelial cells and BEAS-2B cells. Human primary airway epithelial cells and BEAS-2B cells were cultured for 24h in the presence of the nitric oxide donor, NOC-18 (A). HO activity measured as described by Donnelly and Barnes [25]. (B) In separate experiments, cells were treated for 4h with NOC-18 and RNA extracted and RT-PCR for HO-1 and GAPDH performed. Data are mean ± SEM (n=3-7) where closed bars represent primary cells and open bars BEAS-2B. *p<0.05 and ** p<0.01 compared with control.

epithelial cell function and mechanism of regulation, they do have altered responses when compared with primary cells. Indeed, the author's laboratory has demonstrated that release of the cytokine granulocyte macrophage colony-stimulating factor (GM-CSF) from primary cells is approximately three times greater than that from either A549 or BEAS-2B cells [30]. Furthermore, our observation that the increase in the anti-oxidant enzyme heme oxygenase (HO), and HO-1 expression induced by nitric oxide in human airway epithelial cells [25] cannot be reproduced in BEAS-2B cells (Fig 5). These examples demonstrate the value of using primary cells over established cell lines.

In summary, the culture of human primary airway epithelial cells is a valuable technique for the investigation of the role of the epithelium in airway inflammation. Such studies should shed light on the role of the epithelium in inflammatory airway diseases such as asthma and COPD.

Acknowledgements

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Bronchopulmonary Carcinoids—An Analysis of 26 Cases

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Bronchopulmonary carcinoids comprise about 5% of all primary tumors of the lung. Though more benign in nature, bronchopulmonary carcinoids have a potential for local invasion, regional nodal involvement, and distant metastasis.

From 1977 to 1998, 26 patients were admitted to our section with surgical proof of bronchopulmonary carcinoids. They were classified into two subtypes: typical and atypical carcinoids. We retrospectively analyzed the clinical data, diagnostic rate, surgical results, and prognostic factors. Of these 26 patients, 22 patients had typical carcinoids and 4 atypical. The mean age was 57.4 years, with a range of 34 to 79 years. Sixteen were male and 10 were female. Ten patients were smokers. The most common presenting symptom was cough (76.9%), followed by hemoptysis (38.5%). Carcinoid syndrome was observed in 2 patients. The tumors were predominantly localized in the right middle lobe (34.6%), with a right-sided preference in 73% of the cases. Lobectomy was the treatment of choice for most of our patients. No surgical morbidity or mortality was noted. Eight patients had a 10-year disease-free survival, and 13 patients had a 5-year disease-free survival. The prognostic factors that were analyzed included clinical presentation, surgical method, pathological subtype, regional lymph node metastasis, and distal metastasis. Only distal metastasis could influence survival.

In conclusion, we believe that surgical resection for typical carcinoids is sufficient; but a more aggressive treatment for atypical carcinoids is needed, especially in cases with nodal or distal metastasis. ***(Thorac Med 2001; 16: 228-235)***

Key Words: bronchopulmonary carcinoid, typical carcinoid, atypical carcinoid

Introduction

The large majority of pulmonary neoplasms are carcinomas, and often present in advanced stages and carry a poor prognosis. Next to carcinomas, bronchopulmonary carcinoids are the most common primary neoplasms of the lung. They comprise about 5% of all primary tumors of the lung [1]. Compared to carcinomas, bronchopulmonary carcinoids seem to have a prolonged and relatively benign clinical course, with rare metastasis. Oberndofer first used the term 'Karzinoid' to describe this disease entity in 1907 [2].

The most widely accepted histopathological classification for bronchopulmonary carcinoids was presented in 1972 by Arrigoni et al. [3]. They

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differentiated the tumor into typical and atypical types. Typical carcinoids have a more benign course, whereas atypical carcinoids are more aggressive in nature [1]. Some investigators have considered carcinoids to be a family of neuroendocrine tumors, the Amine Precursor Uptake Decarboxylase (APUD) tumors, which originate in the neural crest [4]. Therefore, a different classification system was developed, which categorized the neuroendocrine tumors of the lung into a) very low-grade neuroendocrine neoplasms-- bronchial carcinoids, b) well-differentiated neuroendocrine carcinomas-- atypical carcinoids, c) intermediate cell neuroendocrine carcinomas-- large cell undifferentiated carcinomas, and d) high-grade neuroendocrine carcinomas-- small cell neuroendocrine carcinomas [5-6].

Like carcinoids in other sites of the body, the morphology of the typical carcinoid of the lung reveals uniform round to oval polygonal cells with small oval nuclei and fine chromatin under microscope. The cells organize as small clusters or cords with highly vascular connective tissue among them. On the other hand, in the pathological specimen of atypical carcinoids, polymorphism with mitotic activity, prominent nucleoli, peripheral palisading, and necrosis are the major features [3,7].

The clinical presentations of bronchopulmonary carcinoids are usually nonspecific, such as cough, hemoptysis, dyspnea, and obstructive pneumonitis [1]. But carcinoid syndrome, Cushing's syndrome, and other endocrinopathies may also be present [8].

Diagnosis may be a challenge for us when using chest roentgenography (CXR) and computed tomography (CT) of the chest. These methods only disclose a mass lesion without specific differentiation from other mass lesions of the lung, such as carcinoma. A pre-operative bronchoscopic biopsy may misdiagnose theses carcinoids as small-cell carcinoma due to the small specimen, even in intra-operative frozen pathological examinations [1]. Only a pathological examination of the complete specimen by surgical resection can yield a definitive diagnosis.

Bronchopulmonary carcinoids are slow-growing tumors with a good long-term prognosis. The factors that influence the prognosis include pathological subtype (typical or atypical), lymph node metastasis, and distal metastasis [1,9].

The aim of our study was to review the clinical data and the results of treatment, and then to find the prognostic factors that influenced survival.

Material and Methods

From 1977 to 1998, 26 patients who had undergone surgical treatment in the Division of Thoracic Surgery, Department of Surgery, Taipei Veterans General Hospital, were diagnosed with bronchopulmonary carcinoids. Their medical records were reviewed. All patients had undergone blood cell analysis, a biochemistry study, CXR, a whole body bone nuclear scan, bronchoscopy, and pulmonary function test pre-operatively. A CT scan of the chest was performed as needed.

A surgical resection, including either enucleation, wedge resection, lobectomy, bilobectomy, sleeve lobectomy, or pneumonectomy, was performed for each patient. The type of resection was based on the surgeon's clinical judgment. Lymph node dissections were performed in most cases. Frozen section examinations were performed intra-operatively if no pathological diagnosis had been made pre-operatively. After discharge from the hospital, all patients were followed-up in our outpatient department, using the routine post-operative program. CXR, a whole abdomen sonography, and a whole body bone nuclear scan, were performed every 3 months for 2 years, then every year there after. Telephone visits were also made at the time the data was reviewed.

We analyzed the distribution of age, sex, smoking status, symptoms, CXR and CT findings, bronchoscopic detection rate, pre-operative biopsy diagnosis rate, tumor subtype, location

and stage, and patient survival.

Results

Of the 26 patients included in the study, 16 were male and 10 were female. The mean age was 57.4 years, ranging from 34 to 79 years. Ten patients were smokers (38.5%).

As seen in Table 1, the most common symptom was cough (20/26,76.9%), followed by hemoptysis (10/26, 38.5%), obstructive pneumonitis (8/26, 30.8%), chest pain (6/26, 23.1%), and carcinoid syndrome (2/26, 7.7%). One patient with carcinoid syndrome suffered from liver metastasis and passed away. The other patient had developed the syndrome before diagnosis, but was still alive and well 1.2 years after surgery. Only 4 (15.4%) patients were asymptomatic, and were diagnosed incidentally.

In Table 2, we analyze the pre-operative tumor detection rate with different diagnostic studies. A CXR was performed for all patients. Lesions could be observed in 22 (84.6%) patients. A CT scan of the chest was done for 18 patients, and only one tumor was not be revealed. A pre-operative bronchoscopy was routinely performed for all patients. Positive flexible fiberoptic bronchoscopic findings were noted in 15 patients (57.7%), which might have been due to the central location of the tumor. Among the 15 patients, only 9 (60%) had a pre-operative, accurate diagnosis by bronchoscopic biopsy. Only one patient among the others had pre-operative CT-guided biopsy tissue proof. There after, in all, 10 patients (38.5%) in our series were able to have a pre-operative diagnosis.

The tumor locations are listed in Table 3. Nineteen patients (73.0%) had a right-side tumor, including 3 in the RUL, 9 in the RML, 7 in the RLL. The others were located in the LUL (2 patients) and LLL (5 patients).

The types of surgical intervention are shown in Table 4. Most of our patients underwent a lobectomy (16/29, 61.5%), followed by a bilobectomy (5/26, 19.2%). Two patients received a wedge resection for their tumor, and one enucleation, one sleeve lobectomy, and one pneumonectomy was also done. Radical lymph node dissections were performed in 11 (42.3%) patients. Lymph node sampling was done in 4 (15.4) patients. Eleven (42.3%) patients did not have a lymph node dissection during the operation. The mean tumor size was 2.3 cm; the largest tumor was 5 cm and the smallest was 0.4 cm.

In the pathological findings, 22 patients were typical carcinoid and the other 4 patients were atypical (Table 5). Only one patient had hilar lymph nodal metastasis, and the tumor belonged to the atypical type. One patient developed liver metastasis 2.3 years after surgery, then died of the disease soon after it was found. His previous tumor was a typical type. The mean follow-up time was 8.0 years (range from 1.2 to 19.6 years). Fifteen patients were alive and disease-free at the time of this study. Six patients went through follow-up for more than 5 years, then were lost to follow-up. Five patients were lost to follow-up after their surgeries. Eight patients were known to have celebrated their

Table 1. The Symptoms of Bronchial Carcinoid

	No. of patients	%
Asymptomatic	4	15.4
Symptomatic	22	84.6
Cough	20	76.9
Hemotpysis	10	38.5
Obstructive pneumonitis	8	30.8
Chest pain	6	23.1
Carcinoid syndrome	2	7.7

Total number=26

Table 2. Detection Rate of Bronchial Carcinoids in Different Tools

Tool	No. of patients	%
CXR	22/26	84.6
CT scan of chest*	17/18	94.4
Bronchoscopy	15/26	57.7
Biopsy	9/15	60

* not done in 8 patients

Table 3. Location of Bronchial Carcinoids

Lobe	No.of patients	%
RUL	3	11.5
RML	9	34.6
RLL	7	26.9
LUL	2	7.7
LLL	5	19.2
Total	26	100

Table 4. Surgical Methods of Bronchial Carcinoids

Methods	No. of patients	%
Enucleation	1	3.8
Wedge resection	2	7.7
Lobectomy	16	61.5
Bilobectomy	5	19.2
Sleeve lobectomy	1	3.8
Pneumonectomy	1	3.8
Total	26	100

Table 5. Pathology and Metastatic Features of Bornchial Carcinoids

Pathology		
Typical carcinoid		Atypical carcinoid
22/26 (84.6%)		4/26 (15.4%)
	LND	
With RLND	Sampling	Without LND
11/26 (42.3%)	4/26 (15.4%)	11/26 (42.3%)
	LN metastasis	
	1/26 (3.8%)	
	Liver metastasis	
	1/26 (3.8%)	

RLND: Radical lymph node dissection
LND: Lymph node dissection

10-year disease-free survival, and 13 patients their 5-year disease-free survival.

Discussion

Bronchopulmonary carcinoids are a true malignancy. They are relatively rare and more benign than carcinomas of the lung. The principle of treatment is also different from that of carcinoma, and the prognosis is better.

In 1999, Soga and Yakuwa reported a large series that described the demography of carcinoids [9]. The male: female ratio was 0.929. Our results showed a ratio of 1.6, but the sex bias of a veterans hospital should be taken into consideration. Compared with Soga's study in which the age distribution was from 6 to 95 years, and the mean age was 47.5 yeas, the mean age of our patients was greater (57.4 years). Once again, our patient bias should be considered.

According to the results of the study performed by Soga and Yakuwa, the symptoms were related to tumor location [9]. Most of them were nonspecific bronchopulmonary symptoms, except for carcinoid syndrome and Cushing's syndrome. When the tumor was located on the periphery of the lung, the patient might be asymptomatic. The presenting symptoms included cough (42.3%), hemoptysis (20.3%), atelectasis (25.4%), fever (23.9%), dyspnea (15.6%), chest pain (11.5%), Cushing's syndrome (6.0%), and carcinoid syndrome (7.9%) [9]. Carcinoid syndrome usually occurred in cases with large primary tumors or liver metastasis [1]. Most of our patients suffered from cough. Hemoptysis and obstructive pneumonitis were also common symptoms. Three of our four asymptomatic patients had peripheral lesions that were occult on bronchoscopic examination. Carcinoid syndrome was present in two patients (7.7%), one of which appeared with liver metastasis.

CXR is often the first-line diagnostic tool employed when a lung carcinoid is suspected. Radiographic findings may include the presence of a nodule or a mass, a picture of pneumonia caused by tumor obstruction, even without any abnormality if the lesion is too small to be detected, or when an endobronchial lesion is encountered. Soga and Yakuwa reported a 68.1% abnormality detected on CXR [9]. The vast majority (84.6%) of our patients had abnormal

findings in the CXR examination.

Chest CT can further identify smaller tumors, tumors within pneumonia patches that are occult on CXR, and endobronchial tumors. A CT of the chest is also important in the pre-operative determination of mediastinal lymph node involvement [1]. Nonetheless, neither CXR nor CT of the chest is able to diagnose a carcinoid tumor. Only 69.2% of our patients received a chest CT. The tumor detection rate was 81.3% in Soga and Yakuwa's series, and 94.4% in our series. Chest CT still failed to detect the tumor mass in one of our patients.

Approximately 50.9% of the lung carcinoids could be identified by bronchoscopy [9]. These tumors often appear as submucosal lesions, and the term 'iceberg' is frequently used to describe them. Among our patients, 57.7% of the tumors were localized by bronchoscopy. These lesions are defined as central lesions in our study. However, only one in 4 of our atypical carcinoids was identified by bronchoscopy, and 75% of the atypical carcinoids were peripheral in location. This trend has also been observed by other authors [9]. A biopsy should be performed to reach a final diagnosis, though the risk of hemorrhage poses a problem [1]. Even with biopsy, the morphological resemblance, micro-scop-ically, to small-cell carcinoma may lead to the wrong diagnosis [1]. Special immunohistochemical staining for hormonal peptides such as adrenocorticotropic hormone, vasopressin, calcitonin, bombesin, and serotonin, may be positive in carcinoids. But the same special staining may also be positive in small-cell carcinoma [6]. Hence immunohistochemical staining offers little value in distinguishing between carcinoids and small-cell carcinoma.

Bronchial carcinoids had a distribution significantly more on the right side, comprising 61.4% of them [9]. In our series, 73.1% of the carcinoids were distributed on the right side, and most were located in the right middle lobe. The same preferential localization of the carcinoid tumor has also been observed by other authors [10]. Eight of the 9 RML patients had a centrally located carcinoid, and all of the 9 patients were symptomatic in our study. That the calibration of the RML was smaller than that of the other lobes, which revealed earlier symptoms, may explain the trend.

Surgical resection is the mainstay of treatment if the tumor is deemed resectable [1]. In dealing with a malignant disease, lobectomy is the treatment of choice for most of the patients in our hospital (61.5%), and in other thoracic surgical institutions [10-11], as well. In our studies, 11.5% of the patients underwent local resections without tumor recurrence or distant metastasis. The extent of surgery did not alter patient survival or the local recurrence rate. Wedge resection yielded results comparable to lobectomy for our patients. The same trend was also observed in other series [11]. As the bronchopulmonary carcinoid is often centrally located, bilobectomy or pneumonectomy may be required in some cases. Twenty-three percents of our patients received a bilobectomy or pneu-monectomy, compared with McCaughan *et al.*, who reported 22.8% [10]. Most of the bronchopulmonary carcinoids were small in size [9]. The average size of our tumors was only 2.3 cm. For a small central lesion, a sleeve resection is a reasonable choice. One (3.8%) of our patients with a 1.2 cm tumor underwent this surgery, compared with the 5% reported by McCaughan *et al* [10]. One other main purpose of surgical intervention is to prove the diagnosis. The pre-operative diagnostic rate was only 38.5% in our series, and 29.2% in Soga and Yakuwa's report [9]. A frozen examination is very important in the determination of the type of surgical approach, but carcinoids may be frequently misdiagnosed as small-cell carcinoma [1].

The surgical staging of mediastinal lymph node involvement is another crucial factor in the diagnosis. Mediastinal lymph node sampling is often sufficient for most apparent mediastinal lymph node-negative patients, though radical

lymph node dissection is also recommended by some authors [1]. However, if the tumor is an atypical carcinoid, or if regional lymph nodes are involved, more aggressive surgery consisting of a lobectomy with radical lymph node dissection should be preferred. One of our patients underwent a bilobectomy due to the critical tumor location, with distant metastasis developing later. Lymph node dissection was not performed in this patient. Our sample size prohibited us from making a definitive conclusion on whether or not systemic lymph node dissection should be performed. We recommend the sampling of lymph nodes as a minimum.

The bronchial carcinoids are resistant to radiotherapy. Chemotherapy, following the regimen for small-cell lung cancer, can be considered for atypical carcinoids with mediastinal lymph node spread or distant metastasis. A regimen using the combination of etoposide and cisplatin has yielded satisfactory results [12].

The 5-year survival for stage IA non-small-cell lung cancer patients after surgical treatment was 61%, and 38% for IB patients [13]. The 5-year survival for limited-staged small-cell lung cancer was about 10% [14]. In contrast to the above two malignancies, the bronchopulmonary carcinoid is slow-growing in nature. Our 5-year disease-free survival was 92.9%. Most patients should expect remission after tumor resection. Despite a lymph node metastasis rate of 14.8 % [9], the prognosis is still good. Martini *et al.* reported 12 carcinoid patients with lymph node metastasis. The 5-year disease-free survival rate was 100%, with only one recurrence 8 years after the operation [15]. Our atypical carcinoid patient with lymph node metastasis has lived 14.5 years, up to the time of our study. Mokuno *et al.* reported a liver metastasis 19 years after surgical resection for a typical carcinoid patient. She lived well and disease-free 42 months after the 3.7x3.0x2.5cm liver metastatic tumor was resected [16].

In Soga and Yakuwa's study, the 5-year and 10-year survival for typical carcinoids was 93.3% and 82.1%, respectively [9]. The only patient who suffered from liver metastasis and died in our study was a 52-year-old male non-smoker. The initial symptoms at the time of presentation included cough, chest pain, hemoptysis, and obstructive pneumonitis. The tumor was typical in nature and only 1.5cm in size. However, carcinoid syndrome developed 2.3 years after the surgery, which included a lobectomy without lymph node dissection. The urine 5-HIAA test was negative, but liver metastasis was detected in the subsequent evaluation. Unfortunately, the patient died of the disease.

The pathological features and behaviors of the atypical bronchopulmonary carcinoid are more malignant than those of the typical. About 15% of bronchopulmonary carcinoids were atypical in the Soga and Yakuwa study [9], which is compatible with the results of our study (15.7%). The age distribution was significantly higher than that of the typical, with a mean age of 54.7 years [9]. The trend was also congruous to our series (62.75 years). Atypical carcinoid tumors were predominantly located in the peripheral regions (63.5%), while the typical carcinoids originated mostly in the central area (67.8%) [9]. Our series revealed that 75% of atypical carcinoids are located in the peripheral area. The regional or distant metastatic rate for atypical carcinoids is higher (30.7%). The 5-year and 10-year survival rates were 68.8% and 58.6%, respectively [9]. In our study, the patient with lymph node metastasis turned out to have an atypical carcinoid. But all of the four patients with atypical carcinoids were alive and well, and had undergone lobectomy or bilobectomy, and radical lymph node dissection.

Drawing from our experience, regional or extended resection for bronchopulmonary carcinoids is suggested. Lymph node sampling should be carried out during the operation. We recommend a more aggressive treatment, such as extended resections and radical lymph node dissections for atypical bronchopulmonary carcinoids, especially

in cases with nodal metastasis. For patients with distal metastasis, the surgical resection of all tumors is still advocated. Adjuvants with chemotherapy also provide benefits for patients with distal metastasis.

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支氣管肺類癌—二十六例之病例分析

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支氣管肺類癌大約佔所有原發性肺腫5%。支氣管肺類癌之本質雖較肺癌為良性，然其仍具局部侵犯，區域淋巴轉移，和遠處轉移之能力。自1977至1982年，台北榮民總醫院胸腔外科收集了26個於本院接受手術之支氣管肺類癌病人。這些病人又被分為典型及非典型類癌兩類。 我們迴溯性分析了這些病人的臨床診斷率、手術結果及預後因子。

在這26個病人中，22個病人為典型支氣管肺類癌，4個病人為非典型支氣管肺類癌。十六個病人為男性；十個病人為女性。年齡分佈自34歲至79歲。平均年齡為57.4歲。吸煙的有十個病人。最常見的症狀是咳嗽(76.9%)其次為咳血(38.5)。兩個病人有類癌症候群。腫瘤主要位在右中葉(34.6%)，73%的腫瘤位於右側肺葉。在非典型類癌之病人中有一人有局部淋巴轉移；在典型類癌之病人中有一人有肝臟轉移。大多數的病人接受肺葉切除術。沒有任何手術併發症或者死亡。 有13個病人術後存活超過5年，其中有8人超過10年。預後因子分析包含了臨床症狀，手術方式，病理形態，淋巴節和遠處轉移。在我們的研究中只有遠處轉移會影響預後。

從我們二十二年的經驗中，我們建議對支氣管肺類癌採取手術切除。對非典型支氣管肺類癌，甚至淋巴節或遠處轉移的病人，採取更積極的治療方法。*(胸腔醫學2001; 16: 228-235)*

關鍵詞：支氣管肺類癌，典型類癌，非典型類癌

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台南地區機構呼吸器依賴個案特質探討

葉莉莉

本研究旨在瞭解台南地區機構呼吸器依賴個案之人口學資料、整體性照護需求、個案之家庭經濟狀況與機構照護花費及其主要照顧家屬特質。研究對象為居住於台南地區 9 家呼吸照護機構之個案，依研究者自擬並經專家確認之資料收集表收集資料，以 SPSS8.0 系統進行分析。結果顯示，100 位個案中，男性佔 58%，平均年齡 73.1 歲，轉入機構之疾病診斷以呼吸衰竭為多，計 30%。全日使用呼吸器者計 88%，曾接受呼吸器脫離訓練者有 36%；個案中意識清醒警覺者有 29%；身上有二種以上管路者達 94%；家屬探訪狀況以每天探訪至少 1 次者為多，計 43%。身體功能狀態由巴氏量表平均得分僅 7.3 分，顯示日常生活需求他人完全協助者多。個案住機構花費以自付 2 萬 5 仟至 3 萬者為多，計 44%，家屬主訴之經濟負荷以可平衡為多（87%）。本研究結果對居住機構呼吸器個案及其家屬特質有初步了解，可做為政策制訂與機構服務提供之參考。 ***(胸腔醫學 2001; 16: 236-243)***

關鍵詞：機構呼吸器依賴、個案特質

前　言

Ferns [1]指出長期使用呼吸器可以維持生命的疾病包括：呼吸肌功能障礙、中樞神經系統疾病、多發性神經病變及肌肉疾病或萎縮、胸壁疾病（如多神經根病變）、中樞換氣不足症候群、阻滯性肺疾病、慢性肺阻塞疾病、皮下氣腫及慢性支氣管炎等。罹患上述疾病個案若無法成功的戒斷呼吸器的使用，則如何讓個案及家屬能放心的轉院或回家而不要佔據急性病床，是急症照護單位極大的挑戰，亦是近十年來健康照顧體系所努力的方向之一。

依健保局統計，民國 86 年呼吸器依賴患者（連續使用呼吸器超過 21 天以上者），約 7,326 人。整體而言，此類病患一年之門、住診費用合計約為 60 億元，約佔全民健保一年醫療費用的 3%，住院費用約為 59 億元，約佔全民健保一年住院費用的 8%；有鑑於這些個案滯留於急性醫院所造成之健保負擔，衛生署於 1998 提出「改善醫院急診重症醫療計劃」，規範「急性呼吸治療病床」及「呼吸照護病床」之設置標準。計劃中有關醫療費用的支付方式及支付標準，則由健保局邀請中華民國胸腔暨重症加護醫學之臨床專家及學者組成的「工作小組」，進行呼吸器依賴患者照護模式及支付方式的規劃。小組最終決定依照護時程分四個階段，採不同支付方式給付，並建立管理式照護之整合性照護模式（Integrated delivery system，簡稱 IDS）；期望藉由改善論量計酬的支付方式，鼓勵院所引進管理式照護，使醫療資源合理使用；將使用呼吸器超過 63 天且狀況穩定個案，遷移慢性長期照護場所---包括呼吸照護病房（RCW）與居家呼吸照護；本文所指之機構呼吸器依賴（Institutionalized Ventilator Dependent，簡稱 IVD）個案，定義為居住於慢性醫院（某些機構未加入 IDS 系統，會將呼吸器個案放在慢性病床照顧）、RCW、護理之家或安療養機構之呼吸器依賴個案。

現階段我們僅能由民國 86 年健保局之統計資料，發現使用呼吸器超過 63 天以上且完全不住加護病房者，一年中計有 547 人，散佈全台灣且分佈各年齡層[2]。然而這些個案中究竟有多少人於住院 63 天、狀況穩定後仍持續住院？或安置於機構？或返家？其詳細數目無從考查。惟可確定的是此健保給付政策之實施，將使呼吸器依賴個案之遷移照護率增加。

近年來，在準醫學中心以上之醫療資源豐富的情況下，台南地區（含縣市）IVD 個案有越來越多的現象[3]。研究者於 89 年 11 月由負責台南地區 IDS 系統之某醫學中心個案管理師，以及四家提供大台南地區之呼吸器租借

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公司，確認有 10 家機構接受呼吸器依賴個案。

本研究目的爲瞭解台南地區機構呼吸器依賴個案之下列概況：

1.IVD 個案人口學資料。

2.IVD 個案之整體性照護需求包括

(1)IVD 個案於機構內之呼吸器使用及照護情形。

(2)IVD 個案之意識與溝通表達、留置導管、傷口及日常生活功能狀態。

3.IVD 個案之家庭經濟狀況與機構照護花費。

4.分析 IDS 與非 IDS 系統個案於上述狀況之差異。

5.IVD 個案之主要照顧家屬特質。

材料與方法

一、研究對象

研究對象爲居住於台南地區 9 家呼吸照護機構之個案(原有之 10 個機構中，僅某機構因特殊狀況拒絕筆者進行資料收集)。9 家機構中，屬 IDS 之 RCW 者有 6 家，餘 3 家爲慢性醫院，機構所在位置於台南市者有 4 家，3 家位於永康市，新營、歸仁各一家。

二、研究工具

(一)資料收集表

由研究者依研究目的自擬，收集資料包括機構呼吸器依賴個案之

1.IVD 個案人口學資料：性別、年齡、婚姻狀況、教育程度、是否爲榮民、住機構前居住狀況。

2.IVD 個案醫療狀況：是否爲 IDS 個案、有無健保、轉入機構疾病診斷、轉入機構性質、住機構月數、入機構後生理變化，以及主要照顧家屬探訪狀況。

3.IVD 個案整體性照護需求

(1)呼吸器使用與相關復健狀況：每日呼吸器使用時數、潮濕器種類、呼吸器管路種類、呼吸器連接方式、有無蒸汽吸入、抽痰、胸腔物理治療（拍痰）、是否執行呼吸器脫離訓練，以及是否有肢體復健。

(2)意識與溝通表達：外表意識、聽力、表達能力、表達方式及其訊息理解程度。

(3)留置導管狀態：是否留置氣切管、胃管、尿管或其他管路，以及留置管路的總數。

(4)排泄狀態：主要之排尿與排便型態。

(5)傷口狀態：傷口數目與級數，採用中華民國長期照護專業協會居家照護病歷中傷口記錄單加以評估(傷口等級分 0-4 級，爲全球性被接受之分級方法)。

(6)日常生活功能狀態：由巴氏與柯氏量表進行資料收集，此二量表爲現行健保制度長期照護（居家護理）收案對象篩選量表，國內採用多年，已具相當信效度。巴氏量表測量病患進食、移位、衛生、如廁、洗澡、步行、爬樓梯、穿衣、大小便控制等十項能力，每項依病患目前的能力給分，總分爲 0 分至 100 分，分數越高越獨立。柯氏量表協助健康專業人員評等病人的活動狀態，最早用於癌症病人，此量表共分五級，從零級到四級，零級代表完全獨立，一級代表可步行，二級代表 50%以上清醒時間不受限床椅，三級代表 50%以上清醒時間受限床椅，四級代表完全受限床椅。

(7)活動狀態：機構活動安排與個案每日活動型態。

4.IVD 個案家庭經濟狀況與機構照護花費：家庭經濟包括是否有低收入補助、主要付費來源、經濟負荷；機構照護花費包括看護費、醫療耗材費、日用品消耗量、機構照護費等加總，所有花費均以本地之通用貨幣(台幣)爲計算單位。

5.IVD 個案之主要照顧家屬特質：性別、年齡、與個案關係、教育程度、職業、探訪個案狀況。

(二)問卷之信效度

研究者依研究目的自擬問卷後，進行專家效度之修訂。邀請專家包括胸腔科醫師、呼吸照護病房護理長、居家護理師（提供呼吸器依賴個案居家照護之）及呼吸治療師，於整合相關建議後修改問卷，方進行資料收集。

三、資料收集與分析

研究者於資料收集前，先參訪機構了解各機構之運作。於徵得同意後，委請該機構熟悉個案之呼吸治療師或護理長協助資料收集。於資料收集前指導其認識問卷各項目及填寫方法。資料收集時間爲 89.12.11-90.02.27，凡於此段時間居住於機構內之個案皆列爲收集對象。問卷回收後，由固定之研究助理協助資料查核，確認其填寫無誤，再將資料鍵入電腦，以 SPSS8.0 系統進行分析。研究結果主要以描述性統計如次數、百分比呈現，另以卡方檢定 IDS 與非 IDS 系統之個案於上述各項是否具差異存在。

結　果

總計由 9 家機構收集 100 位機構呼吸器依賴個案之有效問卷，結果依研究目的分述：

一、IVD 個案人口學資料

機構呼吸器個案特質由表一呈現，個案中以男性居多 58%，年齡分佈廣泛，範圍 16 至 93 歲，以 65 歲以上最多，有 83%；已婚者 62%，教育程度亦有 71%在國小以下。榮民者佔 25%。住機構前之居住狀況顯示與家人同住者有 75%，次爲住機構（安養中心、榮家）計 18%。

表一 台南地區機構呼吸器依賴個案特質 N=100

項目	人數	項目	人數
性別		教育程度	
男	58	國小以下	71
女	42	國（初）中	13
年齡		高中（職）以上	13
（範圍 16-93，平均 73.1		不詳	3
17 歲以下	2	榮民	
18-64 歲	15	是	25
65 歲以上	83	否	75
婚姻狀況		住機構前居住狀況	
未婚	17	獨居	6
已婚	62	與家人同住	75
鰥寡	20	住機構	18
不詳	1	不詳	1

二、IVD 個案之整體性照護需求

(一)醫療狀況

IVD 個案之醫療狀況由表二呈現，資料顯示僅 39%爲 IDS 個案，99%有健保，轉入機構疾病診斷前三項爲呼吸衰竭（30%），心血管疾病（24%）與慢性阻塞性肺疾（21%），由外院或他處轉入者共計 73%；住機構月數 51%集中於 4-6 個月內，超過一年的有 7 案。住機構後之生理變化以穩定無變化 43%，及有變化但可控制 43%爲主，持續惡化僅佔 3%，顯示 IVD 個案狀況多平穩。

表二 台南地區機構呼吸器依賴個案之醫療狀況 N=100

項目	人數	項目	人數
IDS 個案		住機構月數	
是	39	(範圍 1-31 個月,中數 2.5 月)	
否	61	1-3 月	27
健保		4-6 月	51
有	99	7-12 月	15
無	1	一年以上	7
轉入機構疾病診斷		住機構後生理變化	
呼吸衰竭	30	狀況變好	11
心血管疾病	24	穩定無變化	43
慢性阻塞性肺病	21	有變化，可控制	43
腦血管疾病	9	持續惡化	3
脊髓損傷	6		
其他	10		
何處轉入			
外院 ICU	13		
外院 RCC	16		
外院一般病房	34		
外院 RCW	5		
本院 ICU	12		
本院一般病房	15		
護理之家/安養院	3		
家裡	2		

(二)呼吸器使用及相關復健狀況

表三呈現 88% 需 24 小時使用呼吸器，僅 10%於白天使用呼吸器。潮濕器使用以人工鼻較多，計 87%；過半數(60%)之呼吸器管路爲拋棄式；呼吸器連接方式，以氣切佔多數，有 97%。蒸汽吸入方面，每日皆給予者有 46%，51%爲需要時才用。抽痰方面，顯示每位個案每日皆需抽痰以維持呼吸道通暢；拍痰方面則超過九成個案接受此照護；僅有 36%接受呼吸器脫離訓練；肢體復健率顯低，如接受被動性關節運動者僅 11%。

(三)IVD 個案之意識與溝通表達

IVD 個案的意識與溝通表達，由表四呈現，其中外表意識清醒警覺的有 29%，有超過半數（58%）呈現植物人狀態。上述 58 案是否保有聽力無法評估，聽力正常者有 23%，其餘則有重聽情形。個案之表達及表達方式，顯示 58%無法評估，而其他個案則可使用口述、唇語或肢體動作的方式與旁人溝通。個案中 17%可完全瞭解外界之互動的內容，3%只遺漏部分，21%僅能對簡單內容作反應。

(四)IVD 個案留置導管、排泄及傷口狀態

留置導管方面，表五呈現個案中 97%有氣切管，92%有胃管留置，37%有尿管留置。留置導管種數顯示留置兩

表三 台南地區呼吸器依賴個案呼吸器使用及相關復健狀況 N=100

項目	人數	項目	人數
每日呼吸器使用時數		蒸汽吸入	
全日	88	有	46
白天	10	無	3
夜間	2	需要時使用	51
潮濕器種類		抽痰	
人工鼻	78	有	100
一般加熱型	22	無	0
呼吸器管路		胸腔物理治療（拍痰	
拋棄式	60	有	96
消毒式	40	無	4
呼吸器連接方式		呼吸器脫離訓練	
口內氣管	3	是	36
氣切	97	否	64
		肢體復健	
		有	11
		無	89

表四 台南地區機構呼吸器依賴個案意識與溝通表達狀態 N=100

項目	人數	項目	人數
外表意識		表達方式	
清醒警覺	29	口述	4
植物人	58	唇語	6
人時地混淆	13	肢體動作	14
聽力		合併至少 2 種	18
正常	23	無法評估	58
微重聽	13	訊息理解程度	
嚴重重聽	6	完全瞭解	17
無法評估	58	只遺漏部分	3
表達能力		對簡單內容反應	21
旁人可明白	14	完全不瞭解	1
明白但用字困難	3	無法評估	58
有時能被理解	21		
無法表達	4		
無法評估	58		

表五 台南地區機構呼吸器依賴個案留置導管、排泄及傷口狀態 N=100

項目	人數	項目	人數
氣切管		主要排尿型態	
有	97	尿片或尿褲	42
無	3	尿套	18
胃管		導尿管	37
有	92	廁所或尿壺	1
無	8	其他	2
尿管		主要排便型態	
有	37	可自解	74
無	63	腸造口	24
留置管路種數		需挖便或灌腸	1
3 種	32	傷口數目與級數	
2 種	62	無	85
1 種	6	1 級	7
		2 級	5
		3 級	2
		4 級	1

種導管者人數最多，計 62%。主要之排尿型態以穿著尿片或尿褲居多，有 41%，其次爲導尿管，有 38%；主要之排便型態，逾七成個案可自解；傷口部份顯示 15%的個案有傷口。

(五)日常生活功能與活動狀態

IVD 個案之功能狀態由表六呈現，65%之巴氏量表分數爲零分，顯示其日常生活各項需求皆需照護者代爲完成；35 位非零分者以 5-20 分佔多數。柯氏等級顯示 90%的個案級數爲四級，意味這些個案的活動完全限制於床

表六 台南地區機構呼吸器依賴個案日常生活功能與活動狀態 N=100

項目	人數	項目	人數
巴氏量(0-75 分)		機構活動安排	
0 分	65	否	91
非 0 分	35	是	9
柯氏等級		一日活動型態	
1 級	3	完全臥床	91
2 級	0	離床 30 分內	6
3 級	7	離床 30-60 分	1
4 級	90	離床一小時以上	2

上。於機構中有安排活動者僅 9 案，餘 91%個案之一日活動型態爲完全臥床，能離床 30 分鐘內者僅有 6 案。

三、家庭經濟狀況與住機構花費

由表七呈現之家庭經濟狀況，顯示有低收入補助者僅 2 案，主要付費來源有 25%爲自己積蓄，自述之經濟負荷多數可平衡，佔 87%，但仍有 1 案需借貸過日。居住機構之每月花費總額，大多爲 2 萬 5 千元至 3 萬元，計 44%，2 萬元以下，以及 3 萬至 3 萬 5 千元，皆佔 10%。值得注意的是有 27%的問卷未註明價錢，探究原因爲資料收集者表示不方便透露住院費用。

四、機構中 IDS 個案與非 IDS 個案其於上述各項之差異檢定

100 位 IVD 個案中，39%爲 IDS 系統內之個案，以卡方檢定兩類個案於個案特質之差異，41 個項目中，僅婚姻、教育程度及蒸汽吸入三項有差異（表八）；吾人發現 IDS 個案以鰥寡居多，教育程度以國(初)中以上較多，而

表七 台南地區機構呼吸器依賴個案家庭經濟狀況與機構照護花費 N=100

項目	人數	項目	人數
低收入補助		住機構每月花費	
是	2	2 萬以下	10
否	98	2 萬-2 萬 5 千	9
主要付費來源		2 萬 5 千-3 萬	44
自己積蓄	25	3 萬-3 萬 5 千	10
親屬	13	未註明	27
補助	7		
其他	54		
經濟負荷			
可平衡	87		
經濟吃緊	12		
借貸過日	1		

表八 台南地區機構 IDS 與非 IDS 呼吸器個案之比較 N=100

項目	IDS 個案(n=39) n(%)	非 IDS 個案(n=61) n(%)	X^2	p
+婚姻				
未婚	3（7.7）	14（23.0）		
已婚	22（56.4）	40（65.6）		
鰥寡	14（35.9）	6 （9.8）	11.611	0.003**
+教育程度				
國小以下	24（61.5）	47（77.1）		
國（初）中以上	15（38.5）	11（18.0）	4.518	0.039*
++蒸汽吸入				
有	26（66.7）	20（32.8）		
需要時才用	13（33.3）	38（62.3）	9.688	0.003**

* p≦ .05，** p≦ .01

+爲該項目不包含表一之不詳者，++爲該項目不包含表三之無者。

IDS 個案接受蒸氣吸入的比率較高。

五、機構呼吸器依賴個案照顧家屬特質

主要照顧家屬特質由表九呈現，顯示有家屬者佔多數，計 89%，11%無家屬，深入瞭解發現其多爲單身榮民；家屬性別以男性爲主，計 50%；年齡顯示 64%不清楚年齡，主要原因爲機構僅做個案資料建檔，故多不清楚家屬之年齡，清楚年齡者中，以 41-60 歲佔多數 19%。與個案關係中，55 人是子女，22 人是配偶。教育程度半數在高中職以上，國小及以下有 27 案。職業狀態顯示 40 人有專職工作，22 人無業，另 14 人兼家庭副業。由探訪個案狀況顯示照顧家屬至少每天探訪一次者居多，有 43%，每週至少 2 次者次之，有 19%，也有機構通知時才探訪者，計 8%。

討 論

一、IVD 個案與照顧家屬特質

高[4]指出呼吸器依賴個案欲出急性醫院後返家，需面對的問題包括居家照護設備不足與照護知識技能不足等。本研究之個案 88%需求 24 小時呼吸器使用；身上留置一種以上導管者達 94%，日常生活需完全依賴他人協助。相關照護需求除呼吸照護外，尚包含神經、活動、營養、排泄、溝通等，若欲返家則必須學習如何給予呼吸照顧(包括評估呼吸功能、查核呼吸器、抽痰、使用人工甦醒球及電力無效時的緊急處置，知道如何監測及轉介)、協助移位、灌食、處理尿管及大小便照護等[5-7]。面對這些照護需求，發生在老人身上（65 歲以上者高達 83%），對家屬而言，要帶回家照顧的困難似乎難以承受。此外，Dellasega 等[8]指出雖然許多慢性病患家屬多會思考未來的安置，但急性住院卻催化送入機構之決策；本研究發現個案之轉入來源有 98% 由醫療單位（外院或自院之 ICU、RCC、一般病房、RCW）轉入，此或可印證學者所言。

文獻查閱發現，家屬送個案入住機構之預測因子包括：個案之年齡越大者[9-12]、身體功能越差者[9-12]、家屬與老人分開居住[9]、家屬爲男性者[10]、照顧者爲成年子女者[10-11]、照顧者工作與照顧時間有衝突者[9]、照顧負荷越大者[9-11]，越容易將個案送入機構。以本研究結果與上述文獻相對照，發現 IVD 個案年齡確實偏高，平均達 73.1 歲，反應身體功能之巴氏量表平均分數爲 7.3 分，日常生活需求完全協助，家屬與老人分開居住者計 22%，主要家屬爲男性者 50%，照顧者爲成年子女者 55%，照顧者有專職工作者 40%，兼副業者 14%，其工作與照顧時間應是有所衝突的，故將個案送入機構是可想像的。

IDS 與非 IDS 系統個案，於 41 項特質檢定上，發現僅婚姻、教育程度及蒸氣吸入三項有不同，顯示兩群個案並無大差異。以上或可由 Kao 等[13]之本土化研究結果，瞭解國人於送個案入住機構的過程中，主要決策所考慮的原則是：機構與案家距離、是否爲醫院附設、每月收費金額及環境的乾淨度：印證本研究之 9 家機構皆屬醫院附設，有其一定之照護品質，加上機構間收費差距不大，故家屬皆就近選擇離家近之機構，以方便探視個案。

二、呼吸器依賴個案照護資源之省思

Coulton 等人[14]之研究顯示出院準備服務中，安置

表九　台南地區機構呼吸器依賴個案主要照顧家屬特質

N=100

項目	人數	項目	人數
是否有家屬		教育程度	
是	89	國小及以下	27
否	11	高中(職)以上	52
性別		不清楚	10
男	50	無家屬	11
女	39	職業	
無家屬	11	專職	40
年齡		無	22
（範圍 27-81 歲		兼家庭副業	14
中數 48 歲）	15	無家屬	11
21-40 歲	19	不清楚	5
41-60 歲	2	其他	8
60 歲以上	64	探訪個案狀況	
不清楚		每天	43
與個案關係		每週至少 2 次	19
子女	55	每週至少 1 次	7
配偶	22	2 週 1 次	7
父母親	3	1 個月一次	5
兄弟姊妹	2	通知才來	8
媳婦	2	無家屬	11
其他	5		
無家屬	11		

場所的決定受病人與家庭特質、健康專業人員的行爲與決策時周邊資源影響。就呼吸器依賴個案照顧者而言，筆者發現替代居家照護資源的充足與否，對於決策安置點是重要的關鍵因素，此由葉等[15]於台南地區，訪問 12 位居家呼吸器依賴個案之返家決策得到確認，該研究發現強化返家動機之原因爲後續照護資源取得困難，且照護品質不佳。以後續照護資源而言，該研究收集資料的時間爲民國 87 年，當時台南地區僅於台南縣有 2 家機構願意接受呼吸器依賴個案；而 IDS 制度的推展，創造了照護資源，本研究之 9 家機構，於民國 89 年始收呼吸器依賴個案者，即有 6 家，且分布台南縣市，因此不難理解證環境中的資源狀況，確實影響出院後安置場所之決策。

三、IVD 個案家庭之照顧者角色

本研究之家屬，每天探訪個案至少一次者高達 43%，僅 20%之家屬沒有每週探望個案，而 IVD 個案中僅 29%爲意識清醒警覺，可與旁人互動溝通，以上顯示即使個案之意識狀態不佳，家屬仍時常探望。

Stevens 等[16]在查閱多篇文獻後發現，送個案入機構後，家屬仍會執行一些所謂隱藏式的照顧工作，且需因應探訪個案時感受到的社會心理壓力，這種隱藏式的照顧工作及壓力，在與病人仍密切互動者身上尤其顯著，其所感受的壓力可能包括：經濟困難、有罪惡感、對其決定有愛恨交集的衝突、需協助照顧個案、需因應個案住機構後的狀況惡化等。其研究發現，送個案入機構不代表壓力的結束，而是有新的關注點；此外，Rosenthal 等[17]發現送個案入機構後，家屬因有較多的時間，如果機構能將家庭視爲照護對象，則可增加家庭的整合性，因而學者們呼籲機構經營者應將家屬視爲照護對象，依家屬期望，將家庭包含在服務提供與照護計劃內[16-17]。

四、呼吸器依賴個案長期安置場所之省思

呼吸器依賴個案適切之長期安置場所，值得吾人深入省思。由葉等之居家呼吸器依賴個案研究[15]，發現 75%的居家個案，居家期間超過半年，最久者已超過四年，而個案狀況仍多穩定，預期居家期間可以更長。本研究發現 IVD 個案住機構時間大於三個月者高達 73%，其狀況可穩定控制者高達 86%，顯示長期居住的潛在性高，以上顯示呼吸器依賴個案需求長期照護之事實。

Pierson[18]指出，後續照顧期間越長，越需考慮照護資源所能提供的照護內涵，以決定照護資源的適切性，其以爲呼吸器依賴個案，接受機構照護不僅花費高（本研究發現於 IDS 之經費補助下，仍有 54%的家屬每月需付 25000 元以上之費用）、且多數機構僅提供保護性照護，未考慮復健需求(活動力之強化與人際社會化活動之增加)，因而機構照護的適切性值得思考；然而再看葉等[15]之研究，發現居家呼吸器依賴個案照顧者雖肯定返家照護之益處，亦傳達照護負荷甚重之感受，對這些返家後需求高科技設備才能維生之個案，以台灣現況---多重專業照護團隊未形成、社會福利資源不足且多未整合、決策返家是否符合醫學期望與倫理考量亦值得重視：如是言，呼吸器依賴個案之後續照護應何去何從，值得產官學界深思。

結　論

本研究對象侷限台南地區之 IVD 個案，且爲橫段式研究，無法了解 IVD 個案接受機構照顧之完整狀況；而資料收集亦只能確認填寫的真確性，對某些（如入機構之主要診斷）則無法判別其正確狀況，以上應爲本研究之限制。未來期望在健保之 IDS 制度規範下，可以收集完整之 IVD 個案資料，以確認資源使用及相關照護成果，做爲政策制定或服務提供之參考。

致　謝

本研究爲「呼吸器依賴個案標準化遷移照護服務模式之建立與評值」（NSC89-2314-B-006-215）第一階段之資料結果，感謝國科會所提供之經費補助；以及九家機構負責人與護理長等對資料收集的協助；同時感謝助理顏佳慧與陳聯儀對本研究投入之心力，在此致以最大謝忱。

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Characterisitcs of Institutionalized Ventilator Dependent Client in Tainan Area

Lily Yeh

This exploratory study was conducted to identify the following characteristics of institutionalized ventilator-dependent clients: demographic distribution, physical care needs, monthly payment to the institution, family economic sufficiency, and family caregiver characteristics. Nine institutions located in the Tainan area participated this study. Data was gathered using a data collection tool, and analyzed with SPSS 8.0 software. Of the 100 clients studied, the following characteristics were revealed: 58% were male; the average age was 73.1years old; the leading diagnosis was respiratory failure (30%); 88% needed 24-hour ventilator use; 36% were trained to wean the ventilator; 44% had family visits at least once a day; 29% were conscious clearly; and 94% had more than two kinds of catheter. The average score on the Barthel's Index was 7.3, showing that most of the clients were completely dependent on help in their daily living activities. Forty-four percent of the families paid from NT$ 25,000 to NT$ 30,000 to the institution monthly, and 87% said they could afford it. The results of this study can be used as a reference in policy-making and for the services provided by the institution. ***(Thorac Med 2001; 16: 236-243)***

Key Words: institutionalized ventilator dependent, characteristics

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Primary Pulmonary Meningioma

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Primary extraneuraxial meningiomas (PEMs) outside of the head and neck regions are extremely rare. To the best of our knowledge, fewer than 20 cases of PEMs of the thorax have been reported in the past 25 years. We report a case of PEM incidentally detected by chest radiography (CXR) and a computed tomographic (CT) scan of the chest, with an initial impression of mediastinal tumor. Thoracic exploration revealed an intrapulmonary mass 3 cm x 3 cm x 3 cm in dimension. The histologic picture was compatible with meningioma, and immunostaining showed a positive epithelial membrane antigen (EMA) and vimentin stain. No intracranial lesion could be found in the subsequent brain CT scan, nor could focal neurological signs be identified. We report this case as the first documented primary pulmonary meningioma in Taiwan. ***(Thorac Med 2001; 16: 244-249)***

Key words: meningioma, mediastinal tumor, primary pulmonary meningioma

Introduction

Meningiomas outside the central nervous system have been called primary extraneuraxial meningiomas (PEM), or extopic meningiomas. Another term, extracranial meningioma, is more familiar, but has limited meaning for our report, since the spinal cord, an extracranial structure, is still a part of the central nervous system. According to statistics reported by Shuangshoti et al [1], PEMs comprise 8% of all meningiomas, and most of them occur in the head and neck region [7]. To the best of our knowledge, fewer than 20 cases of PEMs have been found in the thorax [2,7]. We describe herein the first case of intrapulmonary primary pulmonary meningioma in Taiwan.

Case Report

A 70-year-old man, with hypertension for 30 years without regular treatment, was presented to our hospital with a sudden onset of precordialgia 2 hours previously. On admission, his blood pressure was 140/85 mm Hg, respiratory rate was 20 breaths/minute, pulse rate 55 beats/minute, and body temperature 36.7℃. Physical examination revealed nothing of particular interest, except for his acute ill-looking appearance. The electrocardiogram (EKG) showed sinus bradycardia and a low voltage of the limb leads. The CBC, biochemical analysis, and CK enzymes were all within normal limits. The chest roentgenogram (CXR), however, showed a mass lesion at the right hilum (Figure 1).

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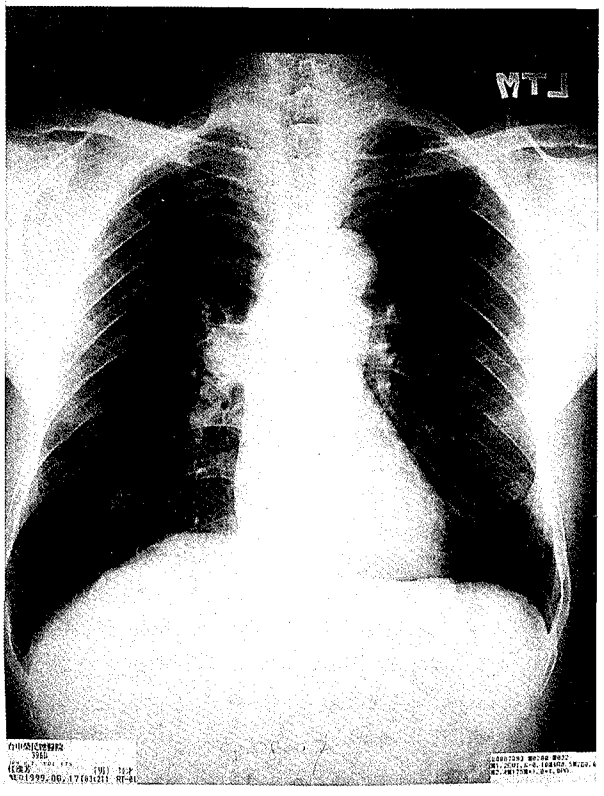

Fig. 1. Chest roentgenogram, anterior posterior view, showing a well-defined nodular lesion in the right hilum with an obtuse angle attaching to the lung parenchyma.

A well-defined soft tissue lesion at the right anterior mediastinum was further demonstrated in the contrast-enhanced chest CT scan (Figure 2).

Thoracic exploration was done under the impression of an anterior mediastinal tumor. Surgical findings were a yellowish, sharply defined mass (3 cm x 3 cm x 3 cm) located inside the upper right lobe, without pleural invasion. A lobectomy of the upper right lobe was done to remove the tumor.

The gross appearance of the surgical specimen showed a well-demarcated mass, 3.5 cm x 2.5 cm x 2 cm in size, with a whitish-yellow cut surface. No necrosis, hemorrhage, nor calcification was found (Figure 3). Histologically, the tumor showed areas of lobular arrangement, and areas of collagen bundles with spindle cells (Figure 4). The lobular microarchitectures were populated by cells having delicate round or oval nuclei, inconspicuous nucleoli, lightly eosinophic

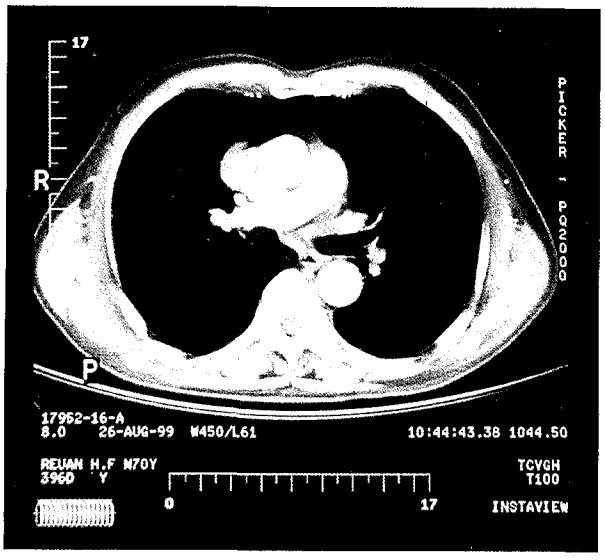

Fig. 2. Contrast-enhanced computed tomographic scan of the chest demonstrating a well-defined soft tissue lesion about 3 cm in diameter in the right anterior mediastinum, abutting the lateral margin of the adjacent ascending aorta and superior vena.

cytoplasma, and indistinct cytoplasmic borders. Some of these cells were in tight whorls with pale nuclear "pseudo-inclusion" consisting of invaginated cytoplasma. Few mitotic figures (less than one mitosis per 50 high-power fields), and no anaplastic change, necrosis, or hemorrhage was seen (Figure 5). Immunostaining also showed a positive reaction for epithelial membrane antigen and vimentin. All of the histological findings were typical for PEM. A post-operative brain CT scan was done, but no intracranial lesion was seen. The patient withstood the surgical intervention well.

Discussion

Meningiomas usually arise in the cranial cavity or spinal canal. Fewer than one in 1000 meningiomas metastasize [5]. A study of 225 sites of metastatic meningiomas in 113 patients revealed the following data regarding location: lungs/pleura, 35%; musculoskeletal, 17%; liver, 13%; lymph nodes/spleen, 11%; kidney, 8%; and other, 16% [9]. Primary extraneuraxial meningiomas were not common.

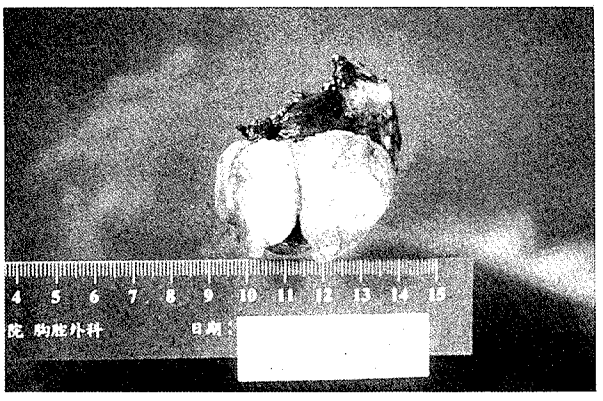

Fig. 3. The gross appearance of the surgical specimen showing a well-demarcated nodule, 3.5 cm x 2.5 cm x 2 cm in size, with a whitish-yellow cut surface, and without necrosis, hemorrhage, or calcification.

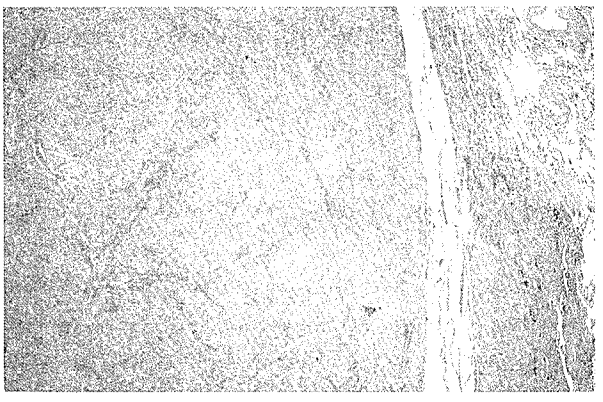

Fig. 4. This picture shows areas of lobular arrangement and a tendency to cellular elongation and streaming (H & E, x 40).

Meningiomas outside of the cranial cavity and spinal canal are rare, according to Hoye *et al*, and can be subdivided into 4 groups: 1), primarily intracranial tumors with direct extracranial growth; 2), those originating from arachnoid cell nests with extracranial growth; 3), extracranial growth without any apparent connection to the cranial foramina or cranial nerves; and 4), extracranial metastasis from intracranial meningiomas [4-6]. Distant metastases usually occur in the lung, pleura, musculoskeletal system, liver, reticuloepithelial system, and the kidney [9], but whorl tumor cells seldom appear in metastatic lesions.

Primary extraneuraxial meningiomas (PEMs) are defined as group 3 in the classification system

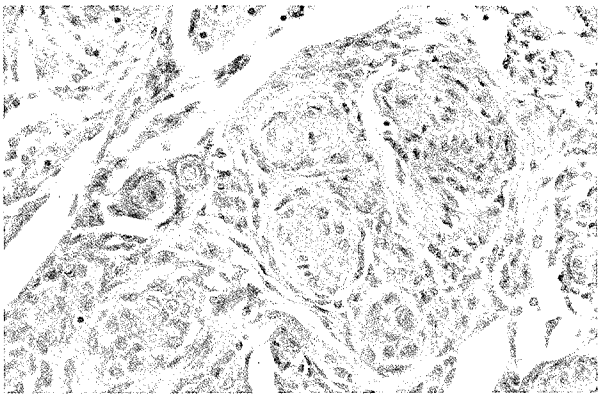

Fig. 5. The cellular whorls' indistinct cytoplasmic boundaries and nuclear clearing are noted. (H & E, x 400).

of Hoye *et al.* Another term, extracranial meningioma, is more familiar but has a limited meaning for our present purpose, since intraspinal meningiomas are also of an extracranial location. Shuangshoti *et al.* studied 504 cases of PEMs from 1962 to 1986 [1], and reported that the female to male ratio of 5:3 is near the 3:2 ratio of all meningiomas. The average age for males with PEMs is 34 years, and 39 years for females. The most frequent locations of the PEMs, in decreasing order of frequency, are as follows: orbit (58%), skin and subcutis (16%), bone (14%), nasal cavity, nasopharynx, and paranasal sinus (11%), lung (1%), mediastinum (0.2%), and adrenal gland (0.2%).

Fewer than 20 cases of primary pulmonary meningiomas have been reported in the past 25 year, and they have occurred more frequently in older women [5].

The majority of the CXR pictures in these cases show a single pulmonary nodule, but only one case presented multiple pulmonary nodules [6]. The histological pictures of those cases were almost benign, except for one which showed malignant change [7]. Wilson *et al* reported a case which had a long-term, gradually enlarging mass in the right lung apex associated with ipsilateral Horner's syndrome [8]. The lesion was found in the pleural space at thoracotomy, and the sympathetic chain was found to have been inverted into a mass. However, no similar case in

the mediastinum has been reported in the past 20 years.

The imaging study in our case incidentally showed a well-defined mass at the right hilum. The patient complained of precordialgia only when he arrived at our hospital. The signs and symptoms of PEM may sometimes be nonspecific. The typical symptoms of meningiomas depend on their location, growth rate, and adherence to the adjacent structures, rather than their histological types. The previous reported cases of primary pulmonary meningioma were also usually found incidentally in routine health examinations or by roentgenograms done for other reasons [5-7].

Kemnitz, Robinson, Chumas and Lorelle, and Erlandson have put forth theories regarding the origin of ectopic pulmonary meningiomas [5]. They are 1), proliferations of arachnoid cells, which give rise to pulmonary chemodectomas from which meningiomas might arise; 2), arising from Schwann cells, which differentiate into meningocytes; 3), arising from fibroblasts, which differentiate into meningocytes; 4), a derivation of pleuropotential or subpleural mesenchyma; and 5), heterotopic arachnoid cell rests within the pleura.

Commonly encountered variants of meningioma in cytological and histological appearances are: 1), meningothelial (syncytial) meningioma: typical meningothelial cells arranged in sheets or lobules; 2), transitional (mixed) meningioma: there may be a pronounced formation of cell whorls and lobules, and psammoma bodies are often identifiable; 3), psammomatous meningioma: almost invariably occuring in the spinal canal; and 4), fibrous (fibroblastic) meningioma: spindle-shaped, usually lacking specific meningothelial features, and arranged into ill-defined fascicles, giving an appearance closely resembling that seen in a schwannoma. In specimens which prove difficult to identify on smear preparations because of the absence of the characteristic meningothelial nuclear morphology, it is worth spending considerable time looking for whorls because, if fond, even one will provide reassurance that meningioma is the correct diagnosis [2]. The typical immuno-profile of meningioma is positive staining for vimentin and EMA and negative for keratin [6-7].

The major differential diagnostic [7] considerations include distinguishing this tumor from sarcomas with epithelioid features, schwannomas, metastatic carcinomas and mesotheliomas, and solitary fibrous tumors. Most of these lesions have distinctive histopathologic, immunohistochemical or ultrastructural features that allow for their distinction from meningiomas.

Based on the clinical symptoms, signs, physical examination, CXR, chest CT scan, surgical findings, surgical pathology, and brain CT scan, we can exclude the possibility of a metastatic meningioma of intraneuraxial origin. We did not perform a MRI scan of the spinal cord to rule out intraspinal meningioma, because spinal meninigiomas occur infrequently and there is almost no distant metastasis if there is no focal neurological deficit. This may be the first case of PEMs of the lung ever reported in Taiwan. Because the case number is so low, we could not determine the typical presentation of this case in the CXR or chest CT scan, and the tumor seemed to be hard to distinguish from other mediastinal lesions.

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原發性肺部腦膜腦瘤

覃俊士　劉杜鎮　江自得　徐中平*　謝品本**　何霖**

有少數的腦膜腦瘤(meningioma)並非源發於中樞神經系統，它們被統稱為原發性神經軸外腦膜腦瘤(primary extraneuraxial meningiomas, PEMs)或者是異位性腦膜腦瘤(ectopic meningioma)。PEMs 經統計約佔所有腦膜腦瘤案例中約 7% 至 10% 左右，其中原發於胸腔(lung, pleura, and mediastinum)者更是罕見。本例報導一位 70 歲男性患者意外由胸部 X 光檢查發現一疑似前縱隔腔腫瘤，經手術病理組織切片證實為罕見之原發性肺部腦膜腦瘤，且為台灣地區首次發現之原發性肺部腦膜腦瘤病例報導。*(胸腔醫學 2001; 16: 244-249)*

關鍵詞：腦膜腦瘤，縱隔腔腫瘤，原發性肺部腦膜腦瘤

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Adult Langerhans Cell Histiocytosis in the Form of Oligo-organic Involvement—A Case Report

Ching-Lih Shyu, Yu-Chin Lee, Ming-Sheng Chern*, Reury-Perng Perng

We herein report the case of a 25-year-old male with a rare disease: Langerhans cell histiocytosis in the form of an oligo-organic (lung and bone) involvement. The patient presented himself to our OPD with a non-specific complaint, and the radiologic findings prompted the suspicion of this diagnosis, which was later proved by open lung biopsy and pathology examinations. Treatment should be tailored to suit the extent of involvement and the clinical activity of the disease. The increased incidence of malignancy in patients with this disease is emphasized in this article, so the patient will be followed regularly and carefully. ***(Thorac Med 2001; 16: 250-255)***

Key words: Langerhans cell histiocytosis, histiocytosis X

Introduction

Langerhans cell histiocytosis is a spectrum of diseases characterized by an inappropriate proliferation and infiltration, into various tissues, of cells that are morphologically and immunologically similar to normal Langerhans cells. With an estimated incidence as low as 0.18/100,000 annually, adult cases comprise about 30% of all those diagnosed as Langerhans cell histiocytosis [1]. The gender preponderance, manifestations, and prognosis of the adult form are different from those of the more common form in children. We report a case of a young male adult with Langerhans cell histiocytosis with lung and bone involvement, presenting with non-specific chest complaints and characteristic image findings, and diagnosed by open lung biopsy and pathology examinations.

Case Report

A 25-year-old male, with a smoking history of 1 pack-per-day for 8 years, suffered from dry cough for 4-5 months prior to admission. He had visited a clinic previously, where pulmonary tuberculosis was suspected and anti-tuberculous drugs had been given for 2 months. Due to the absence of improvement, he came to our OPD, where auscultation revealed normal conditions. No sign of dyspnea was noted at rest or on exertion, and he denied any other systemic diseases, except for a subjective sense of wasting away. The chest X-ray image revealed multiple uneven-sized cystic lesions on the bilateral upper

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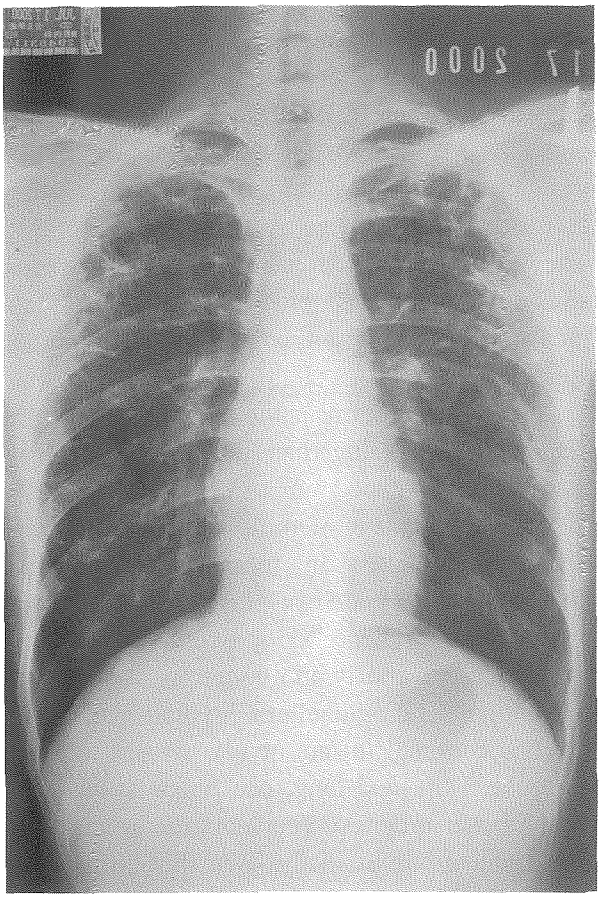

Fig. 1. Chest X-ray image shows multiple cystic lesions in the bilateral upper lung fields, and bony destruction of the left 7th rib.

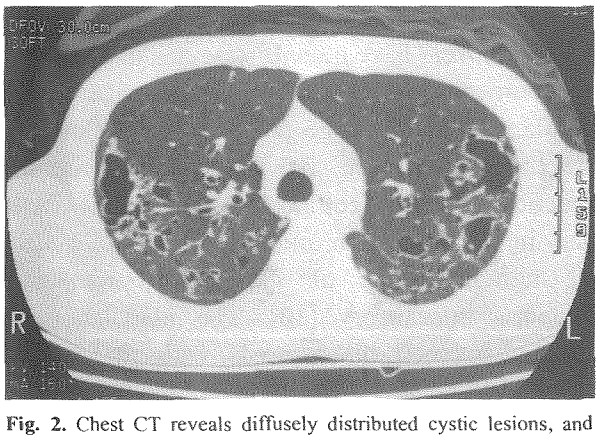

Fig. 2. Chest CT reveals diffusely distributed cystic lesions, and thin-walled cavitary nodules, which are more prominent in the upper lobes.

lung fields, and a cystic bony destruction of the posterior segment of the left 7th rib (Figure 1). This prompted the suspicion of Langerhans cell histiocytosis, and he was then admitted for further study.

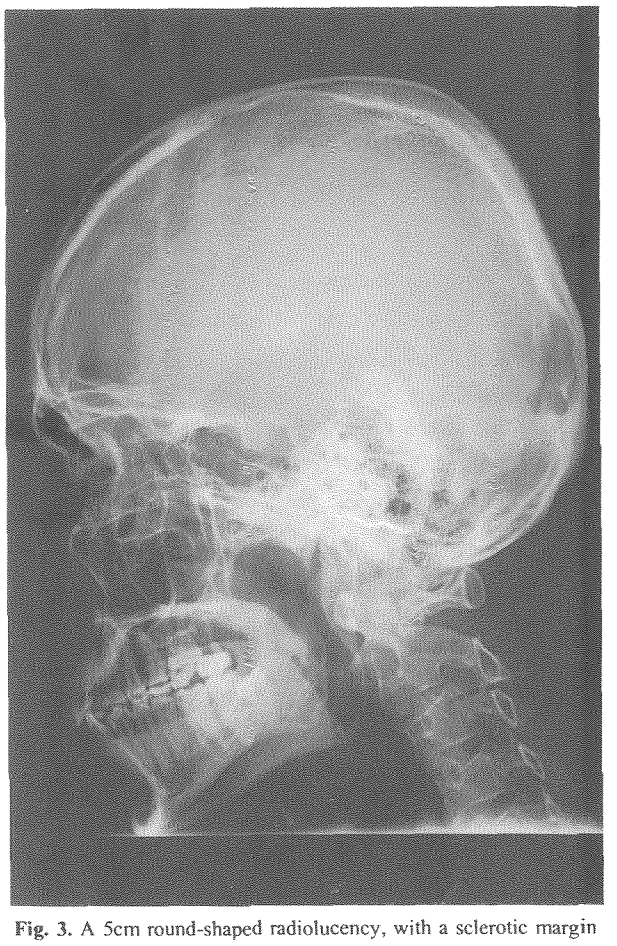

Fig. 3. A 5cm round-shaped radiolucency, with a sclerotic margin in the occipital region.

After admission, a series of exams was done. High resolution computed tomography (HRCT) of the chest showed diffusely distributed cystic lesions and thin-walled cavitary nodules in the bilateral lung fields, which were more prominent in the upper lobes (Figure 2).

Routine X-ray films of the skull revealed an ill-defined round-shaped radiolucency, 5 cm in diameter, with a sclerotic margin at the occipital region (Figure 3). The whole body bone scan showed increased radioactivity at the left 7th rib. A gallium inflammation scan revealed a mildly increased uptake in the upper lobe of the right lung, and a strip of increased radioactivity in the middle left thorax.

The results of the pulmonary function tests were as follows: FEV1=2.71L (70% of predicted);

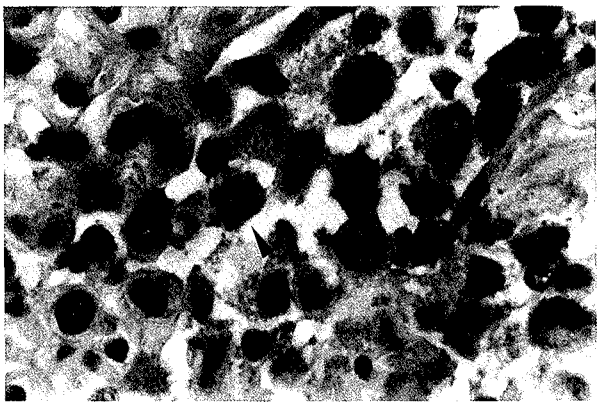

Fig. 4. Histiocytoid cells with characteristic grooved, vesicular nuclei and pale cytoplasm (arrowhead).

FVC=2.74L (61% of predicted); FEV1/FVC= 99%; TLC=4.41L (77% of predicted); RV=1.67L (133% of predicted); and DLCO=19.34mL/min/mmHg (56%), showing a picture of a moderately restrictive ventilatory function, and a moderate reduction of gas exchange.

For the definite diagnosis, the patient received a limited exploratory thoracotomy, and a biopsy was done from the upper right lobe. Pathology reported the following: (1) fibrotic lung tissue infiltrated with chronic inflammatory cells and macrophages; (2) a nodular aggregation of histiocytoid cells with grooved, vesicular nuclei, and pale eosinophilic cytoplasm; (3) the nodules were infiltrated by eosinophils and had undergone cystic degeneration (Figure 4); (4) the immunostain with S-100 protein was positive; and (5) ultrastructurally, rod-shaped Birbeck granules were barely discernible (due to fragmentation) and the membrane structure and a striated core were seen. According to the morphologic features of the lung tissue and the immunostaining, these nodules were diagnosed as Langerhans cell histiocytosis.

Discussion

Langerhans cell histiocytosis was formerly known as histiocytosis X, with the "X" representing a lack of knowledge about its etiology and pathogenesis when this name was first coined by Louis Lichtenstein in 1953 [2]. With the use of modern immunologic and molecular biological techniques, the properties of Langerhans cells are much more clearly understood. They stem from bone marrow, depart, and then enter the circulation, where they constitute 0.1% of the mononuclear cells [3]. They eventually reside in the skin, lung, thymus, and lymph nodes, functioning as antigen-presenting cells, a component of the immune system.

With a uniform pathological finding, the diagnosis of Langerhans cell histiocytosis includes a wide spectrum of disease forms. The diffuse involvement of multiple visceral organs occurs most often in infants, with a poor prognosis (Letterer-Siwe disease). Multifocal involvement of bone, skin, liver, spleen, lung, hypothalamus, and lymph nodes, is usually seen in children (Hand-Schuller-Christian syndrome). Lesions confined to one or two tissues, such as the bone, skin, and lung, can occur at any age, with a better prognosis (eosinophilic granuloma). Adult patients most likely have this form of the disease, with only one or two discrete sites involved [4]. There is no sex preponderence in adult patients, according to updated reports [5].

The etiology seems to be multifactorial. Since smokers have more histiocytes in their lung parenchyma [6], and most of the patients are smokers [7-8], an exogenous origin of the disease has been speculated. An uncontrolled immune reaction, with a component of the cigarette serving as the antigen, might be a possibility [9]. A high incidence of spontaneous remission supports this theory [10]. The association of Langerhans cell histiocytosis with malignancy has been known [11]. Leukemia, lymphoma, myeloma, and solid tumors, including adenocarcinoma of the lung, can occur before or after the diagnosis of Langerhans cell histiocytosis [12-14]. This concurrence may suggest a neoplastic nature [1]. Reports have also indicated a familial coincidence, pointing to a possible genetic predisposition [15].

Clinically, the adult pulmonary disease may

occur in episodes, with a typical episode running for months [4]. In each episode, the process begins with the formation of an infiltration in the bronchioles. These lesions will progress to nodular lesions, which can be seen on the X-ray or high-resolution CT image [16-17]. At this stage, the pulmonary function may be normal, with a mild restrictive change, or with a reduction in the diffusion capacity for carbon monoxide (CO), the most sensitive item of the pulmonary test for this disease [18]. As the bronchiolar destruction becomes prominent, both cystic and nodular lesions may be seen spontaneously on high resolution CT. At this stage, clinical symptoms such as cough and dyspnea exacerbate. When the lesion heals by scarring, cystic lesions of variable size, without nodules, are manifested on high-resolution CT. And at this stage, pulmonary function test may show a pattern of mild airway obstruction with increased residual volume (air trapping) [19]. The disease may then never recur, or may recur with more loss in the pulmonary function. Judging from the pulmonary function test results and image study findings, our patient should have been somewhere between the last 2 stages mentioned.

Extrapulmonary involvement occurs in only a minority of patients with pulmonary Langerhans cell histiocytosis [20], and usually only bone, pituitary glands, or skin are involved. Involvement of the liver, spleen, lymph nodes, or bone marrow is infrequent in adult cases [1]. Extraplumonary lesions can occur earlier or later than those in the lungs [4]. Because the prognosis of Langerhans cell histiocytosis is related to the degree of involvement of the various organs at the time of diagnosis [21], it is important to determine the extent of involvement at that time. The characteristic diagnostic criteria include the finding of aggregates of grooved Langerhans cells in the biopsy specimen, or a positive immunostain for S-100 protein or CD1a. Birbeck granules in the ultrastructure study are the most favored diagnostic finding. In our case, no intact Birbeck granules were detected due to specimen fragmentation, but the morphology in light microscopy and immunostaining was specific enough to meet a practical diagnostic requirement.

Given the great variation in adult Langerhans cell histiocytosis, there has not been a strict guideline for treatment. Classification into a single-system or multiple-system disease is helpful [21]. The single-system disease has a chance of spontaneous remission or stabilization without treatment, so conservative treatment is warranted. For pulmonary victims, smoking cessation is needed, and early treatment of the infection is important, as bronchitis and pneumonia are more common in these patients. Pulmonary lesions with active systemic symptoms or nodular lesions on the chest X-ray image may be treated empirically with oral steroids 0.5-1 mg/kg/d, then tapered off within 6-12 months [22]. This leads to radiologic improvement, but no improvement in the pulmonary function test has been documented. Pneumothorax, most often seen in young adult patients [1], should be treated as usual, while pleurectomy should be avoided in end-stage patients as potential transplantation recipients [22].

For extrapulmonary lesions, involvement of the weight-bearing bones should be treated to prevent fracture and disability, using low-dose radiation or steroid injection. Due to the high rate (one-third) of mortality in multi-organ disease, patients with multifocal bone involvement, soft tissue involvement without organ dysfunction, or with organ dysfunction, should be treated with cytotoxic drugs. The optimal regimen is still under investigation. Treatment candidates are alkylating agents, cytostatics, antimetabolites, and vinka alkaloids [18]. Recurrence has been reported in post-lung transplantation patients.

In our case, the disease seemed to be quiescent, and no diabetes insipitus or skin lesions were noticeable. So, only conservative management was implemented at that time. Smoking cessation was suggested and regular follow-up with X-ray images and pulmonary function tests were arranged. Associated diseases, especially malignancy, warrant

continual awareness, given the body weight loss or wasting-away revealed by patients.

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侵犯少數器官之成人藍格罕士氏細胞組織球症—病例報告

徐青立　李毓芹　陳名聖*　彭瑞鵬

本篇報告一例僅侵犯肺及骨之成人藍格罕士氏細胞組織球症之25歲男性。患者因非特異性之主訴至本院門診，因胸部X光之特徵而被疑有此症，後經開胸切片及病理檢查得到確定診斷。其治療方式當依其侵犯範圍及疾病臨床表現而定。本篇也強調其與較高之癌變發生率相關，後續定期追蹤之處置將做此考慮。*(胸腔醫學2001; 16: 250-255)*

關鍵詞：藍格罕士氏細胞組織球症，組織球症－X

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Malignant Pleural Mesothelioma Appearing as A Bronchogenic Malignancy—A Case Report

Shih-Hsin Hsiao, Horng-Chyuan Lin, Shiu-Feng Huang*, Han-Pin Kuo

A 72-year-old male patient with no obvious asbestos exposure history complained of a nonproductive cough lasting for months, and presented with an unusual upper right lobe mass with a cavity and pleural invasion on the chest radiograph. Fluorescence bronchoscopy revealed a bronchogenic malignancy in the upper right lobe bronchus. An exploratory thoracotomy was performed and demonstrated an upper right lung mass with severe pleural adhesion. An upper right lobectomy and a palliative resection of the right 6th and 7th rib tumors were done. Detailed pathologic studies, including immunohisto-cytochemical staining, proved an extensive malignant mesothelioma with a right main bronchus invasion and lymph node metastasis. This pattern of the clinical and radiographic presentation has seldom been reported, and the fluorescence bronchoscopic finding has never been described as an indication of malignant mesothelioma. ***(Thorac Med 2001; 16: 256-263)***

Key words: malignant mesothelioma, asbestos, fluorescence bronchoscopy

Introduction

Malignant pleural mesothelioma, which occurs in 62% to 85% of patients with occupational asbestos exposure [1], is a rare fatal neoplasm with a rising incidence expected to peak sometime between 2010 and 2020 [2], because of its long latency period of up to 30-40 years and after the application of strict laws on the use of asbestos at the end of 1970s and at the beginning of 1980s. The mean age of patients is approximately 60 years [3]. They usually present with an insidious onset of either chest tightness with progressive chest pain, dyspnea, cough, malaise, or weight loss, and the thoracic radiograph typically demonstrates unilateral pleural effusion with or without ipsilateral pleural thickening or multiple tumors. Theoretically, diagnosis could be achieved by ultrasound-guided pleural biopsy or needle aspiration, thoracotomy, or thoracoscopy. However, up to now, thoracoscopy has provided the most sensitive and specific diagnosis in 95% of the cases. Therefore, thoracoscopy, a good alternative to thoracotomy, is currently the technique of choice for mesothelioma [4]. Generally, the diagnosis of malignant pleural mesothelioma is based on a histological examination in about 80%, on a cytologic examination in 15%, and on other

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forms of examination, e.g. high-resolution computerized tomography, in 6% of the cases [5]. However, the definite diagnosis of malignant pleural methothelioma should be made according to the histopathologic evidence. Furthermore, the differential diagnosis of malignant epithelial mesothelioma and adenocarcinoma metastatic to the serosal membrane is challenging, but now greatly facilitated by the use of the newly developed immunohistochemical markers [6]. The staging of malignant mesothelioma remains a controversial area. Several systems based on TNM staging have been proposed, but have been largely superseded by a new staging system proposed by the International Mesothelioma Interest Group (IMIG) [7], which is awaiting universal acceptance. Malignant mesothelioma is a solid tumor of the mesothelium for which there is no curative treatment, as documented by numerous papers. Treatment is judged by disease staging, but no single therapy such as chemotherapy, radiotherapy, or surgery has proven universally effective. The median survival ranges from 12 to 17 months [8], and 5-yr survival is less than 5%. Recently, multimodal treatments such as extended extrapleural pneumonectomy plus chemotherapy or radiotherapy seem to bring some promise, with a 5-yr survival rate up to 45% in some series [9]. Intrapleural immunotherapies such as TNF-α, interleukin (IL)-12 and gene therapy provide a future therapeutic direction. Herein, we report a case proven to be malignant mesothelioma with an unusual clinical and imaging presentation as well as an atypical bronchoscopic finding--main bronchial invasion, which was easily mistaken as a bronchogenic carcinoma.

Case Report

A 72-year-old male who smoked complained of a nonproductive cough of several months' duration in 2000. He denied any aggravating factor or associated symptoms such as dyspnea, chest pain, hemoptysis, anorexia, fever or body weight loss. Chest radiography (Figure 1) at another hospital showed a mass lesion in the upper right lung, associated with the central cavity, and adjacent infiltration extending to the upper right pleura. Otherwise, there was no tracheal deviation, pleural effusion, lymphadenopathy, or rib destruction. He was transferred to our OPD under the impression of a cavitative upper right lobe mass. Either pulmonary tuberculosis or lung cancer was suspected.

As a schoolteacher for more than 40 years, he had neither occupational nor possible environmental exposure to asbestos. He had no history of pulmonary tuberculosis or asthma. Physical examination revealed decreased breathing sounds in the upper right back, and adequate diaphragmatic movement. No lymphadenopathy or finger-clubbing was observed. The sputum smear

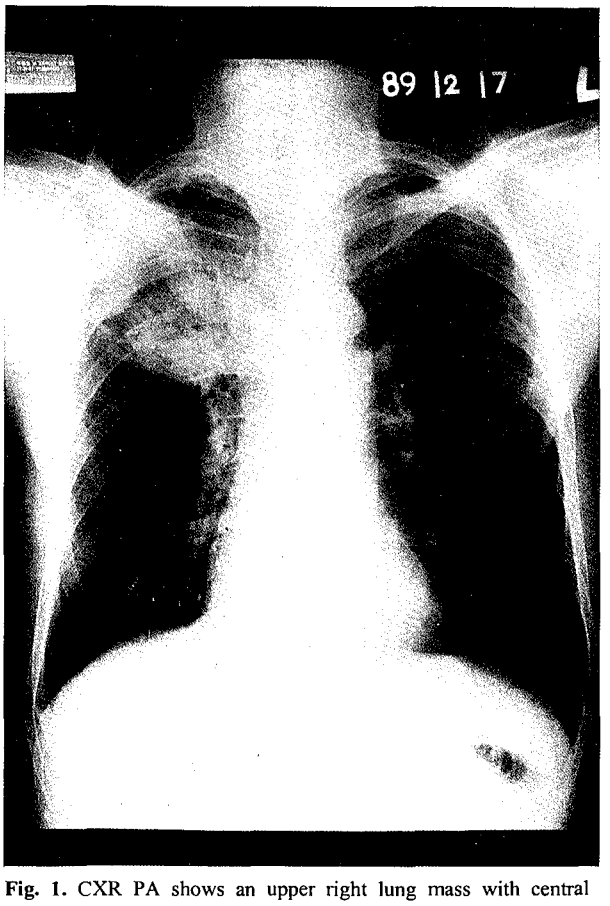

Fig. 1. CXR PA shows an upper right lung mass with central lucency, adjacent infiltration, and localized pleural thickening. No pleural effusion or lymphadenopathy is seen. Either pulmonary tuberculosis or lung cancer is suspected.

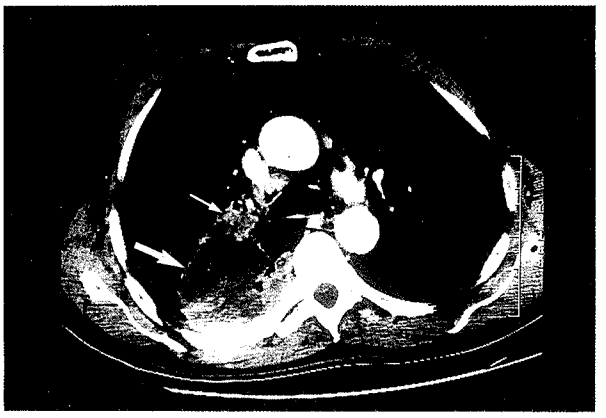

Fig. 2. Enhanced chest CT scan at the level of the main carina demonstrates a 5x7 cm low density mass (long arrow), with adjacent peribronchial infiltration and endobronchial invasion (short arrow) as well as pleural involvement.

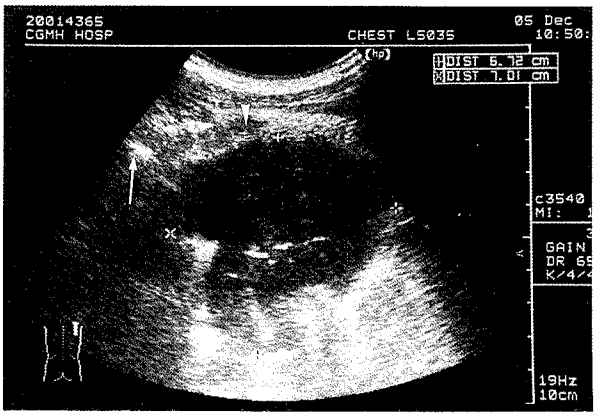

Fig. 4. Chest echo shows a 6.7x7.0 cm mass, containing central necrosis and air-bronchograms, and invading the adjacent pleura (arrow) and muscle layer (arrowhead). Lung or pleural origin can't be confirmed.

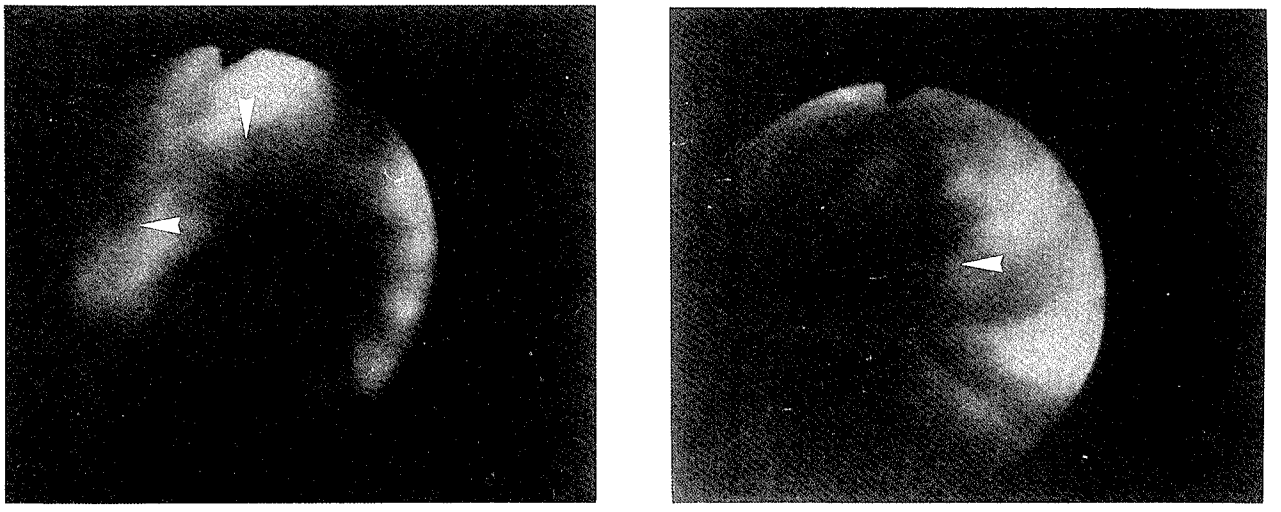

Fig. 3. Fluorescence bronchoscopy illustrates a typically dark brownish to black color change (arrowhead) of the upper right lobe bronchial mucosa. Note the normal mucosa with a greenish color.

disclosed a negative acid-fast stain. Mild normocytic and normochromatic anemia without remarkable etiologies was revealed. The pulmonary function test demonstrated mild airway obstruction (FEV1/FVC: 73%) without response to a bronchodilator. The chest computerized tomography (CT), with and without enhancement (Figure 2), demonstrated an irregular low-density mass on the over right apical-posterior segments, invading both the large bronchi and the posterior pleura.

White light bronchoscopy disclosed patchy hyperemic mucosa with prominent vascularization extending from the entrance of the right main bronchus into the upper and posterior segments of the upper right lobe. The anterior segment of upper right lobe bronchus was obstructed by a protruding tumor with marked submucosal infiltration, which showed a dark brownish to black color change with fluorescence bronchoscopy (Figure 3). The pathology of the two bronchial tissues obtained by bronchial biopsies from the above mentioned mucosa showed no malignancy. Chest ultrasono- graphy revealed a 7 x 6 cm mass, containing central necrosis and air-bronchograms, invading the adjacent pleura and muscle layer (Figure 4). Specimens of echo-guided true-cut biopsy showed bronchial tissue infiltrated by

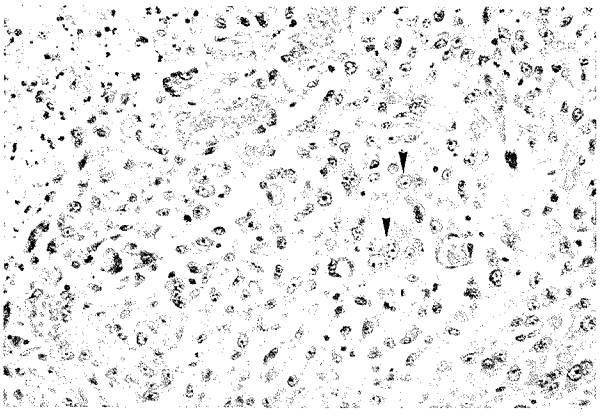

Fig. 5. This section of the echo-guided biopsy specimen shows large polygonal bizarre cells (arrowhead) or large hyperchromatic spindle cells. Adenocarcinoma or malignant mesothelioma can't be differentiated. (H&E stain 200X)

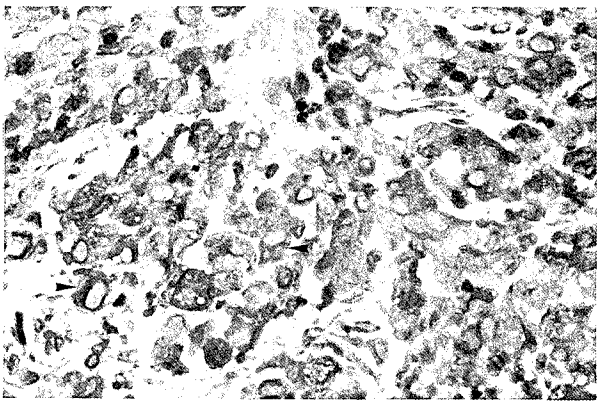

Fig. 6. Strongly positive epithelial immunostaining marker proves malignant mesothelioma. (AE1/AE3 stain 400X)

large anaplastic cells with abundant cytoplasm; no definite epithelial structure was seen (Figure 5). Malignant mesthelioma was diagnosed by special immunohistochemical staining which revealed positive staining for epithelial markers and for mesenchymal markers (Figure 6, 7) and negative for CEA (Figure 8).

Surgical intervention was suggested. A video-assisted thoracotomy was performed and a 7x 9cm mass with central necrosis in the upper right lobe (Figure 9) was seen. An upper right lobectomy with lymph node dissection, bronchoplasty, and palliative resection of the right 6th and 7th rib tumor, as well as extrapleural pneumolysis due to severe pleural adhesion, were performed. The detailed pathologic examination illustrated a malignant pleural mesothelioma with invasion to the right main and upper lobe bronchi, an a large infarct of the upper right lung parenchyma, sixth and seventh ribs. The hilar and paratracheal lymph nodes showed no direct connection to the pleural tumor, and they were metastasized. Local radiation therapy was given latterly at the follow-up visit.

Discussion

Malignant mesothelioma is a rare malignant neoplasm with an incidence of 10-30 per million in males and 2 per million in females in industrialized countries [10], and typically affects individuals occupationally exposed to asbestos. However, insufficient evidence exists of the risk of pleural mesothelioma from non-occupational

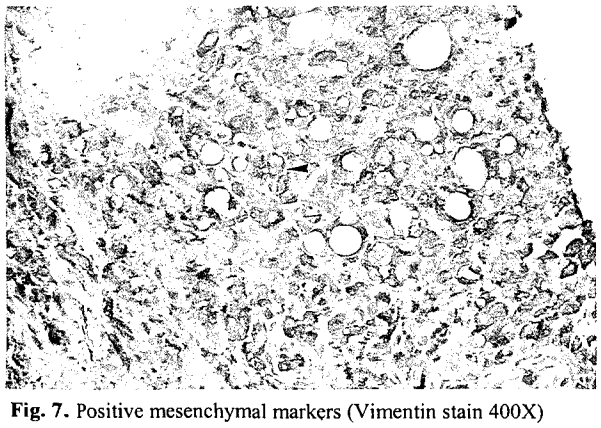

Fig. 7. Positive mesenchymal markers (Vimentin stain 400X)

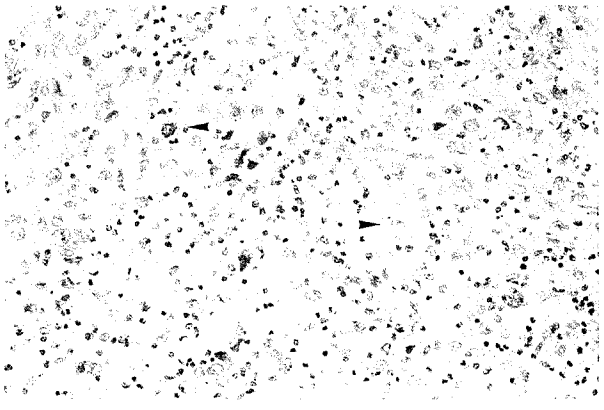

Fig. 8. Malignant cells with positive epithelial and mesenchymal markers show negative CEA staining, consistent with malignant mesothelioma (CEA stain 200X)

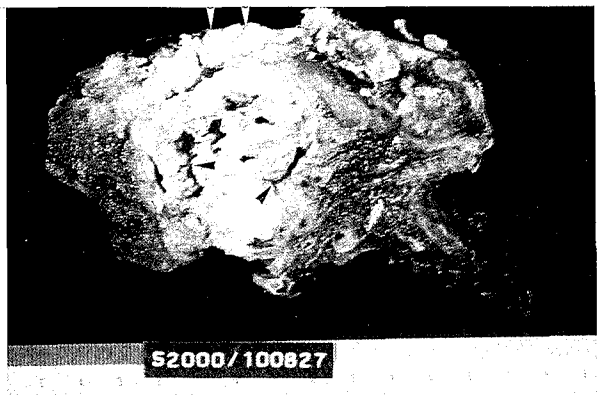

Fig. 9. Gross view of resected URL demonstrates the pleural tumor invading the lung parenchyma (white arrowheads) and bronchi (black arrowheads), forming a thick band-like lung mass.

exposure to asbestos. A population-based case-control study was carried out in six areas of Italy, Spain, and Switzerland. It was suggested that low-dose exposure to asbestos at home or in the general environment carried a measurable risk of malignant pleural mesothelioma [11]. Kumar and Gaur [12] reported a 45-year-old male with malignant pleural mesothelioma without asbestos exposure, which was a rare case. In this case, no obvious asbestos exposure could be noted, suggesting our patient was either one of the rarities, or long term low-dose exposure in the general environment, including home and school, should be considered.

Brenner et al [13] reviewed 123 cases of malignant pleural mesothelioma. With exception of nine patients, the tumor was confined to the chest at the time of diagnosis; in 33 of the remaining 114 patients, a spread to the abdomen or distant metastasis was seen during the course of the disease. Ninety-two percent of malignant pleural mesothelioma patients presented with pleural effusion, 7% with multinodular pleural tumors without fluid, 0.5% with empyema, and 0.5% with pneumothorax on the thoracic radiograph [14]. Presentations such as lung mass or multiple lung nodules have been rarely reported. Herminio et al. [15] published a report of a patient with occupational exposure to asbestos for 35 years, who revealed a left lung mass on the chest X-ray and a well-defined posterior pleura-based tumor on the chest CT scan. However, no evidence of lung parenchyma involvement was confirmed. In our case, a thoracic radiograph revealed an upper right lung mass with cavity-like lucency, and an adjacent ipsilateral pleural tumor without any pleural effusion. An enhanced study of the chest CT scan through the main carina level showed not only a pleural mass, but also an inhomogeneous mass with marked peribronchial infiltration and endobronchial invasion, which was an unusual presentation of malignant pleural mesothelioma. To our knowledge, this is the first case that has been demonstrated to be a malignant pleural mesothelioma associated with lung parenchyma and endobronchial involvement.

In this case, an exploratory thoracotomy was performed and an extensive malignant mesothelioma was diagnosed. At the present time, thoracoscopy is the most sensitive method to obtain lesion tissue for a definite diagnosis of mesothelioma, and is a good alternative to thoracotomy [16]. Because of the difficulties in distinguishing mesothelioma from metastatic adenocarcinoma and reactive pleural inflammation, a thoracoscopy or open lung biopsy is usually required to obtain adequate samples for pathologic evaluation. Thoracoscopy, an essential technique for the early diagnosis of mesothelioma, enables an accurate staging of the tumor involvement, which is an important prognostic finding.

Mesothelioma is a rare disease, but its incidence is rising. Diagnosis is still difficult, but has been improved by immunohistochemical techniques and panels of pathologists[6]. Practically, immunohistochemical studies of epithelial or biphasic tumors should be done with a panel of reagents that has at least four antibodies, including high-molecular weight cytokeratins, CEA, and calretinin, as well as another carcinoma-associated marker. In this patient, the tumor biopsy specimen revealed large anaplastic cells with H&E staining, and the immunohistochemistry staining proved the diagnosis of

malignant mesothelioma with positive Vimentin and AE1/AE3 stains, and a negative CEA stain. Skov BG, et al [17] reported that Vimentin, a monoclonal antibody with specificity against intermediate filament M*r 57,* had a sensitivity of 48.7% and a specificity of 95.6% for malignant mesothelioma. AE1/AE3, a cocktail of monoclonal antibodies for cytokeratins, had a sensitivity of 75.4% and a specificity of 12.8% for the lung adenocarcinoma. Furthermore, CEA had a sensitivity and specificity of 72.5% and 100% for lung adenocarcinomas. In a word, it is suggested that specific immunohistochemical staining should be done for all pleural malignancies order to differentiate the malignant pleural mesothelioma from adenocarcinoma.

Ohishi et al [18] previously reported a case of malignant pleural mesothelioma with contralateral lung metastasis presenting as a reticulonodular shadow on the chest radiograph. However, the specimen obtained by transbronchial lung biopsy was too tiny to make a convincing diagnosis. In addition, their bronchoscopic findings in the tracheobronchial trees were unremarkable. In our case, conventional white light bronchoscopy disclosed the narrowing divisions of the upper right lobe bronchus because of extensive submucosal infiltration and tumor-like protrusion, which could be benign, premalignant or malignant change. Compared with the conventional bronchoscopy, fluorescence bronchoscopy can raise the diagnostic yield of moderate to severe dysplasia and carcinoma in situ from 25% to 67%, and that of invasive bronchogenic malignancy, from 65% to 95%; so we performed fluorescence bronchosocopy which illustrated the the dark brownish to black color changes of those lesions, which were characteristic of premalignant change or carcinoma in situ [19]. Based on this finding, we believed the bronchial mucosa had transformed to moderate or severe dysplasia at least, or even to become malignant. Although the direct bronchial biopsy by bronchoscopy did not provide enough evidence of malignancy, but a further detailed pathology of the resected tumor proved itto be lung and endobronchial metastasis of mesothelioma, which was a unique presentation and has never been described in any published report.

Falconieri et al [20] reported three cases of brain metastases from malignant pleural mesothelioma at autopsy. It was concluded that metastases to the brain from malignant pleural mesothelioma, although rare, are not exceptional, even if their clinical relevance is not prominent. They are seen concomitantly with high-grade tumors. Local and regional tumor spread provides an aid to prognosis, but authentic metastases will further worsen the prognosis [20]. Worn [21] reported a series of 248 surgical cases in which survival was the same after palliative and curative surgery. Probst et al [22] described a series of 111 patients in which the median survival was longer after extended pneumonectomy than after other methods, but the difference was only 1.4 months. In this case, an upper right lobe lobectomy and palliative resection of the 6th and 7th rib tumors were performed. Palliative radiotherapy followed. However, experience with malignant pleural mesothelioma associated with lung parenchyma and endobronchial involvement is so rare that it was difficult to predict the therapeutic outcome and global prognosis of this case by comparing it with previous reports. Long-term follow-up and more cases as reference are needed to reach a conclusion.

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以惡性支氣管性腫瘤為表現之惡性肋膜間皮瘤—病例報告

蕭世欣　林鴻銓　黃秀芬*　郭漢彬

一位缺乏明顯石棉暴露經歷的七十二歲男性病患抱怨乾咳達數月之久，而其胸部X光在右上肺部呈現出一個開洞性腫瘤合併局部肋膜侵犯。透過螢光支氣管鏡可見右上肺葉支氣管處有一個惡性支氣管性腫瘤，而經開胸手術後，切除了右上肺葉腫瘤及被腫瘤侵犯的第六第七肋骨。利用包括免疫組織化學染色法在內的病理組織檢驗，證實這是個不尋常的廣泛性惡性肋膜間皮瘤合併有右主氣管侵犯及淋巴節結轉移。這樣的臨床及X光表現不但極為少見 而其在螢光支氣管鏡的發現更是世界上首見。*(胸腔醫學2001; 16: 256-263)*

關鍵詞：惡性間皮瘤，石棉，螢光支氣管鏡

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Pleural Empyema Following A Silent Cholecystoduodenocolic Fistula—A Case Report

Yeong-Long Hsu, Yuang-Shuang Liaw, Wen-Chih Chiang*

A cholecystoduodenocolic fistula associated with pleural empyema is a rare pulmonary complication. We report a case of a 66-year-old man with fever, right pleural effusion, and common bile duct stones with pneumobilia. The examination of the right pleural effusion revealed an exudate with a high pleural effusion/serum total bilirubin ratio and *E. coli, Bacteroides* and *Candida albicans* in culture. The endoscopic retrograde cholangiogram showed a cholecystoduodenocolic fistula. The right pleural empyema could have been caused by a leakage of pathogens from the gastrointestinal tract through the diaphragm into the pleural cavity. Proper antibiotics treatment with drainage and repair of the digestive organ defects would be mandatory for such a patient. ***(Thorac Med 2001; 16: 264-270)***

Key words: Pleural empyema, Cholecystoduodenocolic fistula

Introduction

Failure to recognize and treat empyema and its underlying disease is generally associated with a poor prognosis [1]. Bilious pleural effusion empyema is a rare complication related to biliary tract abnormalities such as a cholecystopleural, or biliopleural fistula [2-4]. The causes of the fistula include penetrating and non-penetrating traumas [5-6], parasite liver disease [7], and postoperative strictures [3]. The biliopleural fistula is frequently associated with empyema and may adversely affect the success of therapy if it remains undetected or persistent. Subdiaphragmatic infection may extend to the lungs or pleural space by way of lymphatics, directly through the diaphragm or through defects in it, or by way of the blood stream. However, the relationship between pleural empyema and intra-abdominal lesions may be confusing after the communicating lesion has healed. We describe a patient diagnosed as having a cholecystoduodenocolic fistula with an initial presentation of right pleural empyema, whom we treated successfully.

Case report

A 66-year-old man, with no history of abdominal operation, trauma, or gall bladder disease, was admitted to National Taiwan University Hospital due to fever and chest pain for a week. This patient had had occasional right hypochondral discomfort for one year, and developed malaise and a poor appetite two months before admission. Right lower chest pain and dyspnea occurred 8 days before admission. Initially he was treated at a local hospital where

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fever was noticed. His chest radiograph showed a massive pleural effusion on the right side. Thoracentesis yielded a dark brownish- green turbid fluid, with a 7.52 pH, 5.2 g/dl total proteins, 49600/μl WBC count, and 90% polymorphonuclear leukocytes (PMN). He was treated with penicillin, clindamycin, and cefperazone for pleural empyema, and was transferred to our hospital because of persistent fever.

This patient had a 10-year history of essential hypertension and gout. In August 1993, he had an ischemic stroke resulting in mild left hemiparesis. Normocytic anemia was diagnosed in 1994 at our OPD service. However, a bone marrow study revealed normal cellular marrow.

Upon hospital admission, the pertinent physical findings demonstrated a dyspnic man with a blood pressure of 100 /60 mmHg, a pulse rate of 110/min, a respiratory rate of 38/min, and a temperature of 37.9℃. The patient appeared drowsy. The right inferior hemithorax was dull to percussion and no breathing sounds were audible; the heart sound was distant with no friction rub; deep palpation of the abdomen elicited mild tenderness in the right upper quadrant, and no mass was felt.

The initial hemoglobulin value was 7.0 g/dl; the WBC count was 24,460 /μl with 85% PMNS, 9% lymphocytes, and 1% eosinophils. Biochemical tests of the blood revealed the following: total protein, 7.5 g/dl; glucose, 194 g/dI; alkaline phosphatase, 339 U/L; γ- glutamyltransferase, 84 U/L; alanine aminotransferase, 12 U/L; total bilirubin, 0.7 mg/dl; direct bilirubin, 0.4 mg/dl; LDH, 468U/L; blood urea nitrogen, 36.4 mg/dl; and creatinine, 2.2 mg/dl. The arterial blood-gas analysis showed a pH level of 7.367, a $PaCO_2$ value of 46.4 mmHg, a PaO_2 value of 85 mmHg, and HCO_3 of 26 mEq/L (FIO_2 of 44% of the O_2 mask).

Chest radiograph and computed tomography showed a large amount of gas-containing pleural effusion in the right thorax, and a small to moderate amount of pericardial effusion (Figure 1). Chest ultrasonography revealed multiple loculated pleural effusion, and thoracentesis yielded a foul-smelling, turbid, dark-brownish fluid with an LDH of 43000 U/L, a WBC count of 11620 /μl (predominantly neutrophils), and total protein of 4.7 g/dI. The bilirubin of the pleural effusion was 3.8 mg/dl, 2.6 of which was direct. Meanwhile, serum total bilirubin was 0.7 mg/dl and direct bilirubin was 0.4 mg/dI. *E. coli, Bacteroides fragilis, Bacteroides thetaiotaomicron, Bacteroides uniformis*, and *Candida albicans* were isolated from the right pleural effusion simultaneously. *Bacteroides fragilis* was also isolated from the blood. A chest tube was inserted for complex empyema, and antimicrobial therapy with parenteral ceftizoxime, metronidazole, and fluconazole was began. Fibrinolytic therapy with daily 250,000 U streptokinase (Streptase; Hoechst, Uxbridge, UK) dissolved in 100 ml 0.9% saline, administrated through the chest tube and retained in the pleural space for 2 hours after each administration, was given for three days. However, bronchospasms occurred after the second and third doses of streptokinase.

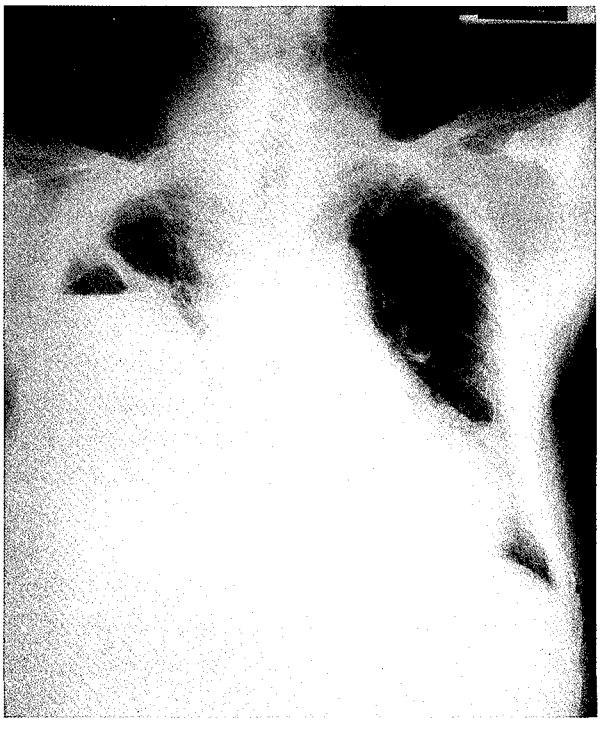

Fig. 1. Chest radiograph showing a large amount of pleural effusion in the right lung, and cardiomegaly.

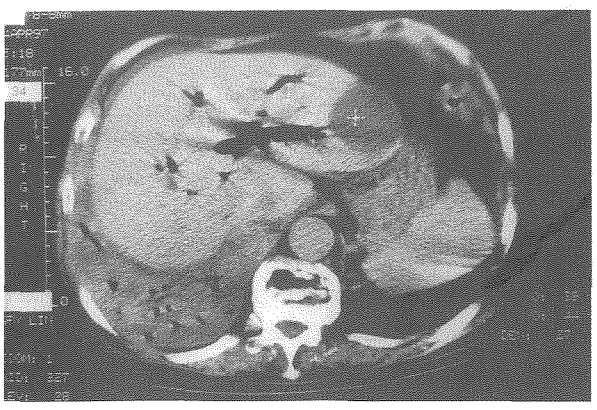

Fig. 2. Abdominal computed tomography revealing pneumobilia and a dilated bile duct. There are some ascites accumulating between the liver and the right diaphragm, and one hepatic cyst is located in the left lobe. Gas-containing pleural effusion in the right hemithorax can be noticed.

Pneumobilia and common bile duct stones were demonstrated by abdominal computed tomography. In addition, a small amount of ascites around the liver, and one hepatic cyst on the left lobe, were noticed (Figure 2). The panendoscopy showed only superficial gastritis without evidence of an esophageal lesion. Endoscopic retrograde cholangiography showed a dilated biliary tree with filling defects in the common bile duct. Although we could not demonstrate that the contrast medium leaked into the pleural space, the injected medium was noted in the proximal transverse colon, soon after appearing in the gall bladder (Figure 3). Therefore, a fistula between the gall bladder and the colon was suspected. He underwent exploratory abdominal surgery 24 days later after hemodyamics were stabilized and the infection was under control. A small contracted gall bladder with some stones was found. The common bile duct also had multiple stones. Some greenish to dark brown fluid had accumulated around the subdiaphragmatic area. Fistulas from the gall bladder to the proximal transverse colon, and to the second portion of the duodenum, were found. Cholecystectomy, fistula resection, and choledocholithotomy with T-tube insertion, were undertaken. Five days later the chest tube was removed without complication. The recovery was

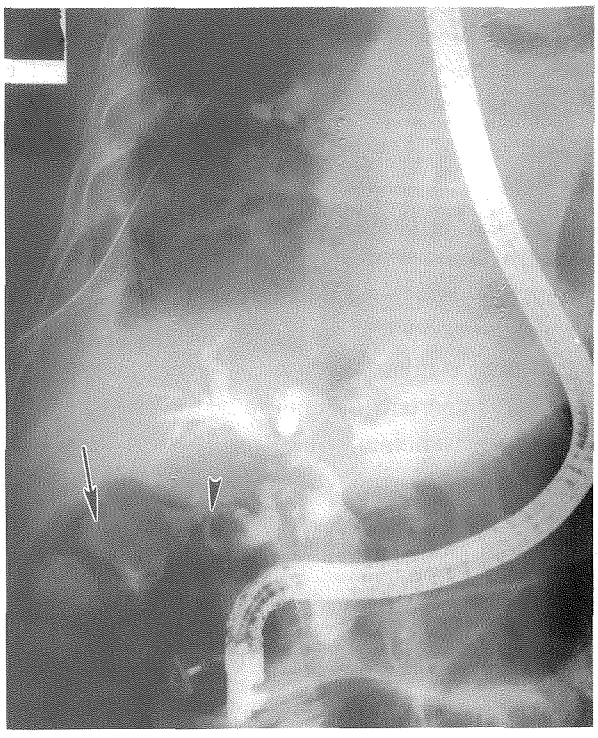

Fig. 3. Endoscopic retrograde cholangiogram showing a dilated common bile duct, the common hepatic duct, and intrahepatic ducts. Several filling defects are noticed in the common bile duct and gallbladder. A leakage of the contrast medium can be seen in the transverse colon (arrow), and appeared soon after the gall bladder was visualized. There is also one suspected fistula tract between the gall bladder and the colon (arrowhead).

uneventful, and the patient was discharged 7 days later.

Discussion

The pleuropulmonary complications of gallbladder disease include pleural effusion, basilar atelectasis, effusions associated with gall stone pancreatitis, and empyema from the perforation of a subhepatic abscess with a fistular formation. The cholecystoduodenocolic fistula is rarely seen and is often associated with cholelithiasis [8]. Its clinical presentations include cholangitis, stone obstruction, and bile acid diarrhea [9]. There has been considerable debate in the past about the pathway of infectious spread from the abdomen to the chest. The transdiaphragmatic spread of infection can occur by means of spontaneous diaphragmatic

perforation, which may not be detected if the size of the perforation is small.

We believe the pleural empyema in our patient was a complication of intra-abdominal sepsis. We had noticed some evidence indicating the correlation between pleural empyema and a biliopleural fistula.

First, the coexistence of bacteria *(E. coli* and *Bacteroides)* and *C. albicans* isolated from the pleural effusion would indicate that there were some possible subdiaphragmatic lesions or communication between the pleural space and the gastrointestinal tract. Although the presence of several pathogens in infected pleural fluid has been frequently seen, mixed aerobic-anaerobic infections are usually related to a subdiaphragmatic process. In our patient, the isolation of four intestinal floras from the pleural fluid is very unusual. In addition, the isolation of *Candida* from the pleural fluid is rare, and is often reported with the presence of a bronchopleural fistula, esophageopleural fistula [10], gastropleural fistula [11], or previous thoracic operation [12]. Since there was no evidence of such a condition in our patient, the entry of bacteria and yeast from a subdiaphragmatic lesion should be considered.

Second, the pleural effusion to serum total bilirubin concentration ratio in our patient indicated the possibility of bile leakage into the pleural space. Meisel et al have reported that most (45 in 46 samples) of the pleural fluid to serum total bilirubin concentration ratio remained below 3, whether the effusion was exudate or transudate. Otherwise, the possibility of bile in the pleural fluid should be considered [13]. Strange et al suggested that the diagnosis of a biliopleural fistula should be suspected if the ratio of total bilirubin levels between the pleural effusion and the serum was greater than 1.0 [3]. In our patient, this ratio was 5.4, indicating the presence of bile in the pleural space.

Third, bile leakage from the biliary tree was suspected because of the greenish color of the ascites in the subdiaphragmatic region. In our patient, gall bladder stones might have caused an inflammatory process and further eroded the wall of the gall bladder, duodenum, and colon. This would result in fistula formation and possible bile or pathogen leakage from the biliary tree or colon. The fistula might heal after days of antibiotic treatment, and might not be noticed during operation.

In determining the pathogenesis of empyema in our patient, a transient biliopleural fistula or a cholecystopleural fistula may have been the possible cause [2,10,14]. It is known that there may be small congenital defects in the diaphragms of some patients [15]. There have also been some reports relating pleural empyema to a subdiaphragmatic infectious lesion, such as an abscess. Based on this, we therefore proposed that the microorganisms from the digestive system and the biliary tree leaked into the peritoneal cavity, through the diaphragm, and then into the pleural space. This possible mechanism of pathogenesis would eventually lead to the empyema in our patient.

Although there was no direct evidence of communication between the pleural space and the digestive organs in our patient, the biochemical and bacteriological data suggested a high probability of a relationship between a cholecystoduodenocolic fistula and the pleural empyema. Early diagnosis with proper drainage, antibiotics therapy, cholecystectomy, and surgical repair of the duodenal and colonic defects would be mandatory for such a patient.

A reconsideration of the presenting signs and symptoms indicated that an early diagnosis was possible and that a diagnosis of empyema should be considered in any patient with a sudden onset of respiratory distress and recent abdominal pain, particularly if there are signs of pleural effusion. We would suggest that all patients presenting with pleural effusion following recent abdominal pain undergo an early pleural aspiration in order to exclude the diagnosis of empyema. We also believe that the presence of empyema following recent abdominal pain suggests the likelihood of intra-abdominal sepsis.

In this situation, the techniques of ultrasound, computed tomography, and ERCP may be helpful in clarifying the diagnosis.

Several studies have suggested that the catheter drainage of the empyema can be improved with the introduction of a fibrinolytic agent into the pleural space [16-18]. Other studies have also revealed that there were no physiologic or statistical differences in clinical coagulation, venous blood prothrombin time, activated partial thromboplastin time, thrombin time, fibrinogen, and D-dimers, between therapeutic and control groups [19]. Our patient received the same dosage of streptokinase as those in previous studies. He had suffered from an ischemic stroke 6 years before this admission, and there was no contraindication for an intrapleural administration of streptokinase. He had no history of penicillin allergy and his penicillin skin test was negative before the fibrinolytic therapy. Although bronchospasms occurred after the second and third doses of streptokinase, they improved after short-acting beta-2 agonist inhalation therapy.

In our review of pulmonary textbooks and the related literature of the past, we failed to find case reports or descriptions of patients with a cholecystoduodenocolic fistula resulting in pleural empyema complications. The presentation of a cholecytoduodenocolic fistula with pleural empyema can be added to the differential diagnosis of pleuropulmonary complications of gallbadder disease.

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膽囊十二指腸結腸廔管合併膿胸—病例報告

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膽囊十二指腸結腸廔管併膿胸在臨床上是一種少見的肺部併發症。我們描述一位66歲男性，因膽囊及總膽管結石合併感染，造成膽囊十二指腸結腸廔管、膽道充氣顯影及發燒、右側肋膜積液入院。右側肋膜積液抽吸檢查發現為滲出液，其肋膜積液與血清之總膽紅素比值偏高且培養長出 *E. coli, Bacteroides* 及 *Candida albicans* 混合感染。內視鏡逆流膽道攝影證實為膽囊十二指腸結腸廔管。我們探討其右側膿胸的原因，認為可能是腸道溢出之病原菌，經由橫膈膜的缺口進入肋膜腔後再併發感染。我們回顧過去的文獻報告並探討其原因與處理方式。 ***(胸腔醫學 2001; 16: 264-270)***

關鍵詞：膿胸，膽囊十二指腸結腸廔管

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Pulmonary Melioidosis—A Case Report

Heng-Ching Huang, Hsin-Chun Lee*, Cheng-Hung Lee*, Chang-Wen Chen*

Melioidosis, caused by the bacterium *Burkholderia pseudomallei*, is a tropical disease. It is a rare but potentially fatal infectious disease in Taiwan. In this article, we report a 52-year-old female diabetic patient with pneumonia caused by *B. pseudomallei*. The patient had never been abroad. The initial presentations included fever, chills, and productive cough. She visited our hospital because of a lack of response to previous antibiotic treatment in a local hospital. The image study in our hospital revealed left upper lobe lesions, and the patient was treated as pulmonary tuberculosis (TB) initially. The antibiotic therapy was later shifted to ciprofloxacin, for lack of evidence of TB. However, her symptoms persisted despite ciprofloxacin treatment. The pneumonia was cured after a 2-month treatment with amoxicillin/clauvulanic acid, and there was no recurrence in the subsequent 3 months' follow-up. This case implicates that pulmonary melioidosis should be included in the differential diagnosis list of community-acquired pneumonia in Taiwan, since the patient had never been abroad. ***(Thorac Med 2001; 16: 271-276)***

Key words: melioidosis, *Burkholderia pseudomallei*.

Introduction

Melioidosis, caused by an aerobic gram-negative bacillus *Burkholderia pseudomallei*, is a glander-like granulomatous infection, found in tropical areas. It was first described by Whitmore and Krishnasuami in 1911 [1]. The major endemic area is between latitudes 20° north and 20° south. Though Southern Taiwan is geographically close to this area, there have been only a few cases reported since 1985 [2-5]. With the import of foreign labors from endemic areas and the finding of indigenous cases in recent years, the potential risk of melioidosis becoming endemic to Taiwan can not be ignored. We report an indigenous case of pulmonary melioidosis diagnosed by a positive bronchoalveolar lavage culture. The patient did not recover until the bacterium was isolated and an effective antibiotic was given.

Case Report

A 52-year-old female farmer with diabetes mellitus (DM) had suffered from high fever, chills, and productive cough for 2 weeks before admission to our hospital. She had visited a local hospital and was admitted under the impression of pneumonia for 10 days. The initial chest

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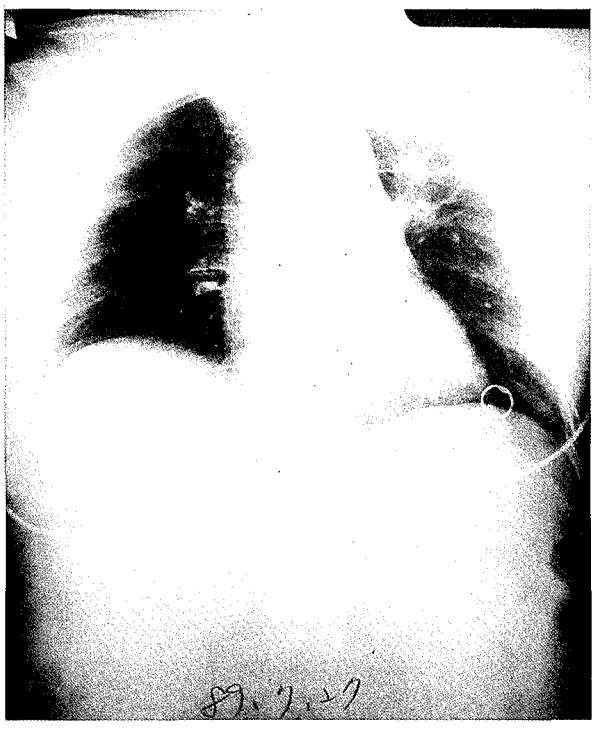

Fig. 1. CXR taken in a local hospital when the patient was initially admitted.

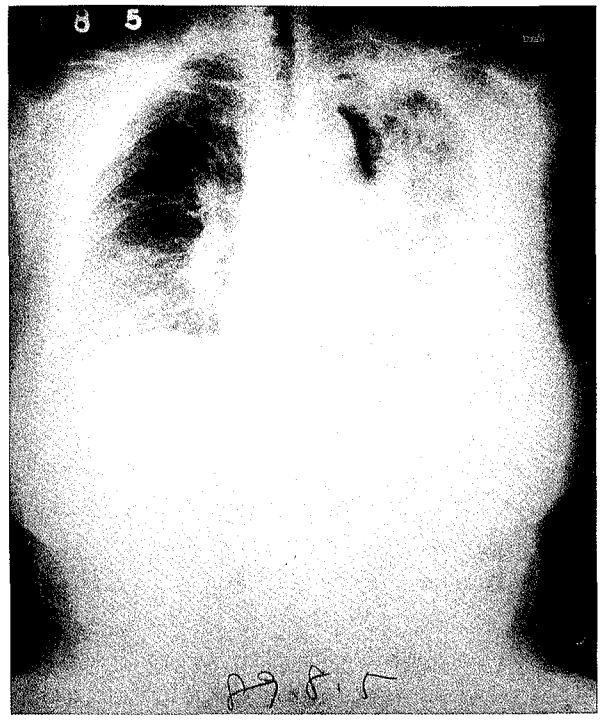

Fig. 2. After one week of hospitalization, the lesion progressed.

radiograph showed a small consolidation patch in the left upper lobe (Figure 1). She visited our hospital because of a lack of response to the previous antibiotic treatment. Upon arrival at our hospital, she remained febrile (body temperature 38.2℃) and her right foot was mildly swollen with local heat and tenderness. The chest radiograph showed the progression of the lesion on the left upper lobe (Figure 2), and the chest computed tomography revealed a cavitary lesion in the posterior segment of the left upper lobe, with multiple patchy nodular lesions in the left lung field (Figure 3,4). The abnormal laboratory data included leukocytosis (WBC 14,100/cmm), a mildly elevated bilirubin level (2.3mg/dl), and a high C-reactive protein value (130mg/l). Antituberculosis therapy, including isoniazide, rifampin, and ethambutol, were given under the suspicion of pulmonary tuberculosis (TB). Pyrizinamide was replaced with an intravenous form of ciprofloxacin, because of a suspicion of gout in this patient. Bronchoalveolar lavage (BAL) was performed one week later for persistent fever, despite the anti-TB drug treatment and negative sputum acid-fast stain. The results of bronchoscopy showed that the bronchial mucosa of the left main bronchus and left upper bronchi were hyperemic. The lavage samples sent for tuberculosis bacilli-polymerase chain reaction (TB-PCR), cytology, cryptococcal antigen, and acid-fast stain were all negative. The anti-TB drugs were stopped for lack of evidence of mycobacterium infection. The ciprofloxacin was continued, and shifted to an oral form (200mg q12h), for the pneumonia. After 12-day's hospitalization, the patient's symptoms lessened and the CXR showed some resolution. At the patient's request, she was discharged with oral ciprofloxacin. One week after discharge, she visited our hospital again because of fever, chills, productive cough and general malaise. The BAL culture during the last admission grew *B. pseudomallei*, which was identified by conventional biochemical methods and confirmed with the API 20NE identification system (BioMerieux Inc, Hazelwood, MO, USA). The minimal

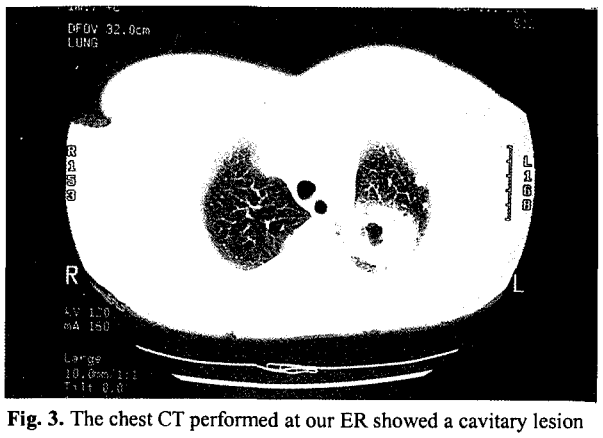

Fig. 3. The chest CT performed at our ER showed a cavitary lesion in the left upper lobe, posterior segment.

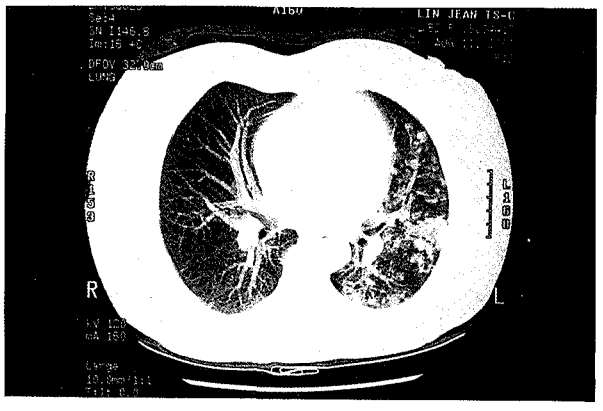

Fig. 4. Multiple patchy nodular lesions in the left lung.

inhibitory concentration (MIC) of amoxicillin/clauvulanic acid was 3 μg/ml using the Etest method (AB Biodisk). Her symptoms completely resolved after treatment with amoxicillin/clauvulanic acid for 2 months, and the CXR became clear (Figure 5). There was no recurrence during the subsequent 3-month follow-up.

Discussion

Melioidosis is a disease caused by *B. pseudomallei*, which is an aerobic, motile, non-spore-forming, gram-negative bacillus, and is widely distributed in water and soil, and on plants, in the tropics. Humans usually acquire this infection by direct contact with contaminated soil or water, or through cutaneous inoculation, and less commonly by the inhalation or ingestion of this organism. Animal-to-human transmission has

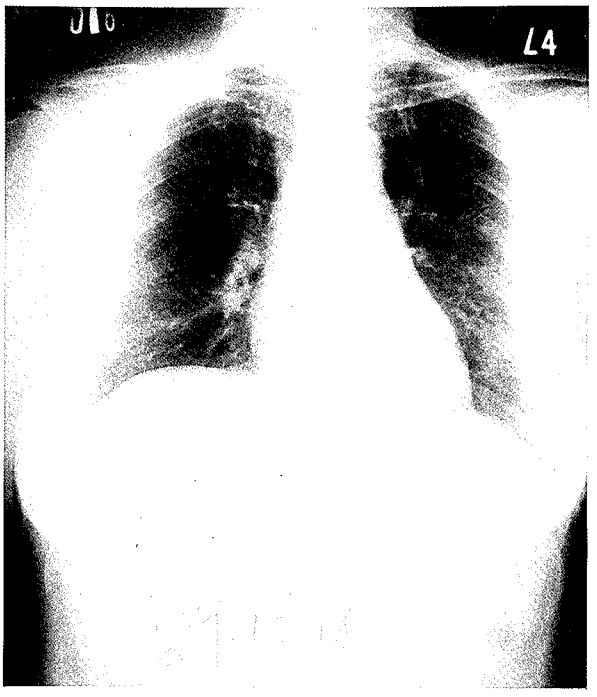

Fig. 5. After 2 more months' treatment, the lesion resolved itself.

been described, but only one case of human-to-human transmission by sexual contact has been reported [6,7]. The disease occurs in all age groups and is found year-round. It has been reported that the incidence is higher in the rainy season [8]. Taiwan is geographically close to the endemic area. However, only a few case reports have been published since 1985 [2-5]. Our patient is a female farmer who has never been abroad. She also denied contact with other patients with melioidosis, and with foreign laborers who might be subclinical carriers. This implies that *B. pseudomallei* may also be present in our soil and water.

Melioidosis has been termed "the great imitator," due to its diverse clinical spectrum. It consists of four forms of disease: acute fulminant septicemia, subacute illness, chronic infection, and subclinical disease [9]. The clinical presentations may be similar to acute or chronic infections caused by other bacteria, mycobacterium, or fungi. Our patient had been misdiagnosed as pulmonary TB. The mortality rate of melioidosis is from 87% for disseminated

septicemia to 9% for localized disease [6]. Melioidosis can remain quiescent for long periods after initial exposure. The longest interval of latency reported has been 26 years [10].

The lung is the most commonly affected organ in melioidosis. It may present in the form of an acute or chronic pneumonitis or as part of the multiorgan dissemination with septicemia [9]. Chest radiographs may reveal consolidation, lung abscess, or nodular densities. Cavitation and pleural effusion can sometimes be found. Disseminated nodular lesions and consolidation are the most common features in acute septicemic form. However, in the subacute and chronic forms, mixed infiltrates with cavities are predominant. The upper lobes are most frequently involved [9,11].

The presumptive diagnosis of melioidosis may be made by serologic testings that are not available in Taiwan [3]. The definitive diagnosis requires bacteriological culture from the blood or other specimens, such as pus, sputum, or bronchoalveolar lavage (as in our patient). The characteristics of *B. pseudomallei* in a specimen culture include: a sweet smell of putrefaction in fresh culture; a wrinkled appearance after incubation for 2 to 3 days; an oxidase-positive, gram-negative bacillus with bipolar or irregular staining; and resistance to aminoglycoside and older generation penicillins and cephalosporins [10]. *B. pseudomalli* may be overlooked or reported simply as "*Pseudomonas* spp." So, clinician awareness and good communication with a microbiologist are important to reach a correct diagnosis. At present, there are some commercial kits that can be used for bacterial identification, such as the API 20NE, Microbact 24E, and Titertek NF systems, enabling laboratories in non-endemic areas to identify and confirm this pathogen [12]. However, one must keep in mind that misidentification due to a premature reading (at 24 hours) has been reported [3].

It is difficult to treat melioidosis, as *B. pseudomallei* is resistant to many antibiotics. The conventional combination therapy of chloramphenical, doxycycline, trimethoprim, and sulfomethoxazole are bacteriostatic and potentially toxic. In vitro data suggests that many newer broad-spectrum β-lactam antibiotics, such as ceftazidime, imipenem, piperacillin, carbenicillin, ampicillin/sulbactam, and ticarcillin/clauvulanate, are effective against *B. pseudomallei*. Quinolone compounds, such as ciprofloxacin and ofloxacin have MIC_{90} values of 4-8 mg/L, which are considered only marginally active against *B. pseudomallei*, and not optimal for the treatment of melioidosis [6,9,13]. The latter should be reserved as third-line agents, and not used for the maintenance treatment of melioidosis, unless there is resistance to or intolerance of the other available antimicrobial compounds [14]. The optimum duration for antibiotic therapy is uncertain. In most reported series, the course of treatment is suggested to be at least 2 months or more. Recently, prolonged treatment for 6 to 12 months has been suggested. Surgical drainage of abscesses, whenever indicated, should be performed, but only after the institution of adequate antibiotic coverage. Our patient's initial treatment failure was possibly due to inappropriate antibiotics. The pneumonia was successfully controlled after an effective antibiotic was used for 2 months. There was no relapse during 3-month follow-up.

In conclusion, with the increase of imported laborers from Southeast Asia, overseas sightseeing in endemic areas, and the reports of domestic cases, melioidosis may become a public health problem in Taiwan. Physicians should include melioidosis in the differential diagnosis list of community-acquired pneumonia in Taiwan, especially in those patients with DM, renal insufficiency, and other immune compromised conditions. Early diagnosis and treatment with a recommended regimen for an adequate duration could significantly decrease the threat of this disease.

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肺類鼻疽——一案例報告

黃恆慶　李欣純*　李政宏*　陳昌文*

類鼻疽是由 *Burkholderia pseudomallei* 所引起的一種熱帶疾病。在台灣很少見，但卻可能造成致命性的感染。我們在此報告一例由 *B. pseudomallei* 引起肺炎的 52 歲糖尿病女性病患。此位病患從未出國。一開始的臨床表現，包括發燒、寒顫、及咳嗽。影像學檢查顯示左上肺葉病變。起初曾被當做肺結核治療，由於無明顯結核感染證據，而改用 ciprofloxacin 治療。但病人症狀仍然持續，直到改用 amoxicillin/clauvulanic acid 治療 2 個月後，病人完全康復。且經三個月後續追蹤，並無復發。由此案例提醒我們，在台灣即使病人並未到過流行地區，也應將肺類鼻疽列入社區感染肺炎的鑑別診斷中。 ***(胸腔醫學 2001; 16: 271-276)***

關鍵詞：類鼻疽，*Burkholderia pseudomallei*

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Malignant Melanoma Presenting as an Endobronchial Pulmonary Mass—A Case Report and Literature Review

Kuo-Hwa Chiang, Jiunn-Min Hsieh, Ching-Nan Lin*

Malignant melanomas in the lung are frequently seen with multiple nodular lesions, and as a complication of cutaneous melanoma. However, solitary endobronchial lesions, either as metastasis or a primary neoplasm, are rarely seen. We report a 26-year-old female who suffered from hemoptysis and chest pain for month. The CXR showed a left lingual collapse and the following bronchoscopy revealed a blackish endobronchial lesion in the LUL bronchus, with nearly total occlusion. pathology with a special stain disclosed malignant melanoma. The patient had no other occult skin lesion, nor did she demonstrate melanoma in other organs at the time of presentation. ***(Thorac Med 2001; 16: 277-281)***

Key words: malignant melanoma, endobronchial lesion, lung collapse

Introduction

Malignant melanoma is the most common fatal neoplasm of the skin. Pulmonary metastases are typically with multiple pulmonary nodules rather than a solitary nodule. [1,2] Solitary metastases are rare, occurring in less than 1% of all cases. A solitary pulmonary melanoma could represent either a metastasis or a primary lung neoplasm. [1,3] Because melanoma frequently metastasizes to the lung, any pulmonary lesion must be assumed to represent metastatic disease until proved otherwise. Both endobronchial and solitary involvement, rather than multiple involvement, are more common in primary pulmonary melanoma, in contrast to melanoma that has metastasized to the lung. [3] However, primary pulmonary melanoma is extremely rare; to establish a melanoma as a primary lesion in the lung during one's lifetime is a very difficult and even impossible task. Herein, we present this interesting case, and briefly review the current literature.

Case Report

A 26-year-old female patient was admitted to our hospital with the chief complaint of hemoptysis and anterior chest pain of one month's duration. She denied any other systemic disease before that. The patient had had no skin lesions excised, and had no prior history of suspicious skin lesions or skin biopsy specimens. No specific past or family history could be traced. Physical examination revealed crackles and diminished breathing sounds in the lower left lung field. No skin lesions could be detected. Complete blood

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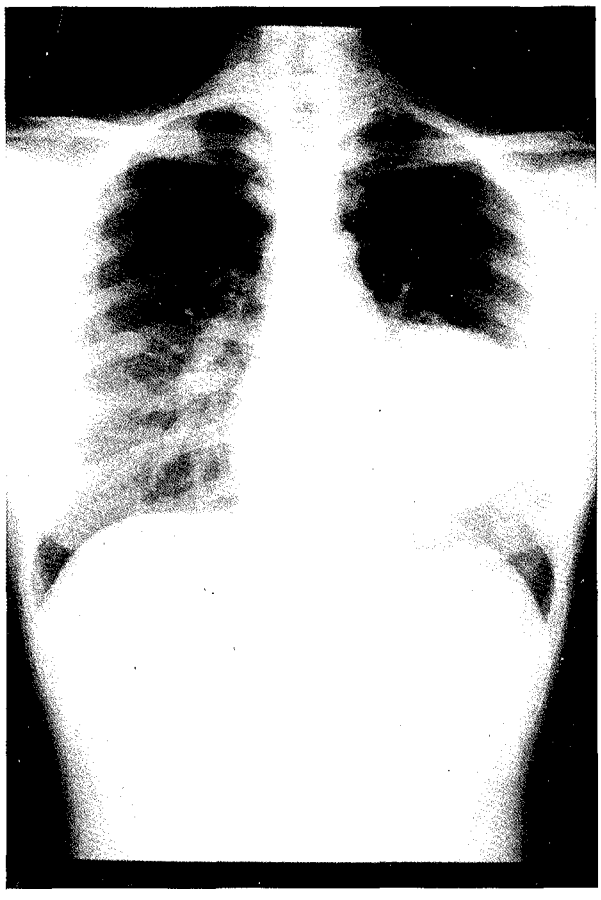

Fig. 1. CXR showing a radio-opaque soft tissue mass over the left lingual with lobar collapse.

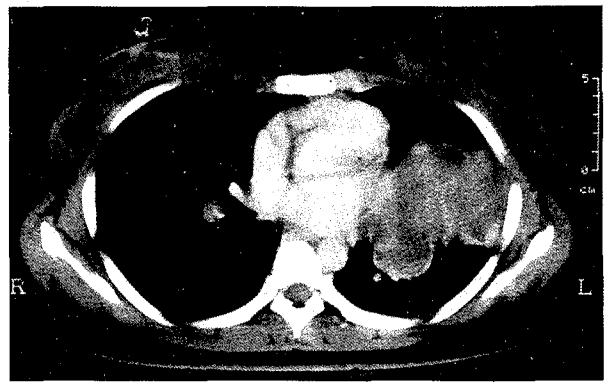

Fig. 2. Chest CT scan showing a soft tissue mass in the lingual division of the upper left lobe bronchus with, occlusion of the bronchus, and no obvious enlarged lymph node within the mediastinum.

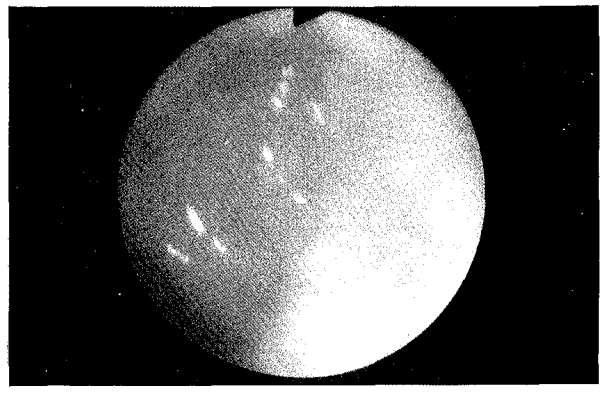

Fig. 3. Bronchoscopic study revealed an endobronchial tumor lesion with a blackish surface appearance on the LUL bronchus, with occlusion.

count and serum biochemistry studies showed no specific findings .The plain chest films revealed soft tissue mass density in the left lingual, with a suspicious lobar collapse. (Figure 1) The chest CT disclosed a non-homogenous soft tissue mass, about 9x8x7cm in size, in the lingual division of the upper left lobe, with occlusion of the associated bronchus, and no obvious enlarged lymph node within the mediastinum. (Figure 2)

Pulmonary function studies showed mildly restrictive ventilatory impairment. The fiberoptic bronchoscopy study revealed a tumor growth with a somewhat polypoid, blackish surface appearance on LUL bronchus, causing a nearly total obliteration of the orifice of the bronchus, such that the scope wouldn't pass through (Figure 3) Brushing cytology revealed clusters or single cells with a high N/C ratio and coarsely granular chromatin, as well as a thick irregular nuclear membrane that was compatible with malignancy. The pathology of the bronchial biopsy demonstrated a nesting of malignant cells beneath the bronchial epithilium (Figure 4), with spindle cells and epithelioid cells in a foamy cytoplasma. Immunohistochemical stains for HMB-45 proteins showed a strong positive staining of the tumor cells (Figure 5), a finding supporting the diagnosis of malignant melanoma. She received a LUL lobectomy at another hospital later.

Discussion

Malignant melanoma is the most common

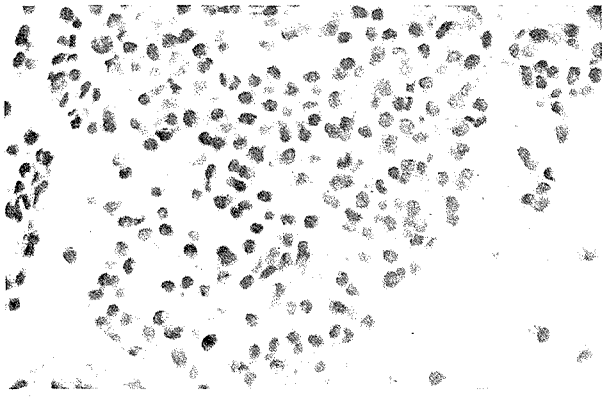

Fig. 4. Bronchial biopsy revealed a nesting of malignant cells beneath the bronchial epithelium, with some spindle and epithelioid cells with foamy cytoplasma. (H&E stain 200*)

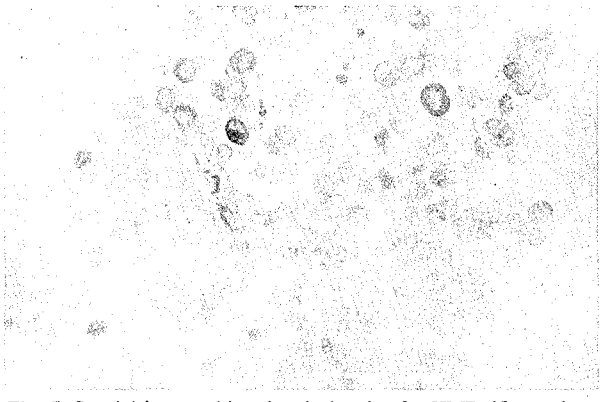

Fig. 5. Special immunohistochemical stains for HMB-45 proteins revealing strong positive staining for tumor cells. (special stain 200*)

fatal neoplasm of the skin. Pulmonary metastases in melanoma are common, but solitary metastases are rare, occurring in less than 1% of the cases. [1-2] A solitary pulmonary melanoma could represent either metastasis or primary lung neoplasm. Melanoma metastasizing to the lung usually consists of multiple bilateral nodules varying between several milliliters and 2.5cm, and favoring the periphery of the lungs. These nodules are most common in areas of high blood flow, especially in the lower lobes. [1-6]

Extracutaneous melanoma is rare, and primary pulmonary melanoma is among the rarest types of melanoma only 20 cases have been previously reported in the literature [3,7-14]. Primary pulmonary melanoma is frequently endobronchial and often manifests itself with the symptoms of cough, hemoptysis, and lobar collapse [3,7-11]. Because primary pulmonary melanoma is so rare, the manifestations, natural history, prognosis, and treatment options are so far poorly defined. Any pulmonary lesion must be assumed to represent metastatic disease until proved otherwise [4-5].

Allen and Drash [7] proposed three histologic criteria to help differentiate primary pulmonary melanoma from metastatic disease. These criteria include junctional change with a nesting of malignant cells beneath the bronchial epithelium, an invasion of the bronchial epithelium in an area without epithelial ulceration, and a demonstration of melanoma beneath the aforementioned described changes. Jensen and Egedorf [8] proposed clinical criteria for the diagnosis of primary pulmonary melanoma, which include no previously removed pigmented skin tumors and no demonstrable melanoma in other organs at the time of surgical resection, no history of excised ocular tumors, a solitary tumor with morphologic features compatible with a primary tumor, and if autopsy is possible, no other primary malignant melanoma that is evident. Some investigators have hypothesized that primary pulmonary melanoma arises in areas of squamous metaplasia [9-10]. A review of the cases of primary pulmonary melanoma favors the hypothesis that this condition arises from residual melanoblasts, which have a common origin with other melanoblasts [7-9].

Common manifestations of primary pulmonary melanoma in the literature and in our patient included cough (50%), hemoptysis (40%), post-obstructive pneumonia (25%), lobar collapse (25%), and an incidental finding on chest radiograpy (30%) [10-14]. Endobronchial disease was more common in patients with primary pulmonary melanoma. The bronchoscopy was able to detect the tumors in some of the patients; the tumor was described as black or pigmented in color in some and appeared as a nonpigmented mass in others. [3,13-14].

The success of resection, and it's long term survival, suggest that an aggressive surgical

approach is warranted. If the tumor is encountered unexpectedly during thoracotomy, a resection of the melanoma may be curative. Lymph node involvement at the time of operation did not preclude long-term survival. The most common sites of lymph node involvement were the hilum and the mediastinum. If the tumor is diagnosed as a solitary pulmonary melanoma before thoracotomy, a thorough search for a primary lesion and other sites of metastatic disease should be conducted before surgical resection. This evaluation should include a thorough ocular examination, skin examination, and search for other mucosal melanomas [3, 14]. If no other sites of metastatic disease are present, an operation should be performed. A complete lobectomy should be done because lesser resections are associated with recurrence [6,12-13]. A complete lymph node dissection is also advisable in light of the fact that approximately half of all patients will have nodal involvement, and some will have prolonged survival. Both endobronchial and lymph node involvement are common in primary pulmonary melanoma, in contrast to melanoma that has metastasized to the lung.

In conclusion, malignant melanoma manifestating with a solitary pulmonary mass is rare, especially when with an endobronchial polypoid lesion is present. This condition is difficult to diagnose without further intervention. Distinguishing often difficult, and even impossible during life. Surgical resection offers the possibility of long-term survival for some patients.

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以支氣管內病灶表現之惡性黑色素瘤—病例報告及文獻回顧

江國華　謝俊民　林靖南*

肺部之惡性黑色素瘤通常以多發之轉移性病灶為常見，以單一肺質塊支氣管內病灶表現者較少見，本篇報告一位 26 歲女性病人，主訴咳血及前胸痛達 1 個月，胸部 X 光片顯示左上肺塌陷，支氣管鏡檢見左上肺支氣管內病灶，病理切片經特殊染色為惡性黑色素瘤，但病人全身上下並無任何皮膚病灶，先前亦無任何皮膚切片之病史。*(胸腔醫學 2001; 16: 277-281)*

關鍵詞：惡性黑色素瘤，支氣管內病灶，肺塌陷

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Pulmonary Lymphangioleiomyomatosis (LAM) with Initial Presentations Mimicking Bronchial Asthma —A Case Report

Kuang-Yu Chen,Meng-Jer Hsieh, Meng-Chih Lin, Ying-Huang Tsai, Thomas C-Y Tsao

Pulmonary lymphagioleiomyomatosis is a rare disease occurring in women of reproductive age, and leads to progressive respiratory failure in spite of treatment. Patients with pulmonary lymphangioleiomyomatosis frequently present with dyspea, chest pain, pneumothorax, or chylous pleural effusion at the time of diagnosis. We report a case of pulmonary lymphangioleiomyomatosis, wich presented with dyspnea, wheezing, airway hyper-responsiveness mimicking bronchial asthma, and a normal chest radiography, but not pneumothorax or chylothorax initially. Diagnosis was made when exertional oxygen desaturation was found during a 6-minute walking test. Typical findings in the high-resolution computerized tomography and histology were also present. ***(Thorac Med 2001; 16: 282-288)***

Key words: lymphangioleiomyomatosis, bronchial asthma

Introduction

Pulmonary lymphangioleiomyomatosis (LAM) is a rare disease of female patients of reproductive age, and presents mostly with progressive dyspnea and non-specific cough. Many of the patients suffer from spontaneous pneumothorax, hemoptysis, chest pain, and occasionally, chylothorax. Pulmonary function tests usually reveal remarkable obstructive ventilatory impairment and decreased diffusion capacity, which might progress to severe airflow limitation and finally respiratory failure. There is no definite relationship between LAM and airway hyperresponsiveness. We report a patient with LAM, with initial presentations of dyspnea, wheezing, airway hyperresponsiveness and normal chest radiography.

Case Presentation

A 46-year-old female visited Chang Gung Memorial Hospital (CGMH) with an initial manifestation of intermittent and progressive dyspnea on exertion. There was no cough, fever, chest pain, or hemoptysis. On physical examination, expiratory wheezing was noted. The spirometry revealed a moderately severe obstructive ventilatory defect with reversibility after using an inhaled bronchodilator. She had a PC_{20} methacholine of 8.7 mg/ml, which was interpreted as a borderline positive result (Tables 1 and 2). The patient was treated under a global standard asthma therapeutic guideline with inhaled budesonide, inhaled

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Table 1. The pulmonary function test which was performed by the patient from the early stage of diagnosis (including serum IgE and CAP level).

Provoation	Positive	$DL_{co}\%_{pred}$	23
PC20	8.7 mg/ml	$Dl_{co}/VA\%_{pred}$	41
IgE	73.8 KU/l	VC $\%_{pred}$	72
CAP	92.1 (*N)	TLC $\%_{pred}$	94
ECP	16.5 ug/l	FRC $\%_{pred}$	101

*N:negative

Table 2. The chages in FEV 1% pred and FVC% from the patient who performed one year before the diagnosis of LAM, four months, ten months and thirteen months after the diagnosis. Most of the FEV 1% pred values revealed mild airflow obstruction except that was recorded after the patient received open lung biopsy.

	A	B	C	D
$FEV_1\%_{pre}$	73	53	61	69.3
FVC%	111	90	72	68.6

A: 1 yr Pre-Dx
B: 4m after Dx (after open lung biopsy)
C: 10m after Dx (after rehabilitation)
D: 13m after Dx (follow-up after rehabilitation)

salmeterol, and oral theophyllin in addition to oral methylprednisolone. Chest radiography at that time revealed no specific finding (Figure 1). The patient still suffered from dyspnea on exertion and intermittent wheezes in spite of steroid and bronchodilator therapy. Follow-up chest radiography one year later revealed a mild diffuse reticular pattern, but neither blunting of the bilateral costo-phrenic angle nor regions of radio-hyperlucency (Figure 2). A 6-minute timed walking test was arranged to determinate the severity, and to differentiate the possible etiology of the dyspnea. Although the patient completed the 6-minute walking test with a total ambulating distance of 399 meters, estimated $\dot{V}O_2$ was 671

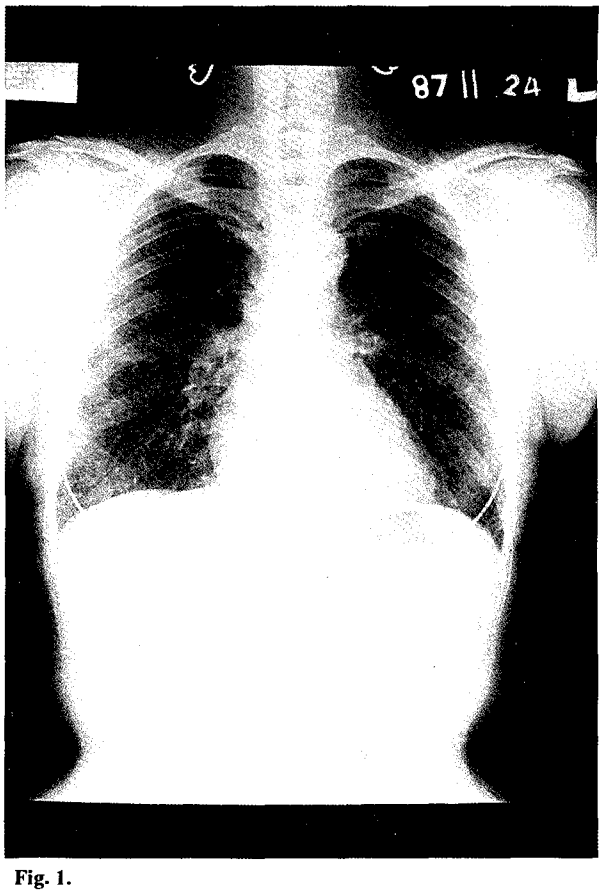

Fig. 1.

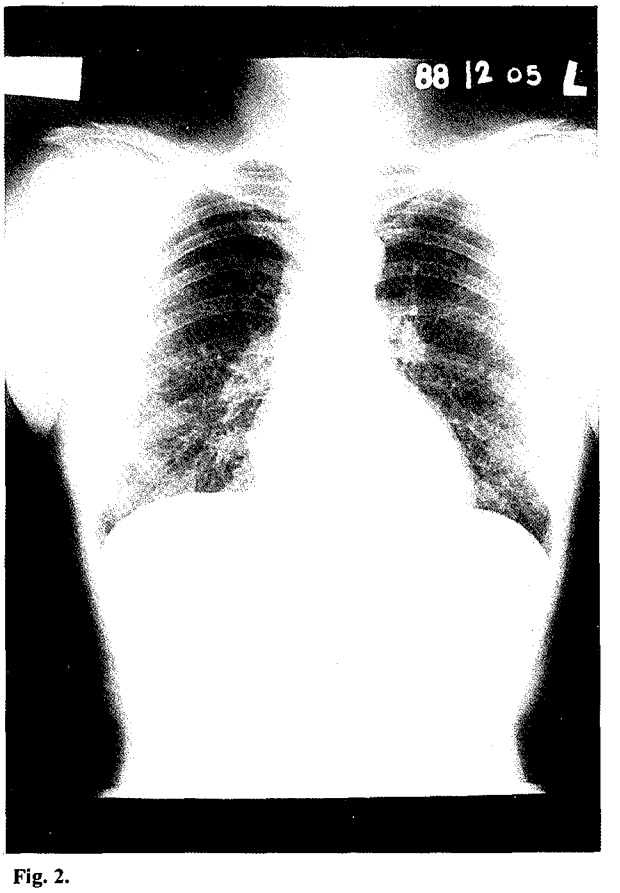

Fig. 2.

Fig. 1. & Fig. 2. The chest X-ray films before and after the pathologic diagnosis were compared. There was only mildly increased infiltration in reticular pattern noted, but the attenuation of the infiltration density was still noted before the diagnosis.

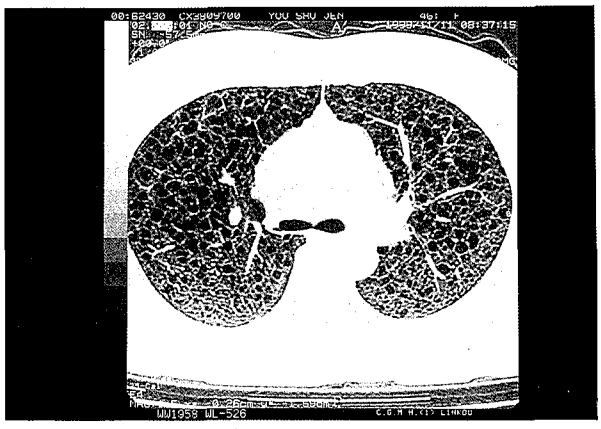

Fig. 3. The computerized tomography revealed diffuse cyst-like lesions with variable sizes of about 1.5cm on the bilateral lung fields, which was highly suspicious for pulmonary lymphangioleiomyomatosis.

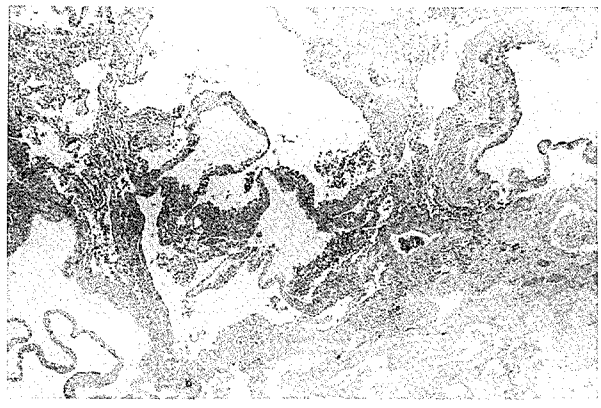

Fig. 4. The pathology revealed a positive staining with HMB-45 antibody stain under 100X light micoscopy

ml/min [1], equaling 48% of predicted $\dot{V}O_{2max}$. The Borg's scale was worse, moving from zero with rest to five at the 6th minute of walking, while the O_2 saturation was noted to be only 77%. This revealed a significant exercise-related oxygen desaturation. Then, a high-resolution computerized tomography (HRCT), was ordered for her because of a high suspicion of an interstitial lung disease. The computerized tomography revealed diffuse cyst-like lesions with variable sizes of about 1.5 cm on the bilateral lung fields, which was highly suspicious for pulmonary lymphangioleiomyomatosis (Figure 3). The patient then received an open lung biopsy in our hospital, with a video-assisted thoracoscopy (VAT) for pathology sampling. The surface of the entire right lung was revealed to be multiply cystic and bulbous. The microstructure of the resected specimen was characterized by increased smooth muscle fibers along the airways, from the small bronchus extending to the respiratory ducts. There were significant cystic dilatations of many terminal airways associated with the smooth muscle proliferation along the cyst wall. A dilated lymphatic was also seen in the interstitium (Figure 4). The alveolar spaces contained abundant hemosiderin-laden macrophages. A marked emphysematous change was found in the subpleural region. Immunochemical staining studies revealed positive results for ACTIN, HMB-45, and DESMIN, focally positive results for PR, but negative for ER. After recovery from the diagnostic surgery, she was recommended to take hormone therapy with a low dose medroxyprogesterone (100 mg daily), and assigned to a pulmonary rehabilitation program. The pulmonary rehabilitation program was designed at the Cardiopulmonary Exercise Laboratory and Rehabilitation Unit of the Department of Pulmonary and Critical Care Medicine in Chung-Gung Memorial Hospital. Based on the results of a previous cardiopulmonary exercise test (CPET), the exercise load for the patient was 60~85% of $\dot{V}O_{2max}$, and 20 to 30 minutes every section. She received 2 to 3 sections every week, and continued for a total of 6 weeks. The patient has been followed-up at the Outpatient Department regularly, and has maintained an active exercise capability without handicap up to the time of this writing.

Discussion

There has been little discussion of the relationship between airway hyperresponsiveness and pulmonary LAM until now. This young female patient had been initially diagnosed and treated as bronchial asthma, with the clinical manifestations of mild to moderately severe airflow obstruction and a positive provocation

test. The patient did not response well to conventional treatment for bronchial asthma, or even the oral and inhaled corticosteroid treatment. Pulmonary LAM was finally diagnosed with the aid of an HRCT and an open lung biopsy after exertional oxygen desaturation was discovered in the 6-minute walking test.

We reported a case of pulmonary LAM in 1992 [2], and the patient has been continuously followed-up for more than 9 years at CGMH. Most patients suffer from severe pulmonary complications on diagnosis and even a life-threatening event while bearing a child. LAM is a rare disease usually presenting clinically with recurrent pneumothorax. Chu SC *et al* have reported the number of mean episodes of pneumothorax to be 5 [3]. Recurrent pneumothorax was present in approximately 41% of the patients in one study [4]. Cough is another common presentation of LAM, and was reported to have a 61% (25/41) occurrence in another study. [5] However, cough is a nonspecific complaint for most patients. Dyspnea has been noted variably, from 46% to 83% of the time [3, 6]. Pleural effusion was found in 30% of the patients, and might be the initial finding or occur at some point during the course of the disease [4]. Less common sym ptoms or signs are chylothorax, hemoptysis, ascites, pericardial effusion, chyloptysis, and chyluria [3]. The chest roentgenogram usually shows a diffuse, lacy, interstitial pattern with occasional Kerley B lines, hyperinflation with cysts and bullae, and frequently, pleural (chylous) effusion [7]. The chest roentgenogram of this patient was interpreted to be non-specific in the first year, when it had only a mild reticulo-cystic pattern without pleural effusion or pneumothroax. The chest roentgenographic findings may be normal or vary according to the disease severity, and in later stages of the disease, it may reveal a more "delicate" appearance than other end-stage diseases, reflecting the absence of significant fibrosis [8]. Although a radiologic study might reveal the characteristic diffuse reticulo-cystic lesions on the HRCT, the differential diagnosis for such lesions have included histiocytosis X, idiopathic pulmonary fibrosis, emphysema, and bronchiectasis [9]. Our patient did not have systemic disease or renal angiomyolipoma, which was found in up to 47% of those affected in one series [10]. Long-term follow-up is still necessary.

The physical examination of this patient revealed bilateral wheezing but no crackles or rhonchi. Crackles and rhonchi were reported to be present in about 10 (22%) and 6 (14%) patients, respectively, in the series of 42 patients by Kitaichi *et al* [5]. There were much earlier manifestations in this reported case, and those symptoms and signs made diagnosis more difficult at this stage without obvious complications. The patient had received spirometry and a methacholine provocation test for airway reversibility, which revealed a borderline positive result for bronchial hyperresponsiveness [7].

DeRemee RA *et al* reviewed the pulmonary function tests of LAM patients, and found the mean total lung capacity to be 87% of predicted value (range, 46% to 150%). For the FEV_1, the mean was 54% of predicted value and the mean diffusion capacity of the lung was 50% of the lower limit of predicted value. [11] Chu SC *et al* has reported that most patients with LAM had a normal pulmonary function test, except for a decrease of DLCO in the initial evaluation. Bronchodilator reversibility had been noted in only 26% of the patients (9/35) in their studies [3]. The patient in this report had been managed as bronchial asthma for more than one year at a local hospital and at clinics, but still suffered from dyspnea on exertion and intermittent wheezes. This alerted us to the importance of performing a further evaluation of exercise capacity, and not only studies of airway hyperresponsiveness. The 6-minute walking test (SMWT) revealed exercise-related oxygen desaturation using a pulse oxymeter at maximal effort. This is a very important clue before the early diagnosis of LAM in a childbearing female who suffers from an intractable reversible obstructive ventilatory

limitation condition.

We performed HRCT with this patient, and the highly characteristic HRCT results did help us make a diagnosis before any complication developed. Although VAT diagnostic tissue sampling by wedge resection was done, recent consensus recommendations have not pointed toward an open lung biopsy but agreed to a HRCT instead. Once the patient underwent a biopsy, the microstructure of the specimen would be very characteristic, but sometimes it would be missing due to insufficient sampling. However, a special smooth muscle actin (SMA) immunostaining, using HMB-45, would be more sensitive and useful [12].

We prescribed pulmonary rehabilitation for this patient using an ergometer for 20 to 30 minutes at 60% to 85% of maximal working capacity 2 or 3 days a week for a total of six weeks. The decline in FEV1% before pulmonary rehabilitation was marked (70% to 53%). Six months after pulmonary exercise training, the FEV1% returned to 61%, and the parameters of $\dot{V}O_{2max}$, A-aDO2, and diffusion capacity had improved significantly. There have been many studies in favor of using pulmonary rehabilitation to improve the overall life quality, transitional dyspnea index (TDI), and functional exercise capacity of patients with chronic obstructive pulmonary disease [13]. The effect on survival was positive but not significant in Ries's study [14]. Clinical improvement in dyspnea sensation, physical exercise, and activity limitation were noted subjectively, and by cardiopulmonary exercise test data. With the aid of HRCT, an early diagnosis before overt clinical complications develop might be achieved in suspected patients. With the assistance of a well-established cardiopulmonary exercise test laboratory that actually reflects the working capacity and $\dot{V}O_{2max}$ condition of the patient, a pulmonary rehabilitation program might contribute significantly to clinical improvement, and have some benefit on long-term medical treatment compliance. The early identification of a LAM patient should be made when considering a characteristic reticulocystic pattern in the chest roentgenogram, a possibly normal or even mildly reticular pattern, limited responsiveness after standard treatment for a moderate-to-severe obstructive ventilatory defect, or a positive or borderline airway hyperresponsiveness in the methacholine test. Childbearing-age females who suffer from exercise incapacity in the 6-minute walking test (SMWT) or the cardiopulmonary exercise test (CPET) and who have limited response to bronchial asthma therapy, should be evaluated for other diseases including pulmonary lymphangioleiomyomatosis.

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肺淋巴血管平滑肌增生症以類似支氣管氣喘表現之一病例報告

陳光裕 謝孟哲 林孟志 蔡熒煌 曹昌堯

肺淋巴血管平滑肌增生症(Lymphangioleiomyomatosis)是一個好發在生殖年齡婦女之罕見病症，往往無論施以各式方法治療卻仍導致漸進性呼吸衰竭。罹患本疾病之患者，經常是以呼吸困難，自發性氣胸，乳糜樣肋膜積水構成診斷。我們在此個案報告一位以呼吸困難和哮喘，呼吸氣道高度敏感性類似支氣管氣喘症狀呈現臨床病症，並且胸部放射檢查並無氣胸發生或是乳糜胸合併發作來呈現其肺淋巴血管平滑肌增生症病症之案例。在病患接受了六分鐘步行運動測驗而表現出明顯運動中氧氣去飽和而獲得診斷。典型的高解析胸部電腦斷層和組織學特徵亦加以說明。 ***(胸腔醫學 2001; 16: 282-288)***

關鍵詞：淋巴血管平滑肌增生症，支氣管氣喘

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Pulmonary Histiocytosis X Presenting as Prolonged Fever—A Case Report and Review of the Literature

Chien-Wen Chen, Chi-Huei Chiang*, Cheng-Ping Yu**, Wann-Cherng Perng, Horng-Chin Yan, Chun-Hu Chen, Kun-Lun Huang, Chin-Pyng Wu

Pulmonary histiocytosis X is an uncommon interstitial lung disease that primarily affects young adults. Patients commonly present symptoms of cough and dyspnea. The diagnosis can be made with confidence when the patient is a young adult with a smoking habit、a classic HRCT pattern and there is a typical histologic appearance. There are of limited value in the treatment of this disorder, but some reports have suggested that positive responses to corticosteroid therapy in the early stage.

Herein, we report a young male without a smoking habit who presented with a persistent high fever of 6 months duration. The diagnosis was made only after the second open lung biopsy, and with diagnostic pathologic confirmation. The response to pulse corticosteroid therapy was dramatic and the clinical outcome was favorable. ***(Thorac Med 2001; 16: 289-296)***

Key words: pulmonary histiocytosis X, HRCT, corticosteroid therapy

Introduction

Pulmonary histiocytosis X is a rare interstitial lung disease. The etiology, true incidence, and prevalence of pulmonary histiocytosis X remain unknown. The synonymies of pulmonary histiocytosis X include eosinophilic granuloma of the lung, pulmonary Langerhans cell histiocytosis, and pulmonary Langerhans cell granulomatosis.

The clinical manifestations of pulmonary histiocytosis X are non-specific. Some patients are asymptomatic, and the disease is identified on a screening chest radiograph. In symptomatic patients, the most common complaints include cough and dyspnea [1-2]. Fever, as well as chest pain, fatigue, and weight loss, is seen less often.

The natural course of pulmonary histiocytosis X is quite variable, difficult to predict, and ranges from spontaneous remission to progressive respiratory insufficiency and death [3]. For symptomatic patients, there are no reliable data concerning the efficacy of various treatment regimens, including corticosteroids and cytotoxic agents on survival [4-5]. However, some investigators suggest that positive responses to corticosteroid therapy can be seen only when

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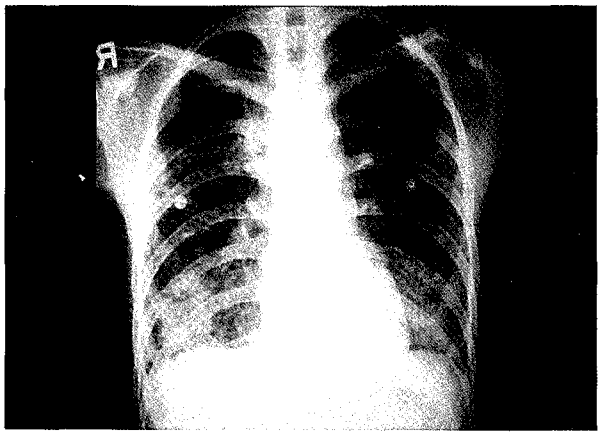

Fig. 1. Chest radiograph demonstrates profuse ill-defined nodules and patch opacities, as well as a reticulonodular appearance predominant in the lower lung zones.

nodular opacities are prominent [6-7].

Case report

A 20-year-old male was referred to our hospital because of persistent fever, productive cough, and bilateral pulmonary infiltration lasting for more than 2 weeks. He had visited the first hospital 9 months before because of fever. The chest radiographs showed reticulonodular infiltration in the left upper lung. An anti-TB regimen was prescribed for 6 months, with clinical and radiological improvement. He then began to experience progressive exertional dyspnea, followed by intermittent fever and a weight loss of 5 kg within 2 weeks, about 2 months before this admission. He returned to that hospital and a mass lesion on the right upper lung was found. He was then transferred to another hospital. The initial workup at the 2nd hospital, including sputum acid fast stain, blood and sputum bacterial culture, and serum tumor markers, revealed negative findings. The spiking fever and extensive bilateral pulmonary infiltration persisted, despite broad spectrum antibiotics treatment. An anti-TB regimen was prescribed again, and he was referred to our hospital because of ineffective treatment.

He denied a history of any other systemic disease. He also denied any smoking habit, substance abuse, or homosexual activities. He had no drug or food allergy history. He had been a worker in a metal grinding factory for two and a half years, but he had had no episodes of asthma or dyspnea. He denied any history of travel or specific allergen exposure during the preceding years.

On admission, the patient was acutely ill-looking, with a high fever (38.9° C), dyspnea (RR 24-28/min), mild pale conjunctiva, and coarse rales in both lung bases. Laboratory tests disclosed severe leukocytosis (white blood cell count: 47,000/mm^3; neutrophil/lymphocyte: 93/5), an increased erythrocyte sedimentation rate (120 mm/hr), and C-reactive protein (13.99 mg/dl); blood gas analysis revealed hypoxemia (PaO_2: 65 mmHg in room air). Other negative laboratory tests included cultures of bacteria and fungus, virus identification, acid fast stain of sputum, PCR for *mycobacterium tuberculosis* and *Pneumocystis carinii*, urine legionella antigen, serum cryptococcus antigen, ANA, ANCA, CEA, and SCC. Radiographs of the chest revealed a diffuse reticulonodular pattern in both lower lung fields (Figure 1). A high-resolution CT scan of the chest showed multiple patches of air-space consolidation, ground-glass opacities in both lungs, and a cavitary nodule in the left upper lobe.

Broad spectrum empiric antibiotics, including Maxipime® (Cefepine), Netromycin® (Netilmicin), and Baktar® (Trimethoprim-sulfamethoxazole), were prescribed after obtaining specimens for blood, sputum, and urine cultures, but failed to control the clinical manifestations. Bone marrow biopsy showed only hypercellularity. Due to the persistent symptoms, an open lung biopsy from the right middle lobe was performed on the 6th hospital day. The pathologic examination revealed evidence of an acute interstitial pneumonitis. Prednisolone 20 mg per day was prescribed, with only a partial response. The productive cough and dyspnea on exertional were alleviated, but not the intermittent high spiking fever.

The subsequent chest radiographs revealed

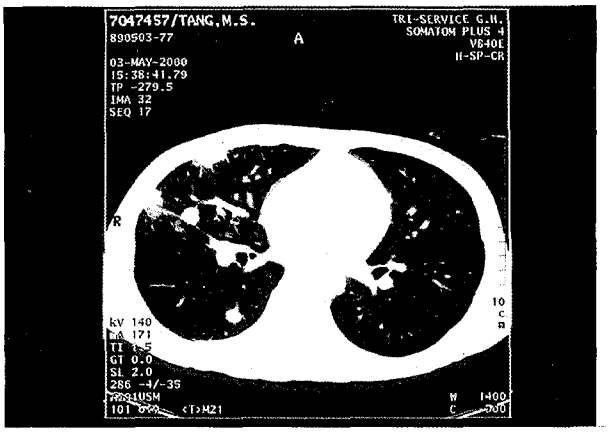

Fig. 2. High resolution CT shows larger solid nodules and pleural-based nodules.

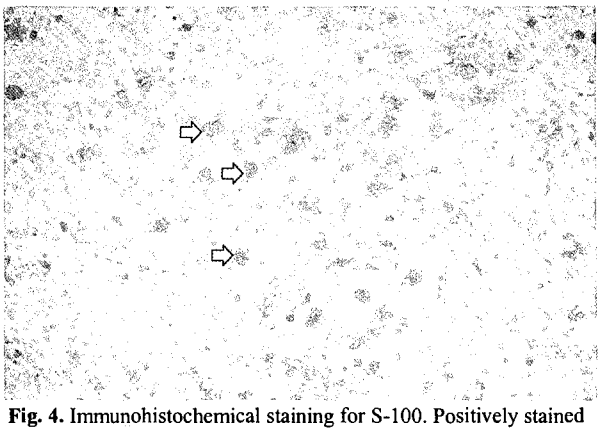

Fig. 4. Immunohistochemical staining for S-100. Positively stained pulmonary histiocytosis X cells (Langerhans cells) are scattered within the nodules. (arrows) (200 X).

disease progression with more newly developed peripheral nodules (Figure 2). The second open lung biopsy of the right lower lobe was performed more than 4 months after admission. The pathology reported a picture of intersitial pneumonitis with nodules formation composed of many histiocytic cells and various inflammatory cells. The histiocytic cells were medium to large in size, and had pale convoluted nuclei with small- to medium-sized nucleoli in hematoxylin- and eosin-stained sections (Figure 3). These histiocytic cells were positive for S-100 protein (Figure 4), but negative for lysozyme immuno-histochemically. Based on the histopathologic and immunohistochemical findings, pulmonary histiocytosis X was diagnosed. Pulse therapy with parenteral Solumedrol® (Methylprednisolone) 500mg per day was given for 3 days, followed by a maintenance dose of prednisolone at 15 mg/day. The fever subsided completely, the clinical symptoms improved, and the abnormal findings on the chest radiograph resolved themselves significantly. The prednisolone was tapered off gradually during the following 4 months. The patient was well and regularly followed at our OPD for one year. There was no further episode of fever and the chest radiograph showed only a mild fibrotic scar. The pulmonary function test just before discharge showed a mild restrictive ventilatory impairment (TLC: 70.5% of the predicted value). The patient keeps up good daily activity, and has been able to go back to work.

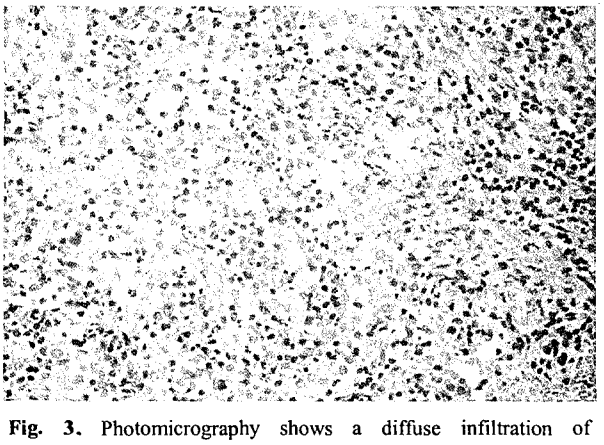

Fig. 3. Photomicrography shows a diffuse infiltration of histiocytes, lymphocytes, plasma cells, and neutrophils, which are adjacent to the dense fibrotic area. (H & E stain 200 X)

During the course of the present illness, disseminated intravascular coagulation and deep vein thrombosis in the left lower limb occurred, and was properly treated. A repeated bone marrow biopsy disclosed evidence of increased hemophagocytic cells.

In summary, we report a young male who denied smoking and presented with a high spiking fever of 6 months duration, with a body weight loss of more than 10 kgs. The diagnosis was not made until after a repeated open lung biopsy. The response to pulse corticosteroid therapy was dramatic, and the clinical outcome was favorable.

Discussion

Histiocytosis X generally refers to a spectrum of three diseases: eosinophilic granuloma, Hand-Schuller-Christian disease, and Letterer-Siwe disease. These diseases are characterized by the abnormal clonal proliferation of a unique type of cell in the monocyte-macrophage cell lineage known as the Langerhans cell. Histiocytosis X may infiltrate many tissues, including the skin, lymph node, bone, bone marrow, lung, liver, spleen, brain, and kidney. Two clinical forms of lung involvement of histiocytosis are seen: lung involvement as part of the generalized disease, and as a separate entity known as primary pulmonary histiocytosis X. These two forms are indistinguishable pathologically [8].

Pulmonary histiocytosis X is a rare disease. Gaensler and colleagues found that only 3.4% of 502 patients underwent open lung biopsy for chronic diffuse infiltrative lung disease [9]. Most cases are found in young adults (20 to 40 years of age), and current data suggest an equal gender distribution. There is no familial tendency. Cigarette smoking is reported in over 90% of patients, which may be important in the pathogenesis of pulmonary histiocytosis X, but the precise mechanisms remain unknown [1, 10, 11].

Many pulmonary histiocytosis X patients are asymptomatic, but progressive dyspnea may occur. Basset and colleagues reviewed 78 cases in 1978 [3], and found that patients presented in 5 ways, including chance discovery by chest radiograph in asymptomatic persons, pneumothorax, cough and dyspnea, constitutional symptoms, especially fever and weight loss, and in follow-up chest radiography in cases of known disseminated histiocytosis X. Travis and colleagues reviewed 48 cases in 1993 [1], and reported that the most common symptoms were cough (58%), dyspnea (48%), chills/fever (17%), weight loss (15%), and chest pain (10%). Crausman and colleagues [2] recently reported 23 cases in which dyspnea (87%) and cough (70%) were the most common presenting symptoms, followed by fatigue and weight loss (30%), pneumothorax (17%), hemoptysis (13%), and chest pain (9%). However, in these literatures, a prolonged fever has never been mentioned as the major symptom of pulmonary histiocytosis X.

The most common radiographic abnormalities are reticular, nodular, reticulonodular, and cystic lesions, often in combination. Rarely, alveolar opacities may occur [3, 12-14]. Characteristic ill-defined or stellate nodules, ranging from 2 to 10 mm in diameter, can usually be found. The interstitial infiltration is usually bilateral and diffuse, with upper- and mid-lung zones predominanting, and costophrenic angles sparing; lung volumes are usually normal or increased; pleural effusion and mediastinal or hilar lymphadenopathy are unusual. The chest HRCT scan is a very useful diagnostic tool for pulmonary histiocytosis X. The small and large cysts, micronodules, and cavitated nodules are better detected than chest radiographs [14]. Brauner and colleagues [12] reported in 18 patients that on HRCT, thin-walled cysts were usually found (n=17). The other abnormalities included nodules (n=14), cavitated nodules (n=3), thick-walled cysts (n=7), reticulation (n=4), ground-glass opacities (n=4), and irregular interfaces (n=4). Serial chest CT scan patterns, progressing from nodules to cavitated nodules, and thick-walled cysts to cysts to confluent cysts were typical of patients in the early and late stages of the disease [12, 15]. In our case, there was an unusual presentation with air-space consolidation, micronodules, and larger nodules, but no typical cystic lesions were found. Early-stage pulmonary histiocytosis X should be considered in these radiographic patterns.

Patients with pulmonary histiocytosis X usually present with either a normal or predominantly restrictive pulmonary physiology. The earliest abnormality is disproportionately reduced in diffusing capacity [2-5]. Exercise

impairment is common and appears to reflect pulmonary vascular dysfunction, which presents with reduced diffusing capacity and elevated resting and exercise dead space to tidal volume ratio (V_D/V_T) [2,16].

The need for confirmation of the diagnosis of pulmonary histiocytosis X by lung biopsy has been questioned, due to the discovery of a variety of techniques, including HRCT and the identification of Langerhans cells in bronchoalveolar lavage (BAL) fluid or sputum, Langerhans cell differential counts of >5% in BAL fluid have been suggested as criteria for the diagnosis [1,17]. Although these alternative techniques may strongly suggest the diagnosis, pathologic confirmation by transbronchial biopsy or open lung biopsy is still the most definite way to establish the diagnosis. The pathologic differential diagnosis includes idiopathic pulmonary fibrosis, eosinophilic pneumonia, reactive eosinophilic pleuritis, and desquamative intersitital pneumonia [1,3]. Langerhans cells can be recognized by the demonstration of Birbeck granules (X-bodies) by electron microscope (EM), or immunohistochemical staining with antibodies to OKT-1 (CD1) or S-100 protein. However, these techniques are not necessary unless lesions are only suggestive, rather than diagnostic, using light microscopy [1, 18-21]. Our patient was diagnosed after repeated open lung biopsy, and confirmed by typical histopathalogic findings and immunohistochemical stain. The reason for a non-diagnosis in the first open lung biopsy might be because infection or an inflammation reaction was more favored then, the radiographic patterns were atypical, and there was inadequate sampling from the consolidation area in the middle lobe.

The natural history of pulmonary histiocytosis X is variable. Spontaneous resolution occurs in 25% of the cases, stabilization with a mild loss in pulmonary function occurs in 50%, and progressive disease in 25%. Death from respiratory failure or cor pulmonale occurs in approximately 5% [22]. Factors leading to a poor prognosis include older age with disseminated disease, functional airflow obstruction (lower FEV_1/FVC ratio and higher RV/TLC ratio), and radiographic evidence of honeycombing, especially associated with repeated pneumothorax [3, 11, 13]. Extrapulmonary manifestations such as diabetes insipidus and cystic bone lesions may occur [1, 11]. A number of malignant and nonmalignant tumors have been found in association with pulmonary histiocytosis X. These include bronchogenic carcinoma (about 5% of the patients), Hodgkin's and non-Hodgkin's lymphoma, pulmonary carcinoid tumor, and mediastinal ganglioneuroma [23-26]. There was no pneumothorax, extrapulmonary involvement such as diabetic insipidus, significant bone pain, or fracture found in our patient. The tumor survey, including tumor markers, repeated bone marrow biopsy, abdominal sonogram, and chest HRCT scan, showed negative results. Our patient presented with disseminated intravascular coagulation and deep vein thrombosis, which may be related to an infectious process and his being bed-ridden in the early stage of admission, but we didn't find any correlation between pulmonary histiocytosis X and these abnormalities in our literature review.

In patients who do not display prominent signs and symptoms, treatment should be discrete, because spontaneous remissions may occur. Von Essen and colleagues presented a case with a subsequent resolution of all roentgenographic changes after smoking cessation [27]. If the patients display the relevant signs and symptoms, progressive X-ray changes, and decreasing pulmonary function, several studies have reported success with of corticosteroids combined or not with cytotoxic agents [3-6, 28-29]. Loddenkemper suggested that early corticosteroid therapy seems to prevent progression to the fibrotic-bullous end-stage [6]. Schonfeld and colleagues showed that 85% of patients with radiographic evidence of progressive disease improved after the administration of corticosteroids [4]. However, none of these studies have reported the effectiveness of such treatments on survival and on the long-term course of the disease. Lung

transplantation should be considered in patients with advanced, progressive disease; unfortunately, recurrence of the condition in the transplanted lung may occur [10, 22, 30].

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肺組織細胞症X以持續發燒作為表現——一病例報告及文獻回顧

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肺組織細胞症 X 是一種罕見的間質性肺病，常影響年輕成人病患。最常見的臨床症狀為咳嗽及呼吸困難。此病的確定診斷有幾種方法，包括年輕成人有抽煙習性且胸部高解析度電腦斷層呈現典型之異常發現，或病理切片發現典型之組織細胞變化。此病之藥物治療效果有限，但數篇文獻指出，在疾病早期以類固醇治療會有良好療效。我們報告一位 20 歲男性病患，無抽煙習慣，以持續高燒達六個月作為臨床表現。在開胸切片檢查確定診斷後，給予脈衝式靜注類固醇治療，發現有顯著療效，其臨床症狀亦呈現明顯進步。*(胸腔醫學 2001; 16: 289-296)*

關鍵詞：肺組織細胞症X，胸部高解析度電腦斷層，類固醇治療

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