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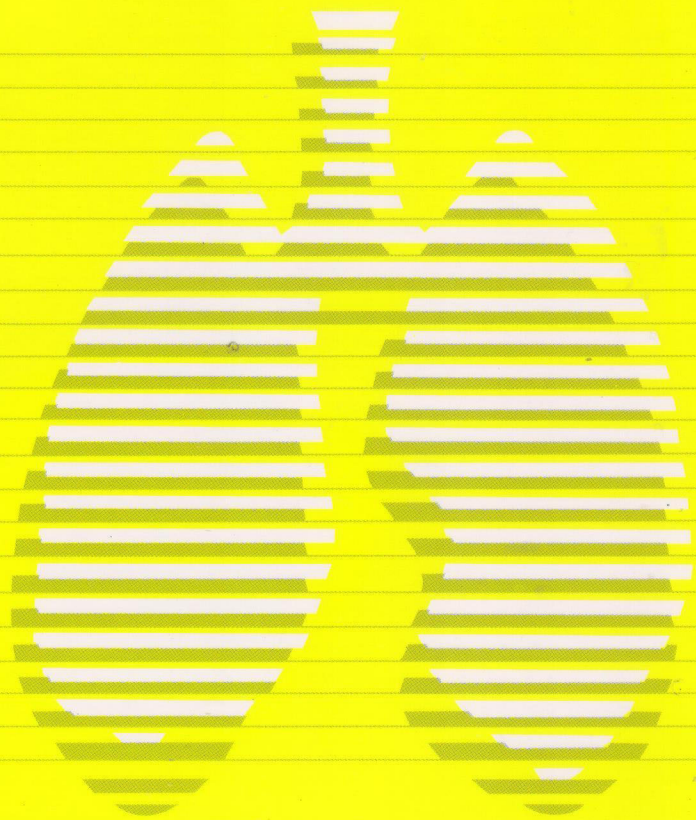

台灣胸腔暨重症加護醫學會

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原著

病例報告

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Orginial Articles

Case Reports

Chemotherapy-Induced Neutropenia as a Predictor of Survival in Patients with Advanced Non-Small Cell Lung Cancer

Chin-Shui Yeh, Cheng-Hsiung Chen, Bin-Chuan Ji, Ching-Hsiung Lin

Introduction: Neutropenia during chemotherapy was reported to be associated with the increased survival of patients with advanced non-small-cell lung cancer. No available data for Asian patients has been analyzed.

Methods: The baseline patient characteristics, overall survival and length of stay in the hospital of 130 advanced non-small cell lung cancer patients treated with chemotherapy were retrospectively compared between patients without neutropenia of grade 0 (n=65), with mild neutropenia, grade I/II (n=41) and those with severe neutropenia, grade III/IV (n=24).

Results: The median overall survival was 3.0, 9.6 and 9.9 months for the grade 0, grade I/II, and grade III/IV patient groups, respectively. Survival was significantly shorter in patients with grade 0 than in patients with grade I/II (p=0.0019) and grade III/IV (p=0.0488) neutropenia, and was similar between patients with grade I/II and grade III/IV (p=0.710) neutropenia. The hazard ratios for death were 0.507 for grade I/II vs. 0 (95% CI 0.317-0.813) and 0.559 for grade III/IV vs. 0 (95% CI 0.320-0.976). Grade I/II, grade III/IV chemotherapy-induced neutropenia, gender and tumor stage were independent factors in multivariate analysis for overall survival. The patients mean cumulative length of stay in the hospital from their initial chemotherapy to the time of death was 34, 35, 39 and 37 days for those with grade 0, grade I/II, grade III/IV and grade I to IV neutropenia, respectively, without a statistically significant difference.

Conclusions: Survival was superior in advanced non-small-cell lung cancer patients with mild or severe chemotherapy-induced neutropenia. ***(Thorac Med 2010; 25: 110-118)***

Key words: chemotherapy, neutropenia, non-small cell lung cancer

Introduction

Lung cancer became the first and second leading cause of cancer-related death in women and men, respectively, during the last decade in Taiwan [1]. The number of deaths related to lung malignancy has been increasing steadily. Systemic chemotherapy was recommended in patients with advanced non-small cell lung cancer (NSCLC) to prolong survival and improve the quality of life, as compared with the best supportive care alone [2].

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Systemic chemotherapy probably suppresses the hematopoietic system, impairing the host protective mechanism. The hematologic toxicity of myelosuppressive chemotherapy may result in neutropenia. Myelosuppression continues to represent the major dose-limiting toxicity of cancer chemotherapy, resulting in morbidity and mortality along with frequent reductions in chemotherapy dose intensity, which may compromise disease control and survival [3, 5]. Neutropenic complications associated with myelosuppressive chemotherapy are a significant cause of morbidity and mortality, possibly compromising treatment outcomes, and leading to excess healthcare costs [5]. In addition, chemotherapy-induced neutropenia has an impact on the quality of life and increases the physical and psychological symptom burden of patients [4, 6].

Neutropenia is a decrease in circulating neutrophils in the peripheral blood. The risk of bacterial infection is related to both the severity and duration of neutropenia. A study of breast cancer has shown that neutropenia during adjuvant chemotherapy is associated with favorable distant disease-free survival, and may be a useful biological marker for chemotherapy efficacy [7]. An analysis demonstrated that patients with chemotherapy-induced neutropenia were associated with a survival advantage in ovarian cancer [8]. Another study suggested that the occurrence of neutropenia during chemotherapy is an independent predictor of increased survival in patients with advanced gastric cancer [9]. Contrary results in another study indicated that neutropenia during adjuvant chemotherapy for breast cancer is not a predictor of outcome [10]. A very limited number of studies have reported on the correlation of neutropenia and clinical outcome in NSCLC patients. A multivariate analysis of patients with advanced NSCLC revealed that both mild and severe chemotherapy-induced neutropenia were independent factors associated with a better time to tumor progression and overall survival [11]. A pooled analysis of 3 randomized trials has also shown that neutropenia during chemotherapy is associated with increased survival of patients with advanced NSCLC, and its absence might be a result of underdosing [12].

The aim of the present study was to investigate the association between chemotherapy-induced neutropenia and the clinical outcome of patients with advanced NSCLC in Taiwan.

Patients and Methods

Patients

We retrospectively selected all NSCLC patients who were diagnosed between 2006 and 2007 in Changhua Christian Hospital, a medical center in Taiwan. All patients underwent standardized TNM staging. Clinical stage was assessed based on the physical examination, computed tomography (CT) scans of the chest, CT scans or magnetic resonance imaging (MRI) of the brain, and bone scintigraphy.

Patients with NSCLC at advanced stage IIIA, IIIB and IV and who had received chemotherapy were eligible. Patients were excluded if they had undergone a surgical operation or radiotherapy only, without chemotherapy, or monotherapy with EGFR tyrosine kinase inhibitor. Overall survival was assessed as the duration from the time of first chemotherapy administration to death, or to the last information on the vital status as of Feb. 2009. Cumulative length of stay (LOS) indicated the days of hospitalization for all causes, from the initial chemotherapy to the death of the patient.

Assessment of neutropenia

A complete blood count with differential count had to be performed before chemotherapy. Patients with chemotherapy-induced neutropenia were assessed and graded by the investigator, using the Common Toxicity Criteria of the National Cancer Institute, version 3.0 [13]. We divided the patients into 3 groups, based on the worst neutropenia grade: absent (grade 0), mild (grade I/II), and severe (grade III/IV).

Statistical analysis

Overall survival was the primary measure of the analysis. Survival was defined as the duration from the time of first chemotherapy administration to death, or to the last information on the vital status. To compare the baseline characteristics of the patients, we used Pearson's χ^2-test for categorical variables. The Mann-Whitney test was used for comparison of the continuous variables. The survival curve was derived using the Kaplan-Meier method. Differences in survival data between groups were assessed with the Wilcoxon test and log-rank test. Hazard ratios of death and 95% CI were estimated with Cox's proportional model. The comparison of concurrent chemoradiotherapy (CCR) with each neutropenia group was performed with Fisher's exact test. A *P*-value of <0.05 was regarded as statistically significant.

Results

A total of 323 lung cancer patients were diagnosed between 2006 and 2007 at Changhua Christian Hospital. Among them, 130 patients with advanced NSCLC who had received chemotherapy were eligible, including 61 patients with adenocarcinoma, 47 with squamous cell carcinoma, and 22 with other histologic types. Most patients were male (71.5%). Of these advanced NSCLC patients, 13 were with stage IIIA, 30 stage IIIB, and 87 stage IV. Grade 0, grade I/II, and grade III/IV neutropenia was observed in 65, 41 and 24 patients, respectively.

There was no significant difference between the patients with chemotherapy-induced neutropenia and those without in terms of age, gender, performance status, histologic subtypes or regimens of chemotherapy. Of the patients receiving chemotherapy, 75 were treated with gemcitabine plus cisplatin (G+C), 52 with docetaxel plus cisplatin/carboplastin (T+C), and 9 with pemetrexed or vinorelbine. Among them, 6 patients received more than 1 kind of regimen for chemotherapy. There was no significant difference between the regimens in terms of inducing neutropenia among grade 0 vs. grade I/II (p=0.525), and grade 0 vs. grade III/IV (p=0.736) (Table 1).

In comparing the TNM stage with the neutropenia grade, the patients with stage IIIA/IIIB lung cancer were more prone to developing grade I/II neutropenia than those with stage IV (p=0.029). Of the 130 patients who received chemotherapy, 39 had undergone radiotherapy, 15 surgery and 5 both radiotherapy and surgery. Nine patients received sequential chemoradiotherapy and 30 received CCR. Neutropenia developed in 11 of 30 patients (36.7%) that received CCR and 5 of 9 (55.6%) that received sequential radiotherapy. Fisher's exact test indicated that CCR had no significant effect on the development of neutropenia in NSCLC patients (p=0.286 for grade I/II, p=0.718 for grade III/IV) (Table 1).

The median survival was 3.0, 9.6 and 9.9 months for the grade 0, grade I/II, and grade III/IV groups, respectively (Table 2). Kaplan-Meier survival analysis showed significantly

Table 1. Patient characteristics according to worst neutropenia grade

	Grade 0 (n=65)	Grade I/II (n=41)		Grade III/IV (n=24)	
	No.(%)	No.(%)	*p*-Value*	No.(%)	*p*-Value*
Age(years) Median(range)	70 (45-90)	65 (29-89)	0.357	68 (43-86)	0.771
Gender					
Male	48 (73.8%)	30 (73.2%)	0.939	15 (62.5%)	0.296
Female	17 (26.2%)	11 (26.8%)		9 (37.5%)	
Performance Status					
0, 1	55 (84.6%)	37 (90.2%)	0.405	21 (87.5%)	0.732
≥ 2	10 (15.4%)	4 (9.8%)		3 (12.5%)	
Histology					
Adeno Ca	25 (38.5%)	20 (48.8%)	0.559	16 (66.7%)	0.057
Squamous	28 (43.1%)	14 (34.1%)		5 (20.8%)	
others	12 (18.4%)	7 (17.1%)		3 (12.5%)	
Stage					
IIIA	7 (10.8%)	5 (12.2%)	0.029	1 (4.2%)	0.509
IIIB	11 (16.9%)	16 (39.0%)		3 (12.5%)	
IV	47 (72.3%)	20 (48.8%)		20 (83.3%)	
Chemotherapy					
G+C	38 (54.3%)	25 (61.0%)	0.525	12 (50.0%)	0.736
T+C	29 (41.4%)	13 (31.7%)		10 (41.7%)	
others	3 (4.3%)	3 (7.3%)		2 (8.3%)	
Radiotherapy					
Sequential	4 (17.4%)	4 (33.3%)	0.286	1 (25.0%)	0.718
CCR	19 (82.6%)	8 (67.7%)		3 (75.0%)	

* Vs. Grade 0. Adeno Ca, adenocarcinoma; Squamous, squamous cell carcinoma; G+C, Gemcitabine and cisplatin; T+C, Docetaxel and cisplatin/carboplatin; CCR, concurrent chemoradiotherapy.

shorter survival in patients with grade 0 than in patients with grade I/II (log rank test p=0.0019), grade III/IV (log rank test p=0.0488) or grade I to IV neutropenia (log rank test p=0.0009). Survival was similar between patients with grade I/II and grade III/IV neutropenia (p=0.710). The Kaplan-Meier survival curves are presented in Figures 1 and 2.

Multivariate analysis showed that grade I/II and grade III/IV chemotherapy-induced neutropenia, gender, and tumor stage were significant prognostic factors (Table 3). The hazard ratios of death were 0.507 (95% CI 0.317-0.813) for grade I/II vs. 0, and 0.559 (95% CI 0.320-0.976) for grade III/IV vs. 0. Both were statistically significant.

The patients' mean cumulative LOS in the hospital from their initial chemotherapy to the time of death was 34, 35, 39 and 37 days in patients with grade 0, grade I/II, grade III/IV and grade I to IV neutropenia, respectively. There was no significant difference in grade 0 vs. grade

Table 2. Over all survival according to neutropenia grade

	0 (n=65)	I/II (n=41)	III/IV (n=24)	I/IV (n=65)
Median survival (months)	3.0	9.6	9.9	9.7
95% CI	2.08-3.92	7.48-11.72	7.50-12.30	8.44-10.96
Log rank test p*		0.0019	0.0488	0.0009

* Vs. Grade 0

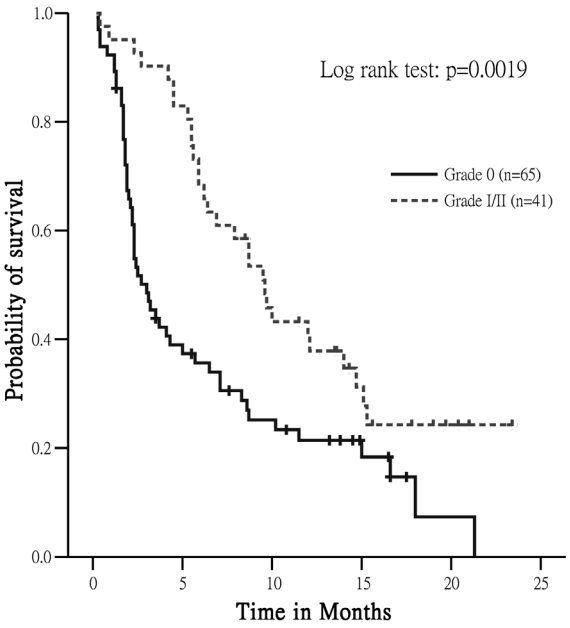

Fig. 1. Kaplan-Meier curves for overall survival of patients with grade 0 vs. grade I/II neutropenia.

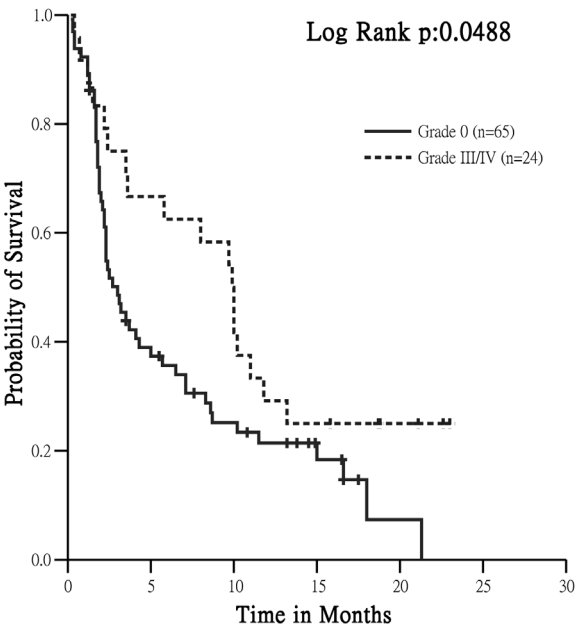

Fig. 2. Kaplan-Meier curves for overall survival of patients with grade 0 vs. grade III/IV neutropenia.

I/II (p=0.820), grade 0 vs. grade III/IV (p= 0.275), and grade 0 vs. grade I to IV (p=0.464) (Figure 3).

Discussion

This retrospective analysis studied the possible correlation between overall survival and the chemotherapy-induced neutropenia of patients with advanced NSCLC. Our data revealed that patients with chemotherapy-induced neutropenia had significantly better survival than those without neutropenia. The survival benefit was observed in grade I/II, grade III/IV and all neutropenic patients.

Neutropenic events were common during adjuvant chemotherapy for primary breast cancer, and had a significant impact on receiving the planned dose intensity [14]. Studies on breast cancer reported neutropenia was associated with a better clinical outcome [7, 15], but there was a contrary result in another study of adjuvant chemotherapy for breast cancer, which showed that neutropenia was not a predictor of outcome [10]. In this study the survival follow-up was longer than that of other previous stud-

Table 3. Multivariate analysis for overall survival

	Hazard	95% CI	*p*-value
Neutropenia			
I/II vs. 0	0.507	0.317-0.813	0.005
III/IV vs. 0	0.559	0.320-0.976	0.041
Age			
Increasing	1.013	0.993-1.033	0.196
Gender			
Women vs. men	2.314	1.406-3.809	0.001
Performance Status			
0, 1 vs. ≥2	1.397	0.781-2.499	0.260
Stage			
IIIA vs. IV	0.469	0.218-1.008	0.052
IIIB vs. IV	0.439	0.258-0.748	0.002
Histological subtype			
Adeno. Ca vs. Squamous	0.798	0.500-1.276	0.346
Other vs. Squamous	0.786	0.434-1.423	0.426

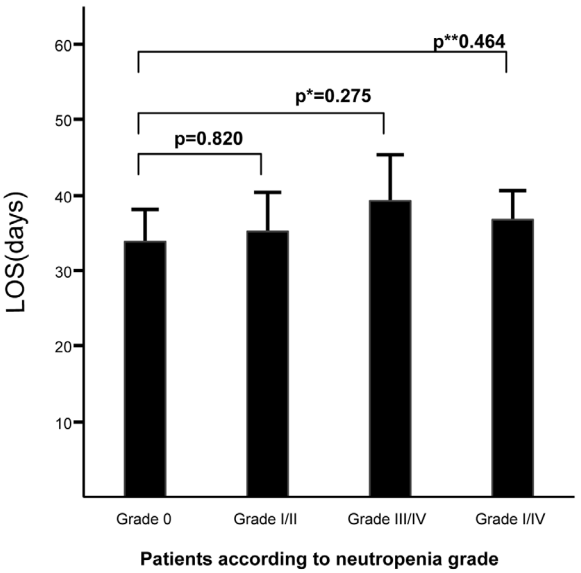

Fig. 3. Cumulative length of stay(LOS) of NSCLC patients undergoing chemotherapy, from the initial chemotherapy to the time of death.
Mean (+ SEM) of the LOS of each grade.
P = grade 0 vs. grade I/II, p*= grade 0 vs. grade III/IV, p**= grade 0 vs. grade I/IV

ies (20 years vs. 10 years), which may have lead to different results.

Neutropenia was implicated as an independent predictor of increased survival in patients with advanced gastric cancer [9] and was associated with a survival advantage in ovarian cancer [8]. Both mild and severe neutropenia during chemotherapy were associated with improved survival in patients with metastatic colorectal cancer [16].

Only a limited number of reports have mentioned the relationship between neutropenia and survival in NSCLC. However, patients with an inherently good prognosis survive longer and thus receive more cycles of chemotherapy, so they have a greater possibility of developing chemotherapy-induced neutropenia. To reduce the likelihood of such a selection bias, Di Maio *et al*. studied the association between neutropenia and increased survival by analyzing patients who had completed 6 cycles of chemotherapy, and confirmed the association [12].

In a study by Pallis *et al*. [11], 858 patients with locally advanced/metastatic NSCLC treat-

ed with front-line docetaxel-gemcitabine were retrospectively analyzed. Multivariate analysis revealed that both mild and severe chemotherapy-induced neutropenia were independent factors associated with a better time-to-tumor progression and overall survival.

In our study, Kaplan-Meier survival analysis revealed a significantly superior survival in grade I/II and III/IV neutropenia patients. However, in multivariate analysis, grade I/II, grade III/IV neutropenia, gender and stage of disease were significant prognostic factors.

Leucocytosis was found to be a significantly negative prognostic factor for overall survival and time-to-progression in patients with advanced-stage NSCLC in a pooled analysis of North Central Cancer Treatment Group trials, with data from about 1000 patients [17]. A review study attempted to hypothesize a correlation between tumor-related leucocytosis and chemotherapy-induced neutropenia [18]. The results showed that patients who do not experience chemotherapy-induced neutropenia may be associated with a worst prognosis because they may be characterized by base-line tumor-related leucocytosis and an autonomous production of hematopoietic cytokines protecting them from chemotherapy-induced neutropenia.

One study reported high medical resource consumption by patients with unresectable advanced NSCLC in the Netherlands [19]. Hospitalization was the main cost driver in patients who received only the best supportive care (BSC) and in those who received chemotherapy as a second-line treatment in addition to the BSC. In our analysis, we assessed the cumulative LOS to compare the disease burden of NSCLC patients with and without neutropenia. Our data revealed no significant difference in LOS between patients with neutropenia and those without. This indicated that there is similar resource consumption by NSCLC patients receiving chemotherapy, whether neutropenia is induced or not.

Nakamura reported neutropenia development in 23.5% of patients with stage III NSCLC who received CCR with cisplatin plus weekly divided-dose docetaxel [20]. One phase II study assessed CCR with twice-weekly gemcitabine in stage III NSCLC. Neutropenia developed in 23% of these patients [21]. Our data showed that neutropenia developed in 11 of 30 (36.7%) patients that received CCR and in 5 of 9 (55.6%) patients that received sequential chemoradiotherapy. The data from our small sample size showed no significant difference in patients that received CCR or sequential chemoradiotherapy, although many trials have demonstrated an increase in host toxicity for those undergoing CCR. A randomized study comparing CCR (n=51) versus sequential chemoradiotherapy (n=48) with cisplatin and vinorelbine in locally advanced NSCLC also revealed no significantly greater incidence of neutropenia (65% vs. 40%, p=0.057) [22].

Although the present study was a retrospective, unicenter analysis, our data indicate chemotherapy-induced neutropenia as a prognostic factor of survival. We further assessed the cumulative LOS in the hospital, and found that patients with chemotherapy-induced neutropenia consumed no more medical resources than those patients without neutropenia. However, further prospective randomized trials are needed to evaluate the efficacy of standard chemotherapy and incremental drug doses in patients who do not develop neutropenia.

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化學治療誘發之嗜中性白血球減少症可作爲非小細胞肺癌患者存活之預測因子

葉金水　陳正雄　紀炳銓　林慶雄

有醫學研究報告非小細胞肺癌晚期患者接受化學治療時導致嗜中性白血球減少症有較佳之存活期。本研究回溯性分析一醫學中心之晚期非小細胞肺癌患者接受化學治療時導致嗜中性白血球減少症與總存活的相關性。130名患者接受化學治療，其中未發生嗜中性白血球減少症為0級（n=65），輕度白血球減少症者為I/II級（n=41），嚴重白血球減少症者為III/IV級（n=24），總存活期中位數分別為3.0、9.6及9.9個月，達統計學差異顯著。未發生嗜中性白血球減少症、輕度及嚴重白血球減少症的肺癌患者平均累計住院日數為34、35和39日，顯示化學治療時導致嗜中性白血球減少症並不會明顯增加醫療資源耗費。*(胸腔醫學* ***2010; 25: 110-118)***

關鍵詞：化學治療，嗜中性白血球減少症，非小細胞肺癌

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Chemotherapy-Sensitive Ectopic Hepatocellular Carcinoma with Multiple Mediastinal Metastasis – A Case Report

Ruei-Lin Liang, Shyh-Sheng Yang, Chung-Ping Hsu, Fang-Yi Lee*

Ectopic hepatocellular carcinoma (HCC) is an extremely rare disease. It is defined as an HCC arising from the hepatic parenchyma located in an extrahepatic organ or tissue. To the best of our knowledge, there have been only 36 cases reported in the literature, but there has not been a diagnosed case of multiple mediastinal metastases, such as ours. Treatment has been surgery, for the most part, and no effective chemotherapy regimens have been reported. We reported a 41-year-old man referred to our hospital because of upper abdominal pain. Chest X-ray disclosed a mass lesion at the right pulmonary hilum. Abdominal computed tomography (CT) disclosed a 8x6-cm heterogeneous enhanced mass near the proximal jejunum. The mother liver was intact without cirrhosis or tumor. His alpha fetoprotein was at an extremely high level (25276 ng/ml). Multiple neck lymphadenopathy was noted and biopsy proved metastatic HCC. We treated this patient with the combined chemotherapy regimen of cisplatin, doxorubicin and cylophosphamide. After 1 year of follow-up, the result was satisfactory, with a marked decrease in the size of the lymph nodes, and his alpha fetoprotein level returned to normal. In addition, the size of the lesion near the proximal jejunum had decreased. ***(Thorac Med 2010; 25: 119-124)***

Key words: ectopic hepatocellular carcinoma, chemotherapy

Introduction

Hepatocellular carcinoma (HCC) is an aggressive tumor that often occurs in the setting of chronic liver disease and cirrhosis. Ectopic HCC, however, can be defined as an HCC arising from the hepatic parenchyma located in an extrahepatic organ or tissue. The incidence of ectopic HCC is extremely low: Only 36 cases have been reported from 1965 to 2007 [1-13]. Ectopic liver is usually asymptomatic, but occasionally causes unexpected problems such as intra-abdominal bleeding; most importantly, ectopic livers are predisposed to developing neoplastic transformation [1-2]. All 36 reported cases of HCC arose in ectopic livers, while the mother liver contained no tumor. Most of the patients were Asian [1-13]. Surgery, if possible,

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is the most preferable treatment option. We report a rare case of ectopic HCC presenting with multiple metastasis in the abdominal, mediastinal and supraclavicular regions when diagnosed. To the best of our knowledge, there has been no similar case reported in the literature. Due to the advanced stage, operation was not the first choice, so the patient received neoadjuvant chemotherapy.

Case Report

A 41-year-old man was referred because of upper abdominal pain. He had no past medical history. He was not taking medications and was not abusing alcohol. Physical examination disclosed multiple enlarged left neck masses. No abdominal distention or intestinal obstruction was noted. Hepatitis B virus (HBV) and hepatitis C virus (HCV) tests were negative. Alpha fetoprotein, which was checked at another hospital, was at an extremely high level (over 18000 ng/ml). A chest X-ray disclosed a mass lesion at the right pulmonary hilum (Figure 1). Abdominal computed tomography (CT) disclosed an 8×6×5 cm heterogeneous enhanced mass located near the proximal jejunum; the mother liver was intact without cirrhosis or tumor (Figure 2). Chest CT disclosed multiple enlarged lymph nodes in the bilateral supraclavicular, paratracheal, anterior mediastinal and right hilar regions with compression of the superior vena cava (Figure 3). In order to obtain pathological proof, an incisional biopsy of the left neck mass was performed. Histology showed tumor cells arranged in sheets, cords and trabeculae with a moderate to abundant amount of eosinophilic

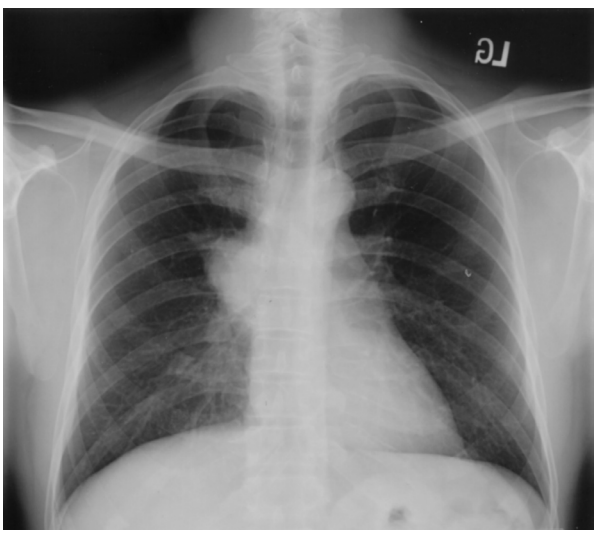

Fig. 1. A mass lesion at the right pulmonary hilum.

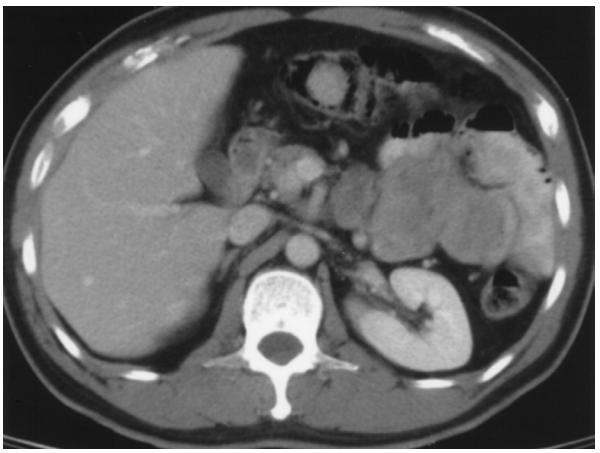

Fig. 2. Abdominal computed tomography (CT) disclosed a 5-cm heterogeneous enhanced mass near the proximal jejunum; the mother liver was intact without cirrhosis or tumor.

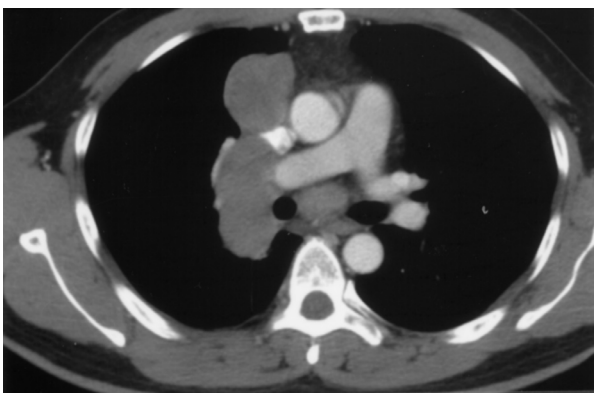

Fig. 3. Chest CT disclosed multiple enlarged lymph nodes in the anterior mediastinal and right hilar regions with compression of the superior vena cava.

cytoplasm and distinctive cell borders resembling HCC (Figure 4). Immunohistochemical stains for AFP and hepatocyte antigen showed positive results and confirmed the diagnosis (Figure 5, 6). Due to the advanced stage, he received systemic chemotherapy for 1 day at 3-week intervals, with the regimen of cisplatin 50 mg/m^2, doxorubicin 40 mg/m^2 and cylophosphamide 500 mg/m^2. After 2 courses of chemotherapy, the follow-up alpha fetoprotein level decreased to 6507 ng/ml. The follow up chest X-ray also disclosed a marked reduction in the size of the tumor at the right pulmonary hilum (Figure 7). After 6 courses, the follow-up chest X-ray disclosed complete remission of the right hilar mass, and chest CT showed a marked decrease in the bilateral supraclavicular, paratracheal, anterior mediastinal and right hilar region lymph nodes (Figure 8). In addition, the serum level of alpha fetoprotein had dramatically de-

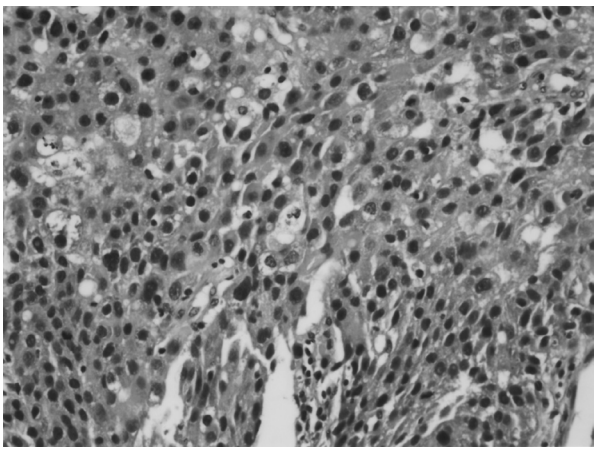

Fig. 4. Tumor cells arranged in sheets, cords and trabeculae with a moderate to abundant amount of eosinophilic cytoplasm and distinctive cell borders resembling hepatocellular carcinoma. (H & E stain 400X)

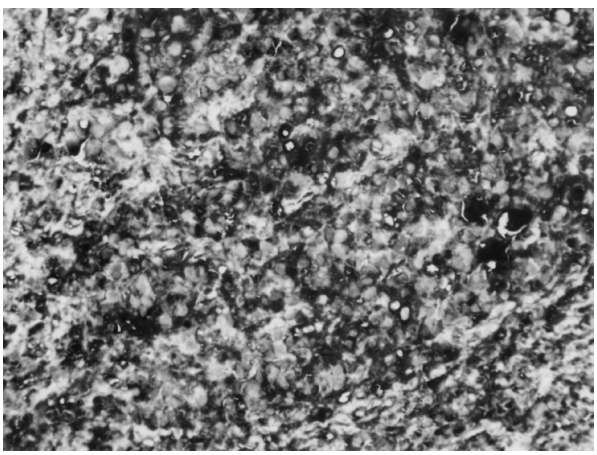

Fig. 5. Tumor cells present diffuse and strong cytoplasmic staining of alpha-fetoprotein. (immunohistochemical stain for alpha-fetoprotein 400X)

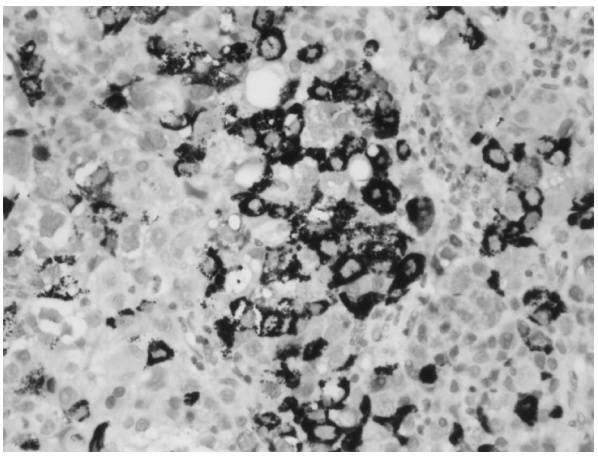

Fig. 6. Hepatocyte antigen staining shows focal and dense granular cytoplasmic staining. (immunohistochemical stain for hepatocyte 400X)

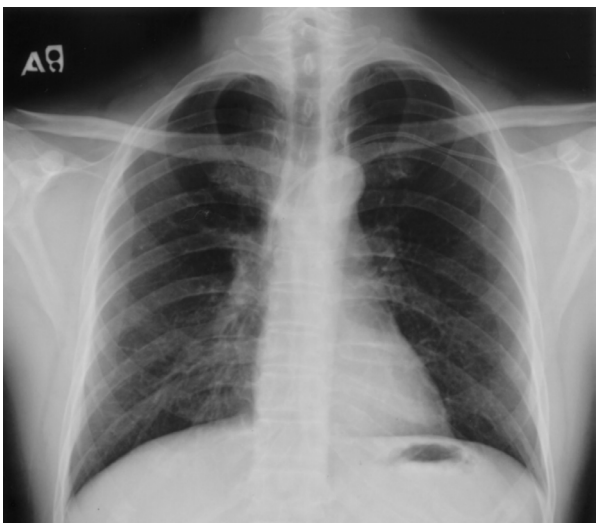

Fig. 7. Chest X-ray disclosed a marked reduction in the size of the tumor at the right pulmonary hilum.

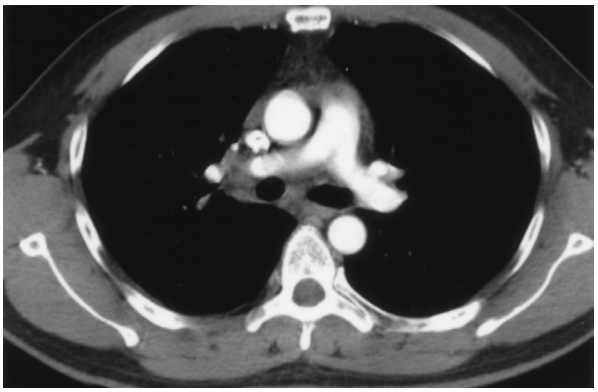

Fig. 8. Chest CT showed a marked decrease in anterior mediastinal and right hilar region lymph nodes.

creased to 1.15 IU/ml, and the size of the lesion near the proximal jejunum decreased to 6×4×3 cm.

Discussion

Ectopic livers are islands of normal liver parenchyma separated from the mother liver. They may occur in various sites distant from the liver [7], including the gallbladder, spleen, retroperitoneum, pancreas, adrenal gland, portal vein, omentum, diaphragm, thorax, gastric serosa, testes and umbilical vein. The most common location is on the gallbladder [6].

Only 36 cases of ectopic liver HCC have been reported; most of the patients were Asian, 26 were reported in Japan [1, 3, 8-11], and a few have been reported among Caucasian patients [2, 4, 6, 10]. Only 2 Taiwanese patients have been reported [12-13]. Males are predominantly affected, with ages ranging from 34 to 77 years. The mother livers were intact in all of the patients, and only 20% had a cirrhotic liver [11]. Chronic hepatitis was found in only 4 patients [11]. This finding implicates that ectopic livers are prone to develop HCC, regardless of the presence or absence of a predisposing liver parenchymal disease. The reason why ectopic livers are particularly predisposed to neoplastic degeneration remains unknown [11].

On the other hand, most patients were free of HBV or HCV infection. Kubota K *et al*. reviewed the literature and found anti-HCV antibody was positive in 2 of 15 patients, and hepatitis B surface antigen was positive in 2 of 27. It is likely that non-viral factors were involved in the carcinogenesis.

Extrahepatic spread of primary HCC at the time of diagnosis or disease recurrence is found in 10-20% of patients. The most common sites are the lung, intraabdominal lymph nodes, bone, and adrenal gland. The definite pathway of ectopic HCC spread is unknown. However, there has been no patient such as ours reported with multiple metastases in the bilateral supraclavicular, paratracheal, anterior mediastinal and right pulmonary hilar regions. Because the incidence is rare, ectopic HCC is difficult to diagnose preoperatively. In about 20% of cases, ectopic HCC was suspected, based on the diagnostic imaging, and a high level of AFP or biopsy findings helped establish the diagnosis [11]. Like most cases, our patient was diagnosed based on the histological examinations of the surgical biopsy specimens. Due to the advanced stage, exploratory laparotomy for primary tumor removal was not indicated. The easiest method to obtain tissue proof was neck mass biopsy. Immunohistochemistry with a monoclonal antibody to human hepatocyte and alpha-fetoprotein confirmed the hepatocellular nature of the specimen.

HCC is moderately responsive to systemically administered chemotherapy. For patients with end-stage HCC, the regimens producing the highest response are the combination of cisplatin, interferon, doxorubicin, and 5-fluoroura-

cil (PIAF), and the combination of epirubicin, cisplatinum and infusional 5-fluorouracil (ECF) [15-17]. However, no effective chemotherapy regimens have been reported for treating ectopic HCC. We treated this patient with cisplatin 50 mg/m^2, doxorubicin 40 mg/m^2 and cylophosphamide 500 mg/m^2 once every 3 weeks. After 6 courses, the follow-up chest X-ray disclosed complete remission of the right hilar mass, and chest CT showed a marked decrease of bilateral supraclavicular, paratracheal, anterior mediastinal and right hilar region lymph nodes. In addition, the serum level of alpha fetoprotein had dramatically decreased to 1.15 IU/ml.

In conclusion, in a well-defined setting of patients characterized by an absence of cirrhosis and a good performance status, we suggest combination chemotherapy may potentially produce a good shrinkage of the tumor (even up to a complete pathological response), and thereby possibly improve overall survival.

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對化學治療敏感的異位性肝細胞癌合併多發性縱膈腔轉移：病例報告

梁瑞麟　楊適生　徐中平　李芳儀*

異位性肝細胞癌是一個罕見疾病。定義為發生在肝臟外組織或器官的肝細胞癌。據我們所知目前只有36例病例報告發表在文獻上，但是沒有一例像我們的病人一樣在診斷時就已經合併多發性縱膈腔轉移。治療方式多是手術移除，並沒有文獻指出化學藥物治療的效果。我們報告一位病人因為上腹痛來到我們醫院，胸部X光攝影發現右肺門處有腫瘤。腹部電腦斷層發現靠近近端空腸有一8×6公分不規則顯影之腫瘤。此外病人的肝臟顯示為正常無腫瘤。而且他的胎兒蛋白指數高達25276 ng/ml。理學檢查發現雙側頸部有多發腫瘤，經病理切片證實為轉移性肝細胞癌。我們用cisplatin，doxorubicinc和cylophosphamide合併治療，結果令人滿意。治療後經一年追蹤，上述轉移性腫瘤在影像學上有明顯變小，病人胎兒蛋白指數也回復到正常，而且腹腔腫瘤的大小也有縮小。*(胸腔醫學* ***2010; 25: 119-124)***

關鍵詞：異位性肝細胞癌，化學治療

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Negative Pressure Pulmonary Edema Related to Deep Neck Infection – A Case Report

Huan-Ting Shen, Shuo-Chueh Chen, Wei-Erh Cheng, Kuo-Liang Chiu, Chuen-Ming Shih, Wu-Huei Hsu

Negative pressure pulmonary edema (NPPE) is a rare, but potentially life-threatening complication of upper airway obstruction (UAO). It is usually reported following general anesthesia, in which an intubated patient experiences complications with laryngospasm after extubation. We reported a patient suffering from a deep neck infection with the initial presentation of allodynia in the 2nd cervical nerve dermatome area, manifesting as NPPE induced by deep neck infection related to nasopharyngeal and oropharyngeal swelling and UAO. ***(Thorac Med 2010; 25: 125-130)***

Key words: negative pressure pulmonary edema, deep neck infection

Introduction

Negative pressure pulmonary edema (NPPE) caused by upper airway obstruction (UAO) was first clinically recognized in 1983 [1]. NPPE is a rare, but life-threatening complication of acute UAO, classified as a kind of non-cardiogenic pulmonary edema. Fewer than 150 adult cases have been cited in the world literature, and independent studies demonstrated a 0.05 to 1% incidence of laryngospasm [2-3]. The major physiological mechanism contributing to the formation of edema in this setting involves the generation of markedly negative intrathoracic pressure, leading to a net increase in pulmonary vascular volume and pulmonary capillary transmural pressure [4]. NPPE is reported to be more common in young patients after surgery involving the upper aero-digestive tract when laryngospasm complicates extubation. Neck strangulation, laryngeal trauma, epiglottitis, croup, hematoma in the upper aero-digestive tract, foreign-body aspiration in the respiratory tract, hiccup, endotracheal tube obstruction, and goiter have also been reported to precipitate NPPE [3, 5]. While most NPPE patients respond to treatment, especially positive end-expiratory pressure (PEEP), some experience deterioration [5-6]. Currently, there are no reports describing the relationship between NPPE and deep neck infection. Herein, we report a case of NPPE induced by deep neck

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infection related to nasopharyngeal and oropharyngeal swelling and UAO, which initially presented with allodynia of the 2nd cervical nerve dermatome area. Relevant literature is also reviewed.

Case Report

A 68-year-old man with a history of nasopharyngeal cancer (T2N2M0 status) and concurrent chemo-radiotherapy 10 years ago was admitted via the emergency room because of shortness of breath for 1 day. He suffered from episodic shooting pain from the posterior neck to the occipital and parietal areas, which started 1 week prior to admission. He had already visited the emergency room twice. Brain computed tomography (CT) demonstrated only several mildly enlarged lymph nodes in the bilateral submental spaces and no local recurrence or metastasis to the brain.

Two days prior to this admission, the patient began experiencing fever and frequent choking when drinking water. Owing to the progressive dyspnea, he visited the emergency room. On physical examination, he was alert, with blood pressure of 150/90 mmHg, heart rate of 93 beats/min, respiratory rate of 24/min, and body temperature of 37°C. Chest examination showed diffuse rhonchi. Arterial blood gas under 3 L/min of oxygenation via a nasal cannula showed pH 7.4, $PaCO_2$ 34 mmHg, PaO_2 134 mmHg, HCO_3^- 22.8 mmole/L and SaO_2 99%; the white blood cell count was 11400/μL, neutrophil count 77%, and C-reaction protein level 17.12 mg/dL. The chest radiograph revealed mild infiltration in the right lower lung field (Figure l). The patient was admitted to the general ward under the impression of aspiration pneumonia.

Fig. 1. Chest X-ray on admission showing alveolar infiltration in the right lower lung field.

A neurologist was consulted for the persistent neck pain, and ampicillin-sulbactum 1.5 gm per 6 hours was given for the aspiration pneumonia. The neurologist suspected allodynia resulting from a lesion in the 2nd cervical spine. Magnetic resonance imaging (MRI) confirmed an abnormal fluid accumulation with an overgrowth of adjacent soft tissue in the prevertebral spaces, from the 1st to the 5th cervical spinal vertebra (Figure 2). Deep neck infection with abscess formation was then highly suspected. Progressive orthopnea was also noted during hospitalization, and mild stridor sometimes occurred when he took a deep breath or was in the supine position. An otolaryngologist was consulted immediately and suggested medical treatment first, because there was no evidence of epiglottitis or obvious swelling on the vocal cord. A sudden onset of severe respiratory distress with loud stridor, cyanosis and desaturation (SpO_2 50% by pulse oximetry) occurred at midnight on the 3rd hospital day. The patient immediately received endotracheal

Fig. 2. Neck MRI revealed an abnormal fluid collection (arrow) with increased adjacent soft tissue enhancement in the pre-vertebral space, from the 1st to the 5th cervical spine.

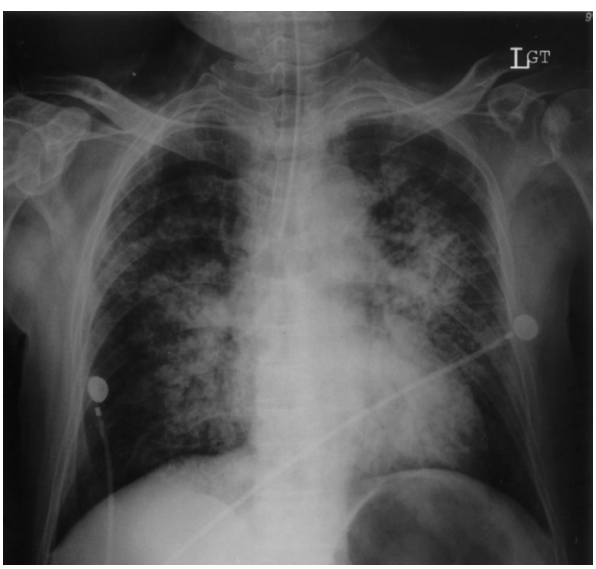

Fig. 3. Chest X-ray showing diffuse alveolar infiltration in both lung fields immediately after intubation.

intubation with respiratory assistance through a mechanical ventilator, and was then transferred to the medical intensive care unit (MICU). Pink frothy sputum was aspirated from the endotracheal tube. Chest radiography revealed acute pulmonary edema (Figure 3).

Fig. 4. Neck CT on the 2nd MICU day revealing generalized soft tissue swelling in the nasopharynx and oropharynx. Focal mild hypo-dense lesions (arrow) in the prevertebral space at the 1st and 2nd cervical spine level, with small amounts of abscess formation.

In the MICU, the antibiotic regimen was shifted to piperacillin-tazobactum, to cover the deep neck infection. Neck CT revealed generalized swollen soft tissue in the nasopharynx and oropharynx, causing airway stenosis, and a focal mild hypo-dense lesion in the prevertebral space at the 1st and 2nd cervical spinal level, together with suspicious, small amounts of abscess formation (Figure 4). Echocardiography showed a preserved left ventricular function without obvious valvular heart disease. NPPE secondary to upper airway obstruction (UAO) was then diagnosed. The patient had relatively

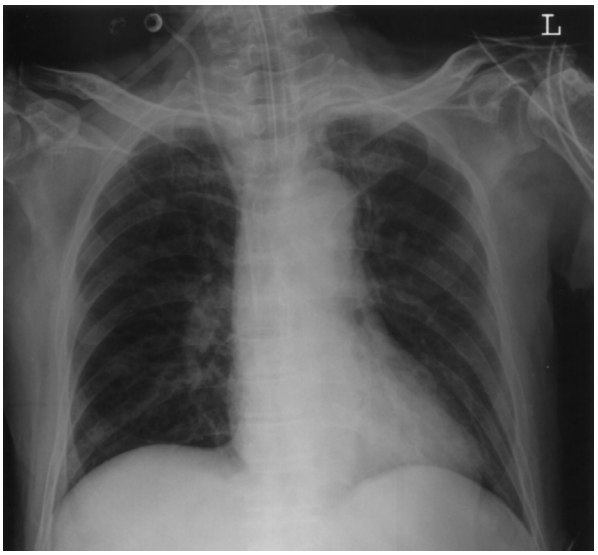

Fig. 5. Chest X-ray showing a resolving alveolar infiltration in both lung fields 4 days after intubation.

low blood pressure (systolic blood pressure 85~90 mmHg) after endotracheal intubation and use of midazolam for sedation. The arterial blood gas under FiO_2 50% of oxygenation showed SpO_2 90~92%. Intravenous furosemide mixed with albumin was used to increase the colloid oncotic pressure and avoid compromising the hemodynamic status. The PEEP was also set to 10 cmH_2O for the NPPE. The patient's hemodynamic status stabilized and the fever subsided within 3 days. The pulmonary edema also improved rapidly and was completely resolved 4 days later, as shown in the chest radiography (Figure 5). Weaning from the ventilator started on the 4th MICU day, and the patient was extubated smoothly under bronchoscopic guidance on the 8th MICU day. The patient was then transferred to the general ward, and discharged after a 14-day treatment of piperacillin-tazobactum.

Discussion

This is the first case report describing deep neck infection-induced NPPE. Previous studies [2-5] have given clinicians a better understanding of the pathogenesis of and treatment for NPPE. Based on etiology, NPPE can be divided into 2 subtypes: Type 1, which results from acute UAO and Type 2, which occurs after relief from a chronic obstructive process [3]. Different underlying mechanisms for the pathogenesis of NPPE have been proposed, based on type. Type 1 involves high negative intrathoracic pressure (ITP) due to forceful attempts at inspiration against the obstruction. Such pressure causes an alteration in venous return and cardiac output, which leads to fluid transudation into the alveolar space. Type 2 is associated with the loss of auto-PEEP due to obstruction by a lesion. It is suggested that unresolved altered permeability and pre-existing occult interstitial fluid result in interstitial fluid transduction and pulmonary edema upon the sudden loss of PEEP [7]. Kollef *et al*. postulated that a high negative ITP enhances venous return to the right heart, resulting in a concomitant increase in pulmonary micro-vascular hydrostatic pressure. This favors transudation of fluid from the pulmonary capillary space to the pulmonary interstitial space, progressing to pulmonary edema [8]. Palvin's hypothesis indicates that the disruption of the alveolar-capillary membrane due to high ITP may cause increased pulmonary capillary permeability and pulmonary edema [9]. This capillary leak of proteinaceous material may account for the classic description of serosanguineous or pink, frothy secretions in NPPE. A hypothesis put forth by Schwartz *et al*. proposed that a hypoxic, hyper-carbic and hyperepinephric status that develops after acute UAO results in increased pulmonary blood volume. This causes distension of the right ventricle, leading to an inter-ventricular septum shift and

a reduction in cardiac output [4].

In the current case report, Type 1 NPPE developed after forced inspiration due to acute UAO, which was caused by deep neck infection-related oropharyngeal and nasopharyngeal swelling. This patient's condition resolved after a 4-day treatment with diuretics and invasive positive pressure mechanical ventilator with PEEP.

Treatment for NPPE generally requires early recognition of the condition and resuscitation with oxygen supplementation and mechanical ventilation, if necessary [5]. Specific treatment of the underlying condition, such as the deep neck infection in the present case, is also vital. Preventive measures include the use of a bite block for patients during recovery from anesthesia [5]. Chest radiographs should be obtained at the onset of symptoms and every 12-24 hours thereafter, until complete resolution of the pulmonary edema. While most cases of NPPE will completely resolve after 24 hours, some may take several days or weeks [3]. The prognosis of NPPE is generally good; however, it can be potentially life-threatening, as illustrated by this patient with deep neck infection. NPPE in the presence of an upper airway obstruction can further compromise gaseous exchange and result in irreversible hypoxic brain damage and even death [5].

In this report, the patient's deep neck infection may have been related to his dental problems. The patient completed concurrent chemoradiotherapy 10 years ago, and has had frequent episodes of dental caries since then. As such, this patient's dental problems were sequelae of the neck radiation therapy, which can decrease salivary secretion and increase the risk of developing dental caries.

In conclusion, NPPE secondary to UAO is a rare, but potentially lethal medical condition. It occurs more commonly in young patients after surgery involving the upper aero-digestive tract, when laryngospasm complicates extubation. This is the first case report describing the correlation between deep neck infection and NPPE. Adequate management includes the early recognition of the condition and correct treatment for the underlying disease with the best supportive care, such as a positive pressure ventilator with PEEP and low-dose diuretics.

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起因於深頸部感染的負壓肺水腫—病例報告

沈煥庭　陳碩爵　程味兒　邱國樑　施純明　徐武輝

負壓肺水腫是上呼吸道阻塞時，一種不常見但卻可能致命的併發症。接受全身麻醉的病人拔除氣管內管後所引發的喉部痙攣是最常被報導造成負壓肺水腫的原因。我們報導一位深頸部感染且伴有頸部C2皮節區疼痛的病人，因為深頸部感染造成鼻咽及口咽部的腫脹，進而導致上呼吸道阻塞及負壓肺水腫。*(胸腔醫學* ***2010; 25: 125-130****)*

關鍵詞：負壓肺水腫，深頸部感染

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Influenza A Infection with Rhabdomyolysis and Acute Renal Failure

Cheng-Chi Lin*,**, Chih-Feng Chian*, Wann-Cherng Perng*

Influenza A virus can be transmitted widely throughout the community. Although patients with influenza often present with myalgia, rhabdomyolysis is rarely seen. Very few results were obtained in an online search for case reports on rhabdomyolysis and acute renal failure associated with influenza. We present the case of a 78-year-old man who was admitted to our emergency department with myalgia, dry cough, fever, progressive lower limb pain, and tea-colored urine. On investigation, the serum creatine kinase level was found to be elevated and myoglobinuria was detected; these signs were indicative of rhabdomyolysis. Renal function impairment was also noted. Influenza A infection was confirmed by the positive antigen test of a nasal swab. The clinical presentation and medical history of the patient strongly suggested that rhabdomyolysis was caused by influenza A virus. The patient's renal function was restored and he was discharged after appropriate therapy for rhabdomyolysis. This case highlights the importance of recognizing influenza A infection as a cause of acute renal failure secondary to rhabdomyolysis during influenza pandemics, despite the fact that rhabdomyolysis complicated by acute renal failure is rarely seen in patients with influenza A. ***(Thorac Med 2010; 25: 131-136)***

Key words: acute renal failure, influenza A, rhabdomyolysis

Introduction

The classical clinical presentations of influenza A include fever, chills, cough, sore throat, rhinorrhea, headache, and myalgia. Patients affected during the 2009 influenza A pandemic were reported to develop severe complications, namely, rapidly progressive pneumonia, respiratory failure, and acute respiratory distress syndrome [1]. Acute renal failure (ARF), a life-threatening disease, is a rare complication of influenza A, but if present, may affect the treatment and survival of the patient [2]. ARF is mostly caused by septic shock or multiple organ dysfunctions; however some reports have indicated that reversible renal failure can develop due to rhabdomyolysis and myoglobinuria secondary to influenza A infection [2-5].

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Rhabdomyolysis can cause oligouric pigment-induced intrinsic renal failure through the nephrotoxic effects of lytic myocyte components [6]. We present the case of a patient whose renal dysfunction, caused by influenza-associated rhabdomyolysis, was restored after adequate treatment.

Case Report

A 78-year-old man had developed generalized muscle ache, nonproductive cough, and intermittent fever 3 days before admission. He visited our hospital for progressive pain in both lower limbs, which started 1 day before admission. He had passed dark tea-colored urine 2 hours before visiting our emergency department. He had no history of excessive physical exertion or trauma during the past few days, nor did he have diarrhea, vomiting, or polyuria during the past 2 months. He had smoked 30 cigarettes per day for the past 30 years, but denied any history of alcohol or drug abuse. The patient had been diagnosed with chronic obstructive pulmonary disease 4 years ago. He lived with his wife and son and had no history of contact with ill patients or animals, nor did he travel outside of metropolitan areas. Physical examination did not reveal a toxic appearance, but the patient was febrile (body temperature, 39.2°C) and chest auscultation revealed coarse crackles and bronchial sounds in both the lower lung fields. Moreover, neither abnormal lymph node enlargement nor heart murmur was detected. He was unable to walk because of leg pain.

Laboratory test results revealed hematocrit 44.6%, white blood cell count 12,630/mm^3 with 88% neutrophils, C-reactive protein 12 mg/dL, sodium 137 meq/L, potassium 3.8 meq/L, creatinine 2.0 mg/dL, creatine kinase (CK) 1,819 IU/L, aspartate aminotransferase (AST) 191 IU/L and alanine transaminase (ALT) 25 IU/L. The urine was dark brown and the hematest result was positive. Microscopic examination revealed 1-2 red blood cells per high power field and an absence of casts. The rapid screen test and serological tests for acute influenza infection were positive for influenza A, but negative for influenza B. Chest radiography revealed an increase in the linear and reticular infiltrations and bronchial wall thickening in both lungs (Figure 1). The electrocardiogram was normal, and blood cultures, sputum cultures, urine cultures and viral throat cultures were all negative for microbial growth.

Since the patient had progressive general muscle pain, he was given analgesics 2 days after admission. The serum CK level was elevated to 40,557 IU/L on the second day after admission. The muscle pain, elevated serum creatine kinase level, and myoglobinuria indicated rhabdomyolysis. The classical symptoms of influen-

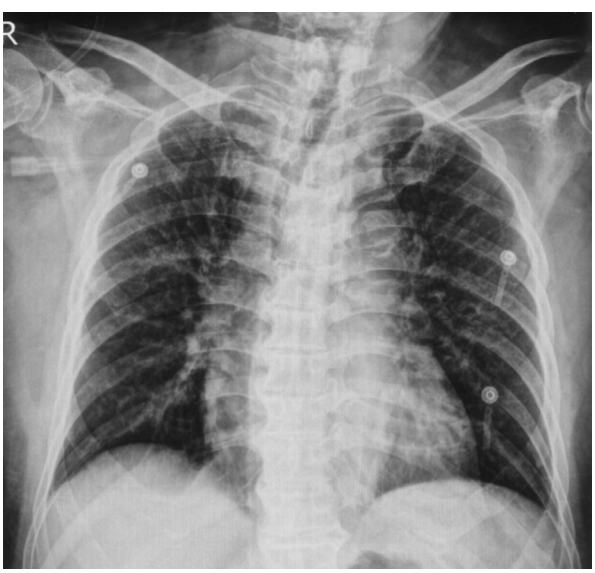

Fig. 1. Chest radiography showed an increase of linear and reticular infiltrations in both lungs and bronchial wall thickening in both lungs.

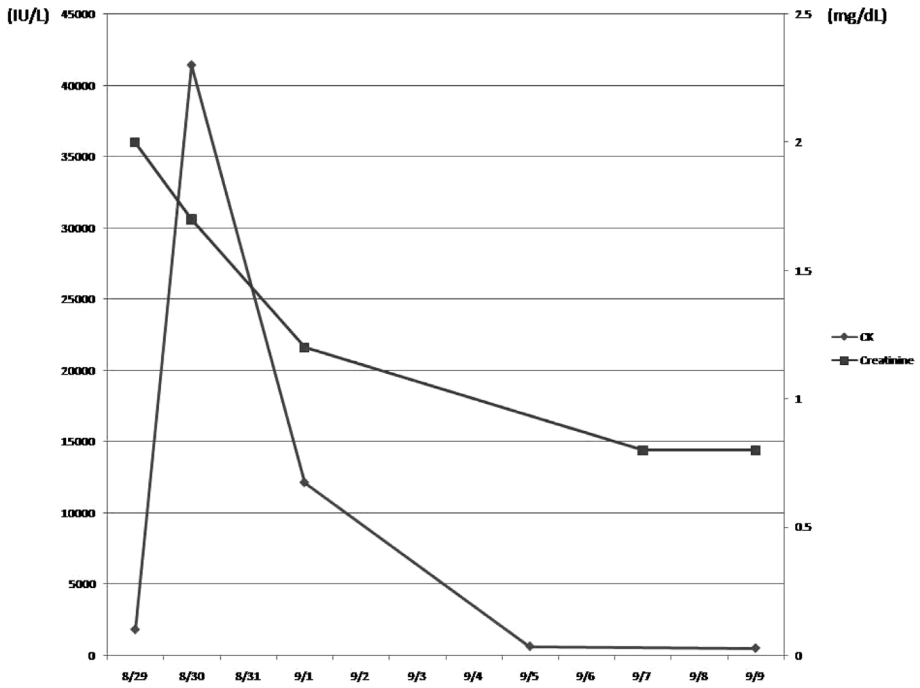

Fig. 2. Serial changes in the serum CK and creatinine levels of the patient. The horizontal axis shows the dates, the left vertical axis serum CK levels, and the right vertical axis creatinine levels.

za, thrombocytopenia and a positive influenza A rapid screen test confirmed the diagnosis of influenza A infection. On the basis of the signs and symptoms, medical history, and laboratory findings of the patient, we ruled out common causes of rhabdomyolysis (such as alcohol overdose, drug toxicity, compression injuries, seizures, hypothermia, and sepsis). These findings strongly suggested that the rhabdomyolysis in this case was caused by influenza A infection. The patient was treated with intravenous fluid hydration and the amount of urine output was measured. In addition, the patient was managed with bed rest, administered sodium bicarbonate for alkalinization of the urine, and given antiviral therapy (oseltamivir). The pain in the lower limbs and fever gradually resolved during the 7 days of hospitalization; the renal function was restored to normal 10 days after admission, and the serum levels of the muscle enzymes CK and AST decreased rapidly, to 506 IU/L and 28 IU/L, respectively, at discharge (14 days after admission) (Figure 2). Four weeks after discharge, the patient visited our outpatient department for follow-up; he reported no muscle tenderness or weakness, and the serum CK level had returned to normal.

Discussion

ARF in association with influenza A has been reported previously, but usually only in relation to septic shock, disseminated intravascular coagulation (DIC) or myoglobinuria [2]. In 2003, Watanabe *et al*. reviewed 45 hospitalized children with influenza A virus infection and found that 11 had renal involvement. The role of viruses in the pathogenesis of renal in-

volvement is still inconclusive. Some patients with ARF have no influenza A RNA in their renal tissues, suggesting that human renal disease may not be caused by direct viral injury to the kidneys [2, 5]. The most likely mechanism for ARF may involve multifactorial effects, including deposition of myoglobin casts causing proximal tubular cell necrosis, oxidant injury and the direct toxic effects of myoglobin, and alterations in renal blood flow leading to renal ischemia [7]. Although ARF is a life-threatening disease, it may be reversible if treated promptly and appropriately. Differentiation of the etiologies of ARF is important for treatment choice. Rhabdomyolysis-induced ARF can be reversed by aggressive hydration. Hyperkalemia is another fatal complication caused by ARF that medical clinicians should keep in mind. However, our patient presented with hypokalemia during hospitalization. This may be explained by the preservation of his renal function, inducing an over-excretion of potassium without an adequate potassium supply.

Rhabdomyolysis is defined as a clinical and laboratory syndrome resulting from skeletal muscle breakdown with leakage of muscle cell contents into the systemic circulation. It is characterized by an elevated serum creatine kinase level and myoglobinuria, and may lead to renal dysfunction. Three studies reviewed 331 cases with rhabdomyolysis and found the following predisposing factors: alcohol abuse, drug overdose, crush or compression injuries, generalized seizures, hypokalemia, hypophosphatemia, hypothermia, sepsis, and virus illness [6, 8-9]. The patient did not have a history of alcohol consumption, drug abuse, compression injuries or seizure. The clinical presentation and laboratory examination of the patient during illness ruled out hypokalemia, hypophosphatemia, and hypothermia as a cause of rhabdomyolysis. Rhabdomyolysis can cause life-threatening complications, including hypovolemia, hyperkalemia, metabolic acidosis, ARF and DIC. ARF often results from the nephrotoxic effects of lytic myocyte components and usually presents as oligouric pigment-induced intrinsic renal failure [7-9].

Although the association of virus infection and myositis is definite, rhabdomyolysis is an uncommon and underestimated complication of influenza infection. Three pathophysiologic mechanisms have been proposed to explain this association. The identification of viral particles in an affected muscle supports the theory of direct invasion of muscle tissue by the virus or its particles [10]. However, not all muscle samples from patients with myositis have been demonstrated to present viral particles. So it may be explained by the second possible mechanism of autoimmune myositis induced by viral infection [11]. The last possibility is that a virus infection induces viral-related myotoxic cytokine release. Fodili *et al*. conducted an animal study and demonstrated that tumor necrosis factor could induce skeletal muscle breakdown [12]. This finding supports that of a report in which the serum of a patient with Coxsackie virus myositis contained an elevated level of tumor necrosis factor [13]. These theories explain the mechanism of viral myositis and the association of rhabdomyolysis, and may be applied to influenza virus infections with myositis, as in our case.

In conclusion, this case highlights the importance of recognizing influenza A infection as a cause of ARF secondary to rhabdomyolysis, despite the fact that rhabdomyolysis complicated by ARF is rarely seen in patients with influenza A. Clinicians should be alert to patients

with flu-like symptoms with severe muscle pain and dark brown urine. Although influenza-related rhabdomyolysis may cause the fatal complication of ARF, early diagnosis can lead to appropriate therapy, and the minimizing or recovering from renal dysfunction.

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A型流感引起橫紋肌溶解症合併急性腎衰竭—病例報告

林承志*,** 簡志峯* 彭萬誠*

目前正當A型流感盛行，流感常表現肌肉酸痛，但真正造成橫紋肌溶解症並不常見。搜尋相關文獻發現流感引起橫紋肌溶解症合併急性腎衰竭只有少數個案報告。我們提出一78歲病患因肌肉酸痛、咳嗽、發燒、持續惡化之下肢疼痛及茶色尿至醫院求診，經小便及血液檢查發現橫紋肌溶解症及腎功能異常，經快篩證實感染A型流感。根據病患病史及臨床表現可推論其橫紋肌溶解症應由A型流感所造成。於治療後病患腎功能及肌酐酸恢復正常且出院。此病例可提醒臨床醫師，當發現病人有橫紋肌溶解症併發急性腎衰竭，A型流感雖不是橫紋肌溶解症併腎衰竭常見致病因，但在此A型流感大流行之際因將其列入考慮。*(胸腔醫學* ***2010; 25: 131-136)***

關鍵詞：急性腎衰竭，A型流感，橫紋肌溶解症

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Adult Bochdalek Hernia with Gastric Volvulus: Case Report

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Acute gastric volvulus associated with congenital diaphragmatic hernia is an unusual surgical emergency. It is difficult to diagnose, as it is non-specific with vague symptoms, but any delay in the diagnosis and treatment can be fatal. Diagnosis requires a high index of suspicion and CT scanning. We described the case of a 76-year-old woman with dyspepsia and intermittent epigastric pain for 1 week. Multidetector-row CT confirmed the diagnosis and she underwent surgical reduction and repair of the diaphragm. This accurate diagnosis and surgical repair resulted in a good prognosis. ***(Thorac Med 2010; 25: 137-141)***

Key words: diaphragmatic hernia, gastric volvulus

Introduction

Congenital diaphragmatic hernia (CDH) is usually detected prenatally or presents neonatally. Only rare cases present in the adult, and are usually asymptomatic and discovered incidentally by chest radiography or CT. CDH with acute gastric volvulus can cause death if there is any delay in the diagnosis and treatment. Preoperative diagnosis is difficult because the symptoms are non-specific. Herein, we report the unusual case of a 76-year-old woman with CDH complicated with gastric volvulus.

Case Report

A 76-year-old woman had had intermittent epigastric pain, regurgitation and constipation during treatment for a peptic ulcer for several years. One week before admission, she developed dyspepsia and intermittent epigastric pain, and went to a local hospital. A chest X-ray revealed part of the stomach in the left hemithorax (Figure 1A). She received nasogastric tube decompression immediately, and was intubated endotracheally to treat her acute respiratory distress. The patient was then transferred to our emergency department. A physical examination revealed decreased breathing sounds and hyperresonance percussion in the left hemithorax. There was local tenderness in the epigastric region, but no rebounding pain. She denied a recent history of trauma. The laboratory data were as follows: hemoglobin 13.9 g/dL, white blood cell count 18.1 $\times 10^3$ μL^{-1}, platelets 237 $\times 10^3$ μL^{-1}, glucose 236 mg/dL; other measures

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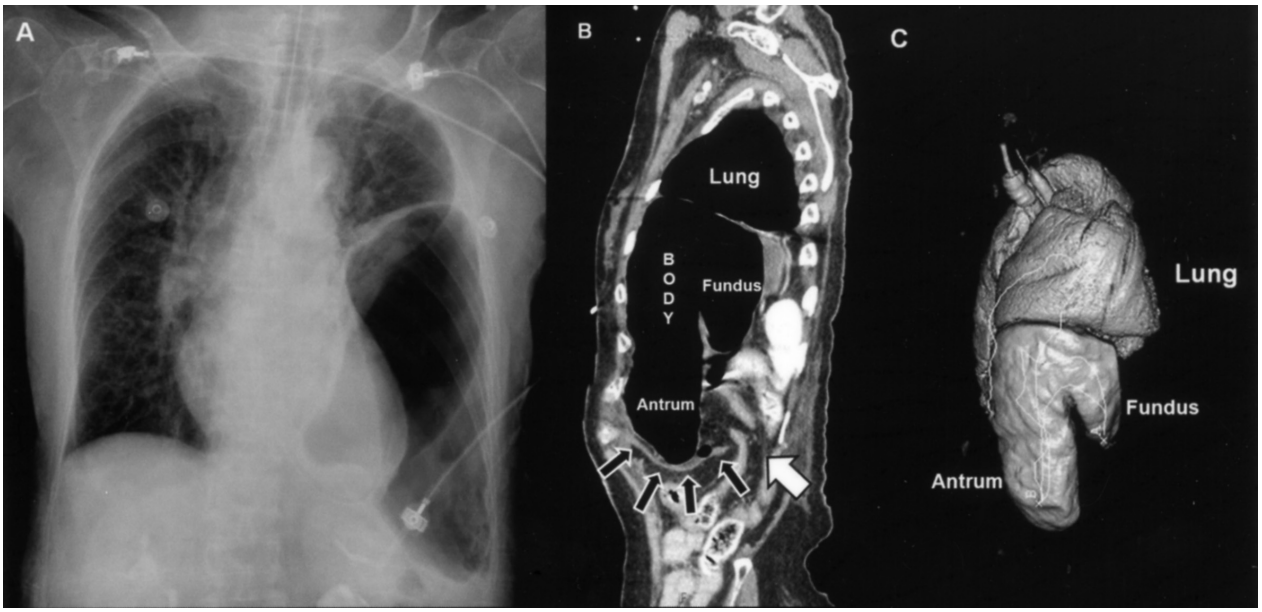

Fig. 1. (A) A chest X-ray shows herniation of the stomach into the left hemithorax. (B) This sagittal multidetector-row CT scan clearly demonstrates intrathoracic herniation of the omentum and gastric volvulus through the posterior defect (white arrow) of the diaphragm (black arrows). (C) A selected volume-rendering view shows an organo-axial volvulus of the stomach with compression of the lung.

were unremarkable. Multidetector-row CT (MDCT) with multiplanar reformatted images of the patient's chest clearly demonstrated a left diaphragmatic defect with herniation of the spleen, and a gastric volvulus (Figures 1B, 1C). The patient underwent thoracoscopy, during which a 3 × 3 cm posterolateral diaphragmatic defect with herniation of the fundus of the stomach, omentum and splenic flexure of the colon and spleen through the defect were found, consistent with a Bochdalek hernia (Figure 2). The lung was essentially healthy in appearance. Because we experienced difficulty in reducing these herniating organs, we shifted to a limited thoracotomy. The incision was created at the 7th intercostal space, and was about 15 cm in length. The adhesions between the lungs, the diaphragmatic defect and the herniating organs were freed using blunt dissection. The herniating organs were returned to the abdominal cavity after the diaphragmatic defect had been enlarged. The defect was repaired with 1-0 silk. The patient had an uneventful recovery and was discharged 10 days later in good condition.

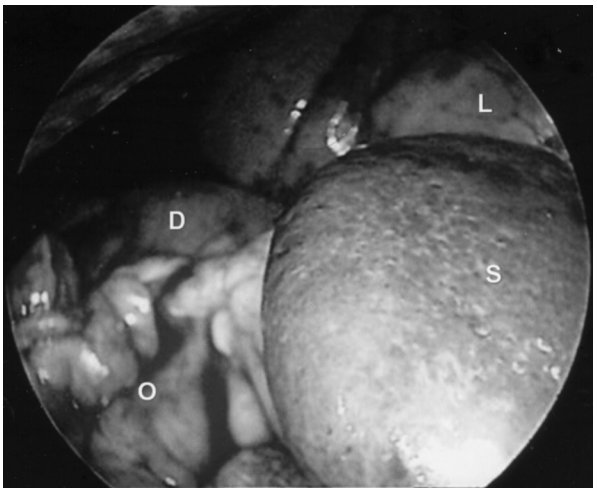

Fig. 2. Thoracoscopy shows herniation of the spleen (S) and omentum (O) through the diaphragm (D) with a healthy appearance of the lung (L).

Discussion

CDHs are usually found neonatally and rarely present in adults. In an adult, a Bochdalek hernia is usually asymptomatic and discovered incidentally by chest radiography or CT scans. Gastric volvulus together with a CDH is rare. A gastric volvulus can be classified as primary or secondary, based on its etiology. A primary gastric volvulus is caused by hyperlaxity of the stabilizing ligaments. Secondary gastric volvulus, which is the major form, is caused by a diaphragmatic defect, a para-esophageal hernia, abdominal bands or abdominal adhesions [1]. Gastric volvuli can also be classified as organo-axial, mesenterico-axial or combined, based on the axis of rotation. In an organo-axial volvulus, the stomach rotates along the axis extending from the hiatus to the pylorus. In a mesenterico-axial volvulus, the stomach rotates around the axis transecting the lesser and greater curvatures. In a combined volvulus, the stomach rotates along both axes [2].

The signs and symptoms of gastric volvulus depend on the extent of gastric rotation and obstruction, and usually are non-specific. Classic symptoms consist of epigastric pain, abdominal distension, vomiting or upper gastrointestinal hemorrhage, anemia, dysphagia, reflux and shortness of breath. Borchardt described the triad presentation of acute gastric volvulus, which includes severe epigastric pain and distension, non-productive retching and vomiting, and inability to receive a nasogastric tube [3]. If undetected, these findings, indicating complete obstruction of the pylorus and cardia, can lead to vascular compromise, viscus ulceration, strangulation, perforation, hemorrhage, ischemia and necrosis, which are the major causes of death [4].

There are many diagnostic methods for identifying a diaphragmatic hernia; these include chest plain radiographs, barium-swallowing fluoroscopy, ultrasound, CT scans and magnetic resonance imaging. Chest radiography is usually pathognomonic for the diagnosis of diaphragmatic hernias, which appear as gas-containing structures or nasogastric tubes *in situ* above the dome of the diaphragm [5]. CT scanning is another very useful and reliable tool in detecting a diaphragmatic hernia and its associated complications [6]. In particular, using MDCT technology with sagittal, coronal and three-dimensional reformatted images, the diaphragmatic discontinuity and herniated organs are all clearly visualized in most cases [6]. Here we wish to highlight the importance and convenience of this modern technology. The MDCT images in this case clearly demonstrated the herniation site, the herniated organs and the presence of gastric volvulus. MDCT technology facilitates making the right diagnosis quickly, and treatment can be given immediately, which is important to the patient and surgeon.

Once a diagnosis of acute gastric volvulus has been made, a nasogastric tube should be put in place promptly to decompress the dilated stomach and prevent gastric wall ischemia or necrosis. The treatment of acute gastric volvulus entails emergency surgery, and includes reduction of the volvulus, correction of any predisposing factors (repair of diaphragmatic defects or fixation of the hyperlax stabilizing ligaments) and gastropexy. The traditional method is laparotomy or thoracotomy. However, an endoscopic approach can provide a better outcome and has been used successfully in these cases [7]. Some authors advocate performing gastropexy with anterior fixation, fundal fixation or gastrostomy in all patients. Others ad-

vocate that gastropexy is not necessary for a secondary volvulus because the space needed for any recurrence of volvulus is obliterated after the diaphragmatic defect has been closed [8]. In this case, we started with thoracoscopic surgery, but shifted to thoracotomy to widen the diaphragmatic defect. We simply reduced these herniating organs, closed the diaphragmatic defect, and did not perform gastropexy; the patient recovered uneventfully and has been symptom-free, as of this writing.

In conclusion, despite the rarity and non-specific and vague clinical symptoms of acute gastric volvulus in adults, clinicians should keep in mind that an adult Bochdalek hernia with acute gastric volvulus is one of the possible differential diagnoses of dyspnea and abdominal pain. MDCT scanning is useful in detecting a diaphragmatic hernia. Early detection and intervention is of the utmost importance to decrease related morbidity and mortality in adults.

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成人Bochdalek型橫膈疝氣合併胃扭轉：病例報告

吳悌暉　李世俊　謝志明

成人先天性橫膈疝氣合併急性胃扭轉是非常少見的緊急手術適應症。它因為沒有特異性的症狀因此診斷困難，但延遲診斷及治療卻是致命的。正確的診斷需要高度的警覺及電腦斷層的輔助。本文報導一位76歲的女性，食慾不良及間歇上腹疼痛一個星期。藉著多層螺旋電腦斷層（multidetector-row CT）的幫忙確定了橫膈疝氣合併胃扭轉的診斷，及時的疝氣復位及橫膈修補治癒了病人。好的預後靠的是早期診斷及手術介入。*(胸腔醫學* ***2010; 25: 137-141)***

關鍵詞：橫膈疝氣，胃扭轉

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Successful Removal of an Endobronchial Hamartoma by Bronchoscopic Electrosurgical Snare Loop – A Case Report

Mei-Chen Yang, Chih-Hsin Lee, Chung-Tai Yue*, Shing-Zeng Dung**, Kun-Eng Lim***, Thomas Chang-Yao Tsao****

Endobronchial hamartomas (EH) are rare, but they often cause irreversible lung damage due to bronchial obstruction if not diagnosed early and treated properly. They are mainly treated with surgery; including rigid bronchoscopy and surgical lung resection.

We report an EH that occurred in a long-term bed-ridden patient who had had a cerebral vascular accident 20 years before, and that presented with repetitive pulmonary infection of the right lower lobe during the past 5 years. Bronchoscopy revealed a right lower lobe endobronchial tumor with total occlusion. The tumor was firm and could not be eradicated by flexible fiberoptic bronchoscopic electrocautery. Since the patient had a history of tooth loss many years before, we highly suspected that the tumor was tooth impaction-related with chronic granulation formation. During fiberoptic bronchoscopic electrocautery, we unexpectedly "extracted" the tumor with an electrosurgical snare loop. Bronchial mucosa defect was also noted but no complications (such as pneumothorax or massive bleeding) occurred because of the right lower lung chronic atelectasis. The tumor had a tooth-like appearance; however, it showed popcorn calcification on radiography. Pathology confirmed that it was an EH.

With the recent developments in fiberoptic bronchoscopy, such as laser therapy and electrocautery, patients with EH have a greater possibility of successful medical treatment initially, thus avoiding the risk of surgery and general anesthesia. Although we suggest that fiberoptic bronchoscopic electrocautery is a feasible treatment for EH, it should be performed selectively. ***(Thorac Med 2010; 25: 142-148)***

Key words: electrosurgical snare loop, endobronchial hamartoma, fiberoptic bronchoscopy

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Introduction

Lung hamartomas are the most common benign lung tumors; however, a pulmonary hamartoma in an endobronchial location is extremely rare [1-7]. Even though endobronchial hamartomas (EH) are considered benign in nature, they still pose potentially fatal complications. The treatment for hamartomas is individualized [1, 4]. Although rigid bronchoscopy is usually the first choice [1, 8-9], in some cases, surgical intervention is needed [2-4, 7]. With recent advances in fiberoptic bronchoscopy, patients with endobronchial lesions have a greater possibility of being diagnosed early and treated medically, thereby avoiding the risk of surgery [10-11]. We report a 78-year-old man suffering from an EH who had repeated pulmonary infections. The tumor was unexpectedly removed by an electrosurgical snare loop during a fiberoptic bronchoscopy electrocautery procedure.

Case Report

This 78-year-old man was a heavy smoker. He had had a cerebrovascular accident 20 years before with the sequela of right-side hemiplegia. In the past 5 years, he had had several episodes of right lower lobe (RLL) pneumonia with respiratory failure. He had received a tracheostomy 2 years previously to assist with sputum clearance. Unfortunately, airway secretion and dyspnea were not improved after the tracheostomy. Bronchoscopy showed a granulation-like tumor with total occlusion of the RLL orifice. Surgical intervention with RLL lobectomy had been suggested at another hospital. He was then transferred to our hospital for surgical intervention.

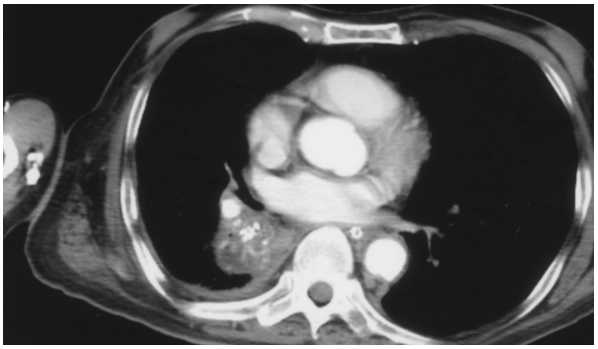
At admission, he was drowsy and had an intractable cough with much purulent sputum. The hemogram showed mild anemia without leukocytosis (WBC count 4900/μL and Hb 10.5 g/dL). The biochemistry tests were normal except for hyponatremia (Na^+ 127 mmol/L). Arterial blood gas under a tracheostomy mask with FiO_2 35% showed $PaCO_2$ 40.5 mmHg, PaO_2 99.6 mmHg and HCO_3 27.1 mmol/L. A sputum culture revealed both *Pseudomonas aeruginosa* and *Acinetobacter baumannii* infections.

Chest radiography showed reticulonodular opacities of both lungs and collapse of the RLL with cystic bronchiectasis (Figure 1A). Chest computed tomography (CT) showed irregular calcification within a soft tissue density in the RLL (Figure 1B). Bronchoscopy revealed a well-circumscribed polypoid tumor that occluded the RLL orifice (Figure 1C). An endobronchial ultrasound image revealed a well-defined hypoechoic lesion with discrete, eccentric calcification, a small area of acoustic shadow and an intact bronchial wall, all indicating the benign characteristics of this lesion (Figure 1D). Bronchoscopic biopsy of the lesion showed chronic inflammation only.

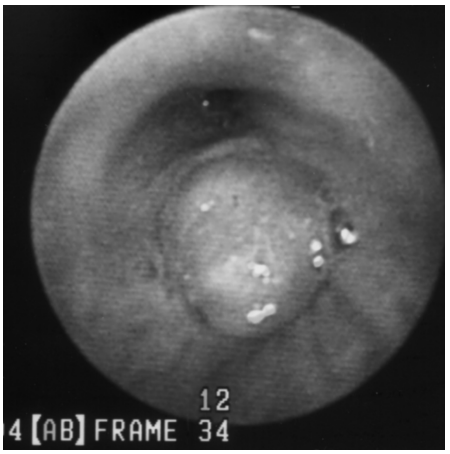
During manipulation with biopsy forceps, we noted the partially movable characteristic of this lesion. Tracing his past history, his wife remembered that he had lost some of his teeth 2 years before. Tooth choked was therefore considered in the differential diagnosis.

Another bronchoscopy was performed 1 week later. We attempted to remove the suspected tooth from the granulation tissue with foreign body forceps and grasping baskets as much as possible, using an electrosurgical knife and heat probe, but this failed. We then encircled the lesion with an electrosurgical snare (SD-7C-1, Olympus, Tokyo, Japan) and strenuously extracted the suspected “tooth”. This pro-

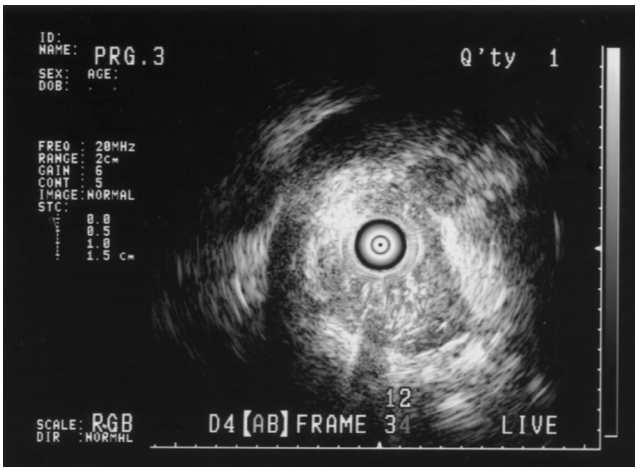
(A)



(B)



(C)

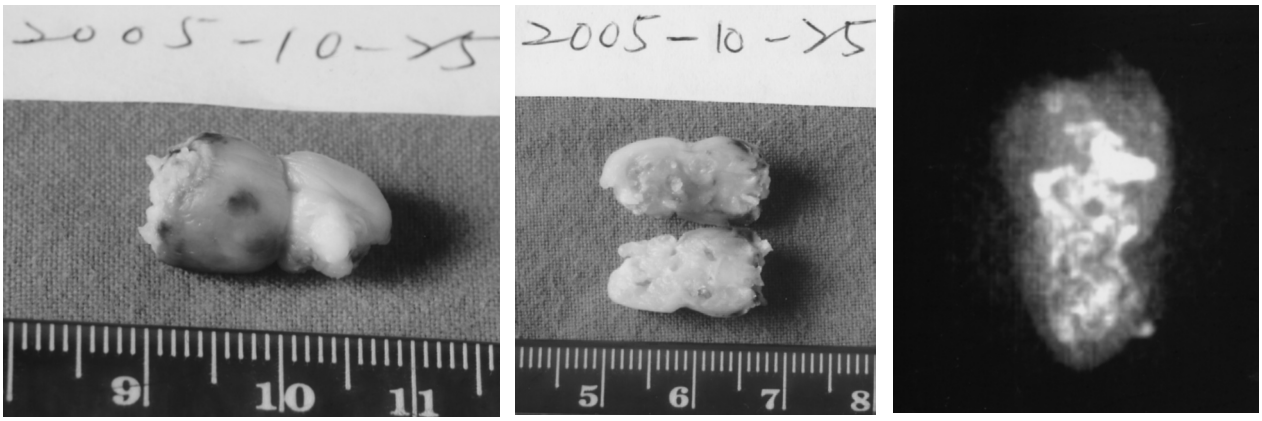


(D)

Fig. 1. (A) Chest radiography showed reticulonodular opacities of both lungs and collapse of the RLL with cystic bronchiectasis. (B) Chest CT showed irregular calcification within a soft tissue density in the RLL. (C) Bronchoscopy revealed a well-circumscribed polypoid tumor that occluded the RLL orifice. (D) EBUS showed a well-defined hypoechoic lesion with discrete, eccentric calcification, a small area of acoustic shadow and an intact bronchial wall.

cess gave the removed tumor a "waistline" appearance, causing it to look grossly like a tooth (Figure 2A). The removed tumor was easily halved with a surgical knife and we could see the cartilage and fat components inside (Figure 2B). However, it did not show the typical radiological characteristics of a real human tooth under X-ray examination. On the contrary, it showed "popcorn" calcification, which is a radiographically typical characteristic of a hamartoma (Figure 2C). Histologically, the tumor consisted predominantly of fat tissue, collagen fibers and cartilage, and was lined with normal bronchial epithelium (Figure 3). In another section (not shown here), we also found a small area of bony spicules with viable blood vessels. An EH was diagnosed.

After unexpectedly removing the EH, we noted some mucosal defects in the RLL bronchial wall. As the surrounding lung was chroni-



(A) (B) (C)

Fig. 2. (A) Grossly, this lesion looked like a tooth, having a "waistline" appearance made by the electrosurgical snare loop. (B) When halved with a surgical knife, it showed grossly the cartilage and fat components. (C) It also showed a radiographically typical "popcorn" calcification pattern.

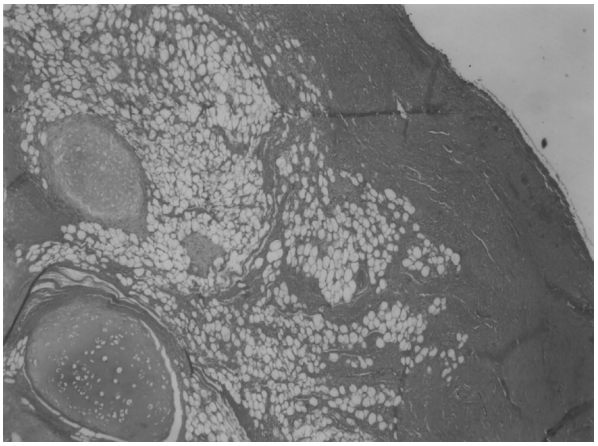


Fig. 3. Histologically, the tumor consisted predominantly of fat tissue, collagen fibers and cartilage, and was lined with normal bronchial epithelium (H&E stain, 100X).

cally atelectatic and consolidated, the patient did not develop complications such as pneumothorax or bleeding. Clinically, the patient showed a dramatic improvement in his cough and copious sputum after removal of the EH and was discharged smoothly days later.

Discussion

Lung hamartomas are the most common benign lung tumors, but are still rare, with an incidence of only 0.025% to 0.96% [1-6, 12-13]. The incidence of pulmonary hamartoma with an endobronchial location is around 1.4% to 20% [1-7, 12-13]. EH occurs mostly in elderly men who smoke, with a mean age between the sixth and seventh decades [1-7, 12-13]. It is usually a single occurrence with a very low risk of malignancy, even though it has been observed concomitantly in some lung cancer patients [1, 10, 12-14]. It has no reported association with parenchymal hamartomas and recurrence is rare [1, 2, 5].

Most patients with peripherally located pulmonary hamartomas are asymptomatic at the time of diagnosis [4-7, 12-13]. In contrast, 80% of EH are usually symptomatic and need treatment [1, 4-7]. The most common presentations are productive cough, hemoptysis and obstructive pneumonia [1-5, 12].

EH often has radiographic abnormalities,

although they are non-specific [1, 15]. Chest radiography often shows lobar atelectasis, pneumonitis or a hilar mass, but fails to reveal the primary lesion because "popcorn" calcification is not always present [3-4, 8, 10-13, 15]. EH tends to have relatively more fat than parenchymal hamartomas due to a relative abundance of fat in the bronchial walls, as opposed to the lung parenchyma [15-16]. This may contribute to the suspicion of EH when fatty endobronchial lesions are identified on chest CT scans [15-16]. The chest CT scan of our patient showed irregular calcification within soft tissue. The surrounding lung parenchyma was destroyed and atelectatic, and we failed to recognize the fat density within it, thus failing to make the right diagnosis using chest CT images. Although some investigators think that EH can be diagnosed with chest CT [14-16], most agree that preoperative diagnosis is difficult and perhaps even impossible [3, 5-7, 15]. An operation for histological examination is usually necessary for a definite diagnosis [5, 8, 13]. Lobectomy or even pneumonectomy has been performed for the suspicion of malignancy [2].

Treatment of EH is considered when patients are symptomatic or in patients with serious radiographic abnormalities, but it must still be individualized [1, 4]. Rigid bronchoscopy with laser or other fiberoptic bronchoscopic procedures are the first choice of treatment for EH and might avoid the risk of thoracotomy [1, 8-9]. Nevertheless, if the EH is bulky, the lung behind the EH is irreversibly destroyed, or malignancy is suspected, surgical resection of the destroyed lung should be considered, including lobectomy and pneumonectomy [2-4, 7, 13, 17-18].

In rare cases, EH can be removed by fiberoptic bronchoscopy [10-11, 19]. However, the recent rapid advances in fiberoptic bronchoscopy, such as laser therapy, electrocautery and endobronchial ultrasound, may offer alternative choices of therapy for EH [11, 17, 19]. Our patient was symptomatic and the lung behind the EH was severely destroyed. Lobectomy might have been the other choice of treatment. However, due to concerns about his poor performance status, we removed the lesion by fiberoptic bronchoscopy and avoided the high risks of operation and anesthesia.

In conclusion, we suggest that fiberoptic bronchoscopy with electrocautery might be a feasible treatment for EH, especially for patients at high risk for surgical intervention. However, it should be performed selectively.

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支氣管內過誤瘤以支氣管鏡電燒環成功地移除—病例報告

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支氣管內過誤瘤很少見，但若未及早診斷和適當處理，常常因引起支氣管阻塞而造成不可逆之肺傷害。一般是用外科手術治療，包括硬式支氣管鏡和外科肺切除術。

我們在這兒報告一中風二十年長期臥牀患者，近五年出現反覆右下肺肺炎。支氣管鏡發現右下肺支氣管出口有一支氣管內腫瘤造成完全阻塞。由於做纖維式支氣管鏡電燒灼術過程中發現此腫瘤很結實，無法以電燒灼術移除，加上數年前牙齒嗆入病史，故高度懷疑為牙齒嗆入併慢性肉芽形成，在用電燒環套住做電燒過程中不預期地拔出了此腫瘤。拔出後發現支氣管粘膜有些微破損，但因患者右下肺早已慢性萎縮無通氣功能，故無氣胸或出血之併發症。拔出之腫瘤外觀像牙齒，但X光下卻不是牙齒而是呈現“popcorn”之鈣化，病理下發現此腫瘤其實是一支氣管內過誤瘤。

近年來隨著纖維式支氣管鏡術的進步，例如雷射和電燒灼術，支氣管內過誤瘤之患者有了更多的機會先接受內科治療，以避免開刀和全身麻醉之風險。雖然電燒灼術是治療支氣管內過誤瘤之一種可行的方法，但仍然要選擇性地進行。*(胸腔醫學* ***2010; 25: 142-148)***

關鍵詞：電燒環，支氣管內過誤瘤，纖維式支氣管鏡術

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Iatrogenic Metastasis Associated with Implanted Venous Access Port – A Case Report

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Cancer patients are always concerned about metastases associated with the diagnostic or therapeutic procedures. Though uncommon, iatrogenic metastasis is nevertheless not as rare as once thought and merits close attention. We herein report a 47-year-old man with small-cell lung cancer who developed a metastasis at the injection site of a totally implanted venous access port 7 months after its establishment. On searching the Medline database, no similar cases were found. We also highlighted the importance of early detection as aggressive surgical intervention or radiotherapy may offer a satisfactory long-term outcome in isolated iatrogenic seeding metastasis. ***(Thorac Med 2010; 25: 149-154)***

Key words: cancer, implanted venous port, metastasis

Introduction

Cancer patients are always concerned about the potential risk of metastases associated with diagnostic or therapeutic procedures. Though uncommon, iatrogenic metastasis is nevertheless not as rare as once thought and merits close attention. We herein report the case of a 47-year-old man with small-cell lung cancer in which metastasis developed at the injection site of a totally implanted venous access port 7 months after its establishment. In a Medline database search, previous reports of iatrogenic metastasis were mostly related to needle biopsy tracts or therapeutic drainage catheters. No metastasis associated with permanent venous access ports has been reported. Of note, in cases with isolated "tract" metastasis, aggressive surgical intervention or radiation therapy may provide an optimistic long-term outcome.

Case Report

A 47-year-old man with limited-stage small-cell lung cancer diagnosed 7 months earlier was admitted for evaluation of dyspnea and right-side pleural effusion. The patient had undergone a totally implanted venous access port procedure (BardPort@ Implanted Ports with Groshong Catheters, Bard Inc., Utah) soon after the diagnosis and had since received 6 cycles of chemotherapy with cisplatin plus etoposide, followed

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by radiation therapy with 6,660 cGy (centigray) in 37 fractions. The response to treatment was poor. Five months after diagnosis, right hilar invasion and cervical spine metastasis developed and the disease was redesignated as extensive stage.

On physical examination, the patient appeared chronically ill and had bilateral lower leg edema. The right chest wall was dull to percussion and the breathing sounds were decreased in the right lung base. A 3-cm, non-tender erythematous nodule was noted at the injection site of the venous port (Figure 1). A computed tomography (Figure 2) of the chest revealed the presence of a nodule located precisely over the portal of the implanted device. An excisional biopsy was performed and the histologic examination revealed a picture of metastatic small-cell carcinoma. Despite our treatment, the patient succumbed to his disease 3 weeks later.

Fig. 1. A 3-cm, non-tender erythematous nodule at the injection site of the venous port on the right chest wall

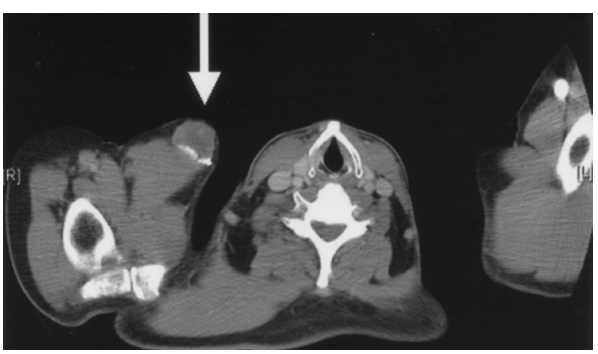

Fig. 2. Computed tomography of the chest reveals the presence of a nodule (arrow) located precisely over the portal of the implanted device.

Discussion

Venous access is crucial in the management of cancer patients, not only in the early phase of surgery or chemotherapy, but also in the chronic and late phases of palliative care. Before the advent of totally implanted vascular access ports, venous access was always a major problem for cancer patients and healthcare professionals. It has been noted that pain associated with the search for suitable veins was the most distressing unwanted side effect of chemotherapy [1]. The causes of gradual obliteration of available veins include the relatively old age of cancer patients, chemical irritation, and repeated venipunctures resulting in thrombophlebitis and sclerosis of the surface veins [2].

An innovative design -- a long-term, totally implanted vascular access port -- has brought dramatic change to the situation. In addition to retaining all the advantages of external venous catheters, the subcutaneous location of the injection site allows uninhibited activity for the patient when the catheter is not in use. The risk of catheter-associated infections is also reduced because of the lack of externally exposed parts and decreased manipulation [3]. Clinical experience has proven the usefulness of these implanted vascular access systems, and yet complications, such as malpositioning or migra-

tion [4-5], fracture with dislodgement [6], and embolization [7], are emerging as well. Most of the reported complications were related to insufficient information provided to the patient or healthcare provider, or inappropriate device placement techniques and nursing care [8].

The BardPort Implanted Ports with Groshong catheters are designed to provide repeated access to the vascular system for the delivery of medications and intravenous fluids. They are also indicated for withdrawal of blood samples. The Groshong 3-position valve helps provide security against blood reflux and air embolism into the system. The catheter is flushed with normal saline and does not require anticoagulants to maintain patency. In our hospital, withdrawal of blood from implanted venous ports of any kind is prohibited and the device in the present case had never been used for blood sampling.

Percutaneous procedures are performed increasingly for both diagnostic and therapeutic purposes in cancer patients. However, despite the great care given to the performance of these procedures, iatrogenic tumor spread remains a potential complication [9]. Tumor seeding associated with medical procedures has been reported previously and is not as rare as once thought.

In a variety of tumors, the incidence of tumor seeding related to a biopsy needle tract is between 0.003% and 0.009% [10]. Most of the reported cases were in pancreatic tumors, hepatocellular carcinoma, papillary thyroid carcinoma, renal cell carcinoma, osteosarcoma, and peritoneal carcinoid tumors [10]. In breast cancer, the frequency of implantation along the biopsy tract has been reported to be up to 38% [11]. Seeding along the tract of a stereotactic needle biopsy has been reported in brain tumors that have a very low propensity for distant metastasis [9, 12].

Subcutaneous seeding also has been reportedly associated with therapeutic measures such as radiofrequency ablation of hepatic tumor [13], percutaneous drainage for renal tumor with obstructive uropathy [14-15], cryosurgery for prostate cancer [16], drainage for malignant pleural effusion [17], and surgery for carcinoma of the common bile duct [18].

Although the prognosis for cancer patients with distant metastasis is generally poor, the excision of the catheter tract may enable long-term survival in selected patients with isolated metastases along the tract [18-19]. In patients with metastases associated with chronic indwelling pleural catheters, successful treatment has been achieved by external-beam radiotherapy [20].

Subcutaneous metastasis in advanced cancer is a possible explanation for the present case. However, the precise location at the injection site over the venous port makes direct seeding more likely. We assume that repeated punctures resulted in a small volume of extravasations, which in turn led to metastasis. Our assumption is further supported by a recent study of 88 small-cell lung cancer patients [21]. In the report, circulating tumor cells (CTCs) were detected in 43 of the 50 patients assessed. The mean number of CTCs in the study was substantially higher than that of 964 cancer patients and 90 lung cancer patients of unspecified cell type in a report by Allard *et al*. [22]. In a study using the commercially available system CellSearch, Takana *et al*. found the CTC test to have a significant diagnostic performance in predicting the presence or absence of distant metastasis and concluded that CTC is a surrogate of distant metastasis in primary lung can-

cer patients [23].

The complication is probably not very rare, and with continuing improvements in cancer survival, the incidence of catheter tract-related metastasis is expected to increase, as well. In a Medline database search (National Library of Medicine, National Institutes of Health, USA), no reports on metastasis associated with implanted venous ports could be found.

In conclusion, we report the first case of an iatrogenic metastasis associated with a totally implanted venous access port. The incidence is probably not very rare and represents a well-recognized complication. Patients should be warned of this potential complication and close attention should be paid to any nodule developing at the injection site. Early detection and aggressive treatment may provide an optimistic long-term outcome.

Acknowledgments

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於植入式靜脈導管發生之醫源性轉移

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對於診斷性或治療性處置是否會導致轉移一直是癌症病患最在意的問題。醫源性轉移雖不常見，但亦不如以前想像般罕見。我們在此報告一名罹難小細胞肺癌的47歲男性，在接受植入式靜脈導管七個月後，於注射處發生了一個轉移。經搜尋Medline database，並無類似報導。我們也強調早期發現的重要性，因積極性手術或放射治療在單一轉移有可能會有令人滿意的長期預後。*(胸腔醫學* ***2010; 25: 149-154)***

關鍵詞：癌症，植入式靜脈導管，轉移

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Tuberculosis Treatment Failure Due to Multiple-Strain *Mycobacterium tuberculosis* Infection – A Case Report

You-Cheng Chang, Ruwen Jou*, Shun-Tien Chien, Ying-Hsun Wu, Ruay-Ming Huang

Treatment failure in a tuberculosis patient has been defined as continued or recurrent positive cultures after 4 months of treatment. The common reasons for this are the poor compliance of the patient or an inappropriate regimen of anti-tuberculosis drugs. Multiple-strain *Mycobacterium tuberculosis* infection with different drug susceptibility results is another reason that has seldom been considered in the past. The development of genotyping methods, such as restriction fragment length polymorphism, has considerably improved the ability to distinguish *M. tuberculosis*. ***(Thorac Med 2010; 25: 155-160)***

Key words: tuberculosis, *Mycobacterium tuberculosis*, multiple-strain *Mycobacterium tuberculosis* infection, restriction fragment length polymorphism

Introduction

Tuberculosis (TB) can develop through progression of a recently acquired infection (primary disease), reactivation of a latent infection, or exogenous re-infection. In the past, it was estimated that approximately 90% of adult cases of TB were the result of endogenous reactivation of latent infection. More recently, with the aid of molecular genotyping techniques, it was found that approximately 60% to 70%, and 30% to 40% of TB cases, respectively, were reactivation and recent infection [1]. Multiple-strain *Mycobacterium tuberculosis* infection can also be identified by using molecular biological methods. We herein describe a case of pulmonary TB treatment failure due to a multiple-strain infection.

Case Report

A 33-year-old female diabetes mellitus patient under insulin control for 5 years visited the Chest Hospital, Department of Health, Executive Yuan on 16 February 2005 with the chief complaint of cough and generalized malaise for 2 months. Chest radiography (CXR) demonstrated right upper lung consolidation with cavity and satellite lesions, and left upper lung infiltration (Figure 1). Sputum acid-fast stain was positive, and anti-TB drugs, including ethambutol and rifater (containing isoniazid, rifampin, and pyrazinamide) were prescribed at that time. Mycobacterial culture revealed a

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positive *M. tuberculosis* complex that showed sensitivity to first-line anti-TB drugs in conventional 7H10 agar proportion drug susceptibility testing (DST). The patient's symptoms improved after anti-TB treatment. Sputum conversion was noted after 15 June 2005. The anti-TB regimen was shifted to ethambutol and rifinah (containing isoniazid and rifampin) after 1 June 2005. Follow-up CXR showed improvement on 9 December 2005 (Figure 2). Since the sputum mycobacterial culture was still positive after a 2-month treatment, we extended the treatment duration to at least 9 months.

Unfortunately, she suffered from hemoptysis in February 2006. CXR demonstrated increased right upper lung infiltration (Figure 3), and the sputum acid-fast stain was positive on 23 February 2006. Under the impression of treatment failure, she was admitted to our hospital. First and second-line anti-TB drugs, including ethambutol, rifater, kanamycin, levofloxacin, para-amino-salicylic acid (PAS), prothionamide, and cycloserine, were prescribed. The mycobacterial cultures remained *M. tuberculosis* complex-positive throughout February 2006. Cultures from sputum collected on 23 and 24 February 2006 were both resistant to isoniazide, rifampin, and streptomycin. However, the culture of the sputum sample on 26 February 2006 was *M. tuberculosis* complex and was resistant to isoniazide, rifampin, ethambutol,

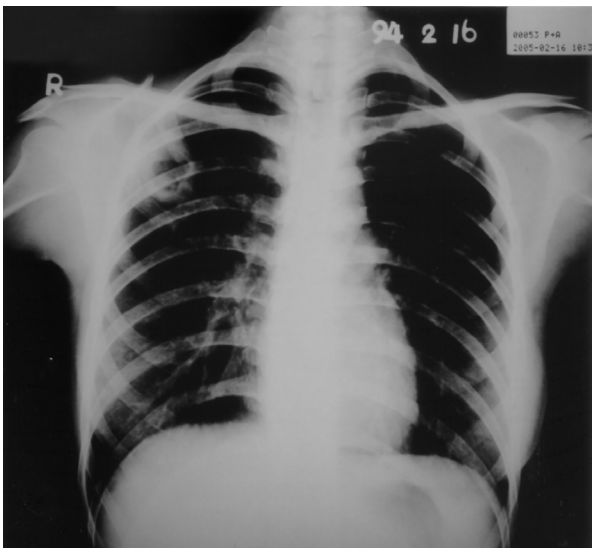

Fig. 1. Posteroanterior chest radiograph shows right upper lung consolidation with cavity and satellite lesions, and left upper lung infiltration.

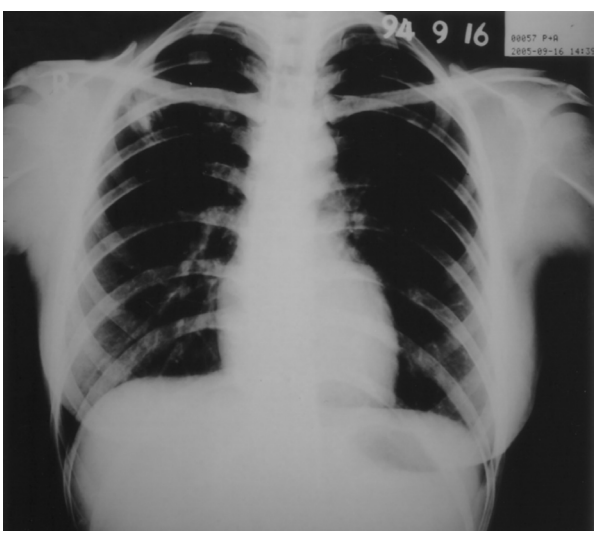

Fig. 2. Posteroanterior chest radiograph shows right upper lung fibrocalcified lesion and left upper lung fibrosis change.

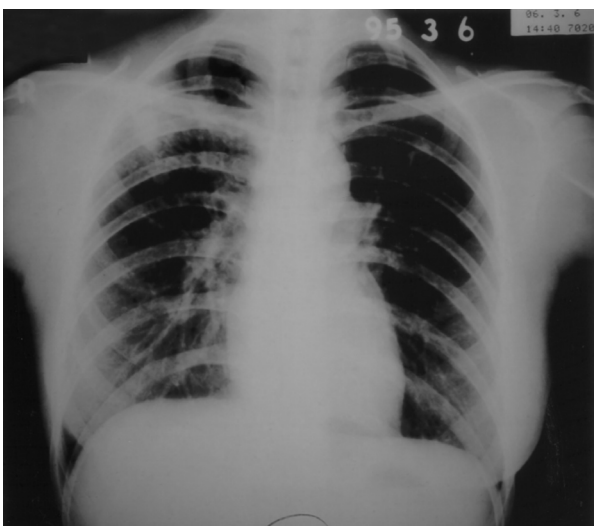

Fig. 3. Posteroanterior chest radiograph shows increased right upper lung infiltration.

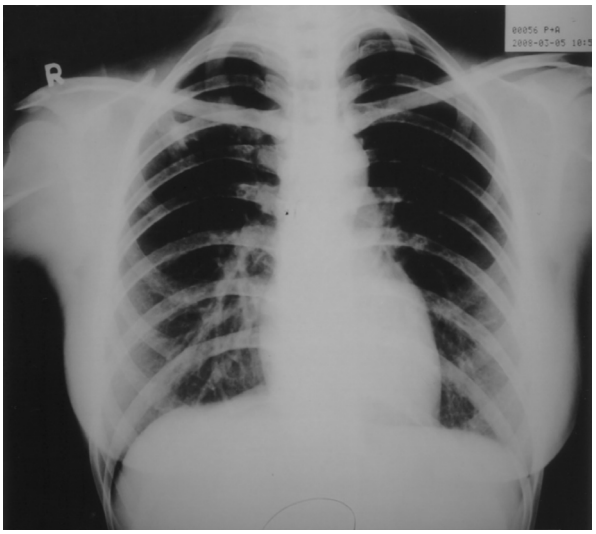

Fig. 4. Posteroanterior chest radiograph shows right upper lung fibrocalcified lesion and left upper lung fibrosis change.

and streptomycin. The sputum mycobacterial culture converted to negative after May 2006. Pulmonary TB treatment was completed in March 2008, and the follow-up CXR showed improvement (Figure 4). The treatment course, including regimens and sputum smear with culture results, is listed in Table 1.

The 4 isolates were sent for genotyping using the restriction fragment length polymorphism (RFLP) method. The RFLP pattern of the first isolate cultured on 16 February 2005 was different from that of the other 3 cultures in 2006. The RFLP results were compatible with DST profiles and the clinical course (Figure 5). Multiple-strain *M. tuberculosis* infection was confirmed in the patient.

Discussion

For years, there has been much discussion and many opinions about the relative importance of exogenous re-infection and endogenous reactivation in the development of clinical TB disease following the initial infection with *M. tuberculosis* [2]. Patients with TB have often been assumed to be infected with single *M. tuberculosis*, and infection with 1 strain was thought to confer immunity to additional *M. tuberculosis* infection [3]. Therefore, recurrence of disease after treatment is often considered to be caused by the same strain that caused the initial infection. Mankiewicz and Liivak

Table 1. Clinical course of anti-TB treatment included anti-TB drugs, and sputum smears with culture results. INH = isoniazid, RIF = rifampin, EMB = ethambutol, PZA = pyrazinamide, KM = kanamycin, LVX = levofloxacin, TBN = prothionamide, CS = cycloserine, PAS = para-aminosalicylic acid.

date	year	2005											2006											2007											2008		
	month	2	3	4	5	6	7	8	9	10	11	12	1	2	3	4	5	6	7	8	9	10	11	12	1	2	3	4	5	6	7	8	9	10	11	12	1	2	3
sputum	smear	+	+	+	+	−		−	−		−		−	+	+	−	−	−		−		−	−		−	−			−		−	−		−	−		−	−	
	culture	+	+	+	+	−		−	−		−		−	+	+	−	−	−		−		−	−		−	−			−		−	−		−	−		−	−	
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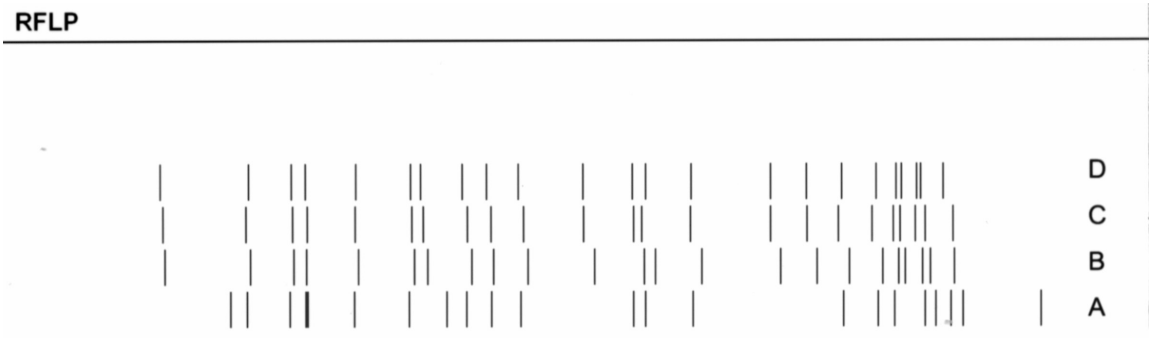

Fig. 5. Specimen A was cultured on 16 February 2005. Specimen B was cultured on 23 February 2006. Specimen C was cultured on 24 February 2006. Specimen D was cultured on 26 February 2006. The RFLP pattern of the first specimen which was cultured on 16 February 2005 was different from the other 3 sets of specimens which were cultured from 23 February 2006 to 26 February 2006.

used phage typing to analyze the heterogeneity among individual colonies obtained from cultures of specimens isolated from 233 Eskimo patients, leading to the conclusion that 14.1% of patients tested were simultaneously infected with more than 1 strain of *M. tuberculosis* [4]. The development of molecular biological methods, including RFLP, has considerably improved the capacity to distinguish *M. tuberculosis* [5-6]. Multiple-strain *M. tuberculosis* infection with distinct DST results seriously confuses the prognosis of treatment [7-8]. Multiple infections in patients with TB have been described in the form of mixed or simultaneous infections with 2 or more different strains, or in the form of exogenous re-infection, in which an initial infection with a strain is followed by a second infection with a new strain. Mixed infections are defined as simultaneous infection by 2 or more *M. tuberculosis* strains, as evidenced by very distinct molecular biological methods. When we provide regular treatment for a TB patient but fail, multiple-strain infection should be considered [9]. Furthermore, it is possible that undetected drug-resistant strains may emerge under the pressure of initial antibiotics. Our findings suggested that antibiotics pressure with a standard first-line regimen might have led to a reduction in the growth of the drug-susceptible strain, and the selection of a previously undetected genetically distinct drug-resistant strain [10]. To understand the causes of TB treatment failure, we recommend performing conservative bacteriological examinations, including mycobacterial culture, DST, and genotyping to analyze the possibility of multiple-strain infection.

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結核病治療失敗導因於多重菌株感染：病例報告

張祐汪　周如文*　簡順添　吳盈勳　黃瑞明

結核病治療失敗的定義是經治療四個月後，痰培養持續或再次陽性，常見的原因為病人醫囑順從性不好或處方的不適當。此外，多重結核菌株感染合併不同的藥物抗藥性，也可能是治療失敗的一種可能，過往這種情況較少被考慮到，但是伴隨著分子生物學的發展，使用基因分型方法（如限制酵素片段長度多形性），可以鑑別及釐清不同的結核菌感染導致的治療失敗。*(胸腔醫學* ***2010; 25: 155-160)***

關鍵詞：結核病，結核菌，多重結核菌株感染，限制酵素片段長度多形性

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Co-infection of Pulmonary *Mycobacterium chelonae* and Spinal *Mycobacterium tuberculosis*: A Case Report

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Co-infection of pulmonary *M. chelonae* and spinal *M. tuberculosis* in an immunocompetent adult is a rare condition. We reported a 32-year-old woman who developed chronic productive cough and nonspecific bilateral flank pain. Acid-fast bacterial cultures isolated *M. chelonae* from sputum samples and *M. tuberculosis* from a paraspinal abscess. She was finally cured by standard anti-tuberculosis regimens plus surgical intervention, and anti-chelonae therapy according to *in vitro* susceptibility testing. The diagnosis and treatment of both pulmonary and extrapulmonary mycobacterial infection require a high index of suspicion, adequate samples for smears and cultures, and *in vitro* susceptibility testing. ***(Thorac Med 2010; 25: 161-167)***

Key words: co-infection, *Mycobacterium tuberculosis*, *Mycobacteria chelonae*, susceptibility testing

Introduction

Mycobacterium tuberculosis (MTB) remains a major global public health problem worldwide, but increasing environmental non-tuberculous mycobacteria (NTM)-related infection has been observed. Spinal MTB may cause prolonged nonspecific constitutional symptoms and lead to a delayed diagnosis. Similarly, the diagnosis of NTM infection requires clinical suspicion and adequate sampling. Since susceptibility testing varies with different species of NTM, the clinician should use *in vitro* susceptibility data to treat NTM.

We report a young and previously healthy woman diagnosed with pulmonary *M. chelonae* and T12-L1 MTB spondylitis with psoas abscess coinfection. The patient was cured after a full course of anti-*M. chelonae* therapy and anti-MTB treatment with surgical intervention to the spine.

Case Report

A 32-year-old woman first presented to our hospital because of a nodule-like lesion noted on her left breast. She worked in an office, was a non-smoker, and had a generally unremarkable past history. Fine-needle aspiration revealed necrotizing mastitis composed of diffuse necro-

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Fig. 1. (a) Thoraco-lumbar spinal radiograph showing wedge deformity of the vertebral body of L1 and narrowing of the T12-L1 disc space. (b) T-L spinal MRI revealing infectious spondylitis involving T12-L1 with epidural extension resulting in spinal stenosis, and suspicious abscess formation involving bilateral psoas muscles.

sis interspersed with multinucleated giant cells. About 3 months later, she presented again with intermittent bilateral flank pain and productive cough lasting 2 months. The thoraco-lumbar spine radiograph showed wedge deformity of the vertebral body of L1 and narrowing of the T12-L1 disc space (Figure 1a). Osteomyelitis bone scan with gallium-67 and technetium-99m methylene diphosphonate showed no significant inflammation or infection, but T-L spinal magnetic resonance imaging (MRI) revealed infectious spondylitis involving T12-L1 with epidural extension resulting in spinal stenosis, and suspicious abscess formation involving the bilateral psoas muscles (Figure 1b).

Laboratory studies revealed white blood cells within the normal range (6500/uL), an elevated serum C-reactive protein level (3.36 mg/dL), an elevated erythrocyte sedimentation rate (42 mm/hr), and negative for human immunodeficiency virus infection. Computed tomography (CT)-guided biopsy samples were sent for Gram's stain, acid-fast bacteria (AFB) stains and cultures, routine bacterial cultures, and histologic tests. All of the above studies were negative, except that the histologic sections revealed granulomatous inflammation composed of a few giant cells and some histiocytes. No caseous necrosis or acid-fast bacilli was found.

The chest radiograph showed fibrocalcification in the right upper lung field, irregular patch opacification in the right lower lung field, and pleural thickening on the right side with blunting of the right costophrenic angle (Figure 2a). High-resolution computed tomography (HRCT) scan of the chest showed multifocal bronchiectasis at the right lower lung. Three sputum samples were collected for AFB smears and cultures. Despite the negative AFB smears results, standard anti-MTB therapy with rifampicin (RMP), isoniazid (INH), ethambutol (EMB), and pyrazinamide (PZA) was initiated for 2 months, followed by RMP, INH, and EMB for 4 months for both the suspicious pulmonary and the extrapulmonary MTB infection.

The productive cough with intermittent dyspnea persisted despite 2 weeks of anti-MTB therapy and oral amoxicillin/clavulanate, and all of the previous AFB-stain negative sputa finally grew *M. chelonae*. In accordance with NTM pulmonary disease criteria [1] and the *in vitro* susceptibility test results, clarithromycin and ciprofloxacin were given orally. The flank pain and productive cough both improved after 2 months of anti-MTB and anti-NTM therapy. The final culture from the paraspinal abscess isolated MTB bacilli.

Four months after anti-MTB and anti-NTM

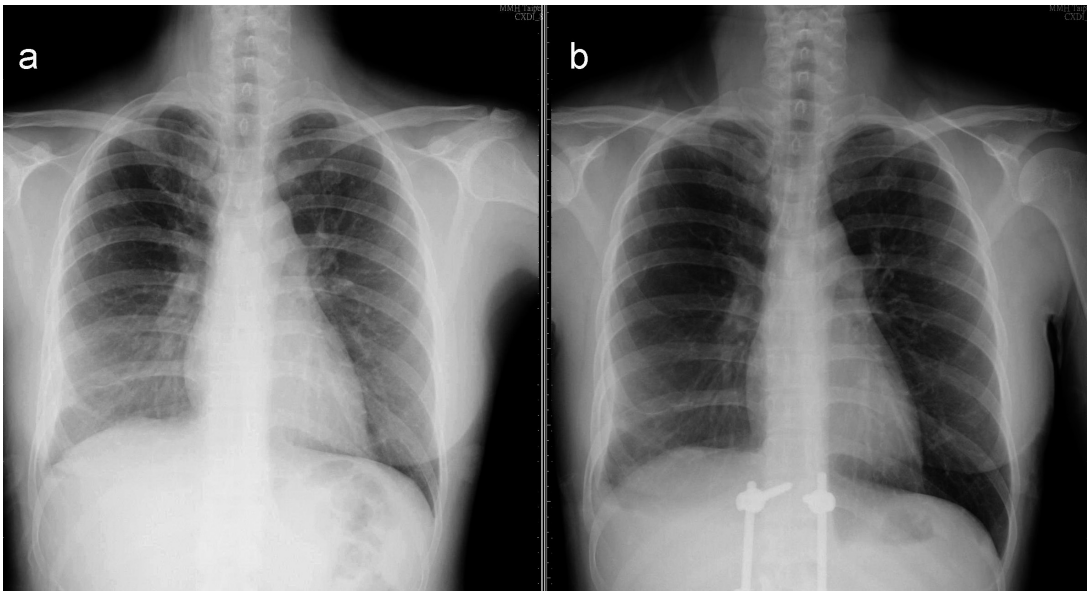

Fig. 2. (a) Chest radiograph showing fibrocalcification in the right upper lung field, irregular patch opacification in the right lower lung field, and pleural thickening on the right side with blunting of the right costophrenic angle. (b) Chest radiograph showing mild blunting of the right costophrenic angle with pleural change. The post-operative status of the lumbar spine with metallic device fixation is also noted.

therapy, the nodule lesion on her left breast was removed and showed granulomatous inflammation with central caseous necrosis surrounded by epithelioid cells and Langerhans' giant cells histologically. Despite the fact that the histologic picture was consistent with tuberculous infection, the AFB smear and culture from the section were both negative. Repeated sputum AFB smears and cultures were negative at the same time.

After 6-months of anti-MTB and anti-NTM therapy, there was no more muscle rigidity or focal neurological complications. However, the patient still complained of bilateral flank pain, so she underwent posterior decompression with internal fixation at another hospital (Figure 2b). Meanwhile, no further productive cough or dyspnea was noted after 12 months of anti-chelonae therapy.

Discussion

MTB remains a major global public health problem. It is estimated that about one-third of the world's population is infected with MTB [2]. After primary infection, MTB may reactivate at anytime and anywhere in the body. About 10% of MTB infection is diagnosed as extrapulmonary tuberculosis (EPTB) in Taiwan [3], and spinal MTB infection is a serious clinical problem. Among spinal MTB infection sites, the lumbar and lower thoracic regions are most commonly affected. These patients may develop varying degrees of kyphotic deformity, vertebral destruction, and neurologic complications [4-5].

Progressive local back pain for weeks to months, with or without associated muscle spasm and rigidity, is a common clinical presentation. Fever, weight loss, and constitutional symptoms are encountered in less than 40% of

cases [5]. Late manifestations, such as spinal cord compression or vertebral destruction, may lead to delayed diagnosis and inadequate access to medical care. A retrospective analysis of MTB patients diagnosed in western Nepal revealed that younger age and female gender were strongly associated with EPTB [2].

A high index of clinical suspicion and an accurate history of possible MTB exposure are essential to the diagnosis of spinal MTB. Physicians should consider spinal MTB in patients with an indolent clinical course manifesting as osteomyelitis involving the lumbar or thoracic spine with negative bacterial cultures [5-6]. Patients with suspected MTB infection should have appropriate specimens, such as bone biopsy, sent for AFB staining, mycobacterial culture, and histology for diagnosis of tuberculous osteomyelitis [6]. The most common granulomatous spinal infection in the world by far is MTB; however, fungi, certain bacteria and spirochetes may cause similar clinical and histologic features. Of the newer investigative modalities (ultrasound, CT scan, and MRI), MRI has been proven to be most useful for detection, assessment, and diagnosis [7].

Testing of anti-MTB drug sensitivity should be performed, given the increasing prevalence of multidrug-resistant spinal MTB. A multidrug combination is the mainstay of spinal MTB treatment. A 6-to-9-month treatment course is recommended for EPTB as initial therapy. Prolongation of therapy may be considered if the response to therapy is deemed slow [8]. Surgery may be necessary to drain abscesses, debride infected tissue, or stabilize the spine and relieve spinal cord compression. Otherwise, medical therapy alone should result in an excellent response [6].

In our case, the patient still complained of persistent bilateral flank pain despite anti-MTB therapy; therefore, she underwent surgery for spinal stabilization. The proper role of surgery in the treatment of tuberculous spondylitis remains an ongoing controversy. One large series showed similar recovery rates in both operative and nonoperative groups, but the nonoperative group required a longer period of treatment [9].

The term "nontuberculous mycobacteria" (NTM) is used to distinguish environmental mycobacteria from *M. leprae* and MTB. NTM are found primarily in water, both natural and tap water, but are also found in soil, dust, animals, and food. They most commonly cause skin and soft tissue infections, lymphadenitis, and lung diseases [10]. *M. chelonae* was isolated from sea turtles (*Chelona corticata*) by Friedman. In a review of 125 cases of rapidly growing mycobacterial infection, only 17 cases were primary pulmonary infection caused by *M. chelona*e, which would be a rare phenomenon [11].

The radiologic manifestations of pulmonary *M. chelonae* infection were fibronodular bronchiectasis or hypersensitivity pneumonitis rather than the classic cavitary form [10, 12-13]. A previous history of COPD, cystic fibrosis, scarring from previous MTB and pneumoconiosis, pulmonary alveolar proteinosis, gastroesophageal reflux disease, vomiting, and chest well disorders has been associated with *M. chelonae* infection, which may occur in younger persons. The clinical signs and symptoms of *M. chelonae* lung disease are generally nonspecific, and include chronic cough, sputum production, and fatigue. Fever and sweats are less frequent. Dyspnea, malaise, hemoptysis, weight loss, and wasting are uncommon and usually reflect advanced disease [10, 12].

Microbiologic study is an essential comple-

ment for the diagnosis of *M. chelonae* lung infection. A minimum of 3 sputum specimens in sterile disposable containers should be stained and cultured for mycobacteria. Fluorochrome staining is preferred because it can be done more rapidly and is more sensitive than conventional staining, with which *M. chelonae* are easily decolorized. The observation of high colony counts (ie, >100) and/or multiple isolates with any number of colonies has been frequently associated with clinical disease [1, 10, 12].

Susceptibility testing varies with different species of NTM; rapidly growing Mycobacterium, especially *M. chelonae*, *M. abscessus*, and *M. fortuitum*, they are not responsive to "standard" antituberculosis agents. Testing should be done against amikacin, cefoxitin, clarithromycin, ciprofloxacin, doxycycline, sulfamethoxazole, imipenem, and tobramycin. Linezolid and tigecycline may also be active. The optimal therapy for *M. chelonae* lung disease is unknown. On the basis of *in vitro* susceptibilities, 2 or more drugs including clarithromycin would likely be successful. Treatment for more than 12 months of negative sputum cultures is recommended [1, 12]. A study including 39 *M. chelonae* isolates from a medical center in Taiwan revealed high variations in susceptibility testing results. Among the 39 isolates, amikacin exhibited the best activity (100%), followed by linezolid (82%), clarithromycin (49%), and tobramycin (31%). The newer fluoroquinolones (moxifloxacin, gatifloxacin) showed poor potency against *M. chelonae*, as did azithromycin and imipenem. Therefore, accurate identification and susceptibility testing should be done for any isolates [14].

In our case, the initial findings, including chronic cough, sputum production, and irregular patch opacification on the chest radiograph, implied nonspecific pulmonary infection. Suspicious pulmonary MTB infection followed the granulomatous inflammation microscopically from the paraspinal abscess, but clinical respiratory improvement was not observed, despite initiating anti-MTB therapy. Fortunately, all 3 sputum cultures isolated *M. chelonae*, which met the diagnostic criteria of pulmonary infection, and anti-chelonae therapy was started. After a complete course of medical anti-MTB and anti-NTM therapy and surgical intervention in the spine, the flank pain and pulmonary symptoms resolved successfully.

Co-infection of pulmonary *M. chelonae* and spinal MTB in an immunocompetent young female patient in Taiwan has not been reported before. Patients with early diagnosis, sensitive organisms, and favorable pathologic lesions (i.e., an absence of large cavitations, ischemic tissue, and infarcted bone) can achieve full clinical healing without surgical intervention. The clinician should use *in vitro* susceptibility data for treatment of both MTB and NTM disease. Empiric therapy for suspected NTM lung disease is not recommended [14].

In summary, we would like to remind all physicians that MTB should be considered in patients with vertebral osteomyelitis, psoas abscess, and appropriate risk factors, and that pulmonary NTM infection is an increasingly important cause of morbidity and even mortality. Adequate sampling of every possible material is very important, because co-infection with different mycobacteria species at different sites is possible.

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同時感染肺龜鱉型分枝桿菌與脊椎結核分枝桿菌—一病例報告

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臨床上同時感染肺龜鱉型分枝桿菌和脊椎結核分枝桿菌的案例相當罕見。本文報告一例32歲年輕女性病人，起初的臨床表現為長期咳嗽與非特異性的側腹疼痛，胸部X光片呈現右上肺葉纖維鈣化、右下肺葉不規則實質化病變及肋模增厚，脊椎磁振影像檢查呈現T12-L1感染性脊椎炎及疑似腰肌膿瘍。檢驗結果三套痰液均培養出龜鱉型分枝桿菌，但脊椎膿瘍培養結果為結核分枝桿菌。病人接受抗龜鱉型分枝桿菌治療治癒肺部感染，並且以標準抗結核藥物及手術治癒脊椎結核感染。臨床上診斷及治療不同分枝桿菌同時感染肺內和肺外部位，有賴於醫師的警覺、適當的樣本處理切片、耐酸性染色與細菌培養、以及抗結核藥物的敏感性測試結果，作為治療的依據。*(胸腔醫學* ***2010; 25: 161-167)***

關鍵詞：雙重感染，結核分枝桿菌，龜鱉型分枝桿菌，體外藥物敏感性試驗

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