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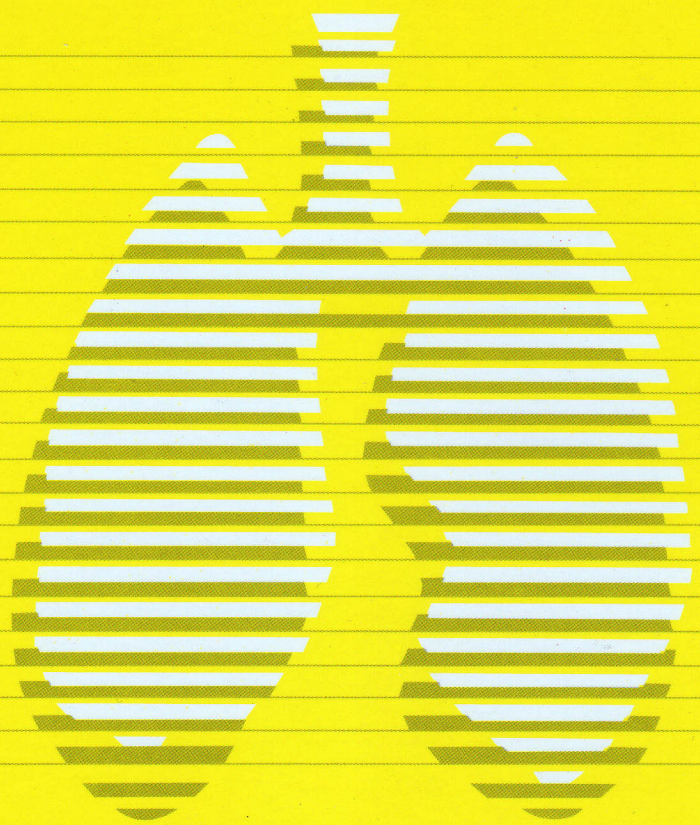

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原著

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Thoracic Medicine

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Orginial Articles

Case Reports

Pretreatment Neutrophil/Lymphocyte Ratio as a Prognostic Factor for Survival in Patients with Advanced Non-Small Cell Lung Cancer

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

Introduction: Peripheral neutrophils, lymphocyte counts and the neutrophil/lymphocyte ratio (NLR) have been associated with survival of patients with non-small cell lung cancer (NSCLC). In this study, we investigated the prognostic effect of NLR on overall survival of stage IIIB and IV NSCLC patients.

Methods: Patients with stage IIIB and IV NSCLC who underwent radiotherapy or chemotherapy between January 2004 and December 2006 were studied retrospectively. The complete blood count data with differential counts of peripheral blood before chemotherapy or radiotherapy were analyzed. The prognostic effect of clinicopathological factors and NLR were examined by univariate and multivariate analysis. Overall survival curves were derived using the Kaplan-Meier method, and the difference between the high and low NLR groups was assessed by log-rank test.

Results: In all, 375 eligible NSCLC patients, including 246 men and 129 women with a mean age of 66.7 years, were enrolled. Median overall survival durations of the low NLR (NLR<8.91) and high NLR groups (NLR≥8.91) were 10.15 and 2.20 months, respectively (p<0.001). The pretreatment NLR was an independent prognostic factor for overall survival (hazard ratio: 1.966; 95% CI: 1.527-2.532; p<0.001), Multivariate analysis showed that age younger 66 years and performance status were independent prognostic factors. Increased pretreatment NLR was associated with a poor prognosis for advanced NSCLC patients.

Conclusions: NLR is easily measured and may be utilized as a reliable prognostic predictor for advanced NSCLC. ***(Thorac Med 2013; 28: 321-329)***

Key words: neutrophil/lymphocyte ratio, prognostic factor, non-small cell lung cancer

Introduction

Non-small cell lung cancer (NSCLC) is the leading cause of cancer-related death worldwide [1]. There have been advances in many aspects of the classification, diagnosis, and treatment of NSCLC in the last decade, but the duration of overall survival (OS) remains poor. Many prognostic factors for NSCLC, such as tumor size, performance status, age, gender,

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lymph node metastasis and distant metastasis, affect survival significantly. Several studies of the inflammatory conditions associated with the prognosis of NSCLC have been published recently. Preoperative lymphocyte count was reported to be an independent prognostic factor in node-negative NSCLC [2], and pretreatment neutrophil count was reported to be an independent prognostic factor in advanced NSCLC [3]. The number of lymphocytes observed after the first chemotherapeutic cycle had significantly decreased in advanced NSCLC patients with progressive disease, but increased in patients with partial response or stable disease [4]. An increased preoperative neutrophil/lymphocyte ratio (NLR) was an independent predictor of survival in NSCLC patients [5]. The NLR obtained from percutaneous fine-needle aspiration biopsy specimens was also found to have prognostic significance in advanced NSCLC [6]. The aim of the present study was to investigate the relationship between the NLR and OS of stage IIIB and IV NSCLC patients.

Materials and Methods

Patients

We performed a retrospective analysis of patients diagnosed with stage IIIB and IV NSCLC between January 2004 and December 2006 and that underwent radiotherapy or chemotherapy in a medical center in Taiwan. All patients underwent standardized 6th edition 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 a presentation of pneumonia on chest X-ray, as reported by a radiologist or a chest medicine physician at the time of the complete blood count, urinary tract infection, or other infections, and those that received corticosteroid therapy were excluded. Clinicopathological data of 375 patients were obtained from the hospital's database.

Assessment of NLR

Complete blood count data with differential counts of peripheral blood before chemotherapy or radiotherapy, as well as the pretreatment NLR, were collected from each patient.

Statistical analysis

OS was the primary measure of this analysis. Survival was defined as the time from initial chemotherapy or radiotherapy to the time of death or the last known information on the patient's vital status. To compare the clinicopathological baseline characteristics of the patients, Pearson's χ^2-test (or Fisher's exact test when appropriate) was used for categorical variables, and the *t* test for continuous variables. Univariate predictors and survival curve were derived using the Kaplan-Meier method. Differences in survival data between the high and low NLR groups were assessed by log-rank test. Multivariate analysis of hazard ratios (HR) of death and 95% confidence intervals (95% CI) were estimated with the Cox's proportional hazards model. A p value of <0.05 was regarded as statistically significant.

Results

Patients' clinicopathological characteristics

Of the 375 eligible NSCLC patients, 246 were men and 129 were women, with a mean age of 66.7 years (ranging from 34 to 92 years) (Table 1). The mean NLR was 8.91, with a standard deviation of 14.08. Of the 375 included

Table 1. Clinicopathological characteristics of the patients

Total No.	375
Age (mean±SD), years	66.7±11.9
Sex (male/female)	246/129
NLR (Mean±SD)	8.91±14.08
Histology	
Squamous, n (%)	110 (29.3%)
Adenocarcinoma, n (%)	200 (53.3%)
Other, n (%)	65 (17.3%)
Clinical stage	
IIIB, n (%)	94 (25.1%)
IV, n (%)	281 (74.9%)
Performance status	
0,1	305 (81.3%)
≥2	70 (18.7%)

NLR: Nneutrophil/Llymphocyte Rratio

patients, 110 had squamous cell carcinoma, 200 had adenocarcinoma, and 65 had other histological types; 94 were stage IIIB and 281 were stage IV. The Eastern Cooperative Oncology Group (ECOG) performance status was 0 to 1 for 305 patients and 2 to 4 for 70.

Relationship between pre-treatment NLR and clinicopathological factors

We compared the clinicopathological factors of patients with low NLR (NLR<8.91) and high NLR (NLR≥8.91) (Table 2). There was no significant difference between those 2 groups of patients in terms of age, gender, histological subtypes or TNM clinical stage. Patients with low NLR had a better ECOG performance status than those with high NLR (p<0.001).

Univariate analysis and multivariate analysis of OS

Age, gender, histology subtypes, performance status and pretreatment NLR had a significant effect on OS, using univariate analysis (Table 3). Median survival times for the low and high NLR groups were 10.15 and 2.20 months, respectively (p<0.001) (Table 4). The pretreatment NLR was an independent prognostic factor for OS (HR: 1.966; 95% CI: 1.527-2.532; p<0.001); age younger than 66 years and ECOG performance status were other independent prognostic factors.

Table 2. Relationship between pretreatment NLR and clinicopathological factors

	NLR<8.91 n=290	NLR≥8.91 n=85	*p*-value
Age (mean±SD), years	66.2±11.7	68.6±12.4	0.740
Sex (male/female)	186/104	60/25	0.301
Histology			
Squamous	85	25	0.833
Adenocarcinoma	154	46	
Other	51	14	
TNM Clinical stage			
IIIB, n (%)	77	17	0.256
IV, n (%)	213	68	
ECOG Performance status			
0,1	251	54	<0.001
≥2	39	31	

Table 3. Univariateble predictors of overall survival

	n	MST in months (95% CI)	*p*-value
Age Median (range)			
<66	149	9.23 (6.38-12.09)	0.008
≥66	226	6.44 (4.89-7.99)	
Gender			
Men	246	6.18 (5.00-7.35)	0.001
Women	129	11.07 (8.06-14.08)	
Histology			
Squaqmous	110	5.65 (4.64-6.66)	<0.001
Adenoc Carcinoma	200	10.12 (8.46-11.78)	
Other	65	5.65 (2.31.8-8.99)	
TNM stage			
IIIB	94	8.64 (6.24-11.04)	0.316
IV	281	6.97 (5.45-8.48)	
ECOG Performance Status			
0,1	305	10.15 (8.85-11.46)	<0.001
≥2	70	1.77 (1.24-2.31)	
Pretreatment N/L ratio			
N/L<8.91	290	10.15 (8.64-11.67)	<0.001
N/L≥8.91	85	2.20 (1.38-3.03)	

MST: median survival time; 95% CI: 95 % confidence interval

Kaplan-Meier curves for OS of patients with high and low NLR

Survival analysis of the NSCLC patients revealed that the low NLR group had a median survival of 10.15 months (95% CI 8.64-11.67) and the high NLR group, 2.2 months (95% CI 1.38-3.03). The low NLR group had significantly better OS than the high NLR group (log rank test: $p<0.001$) (Figure 1).

Discussion

Recent data has revealed that inflammation plays an important role in the microenvironment of tumor progression [7-9]. A number of studies have investigated the prognostic importance of the lymphocyte and neutrophil count of NSCLC patients. The preoperative lymphocyte count was reported to be an independent prognostic factor in node-negative NSCLC [2]. This study showed that high neutrophil counts in the peripheral blood were associated with tumor size and pleural invasion, and that low lymphocyte counts were correlated to vascular invasion. The lymphocyte count in advanced NSCLC patients during chemotherapy was

Table 4. Multivariate analysis for overall survival

	Hazard ratio	(95% CI)	*p*-value
Age Median (range)			
< 66 vs. ≥66	1.364	1.105-1.684	0.004
Gender			
Men vs. Women	0.797	0.633-1.004	0.054
Histology			
Adenocarcinoma Ca vs. Squamous	0.789	0.613-1.016	0.066
Other Vvs. Squamous	1.129	0.825-1.544	0.449
ECOG Performance Status			
0,1 vs. ≥2	3.471	2.619-4.601	<0.001
Pretreatment N/L ratio			
N/L<8.91 vs. N/L≥8.91	1.966	1.527-2.532	<0.001

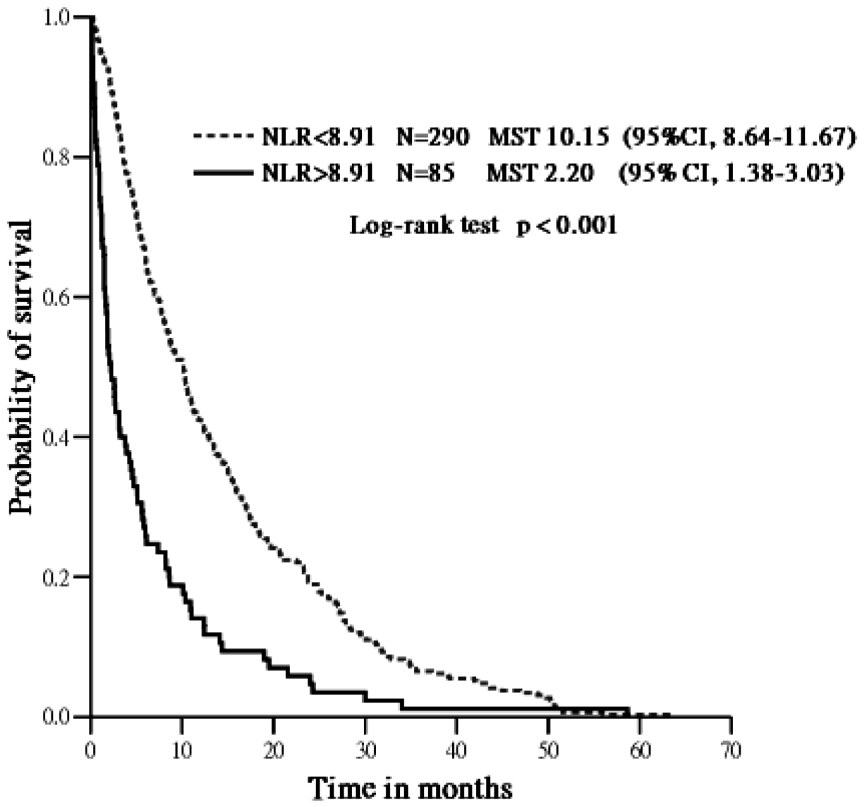

Fig. 1. Kaplan-Meier curves for overall survival of patients with low NLR vs. high NLR.

found to be significantly decreased in those with progressive disease, and increased in patients with a partial response or stable disease [4]. Lymphocyte count was reported to be a significant survival predictor in advanced NSCLC [10].

Also, pretreatment neutrophil count was found to be an independent prognostic factor in advanced NSCLC [3]. Neutrophil was reported to promote the aerogenous spread of lung adenocarcinoma, which was a significant factor in the shorter survival of patients with adenocarcinoma progression [11].

Many studies have reported that NLR, an index of systemic inflammation, was associated with treatment response and outcomes of several cancer types. High NLR (NLR>5) was associated with worse survival in patients with metastatic colorectal cancer, and was reported to be a potentially useful clinical biomarker [12-14]. In patients with advanced gastric cancer, NLR was an independent prognostic factor [15]. Elevated preoperative NLR predicts a poor disease-free survival and OS for late-stage gastric cancer patients [16]. A study demonstrated that pre-therapeutic NLR in patients with advanced esophageal cancer can be used as a predictor for chemosensitivity [17]. In patients with nasopharyngeal carcinoma, elevated NLR predicts a poor prognosis [18]. Among breast cancer patients, those with higher NLR (NLR>3.3) had higher 1-year and 5-year mortality rates than those with lower NLR [19]. All of these studies involving different cancer types revealed a trend, that high NLR was associated with a poor prognosis.

The purpose of the present study was to elucidate whether NLR is associated with the prognosis of NSCLC. NSCLC patients with high NLR were found to have a poor prognosis in several studies. Increasing preoperative NLR was associated with a higher stage, but remained an independent predictor of survival after complete resection of primary lung cancer and was a potential biomarker to stratify high risk of death [5]. The NLR of fine-needle aspiration specimens was found to be an independent prognostic factor for patients with advanced NSCLC [6]. A high preoperative NLR was also reported to be a convenient biomarker to identify patients with a poor prognosis after resection for NSCLC [20].

In our study of advanced NSCLC patients, the high NLR group had a significantly poorer OS than the low NLR group ($p<0.001$). Age, gender, histological type, performance and pretreatment NLR were predictors of survival in univariate analysis. In multivariate analysis, age, performance status and NLR were independent prognostic factors.

The mean value of the NLR of 284 resected NSCLC patients in 1 study was reported as 2.44 (range: 0.56-29.44) [20]. In another study, a median NLR of 3.13 for 177 NSCLC patients that underwent surgical resection was reported; the increased NLR was associated with a more advanced stage, but remained an independent predictor of survival [5]. The mean value of the NLR was 8.91 (range: 0.78-97) in our study. The difference in the NLR value may be related to the TNM stage distribution of the patient population. There were 128 stage I/II and 49 stage III/IV NSCLC patients in the above study [5], and 375 patients with stage IIIB /IV NSCLC in our study.

The median survival time of stage IIIB and IV patients in the current study seemed poorer than that reported in another study from Taiwan [21], although the patient population was somewhat different from that of our study. The above

study enrolled 308 NSCLC patients with deletions in EGFR exon 19. Adenocarcinoma was the principle histology (291 patients, 94.5%) and 210 patients (68.2%) had received EGFR-TKI treatment. The difference in OS may be related to the greater number of adenocarcinoma patients with an EGFR mutation that received EGFR-TKI therapy.

A number of studies in the last 2 decades have suggested an association between the NLR and the prognosis of cancer patients. The mechanism of this observed association remains to be proposed. Inflammation is important in the local microenvironment of tumors, and in some types of cancer, inflammatory conditions are present before a malignant change occurs. In other types of cancer, an oncogenic change induces an inflammatory response that promotes the development of tumors [8]. High neutrophil counts were associated with tumor size and pleural invasion, and low lymphocyte counts were correlated with vascular invasion and recurrence of NSCLC [2].

Conclusion

NLR is easily measured at low cost and is not time-consuming. It may be utilized as a simple, reliable prognostic factor for risk stratification and can be used to provide better treatment allocation for advanced NSCLC patients.

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治療前嗜中性白血球／淋巴球比值可作爲非小細胞肺癌患者存活之預測因子

葉金水　紀炳銓　陳正雄　蔡偉宏　林慶雄

背景：週邊嗜中性白血球，淋巴球數目及嗜中性白血球 / 淋巴球比值（NLR）據研究顯示與非小細胞肺癌患者存活有關。本研究探討 NLR 作為非小細胞肺癌第 IIIB 及第 IV 期患者存活之預測因子。

方法：非小細胞肺癌第 IIIB 及第 IV 期患者於 2004 年 1 月至 2006 年 12 月曾接受放射線治療或化學治療納入此回溯性研究。紀錄分析患者接受治療前週邊血液常規檢查及白血球分類比。臨床病理因子及 NLR 以單變數分析和多變數分析。總存活曲線以 Kaplan-Meier 法行存活分析，高 NLR 比值與低 NLR 比值組的存活差異以 log-rank 法檢定。

結果：375 個非小細胞肺癌患者包含 246 位男性及 129 位女性平均 66.7 歲納入研究。低 NLR 值與高 NLR 值組的存活中數分別為 10.15 及 2.20 個月（p<0.001）。治療前 NLR 值為存活獨立癒後因子。多變數分析顯示年紀小於 66 歲及體能狀態亦為獨立癒後因子 晚期非小細胞肺癌患者NLR值升高可能存活較差。

結論：NLR 值為一容易測量並且可能作為晚期非小細胞肺癌患者存活之預測因子。*(胸腔醫學 **2013; 28: 321-329**)*

關鍵詞：嗜中性白血球 / 淋巴球比例值，存活預測因子，非小細胞肺癌

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Successful Management of Tracheo-innominate Artery Fistula by Endovascular Embolization – A Case Report

Yu-Hung Fang, Yu-Ching Lin, Ying-Huang Tsai, Yuan-Hsiung Tsai*, Tsung-Ming Yang

Tracheostomy is increasingly used in patients receiving prolonged mechanical ventilation (PMV). Tracheo-innominate artery fistula (TIF) is a rare but potentially life-threatening complication of tracheostomy. The incidence of TIF formation usually peaks 7 to 14 days after tracheostomy. Surgical intervention with full or partial median sternotomy followed by ligation of the innominate artery is recommended for definitive management of this fatal complication. Nonetheless, effective hemostasis by endovascular procedures in selected patients has been reported. We herein present a case of TIF that developed on the very next day after a tracheostomy in a 72-year-old man with PMV, which was successfully treated by endovascular embolization. ***(Thorac Med 2013; 28: 330-335)***

Key words: prolonged mechanical ventilation, tracheostomy, tracheo-innominate artery fistula, endovascular embolization

Introduction

Around 5-13% of mechanically ventilated patients ultimately require prolonged mechanical ventilation (PMV) [1]. Tracheostomy has been used increasingly in patients receiving PMV, and has advantages over translaryngeal intubation [2]. The benefits of tracheostomy in mechanically ventilated patients include more patient comfort, less unplanned extubation, faster ventilator weaning, and less ventilator-associated pneumonia [3-4]. Despite the aforementioned advantages and its increasing utilization in PMV patients, tracheostomy does not increase the rate of weaning success in these patients [5]. In addition, complications of tracheostomy include bleeding, wound infection, tracheal stenosis, and death [6], and the early complications include bleeding, wound infection, injury to adjacent structures, airway loss, and malposition of the tracheostomy tube [7]. Late complications include granulation tissue formation, tracheal stenosis, tracheoesophageal fistula, and tracheo-innominate artery fistula (TIF) [8]. TIF is a rare but often life-threatening complication of tracheostomy, and the peak incidence of its formation is 7 to 14 days after tracheostomy [9-10]. The bleeding caused by TIF is usually massive and fatal if surgery is not performed immediately [11]. In addition to sur-

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gical repair, endovascular stent graft repair and embolization have been reported to achieve hemostasis in selected patients [12-16]. We herein report a 72-year-old PMV patient who had massive TIF bleeding 1 day after tracheostomy. In this case, the TIF was successfully repaired by endovascular embolization.

Case Report

A 72-year-old man received PMV via orolaryngeal intubation because of mixed-type respiratory failure and repeated ventilator-associated pneumonia after a large cerebral infarction. He underwent surgical tracheostomy at the level of the second tracheal cartilage with a fenestrated low-pressure cuffed tracheostomy tube (Shiley™ tracheostomy tube, outer diameter: 12.2 mm) after he had been mechanically ventilated for 30 days. The operation was performed smoothly, and the cuff pressure was 20 mmHg after operation. Chest radiography immediately after the surgery demonstrated adequate positioning of the tracheostomy tube (Figure 1). On the second day after tracheostomy, a massive amount of blood suddenly drained from the tracheostomy tube. Over-inflation of the tracheostomy cuff, shifting to orolaryngeal intubation, and manual compression of the stoma failed to control the hemorrhage. Later, hypoxemia and severe hypotension developed because of massive blood loss.

We aggressively resuscitated the patient using intravenous fluids, blood transfusion, and inotropic agents to stabilize the hemodynamics, and kept the airway patent by continuous suction. After stabilizing the respiratory and hemodynamic status, we arranged emergent angiography as a diagnostic and therapeutic approach. No significant contrast medium extravasation

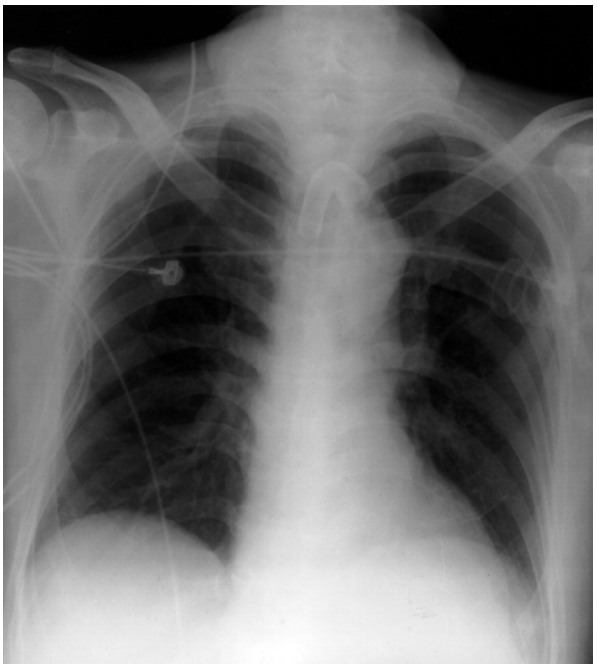

Fig. 1. Chest roentgengraphy taken after tracheostomy demonstrated adequate positioning of the tracheostomy tube with good inflation of bilateral lungs.

was observed in the bilateral common carotid and external carotid angiograms. However, a small vessel arising from the innominate artery and into the region of the tracheostomy was noted during the aortogram (Figure 2A). There was a vascular pouch at the distal end of this artery that was considered to be a pseudoaneurysm. Selective catheterization of this vessel was achieved with a microcatheter (Renegade. Boston Scientific, Natick, MA, USA). A selective angiogram showed active contrast medium extravasation and pooling in the para-tracheal spaces (Figure 2B). This bleeding artery was then successfully embolized with a 50% n-BCA mixture, prepared with 1.0mL of n-BCA (n-butyl cyanoacrylate, Ingenor, Gennevilliers, France) and 1.0 mL of ethiodized oil (Lipiodol Ultra Fluid; Guerbet, Aulnay-sous-Bois, France) (Figure 2C). The bleeding then stopped. A sub-

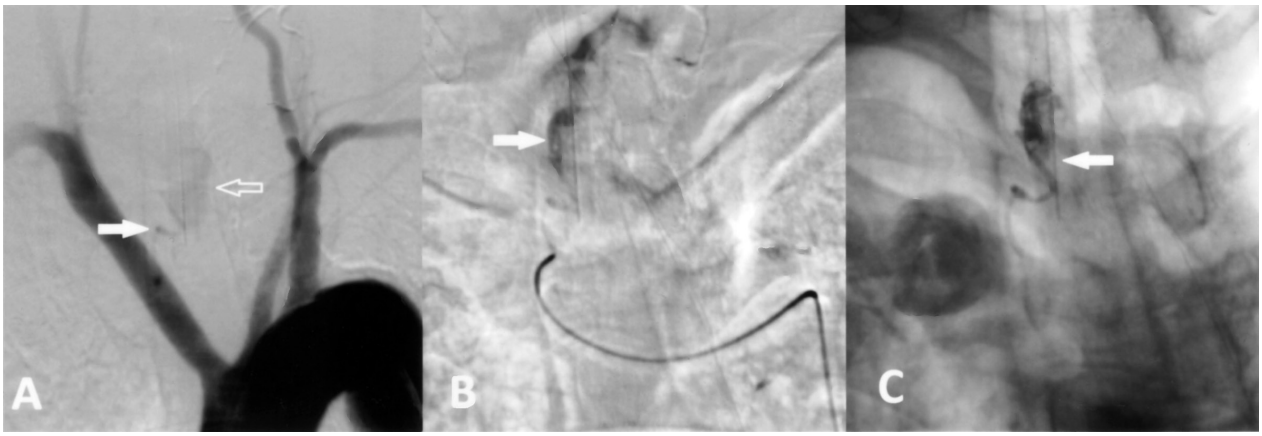

Fig. 2. (A) Aortogram showed a small branch from the innominate artery (arrow) with pseudoaneurysm formation (open arrow). (B) Selective angiogram from the bleeding vessel showed active contrast medium extravasation with pooling of contrast medium in para-tracheal regions (arrow). (C) Retension of embolization material (n-butyl cyanoacrylate mixture) in the para-tracheal region as well as the bleeding vessel after embolization (arrow).

sequent angiogram demonstrated complete occlusion of the fistula and the pseudoaneurysm. The patient's hemodynamic status gradually improved after embolization, and the inotropic agents were discontinued within 12 hours. However, severe sepsis developed afterward, and the patient died of multiple organ failure 8 days later.

Discussion

TIF is a rare but usually fatal complication of tracheostomy, with an incidence of 0.7% [17]. The innominate artery originates from the aortic arch and bifurcates into the right common carotid artery and the right subclavian artery, and supplies blood to the right arm and head. It crosses the trachea approximately at the level of the 9th tracheal ring, varying from the 6th~10th ring. If the tracheostomy tube is correctly placed at the level of 2nd~3th tracheal ring, the tip or cuff of the tracheostomy tube is close to the point at which the innominate artery crosses the trachea. Tracheal damage and erosion by the tip or cuff of the tracheostomy tube may result in fistula formation. In most cases, TIF occurred 7 to 14 days after tracheostomy [10], and more than 70% of TIF happened within the first 3 weeks after the procedure [18]. However, TIF has also been reported as early as 2 days to as late as several years after tracheostomy [19]. It has been suggested that bleeding within 48 hours after tracheostomy is typically associated with local factors (e.g., injury to anterior jugular or inferior thyroid veins, or tracheal suction) or coagulopathy, and TIF almost always occurred late (>48 hours after tracheostomy) [20]. In the case of this patient, however, TIF bleeding happened on the very next day after tracheostomy. Factors contributing to TIF include low-lying tracheostomies below the 3rd or 4th tracheal ring, overinflated cuffs, a sharply bent tracheostomy tube with an adjustable flange, a high innominate artery, and excessive head and neck movement [10,20-22]. Early formation of the TIF in this patient may have resulted from the

vascular abnormality revealed on the aortogram (Figure 2A), which demonstrated an aberrant small vessel arising from the innominate artery and pseudoaneurysm formation. This is an uncommon form of TIF, since the trachea and innominate artery were abnormally connected by a passageway.

The mortality rate of TIF is extremely high if left untreated, and the ideal management approach is to prevent the development of this life-threatening complication. The outcomes following massive TIF bleeding largely depend on its timely diagnosis and prompt management. Warning signs of massive TIF bleeding include minimal bleeding and synchronous pulsation of the tracheostomy tube with the heartbeat. Bronchoscopy has been suggested to confirm the site of bleeding, and to guide the endotracheal tube to stop the bleeding by cuff compression [23]. However, sometimes this may not be practical because of severe active bleeding and a massive amount of blood in the airways, as we saw in this case. When bleeding happens, control of the hemorrhage and restoration of ventilation are mandatory to ensure survival. Overinflation of the tracheostomy cuff has been shown to temporarily control the bleeding in around 85% of cases [18]. If the bleeding does not stop by overinflating the tracheostomy cuff, translaryngeal intubation to keep the airway patent and digital compression of the bleeding vessel via the stoma should be utilized to protect the airway and temporarily stop bleeding.

Full or partial median sternostomy followed by ligation of the innominate artery is the preferred definitive approach for TIF bleeding [11]. Despite the reversal of blood flow in the right internal carotid artery following the procedure, ligation of the innominate artery appears to be safe and reliable [10]. However, the surgical wound can be contaminated by tracheal secretion, thus increasing the risk of mediastinitis in these patients. In addition, patients with PMV are usually weak and prone to a higher risk of emergency surgical intervention. Angiography is a less invasive and readily available procedure in the referral hospital that provides definitive diagnosis of the active bleeding. Recent advances in endovascular procedures provide alternatives to traditional open surgical repair for the management of TIF bleeding in selected patients. Endovascular stent graft has been reported to be successful in the repair of TIF [12-13], and endovascular coil embolization of TIF has also been used to stop bleeding in some patients [15-16]. Although there has been no clinical trial comparing the efficacy of surgical repair and endovascular procedures in the management of TIF bleeding, emerging data indicate that endovascular procedures, including stent graft repair and embolization, can be useful tools to manage this difficult and life-threatening complication of tracheostomy. TIF bleeding was stopped in our patient by endovascular embolization using 50% n-BCA alone rather than an endovascular stent graft, because the aortogram revealed a small aberrant vessel arising from the innominate artery.

We have reported a 72-year-old man with PMV who had massive TIF bleeding on the day following surgical tracheostomy that was successfully repaired by endovascular embolization. Common etiologies of early tracheostomy include injuries to adjacent vessels, tracheal suction, and coagulopathy. However, TIF should be considered, especially when the tracheostomy bleeding is accompanied with synchronous vibration of the tracheostomy tube with the heartbeat. Optional managements in-

clude over-inflation of the tracheostomy cuff, translaryngeal intubation, and digital compression of the bleeding vessel. Bronchoscopy may help confirm the site of bleeding, and guide the positioning of the endotracheal tube. In addition to confirming the etiology of the tracheostomy bleeding, recent advances in endovascular procedures also provide alternative therapeutic choices in carefully selected patients during angiography.

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使用血管栓塞術成功治療併血管異常之氣管無名動脈瘻管出血－病例報告

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氣管切開術的使用在長期使用呼吸器輔助呼吸的病人逐漸地增加，在氣管切開術的併發症中氣管無名動脈瘺管出血雖然少見但卻常常容易致命。氣管無名動脈瘺管最常形成的時間是在接受氣管切開術之後的第 7 到第 14 天之間。以胸骨切開術進行氣管無名動脈瘺管結紮是目前治療這項致命併發症的主要治療方式，但是血管栓塞術也曾被報告過可以成功地治療氣管無名動脈瘺管出血。我們在此報告一位 72 歲長期使用呼吸器的男性病患在接受氣管切開術之後隔天即發生氣管無名動脈瘺管出血，並使用血管栓塞術成功地治療此瘺管出血。*(胸腔醫學 **2013; 28: 330-335**)*

關鍵詞：長期呼吸器，氣管切開術，氣管無名動脈瘺管，血管栓塞術

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Trans-diaphragmatic Actinomycosis from Liver Abscess

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Actinomycosis is a rare and slowly progressive infection. We report a 42-year-old female patient whose computed tomography scan showed liver nodules at first. Biopsy revealed no malignant cells. Five months later, follow-up chest-computed tomography still showed hypodense lesions in the liver. She was admitted for further survey. During admission, we arranged ultrasound-guided liver abscess drainage. However, her liver abscess continued to spread continuously, and pleural empyema and pericardial abscess were identified. All culture reports showed negative findings. She also had respiratory failure and received endotracheal intubation and ventilator support. After decortication, the pathology report showed *Actinomyces*. We changed antibiotics immediately. Her condition gradually improved and extubation was performed successfully. She was discharged with outpatient department follow-up and antibiotics treatment. Trans-diaphragmatic actinomycosis rarely occurs. The initial clinical symptoms and signs are often nonspecific, which led in this case to a delayed diagnosis. It is important to take actinomycosis into consideration in case of liver abscess, pleural empyema, and pericardial abscess. ***(Thorac Med 2013; 28: 336-341)***

Key words: *Actinomyces*, empyema, liver abscess, pericardial effusion

Introduction

Actinomycosis is a rare infection caused by *Actinomyces*, which is a Gram positive, anaerobic, and filamentous bacterium. The clinical course of actinomycosis is usually chronic and indolent. The most common infection site is the cervicofacial area [1]. Pericardiac, thoracic, abdominal and genital areas are reported infection sites [2-3]. The infections have been reported to spread continuously through anatomical barriers and extend to empyema and pericardial effusion [1,4]. We present the first reported case of *Actinomyces* infection that induced liver abscess, pericardial effusion, and empyema.

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Case Report

A 42-year-old female patient had a history of hyperthyroidism and denied other systemic disease. She complained of poor appetite and suffered body weight loss of 10 kg in 1 month. She visited a local hospital for help and 2 hepatic nodules were detected by abdominal computed tomography (CT). CT-guided liver biopsy was performed and the pathology report revealed only fat tissue. Therefore, she came to our hospital for a 2nd opinion on 15 April 2010. Abdominal magnetic resonance imaging (MRI) was arranged and 2 hepatic nodules at S4 (2.9 × 1.8 cm) and S6 (1.3 cm) were found (Figure 1). Abdominal ultrasound-guided biopsy was then arranged, but hepatic nodules could not be detected. The patient was followed up at the outpatient department (OPD) and received regular liver function testing and abdominal sonography. Steroid treatment was begun on 21 October 2010 for suspected autoimmune cholangitis due to persistently elevated biliary enzyme.

About 1 week prior to admission, she began experiencing exertional dyspnea, mild cough, epigastric discomfort, chest tightness, palpitation, dizziness, and lower leg edema. There were also fever and chills. Physical examination revealed bilateral basal rales. Chest X-ray revealed bilateral pleural effusion (Figure 2). She was then admitted to our general ward on 30 November 2010.

After admission, pericardial effusion, massive pleural effusion, and liver abscess were found in the abdominal CT (Figure 3). Pericardiocentesis was performed due to right ventricle and right atrium compression, and turbid fluid was drained immediately at the emergency department (ED). Ordinary culture and tuberculosis (TB) culture of the pericardial effusion were all negative. For treatment of the progressive dyspnea and respiratory failure, she received endotracheal tube intubation and mechanical ventilator support on the 6th day after admission. Pigtail drainage was arranged for her liver abscess on the 15th day after admission and ordinary, anaerobic, and TB cultures of drained fluid all showed negative findings. Thoracentesis was performed for massive pleural effusion in the bilateral lung. The pleural effusion on

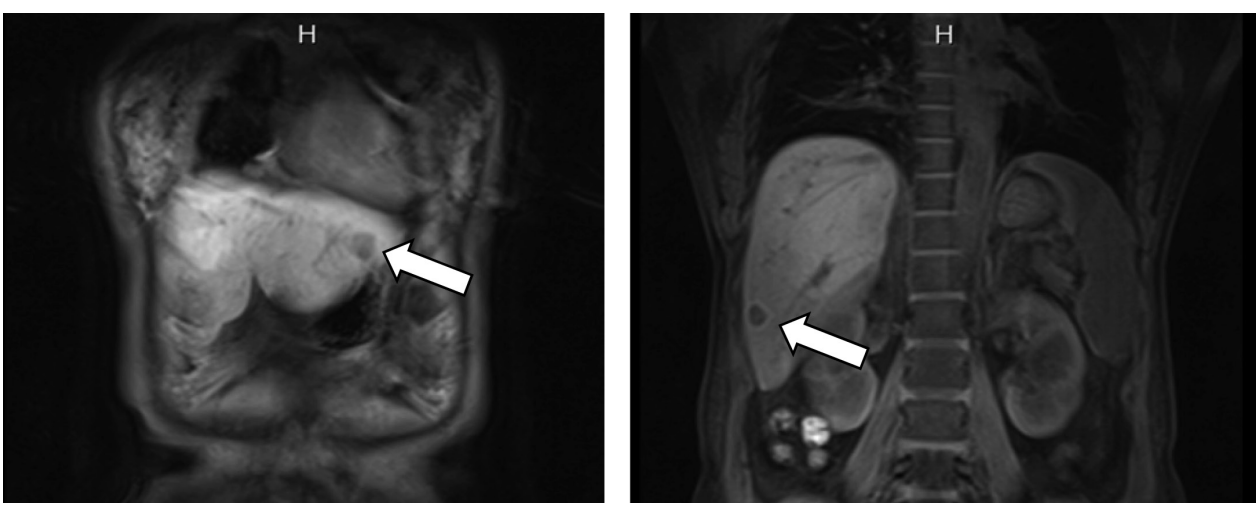

Fig. 1. A subcapsular nodule in the liver S6 (arrow) about 1.3 cm in size, and another (arrow) in the lateral segment about 2.9×1.6 cm

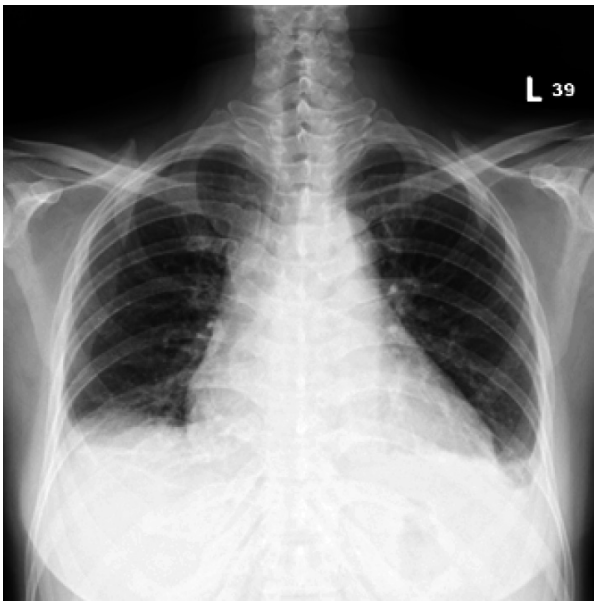

Fig. 2. Bilateral pleural effusion

the left side was exudative and that on the right side was pus-like material. Repetitive decortication of the right-side empyema was then performed. The first decortication was performed because of poor chest tube drainage, the second was for diagnosis, and the third was because of difficulty weaning. Of note, ordinary culture, acid-fast stain, TB culture, anaerobic culture, and fungus culture were still all negative. The pathological report at the 2nd surgery suggested *Actinomyces* (Figure 4). She initially received flomoxef in the ED for liver abscess. Three days after admission, she started Imipenem and teicoplanin in place of flomoxef due to signs of persistent infection for 21 days. When the pathological report showed actinomycosis, we changed antibiotics to unasyn (ampicillin 2000 mg and sulbactam 1000 mg). Her liver abscess, empyema, and pericardial effusion all improved gradually and she was extubated successfully. She was discharged with regular OPD follow-up and chronic antibiotics control.

Discussion

Thoracic and abdomino-pelvic actinomycosis, respectively, account for 15~20% and 20% of *Actinomyces* infections [3]. Cardiac actinomycosis is reported to be less than 2% of all actinomycosis cases [2,5-7]. Actinomycosis infections extending into the surrounding tissue have been reported in approximately 1/3 of cases [5]. Yasuo K *et al*. first described a case of hepatic actinomycosis infiltrating the diaphragm and right lung in 1996 [4]. However, actinomycosis that spreads continuously and involves 3 different areas, including the lung, liver, and pericardium, as in our case has rarely been reported.

Our patient at first had clinical symptoms of poor appetite and body weight loss only. The common clinical presentations include fever, abdominal pain, and body weight loss [4], and all are non-specific, which might lead to a delayed diagnosis. This patient had received low-dose steroid, but steroid may be a risk factor for actinomycosis [3]. However, the relationship between steroid and transdiaphragmatic actinomycosis is still not clear.

The initial image finding in our patient was tumor-like lesions. The most common radiographic finding of hepatic actinomycosis in 1 report was a hypodense mass/abscess (68.4%) [8]. Liver abscess of our patient finally extended to the lung and pericardium. Therefore, we were unable to predict disease progression within the initial imaging findings.

The diagnosis is most often confirmed by microscopic examinations of surgical samples [7]. With our patient, we drained the liver abscess, pericardial effusion, and empyema initially for a definitive diagnosis. It is not surprising that none of the cultures revealed positive findings.

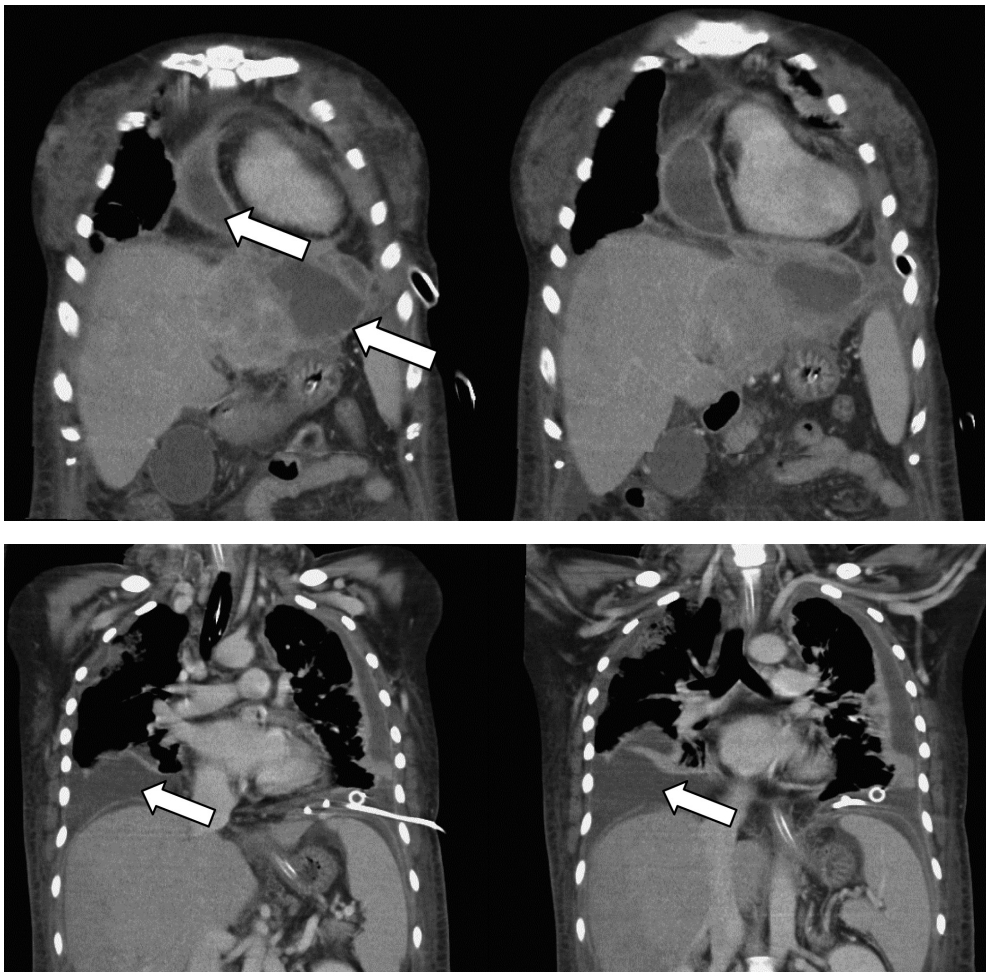

Fig. 3. Serial saggital non-contrast CT scan images showing a low attenuating lesion in the liver, pericardium, and pleural space (arrow), which was suggestive of liver abscess, pericardial effusion, and empyema

One report described a case of actinomycotic liver abscess that extended to the pericardium and finally formed empyema [2]. The patient underwent video-assisted thoracic surgery in addition to antibiotics treatment due to a poor response to antibiotics alone. Our patient underwent decortication 3 times. It seems that surgical intervention is the usual treatment for continuously spreading actinomycosis. Another study also showed a trend toward lower mortality rates for patients that received antibiotics plus surgery than for patients that received antibiotics alone [7]. Therefore, surgical intervention should be considered when the patient is diagnosed as having actinomycosis.

Conclusion

This is a rare case in which liver abscess of actinomycosis directly invaded the lung and pericardium after empiric antibiotics treatment. This case is a reminder that actinomycosis should be taken into consideration in patients developing infections with a trans-diaphragmat-

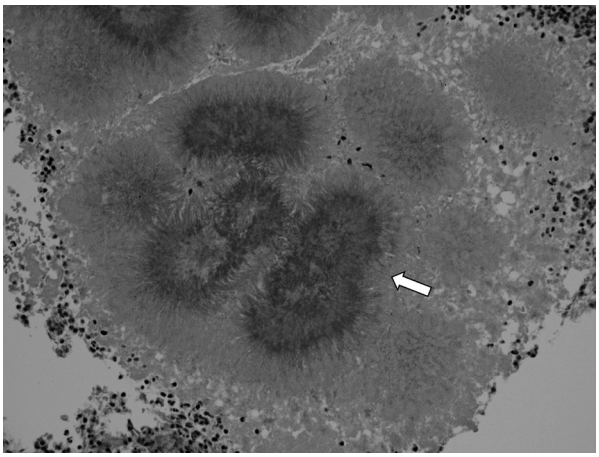

Fig. 4. Actinomycotic granules (arrow) in the abscess. The pathological finding is consistent with actinomycosis (hematoxylin and eosin stain, x200)

ic spread.

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穿越橫膈膜之放射線菌肝膿瘍

曾彥寒 *,** 柯信國 *,*** 曾彥強 **** 余文光 *,** 葉奕成 ***** 黃建勝 ****

放射線菌感染是一種少見及進展緩慢的感染。我們提出一位 42 歲病患。開始時為肝臟出現結節。進行切片後並未發現惡性細胞。5 個月後追蹤發現為肝膿瘍。入院後進行肝膿瘍引流。此時肝膿瘍直接穿過橫膈膜形成肺膿瘍以及心包膜積液。病患因呼吸衰竭使用呼吸器並進入加護病房。肝膿瘍，肺膿瘍和心包膜積液在引流出來後進行細菌培養，結核菌培養，和厭氧菌培養皆呈陰性反應。後來因肺膿瘍狀況未改善進行剝除術，病理報告顯示為放射線菌感染。在改用適當抗生素治療後，病患狀況逐步改善並脫離呼吸器。之後順利出院並接受長期抗生素治療。*(胸腔醫學 **2013; 28: 336-341**)*

關鍵詞：放射線菌，膿胸，肝膿瘍，心包膜積液

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Rare Anterior Tongue Metastasis from Primary Lung Cancer: A Case Report

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Primary tumors metastasizing to the tongue are extremely rare. There is a 1% rate of metastasis to the oral cavity from other primary sites, most commonly the lung, breast, skin, gastrointestinal tract, and liver. There is a 1.6% rate of primary lung cancer metastasized to the tongue. We describe a patient with adenocarcinoma of the lung who developed a metastatic lesion on the tongue. A 71-year-old Taiwanese male was diagnosed with adenocarcinoma of the lung at stage IV (cT4N2M1a, stage IV [lung-to-lung metastasis]) with a tongue tumor. The tumor was painful, palpable, and firm, measuring around 1 x 1 x 1 cm^3 on the anterior part of the tongue. There was no cervical lymphadenopathy. The tumor was thought to be a metastasis of the lung adenocarcinoma. The tongue lesion was excised and revealed adenocarcinoma. The histology of the specimen was consistent with that of the previous lung cancer, so he was considered to have had tongue metastasis from adenocarcinoma of the lung (right upper lung, cT4N2M1b, stage IV [lung-to-lung and tongue metastasis]). ***(Thorac Med 2013; 28: 342-346)***

Key words: lung cancer, adenocarcinoma, tongue metastasis

Introduction

Lung cancer is a leading cause of cancer death in Taiwan and worldwide. The most frequent metastatic sites are the regional lymph nodes and surrounding areas, as well as the liver, adrenal gland, bones and brain. Tongue metastasis during the natural course of many neoplasms, including lung cancer, is extremely rare, and the prognosis of these patients is rather poor. Reported incidences vary from 0.2 to 1.6% [1-3]. We describe a case of anterior tongue metastasis in a patient with adenocarcinoma of the lung.

Case Report

A 71-year-old male visited our ear, nose and throat outpatient department due to a lump sensation for 2 months, and was experiencing

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pain, dysarthria and difficulty in eating. He had smoked a pack of cigarettes per day for more than 40 years. Physical examination showed an elastic, hard, tender and ulcerated mass at the anterior part of tongue, about $1 \times 1 \times 1$ cm^3 in size (Figure 1). Chest X-ray showed a mass lesion in the right upper lung (Figure 2). Chest computed tomography (CT) also showed suspected lung cancer in the anterior segment of the right upper lobe, with its largest dimension at 6.7 cm, adenopathy at the right subcarinal region, and metastases to the left lung (Figure 3). Histological examination of the specimen obtained by bronchial biopsy showed lung adenocarcinoma. No mutation in the epidermal growth factor receptor (EGFR) gene was identified. The patient underwent incision biopsy of the tongue tumor which also showed adenocarcinoma. The immunohistochemical study revealed the tumor cells were CK7 (positive), TTF-1 (positive), and CK20 (negative), and their appearance was similar to that of the lung

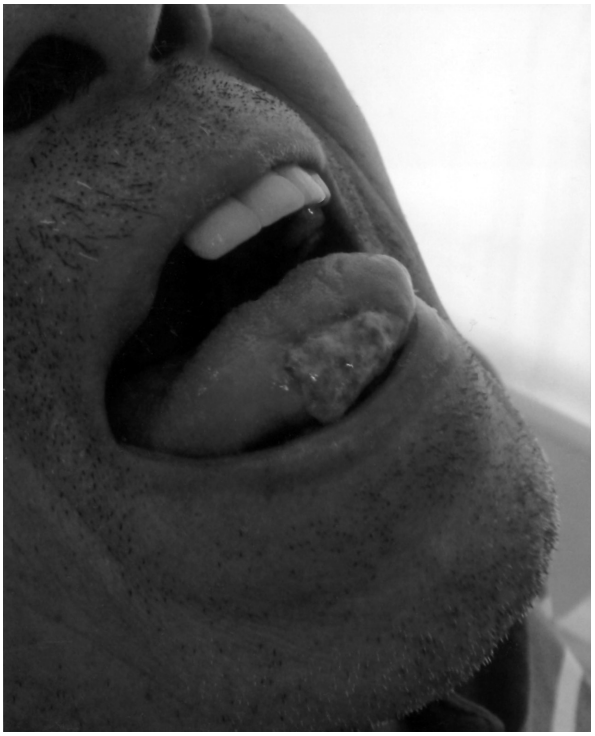

Fig. 1. Anterior side of the tongue showing a mass lesion with ulceration

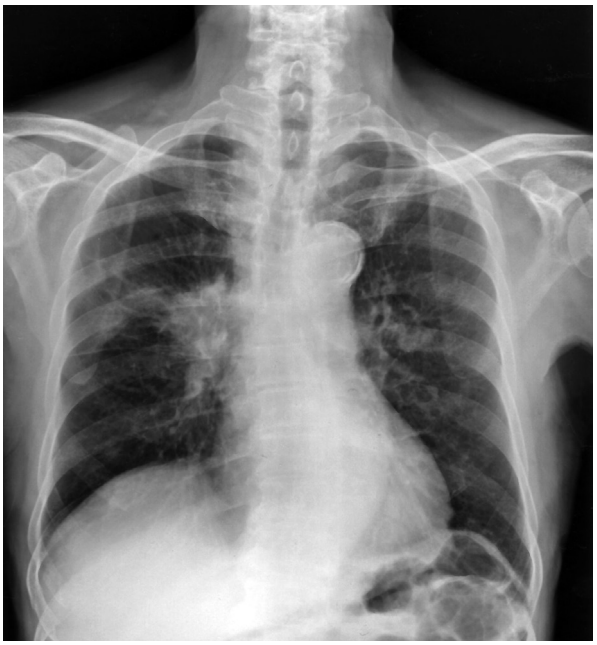

Fig. 2. Chest X-ray showing a mass in the right upper lung

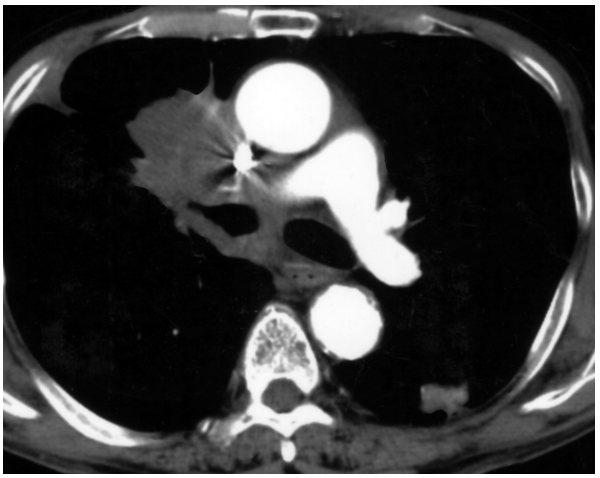

Fig. 3. Chest CT showing a tumor in the anterior segment of the right upper lobe, with subcarinal lymphadenopathy and left lung metastasis

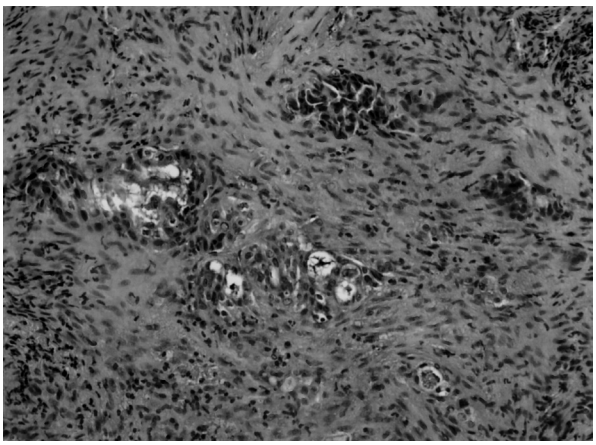

Fig. 4. The incision biopsy of the tongue showing adenocarcinoma (HE stain, x40)

tumor (Figure 4). Based on these findings, the tongue lesion was diagnosed as a metastatic tumor from the lung cancer. With the diagnosis of lung cancer, anterior segment of the right upper lobe, T2bN2M1b, Stage IV (lung-to-lung and tongue metastasis), the patient was given 6 cycles of Alimta 500 mg/M2 plus cisplatin 70 mg/M2 as 1st-line chemotherapy and Alimta 500 mg/M2 as maintenance chemotherapy. However, the disease progressed and the patient expired 7 months after the disease was diagnosed.

Discussion

Common sites of metastasis from lung cancer include the brain, bone, adrenal glands, contralateral lung, liver, pericardium, and kidneys. There is 1% rate of metastasis to the oral cavity from other primary sites, most commonly the lung, breast, skin, gastrointestinal tract, and liver [4]. Primary tumors metastasizing to the tongue are extremely rare. Zegarelli *et al*. [1] reported 12 patients (0.2%) with tongue metastasis among 5933 patients with various malignancies. Another study [3] reported 48 cases (1.6%) of tongue metastasis from 3047 primary lung tumors. Although the number of cases of lung cancer is increasing, tongue metastasis is extremely rare as an initial symptom of the disease [5]. The case we present is unusual in that the patient's initial symptom was related to the tongue lesion without pulmonary symptoms or signs. He is the first reported case of lung adenocarcinoma with tongue metastasis in Taiwan.

Lung cancer is a significant and aggressive primary cancer with a predilection for extrathoracic metastasis. Several routes of metastasis to the tongue have been proposed. The hematogenous route of spread is considered to account for the majority of cases of metastases to the tongue. Lymphatic spread has also been considered; however, since the tonsils do not have afferent lymphatic vessels, malignant cells can be transported to the tongue only in a retrograde manner. Another postulated route is the direct transluminal implantation of malignant cells at the time of bronchoscopy. Although the route of metastasis to the tongue is difficult to determine, in the present case, the hematogenous route was thought to be the most likely because the tongue lesion developed before the bronchoscopy was performed. Lymphatic spread was less likely, since there was no evidence of metastases in the hilar and mediastinal lymph nodes.

One study reported that 66% of patients had metastases localized to the base of the tongue [1], and a literature review on metastasis to the oral cavity found that the base of the tongue was the site most commonly involved [6]. The probable mechanism was that the tongue base is relatively immobile and contains many lymphatic and blood vessels. In this case, however, the metastatic tongue tumor was located in the anterior of the tongue, not in the base.

Metastatic spread to the tongue may occur in advanced stages of tumors. The prognosis of patients with tongue metastasis is poor because most of these patients have widespread disease. Similar to primary tumors of the tongue, metastatic lesions to this organ may be ulcerated or polypoid. Since the tongue is a rare metastatic site, when a lesion is detected, no matter near the base or not, a thorough evaluation to distinguish between metastasis and primary cancer should be made.

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肺腺癌合併舌部轉移－病例報告

吳秉儒 *,*** 陳家弘 *,** 涂智彥 *,***,**** 廖偉志 * 夏德椿 *,** 徐武輝 *,***

舌部轉移是肺癌中少見的轉移，這類轉移多在肺癌晚期才會出現，因此病人大多預後不佳，過去關於這類病例報告並不多，我們描述一個七十一歲的患者，初期以舌部腫瘤的症狀來表現，並意外發現肺部亦有一顆腫瘤，肺部腫瘤的切片結果肺腺癌，舌部腫瘤切片與免疫螢光染色後發現 CK7 與 TTF-1 呈現陽性反應，確定為肺腺癌轉移，在經過六個療程第一線化學治療（Alimta 跟 cisplatin）後，病人於診斷後七個月後死亡。*(胸腔醫學 **2013; 28: 342-346**)*

關鍵詞：肺癌，腺癌，舌部轉移

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Human Herpes Virus 8-Unrelated Primary Effusion Lymphoma-like Lymphoma Presenting with Acute Respiratory Failure – A Case Report

Wei-Lun Chien*, Jeng-Yuan Hsu*,**, Chun-Shih Chin*

Primary effusion lymphoma (PEL) is a high-grade non-Hodgkin lymphoma of B-cell origin that is predominantly found in human immunodeficiency virus (HIV)-seropositive patients, and presents exclusively as a lymphomatous effusion in the absence of a solid mass. It is universally related to herpes virus type 8 (HHV-8) infections. There have been a small number of cases of HHV-8-unrelated PEL-like lymphoma, and it is a rare cause of pericardial effusion. In this report, we describe the case of a 69-year-old man who presented with acute respiratory failure due to massive pericardial effusion. The cytopathologic examination of the pericardial fluid showed diffuse B cell lymphoma in the absence of a solid mass. Extubation was performed successfully after pericardiocentesis. The pericardial effusion resolved after chemotherapy with a regimen of cyclophosphamide, hydroxydaunorubicin, vincristine, prednisolone and rituximab (R-CHOP). Herein, we report this rare case and review the literature. ***(Thorac Med 2013; 28: 347-353)***

Key words: primary effusion lymphoma-like lymphoma, pericardial effusion, acute respiratory failure

Introduction

Primary effusion lymphoma (PEL) is an uncommon and unusual subset of AIDS-related lymphomas that grow mainly in the bodily cavities as lymphomatous effusions without an identifiable contiguous tumor mass [1]. It is a high-grade non-Hodgkin lymphoma of B-cell origin and universally associated with human herpes virus type 8 (HHV-8) infections [2-3]. The majority of cases occur in the presence of human immunodeficiency virus (HIV) infection. However, there have been a small number of cases of HHV-8-unrelated PEL-like lymphoma, the first case of which was described in 1998 [4]. Hepatitis C virus (HCV) has been suggested to be an etiological agent of HHV-8-unrelated PEL-like lymphoma [5]. Herein, we present a rare case of PEL-like lymphoma in an elderly patient without HIV or HHV-8 infection who was followed up for 8 months.

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Case Report

A 69-year-old male had progressive dyspnea of 1 week's duration. He was a smoker (1 pack per day for 30 years) and had a history of pulmonary tuberculosis infection. Poor appetite and body weight loss, from 53 kilograms to 47 kilograms, developed in the most recent 6 months. He visited another hospital first where hypotension and hypercapnia with consciousness disturbance developed. The patient was intubated for airway protection, and was then transferred to our hospital. At the emergency unit, his temperature was 37.5°C, pulse rate 86 beats per minute, blood pressure 89/59 mmHg, and respiratory rate 16 breaths per minute. Physical examination showed distant heart sounds and diminished bilateral lower breathing sounds. Laboratory tests indicated a white blood cell (WBC) count of 9700/μL with 97% neutrophils, and a hemoglobin (Hb) level of 14.7 g/dl (normal range for women: 11.3-15.3 g/dl). The C-reactive protein level was 0.04 mg/L (normal range <0.3 mg/dl). Arterial blood gas revealed respiratory acidosis with metabolic compensation (pH: 7.355, PCO_2: 71.3 mmHg, HCO_3^-: 38.9 mmHg, PO_2: 88.6 mmHg).

Chest X-ray (Figure 1) showed bilateral pleural thickening with a calcified and water-bottle heart. Chest computed tomography (CT) (Figure 2) revealed calcified lymph nodes at the mediastinum, bilateral fibrothorax, and moderate to severe pericardial effusion. Cardiac sonography revealed moderate pericardial effusion. Pericardiocentesis was performed and 520 ml of yellowish pericardial fluid was withdrawn. Pericardial fluid analysis indicated a WBC count of 1350/μL with 83% lymphocytes, a lactic dehydrogenase (LDH) level of 544 U/l, a protein level of 4900 mg/dl, and an adenosine

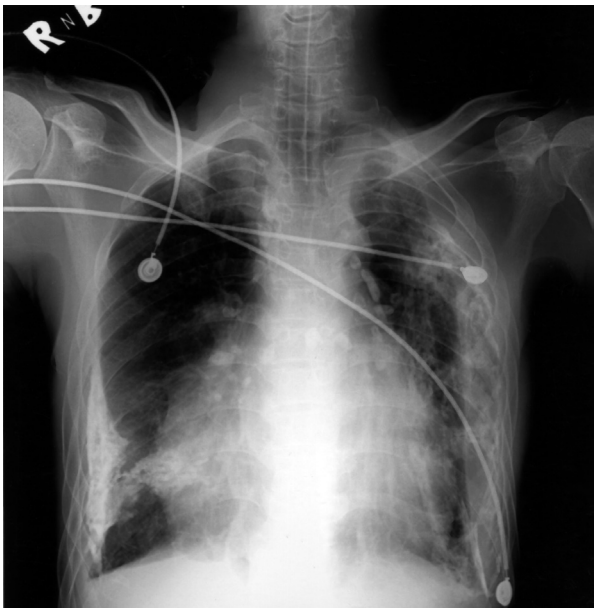

Fig. 1. Chest radiography showing bilateral pleural thickening with a calcified and water-bottle heart compatible with bilateral fibrothorax and pericardial effusion

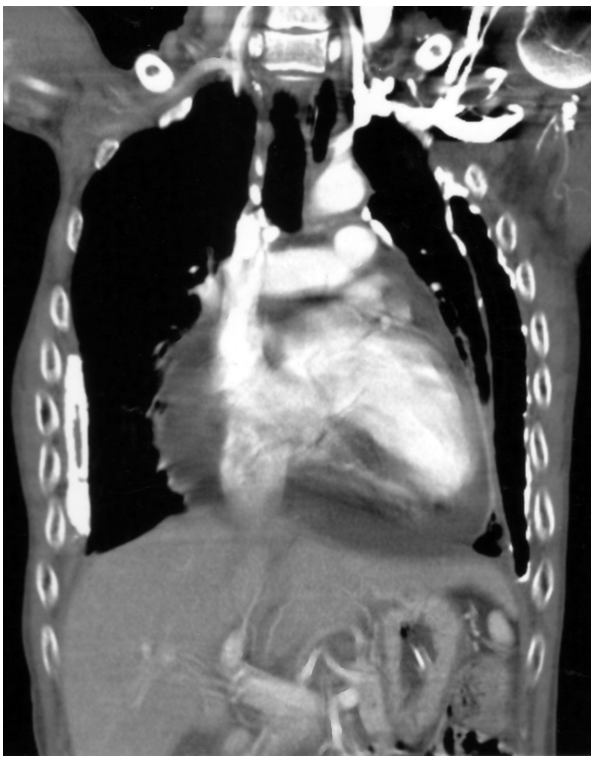

Fig. 2. Chest CT revealed calcified lymph nodes at the mediastinum, bilateral fibrothorax and massive pericardial effusion

deaminase (ADA) level of 42 U/l. Bacterial culture, mycobacterial culture and fungus culture of the pericardial fluid yielded no organism. The cytopathologic examination of the fluid showed huge lymphocytes with hyperchromatic nuclei consistent with diffuse B cell lymphoma (Figure 3). In addition, immunohistochemical analysis showed positivity for CD20 and negativity for CD3 and CD138 (Figure 4). The cells in the pericardial fluid were negative for HHV-8 genomes, using polymerase chain reaction (PCR). Serologic tests were found to be negative for HIV, HCV and HBV. Thoracoabdominal CT scans failed to reveal the primary origin of the pathology. Positron emission tomography (PET) showed increased FDG uptake at the left nasopharyngeal region due to inflammation, or less likely to tumor involvement. The pathology of the bone marrow biopsy revealed mildly hypocellular marrow and no evidence of lymphoma involvement. After the survey, no evidence of a solid mass was noted.

Based on these findings, a diagnosis of HHV8-unrelated PEL-like lymphoma was made for this HIV-negative patient. Extubation was performed successfully after pericardiocentesis. The pulmonary function test after extubation revealed severely restrictive ventilatory impairment with total lung capacity (TLC) of 2.13 liters (prediction value: 5.44 liters).The patient was referred to the department of hematological oncology for further diagnosis and treatment. He received chemotherapy with a regimen of cyclophosphamide, hydroxydaunorubicin, vincristine, prednisolone and rituximab (R-CHOP). The post-treatment follow-up chest X-ray revealed resolution of the pericardial effusion (Figure 5). Throughout an 8-month follow-up, the patient had no symptoms.

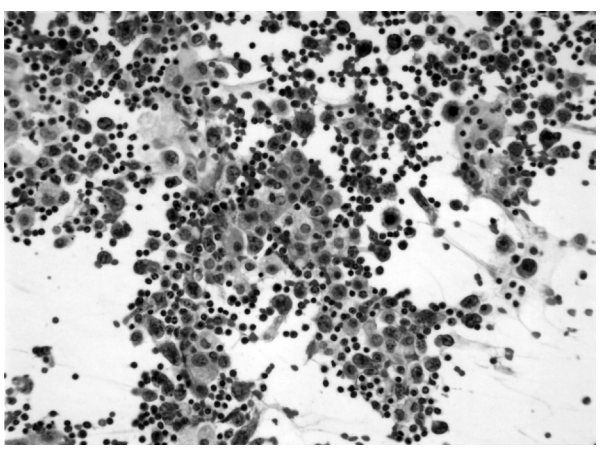

Fig. 3. Cytopathologic examination revealed medium-to-large-sized lymphocytes with scanty cytoplasm and oval nuclei containing fine chromatin compatible with lymphoma

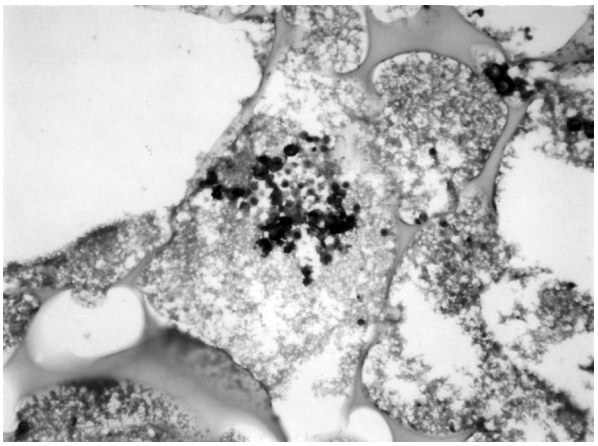

Fig. 4. Immunohistochemistry stain of pleural effusion revealed CD20-positive, which was compatible with diffuse large B cell lymphoma

Discussion

Malignancy has accounted for 13-23% of patients with pericardial effusion [6,7]. It is more commonly seen in large symptomatic pericardial effusions, and was responsible for 33% of cases in 1 report [8]. In this case, the patient had fibrothorax with severely restrictive ventilatory impairment. Chronic hypercapnia

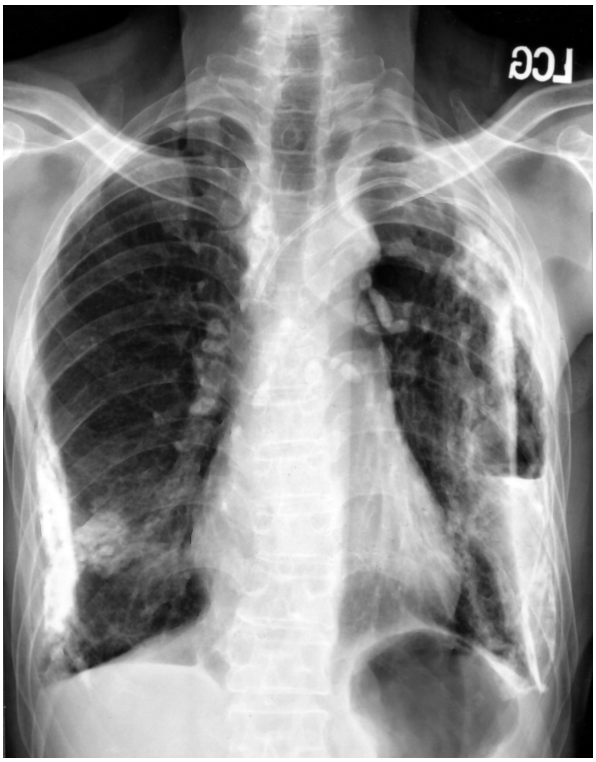

Fig. 5. Chest radiography showing resolution of the pericardial effusion after chemotherapy

may develop in patients with this condition [9]. The progressive pericardial effusion with low cardiac output may aggravate ventilator muscle fatigue. In this situation, acute or chronic hypercapnic respiratory failure may develop. After pericardiocentesis, the low cardiac output improved in our patient. And the aggravating factor of ventilatory failure disappeared. Successful extubation was later performed. The most common causes of pericardial malignant effusion included metastases of lung cancer, breast cancer and leukemia [10]. PEL is a rare cause of pericardial malignant effusion, and presents exclusively as a lymphomatous effusion in the absence of a solid mass [1]. PEL is a high-grade non-Hodgkin lymphoma of B-cell origin that is predominantly found in HIV-seropositive patients, and accounts for less than 4% of AIDS-related lymphoma [2]. However, PEL can occur in the absence of HIV infection, such as in solid organ transplant recipients and in those with hepatitis C virus infection [11,12]. PEL is universally associated with HHV-8 infection [3], and the World Health Organization (WHO) has used the term "PEL" only for HHV-related PEL [13]. The malignant cells of PEL are monoclonal B cells that contain genomic material from HHV-8 [14]. The products of HHV-8, including latency-associated nuclear antigen (LANA-1), viral cyclin (v-cyclin), viral FLICE inhibitory protein (v-FLIP), viral interleukin-6, viral interleukin-8 receptor homolog (vIL8R) and transmembrane protein K1, appear to play significant roles in the development of PEL by promoting proliferation and impairing apoptosis [15]. Loss of the HHV-8 genome results in the death of PEL cells, which shows that genes of the virus play a vital role in PEL cell survival [16].

Other primary lymphomatous effusion cases are described as HHV-8-unrelated PEL-like lymphoma [17]. HHV-8-unrelated PEL-like lymphoma was first described in 1998 [4]. HCV has been suggested to be an etiological agent of HHV-8-unrelated PEL-like lymphoma [5]. Most of the cases of HCV-associated HHV-8-unrelated PEL-like lymphoma involved the peritoneum, and also the pleura and pericardium [18,19]. Multi-step genomic abnormalities such as trisomy 8 chromosomes and amplification of the c-myc gene might be involved in the development of HIV-negative HHV-8-unrelated PEL-like lymphoma [20]. In this case, there was no known possible pathogenesis of HHV-8-unrelated PEL-like lymphoma, such as HIV, HCV, solid organ transplantation, alcoholism, cirrhosis or cancer. However, the advanced age of the patient could be the possible reason for the

HHV-8-unrelated PEL-like lymphoma. Since the immune function is known to be decreased in older populations, it is possible that the unrecognized mechanism of immunodeficiency may cause HHV-8-unrelated PEL-like lymphoma in geriatric patients [21]. There is no standard chemotherapeutic regimen recommended for HHV-8-unrelated PEL-like lymphoma. CHOP-like therapy has been used routinely. Patients would be treated with rituximab if the immunophenotype of the neoplastic cells were positive for CD20 [22-26]. In general, PEL patients are thought to have a poor prognosis with a mean survival time of approximately 4-6 months [2]. However, CD20-positive cases, especially in the HHV-8-negative and HIV-negative groups, might have a better outcome with the addition of rituximab, with a median survival of 7 months [21].

In conclusion, malignancy is more commonly seen in large symptomatic pericardial effusions. HHV-8-negative PEL-like lymphoma is a rare cause of pericardial effusion. Early diagnosis and appropriate treatment with rituximab might result in a better outcome.

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類原發性積液淋巴瘤導致之急性呼吸衰竭－病例報告

簡暐倫 * 許正園 *,** 覃俊士 *

原發性積液淋巴瘤為一高度惡性 B 細胞非何杰金氏淋巴瘤，常見於後天免疫不全病毒陽性病患，常以淋巴性積液表現而無實質性腫瘤。其普遍與第八型人類疱診病毒感染有關。有一小部份的積液淋巴瘤和第八型人類疱診病毒感染無關稱之為類原發性積液淋巴瘤。類原發性積液淋巴瘤為造成心包膜積液之罕見原因。我們報告一位 69 歲男性患者，此次因喘及急性呼吸衰竭之表現就診且檢查發現有大量心包膜積液。心包膜積液經病理診斷為類原發性積液淋巴瘤。病人經心包膜積液放液後成功拔管。並經 cyclophosphamide，hydroxydaunorubicin，vincristine，prednisolone 及 rituximab 治療後心包膜積液消退。我們報告此一罕見個案並做文獻回顧。*(胸腔醫學 **2013; 28: 347-353**)*

關鍵詞：類原發性積液淋巴瘤，心包膜積液，急性呼吸衰竭

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Tension Pneumopericardium after Removal of a Pericardial Drainage Catheter – Case Report

Eng-Guan Khor, Jiunn-Min Shieh, Shian-Chin Ko

Pneumopericardium is an uncommon complication of blunt or penetrating chest trauma. It may also occur iatrogenically, e.g., as a result of thoracic procedures, endoscopy, mechanical ventilation and pericardiocentesis. Tension pneumopericardium may progress rapidly, leading to cardiovascular compromise or circulatory collapse, and require emergent drainage of the pericardial sac. We describe the case of a patient with bilateral pneumonia and pericardial effusion. The patient underwent pericardiocentesis with pigtail drainage; however, subcutaneous emphysema, pneumopericardium, pneumomediastinum and pneumothorax developed immediately after removal of the drain catheter. Cardiac tamponade signs were noted. The patient underwent emergency pericardial window operation. Pneumopericardium is a rare complication of pericardiocentesis, occurring either as a result of direct pleuro-pericardial communication or a leaky drainage system. Although there have been several case reports in the literature describing pneumopericardium associated with pericardiocentesis, none had concurrent pneumothorax and/or pneumomediastinum. ***(Thorac Med 2013; 28: 354-359)***

Key words: pneumopericardium, pericardiocentesis, pericardial drainage

Case Report

A 55-year-old man was referred to our hospital with the presentation of cough, mild pyrexia and exertional dyspnea for 2 weeks. He had a 10-year history of hypertension under regular medical treatment. Physical examination revealed a body temperature of 37.8°C and a respiratory rate of 22 breaths per minute. On auscultation, there were distant heart sounds. Scattered inspiratory crackles were heard in the bilateral lower lung fields. Laboratory data revealed a total white blood cell (WBC) count of 12,200/μL, 83% neutrophils, an erythrocyte sedimentation rate of 43 mm/hr and serum C-reactive protein (CRP) of 14.1 mg/dL. Sputum culture yielded *Citrobacter koseri* and *Haemophilus influenzae* 2 days later.

Electrocardiography (ECG) showed sinus tachycardia (108/min), non-specific ST-T changes and diffuse low voltages on both limb and precordial leads. Chest radiograph revealed an enlarged cardiac silhouette and diffuse interstitial infiltrates in the bilateral lower lung

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fields. A moderate amount of pericardial effusion was found on transthoracic echocardiography. A pigtail catheter was placed in the pericardial space under ultrasound guidance (Figure 1). No complication was noticed during and immediately after the procedure. In all, 350 ml of yellowish clear fluid was evacuated. Analysis of the pericardial effusion showed a pH of 7.5, glucose of 121 mg/dL, lactic dehydrogenase (LDH) 302 IU/L, total protein 4.7 g/dL and WBC 24 /μL with lymphocytes 50%. Cytological study showed no malignant cells.

The drainage catheter was removed 4 days later. However, immediately after removing the pigtail catheter, the patient started to feel dyspnea, palpitation and chest pain. The left-side of the chest wall was swelling with crepitations on palpation. Tachycardia (112/min), relative hypotension (102/66 mmHg) and jugular vein engorgement were found. Follow-up chest radiography (Figure 2) and chest computed tomography (CT) (Figure 3) showed massive pneumopericardium, pneumomediastinum, subcutaneous emphysema and mild left-side pneumothorax.

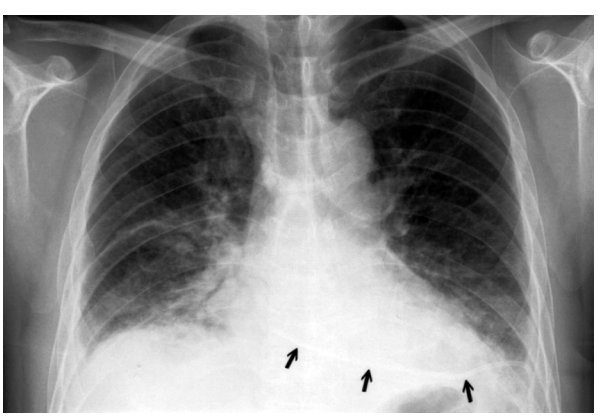

Fig. 1. Chest radiograph before removal of the pericardial drainage catheter. Black arrows denote the indwelling pigtail catheter inserted through the posterolateral aspect of the 7th intercostal space. No evidence of air leak was found at that time. Increased infiltrates in the bilateral lower lung fields indicated pneumonia.

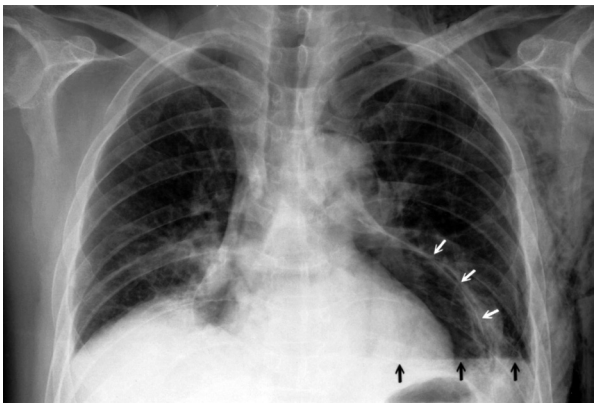

Fig. 2. Chest radiograph after removal of the pericardial drainage catheter. Black arrows denote an air-fluid level in the left lower field which represents hydropneumothorax. White arrows indicate 2 radiopaque lines outlining the pericardial sac. The outer line represents the visceral pleura and the inner line is the pericardium. Concurrent pneumopericardium and pneumothorax is demonstrated. Subcutaneous emphysema in the left-side chest wall and neck was also found.

Under the impression of tension pneumopericardium, pericardial window was performed via a subxyphoid approach for pericardial fluid and air evacuation. The pericardial biopsy showed only chronic inflammation. The patient unfortunately developed acute respiratory distress syndrome after the operation, and finally, succumbed to acute respiratory failure on the 7th postoperative day.

Discussion

Pneumopericardium is a rare occurrence and is defined as the presence of air within the pericardial space. Pneumopericardium can be of traumatic or non-traumatic origin, although most cases are of traumatic origin. It can also develop as a result of mechanical ventilation delivered at high pressure, mediastinal tumors, tuberculosis, and gastropericardial fistulas [3]. A variety of procedures including esophagecto-

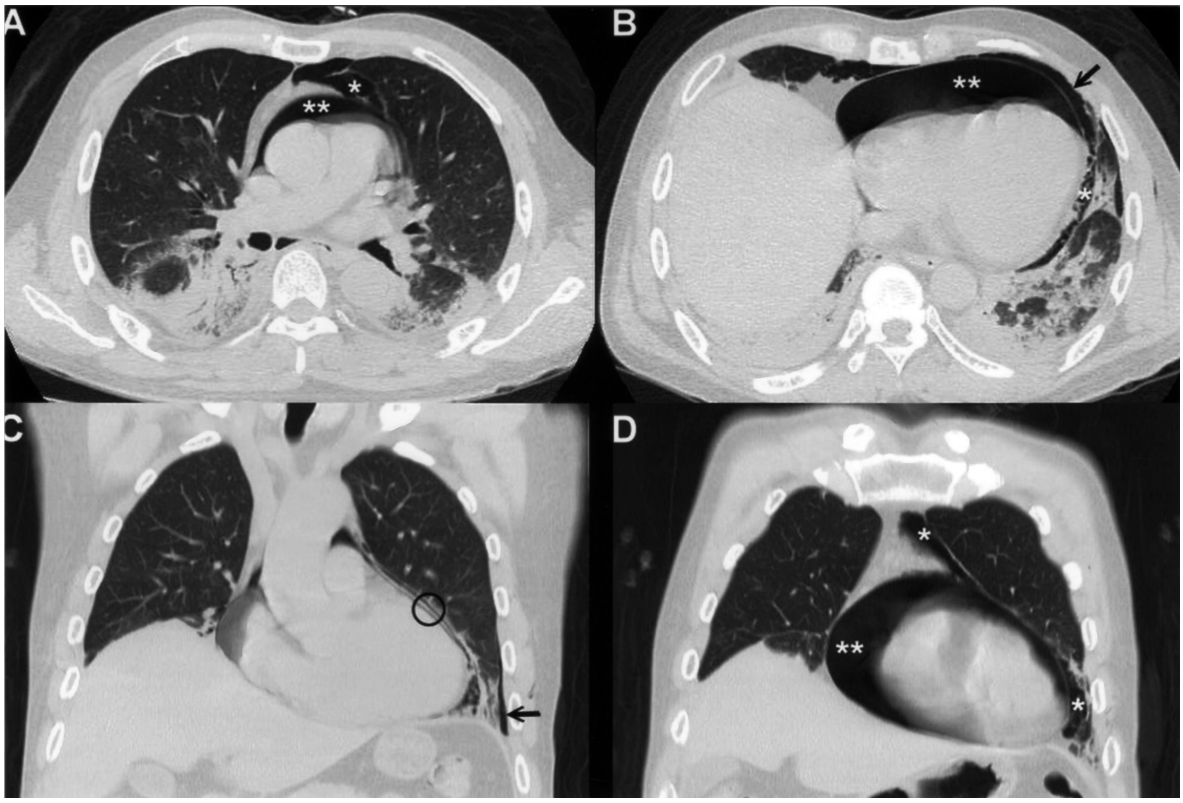

Fig. 3. Lung window setting of the chest CT: Panels A and B are axial views and panels C and D are frontal views. The asterisk (*) denotes pneumomediastium, which extends to the upper mediastinum and comprises a soft tissue web within it. The double-asterisk (**) denotes pneumopericardium, which is confined to the pericardial sac. The heart is surrounded by a broad band of air (halo sign) on panel D. The black arrows denote the mild left-side pneumothorax. The circular area (○) on panel C comprises both the visceral pleura and pericardium, as described in the legend of Fig. 2.

my, endomyocardial biopsy [4], lung transplantation, pericardiocentesis, pacemaker placement [5], sigmoidoscopy [6] and even dental surgery [1] have been associated with pneumopericardium. Pneumopericardium is very rarely caused by gas-forming microorganisms, e.g., *Aspergillosis spp. and Clostridium perfringens* [7]. Spontaneous cases have been reported in neonates and during asthma attacks [8].

Pneumopericardium can be asymptomatic or cause symptoms such as chest pain, shortness of breath, shoulder pain, and fainting. On physical examination, Hamman's sign, a crunching, rasping sound, synchronous with the heartbeat, is heard at the precordium in cases of pneumomediastinum or pneumopericardium. In addition, a murmur resembling the sound of a mill wheel (bruit de moulin) can be heard. On percussion, shifting tympany may be found at the precordial area.

The diagnosis of pneumopericardium is suggested by conventional chest radiography. On posteroanterior chest radiographs, a continuous radiolucent rim of air outlines the cardiac silhouette. It is curved and sharply marginated by the pericardial sac. Pneumopericardium does not extend into the upper mediastinum and neck, which differentiates it from pneumomediastinum. The band of gas can be broad and completely surround the heart, thus creating the

halo sign. A continuous diaphragm sign can be seen on the posteroanterial and lateral views of plain films [9]. Chest CT helps in confirming the presence of air. Reduced ECG voltages may be found as in our case.

Tension pneumopericardium is defined as sufficient intrapericardial pressure to produce cardiovascular instability. It produces the same physiological derangement as cardiac tamponade secondary to accumulation of blood or other fluids. This may result from a "1-way valve" mechanism within a pleuropericardial or bronchopericardial fistula. The amount of air required to produce hemodynamic changes depends on the volume and rate of introduction. Hemodynamic changes may occur with as little as 60 ml of air if it is introduced rapidly. Up to 500 ml may accumulate in the pericardium without marked effect if introduced slowly into the pericardial space.

In our case, there was no remarkable air leak during or immediately after the pericardiocentesis procedure. However, massive pneumopericardium, pneumomediastinum, subcutaneous emphysema and left-side pneumothorax developed soon after removing the drainage catheter. We hypothesized that the left lung was punctured during the placement of the pigtail catheter. No immediate air leakage from the ruptured alveoli would be due to the tamponade effect of the catheter itself. However, the tamponade effect disappeared after removal of the catheter and resulted in air leaking from the alveoli into the pericardium, mediastinum, pleural space and soft tissue layers. To our knowledge, there has been no similar case report in the literature describing the simultaneous development of pneumopericardium, pneumomediastinum and pneumothorax following removal of the pericardiocentesis drainage catheter.

There is no consensus regarding the treatment of pneumopericardium and the clinical course is highly variable. In general, if the hemodynamic condition is stable, the underlying condition should be treated and the patient should be monitored closely. Bed rest is the treatment of choice, and the patient is followed up with chest radiography, echocardiograms, and hemodynamic tests. In patients who do not develop tension pneumopericardium, spontaneous regression can be anticipated [10]. Management of patients with tension pneumopericardium is important because of its possible fatal consequences. Pericardial tamponade requires emergent pericardiocentesis. If the pericardial tamponade communicates directly with hollow organs apart from the lungs, surgical treatment is preferred. Mortality due to tension pneumopericardium can be as high as 50% [2].

In conclusion, pneumopericardium can develop following pericardiocentesis secondary to iatrogenic causes. As in our case, pneumopericardium can occur after removal of the pericardial drainage catheter. Chest radiography should be followed up, especially when there is air leak syndrome, such as subcutaneous emphysema. If pericardial tamponade signs are evident and the hemodynamic status deteriorates, re-pericardiocentesis or surgical intervention should be performed. It is important that clinicians are aware of this rare but potentially fatal complication of pericardiocentesis.

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拔除心包引流導管後產生張力性心包積氣－個案報告

許永毅　謝俊民　柯獻欽

心包積氣是胸腔外傷所造成的罕見併發症，但它也可能由醫源性原因導致，如：使用呼吸器、心包穿刺術。心包積氣可能快速惡化而造成心臟血管循環系統衰竭，此時稱之為張力性心包積氣，需要緊急做心包引流術。我們報告一位成年男性病人，起始表現為兩側肺炎併心包積液，接受心包穿刺術併豬尾巴導管置入，引流數天後在拔除導管時，卻立即發生張力性心包積氣、縱膈積氣、氣胸與皮下氣腫，出現心臟填塞徵候，病人緊急接受心包膜開窗術。張力性心包積氣是可能危及生命的併發症，需要立即診斷與妥善治療。*(胸腔醫學 **2013; 28: 354-359**)*

關鍵詞：心包積氣，心包引流

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Management of Fat Embolism Syndrome Using Extra-Corporeal Membrane Oxygenation: Report of 2 Cases

Hsiang-Wen Liu, Ping-Hung Kuo

Fat embolism syndrome (FES) is a condition characterized by pulmonary dysfunction, changes in mental status and petechial rash. Trauma to the long bones and pelvis is the major cause of FES. The severity of FES can range from sub-clinical to life-threatening. Immediate and appropriate resuscitation is essential to reduce mortality. Although extracorporeal membrane oxygenation (ECMO) has been used for severe respiratory and circulatory failure, its full potential as a rescue therapy for FES has yet to be exploited. In this report, we present 2 trauma cases with fulminant FES that were successfully treated with veno-venous ECMO. On the basis of the results of our report, we suggest that ECMO may be an appropriate therapy for patients with severe pulmonary FES who do not respond to supportive management. ***(Thorac Med 2013; 28: 360-369)***

Key words: fat embolism syndrome, FES, extra-corporeal membrane oxygenation, ECMO

Introduction

Fat embolism is a condition in which fat drops enter the microcirculation with or without clinical symptoms. Fat embolism syndrome (FES), however, is characterized by multiple organ dysfunction including respiratory distress, alternation of mental status and skin petechiae. Trauma to or surgery at the fat-containing bony or soft tissues, especially the long bones and pelvis, is considered to be the major cause of FES. The syndrome usually develops suddenly and rapidly after the culprit event, and may progress quite quickly -- even within several hours in fulminant cases.

Two theories have been proposed. The first is a "mechanical" theory and the second is a "biochemical" theory [1]. The "mechanical" theory is that of fat droplets causing a mechanical obstruction in the pulmonary system. When fat globules enter the systemic circulation by crossing a patent foramen ovale or going through the pulmonary capillaries, embolization to the central nervous system can occur. The "biochemical" theory is that of toxicity caused by free fatty acids from hydrolysis of intravascular fat droplets. However, the pathogenesis of FES remains unclear.

No effective therapies have been documented for FES, and the treatment centers on

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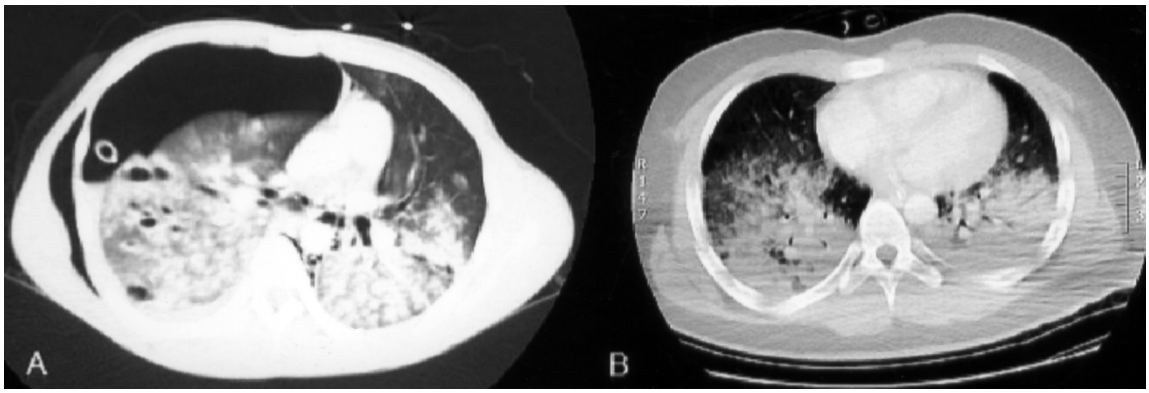

Fig. 1. A. The chest CT of case 1 showed right hemo-pneumothorax and bilateral lower lung consolidations. B. The chest CT of case 2 also showed bilateral lower lung consolidations.

supportive care. In recent years, extra-corporeal membrane oxygenation (ECMO) has been used increasingly for various critical conditions including acute respiratory distress syndrome (ARDS), lung transplantation, and fatal pulmonary embolism.

In this report, we describe 2 cases of FES with refractory hypoxemia under traditional mechanical ventilation. Both patients were successfully managed by the use of ECMO.

Case Presentation

Case 1

A previously healthy 18-year-old man presented to the emergency department (ED) with shortness of breath after a motor vehicle accident. Upon examination, he was afebrile. Tachycardia (146 beats/min), tachypnea (35 breaths/min), and hypotension (blood pressure 78/52 mmHg) were found. Although the patient did not have direct traumatic brain injury, the Glasgow Coma Scale (GCS) decreased to E2V1M2. His breathing sounds in the right lung were decreased. The abdomen was distended, and he could not move his lower limbs. He underwent a whole body computed tomography (CT) examination, which revealed fractures at the right clavicle, right 8^{th} rib and left femur. Right hemo-pneumothorax and liver laceration were also noted. The chest CT also revealed basal consolidation of both lungs (Figure 1A). Volume resuscitation was started, and a right tube thoracotomy was performed. The patient was intubated and ventilated due to hypoxemia. He also underwent a trans-arterial embolization for liver laceration.

Because the patient had respiratory symptoms and evidence of cerebral involvement unrelated to head injury, FES was highly suspected. The syndrome was diagnosed based on the Schonfeld's score [2] (Table 1), which was 10 for this patient.

Severe hypoxemia, with a PaO_2/FiO_2 (P/F) ratio of 61, persisted despite the use of high-level positive end expiratory pressure (PEEP) of 14 cm H_2O and an inspired oxygen faction (FiO_2) of 1.0. A veno-venous ECMO was instituted within the first 24 hours of hospitalization, with a right internal jugular 18-Fr and a right femoral 22-Fr return cannula. Heparin was not used to avoid bleeding complications. The

Table 1. The Schonfeld's score, a quantitative measure to diagnose FES; a score of more than 5 is required to diagnose FES

The Schonfeld's score	Score
Petechiae	5
X-ray chest diffuse infiltrates	4
Hypoxemia	3
Fever	1
Tachycardia	1
Tachypnea	1
Confusion	1

initial running of the ECMO was 2300 rpm and the initial blood flow was 2.5 L/min. The sweep gas flow was 5 L/min.

The patient's oxygenation improved gradually under ECMO support (Figure 2), and the mechanical ventilator settings were adjusted according to the lung-protection ventilator strategy (lowest FiO_2 to maintain SpO_2 >90%, ventilator rate 10 to 20/min, pressure control mode with peak inspiratory pressure <35 cm H_2O, and PEEP maintained from 10 to 16 cm H_2O). The FiO_2 could be tapered to 45% on day 3. Deep vein thrombosis of his right leg occurred on day 6, requiring moving of the right femoral cannula to the left side. He was liberated from ECMO on day 10. The patient underwent an open reduction and internal fixation (ORIF) for left femoral fracture on the 27th hospital day. However, the patient developed an episode of generalized tonic seizure on the next day. Brain magnetic resonance imaging (MRI) disclosed several small cortical lesions at the bilateral frontal and right occipital lobes which were hyperintense on the T2-weighted image (Figure 3).

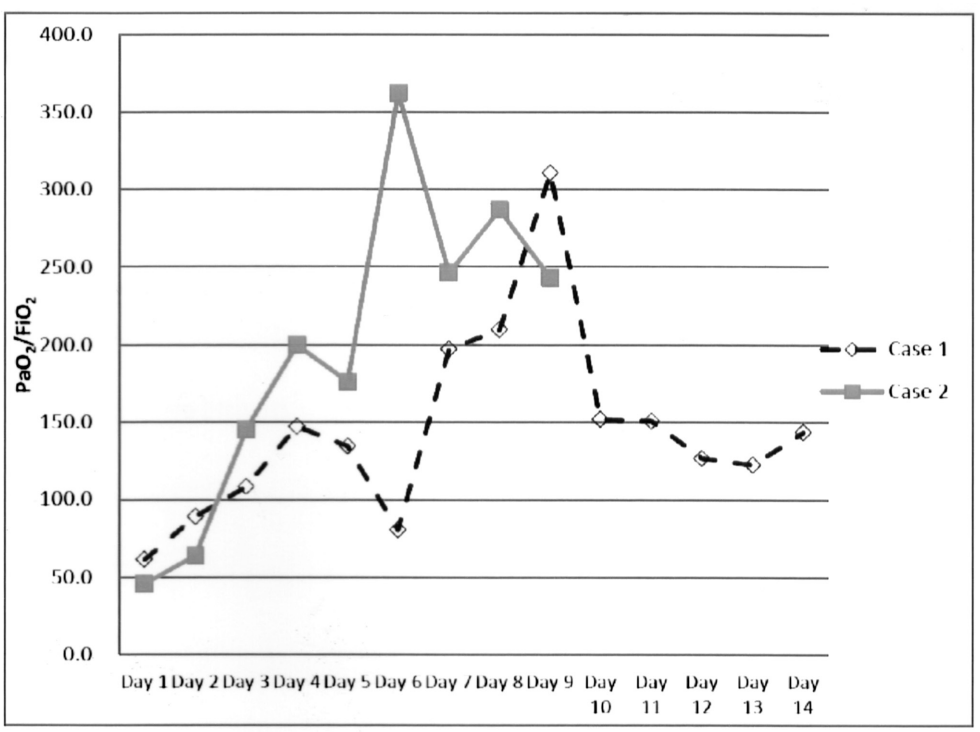

Fig. 2. Changes in the PaO_2/FiO_2 ratio of the 2 patients during hospitalization. The initiation of ECMO was on day 1 in both cases, and withdrawal occurred on day 10 and day 4 in case 1 and case 2, respectively.

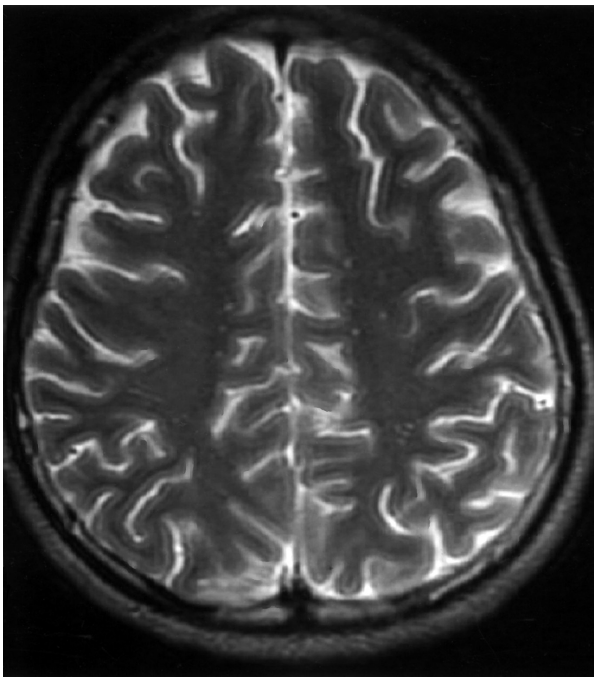

Fig. 3. Brain MRI after seizure revealing multiple hyperintense dots on the T2-weighted image.

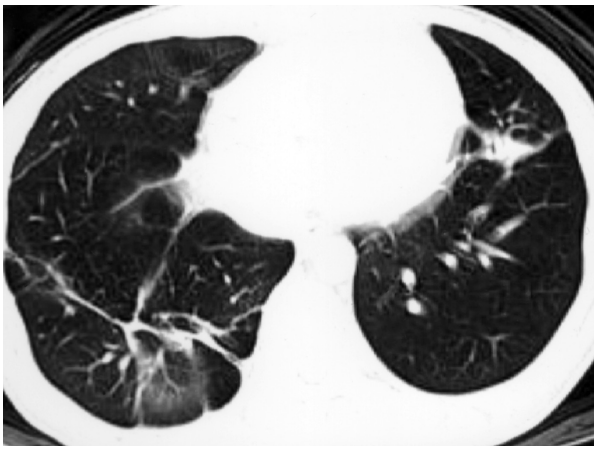

Fig. 4. Follow-up chest CT in case 1, 4 months after discharge, demonstrating mild fibrotic changes.

Because of prolonged ventilator use, a tracheostomy was performed on day 34. He was successfully weaned from mechanical ventilation on the 38th hospital day. Corking succeeded 3 weeks later. He had a complete neurological recovery and was discharged home on day 62. We performed a lung function study soon after discharge which showed a mild to moderate mixed ventilatory defect and moderate impairment of diffusion capacity (DL_{CO}) (FEV_1: 78.81% predicted, DL_{CO}/VA: 60.33% predicted). The follow-up CT scan of the chest showed mild fibrotic changes at the bilateral lower lobes (Figure 4).

Case 2

A previously healthy 16-year-old boy was sent to the ED of our hospital after a motor vehicle accident. Upon examination, he had normal vital signs and was fully-oriented. His bilateral legs were tender on palpation. Other physical examinations were unremarkable. There was no traumatic brain injury. Bilateral femoral and left tibia shaft fractures were noted on the plain radiographic films, and an emergent ORIF was performed on the same day. However, acute changes in consciousness and desaturation developed soon after the surgery. The GCS decreased to E4V1M2. He was intubated and ventilated. The brain CT showed multifocal hemorrhage. Moreover, the patient was noted as having severe hypoxemia, P/F= 45, under a high PEEP, and a FiO_2 of 1.0. The chest CT showed bilateral basal consolidation (Figure 1B). FES was diagnosed by the Schonfeld's score [2] of 9.

Veno-venous ECMO was performed in place immediately in the same fashion as described in the previous case. Again, heparin was not used to prevent hemorrhage. The initial running of the ECMO was 2890 rpm and the initial blood flow was 3680 ml/min. The sweep gas flow was 10 L/min.

The patient's hypoxemia significantly im-

Table 2. The demographics and clinical characteristics of the 2 patients

	Case 1	Case 2
Age (y)	18	16
Male/female	Male	Male
Clinical symptoms	Diffuse infiltrates on chest X-ray, hypoxemia, tachycardia, tachypnea and confusion	Diffuse infiltrates on chest X-ray, hypoxemia, tachypnea and confusion
Schonfeld's score	10	9
The culprit events of FES	Trauma, orthopedic surgery	Trauma, orthopedic surgery
Indication for ECMO	Hypoxia	Hypoxia
PaO_2/FiO_2 ratio when ECMO was set up	61	45
Hospital day of initiation of ECMO	1	1
Duration of ECMO (d)	10	4
Duration of mechanical ventilation (d)	38	13
Outcome	Survival	Survival
Complication of FES		Frontal lobe syndrome

proved after ECMO (Figure 2). The FiO_2 was decreased to 50% on day 3, and he was liberated from ECMO on day 4. There were no severe complications with regard to the ECMO treatment. Tracheostomy was performed on the 7th hospital day. His consciousness fully recovered and he was successfully weaned from mechanical ventilation on the 13th hospital day. The tracheostomy tube was removed a month and a half later. However, he developed a frontal lobe syndrome with decreased short-term memory. He has also received long-term use of anti-epileptic drugs after discharge to prevent seizure. Because of the neurologic sequelae, he was not able to return to a normal social life.

Discussion

We have described the use of ECMO for refractory hypoxemia in 2 cases of severe FES (Table 2). Our experience with regard to ECMO with these patients may provide insight into the optimal management of FES, especially for refractory hypoxemia in the acute ICU setting.

The complications in the surgical ICU following severe multiple trauma may occasionally make the diagnosis of FES rather difficult. Several diagnostic criteria for FES have been proposed, including Gurd's criteria [3], the Lindeque criteria [4], and the Schonfeld's score [2]. Both of the cases reported here met the diagnostic criteria for FES, with a Schonfeld's score of 10 and 9, respectively. It is notable that 2 episodes of FES developed in the first

case, with the second episode occurring several hours after the orthopedic procedure. Similar cases of recurrent FES have been reported, and it has been suggested that multiple bone fractures and movement of fracture segments can increase the risk of such events [5]. Therefore, early fixation of fractures within 12 hours of injury is recommended to prevent recurrence of FES. However, the best surgical technique with which to do this stabilization has not yet been clearly determined. Surgical techniques have been developed in an attempt to decrease the extravasation of fat during long-bone stabilization by reducing intramedullary pressure.

The management of FES is mainly supportive. The efficacy of the use of drugs for the treatment of FES is as yet inconclusive -- drugs have not been shown to reduce the treatment course or mortality. In our first case, methylprednisolone was discontinued after just 1 dose was administered to avoid any further risk of infection.

Severe hypoxemia (the initial PaO_2 < 50 mmHg) has been reported in more than 90% of patients with fulminant FES [6]. The incidence of respiratory failure requiring mechanical ventilation was reported to be 79% [4]. The pathophysiology of hypoxemia due to FES is controversial. However, lung injury is believed to be the result of a combination of the mechanical and biochemical effects of the fat. In previous animal studies, capillary congestion and interstitial edema due to intravascular fat globules were observed soon after the development of FES, followed by extensive inflammation of the interstitium and hemorrhagic edema [7].

With the advances in supportive ICU care, the rate of respiratory failure following FES has decreased to 44% in recent years [8]. The incidence of intubation or tracheostomy was about 50% in previous studies [9]. Because pulmonary presentations of fulminant FES can be similar to those of ARDS, it is difficult to determine the exact morbidity and mortality of FES. However, most authors agree that even severe respiratory failure associated with fat embolism seldom leads to death, with a mortality rate ranging from 5-15% [10].

The treatment of respiratory complications associated with FES focuses on maintaining an acceptable gas exchange with a lung-protective strategy of mechanical ventilation. Extracorporeal support facilitates the use of the lung-protective strategy. Furthermore, it often allows for delivery of a low tidal volume from the ventilator and decreases both the airway pressure and the requirement of FiO_2. These advantages provide the lung a time of rest. The Conventional Ventilation or ECMO for Severe Adult Respiratory Failure (CESAR) trial was a controlled clinical trial using modern ECMO technology [11]. In this trial, the primary outcome, either death or severe disability at 6 months, was lower in cases of patients referred for consideration for ECMO than in those assigned to conventional management. To the best of our knowledge, the use of ECMO to treat respiratory failure due to FES has been described in only a few related case reports [12-14]. Webb *et al*. described the successful use of veno-venous ECMO in a trauma patient who had fractures of the right ulna and femur with rapid deterioration. Despite ventilatory support with a FiO_2 of 100% and a PEEP of 30 cm H_2O, the patient remained profoundly hypoxic. Therefore, ECMO was used for approximately 120 hours. The P/F ratio improved from 39 to 187. Two other reports from Taiwan also demonstrated marked improvement in arterial oxygenation in 2 young men with severe FES [12-13]. These 3 previ-

ously reported cases, along with our 2 cases, all had trauma-related FES. Four episodes of FES developed after orthopedic surgery. Improvement in the P/F ratio after initiation of ECMO support was reported in only 3 cases, and it was 184.6±45.8. Of most importance, these 5 patients survived.

The average duration of ECMO use for these patients with FES was shorter than for patients with ARDS [15]. Patients with ARDS typically require extracorporeal support for a week to 10 days. However, the patients reported here used ECMO for only 6.4±2.3 days. According to our experience and previous reports, the timing of ECMO initiation may be the key to a successful outcome. ECMO therapy was started soon after the failure of conventional ventilatory strategies for 4 patients. Bridging therapies, such as prone positioning or high-frequency oscillatory ventilation, were not applied for our patients due to the severity of the trauma. Both of our cases underwent ECMO on hospital day 1, while the 2 cases reported previously received this treatment on hospital day 3 and 2, respectively. Only 1 patient received volumetric diffusive ventilation as a salvage therapy before application of ECMO. Another issue essential to determining the efficacy of ECMO is that it must be used with the appropriate patient. The 5 reported patients were all young men, with ages ranging from 16 to 38 years, and did not have significant preexisting comorbidities.

Bleeding is 1 of the most undesirable complications of ECMO, although it has been used for traumatic patients, even those with traumatic brain injury [16]. Heparin was not used with our 2 patients to prevent further bleeding. One of our cases developed deep vein thrombosis in the leg that was cannulated for ECMO. Webb et al. used heparin dosages ranging from 2-15 units/kg/h, which were able to maintain the activated clotting time (ACT) between 182 and 240 seconds; no major bleeding in their patient was reported. Continuous improvements in ECMO technology and the development of the anti-coagulability of the circuit have contributed to the decreased use of anticoagulants. Furthermore, the use of centrifugal-type pumps reduces hemolysis [17]. Therefore, putting severe trauma patients with active hemorrhage on ECMO may not be a contraindication.

The majority of patients with FES have a good prognosis. Neurologic sequelae are the most frequently reported complications in these patients. Moreover, the recovery is unpredictable. Even in patients with severe FES complicated with tetraplegia, full recovery has been observed [18]. However, permanent neurologic deficit with FES is not rare. One of the presented cases developed frontal lobe syndrome with inappropriate behavior and bad manners. He also required long-term use of anti-psychotic agents. Transesophageal echocardiography during operation has been recommended for earlier recognition and diagnosis of systemic embolization from FES [19].

The potential long-term effects of FES on the lung are unknown. In a rabbit model, interstitial fibrosis and pleural contraction were noted on the 7th day after FES [7]. Our patient's CT scan showed parallels to reports in the animal study. In the first case, we performed a lung function test about 3 months after the accident that revealed a mild to moderate mixed ventilatory defect and moderate impairment of diffusion capacity (FEV_1: 78.81% of predicted, DL_{CO}/VA: 60.33% of predicted). Decreased diffusion capacity was observed in a post-ARDS study, as well [20]. The mechanism may be the

progressive nature of the fibrotic changes due to a progressive thickening of the septa and also a progressive chronic inflammatory reaction. In particular, the pulmonary vessels still showed some persistent narrowing of the lumen patency and media thickening [7].

In summary, ECMO may be a useful ventilator adjunct for severe hypoxemia in FES patients. It is essential that those involved in the acute management of severely traumatized patients use their expertise and whatever technological aids are available to diagnose FES and treat it appropriately. Although trauma-related FES is usually accompanied with coagulopathy, veno-venous ECMO is typically a safe and beneficial procedure that can be used in such patients. However, special attention should be paid to the prevention of ECMO-related complications. Our experience may provide insight into the optimal management of FES in the acute ICU setting.

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脂肪栓塞症候群病患使用葉克膜之兩病例報告

劉祥雯　郭炳宏

脂肪栓塞症候群是長骨骨折的併發症，主要的症狀有呼吸及神經系統異常和淤斑。脂肪栓塞症候群的嚴重度從輕微到致命都有，快速及正確的支持性療法是減少死亡率重要的一環。最近在世界各地的加護中心，體外循環維生系統常被用來治療嚴重呼吸及循環衰竭的病患，但此裝置對於改善脂肪栓塞而引起之呼吸衰竭仍未有定論。我們報告二例因脂肪栓塞症候群而產生嚴重低血氧情形之病患，在接受靜脈 - 靜脈型體外循環維生系統後，病人血氧明顯改善並在良好的狀況下出院。根據此篇結論，我們建議當病人出現因脂肪栓塞症候群引起之致命呼吸衰竭，在支持性療法失敗後，便可使用靜脈 - 靜脈型體外循環維生系統作為治療。*(胸腔醫學 **2013; 28: 360-369**)*

關鍵詞：脂肪栓塞症候群，體外循環維生系統，葉克膜

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Penetration of Liver, Diaphragm and Lung by Tube Thoracostomy in a Mechanicaly Ventilated Patient: A Rare Case of Chest Tube Malposition

Chi-Lu Chiang*, Heng-Sheng Chao*, Chien-Sheng Huang**, Shi-Chuan Chang*,***

Tube thoracostomy is a standard therapy for a number of pleural disorders. However, the procedure involves a certain rate of complications. We reported a 55-year-old woman who had diabetes and required mechanical ventilation due to respiratory failure at another hospital, and then developed right-side pneumothorax. Her oxygenation showed no improvement after tube thoracostomy. The chest computed tomography scans showed that the chest tube had penetrated the liver, diaphragm, and right lower lung into the pleural cavity. Interstitial pneumonitis was also noted. After insertion of a new chest tube, withdrawal of the original one began inch-by-inch every 2-3 days and, was finally removed uneventfully. This case highlights the importance of performing tube thoracostomy with caution in all patients, especially in those who are mechanically ventilated and with restricted lung. ***(Thorac Med 2013; 28: 370-374)***

Key words: chest tube, mechanical ventilation, pneumothorax, thoracostomy

Introduction

Chest tube thoracostomy is a common procedure used to treat pneumothorax and to drain fluids from pleural spaces. Although the procedure is safe when performed by a trained physician, it has potential complications that may reach 37% in the emergency department [1]. The immediate complications include intercostal vessel laceration and retroperitoneal misplacement; delayed complications include empyema, re-accumulation of pneumothorax and insertion site infection [1]. We report herein a case of chest tube malpositioning with penetration through the liver, diaphragm and lung. The malpositioned chest tube fortunately was removed slowly and unevenfully and required no further surgical intervention.

Case Report

A 55-year-old woman had a history of type 2 diabetes mellitus and idiopathic thrombocytopenic purpura. She underwent a tracheos-

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tomy after an episode of severe pneumonia and required mechanical ventilation. The patient suffered from a sudden onset of dyspnea after assisted ventilation for 3 months. Chest sonography showed an absence of pleural gliding signs in the right chest highly suggestive of pneumonthorax, which was later confirmed by portable chest x-ray film. A trocar-type chest tube was inserted into the right chest along the mid-axillary line by a medical intensivist. One week after tube thoracostomy, a persistent air leak from the chest tube was noted, and a 70% fraction of inspired oxygen (FiO_2) was required for the patient to maintain the arterial oxygen saturation (SpO_2) above 90%. The patient was transferred to the respiratory care unit (RCU) in a tertiary teaching medical center for further management.

Chest radiograph and computed tomography (CT) scans of the chest performed at our hospital showed right-side pneumothorax inadequately drained by a chest tube and right upper lobe passive atelectasis (Figures 1A and 1B). The image studies indicated interstitial lung disease with reduced lung volume. The chest tube traveled from the subphrenic region, through the posterior segment of the liver, the right diaphragm and right lower lung parenchyma into the right hemithorax. Chest tube malposition with liver, diaphragm and lung penetration was diagnosed. There was no CT evidence of injury to the major hepatic vessels or inferior vena cava. A new 28 French chest tube was inserted via the right 7th intercostal space by a chest surgeon. The chest tube appeared to be in the appropriate position as evidenced by a chest film showing full expansion of the right lung. Before removing the malpositioned chest tube, we consulted general and thoracic surgeons regarding the potential risk of hemoperitoneum and bile leakage during the removal. After fully discussing this and reaching a consensus, the malpositioned chest tube was removed inch-by-inch, around 2-5 cm each time, every 2-3 days, with close monitoring of vital signs. We checked the hemoglobin level and liver func-

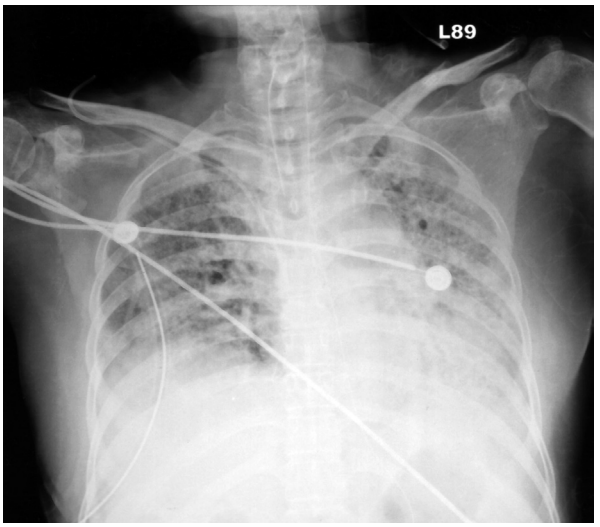

Fig. 1A. Plain chest film of the patient shows the unusual curved path of the chest tube.

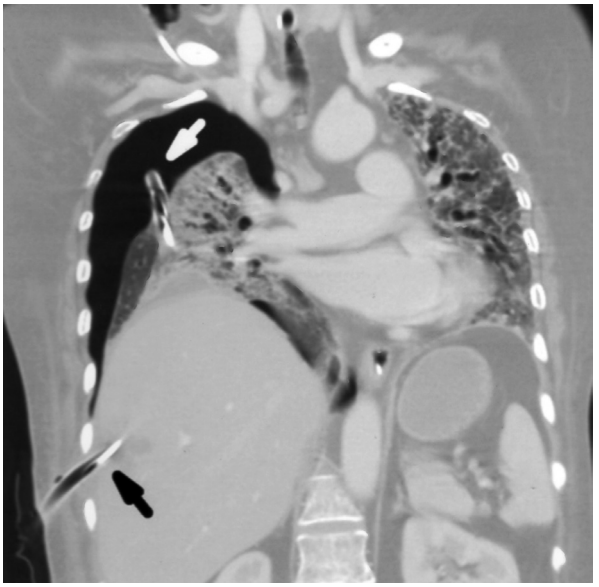

Fig. 1B. CT scan of the chest shows the liver (black arrow) and lung (white arrow) are penetrated by the chest tube.

tion tests, especially alkaline phosphatase and gamma-glutamyl transpeptidase, each time when the tube was pulled out. The malpositioned chest tube was successfully removed without any complications 14 days later. The interstitial lung disease of the patient was proved to be collagen vascular disease in nature during RCU hospitalization. After treatment with high dose methylprednisolone followed by low-dose maintenance steroid therapy, the patient was successfully weaned from the ventilator about 4 months after removal of the malpositioned chest tube.

Discussion

The risk of chest tube insertion in patients requiring with mechanical ventilation has been well described [2]. Chest tube malpositioning is a common complication of tube thoracostomy, and the incidence may be higher in critically ill patients. The rate of malpositioning of the chest tube as demonstrated by thoracic CT was 30% in 75 critically ill patients undergoing 122 chest tube thoracotomies, and the use of a trocar for chest tube insertion appeared to be the only predicting factor [3]. The British Thoracic Society published a guideline for insertion of a chest drain in 2003 [4]. To minimize complications, the insertion site must be within the "safe triangle". This is the triangle demacrated by the anterior border of the latissimus dorsi, the lateral border of the pectoralis major muscle, a line superior to the horizontal level of the nipple, and an apex below the axilla [4]. Access to the pleural cavity is better attained by blunt dissection than the use of a trocar. Furthermore, the use of chest sonography during chest drain insertion may help identify the diaphragm, detect tube position and avoid intraabdominal placement. These key points were relevant to our patient, whose chest images were indicative of a small lung volume with a high diaphragm position. Based on this case report, we suggest that sonographic guidance be mandatory in cases of chest tube insertion, if the equipment is available and clinically indicated.

Malpositioning may be difficult to diagnose by plain films. Landay *et al*. reported 51 instances of chest tube thoracostomy complicated with lung penetration, and none of these malpositioned tubes were observed to be intrapulmonary on plain chest films before the performance of thoracic CT scans [5]. In our reported case, the penetration of the liver, diaphragm and lung by the chest tube was discovered 1 week later at our institute on CT scans of the chest. The diagnostic clues of a malpositioned chest tube in reported patients were deterioration of oxygenation and persistent air leakage from the chest tube.

A reported patient with pneumothorax was subjected to a chest drain resulting in liver penetration. Because of stable hemodynamics, the patient was treated in a nonoperative manner with embolization of the transhepatic track [6]. Unlike this reported patient, removal of the malpositioned chest tube in our patient was delayed to allow granulation tissue to develop in the clinical setting of stable hemodynamics. During the period of slow outward removal of the malpositioned chest tube, the intensivists should closely monitor the homodynamic status of the patient and any signs suggestive of bile leakage, and maintain close contact with general and thoracic surgeons. The malpositioned chest tube in our patient was finally successfully removed without any complications and surgery was avoided in this critically ill patient.

In summary, the use of a trocar technique in

chest tube insertion may increase the likelihood of penetration and laceration of internal organs. In contrast, complications may be relatively rare with open dissection using the finger technique. This case report highlights the potential promise of medical treatment in patients with pneumothorax complicated with penetration of the liver, diaphragm and lung caused by a malpositioned chest tube, in particular in patients who are critically ill and unsuitable for surgical intervention. Further studies with larger populations are needed to substantiate this finding.

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胸管置入造成肺及肝臟穿透：罕見的胸管併發症

江起陸 * 趙恆勝 * 黃建勝 ** 張西川 *,***

胸管置入術是肋膜疾患的標準治療之一，但有一定的比例產生併發症。我們報告一位 55 歲本身有糖尿病及呼吸器依賴的女性患者，伴隨發生氣胸而接受胸管置入術。但胸管置入後病患的氧合情況並未改善。胸部電腦斷層發現胸管穿越肝臟、橫膈膜、右下肺後進入肋膜腔，同時發現肺部的瀰漫性間質性病變。在置入新的胸管後，我們以每天往外拔除一些的方式成功移除原來誤置的胸管。臨床上執行胸管置入術時應小心謹慎，尤其是限制性肺疾及呼吸器使用的患者。*(胸腔醫學 **2013; 28: 370-374**)*

關鍵詞：氣胸，機械通氣，胸管，胸腔造口術

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Ewing's Sarcoma of the Left First Rib: A Case Report

Chi-Wei Duann*, Wen-Hu Hsu*, Yu-Chung Wu*, Wei-Ming Chen**

Ewing's sarcoma is part of a rare group of malignant neoplasms that are localized frequently in the long bone of the lower extremities, the humerus, and the pelvis. However, Ewing's sarcoma can also arise from the rib. We described a 45-year-old male with Ewing's sarcoma of the left first rib, who presented with tenderness and numbness in the upper back and left upper limb for 2 months. CT, MRI and PET were performed and a tumor mass about 2.8 cm at the left first rib was found. Ewing's sarcoma was confirmed by biopsy. He received neoadjuvant chemotherapy, and then tumor-wide excision was performed via the anterior approach. We present this case and discuss its rare presentation, and also provide a literature review. ***(Thorac Med 2013; 28: 375-381)***

Key words: Ewing's sarcoma, rib, wide excision, rare neoplasm

Introduction

Ewing's sarcoma is a rare malignant bone tumor that mainly affects the long bone of the lower extremities, the pelvis and the humerus. It is an extremely aggressive neoplasm and is the 2nd most common primary bone malignancy of childhood and adolescence. With much progress in the treatment of Ewing's sarcoma since the disease was first described in the 1920s, the long-term survival rate for patients with localized disease has reached approximately 70% using multimodal treatment approaches including radiotherapy, surgery and aggressive multiagent chemotherapy. However, relapse is not uncommon and often leads to mortality.

Case Report

A 45-year-old male, an HBV carrier with a past history of chronic hepatitis related to alcohol drinking, presented with tenderness and numbness in the upper back and left upper limb for 2 months. The sensation of numbness started from his back and gradually involved his arm. He went to a hospital for evaluation, where a series of imaging studies including CT, MRI and PET were performed. A tumor mass about 2.8 cm at the left 1st rib was revealed. He was referred to a different institution 2 months later, and to an orthopedics outpatient clinic, where physical examination revealed upper back pain with left arm C7/8 dermatone numb-

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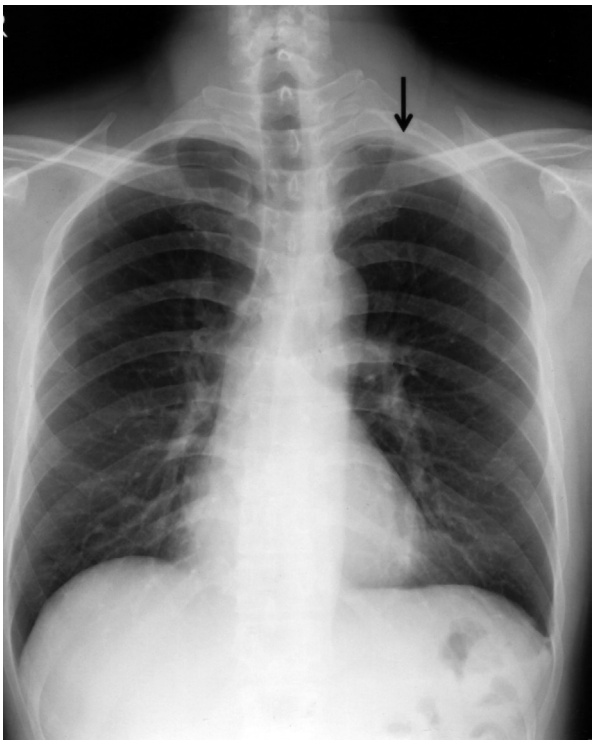

Fig. 1. Initial chest radiograph showed increased soft tissue density at the left apical region (arrow).

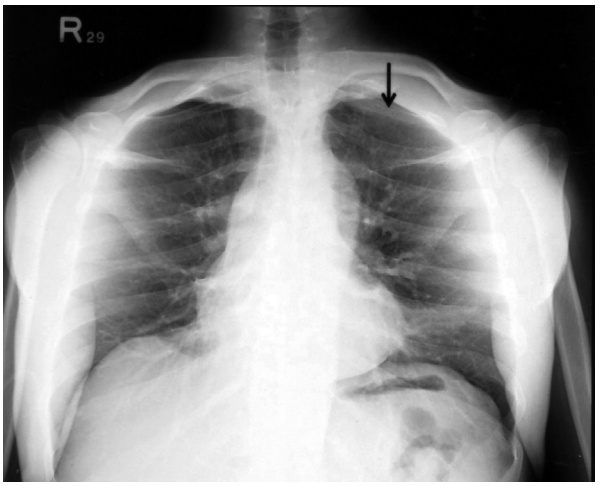

Fig. 2. Lordotic view of the chest radiograph showed increased soft tissue density at the left apical lung region with bony destruction of the left 1st rib (arrow).

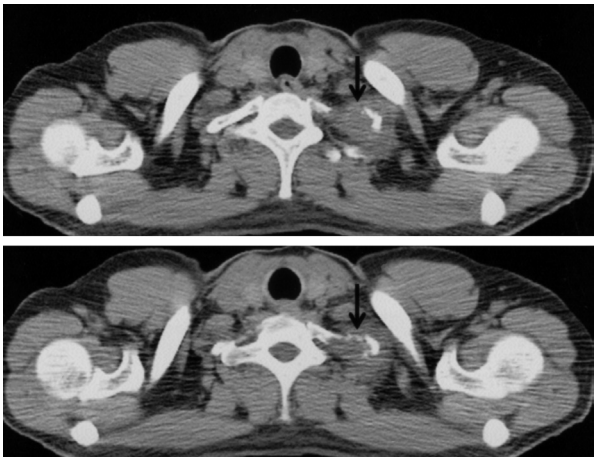

Fig. 3. Chest CT revealed a bony destructive lesion at the left 1st rib. (arrow).

ness. Chest radiographs were taken (Figures 1, 2), and then a PET-CT (Figure 3) was ordered and showed a soft tissue mass located at the left 1st rib with bone destruction and possible T1 nerve root encasement. MRI also revealed a rather well-defined bone mass at the left 1st rib, 4.4 × 6.0 cm in size (Figure 4); it showed cortical destruction, a soft tissue mass, and extension to the left costovertebral junction, with compression to surrounding neurovascular bundles, muscles and the left apex of the lung. The impression was osteosarcoma or malignant bone tumor, and biopsy was suggested. CT-guided biopsy was performed and the pathology report turned out to be round-cell sarcoma. The tumor cells were immunoreactive for FLi-1 and focally for CD99, and a fluorescence in situ hybridization (FISH) analysis using a Vysis LSI EWSR1 Dual Color Break-Apart Rearrangement Probe (30-190059) revealed the cells to be positive for EWS gene translocation, which is consistent with Ewing's sarcoma. The clinical stage was cT2N1M0G4 (High).

The patient was then transferred to the oncology department for neoadjuvant chemotherapy. Whole body bone scan revealed no definite evidence of distant bone metastasis.

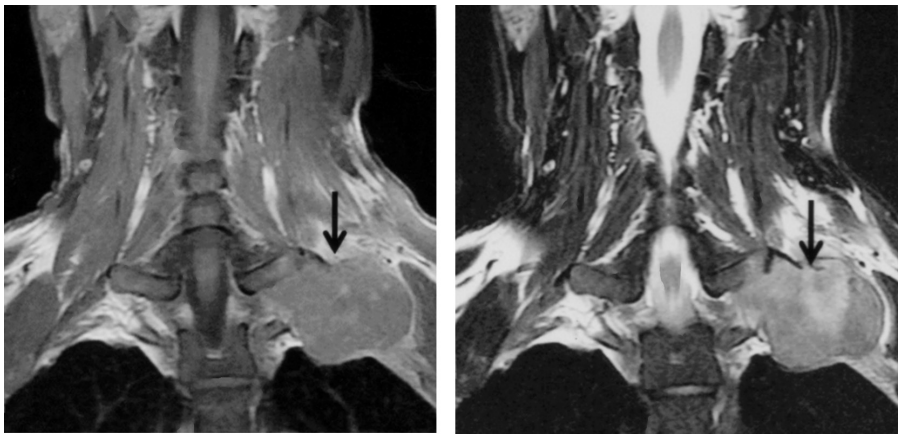

Fig. 4. A rather well-defined bone mass at the left 1st rib, with a low signal on T1WI (left), a relatively high signal on T2WI (right), 4.4 × 6.0 cm in size; cortical destruction, a soft tissue mass, extension to the left costovertebral junction, and compression to surrounding neurovascular bundles, muscles, and the left apex of the lung can be seen.

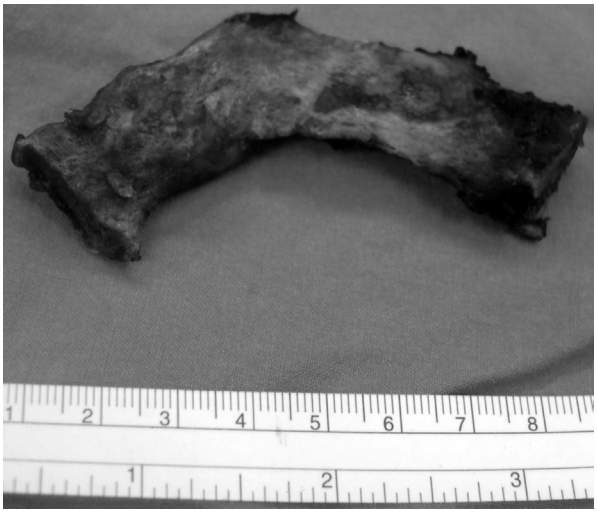

Fig. 5. Osteotomy was performed on the left clavicle for 1st rib dissection, and the left 1st rib was resected as a whole by careful dissection.

After 1 course of combined vincristine, dactinomycin and cyclophosphamide and 1 course of ifosfamide and etoposide some time later, the patient presented with improved muscle power in both hands. The follow-up MRI and CT of the chest revealed the tumor to be decreased in size, measuring 4.1 × 3.0 cm. There was no evidence of distant metastasis. After another course of combined vincristine, dactinomycin and cyclophosphamide, tumor-wide excision was arranged for the patient. At the time of the operation, MRI showed an excellent response with a small residual soft tissue component around the 1st rib.

The operation took place 4 months after the patient first came to the outpatient department. The left clavicle was exposed via the anterior approach. Osteotomy was performed on the left clavicle for 1st rib dissection. Careful dissection of the exposed left 1st rib was done, and then the rib was resected as a whole (Figure 5). The clavicle osteotomy was put back in place and fixed with 2 dynamic compression plates and screws. Five days after the operation, the patient was discharged in a stable condition (Figure 6). Pathological complete response (pCR) was reported with sequestrum and fibrosis in the removed left 1st rib. The proximal cut end was free of tumor cells. (ypT0R0)

After the operation, adjuvant chemotherapy with 2 courses of combined vincristine, dacti-

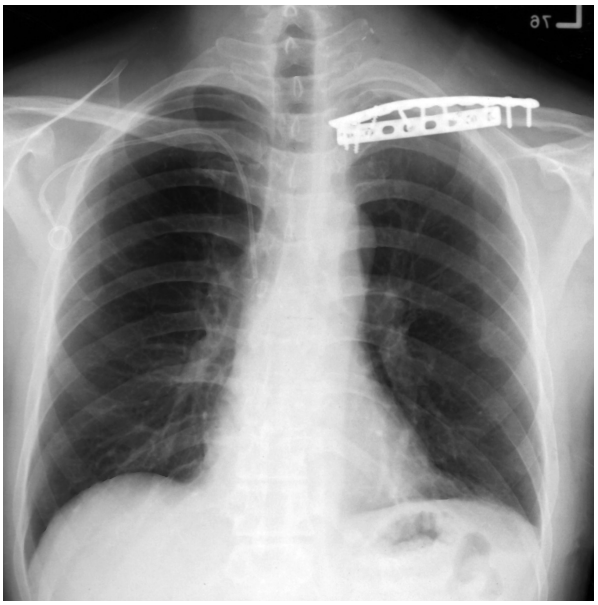

Fig. 6. The chest radiograph showed the status post-osteotomy. The clavicle was placed back in position and fixed with 2 dynamic compression plates and screws.

nomycin and cyclophosphamide and 2 courses of ifosfamide and etoposide was given. There was no specific discomfort except 1 episode of elevated liver function without jaundice or coagulopathy. Six months after the operation, there appeared to be no signs of recurrence.

Discussion

The term Ewing's sarcoma was first used in 1921 by Dr. Ewing [1], and it was originally thought to be a biologically distinct entity. However, over time a spectrum of malignant tumors that shared the histological component of small round blue cells was found. These included primitive neuroectodermal tumor (PNET) of the soft tissue and bone, extraosseous Ewing's sarcoma (EES), and Askin tumor, which were all later classified as the Ewing's sarcoma family of tumors (ESFT). They share a uniformity of immunohistochemical, cytogenic and molecular characteristics, and also have identical responses to Ewing-based chemotherapy regimens [2-3]. Although there is a wide spectrum of neural differentiation in ESFT, with Ewing's sarcoma being least differentiated, the tumors share a common translocation between the EWS gene on chromosome 22 and 1 of 3 ETS-like genes, especially the FLi-1 gene on chromosome 11 [4]. RT-PCR and FISH are 2 of the molecular diagnostic tests that can aid in the detection of the presence of ESFT-specific translocations [5].

Ewing's sarcoma appears grossly to be a gray-white tumor with necrosis, hemorrhage, or cyst formation. It is composed of monotonous sheets of small round cells with medium-size, round or oval nuclei, a high nucleus-to-cytoplasmic ratio, and inconspicuous nucleoli [3,6]. Another common trait of these tumors is an over-expression of CD99, which is a transmembrane protein encoded by the MIC-2 gene, and can be a useful positive marker when ruling out other differential diagnostic considerations [7-8].

Ewing's sarcoma is the 2nd most common primary bone malignancy of childhood and adolescence [9-10]. However, our patient was a 45-year-old male not previously diagnosed with Ewing's sarcoma. Data on adult patients are relatively scarce in the current literature. Some reports suggested that the behavior of Ewing's sarcoma in adults is no different from its behavior in children [11], and in other reports, adults were found to have a worse outcome [12-14]. In a study of 44 adult patients evaluated for Ewing's sarcoma, it was concluded that people over the age of 26 had survival rates inferior to those of younger adults [15].

The long bone of the lower extremities, the pelvis and the humerus are some of the mainly affected sites. In the first Intergroup Ewing's

Sarcoma Study (IESS), comprising 303 patients, the most common distribution of primary sites, in order, was the lower extremities, pelvis, upper extremities, axial skeletal or ribs, and face. The ribs accounted for about 12.9% of all cases [16-17]. Other studies reported that the incidence rate in the ribs was around 10% [18-21]. Patients with tumor localized to the ribs did not seem to present with a poorer prognosis [22]. In a study of 34 patients with Ewing's sarcoma of the ribs, the affected rib was found radiographically to be predominantly lytic in 82% of cases [23], which was in accordance with the finding in our presented case. The initial symptoms included intermittent localized thoracic pain, pleuritic pain, intermittent fever, and dyspnea. The most important clinical finding was pleural effusion and a palpable mass [24].

Treatment options for Ewing's sarcoma include induction chemotherapy, local control with either surgery or radiation or the combination of both, and adjuvant chemotherapy [25]. This is because most patients with localized disease at diagnosis have subclinical micrometastases; therefore, multidrug chemotherapy as well as local control of disease is indicated for all patients. Included among the current standard chemotherapeutic agents are vincristine, doxorubicin, and cyclophosphamide, alternating with ifosfamide and etoposide [3,26]. The disease had an extremely high fatality rate before the use of systemic therapy, which was introduced in the early 1970s: the 5-year survival rate was less than 20% [27]. However, since the use of adjuvant chemotherapy, there has been a marked improvement in the outcome -- localized disease now has a 70% 5-year survival rate [28]. However, there is still an unacceptably high relapse rate of 30%, and the prognosis after relapse is fatal [29].

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發生在左側第一肋骨的 Ewing 氏骨肉瘤之個案報告－病例報告

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Ewing 氏骨肉瘤是罕見的惡性腫瘤之一，它通常位於長骨或是骨盆腔處，不過它也能夠發生在肋骨。本文將簡述一名四十五歲的男性 Ewing 氏骨肉瘤的病人，其病灶正位於左邊的第一肋骨。他一開始表現的症狀是上背及左上肢的壓痛和麻木感長達兩個月的時間，電腦斷層，磁振造影及正子攝影檢查皆發現一個約 2.8 公分的腫瘤，並且經由切片證實為 Ewing 氏骨肉瘤。他接受了手術前的化學治療之後，接受了經前側探查的廣泛性腫瘤切除手術。我們將陳述這個病例並且討論其罕見的表現方式並且進行文獻回顧。*(胸腔醫學 **2013; 28: 375-381**)*

關鍵詞：Ewing 氏骨肉瘤，肋骨

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