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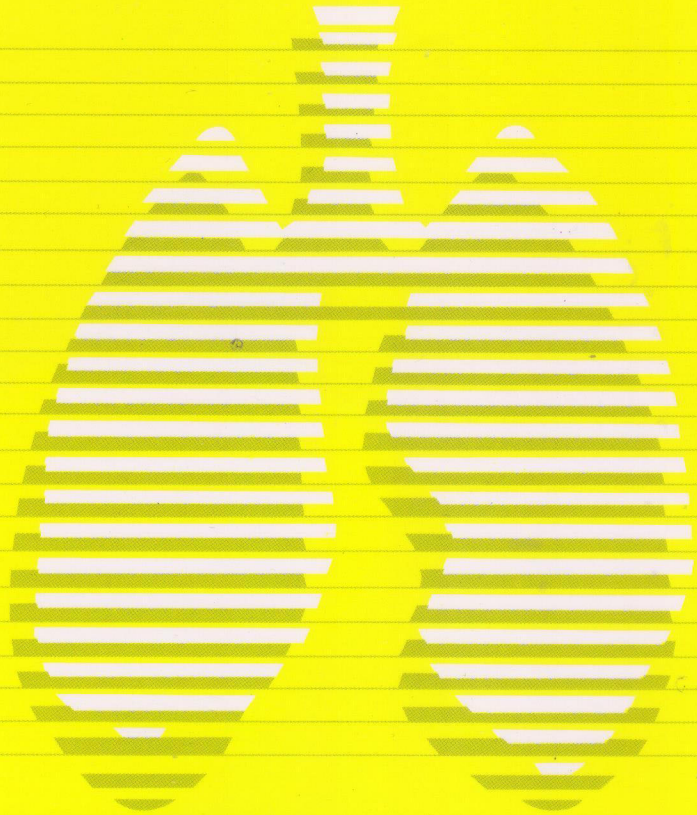

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Orginial Articles

Case Reports

Factors Associated with Compliance with Sepsis Bundle Care in the Intensive Care Unit

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Background: The aim of this study was to determine which factors are associated with compliance with sepsis bundle care in the intensive care unit.

Patients and Methods: Forty-five patients with severe sepsis admitted to the medical intensive care units of Kaohsiung Chang Gung Memorial Hospital from December 2009 through December 2010 were enrolled. We analyzed the factors, including patient, organizational, and process factors, that were most likely associated with compliance with the sepsis bundle.

Results: The total compliance rate with the 6-hour resuscitation bundle was 17.8%, and that with the 24-hour management bundle was 11.1%. When comparing patient groups with compliance or non-compliance with the sepsis bundle (either 6-hour or 24-hour), there was no statistically significant difference among factors, such as using the sepsis code and intubation-to-ICU time. However, admission source, admission time, resident at admission, nurse-to-bed ratio, and number of dysfunctional organs were associated with compliance with detailed bundle elements.

Conclusions: The factors that are associated with compliance with sepsis bundle elements in the intensive care unit include admission source, admission time, resident at admission, nurse-to-bed ratio, and number of dysfunctional organs. We should be aware of these factors, to improve compliance with sepsis bundle elements. ***(Thorac Med 2012; 27: 260-269)***

Key words: surviving sepsis campaign guideline, sepsis bundle, 6-hr resuscitation bundle, 24-hr management bundle

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Introduction

Sepsis is 1 of the most prevalent diseases and 1 of the main causes of death among hospitalized patients [1]. Severe sepsis accounts for 1 in 5 admissions to intensive care units (ICUs) and is a leading cause of death in non-cardiac ICUs [2-3]. The incidence of severe sepsis is high (300 cases per 100,000 population), as is the mortality rate (28.6%), which represents 215,000 deaths annually in the United States alone [2]. Early appropriate antibiotic therapy [4-6], early goal-directed therapy (EGDT) [7], corticosteroids [8], recombinant human activated protein C or drotrecogin alfa (activated) [9], and lung protective strategies [10] have all been associated with survival benefits. These and other therapeutic advances have led to the development of the Surviving Sepsis Campaign (SSC) guidelines [11], as part of a plan to reduce severe sepsis mortality by 25% by the year 2009.

However, the mortality rate from severe sepsis is still high in much of Asia, and compliance with resuscitation and management bundles is generally poor throughout Asia. The hospital mortality rate of severe sepsis patients in Asia was approximately 44.5%, and the compliance rate with resuscitation and management bundles was 7.6% and 3.5%, respectively [12]. Some experts have studied factors that were associated with mortality, such as admission time [13], age, APACHE II score and location at diagnosis of severe sepsis [12]. However, these factors were not included in the evaluation of compliance with the sepsis bundle element. Therefore, we wanted to determine which factors were associated with compliance with the sepsis bundle.

Patients and Methods

Patients

In this retrospective cohort study, we analyzed data from patients with severe sepsis admitted to the medical ICUs of Kaohsiung Chang Gung Memorial Hospital from December 2009 through December 2010.

We enrolled adult patients with severe sepsis, defined as previously reported [14]. Patients who refused resuscitation (including central venous catheter (CVC) placement) for sepsis and those that had active bleeding or cardiogenic pulmonary edema were excluded. Patients with severe decompensated chronic liver disease included on a waiting list for liver transplantation were also excluded from the study.

Study design

When we recognized that the patient had severe sepsis or septic shock at ICU admission, we would start the severe sepsis bundle quality checklist. We defined ICU admission time as 0 hour (hr), and then started the severe sepsis bundle. At 0 hr, 2 hours (hrs), 4 hrs and 6 hrs, we applied the 6-hr resuscitation bundle, including lactate determination, early cultures and antibiotics, and early-goal direct therapy (EGDT). The 24-hr management bundle, including optimization of glycemic control, respiratory-inspiratory plateau pressure, and determination of the need for corticosteroids or drotrecogin alfa (activated) [12] would be evaluated during the following hours. If the patient had severe sepsis or septic shock recognized at the emergency room (ER) or ward, we used a sepsis code to remind the clinical physician to use the SSC guidelines. If the sepsis bundle was started at the ER or ward, we would complete the bundle after ICU admission. However, if the

sepsis bundle was not started at the ER or ward, we would remind the resident at admission to start this bundle at the ICU immediately.

Data collection

We collected the following data from all study patients: demographics (age, gender), Acute Physiology and Chronic Health Evaluation II (APACHE II), source of infection, comorbidities, organ dysfunction on arrival at the ICU, number of organ failures, admission source, resident at admission, nurse-to-bed ratio, sepsis code, intubation-to-ICU time, admission time, patient location at the time severe sepsis was diagnosed (emergency department, ward, ICU), and whether there was time for CVC insertion. Having time for CVC insertion was defined as having no other emergency condition that needed managing when the new patient was admitted. We used patient factors, organizational factors, and process factors to analyze the bundle compliance rate.

Lactate clearance was also used to evaluate the clinical outcome. Lactate clearance (percent) was defined using the following formula: lactate at initial presentation (0 hr) minus lactate at 6 hrs, divided by lactate at initial presentation, and then multiplied by 100. A positive value denoted a decrease or clearance of lactate, whereas a negative value denoted an increase in lactate after 6 hrs of initial intervention [15].

$$\text{Lactate clearance} = (\text{Lactate}^{\text{Initial Presentation}} - \text{Lactate}^{\text{Hour 6}}) \times 100/\text{Lactate}^{\text{Initial Presentation}}$$

To evaluate the initial empirical antibiotic response in treating the underlying sepsis, we defined an antibiotic as adequate if it was able to cover pathogens isolated from culture, clinically improving the condition of the patient assessed at 48 hrs after the start of treatment. Inadequate initial antibiotic treatment was defined as the inability to cover any bacterium and lack of improvement with regards to the patient's clinical condition within 48 hrs after the start of antibiotic treatment. If the initial antibiotic treatment could not be identified as adequate or inadequate, based on the clinical status, it was designated as indeterminate [16].

This study was approved by the Institutional Review Board of Chang Gung Memorial Hospital, and the requirement for patient consent was waived.

Outcome measures

All patients were followed until discharge from or mortality in the hospital. The primary outcome measure was compliance with the 6-hr resuscitation and 24-hr management bundles. The secondary outcome measures were 28 days mortality, ICU mortality and in-hospital mortality. Patients who had complete compliance with all bundle elements were deemed compliance cases, and those otherwise were deemed noncompliance cases.

Statistical analysis

The Statistical Analysis System software (SAS Institute, Cary, NC) was used to perform data analysis. Categorical variables were analyzed using the chi-square test or Fisher's exact test where appropriate, and continuous variables were compared using Student's t-test.

Results

From December 2009 through December 2010, a total of 45 patients were enrolled in the analysis. Baseline characteristics of these patients are shown in Table 1. The average age of

the patients was 69.1 ± 13.4 years, the average APACHE II score was 27.4 ± 5.9, mean ICU length of stay was 17.1 ± 14.6 days, and hospital length of stay was 30.6 ± 40.4 days.

The total compliance rate with the 6-hr resuscitation bundle was 17.8%, and for the 24-hr management bundle, 11.1%. Adherence to less than 3 items of the 6-hr resuscitation bundle revealed no survival benefit, and adherence to 4 items of the 6-hr resuscitation bundle seemed to decrease 28-day mortality (p=0.081). In addition, lactate compliance decreased 28-day mortality (p<0.05), and patients with early lactate clearance had decreased ICU and in-hospital

Table 1. Patient characteristics (n=45)

Parameters	Numbers (%)	6-hr resuscitation bundle	
	All (n=45)	Complete compliance (n=8)	Not complete compliance (n=37)
Age (years; mean ± SD)	69.1 ± 13.4	66.0 ± 16.4	69.8 ± 12.9
Female (n, %)	14 (31.1)	3 (37.5)	11 (29.7)
Apache II score (mean ± SD)	27.4 ± 5.9	28.9 ± 4.5	27.1 ± 6.2
Source of infection			
Pneumonia/lung	32	5	27
Abdomen other than urinary tract	6	1	5
Urinary tract	9	1	8
Multiple sources (≥3)	3	1	2
Co-morbidities			
CNS disorders	12	3	9
Heart disorders	8	3	5
Chronic obstructive pulmonary disease	10	2	8
Liver cirrhosis	8	0	8
Chronic kidney disease	8	1	7
Solid tumors	10	2	8
Organ dysfunction on arrival at ICU:			
Hypotension or on vasopressors	20 (44.4)	5 (62.5)	15 (40.5)
Hyperlactatemia	12 (26.7)	2 (25.0)	10 (27.0)
Acute kidney injury	19 (42.2)	2 (25.0)	17 (45.9)
Acute lung injury	29 (64.4)	6 (75.0)	23 (62.1)
Hyperbilirubinemia	11 (24.4)	2 (25.0)	9 (24.3)
Thrombocytopenia	15 (22.2)	1 (12.5)	14 (37.8)
Coagulopathy	14 (31.1)	1 (12.5)	13 (35.1)
ICU LOS (days; mean ± SD)	17.12 ± 14.6	18.1 ± 16.87	16.9 ± 14.4
Hospital LOS (days; mean ± SD)	30.6 ± 40.4	36.39 ± 32.8	29.4 ± 42.1
ICU mortality (n, %)	30 (66.7)	3 (37.5)	27 (73.0)
In-hospital mortality (n, %)	31 (68.9)	3 (37.5)	28 (75.7)

Definition of abbreviations: SD=standard deviation; ICU=intensive care unit; LOS=length of stay.

mortality (p=0.023 and 0.011, respectively). (Table 2)

Analyzing factors possibly associated with compliance with the sepsis bundle, such as admission source, use of the sepsis code, and intubation-to-ICU time, we found no significant relationship between these factors and total bundle compliance (6-hr resuscitation bundle or 24-hr management bundle compliance) (Table 3). However, when looking into the detailed elements of the sepsis bundle, we found that blood culture compliance was better at the ER than in the ward (p<0.05), better in cases involving senior residents than junior residents (p<0.05), and seemingly better in cases involving 1 nurse: 2 beds than in cases with 1 nurse: ≥3 beds (p=0.059). In addition, central venous pressure (CVP) compliance tended to be better during the week than on weekends (p=0.062). The vasopressor was used less on weekdays than weekends (p<0.05), and more during off-times than office hours (p<0.05). Furthermore, the vasopressor was used less for patients with ≤2 dysfunctional organs than >3 dysfunctional organs (p<0.05) (Table 4).

Discussion

According to our study results, adherence to less than 3 items in the 6-hr resuscitation bundle had no survival benefit, and adherence to 4 items in the 6-hr resuscitation bundle seemed to decrease 28-day mortality. These results confirmed the importance of adherence to

Table 2. Relationship of sepsis bundle compliance with 28-day mortality, ICU mortality and in-hospital mortality (n=45)

		28 days mortality	ICU mortality	In-hospital mortality
Parameters	Compliance (%)	*p* value	*p* value	*p* value
Lac-compliance	26/45 (57.8)	0.036*	0.054	0.102
Lac-clearance >10%	14/45 (31.1)	0.072	0.023*	0.011*
B/C-compliance	37/45 (82.2)	0.059	0.236	0.402
Anti-compliance	44/45 (97.8)	1.000	1.000	1.000
Anti-adequate	31/45 (68.9)	0.722	0.496	0.158
CVP-compliance	15/45 (33.3)	0.565	0.405	0.659
Fluid-compliance	39/45 (86.7)	0.678	1.000	1.000
Vasopressor	20/45 (44.4)	0.592	0.832	0.885
$ScvO_2$-compliance	14/45 (31.1)	0.269	0.204	0.143
6-hr resuscitation bundle	8/45 (17.8)	0.113	0.095	0.085
Steroid-compliance	29/45 (64.4)	0.577	0.660	0.988
APC-compliance	25/45 (55.6)	0.502	0.396	0.614
Sugar-compliance	21/45 (46.7)	0.045*	0.205	0.322
IPP<30 cmH_2O compliance	43/45 (95.6)	0.196	0.545	1.000
24-hr management bundle	5/45 (11.1)	0.362	0.651	1.000

Definition of abbreviations: Lac=lactate; B/C=blood culture; Anti=antibiotics; CVP=central venous pressure; $ScvO_2$=central venous oxygen saturation; APC=activated protein C; IPP=inspiratory plateau pressure.

*Statistical significance based on Chi-square test or Fisher's exact test. *p* value less than 0.05 was considered statistically significant.

Table 3. Univariate analysis of factors influencing compliance with the sepsis bundle (n=45)

		6-hr resuscitation bundle	24-hr management bundle
Parameters	Numbers (%)	*p* value	*p* value
Patient factors			
Age (years)	≤75 (27/45, 60%) >75 (18/45, 40%)	0.694	0.375
APACHE II score≥25	<25 (14/45, 31.1%) ≥25 (31/45, 68.9%)	0.402	0.639
Number of organ failures	≤2 (34/45, 75.6%) >3 (11/45, 24.4%)	1.000	0.582
Organizational factors			
Admission source	ER (21/45, 46.7%) Ward (24/45, 53.3%)	1.000	1.000
Resident at admission	R2 (10, 22.2%) R3 (11, 24.4%) R4 (24, 53.3%)	0.973	0.075
Nurse-to-bed ratio	1 nurse : ≥3 beds (25, 55.6%) 1 nurse : 2 beds (20, 44.4%)	0.269	1.000
Process factors			
Sepsis code	Yes (21/45, 46.7%) No (24/45, 53.3%)	0.121	1.000
Intubation-to-ICU time	<6 hrs (18/45, 40%) >6 hrs (27/45, 60%)	0.699	0.346
	<12 hrs (23/45, 51.1%) >12 hrs (22/45, 48.9%)	0.699	0.346
Admission time	Office time (15/45, 33.3%) Off time (30/45, 66.7%)	0.699	0.315
	Week (38, 84.4%) Weekend (7, 15.6%)	0.590	0.577
Patient location at diagnosis of severe sepsis	ER (18, 40%) Ward (7, 15.6%) ICU (20, 44.4%)	0.443	0.953
Having time for CVC insertion	Yes (17, 37.8%) No (28, 62.2%)	1.000	1.000

Office time defined as 07:30 am to 17:30 pm from Monday to Friday; Off-time defined as 17:30 pm to 07:30 am the next morning. Weekend defined as Saturday and Sunday.

Definition of abbreviations: CVC=central venous catheter.

the sepsis bundle. Nonetheless, implementation of the entire bundle might be no more effective than implementation of selected components [12]. Although we found no significant relationship between the investigated factors and total bundle compliance, when looking into detailed

Table 4. Relationship of factors influencing compliance with the sepsis bundle in detail

		B/C-Compliance	CVP-Compliance	Vasopressor
Parameters		*p* value	*p* value	*p* value
Patient factors				
Number of organ dysfunction	≤2 >3	1.000	0.210	0.041*
Organizational factors				
Admission source	ER Ward	0.004*	0.818	0.841
Resident at admission	R2 R3 R4	0.014*	0.515	0.335
Nurse-to-bed ratio	1 nurse : ≥3 beds 1 nurse : 2 bed	0.059	0.904	0.947
Process factors				
Admission time	Office time Off-time	0.581	0.198	0.027*
	Week Weekend	0.181	0.062	0.034*

*p value less than 0.05 was considered statistically significant

elements of the sepsis bundle, we found some interesting data that could help us to improve compliance with the sepsis bundle.

Early lactate clearance

Researchers found that early lactate clearance is associated with improved outcome in severe sepsis and septic shock. They analyzed 107 patients with a mean age of 64.9 ± 16.7 years, and with an overall in-hospital mortality rate of 42.3%. The baseline APACHE II score was 20.2 ± 6.8 and lactate was 6.9 ± 4.6 mmol/L. Lactate clearance was found to have a significant inverse relationship with mortality (p=0.04) [15]. This finding was compatible with that in our study group. According to our results, increased lactate compliance would decrease 28-day mortality (p<0.05) and early lactate clearance would decrease ICU and in-hospital mortality (p=0.023 and 0.011, respectively). The reason for decreased mortality may be that early lactate clearance indicates a resolution of global tissue hypoxia. Patients with higher lactate clearance after 6 hrs of intensive intervention have improved outcome [15]. Therefore, the earlier the implementation of the sepsis bundle, the better the outcome.

Sepsis code

Implementation of a comprehensive sepsis protocol, facilitated by the activation of the "sepsis code", was associated with better compliance with resuscitation bundle elements [17]. Activation of the sepsis response team in combination with weekly feedback was found to increase compliance with the process of care and reduce the hospital mortality rate [18]. Therefore, we also analyzed this in our study

group, to determine whether using the sepsis code would be associated with better compliance with resuscitation and management bundle elements. Statistical analysis revealed no significant change. We believe this result was due to our not having a sepsis response team in our hospital. If we have a sepsis response team when the sepsis code is used, compliance with the resuscitation and management bundles might also improve. In addition, a national educational effort to promote care bundles for severe sepsis and septic shock patients was associated with improved guideline compliance and lower hospital mortality [13]. Therefore, we also need to seek national education resources.

Intubation-to-ICU time

Many patients who were admitted to the ICU had severe sepsis for more than 6 hrs or even more than 12 hrs (60% and 48.9%, respectively). We analyzed intubation to ICU admission time (intubation-to-ICU time) and compliance with the sepsis bundle (6-hr resuscitation bundle and 24-hr resuscitation bundle). The statistical analysis revealed no significant difference (p=0.699 and 0.346, respectively). However, an important reason why compliance with sepsis bundling was so low was that health care professionals may have thought that starting the severe sepsis bundle in patients in which the discovery of severe sepsis was delayed would have no effect.

Other factors influencing compliance

Patient factors, such as age, APACHE II score, and number of organ failures; organizational factors such as admission source, resident at admission, and nurse-to-bed ratio; and other process factors, such as admission time, patient location at the time severe sepsis was diagnosed, and having time for CVC insertion, were all analyzed to evaluate their respective association with compliance with the sepsis bundle. However, the relationship between the above factors and compliance with the 6-hr resuscitation or 24-hr management bundle showed no significant change. Admission source, admission time, number of dysfunctional organs, resident at admission, and nurse-to-bed ratio were associated with detailed sepsis bundle elements, such as blood culture compliance, and CVP compliance.

Limitations

There are a number of limitations to this study that are worth mentioning. This retrospective study was conducted in medical ICUs with different staffing in a single medical center, with a study sample size that was relatively small. Its weaknesses were the retrospective nature of the study and the heterogenic variety of sepsis sources. On the other hand, this situation reflects the reality of sepsis and sepsis treatment. The strength of the manuscript is the evaluation of a variety of clinical factors and patient characteristics to determine which factors are associated with compliance.

Conclusion

When comparing patient groups with compliance or non-compliance to the sepsis bundle (either 6-hr or 24-hr), there was no statistically significant difference among factors, such as using a sepsis code and intubation-to-ICU time. However, admission source, admission time, and number of dysfunctional organs were associated with compliance with detailed bundle elements. We should be aware of these factors, in order to improve compliance with sepsis bundle

elements.

References

1. Angus DC, Linde-Zwirble WT, Lidicker J, *et al*. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. Crit Care Med 2001; 29(7): 1303-10.
2. Brun-Buisson C, Doyon F, Carlet J, *et al*. French ICU Group for Severe Sepsis. Incidence, risk factors, and outcome of severe sepsis and septic shock in adults: a multicenter prospective study in intensive care units. JAMA 1995; 274(12): 968-74.
3. Guidet B, Aegerter P, Gauzit R, *et al*. Incidence and impact of organ dysfunctions associated with sepsis. Chest 2005; 127(3): 942-51.
4. Garnacho-Montero J, Garcia-Garmendia JL, Barrero-Almodovar A, *et al*. Impact of adequate empirical antibiotic therapy on the outcome of patients admitted to the intensive care unit with sepsis. Crit Care Med 2003; 31(12): 2742-51.
5. Kumar A, Roberts D, Wood KE, *et al*. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. Crit Care Med 2006; 34(6): 1589-96.
6. MacArthur RD, Miller M, Albertson T, *et al*. Adequacy of early empiric antibiotic treatment and survival in severe sepsis: experience from the MONARCS trial. Clin Infect Dis 2004; 38(2): 284-8.
7. Rivers E, Nguyen B, Havstad S, *et al*. Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med 2001; 345(19): 1368-77.
8. Annane D, Sebille V, Charpentier C, *et al*. Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. JAMA 2002; 288(7): 862-71.
9. Bernard GR, Vincent JL, Laterre PF, *et al*. Efficacy and safety of recombinant human activated protein C for severe sepsis. N Engl J Med 2001; 344(10): 699-709.
10. Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med 2000; 342(18): 1301-8.
11. Dellinger RP, Carlet JM, Masur H, *et al*. Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock. Intensive Care Med 2004; 30(4): 536-55.
12. Phua J, Koh Y, Du B, *et al*. Management of severe sepsis in patients admitted to Asian intensive care units: prospective cohort study. BMJ 2011; 342: d3245.
13. Kuijsten HA, Brinkman S, Meynaar IA, *et al*. Hospital mortality is associated with ICU admission time. Intensive Care Med 2010; 36 (10): 1765-71.
14. Ferrer R, Artigas A, Levy MM, *et al*. Improvement in process of care and outcome after a multicenter severe sepsis educational program in Spain. JAMA 2008; 299 (19): 2294-303.
15. Nguyen HB, Rivers EP, Knoblich BP, *et al*. Early lactate clearance is associated with improved outcome in severe sepsis and septic shock. Crit Care Med 2004; 32(8): 1637-42.
16. Tseng CC, Fang WF, Huang KT, *et al*. Risk factors for mortality in patients with nosocomial stenotrophomonas maltophilia pneumonia. Infect Control Hosp Epidemiol 2009; 30(12): 1193-202.
17. Shapiro NI, Howell MD, Talmor D, *et al*. Implementation and outcomes of the Multiple Urgent Sepsis Therapies (MUST) protocol. Cri Care Med 2006; 34(4): 1025-32.
18. Schramm GE, Kashyap R, Mullon JJ, *et al*. Septic shock: A Multidisciplinary response team and weekly feedback to clinicians improve the process of care and mortality. Crit Care Med 2011; 39(2): 252-8.

在加護病房單位有關敗血症準則順從性的因素分析

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林孟志 *,***,**** 方文豐 *,***,****

背景：此研究的目的為找出哪些因素與敗血症準則的順從性相關。

病人及方法：收錄自 2009 年 12 月至 2010 年 12 月，45 個因敗血症重症住進高雄長庚醫院內科加護病房的病人。分析與敗血症準則順從性相關的因素，如病人的來源、是否使用敗血症碼、自插管至加護病房的時間、年齡、APACHE II 分數、器官衰竭的數目、進入加護病房的時間、護理師與照護床數比、病人被診斷出敗血症重症的地點、有無時間置入中央靜脈導管。

結果：6 小時復甦套裝全部完成有 17.8%，而 24 小時處置套裝全部完成有 11.1%。雖然使用敗血症碼，或是自插管至加護病房的時間來比較是否遵循敗血症套裝 (不論 6 小時復甦套裝或是 24 小時處置套裝) 均未達統計學上的意義。但病人的來源，進入加護病房的時間，進入加護病房時的住院醫師，護理師與照護床數比，及器官衰竭的數目與敗血症套裝細項的遵循及完成有關。

結論：有很多的因素與敗血症套裝細項的執行有關，如病人的來源，進入加護病房的時間，進入加護病房時的住院醫師，護理師與照護床數比，及器官衰竭的數目。我們期望透過這個研究能讓我們更注意這些因素，來達到改善敗血症套裝細項的執行。*(胸腔醫學 **2012; 27: 260-269**)*

關鍵詞：戰勝敗血症準則，敗血症套裝，6 小時復甦套裝，24 小時處置套裝

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Unplanned Extubation in Surgical Patients: Clinical Outcomes and Risk Factors for Reintubation

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Objectives: To determine the clinical outcomes of unplanned extubation (UE), and the incidence and risk factors of reintubation in surgical patients.

Design: Retrospective medical chart and electronic database review.

Materials and Methods: All adult patients admitted to the Surgical and Neurosurgical Intensive Care Unit of Chang Gung Memorial Hospital, Chiayi, from January 2007 to December 2009 were included. The medical charts and electronic records, cross-matched with the quality practice database of the Critical Care Audit Committee, were reviewed.

Results: There were 50 episodes of UE involving 42 patients (29 males) from among 2,165 intubated patients during this period. The median age was 61.4 years. UE was categorized as intentional in 42 episodes (84%). The following factors were associated with reintubation in univariate analysis: accidental UE (p=0.03), time on mechanical ventilation (p=0.021), and PaO_2/FIO_2 (p=0.002). In multivariate analysis, accidental UE (p=0.004) and PaO_2/FIO_2 ($p \leq 0.001$) remained as significant risk factors for reintubation. Reintubation was mandatory in 71.4% of patients within 1 hour of UE. Reintubated patients spent an average of 11.7 more days in the intensive care unit (ICU) and had 31.0 more days of hospital stay. Reintubation correlated strongly with ICU stay (p<0.001), hospital stay (p<0.001) and mortality (p<0.001).

Conclusion: The incidence of UE in surgical patients is low. Reintubations occur more frequently within one hour of UE. Accidental extubations are more likely to require reintubation. ***(Thorac Med 2012; 27: 270-275)***

Key words: unplanned extubation, reintubation

Introduction

Weaning from mechanical ventilator support always starts after stabilization of acute respiratory failure due to either surgical or medical causes. Although the average stay in surgical intensive care units (ICUs) tends to be short because acute respiratory failure is not

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the most common reason for admission to these units, the occasional occurrence of unplanned extubation (UE) complicates the clinical course of these patients. Since the effects of UE in surgical patients have not been explored in detail, we wanted to determine which risk factors are associated with reintubation, as well as the outcome of UE in a cohort of surgical patients.

Materials and Methods

The investigation and research board of Chang-Gung Memorial Hospital approved this clinical investigation. Informed consent from individual patients was waived in the absence of any intervention for the purpose of this review.

The clinical record of all patients (>18 years) admitted to the surgical and neurosurgical ICUs at Chang-Gung Memorial Hospital, Chiayi Center, from January 2007 to December 2009, were reviewed retrospectively. The monthly quality practice data submitted by each ICU to the Critical Care Audit Committee were cross-matched for accuracy. Patients ventilated through tracheostomies were excluded.

UE was defined as the premature removal of an artificial airway. UE was considered "intentional" when the endotracheal tube was removed by the patient and "accidental" when it occurred during the routine care process or transportation of the patient. Reintubation was defined as any intubation within 48 hours of UE (≤30 minutes was considered immediate). Restraints were used when deemed necessary by the nursing staff and surgical resident under the strict nursing restraint protocol. The use of intravenous sedation was not mandatory, and was at the discretion of the attending surgeon or critical care specialist. O_2 supplementation by mask with an FIO_2 of 50% was given immediately post-UE, and arterial blood gas analysis was assessed 30 minutes thereafter. The decision to reintubate was at the discretion of the senior duty resident and attending physician. The following clinical and laboratory parameters were collected: age, gender, ICU allocation, admission APACHE II score, admission SAPS II score, time under mechanical ventilation support, Glasgow Coma Scale post-extubation, event nature of UE (intentional or accidental), work shift (morning: 8am-4pm, evening: 4pm-12pm or night: 12pm-8am) and day of the week UE occurred (weekend: Saturday 12pm- Monday 8am vs. weekday), weaning condition, rapid shallow breathing index (RSBI) before UE, partial pressure of arterial oxygen (PaO_2) and carbon dioxide (PCO_2), PaO_2/FIO_2 ratio, fluid balance 48 hours before UE, time to reintubation, ICU and hospital stay, and clinical outcome. Respiratory parameters and ventilator settings were extracted from the respiratory therapist record sheet. The PaO_2, $PaCO_2$, PaO_2/FIO_2 and respiratory rate to tidal volume ratios were calculated based on the last entry by the respiratory therapist. $PaCO_2$ was grouped as normocapnea (35-44.9 mmHg) and hypo/hypercapnea (≤34.9 / ≥44.9 mmHg).

The incidence rate of UE was calculated as follows: [(number of patients with UE) / (number of intubated patients)] × 100.

Statistics

Continuous variables were expressed as mean ± standard deviation, and non-parametric variables as percentages. Student's *t* test was used to compare continuous variables. Differences in proportions were compared using the chi-square or Fisher's exact test, depending on cell size. Multinominal logistic regression

analysis was used for risk factor stratification of significant factors in univariate analysis. Data were analyzed using SPSS software (12.0, SPSS Inc, Chicago, Illinois).

Results

There were 50 episodes of UE involving 42 patients from among 2,165 intubated patients during this period (29 males, 34 episodes). The incidence of UE was 1.9%. The mean age of the cohort was 61.4 years (range 23-95 years). The mean APACHE II score and SAPS II score on admission were 14.5 (range 6-30) and 32.5 (range 13-52), respectively (Table 1). The mean mechanical ventilation time before the UE episode was 76.9 hours. Forty-two episodes (84%) were classified as intentional, and 27 (54%) occurred during the night shift. Forty-three episodes occurred while the patient was being restrained, and 33 episodes during the weaning process (66%).

The incidence of reintubation was 33% (14/42 patients). Reintubation was mandatory in 10 patients within 1 hour, and 3 cases were considered immediate; 85.7% (12/14 patients) were reintubated within 24 hours of UE. The reasons for reintubation were hypoxemia (n=9, 64.2%), tachypnea (n=4, 28.5%) and the general anesthesia effect (n=1). Five of 8 episodes (62.5%) of accidental extubation required reintubation, and only 9 of 42 episodes (21.4%) of intentional self-extubation required reintubation (p=0.03). Reintubated patients had an average ICU stay of 18.7 ± 12.4 days and hospital stay of 55.8 ± 36.4 days, and patients who did not require reintubation had an ICU stay of 6.9 ± 10.1 days and hospital stay of 24.8 ± 19.4 days, respectively. Seven patients died during hospitalization, and 6 of them had been reintubated within 48 hours. Reintubation correlated strongly with ICU stay (p<0.001), hospital stay (p<0.001) and mortality (p<0.001). No death was directly related to UE or reintubation events.

In univariate analysis, the following factors were correlated with the need for reintubation: accidental UE (p=0.03), time on mechanical ventilation (p=0.021), and PaO_2/FIO_2 (p=0.002). Multivariate analysis revealed that accidental UE (p=0.004, OR 18.102, 95% CI 2.165-151.323) and PaO_2/FIO_2 ($p\leq$0.001, OR 20.448, 95% CI 3.284-127.318) were factors that were strongly correlated to reintubation, but time on mechanical ventilation did not reach statistical significance (p=0.338).

Discussion

In this report, the incidence of unplanned extubation was only 1.9%. An appropriate explanation for this is the fast track for extubation adopted for our patients in the surgical ICU. The weaning process in our institution is guided by a supervised non-mandatory respiratory therapist-driven protocol, yet the decision to extubate is at the discretion of the primary care physician. In this study, a weaning trial per se was not a significant risk factor for reintubation, in contrast to a previous study by Betbese *et al*. [1]. A possible reason for this is that there were twice as many cases under a weaning trial as those under controlled ventilation; therefore, more cases were needed to reach a statistically significant level. A higher proportion of UE cases occurred during the night shift and weekdays, but without statistical significance. Published studies have discordant results regarding the effects of work shifts or workdays on UE [2-4]. Other insignificant risk factors in our study included the Glasgow Coma Scale (GCS)

Table 1. Demographic characteristics and statistical analysis

	No Reintubation	Reintubation	Univariate Analysis	Multivariate Analysis	
	mean or (%)	mean or (%)	*p* value	*p* value	Odds Ratio (95% Confidence Interval)
Variable					
Age (years)	58.5	68.9	0.082		
Gender			0.513		
Male (n=34)	70.6%	29.4%			
Female (n=16)	75.0%	25.0%			
ICU Allocation			0.322		
SICU (n=35)	68.6%	31.4%			
NSICU (n=15)	80%	20%			
Type of UE			0.03	0.004	18.102 (2.165-151.323)
Accidental (n=8)	37.5%	62.5%			
Intentional (n=42)	78.6%	21.4%			
Work Shift			0.437		
Morning (n=9)	55.6%	44.4%			
Evening (n=14)	71.4%	28.6%			
Night (n=27)	77.8%	22.2%			
Day of the Week			0.283		
Weekday (n=40)	75.0%	25.0%			
Weekend (n=10)	60.0%	40.0%			
Restraint			0.85		
No (n=7)	42.9%	57.1%			
Yes (n=43)	76.7%	23.3%			
Intravenous Sedation			0.552		
No (n=38)	71.1%	28.9%			
Yes (n=12)	75.0%	25.0%			
On Weaning			0.308		
No (n=17)	64.7%	35.3%			
Yes (n=33)	75.8%	24.2%			
APACHE II score	14.4	15.1	0.7		
SAPS II score	31.4	35.7	0.2		
Glasgow Coma Scale	13.0	12.6	0.699		
Time on MV (hours)	51.8	141.6	0.021	0.338	0.265 (0.017-4.101)
Input/Output	1279.7	2256.3	0.073		
PaO_2/FIO_2	384.3	242.3	0.002	<0.001	20.448 (3.284-127.318)
PaO_2 (mmHg)	153.7	126.6	0.168		
$PaCO_2$ (mmHg)	40.6	36.4	0.084		
RSBI index (f/VT)	29.8	36.7	0.069		

ICU: intensive care unit

SICU: surgical intensive care unit

NSICU: neurosurgical intensive care unit

UE: unplanned extubation

MV: mechanical ventilation

RSBI index: rapid shallow breathing index

APACHE II: acute physiology and chronic health evaluation II score

SAPS II: simplified acute physiology score II

and restraint. The explanation for the lack of association of the GCS is that all our patients had a high GCS, which differs completely from earlier studies [5-6]. The effect of physical restraint on UE remains controversial [5,7].

Three risk factors were associated with reintubation in univariate analysis (Table 1). Only lower PaO_2/FIO_2 ratios and accidental UE were found to be significant in multivariate analysis. The reason for reintubation following lower PaO_2/FIO_2 ratios is self-explanatory, as hypoxemia per se is an indication for reintubation [4,8-9]. Accidental UE as an independent risk factor for reintubation is a finding compatible with published articles [9-11], and is understandable because the underlying causes of acute respiratory failure are usually not under control. Re-intubated cases are associated with increased length of ICU and hospital stay, and hospital mortality.

Conclusion

The incidence of UE in surgical patients is low. Reintubations occur more frequently within 1 hour of UE. Accidental extubations are more likely to require reintubation.

References

1. Betbese AJ, Perez M, Bak E, *et al*. A prospective study of unplanned endotracheal extubation in intensive care unit patients. Crit Care Med 1998; 26: 1180-6.
2. Boulain T. Unplanned extubations in the adult intensive care unit. A prospective multicenter study. Am J Respir Crit Care Med 1998; 157: 1131-7.
3. Chevron V, Menard JF, Richard JC, *et al*. Unplanned extubation: risk factors of development and predictive criteria for reintubation. Crit Care Med 1998; 26: 1049-53.
4. Listello D, Sessler CN. Unplanned extubation clinical predictors for reintubation. Chest 1994; 105: 1496-503.
5. Chang LY, Wang KWK, Chao YF. Influence of physical restrain on unplanned extubation of adult intensive care patients: a case-control study. Am J Crit Care 2008; 17: 408-15.
6. Namen AM, Ely EW, Tatter SB, *et al*. Predictors of successful extubation in neurosurgical patients. Am J Respir Crit Care Med 2001; 163: 658-64.
7. Tanios MA, Epstein SK, Livelo J, *et al*. Can we identify patients at high risk for unplanned extubation? A large-scale multidisciplinary survey. Respiratory Care 2010; 55: 561-8.
8. Bernard GR, Artigas A, Brigham KL, *et al*. The American-European Consensus Conference on ARDS: Definitions, mechanisms, relevant outcomes, and clinical trial coordination. Am J Respir Crit Care Med 1994; 149: 818-24.
9. Razek T, Gracias V, Sullivan D, *et al*. Assessing the need for reintubation: a prospective evaluation of unplanned endotracheal extubation. J Trauma 2000; 48: 466-9.
10. de Groot RI, Dekkers OM, Herold IH, *et al*. Risk factors and outcome after unplanned extubations in the ICU: a case-control study. Crit Care 2011; 15: R19.
11. Curry K, Cobb S, Kutash M, *et al*. Characteristics associated with unplanned extubations in a surgical intensive care unit. Am J Crit Care 2008; 17: 45-51.

外科病患的非預期性拔管：危險因子及預後分析

呂明憲 * 鄭宇凱 ** 王定中 ** 黃文詩 *** 邱麗櫻 **** 黃耀廣 * 蔡熒煌 *****

前言：呼吸器的運用在任何現代重症加護病房是日常活動的一部分。氣管插管，是用於提供安全的呼吸通道及有效的呼吸器的運用的主要途徑。當導致呼吸衰竭的疾病或手術情況穩定後，可考慮脫離呼吸器。外科病患通常在接受重大或高風險的手術後因需要血流動力學監測而轉住加護病房。這些患者通常在加護病房的停留時間較短。不幸的是，非計劃性的拔管，仍然會造成某些病人有較複雜的病程。非計劃性的拔管對外科病患影響尚未有詳細的探討。此論文是探討外科病患在非預期性拔管之後再插管的發生率，危險因子及臨床上之預後。

設計：採回溯性病歷及電子資料檢閱分析。

資料與方法：在此回溯分析研究中之成人病患，皆於 2007 年 1 月至 2009 年 12 月間於長庚紀念醫院嘉義分院，外科及腦神經外科加護病房住院。本研究中分析病患病歷及加護病房委員會交叉比對之電子資料。

結果：從 2007 年 1 月至 2009 年 12 月總共有 2,165 位插管病患。本研究收錄 42 位病患（共 50 次非預期性拔管）。其中有 29 位男性病患，平均年齡為 61.4 歲。這 50 次非預期性拔管中，有 42 次是蓄意的（84%）。單變量的分析顯示：意外性非預期拔管（p=0.03），使用人工呼吸器時間（p=0.021）及 PaO_2/FIO_2 比值（p=0.002）等因子與非預期性拔管後再插管有關。多變量的分析結果顯示：意外性非預期拔管（p=0.004）及 PaO_2/FIO_2 比值（$p \leq 0.001$）仍然是再插管的危險因子。需要再插管的病患中，71.4% 的病患需要在一小時內再插管。再插管使病患的加護病房及總住院平均天數增加 11.7 及 31.0 天。此外，再度插管與加護病房住院天數（p<0.001），總住院天數（p<0.001），及死亡率（p<0.001）有極強烈的相關。

結論：在外科病患中，非預期性拔管是個發生率低的突發事件；而再度插管通常發生在非預期性拔管一小時內。意外性非預期拔管常需要再度插管。*(胸腔醫學 **2012; 27: 270-275**)*

關鍵詞：非預期性拔管，再插管

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A Very Rare Case of Combined Pleomorphic Carcinoma and Small Cell Lung Carcinoma: A Case Report

Jin-Ing Lin*, Kuo-Chin Kao*,**,***, Chih-Wei Wang****, Chien-Ying Liu*, Cheng-Ta Yang*,***, Kuo-Chin Chiu*****

Lung cancer is the most common cause of cancer mortality worldwide. Pleomorphic carcinoma, defined as a poorly differentiated, non-small cell carcinoma, admixed with at least 10% malignant spindle cells and/or giant cells, is a rare tumor with an incidence rate of 0.1-0.3% of all lung tumors. Combined small cell lung carcinoma (SCLC) is also an unusual tumor with a poor prognosis than pure SCLC. A 76-year-old male, a smoker, complained of chest pain and chest X-ray revealed a large lobulated mass in the left lower lung field. Chest computed tomography mainly revealed a 9.7 x 8.7 cm soft tissue mass in the left lower lung. The pathological result of a sample retrieved by thoracotomy revealed combined pleomorphic carcinoma and small cell carcinoma, composed of spindle cell carcinoma (85%), squamous cell carcinoma (10%) and small cell carcinoma (5%). Two months later, the patient died of septic shock with multiple-organ failure without receiving chemotherapy, due to the poor performance status. We reported a relatively rare case of combined pleomorphic carcinoma and SCLC with a poor prognosis. Due to its aggressive behavior and the difficulty of reaching an accurate diagnosis, physicians should be aware of this kind of combined lung cancer, though it is rare. ***(Thorac Med 2012; 27: 276-281)***

Key words: combined pleomorphic carcinoma, lung cancer, spindle cell carcinoma, small cell carcinoma

Introduction

Lung cancer is the most common cause of cancer mortality worldwide. According to the 2004 World Health Organization classification of malignant epithelial lung tumors, sarcomatoid carcinoma encompasses a group of non-small cell carcinomas that are either entirely or partially composed of a component of spindle or/and giant cells. Pleomorphic carcinoma is 1 of 5 subtypes of sarcomatoid carcinoma and is a rare tumor with an incidence rate of 0.1-0.3% of all lung tumors [1-2]. Pleomorphic carcinoma is defined as a poorly differentiated, non-

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small cell carcinoma, specifically adenocarcinoma, squamous cell carcinoma, or large cell carcinoma, closely admixed with at least 10% malignant spindle cells and/or giant cells [3]. Combined small cell lung carcinoma (SCLC) is a rare tumor with an incidence of about 1-3% of SCLC cases [4]. Preoperative diagnosis of mixed tumors is difficult and the prognosis of combined SCLC is worse than that of pure SCLC [5]. Herein, we report a very rare case of combined pleomorphic carcinoma and SCLC presenting with rapid progression.

Case Report

A 76-year-old man presented at the thoracic surgery outpatient department complaining of mild left chest tightness, but chest radiography revealed no significant abnormalities except bilateral upper lung fibrotic change. He was then lost to follow-up. Eight months later, he again suffered from persistent left chest pain and visited the emergency department for help. This time, chest radiography (Figure 1) showed fibrotic cicatrization at the bilateral upper lobes and a large lobulated mass in the left lower lung with left pleural effusion. He had a past medical history of being treated for pulmonary tuberculosis about 30 years before. He had a 50 pack-year smoking history and had quit for 1 year. Physical examination revealed decreased breathing sounds at the left side and no palpable lymph node at both supraclavicular fossae.

After admission, diagnostic thoracocentesis of the left pleural cavity revealed a small amount of exudative pleural effusion with neutrophils predominant, and the pleural effusion cytologic examination result was atypia. Tumor markers showed only mild elevation of the serum carcinoembryonic antigen level to 7 ng/mL (normal, <5 ng/mL). Chest computed tomography (CT) (Figure 2) revealed a 9.7 × 8.7 cm soft tissue mass in the left lower lung, some calcified nodular lesions in both upper lobes, lymphadenopathies in the left hilum and intrapulmonary area, and left pleural effusion. Bone scan revealed no evidence of bony metastasis. Whole body PET/CT ([^{18}F]-2fluoro-deoxy-D-glucose positron emission tomography) (^{18}F-FDG PET) showed a main tumor in the left lower lung with a standardized uptake value of 13.6. Chest CT-guided core needle biopsy of the left lower lung mass was performed, but failed to confirm the diagnosis. In order to halt the progressive decline in pulmonary function due to the rapid enlargement of the tumor and the inconclusive histological result, left lower lobectomy and lymph node sampling were performed, using a left posterolateral thoracotomy

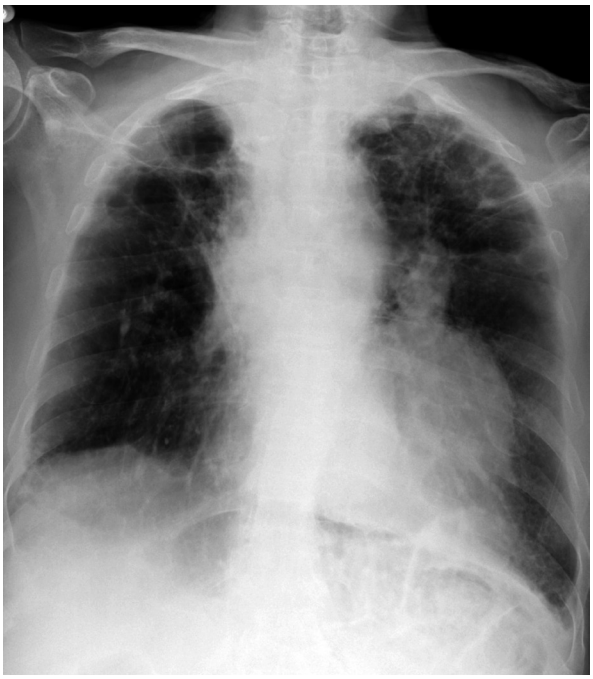

Fig. 1. Chest X-ray showed fibrotic cicatrization at the bilateral upper lobes and a large lobulated mass in the left lower lung with left pleural effusion.

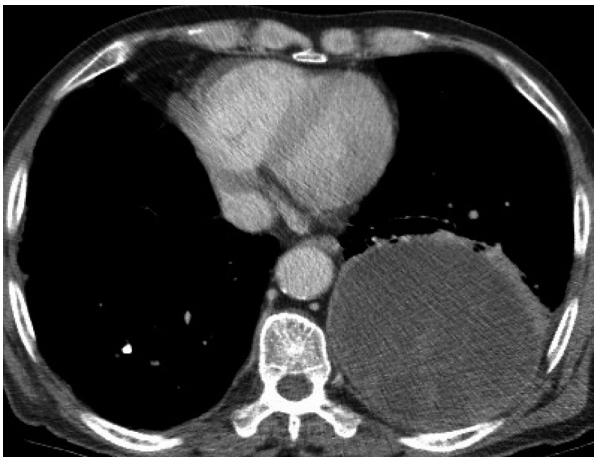

Fig. 2. Chest CT showed a 9.7 × 8.7 cm soft tissue mass in the left lower lung, and left pleural effusion.

operation. Postoperative tumor staging was *p*T-3N1Mx.

The surgical finding was a huge tumor mass with marked tumor necrosis measuring 15 × 15 cm with dense adhesion to the left lower lobe and parietal pleura. The postoperative pathological examination revealed combined pleomorphic carcinoma and small cell carcinoma, composed of spindle cell carcinoma (85%) (Figure 3A), squamous cell carcinoma (10%) (Figure 3B) and small cell carcinoma (5%) (Figure 3C).

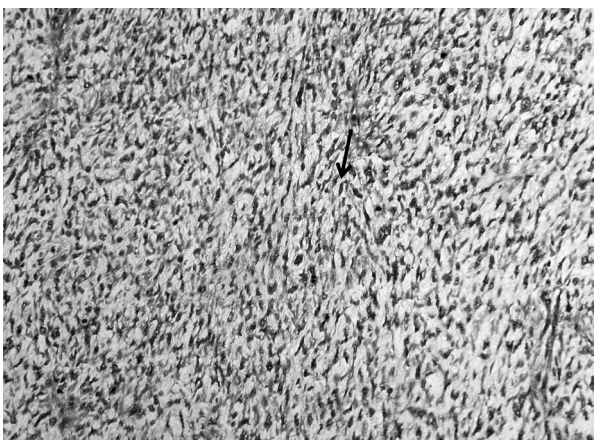

Fig. 3A. The pathological finding revealed spindle cell carcinoma (hematoxylin and eosin stain, X40).

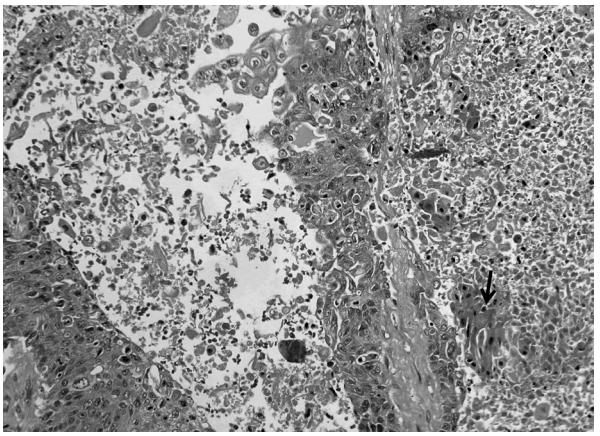

Fig. 3B. The pathological finding revealed squamous cell carcinoma (hematoxylin and eosin stain, X40).

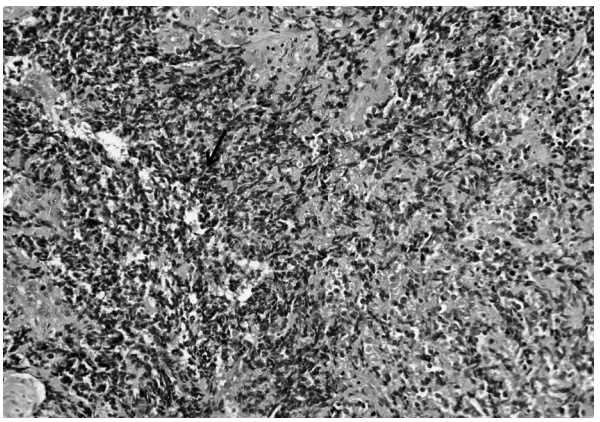

Fig. 3C. The pathological finding revealed small cell carcinoma (hematoxylin and eosin stain, X40).

In addition, metastatic small cell carcinoma with extra-capsular tumor extension was found in the ipsilateral group 11 lymph node. Immunohistochemical study was performed. The components of malignant spindle cells, squamous cell carcinoma and small cell carcinoma were positive for cytokeratin, p63 and synaptophysin, respectively, and therefore the diagnosis of combined pleomorphic carcinoma and SCLC was confirmed.

After operation, while on mechanical ventilation in the intensive care unit, the patient was

initially complicated with subcutaneous emphysema and pneumomediastinum, and subsequently with ventilator-associated pneumonia. The patient did not receive chemotherapy due to the poor performance status. Two months later, the patient died of multiple-organ failure secondary to nosocomial pneumonia.

Discussion

In the present case, spindle cell carcinoma, squamous cell carcinoma and small cell carcinoma were observed in 85%, 10% and 5% of the tumor, respectively. For this kind of combined lung malignancy, several factors, such as the rare heterogeneity of the multiple cellular components and the different lymph nodes metastasized by different cell types, often make a precise diagnosis difficult, unless by surgical biopsy and thorough histopathological examination with immunohistochemical stain [6-8].

Combined SCLC is not easily diagnosed appropriately, not only because of the very low incidence rate, but also the cellular heterogeneity. In this case, the primary tumor consisted of trimorphic histological components with spindle cell, squamous cell and small cell types, bearing the aggressive nature of both spindle cell carcinoma and small cell carcinoma. For the spindle cell carcinoma portion, the aggressive nature was reflected by the huge tumor size, up to 17.8 cm, and parietal pleural invasion by malignant spindle cells, and for the small cell carcinoma component, by histological proof of left interlobar lymph node (group 11) metastasis.

Pleomorphic carcinoma has no characteristic features distinguishing it from other primary lung malignancy. Kim *et al* reported that pleomorphic carcinoma is usually shown to be round or oval masses with a lobulated appearance, often located at the lung periphery with aggressive invasion to the adjacent chest wall or the pleura in radiographic features [9]. The chest X-ray and CT findings in this case were compatible with the previously reported characteristics.

Yuki *et al* reported that pleomophic carcinoma has a high postoperative recurrence rate (95%) within 14 months after operation [10]. Bae *et al* reported the common chemotherapy regimens used in non-small cell lung cancer were absolutely ineffective for advanced pulmonary pleomorphic carcinoma [11]. Even in pleomorphic carcinoma with an adenocarcinomatous component, concomitant EGFR mutations of exon 19 deletions and exon 20 T790M with resistance to gefitinib have been reported [12]. Pelosi *et al* reported that the aggressive course of pleomorphic carcinoma may be correlated with the huge malignant spindle cell burden, reflecting in part and attributable to the sarcomatoid elements with increased tumor cell motility and angiogenic activity [13]. Martin *et al* [14] and Mochizuki *et al* [15] reported that an initial tumor size of >7 cm, a proportion of sarcomatous elements and massive necrosis >25% were independent prognostic factors of pleomorphic carcinoma, and negatively impacted the 5-year survival rate, which was less than 33% compared with stage-matched NSCLC. There were no 5-year survivors among pleomorphic carcinoma cases of pathological stage III or greater [14]. Earlier studies have demonstrated that there are no differences in the clinical performance and outcomes between combined SCLC and pure SCLC, making the initial stage the most significant prognostic factor [4,16]. In terms of outcome, the huge tumor size with marked tumor necrosis and pleural invasion, postoperative tumor staging of IIIA,

and the propensity of small cell carcinoma to metastasize early, were all poor prognostic factors in this case.

In summary, we reported a relatively rare case of combined pleomorphic carcinoma and SCLC with a poor prognosis. Further understanding of and future clinical studies on effective treatment regimens for this kind of combined pleomorphic and small cell carcinoma are needed.

References

1. Beasley MB, Brambilla E, Travis WD. The 2004 World Health Organization classification of lung tumors. Semin Roentgenol 2005; 40: 90-7.
2. Ishida T, Tateishi M, Kaneko S, *et al*. Carcinosarcoma and spindle cell carcinoma of the lung. Clinicopathologic and immunohistochemical studies. J Thorac Cardiovasc Surg 1990; 100: 844-52.
3. Franks TJ, Galvin JR. Sarcomatoid carcinoma of the lung: histologic criteria and common lesions in the differential diagnosis. Arch Pathol & Lab Med 2010; 134: 49-54.
4. Nicholson SA, Beasley MB, Brambilla E, *et al*. Small cell lung carcinoma (SCLC). Am J Surg Pathol 2002; 26: 1184-97.
5. Sehested M, Hirsch FR, Osterlind K, *et al*. Morphologic variations of small cell lung cancer. A histopathologic study of pretreatment and posttreatment specimens in 104 patients. Cancer 1986; 57: 804-7.
6. Kaira K, Endo M, Abe M, *et al*. Biologic correlates of F-FDG uptake on PET in pulmonary pleomorphic carcinoma. Lung Cancer (Amsterdam, Netherlands) 2011; 71: 144-50.
7. Travis WD. Sarcomatoid neoplasms of the lung and pleura. Arch Pathol & Lab Med 2010; 134: 1645-58.
8. Rossi G, Cavazza A, Sturm N, *et al*. Pulmonary carcinomas with pleomorphic, sarcomatoid, or sarcomatous elements - A clinicopathologic and immunohistochemical study of 75 cases. Am J Surg Pathol 2003; 27: 311-24.
9. Kim TH, Lim SJ, Ryu YH, *et al*. Pleomorphic carcinoma of lung: comparison of CT features and pathologic findings. Radiol 2004; 232: 554-9.
10. Yuki T, Sakuma T, Ohbayashi C, *et al*. Pleomorphic carcinoma of the lung: a surgical outcome. J Thorac Cardiovasc Surg 2007; 134: 399-404.
11. Bae HM, Min HS, Lee SH, *et al*. Palliative chemotherapy for pulmonary pleomorphic carcinoma. Lung Cancer 2007; 58: 112-5.
12. Ushiki A, Koizumi T, Kobayashi N, *et al*. Genetic heterogeneity of EGFR mutation in pleomorphic carcinoma of the lung: response to gefitinib and clinical outcome. Jpn J Clin Oncol 2009; 39: 267-70.
13. Pelosi G, Fraggetta F, Nappi O, *et al*. Pleomorphic carcinomas of the lung show a selective distribution of gene products involved in cell differentiation, cell cycle control, tumor growth, and tumor cell motility: a clinicopathologic and immunohistochemical study of 31 cases. Am J Surg Pathol 2003; 27: 1203-15.
14. Martin LW, Correa AM, Ordonez NG, *et al*. Sarcomatoid carcinoma of the lung: a predictor of poor prognosis. Annals of Thorac Surg 2007; 84: 973-80.
15. Mochizuki T, Ishii G, Nagai K, *et al*. Pleomorphic carcinoma of the lung: clinicopathologic characteristics of 70 cases. Am J Surg Pathol 2008; 32: 1727-35.
16. Fraire AE, Johnson EH, Yesner R, *et al*. Prognostic significance of histopathologic subtype and stage in small cell lung cancer. Hum Pathol 1992; 23: 520-8.

多型性細胞與小細胞混合肺癌：一個病例報告

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肺癌是癌症死亡的最大主因。多型性細胞癌是一種分化不良的非小細胞癌、混有至少十分之一以上的惡性梭狀細胞和 / 或巨型細胞。它是一種罕見腫瘤、發生率僅占所有肺腫瘤的 0.1 ～ 0.3%。混合多型性細胞與小細胞肺癌更為罕見、且比單純小細胞肺癌有更差的預後。一位七十六歲抽菸男性主訴胸痛而且胸部放射線圖像顯示左胸有多葉性腫塊。胸腔電腦斷層發現左下肺有 9.7 x 8.7 cm 大小的軟組織腫塊。胸腔手術病理分析顯示是混合多型性細胞與小細胞癌、含有梭形細胞（85%）、鱗狀扁平細胞（10%）與小細胞癌（5%）。病患於兩個月後因敗血症與多器官衰竭而死亡。病患因身體狀況不佳未給予化學藥物治療。吾人於此報告此一罕見與預後不佳的混合多種型態細胞與小細胞肺癌病例。因其具侵犯性佳且不易正確診斷，因此值得注意。*(胸腔醫學* ***2012; 27: 276-281)***

關鍵詞：混合多型性上皮細胞癌，肺癌，梭形細胞癌，小細胞癌

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Infective Endocarditis with Septic Shock in a Rheumatoid Arthritis Patient being Treated with Etanercept

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Rheumatoid arthritis (RA) is a chronic inflammatory polyarticular disorder of unknown cause. Nowadays, biologic agents are widely used to treat RA. Etanercept, a tumor necrosis factor (TNF) type II receptor fused to IgG1, is one of the most commonly used biologic agents. Increased risk of serious infections is recognized as a potential side effect, of which reactivation of tuberculosis is particularly notable. We report the case of a patient with infective endocarditis complicated with septic shock, who had been receiving etanercept for his refractory RA. Through appropriate resuscitation and antibiotic treatment, the patient had a good recovery with resolution of the vegetation on the aortic valve. To the best of our knowledge, this is the first report in the medical literature describing a RA patient taking etanercept complicated with infective endocarditis. Physicians should be cautious when considering the use of biologic agents. ***(Thorac Med 2012; 27: 282-286)***

Key words: infective endocarditis, rheumatoid arthritis, etanercept, sepsis, pneumonia

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory polyarticular disorder of unknown cause. Nowadays, biologic agents are widely used for patients with RA. These agents are not only quite effective in controlling signs and symptoms for most patients, but may also slow the progression of joint damage and improve disability. Etanercept, a tumor necrosis factor (TNF) type II receptor fused to IgG1, is one of the most commonly used biologic agents [1]. Increased risk of serious infections, however, has been recognized as a potential side effect, of which reactivation of tuberculosis is particularly notable. Herein, we report a case of infective endocarditis in a patient receiving etanercept for his refractory RA.

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Case Report

A 68-year-old man with an unremarkable medical history presented to our hospital with a 3-month history of polyarthralgia with swelling, tenderness and local heat in both shoulders, hands, knees and right wrist and ankle. The laboratory examination revealed positive rheumatoid factor (715 IU/mL), positive antinuclear antibody with a titer of 1:80, and positive anti-CCP (cyclic citrullinated polypeptides) (195 U/mL). After the diagnosis of RA was made, he tried different combinations of disease-modifying anti-rheumatic drugs (DMARDs) such as methotrexate, sulfasalazine, leflunomide and cyclosporine. However, he experienced a variety of side effects. Six months later, he started treatment with etanercept (25 mg given subcutaneously 2 times per week). His polyarthralgia improved quickly within 1 month.

Two months later, he began having intermittent fever with chills and productive cough. Then, 3 days later, he presented to the emergency department with progressive dyspnea, blood-tinged sputum, dizziness, postural hypotension which compromised his circulation, and shock with blood pressure of 80/44 mmHg. The nasopharyngeal swab was negative for the influenza antigen rapid test. Chest radiograph (Figure 1) revealed bilateral multiple patchy lesions. After initial fluid resuscitation, he was placed on norepinephrine support. Empirical antibiotic treatment with ceftriaxone and levofloxacin was started soon thereafter, and he was admitted to the intensive care unit under the impression of septic shock. After admission, his vital signs were stabilized, and norepinephrine was tapered gradually. Chest computed tomography (CT) disclosed multiple pulmonary opacities, arousing concern about septic embolism or fungal infection. The serum galactomannan test was negative. The sputum culture and 2 sets of blood culture all yielded oxacillin-susceptible *Staphylococcus aureus*, so the antibiotic was changed to oxacillin. His dyspnea improved gradually, and he was transferred to the ordinary ward for further care. Transthoracic and transesophageal echocardiography (Figure 2) revealed vegetation on the ventricular surface of the aortic valve. Antibiotic treatment with oxacillin was maintained for 4 weeks. Resolution of the lesions on chest radiograph was noted, and the follow-up echocardiography performed on the 20th day of antibiotic treatment revealed that the aortic valve vegetation had disappeared. He had an uneventful recovery except recurrence of his polyarthritis, related to the discontinuation of etanercept.

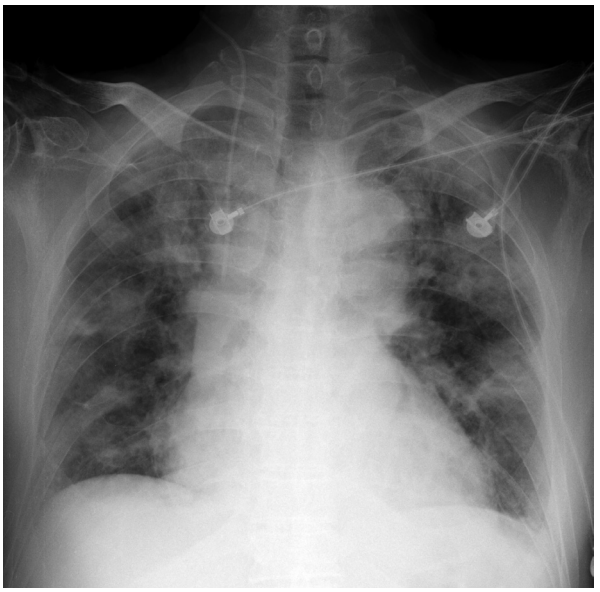

Fig. 1. Chest radiograph revealed bilateral multiple patchy lesions.

Discussion

RA is a chronic multisystem inflammatory

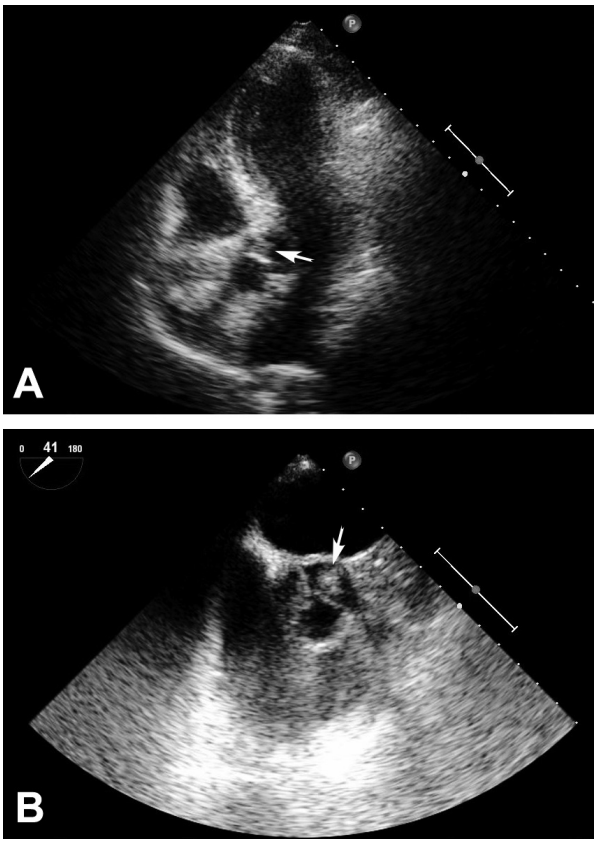

Fig. 2. Transthoracic echocardiography (A) revealed a suspicious lesion (arrow) on the aortic valve. Transesophageal echocardiography (B) confirmed vegetation (arrow) on the ventricular surface of the aortic valve.

disease with varied clinical manifestations. It characteristically presents as persistent inflammatory synovitis, usually involving peripheral joints in a symmetric fashion. The synovial inflammation may lead to cartilage damage and bone erosion, resulting in changes in joint integrity, which may be disabling. In addition to arthritis, it is estimated that about 40% of patients may have extraarticular manifestations, including rheumatoid nodules, vasculitis, pleuropulmonary disorders, cardiac involvement, hematological disorders, and so on.

Cardiac involvement with RA has occurred in up to 50% of affected patients and is usually clinically silent [2]. Pericarditis is the most common presentation, while myocarditis and endocarditis have been reported [2-3]. Although cardiac manifestations with RA are usually silent and asymptomatic, severe rheumatoid valvular heart disease has been reported, and in these cases, etanercept was a useful treatment [2]. Bacterial endocarditis superimposed on a valvular rheumatoid nodule has been reported, as well [4]. In our patient, the rapid progression of bilateral multiple pulmonary lesions led to a concern about infective endocarditis. The sputum culture and 2 sets of blood culture all yielded oxacillin-susceptible *Staphylococcus aureus*. Echocardiography confirmed the presence of vegetation on the aortic valve, which disappeared after antibiotic treatment. Furthermore, etanercept was stopped on admission. Therefore, the vegetation should be attributed to infective endocarditis, not a rheumatoid nodule.

In addition to non-steroidal anti-inflammatory drugs, simple analgesics, glucocorticoids, and DMARDs, many biologic agents are available for treating RA nowadays, including adalimumab, etanercept, infliximab, anakinra, rituximab, abatacept, and so on. Although these biologic agents are generally considered safe and well-tolerated, concerns about a possible increased risk of infection remain a critical issue [5-10]. For example, there is no surprise that the risk of opportunistic infection is increased with TNF antagonists, since TNF is an important constituent of the human immune response to infection [11]. It is widely known that patients using TNF antagonists are at increased risk of developing tuberculosis, and therefore, tuberculosis screening before starting on these agents is mandatory [12-14]. However, to the best of our knowledge, this is the first report in the medical literature to date about infective endocarditis in a rheumatoid arthritis patient receiving etaner-

cept.

Although the theoretically increased risk of infection is of concern for patients receiving etanercept, a few recent systematic reviews with a meta-analysis confirmed the efficacy of etanercept and showed no statistically significant differences between treated patients and controls in terms of serious adverse events, serious infections, malignancy or deaths [15-16]. Many recent studies with long-term follow-up also have demonstrated the favorable safety profile and consistent effectiveness of etanercept, even in elderly patients [8-10,17-18]. Nevertheless, physicians should be cautious when considering the use of biologic agents, especially in patients with a history of recurrent infections or underlying conditions that predispose them to infections.

References

1. Anis A, Zhang W, Emery P, *et al*. The effect of etanercept on work productivity in patients with early active rheumatoid arthritis: results from the COMET study. Rheumatol (Oxford) 2009; 48: 1283-9.
2. Anaya JM. Severe rheumatoid valvular heart disease. Clin Rheumatol 2006; 25: 743-5.
3. DeLong CE, Roldan CA. Noninfective endocarditis in rheumatoid arthritis. Am J Med 2007; 120: e1-2.
4. Giladi H, Sukenik S, Flusser D, *et al*. A rare case of enterobacter endocarditis superimposed on a mitral valve rheumatoid nodule. J Clin Rheumatol 2008; 14: 97-100.
5. Khraishi M. Comparative overview of safety of the biologics in rheumatoid arthritis. J Rheumatol Suppl 2009; 82: 25-32.
6. Weisman MH, Paulus HE, Burch FX, *et al*. A placebo-controlled, randomized, double-blinded study evaluating the safety of etanercept in patients with rheumatoid arthritis and concomitant comorbid diseases. Rheumatol (Oxford) 2007; 46: 1122-5.
7. Weinblatt ME, Bathon JM, Kremer JM, *et al*. Safety and efficacy of etanercept beyond 10 years of therapy in North American patients with early and longstanding rheumatoid arthritis. Arthritis Care & Res 2011; 63: 373-82.
8. Klareskog L, Gaubitz M, Rodriguez-Valverde V, *et al*. Assessment of long-term safety and efficacy of etanercept in a 5-year extension study in patients with rheumatoid arthritis. Clin Exp Rheumatol 2011; 29: 238-47.
9. Senel S, Kisacik B, Ugan Y, *et al*. The efficacy and safety of etanercept in patients with rheumatoid arthritis and spondyloarthropathy on hemodialysis. Clin Rheumatol 2011; 30: 1369-72.
10. Gibofsky A, Palmer WR, Keystone EC, *et al*. Rheumatoid arthritis disease-modifying antirheumatic drug intervention and utilization study: safety and etanercept utilization analyses from the RADIUS 1 and RADIUS 2 registries. J Rheumatol 2011; 38: 21-8.
11. Favalli EG, Desiati F, Atzeni F, *et al*. Serious infections during anti-TNFalpha treatment in rheumatoid arthritis patients. Autoimmun Rev 2009; 8: 266-73.
12. Soderlin M, Blomkvist C, Dahl P, *et al*. Increased risk of infection with biological immunomodifying antirheumatic agents. Clear guidelines are necessary as shown by case reports. Lakartidningen 2005; 102: 3794-6, 9-800. [In Sweden English abstract]
13. Fuchs I, Avnon L, Freud T, *et al*. Repeated tuberculin skin testing following therapy with TNF-alpha inhibitors. Clin Rheumatol 2009; 28: 167-72.
14. Dixon WG, Hyrich KL, Watson KD, *et al*. Drug-specific risk of tuberculosis in patients with rheumatoid arthritis treated with anti-TNF therapy: Results from the British Society for Rheumatology Biologics Register (BSRBR). Ann Rheum Dis 2010; 69: 522-88.
15. Wiens A, Correr CJ, Pontarolo R, *et al*. A systematic review and meta-analysis of the efficacy and safety of etanercept for treating rheumatoid arthritis. Scand J Immunol 2009; 70: 337-44.
16. Wiens A, Venson R, Correr CJ, *et al*. Meta-analysis of the efficacy and safety of adalimumab, etanercept, and infliximab for the treatment of rheumatoid arthritis. Pharmacother 2010; 30: 339-53.
17. Koike T, Harigai M, Inokuma S, *et al*. Postmarketing surveillance of safety and effectiveness of etanercept in Japanese patients with rheumatoid arthritis. Mod Rheumatol 2011; 21: 343-51.
18. Lurati A, Marrazza M, Angela K, *et al*. Safety of etanercept in elderly subjects with rheumatoid arthritis. Biologics 2010; 4: 1-4.

類風濕性關節炎使用 etanercept 的病人併發感染性心內膜炎及敗血性休克

蔡明儒 * 連啟惇 * 蔡忠榮 *,*** 吳正欽 ** 顏正賢 **,****

類風濕性關節炎是一種慢性多關節發炎性疾病，其真正的形成原因目前仍不甚清楚。生物製劑已被廣泛地應用在類風濕性關節炎的治療。其中，etanercept 是一種常被使用的生物製劑，它是由第二型腫瘤壞死因子接受器與免疫球蛋白 G1（IgG1）結合而成。這類生物製劑被認為有可能會增加嚴重感染的風險。在此，我們報告一個使用 etanercept 治療類風濕性關節炎病人所發生的感染性心內膜炎併發敗血性休克。經過適當的復甦與抗生素治療，此病患恢復良好；其主動脈瓣上的贅生物也在治療後消失不見。據我們了解，這是醫學文獻上初次報告感染性心內膜炎併發敗血性休克發生在使用 etanercept 治療類風濕性關節炎病人。我們提出這個報告以提醒臨床醫師在處方這類生物製劑時須特別謹慎。*(胸腔醫學 **2012; 27: 282-286**)*

關鍵詞：感染性心內膜炎，類風濕性關節炎，etanercept，敗血症，肺炎

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Metastatic Pulmonary Calcification in a Patient with End-Stage Renal Disease and Hyperparathyroidism: A Case Report

Chi-Hung Lo, Shih-Wei Wu*, Chin-Pyng Wu**, Kao-Yao Chang, Jen-Hsien Lin, Nan-Hsiung Feng

Metastatic pulmonary calcification (MPC) is an occasionally encountered complication of uremia and a disordered calcium metabolism. Chest radiograph has limited effectiveness in the detection of MPC. Chest computed tomography (CT) scan, particularly high-resolution CT (HRCT), and bone scintigraphy are the preferred methods for detecting small amounts of calcification and diagnosing MPC, obviating the need for open lung biopsy. We report the case of a 58-year-old patient with uremia and secondary hyperparathyroidism who was diagnosed as having metastatic calcification, based on the history, chest x-ray, chest CT, and bone scintigraphy. ***(Thorac Med 2012; 27: 287-293)***

Key words: metastatic pulmonary calcification, uremia

Introduction

Metastatic calcification is an occasionally encountered complication of a disordered calcium metabolism that may occur as a result of destructive bone disease, hyperparathyroidism, chronic renal failure, hypervitaminosis D, or the therapeutic administration of corticosteroids and phosphate [1-2]. Metastatic pulmonary calcification (MPC), a pulmonary manifestation of metastatic calcification, may exhibit a diffuse or localized distribution. Chest radiograph (CXR) is neither specific nor sensitive in the detection of MPC [3-5]. Chest computed tomography (CT) scan, particularly high-resolution CT (HRCT), is the preferred method for detecting small amounts of calcification and for diagnosing MPC, thus obviating the need for open lung biopsy [6]. The mechanism of MPC appears to be complex, as not all patients with end-stage renal disease (ESRD) undergoing hemodialysis (HD) treatment have metastatic calcification. We present the case of a patient with ESRD and secondary hyperparathyroidism who developed bilateral metastatic calcification of the lungs, as a reminder to clinicians of this possible complication.

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Case Report

A 58-year-old married man with a history of autosomal-dominant polycystic kidney disease (ADPKD) and in a uremic status on HD at our hospital for approximately 28 years underwent parathyroidectomy with autotransplantation to his right arm approximately 15 years ago. He visited our outpatient department (OPD) due to a chronic cough lasting several months and an abnormal CXR during a regular health exam. He had no prior history of exposure to tobacco or occupational aerosols. His CXR displayed increased infiltrations and nodular opacity in both upper lung zones (Figure 1).

Sputum cultures revealed normal flora without fungus infection. Acid-fast bacillus (AFB) smears and tuberculosis sputum cultures were negative, and carcinoembryonic antigen (CEA) was within normal limits. Results of serum tests revealed an increased serum creatinine level of 7.5 mg/dL (0.7-12 mg/dL), normal calcium level of 9.3 mg/dL (8.4-10.2 mg/dL), normal phosphate level of 4.2 mg/dL (2.7-4.5 mg/dL), and an increased parathyroid hormone level of 1,118 pg/mL (10.0-69.0 pg/mL). An axial HRCT of the chest was arranged for further evaluation, and the presence of fluffy ground-glass opacities with calcifications mainly in both upper lobes was noted (Figure 2). The largest conglomerated calcification, located in the right apical lung, measured approximately 3.1 × 2.2 cm^2, and diffuse calcifications in the trachea and bilateral bronchi were observed.

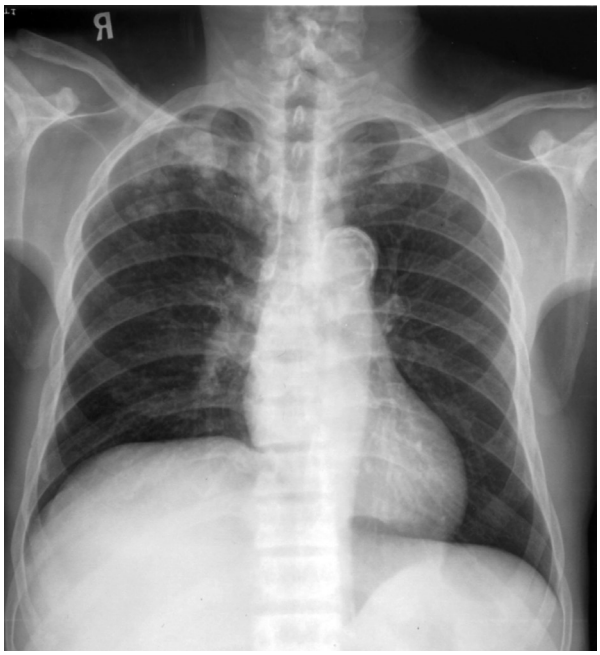
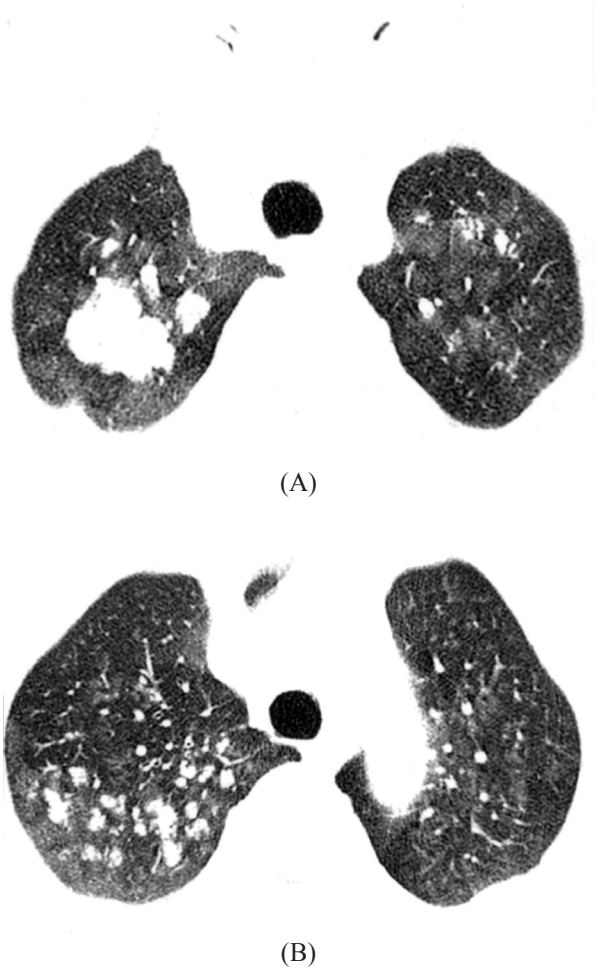


Fig. 1. CXR exhibiting increased infiltrations and nodular opacity in both upper lung zones.



(A)

(B)

Fig. 2A,B. Computed tomography images of fluffy ground-glass opacities with calcifications mainly in both upper lobes.

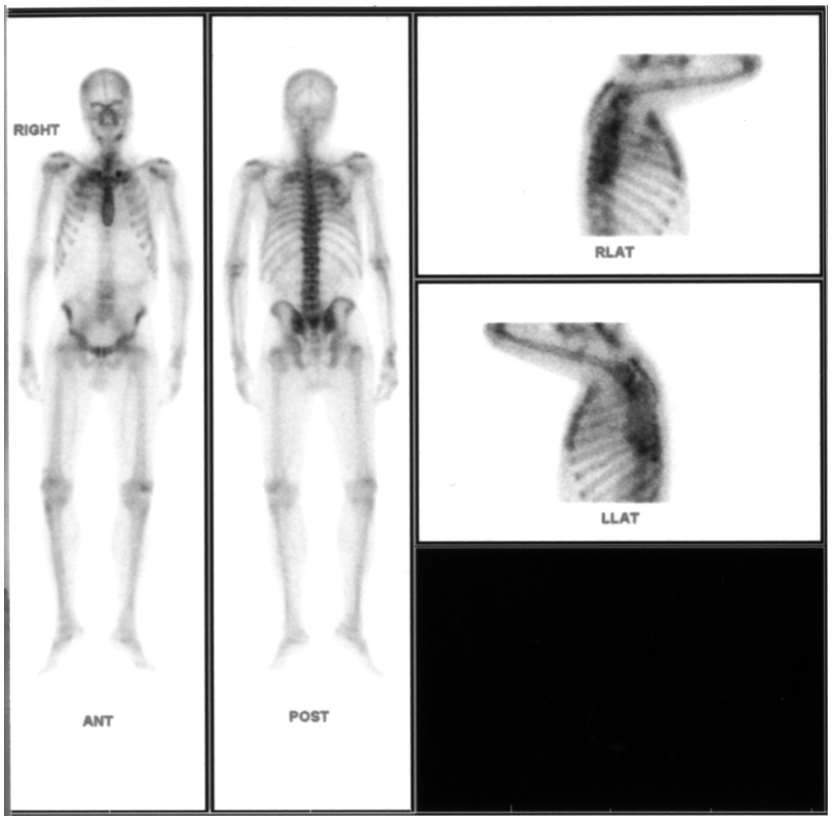


Fig. 3. Whole body bone scan revealing faintly increased uptake in the bilateral upper lung fields, compatible with the clinical impression of extraosseous calcification.

Given the patient's history, a diagnosis of MPC was highly suspected. A whole body bone scan revealed a faintly increased uptake in the bilateral upper lung fields, compatible with the clinical impression of extraosseous calcification (Figure 3). Based on these findings, we made a diagnosis of MPC due to chronic renal impairment and secondary hyperparathyroidism. The patient received supportive treatment at our OPD and regular follow-up CXRs.

Discussion

Metastatic calcification is a process in which calcium deposition occurs in normal tissues as a result of an excessively high serum calcium level [7]. Its pulmonary manifestation, MPC, is an interstitial process involving the deposition of calcium in the alveolar septa and bronchial walls, and to a lesser extent, in the bronchioles and pulmonary arterioles. MPC is most likely to develop when the calcium-phosphorus product exceeds 70, but may also occur with calcium-phosphorus product levels in the normal range [8]. Patients with ESRD undergoing HD may suffer from a number of metabolic derangements; MPCs, as one example, have been shown to be present in 60-80% of autopsied patients with chronic renal failure receiving HD, but are rarely recognized during the patient's life [4]. Risk factors for metastatic calcification have been reported to include elevated plasma calcium-phosphate product, protein C deficiency, hypercalcemia, hyperphosphatemia, chronic

kidney disease, hyperparathyroidism, HD, malignancy, and warfarin therapy. However, no correlation was found with the duration of HD or the type of dialysate [5].

MPC is found less than often on conventional CXRs. When abnormalities are present on CXRs, they most commonly represent pulmonary parenchymal opacification or poorly defined infiltrates that may simulate pneumonia or pulmonary edema [9-10]. MPC may be diffuse or focally distributed, with the upper lobe of the lung being more commonly affected [11]. Tissue alkalosis may be an important causative factor. The higher ventilation: perfusion ratio in the lung apex than in the base, resulting in a lower alveolar carbon dioxide tension (P_ACO_2) and higher tissue pH, may be responsible, given that relative alkalinity favors the deposition of calcium salt [12]. At the apex, blood pH is approximately 7.51, compared with 7.39 at the base [13]. The combined presentation of pulmonary and vascular calcification is also a characteristic of MPC in some patients [14].

Although most patients with MPC are asymptomatic, respiratory failure may develop [3,9-10]. Some patients develop respiratory symptoms that are related to the extent of calcification. Restrictive lung diseases with progressive decreases in carbon monoxide diffusing capacity (DLCO), total lung capacity (TLC), vital capacity (VC), and hypoxemia may be associated with increasing levels of pulmonary calcium [5]. Pulmonary calcification may lead to a slowly diminishing diffusion capacity, and hypoxemia may result [15]. In such cases, the patient may die due to progressive respiratory failure [9,16]. Therefore, it is important to identify such entities early to enable the correct diagnosis of this potentially progressive and fatal cause of respiratory failure. Methods of diagnosis using the pulmonary uptake of bone-seeking radiopharmaceuticals or dual-energy digital CXR have been described [5,17]. However, only isolated cases using CT findings for a diagnosis of MPC have been reported [18-19]. HRCT, with its excellent sensitivity in the detection of small amounts of calcification, is being increasingly used to diagnose MPC. Three CT patterns of pulmonary calcification have been described. The first is diffuse or patchy areas of ground-glass opacity or consolidation. The second is multiple diffuse calcified nodules that either are distributed throughout the whole lung or demonstrate a predilection for the apices or bases [20]. The third pattern appears as a confluent, high-attenuation parenchymal consolidation in a predominantly lobar distribution, mimicking lobar pneumonia [18]. The combined presentation of CT findings may be an important factor in identifying the causes of pulmonary calcification. Both bone scintigraphy and HRCT with mediastinal images are better than standard CXRs in detecting pulmonary calcification. Moreover, bone scintigraphy with the bone-avid radiotracer ^{99m}technetium-methylene diphosphate can help resolve equivocal cases. A critical use of bone scintigraphy and HRCT is in the early and accurate recognition of pulmonary calcification in cases of unexplained and persistent infiltrates.

MPC is an important complication of uremia, but is not often seen in uremic patients. Diagnosing MPC is not easy because it can only be considered if other causes have been excluded. In a patient with a normal calcium-phosphorus product, a diagnosis of MPC cannot be completely excluded if other causes are unlikely. Therefore, increased suspicion is necessary in high-risk patients. As the presentation of MPC on CXR may be similar to that of pulmonary

TB, the exclusion of pulmonary TB should be prioritized, which is the case in Taiwan. MPC should be considered if persistent apical infiltration is noted in uremic patients. A chest CT may help to confirm the diagnosis based on the characteristic CT findings of MPC. Invasive study is seldom indicated for the pathological diagnosis if the patient does not have severe respiratory symptoms.

The treatment of MPC is supportive. Rigorous control of the phosphate and calcium balance may help avoid the metabolic milieu in which metastatic calcification occurs. Such treatment consists of eliminating any known sensitizing or precipitating factors. Lowering the calcium-phosphate product and parathyroidectomy are also appropriate.

Conclusion

MPC is a well-known complication of end-stage renal failure, but it is not often seen in uremic patients in Taiwan. It is usually asymptomatic or has a benign course [6], but in some cases can cause fulminant respiratory failure and early death. Therefore, more attention should be given to the possibility of MPC in high-risk patients. Although MPC is most commonly seen in patients with chronic renal failure [1,3], it has also been described in cases with primary and secondary hyperparathyroidism, hypervitaminosis D, milk-alkali syndrome, diffuse myelomatosis, and extensive bone malignancy. Given that the presentation of MPC on chest radiography may be similar to that of pulmonary TB, the exclusion of pulmonary TB should be made a priority in Taiwan. The advantages of thin-section CT for detecting calcium in solitary pulmonary nodules are well established. Invasive study is seldom indicated for the pathological diagnosis if a patient does not have severe respiratory symptoms. Finally, the management of MPC is supportive.

References

1. Mulligan RM. Metastatic calcification. Arch Pathol 1947; 43: 177-230.
2. Parfitt AM. Soft-tissue calcification in uremia. Arch Intern Med 1969; 124: 544-56.
3. Kaltreider HB, Baum GL, Bogarty G, *et al*. So-called "metastatic" calcification of the lung. Am J Med 1969; 46: 188-96.
4. Conger JD, Hammond WS, Alfrey AC, *et al*. Pulmonary calcification in chronic dialysis patients: clinical and pathologic studies. Ann Intern Med 1975; 83: 330-6.
5. Sanders C, Frank MS, Rostand SG, *et al*. Metastatic calcification of the heart and lungs in end-stage renal disease: detection and quantification by dual-energy digit chest radiography. AJR 1987; 149: 881-7.
6. Romagnoli M, Mourad G, Serre I, *et al*. Diffuse pulmonary calcinosis without calcium metabolism abnormalities in a renal transplant recipient. Eur Respir J 1997; 10: 958-60.
7. Beyzaei A, Francis J, Knight H, *et al*. Metabolic lung disease: diffuse metastatic pulmonary calcifications with progression to calciphylaxis in end-stage renal disease. Adv Perit Dial 2007; 23: 112-7.
8. Stanbary SW, Lamb GA. Parathyroid function in chronic renal failure. Q J Med 1966; 35: 1-23.
9. McLachlan MSF, Wallace N, Senevirante C. Pulmonary calcification in renal failure: report of three cases. BrJ Radiol l986; 41: 99-106.
10. Neff M, Yalcin S, Gupta S, *et al*. Extensive metastatic calcification of the lung in an azotemic patient. Am J Med 1974; 46: 103-9.
11. Jost RG, Sagel SS. Metastatic calcification in the lung apex. AJR 1979; 133: 1188-90.
12. Shear MJ, Kramer B. Composition of bone: physicochemical mechanisms. J Biol Chem 1928; 79: 125-45.
13. West JB. Regional differences in blood flow and ventilation in the lung. In: Caro CG, ed. Advances in respiratory physiology. Baltimore: Williams and Wilkins Company, 1966; 198-254.

14. Hartman TE, Muller N, Primack SL, *et al*. Metastatic pulmonary calcification in patients with hypercalcaemia: findings on chest radiographs and CT scans. AJR 1994; 162: 799-802.
15. Khafif RA, DeLima C, Silverberg A, *et al*: Calciphylaxis and systemic calcinosis: Collective review. Arch Intern Med 1990; 150: 956-9.
16. Davidson RC, Pendros JP: Calcium related cardiorespiratory death in chronic hemodialysis. Trans Am Soc Artif Intern Organs 1967; 13: 36-40.
17. Rosenthal Dl, Chandler HL, Azizi F, *et al*. Uptake of bone imaging agents by diffuse pulmonary metastatic calcification. AJR 1977; 129: 871-4.
18. Kuhlman JE, Ren H, Hutchins GM, *et al*. Fulminant pulmonary calcification complicating renal transplantation: CT demonstration. Radiology 1989; 173: 459-60.
19. Mani TH, Lallemanel 0, Corone S, *et al*. Metastatic pulmonary calcifications after cardiac surgery in children. Radiology 1990; 174: 463-7.
20. Hartman TE, Muller N, Primack SL, *et al*. Metastatic pulmonary calcification in patients with hypercalcaemia: findings on chest radiographs and CT scans. AJR 1994; 162: 799-802.

一位末期腎病變及副甲狀腺高能症病人併發轉移性肺鈣化—病例報告

羅啟紘　吳世偉 *　吳清平 **　張高耀　林任先　馮南雄

轉移性肺鈣化在尿毒症及鈣離子代謝異常的病患是一個偶發的併發症。胸部 X 光對於偵測轉移性肺鈣化的並不非常敏感。電腦斷層，尤其是高分辨電腦斷層，以及骨骼掃描對於偵測小量鈣化及轉移性肺鈣化的診斷是較建議的方法，更可以避免開胸切片檢查的必要性。我們報告一個 58 歲尿毒症病人合併續發性副甲狀腺高能症，經由病史、胸部 X 光、電腦斷層，以及骨骼掃描等檢查，診斷為轉移性肺鈣化。*(胸腔醫學 **2012; 27: 287-293**)*

關鍵詞：轉移性肺鈣化，尿毒症

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Idiopathic Pulmonary Hemosiderosis – A Case Report

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Idiopathic pulmonary hemosiderosis (IPH) is a rare cause of diffuse alveolar hemorrhage and has an unknown etiology and pathogenesis. The clinical presentations of IPH include dyspnea, anemia, and hemoptysis. Chest radiography often reveals diffuse ground glass and ill-defined opacities. Herein, we report a patient with iron-deficiency anemia. The patient had progressive dyspnea, recurrent hemoptysis, hemolytic anemia and alveolar opacities on chest film that were difficult to differentiate from other types of pneumonitis. We excluded autoimmune disease, coagulopathy, renal disease, and pulmonary infection. The pathology report from the transbronchial biopsy revealed hemosiderin-laden macrophages. Intravenous prednisolone was useful in alleviating the symptoms. ***(Thorac Med 2012; 27: 294-298)***

Key words: idiopathic pulmonary hemosiderosis, anemia, hemoptysis, pneumonitis

Introduction

Idiopathic pulmonary hemosiderosis (IPH) is a rare pulmonary disorder that manifests as a triad of hemoptysis, anemia and diffuse parenchymal infiltrates on chest radiograph. IPH results from recurrent bleeding into alveolar spaces and interstitial lung tissue with hemosiderin accumulation in the alveolar spaces. The diagnosis is exclusive of other autoimmune diseases, coagulopathy and renal disease. If left untreated, fibrosis and severe restrictive lung disease will develop and may lead to death. We describe the clinical presentation, and related diagnosis of a patient with IPH.

Case Report

A 46-year-old man with a history of iron deficiency anemia (IDA) presented to our emergency room with a 2-day history of dyspnea. Two days before admission, the patient suffered from progressive exertional dyspnea, accompanied with cough with mild tiny blood-like material in the sputum, and a low-grade fever. Physical examination revealed body temperature of 36.6ºC, pulse rate of 111 per minute, respiratory rate of 23 per minute, blood pressure of 157/88 mmHg, and breathing sounds with crackles in the bilateral lower lung fields. The chest radiography showed increased alveolar infiltration in the bilateral lung fields (Figure A). Pneumonia

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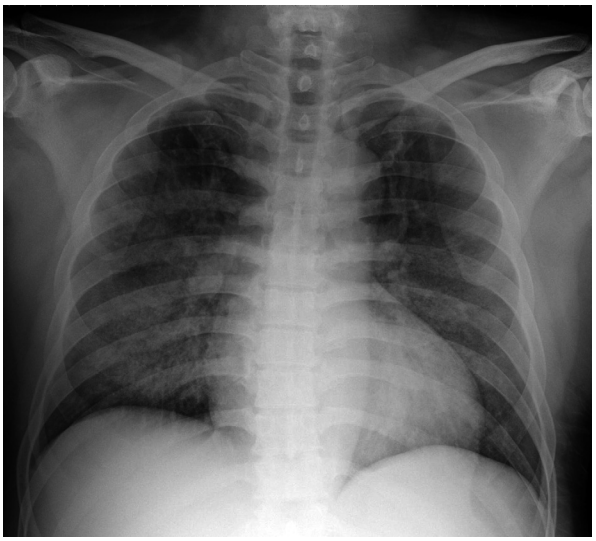

Fig. A. Chest film showing bilateral alveolar infiltration

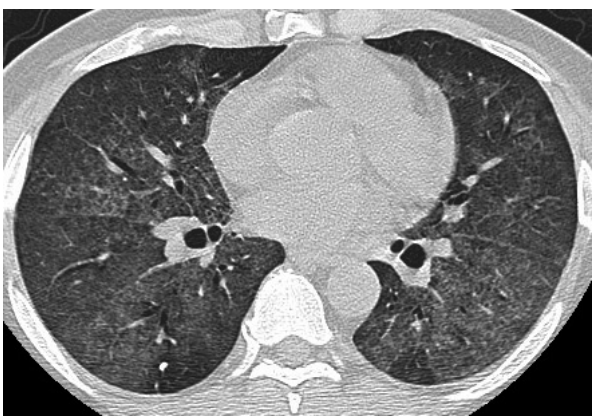

Fig. B. Chest CT scan revealed a ground-glass pattern in the bilateral lung fields

was suspected. Hemolytic anemia was diagnosed based on serum data that revealed a red blood cell count of 3.08×10^6/ul, hemoglobin 8.3 gm/dl, total bilirubin 2.12 mg/dl, a reticulocyte count of 7.6%, lactic dehydrogenase of 466 IU/L, and haptoglobin of less than 5.83 mg/dl. However, Coomb's tests were negative.

The patient had been diagnosed with IDA 3 years earlier without knowing the definite etiology. Tracing back his history, there were abnormal findings in his previous chest radiography, and mildly increasing bilateral alveolar infiltrations in the hilar area, but no attention was paid to it at the time.

During hospitalization, *Mycoplasma pneumoniae* infection was suspected due to the atypical pneumonia symptoms with hemolytic anemia, but the low-grade fever and persistent infiltration in the chest radiography were refractory to moxifloxacin treatment. *Mycoplasma* antibody, *Chlamydiae* antibody and cold agglutinin were also negative. High-resolution computed tomography (HRCT) of the chest revealed a ground-glass pattern in the bilateral lung fields (Figure B). The echocardiography demonstrated a preserved systolic function (left ventricular ejection fraction was 60%) without valvular disease or pulmonary hypertension. In the microscopic examination, the transbronchial biopsy yielded abundant hemosiderin-laden macrophages, indicating an old hemorrhage (Figure C). Alveolar hemorrhage syndrome surveys, including anti-nuclear antibody, rheumatic factor, complements, perinuclear-staining antineutrophil cytoplasmic antibodies, cytoplasmic-

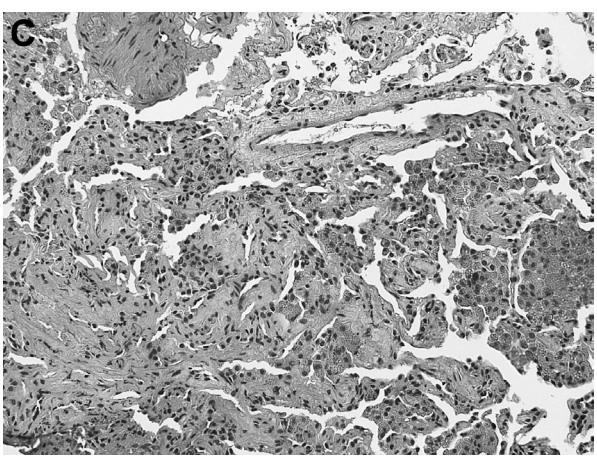

Fig. C. Transbronchial biopsy yielded abundant hemosiderin-laden macrophages, indicating an old hemorrhage

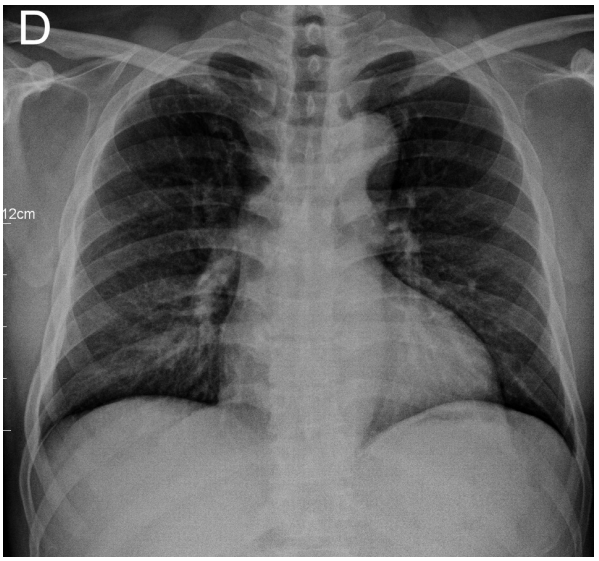

Fig. D. Chest film showed resolution of bilateral alveolar infiltration after 1 week of steroid treatment

staining antineutrophil cytoplasmic antibodies and anti-glomerular basement membrane antibody, were all within normal limits. Under the impression of IPH, the patient was treated with intravenous prednisolone 25 mg every 8 hours. Seven days later, the patient recovered to a level of normal activity and was discharged with oral prednisolone 20 mg daily. A follow-up chest radiograph 1 week after steroid therapy revealed resolution of the bilateral ground-glass opacity (Figure D), and 1 month later, a pulmonary function test disclosed mild restrictive ventilatory defects (FEV_1: 2.66 liter (80.7%), FVC: 3 liter (75%), FEV_1/FVC: 88.61%) and a moderate reduction in diffusing capacity for carbon monoxide (DLCO: 58.3%, reference: 9.32 mmol/min/kPa).

Discussion

IPH is a rare cause of diffuse alveolar hemorrhage and its etiology is unknown [1]. The clinical presentations of IPH include dyspnea, hemoptysis, and even fatigue due to IDA [2]. Chest radiography reveals ill-defined opacities with an alveolar pattern in the unilateral or bilateral middle and lower lung fields. Pulmonary function tests show a restrictive ventilatory pattern. The diffusing capacity for carbon monoxide is elevated in the acute phase, but is normal or low during the chronic phase [1]. The diagnosis of IPH is dependent on a combination of clinical symptoms, imaging studies, and lung biopsy, after excluding coagulopathy, thrombocytopenia, hepatic dysfunction, or glomerulonephritis [1-3]. Although some patients have been observed to have spontaneous remission [6], corticosteroids may be a mainstay treatment worth considering [4-5]. On the other hand, some patients may need immunosuppressive agents such as azathioprine [7].

The *Mycoplasma pneumoniae* infection in this patient was initially suspected due to hemolytic anemia [6] and ill-defined opacities in the chest radiography. However, the poor response to antibiotics and the lower titer of mycoplasma antibody militated against the diagnosis of *Mycoplasma pneumoniae* infection. Later, IPH was diagnosed based on imaging studies and lung biopsy; other etiologies of alveolar hemorrhage syndrome were also excluded by serological exams.

The differential diagnoses of diffuse ground-glass opacities on HRCT include pulmonary edema, hemorrhage, *Pneumocystis jirovecii* pneumonia, *Cytomegalovirus* pneumonia, alveolar proteinosis, and rare eosinophilic pneumonia, acute lung rejection, collagen vascular disease, and desquamative interstitial pneumonitis [9]. Focal pulmonary ground-glass opacities may include adenocarcinoma, bronchioloalveolar carcinoma, and atypical adenomatous hyperplasia [10]. In this patient's case, the ini-

tial poor response to antibiotics impelled us to consider HRCT. With imaging results such as those of our patient, pulmonary edema, atypical pneumonia, and hemorrhage should be considered due to the interstitial pattern or lack of an immunocompromised history. Then, bronchoscopy should be performed for further confirmation.

We have reported a case of IPH that mimicked hemolytic anemia. In patients with ill-defined opacities on chest radiography and suspected hemolytic anemia, IPH must be considered as 1 of the differential diagnoses.

References

1. Ioachimescu OC, Sieber S, Kotch A. Idiopathic pulmonary haemosiderosis revisited. Eur Respir J 2004; 24: 162-70.
2. Milman N, Pedersen FM. Idiopathic pulmonary haemosiderosis. Epidemiology, pathogenic aspects and diagnosis. Respir Med 1998; 92: 902-7.
3. Corte TJ, Tattersall S. Iron deficiency anaemia: a presentation of idiopathic pulmonary haemosiderosis. Intern Med J 2006; 36: 207-9.
4. Kabra SK, Bhargava S, Lodha R, *et al*. Idiopathic pulmonary hemosiderosis: clinical profile and follow up of 26 children. Indian Pediatr 2007; 44 :333-8.
5. Kiper N, Gocmen A, Ozcelik U, *et al*. Long-term clinical course of patients with idiopathic pulmonary hemosiderosis (1979-1994): prolonged survival with low-dose corticosteroid therapy. Pediatr Pulmonol 1999; 27: 180-4.
6. Dolan CJ, Jr., Srodes CH, Duffy FD. Idiopathic pulmonary hemosiderosis. Electron microscopic, immunofluorescent, and iron kinetic studies. Chest 1975; 68: 577-80.
7. Rossi GA, Balzano E, Battistini E, *et al*. Long-term prednisone and azathioprine treatment of a patient with idiopathic pulmonary hemosiderosis. Pediatr Pulmonol 1992; 13(3): 176.
8. Mansel JK, Rosenow EC, 3rd, Smith TF, *et al*. Mycoplasma pneumoniae pneumonia. Chest 1989; 95: 639-46.
9. Collins J, Stern EJ. Ground-glass opacity at CT: The ABCs. AJA 1997; 169: 355-67.
10. Infante M, Lutman RF, Imparato S, *et al*. Differential diagnosis and management of focal ground-glass opacities. Eur Respir J 2009; 33: 821-7.

自發性肺血鐵質沉積症：病例報告

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自發性肺血鐵質沉積症（idiopathic pulmonary hemosiderosis）發生的原因和病理機轉不明。自發性肺血鐵質沉積症的臨床表現以呼吸困難、貧血、咳血。胸部 X 光片以瀰漫性毛玻璃狀陰影表現。我們這裡提出一個病人以漸進式呼吸困難、反覆性咳血、溶血性貧血及肺炎的胸部 X 光表現，我們排除了自體免疫、血液疾病、腎臟疾病及肺炎感染，後經由支氣管鏡取樣病灶部位的病理切片顯示大量血鐵質堆積的巨嗜細胞，後來使用了靜脈注射的類固醇取得良好的療效。*(胸腔醫學 **2012; 27: 294-298**)*

關鍵詞：自發性肺血鐵質沉積症，貧血，咳血，肺炎

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Leiomyosarcoma of the Mediastinum: An Extremely Rare Case

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Malignant smooth muscle tumors usually develop in the uterus and gastrointestinal tract due to the abundance of smooth muscle. They rarely develop in the soft tissue of the mediastinum. We report a 44-year-old male with neurofibromatosis type I who suffered from leiomyosarcoma extending between the left supraclavicle and the left-side middle mediastinum. The patient received debulking surgery to salvage the compromised airway and disabled upper limb. He then refused adjuvant therapy and expired 7 months postoperatively due to recurrence. To our knowledge, this type of case has never been reported in the literature. ***(Thorac Med 2012; 27: 299-304)***

Key words: mediastinum, supraclavicle, leiomyosarcoma

Introduction

Malignant smooth muscle tumors usually develop in the uterus and gastrointestinal tract due to the abundance of smooth muscle [1]. Most of the tumors that occur in the thoracic cavity arise from organs that contain smooth muscle, such as the atrium, esophagus, and great vessels [2-7]. The appearance of these malignant tumors in the soft tissue of the mediastinum is extremely rare [8-12]. There have been no reports of malignant smooth muscle tumor extending between the supraclavicle and middle mediastinum with neurofibromatosis type I. Herein, we report the case of a patient who received debulking surgery, but finally expired due to recurrence.

Case Presentation

A 44-year-old man who was diagnosed with neurofibromatosis type I in his early 3rd decade was admitted to our hospital with the chief complaint of dyspnea, chest pain and a left supraclavicular mass for several months. On admission, physical examination revealed decreased left-side upper chest breathing sounds, a left-side supraclavicular 5 × 5 cm, non-movable, non-tender, hard tumor, and limited left upper limb movement. Chest radiography showed a large left middle mediastinal mass (Figure 1). A reconstructed computed tomography (CT) scan

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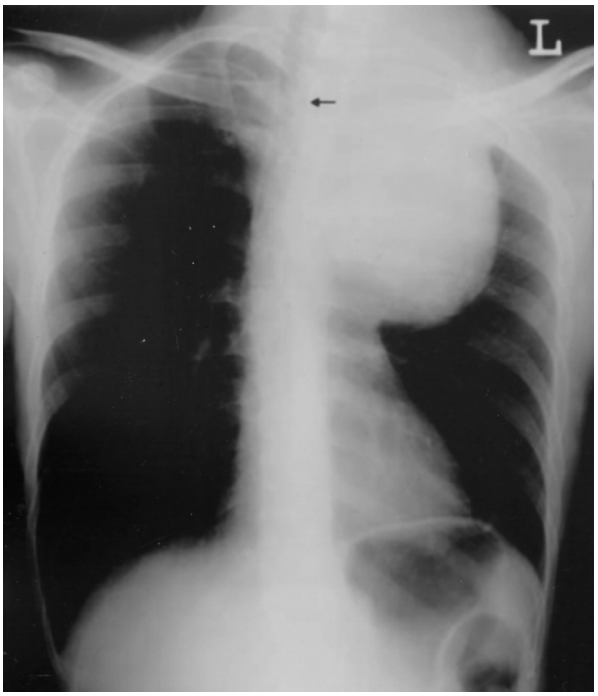

Fig. 1. A large left-side middle mediastinal mass with tracheal deviation and external compression (black arrow)

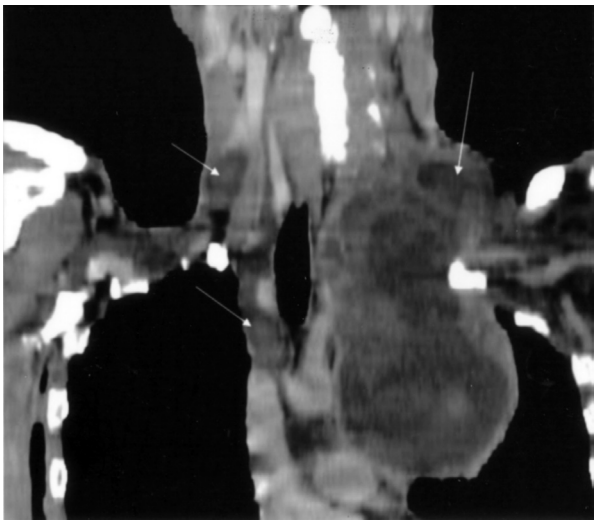

Fig. 2. A huge heterogeneous tumor extends between the left supraclavicular and left-side middle mediastinum, and 2 small tumors in the right-side neck and paratracheal region (white arrow)

showed a huge heterogeneous tumor extending between the left supraclavicle and the left-side middle mediastinum. Tumor was also found in the right-side neck and right paratracheal region (Figure 2). After counseling, the family decided on surgery because of the impending respiratory failure and impaired left upper limb function. Median sternotomy and left-side oblique cervical incision were performed. A firm encapsulated mass filling the entire left-side middle mediastinum and left supraclavicle was noted. The left upper lobe was passively compressed, but there was no invasion of the lung parenchyma. The tumor contained jelly-like material. There were severe adhesions to the soft tissue around the tumor, and especially, the left brachial plexus and left subclavian vessels were enveloped. Hence, the tumor had to be debulked in order to preserve the left upper limb. No obvious origin of the neoplasm could be identified during operation.

After the surgery, the patient recovered well. His symptoms improved and he was discharged 10 days later. The pathology revealed unclassified sarcoma. The immunohistochemical studies of vimentin, smooth muscle actin and sarcomeric actin showed positive staining. On the other hand, S-100 and desmin revealed negative results (Figure 3). Based on the immunohistochemical studies, leiomyosarcoma was the most likely diagnosis. The tumor unfortunately regained its preoperative size just 3 months after discharge (Figure 4). The patient was quite depressed and refused all suggested further management, including chemotherapy and radiotherapy. He died 4 months later.

Discussion

Less than 10% of adult primary mediastinal tumors were mesenchymal tumors, and their prevalence and malignant potential seemed to

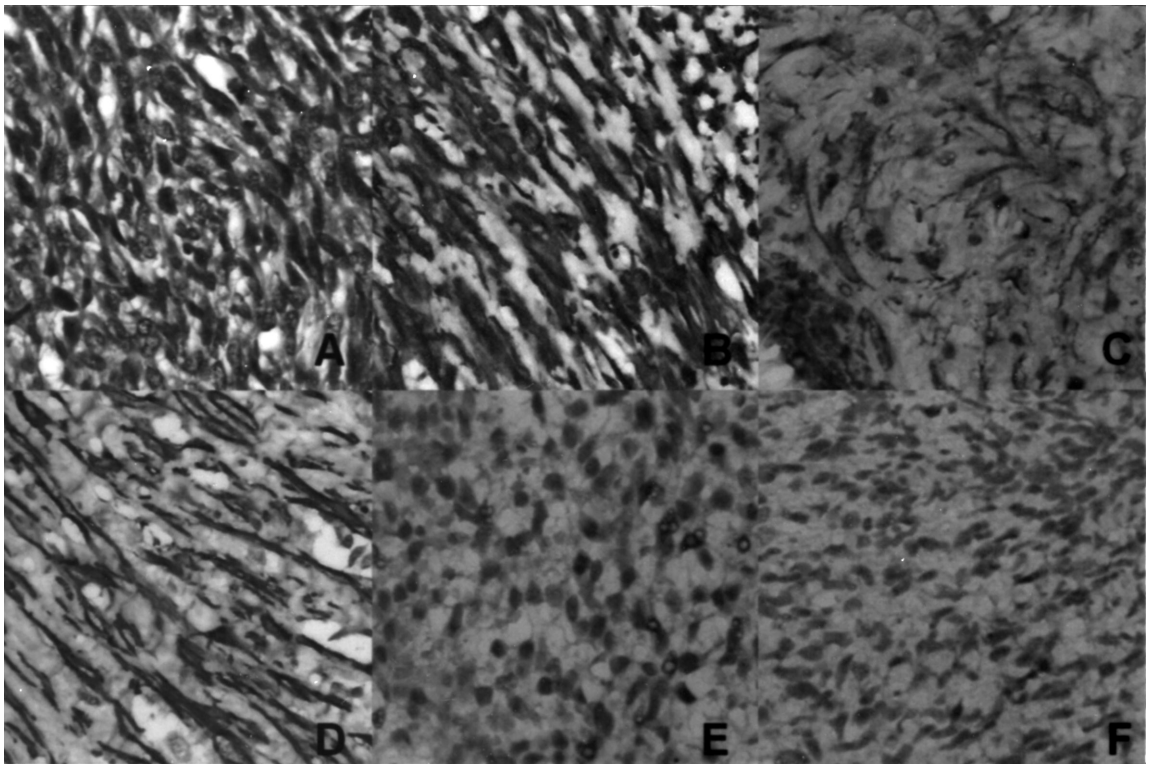

Fig. 3. (A) The hematoxylin and eosin stain revealed unclassified sarcoma. (B) vimentin, (C) smooth muscle actin and (D) sarcomeric actin stains showed a positive result. (E) S-100 and (F) desmin stains demonstrated a negative result. (All pictures are high-power field, 400x)

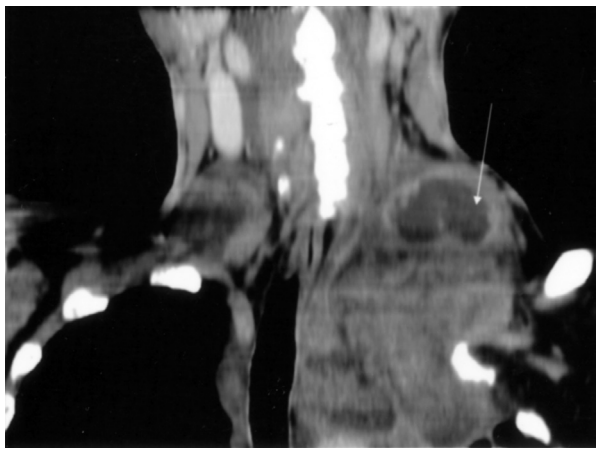

Fig. 4. The tumor regained its preoperative size just 3 months after discharge (white arrow)

be greater in children [13]. Leiomyosarcomas constitute 8% of all malignant mesenchymal lesions, and most of them are located at the uterus, gastrointestinal tract, extremities, and retroperitoneum [14]; leiomyosarcoma at the mediastinum is rare. The origin of these tumors within the mediastinum remains a subject of speculation. They may arise from small vessels within the mediastinum, heterotopic smooth-muscle cells derived from displaced splanchnic mesoderm or parasitic tumors of the esophagus [13]. Leiomyosarcoma arising within the soft tissues of the mediastinum unassociated with neighboring structures is extremely rare [12]. In our case, a 44-year-old man with neurofibromatosis type I had an encapsulated mass with severe adhesions, but there was no obvious relationship between the soft tissue and smooth muscle. Therefore, the tumor may have arisen from soft tissue of the mediastinum unassoci-

ated with smooth muscle. Pathology revealed unclassified sarcoma and the final diagnosis had to rely on immunohistochemistry alone. The immunohistochemical studies, which were reviewed by a pathologist, revealed leiomyosarcoma as the most likely diagnosis [12].

Treatment options for leiomyosarcoma include surgery, chemotherapy and radiotherapy, either alone or in combination. Complete resection is the optimal treatment [15-16]. The surgical method depends on the location and size of the tumor. We chose median sternotomy and a left-side oblique cervical incision because the tumor was located at the left-side middle mediastinum extending to the left supraclavicle. Adjuvant radiotherapy was advised but refused by patient. Adjuvant chemotherapy was not suggested by some physicians due to the toxicity and lack of significant benefit [17]. Several factors such as location, tumor size and resection margin affect local control and metastatic recurrence after operation [15]. The tumor in this case could not be completely excised, as assessed preoperatively, based on the opinion of the neurosurgeon and cardiovascular surgeon. The surgical indication was mainly for the release of compression of the airway and the neurovascular insult. Based on the initial family counseling, CT-guided biopsy for pathologic diagnosis and neoadjuvant radiotherapy could be arranged if the patient agreed. Airway stent implantation should be considered for relief of the compromised airway. Then, surgical intervention would depend on the response to radiotherapy.

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References

1. Ranchod M, Kempson RL. Smooth muscle tumors of the gastrointestinal tract and retroperitoneum. Cancer (Phila) 1977; 39: 255-62.
2. Fabricius AM, Autschbach R, Lochhaas L, *et al*. Primary left atrial leiomyosarcoma. Thorac Cardiovasc Surg 2000; 48: 306-8.
3. Mendes Almeida JM. Leiomyosarcoma of the esophagus. Chest 1982; 81: 761-3.
4. Weiss KS, Zidar BL, Wang S, *et al*. Radiation induced leiomyosarcoma of the great vessels presenting as superior vena cava syndrome. Cancer (Phila) 1987; 60: 1238-42.
5. Davis GL, Bergmann M, O'Kane H. Leiomyosarcoma of the superior vena cava: a first case with resection. Thorac Cardiovasc Surg 1976; 72: 408-12.
6. Sunderrajan EV, Luger AM, Rosenholtz MJ, *et al*. Leiomyosarcoma in the mediastinum presenting as superior vena cava syndrome. Cancer (Phila) 1984; 53: 2553-6.
7. Eng J, Murday AJ. Leiomyosarcoma of the pulmonary artery. Ann Thorac Surg 1992; 53: 905-6.
8. Herlitzka AJ, Gale JW. Tumors and cysts of the mediastinum: survey of one hundred seventy-four mediastinal tumors treated surgically during the past eighteen years at the University of Wisconsin Hospitals. AMA Arch Surg 1958; 76(5): 697-706.
9. Gupta S, Jindal SK, Bashisht R, *et al*. Leiomyosarcoma of the mediastinum. Eur J Respir Dis 1983; 64: 69-71.
10. Rasaretnam R, Panabokke RG. Leiomyosarcoma of the mediastinum. Brit J Dis Chest 1975; 69: 63-9.
11. Lincoln JCR. Leiomyosarcoma of the anterior mediastinum. Thorax 1965; 20: 362-4.
12. Moran CA, Suster S, Perino G, *et al*. Malignant smooth muscle tumors presenting as mediastinal soft tissue masses: a clinicopathologic study of 10 cases. Cancer (Phila) 1994; 74: 2251-60.
13. Macchiarini P, Ostertag H. Uncommon primary mediastinal tumours. Lancet Oncol 2004; 5: 107-18.
14. Kransdorf MJ. Malignant soft-tissue tumors in a large referral population: distribution of diagnosis by age, sex and location. AJR 1995; 164: 129-34.
15. Zagars GK, Ballo MT, Pisters PWT, *et al*. Prognostic

factors for patients with localized soft-tissue sarcoma treated with conservative surgery and radiation therapy: an analysis of 1225 patients. Cancer 2003; 97: 2530-43.
16. Zagars GK, Ballo MT, Pisters PWT, *et al*. Surgical margins and resection in the management of patients with soft tissue sarcoma using conservative surgery and radiation therapy. Cancer 2003; 97: 2544-53.
17. Wesolowski R, Budd GT. Use of chemotherapy for patients with bone and soft-tissue sarcomas. Cleve Clin J Med 2010; 77(Suppl 1): S23-6.

縱膈腔平滑肌惡性肉瘤：極罕見之病例

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惡性平滑肌腫瘤大部分發生在子宮及消化道因其含有大量的平滑肌。在縱膈腔的軟組織中，這些腫瘤是相當罕見的。在此，我們報導了一個 44 歲男性，本身患有第一型神經纖維瘤，因呼吸喘、胸痛及左鎖骨上硬塊就診。經檢查後，診斷出延伸於縱膈腔及鎖骨上的平滑肌惡性肉瘤。因呼吸窘迫及左上肢功能受損，病人接受減瘤手術，術後病人拒絕化學治療及放射線治療。不幸地，三個月後腫瘤復發，七個月後病人死亡。*(胸腔醫學 **2012; 27: 299-304**)*

關鍵詞：縱膈腔，鎖骨上，平滑肌惡性肉瘤

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Transformation of Non-Small Cell Lung Cancer to Combined Squamous Cell and Small Cell Carcinoma after Chemotherapy: Case Report

Yung-Hung Luo*, Yuh-Min Chen*,**

About 5% of small-cell lung cancer (SCLC) may be combined with non-small cell components. The estimated incidence of SCLC combined with squamous cell and/or adenocarcinoma was probably less than 1% to 2% of all SCLC cases. We presented a case with transformation of non-small cell lung cancer to combined squamous cell and small cell carcinoma after chemotherapy. SCLC occurs almost exclusively in smokers. To our knowledge, this is the 2nd reported case of combined small and squamous cell carcinoma occurring in a patient without a smoking history. A histological change in lung cancer after treatment is considered unusual. Tumor heterogeneity may be found at initial diagnosis, may occur spontaneously over time or may be elicited by chemotherapy and/or radiotherapy. This emphasizes the importance of histological confirmation, even at molecular levels, such as epidermal growth factor receptor *(EGFR)* mutation status, in order to make appropriate plans for lung cancer therapy. ***(Thorac Med 2012; 27: 305-310)***

Key words: combined squamous cell and small cell carcinoma, non-small cell lung cancer, transformation

Introduction

Combined small cell lung cancer (SCLC) is defined by the World Health organization (WHO) as small cell carcinoma combined with additional components consisting of any non-small cell histological type, including adenocarcinoma, squamous cell carcinoma (SCC), and large cell neuroendocrine carcinoma [1]. About 5% of SCLC may also be combined with non-small cell components, with large cell carcinoma as the most common, followed by adenocarcinoma and SCC [2]. The estimated incidence of SCLC combined with squamous cell and/or adenocarcinoma probably represents less than 1% to 2% of all SCLC cases [3].

We present a case with transformation of non-small cell lung cancer (NSCLC) to combined squamous cell and small cell carcinoma after chemotherapy. A histological change in lung cancer after treatment is considered unusual. Tumor heterogeneity may be found at

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initial diagnosis, may occur spontaneously over time or may be elicited by chemotherapy and/or radiotherapy. In this report, we discuss the influence of tumor heterogeneity on diagnosis and management.

Case Report

A 47-year-old previously healthy woman suffered from cough with whitish sputum for 2 weeks. She did not have a smoking history. She visited a community hospital where chest X-ray revealed a mass in the right lower lung field. She was then referred to Taipei Veterans General Hospital, and NSCLC in the right lower lobe (RLL) of the lung (Figure 1) was diagnosed by chest CT-guided biopsy. The pathology report revealed that the tumor cells (Figure 2) were diffusely immunoreactive to p63 (Figure 3) and negative for TTF-1 and CK20. Scattered CK7 positive carcinoma cells were identified (Figure 4). Based on the morphology and the immunoprofile, the differential diagnosis of the tumor included poorly differentiated SCC and large cell carcinoma. After serial examinations, clinical staging revealed cT3N2M0 (AJCC 7th edition), stage IIIA. A thoracic surgeon was consulted for the possibility of surgical intervention, and neo-adjuvant chemotherapy was suggested. The patient received 2 cycles of neo-adjuvant chemotherapy with paclitaxel and cisplatin, and then RLL lobectomy and radical lymph node dissection were performed. After surgery, the pathology report showed combined SCC and small cell carcinoma in the right

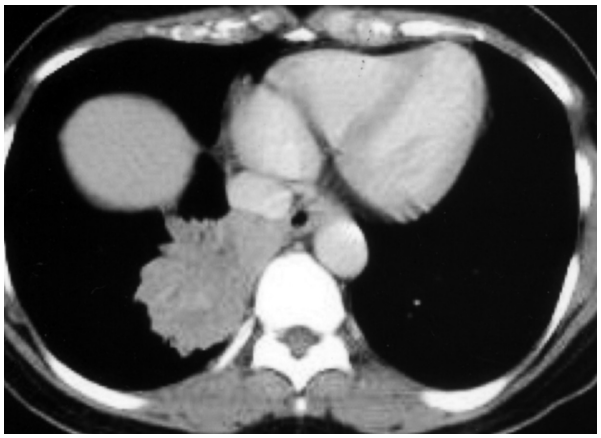

Fig. 1. A mass in the right lower lobe of the lung

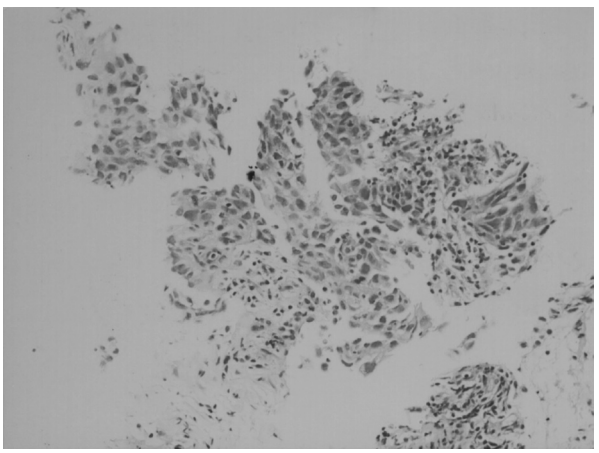

Fig. 2. Poorly differentiated infiltrating carcinoma cells were found in the CT-guided biopsy specimen (hematoxylin and eosin; ×20). No small cell carcinoma component was seen.

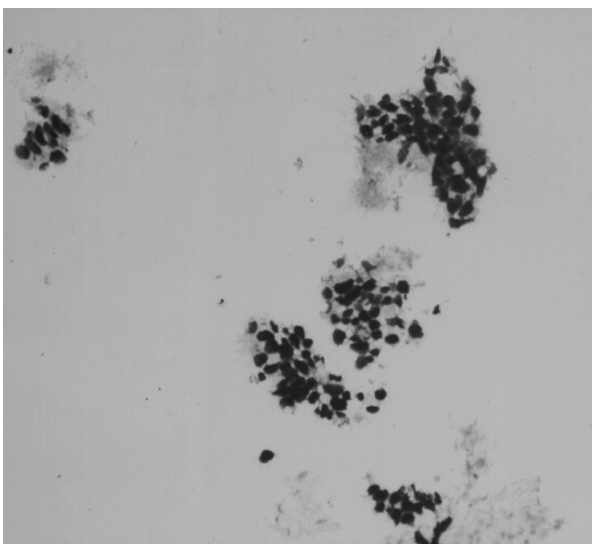

Fig. 3. Immunohistochemical (IHC) studies revealed that the tumor cells were diffusely immunoreactive to p63 (IHC staining; ×20).

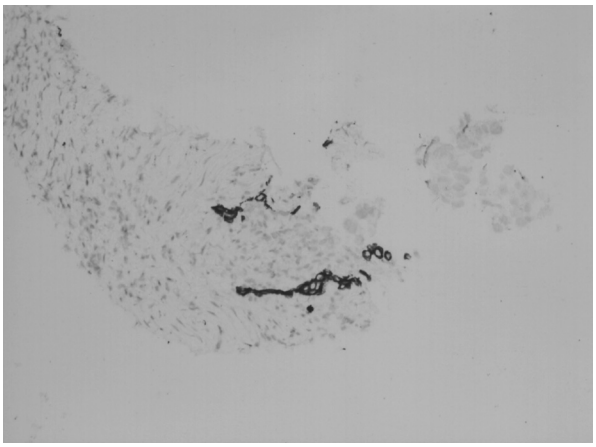

Fig. 4. Immunohistochemical studies revealed that scattered CK7 positive carcinoma cells were found (IHC staining; ×20).

lower lobe, ypT2aN0Mx, stage IB (Figure 5). Thereafter, she received 2 cycles of adjuvant chemotherapy with paclitaxel, etoposide, and cisplatin, and was regularly followed up at our hospital.

Discussion

SCLC differs from other types of NSCLC due to its high growth fraction, rapid doubling time, and early metastatic dissemination. It represents about 15-25% of all lung cancers and occurs almost exclusively in smokers [4]. About 5% of SCLC may also be combined with non-small cell components, with large cell carcinoma as the most common, followed by adenocarcinoma and SCC [2]. Although it is difficult to accurately estimate the incidence of SCLC combined with squamous cell and/or adenocarcinoma, such tumors probably account for less than 1% to 2% of SCLC [3].

This case presented 2 unusual clinical manifestations. First, the patient had never smoked; SCLC occurs almost exclusively in smokers [5]. To the best of our knowledge, this is the 2nd

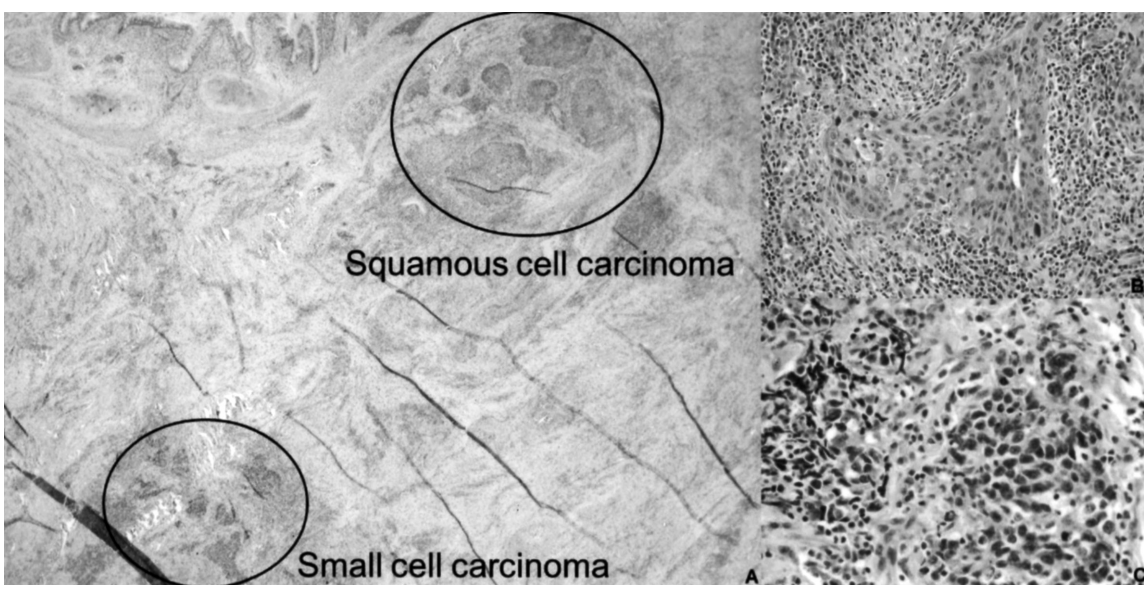

Fig. 5. Squamous cell carcinoma and small cell carcinoma were found simultaneously in the surgical specimen under the optical microscope. (hematoxylin and eosin; ×2) (A) Squamous cell carcinoma (hematoxylin and eosin; ×20) (B) in the right upper site is distinguished from small cell carcinoma (hematoxylin and eosin; ×40) (C) by polygonal cells with prominent nucleoli, vesicular nuclear chromatin, intercellular bridges, and abundant cytoplasm with keratinization in the center of the tumor cell nest. The small cell carcinoma (C) consisted of small, round, ovoid cells with finely granular nuclear chromatin, absent or inconspicuous nucleoli, and scant cytoplasm. Mitosis, crush artifact and necrosis were seen.

reported case of combined small cell and SCC occurring in a patient without a smoking history [6]. Second, transformation of NSCLC to combined squamous cell and small cell carcinoma after chemotherapy is rarely found in lung cancer patients. The limited number of biopsy specimens may not show tumor heterogeneity and the possibility of a histological change. However, one study suggested that the incidence of combined histology (2%, 9 cases in 429 patients) diagnosed with a limited number of biopsy specimens from fiberbronchoscopy or lymph node biopsy (89%, 8 cases) is consistent with previous reports [7]. Therefore, a limited number of specimens are capable of diagnosing combined SCLC and NSCLC. The biphasic components of a neoplasm could represent a divergent evolution from a common cancer stem cell. On the other hand, one component could also represent an outgrowth from the other, due to random acquisition of additional genetic or epigenetic alterations spontaneously over time or in response to treatment, such as chemotherapy or radiotherapy. The histological change in combined SCLC and NSCLC during tumor recurrence or progression has also been reported in a study. This study included 9 combined SCLC and NSCLC cases from among 429 SCLC patients, and reported that 6 (75%) of 8 patients with relapsed or recurrent tumor confirmed by repeated biopsy or autopsy had a histological change [7]. Another study reported that 5 (14%) *EGFR*-mutant adenocarcinomas of the lung transformed into SCLC and were sensitive to standard SCLC therapy [8]. These results emphasize the need to repeat biopsy or surgically resect the tumor when possible. They also emphasize the importance of histological confirmation of recurrences in order to make appropriate plans for salvage therapy. The possible reasons for histological change also include that unrelated separate primary neoplasms have occurred at the same location [1].

Temporal alterations in the histology of lung cancer may have important clinical and therapeutic implications. Combined SCLC and NSCLC reveal clinical, histological and prognostic characteristics that are more similar to pure SCLC than NSCLC. It presents more aggressive clinico-pathologic behavior and reduced survival, compared with a single-histology population of resected lung tumors [9]. Surgical resection in patients with combined SCLC and NSCLC postoperative stage I yields a cumulative 5-year survival rate of 31%, and for those with stage II and III disease, there have been no survivors at 5 years. Thus, surgery can offer a long-term disease-free interval or may even be curative in patients with stage I combined SCLC and NSCLC [10].

Conclusion

Transformation of NSCLC to combined squamous cell and small cell carcinoma after chemotherapy reveals an unusual histological change among lung cancer patients. This finding underscores the importance of repeated biopsy or surgical resection of the tumor when the clinical condition indicates. It also emphasizes the importance of histological confirmation of tumor recurrence or progression in order to make appropriate plans for further treatment. Surgical resection in stage I combined SCLC and NSCLC can offer a long-term disease-free interval or may even be curative, and (neo-) adjuvant chemotherapy may reduce the incidence of distant metastases before or after surgical resection [10].

References

1. Wagner PL, Kitabayashi N, Chen YT, *et al*. Combined small cell lung carcinomas: genotypic and immunophenotypic analysis of the separate morphologic components. Am J Clin Pathol 2009; 131: 376-82.
2. Nicholson SA, Beasley MB, Brambilla E, *et al*. Small cell lung carcinoma (SCLC): a clinicopathologic study of 100 cases with surgical specimens. Am J Surg Pathol 2002 Sep; 26(9): 1184-97.
3. Matthews MJ, Gazdar AF. Changing histology in malignant tumors: Diagnostic and therapeutic significance. Eur J Cancer Clin Oncol 1985; 21: 549-52.
4. Planchard D, Le Péchoux C. Small cell lung cancer: new clinical recommendations and current status of biomarker assessment. Eur J Cancer 2011 Sep; 47 Suppl 3: S272-83. Review.
5. Antony GK, Bertino E, Franklin M, *et al*. Small cell lung cancer in never smokers: Report of two cases. J Thorac Oncol 2010; 5: 747-8.
6. Lee SY, Shim JJ, Kang KH. Curious case of combined small- and squamous cell carcinoma. J Clin Oncol 2011 Mar; 29(8): e186-7.
7. Mangum MD, Greco FA, Hainsworth JD, *et al*, Combined small-cell and non-small-cell lung cancer. J Clin Oncol 1989 May; 7(5): 607-12.
8. Sequist LV, Waltman BA, Dias-Santagata D, *et al*. Genotypic and histological evolution of lung cancers acquiring resistance to EGFR inhibitors, Sci Transl Med 2011 March 23; 3(75): 75ra26.
9. Ruffinia E, Renaa O, Oliaroa A, *et al*. Lung tumors with mixed histologic pattern. clinico-pathologic characteristics and prognostic significance. Eur J Cardiothorac Surg 2002; 22(5): 701-7.
10. Hage R, Elbers JRJ, Rivière AB, *et al*. Surgery for combined type small cell lung carcinoma. Thorax 1998; 53: 450-3.

非小細胞肺癌經化學治療後轉變爲聯合型鱗狀上皮細胞與小細胞癌：病例報告

羅永鴻 * 陳育民 *,**

大約百分之五的小細胞肺癌會同時具有非小細胞癌的成分。據估計聯合型小細胞肺癌與鱗狀上皮細胞癌或腺癌的發生率約占所有小細胞肺癌的百分之一至二以下。我們報告一例非小細胞肺癌經化學治療後轉變為聯合型鱗狀上皮細胞與小細胞癌。小細胞肺癌幾乎只發生在吸菸的人身上。據我們所知，這是第二個被報導的發生在不抽菸患者身上的聯合型鱗狀上皮細胞與小細胞癌。肺癌經治療後發生組織學形態上的變化被認為是不常見的狀況。腫瘤的異質性可能在最初的診斷時就發現，也可能隨著時間的推移而自然發生，或者是被化學治療或放射線治療而誘發。這種現象更加強調了在組織學、及分子檢驗方面，例如上皮生長因子受體基因突變狀態方面作確定診斷的重要性，如此才能對肺癌的治療作出完善之計畫。*(胸腔醫學 **2012; 27: 305-310**)*

關鍵詞：聯合型鱗狀上皮細胞與小細胞癌，非小細胞肺癌，轉變

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Successful Management of Probable Imatinib-Related Pneumonitis in a Gastrointestinal Stromal Tumor Patient without Discontinuing Imatinib – A Case Report and Literature Review

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Imatinib is a tyrosine kinase inhibitor that is used in the treatment of chronic myelogenous leukemia and gastrointestinal stromal tumor (GIST). Imatinib-related pneumonitis has been rarely reported, especially in GIST patients. A 53-year-old man with GIST treated with imatinib for 9 months was referred to our hospital because of progressive exertional dyspnea for 10 days. He developed hypoxemia and required oxygen supply. Chest radiograph and computed tomography revealed bilateral consolidations with peri-bronchovascular bundle distribution. Under the impression of probable drug-related pneumonitis, he was treated with systemic steroid. Although imatinib was not discontinued, his dyspnea improved gradually and he became independent of the oxygen supply within 10 days. The chest radiograph confirmed substantial improvement. To our knowledge, this is the first case of probable imatinib-induced pneumonitis in a GIST patient that was managed efficiently with steroid without discontinuing imatinib. This case demonstrates the possibility of successful management of drug-related pneumonitis without discontinuing the offending drug. ***(Thorac Med 2012; 27: 311-317)***

Key words: imatinib, pneumonitis, steroid

Introduction

Imatinib is commonly used in the treatment of chronic myelogenous leukemia (CML). It is also indicated for high-risk, unresectable, and/or metastatic gastrointestinal stromal tumor (GIST). Imatinib-related pneumonitis is a rare yet clinically significant complication that is potentially lethal if left unrecognized. Although discontinuation of imatinib is almost always suggested as the first step of management, the decision is usually difficult and challeng-

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ing since there are currently few alternative treatments for GIST. We report herein a case of probable imatinib-related pneumonitis in a GIST patient who was successfully treated without discontinuing imatinib.

Case Report

A 53-year-old man with a history of hypertension, seizure and hepatitis B had undergone partial surgical resection for a retroperitoneal tumor that was later pathologically confirmed to be a GIST in September 2010, and started taking imatinib as adjuvant therapy in a local hospital. His long-term medications also included amlodipine, diphenylhydantoin, and entecavir. In June, 2011, he suffered from fever, productive cough with white sputum and progressive dyspnea. Intravenous antibiotics were prescribed for 10 days, the fever resolved and the sputum amount decreased. However, because of persistent severe cough and dyspnea, he was referred to our hospital.

On admission to our hospital, he had severe dyspnea on exertion that limited his activity to the bedside. Due to hypoxemia, he required 4 L/min of oxygen supplement via nasal cannula all day long. Physical examination revealed inspiratory fine crackles in bilateral lung fields, but no signs of fluid overload, such as jugular vein engorgement or pedal edema, were observed. The chest radiograph (Figure 1) revealed bilateral diffuse non-segmental airspace consolidations. Laboratory examination showed leukocytosis (17,800/μL) with neutrophils predominant (85.2%), mildly elevated alanine aminotransferase level (41 IU/L), elevated C-reactive protein (CRP) level (11.39 mg/L), and normal renal function. Although no fever or chills was observed after the referral, antibiotic treatment

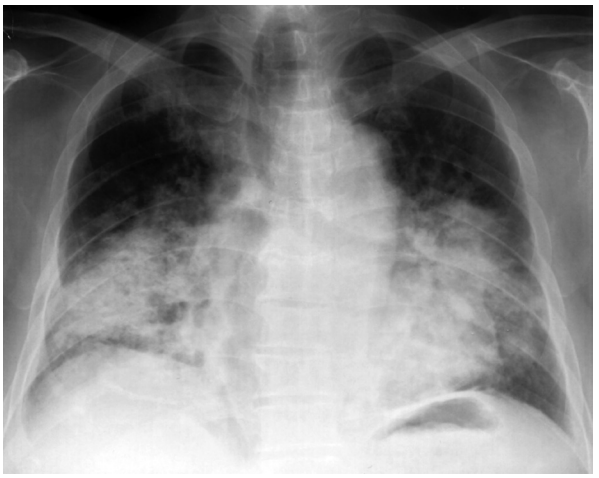

Fig. 1. Chest radiograph on initial presentation at the emergency department of our hospital revealed bilateral diffuse non-segmental airspace lesions.

was still given, since infection could not be totally excluded. After another course of antibiotic treatment in our hospital, the leukocyte count and CRP level both returned to normal range (7,900/μL and 3.15 mg/L, respectively). However, his symptoms and chest radiograph findings did not improve, and eosinophilia (1,225/μL) developed.

Further examination with computed tomography (Figure 2) revealed bilateral airspace consolidations with peri-bronchovascular bundle distribution. Imatinib-related pneumonitis was therefore suspected. Bronchoscopy showed no obvious endobronchial lesion. Culture of the bronchioloalveolar lavage fluid yielded no pathogen and pathological examination of the bronchoscopic biopsy specimens revealed fragments of lung tissue with mild chronic inflammation and slight fibrosis with focal anthracosis. Further examination with video-assisted thoracoscopic lung biopsy was suggested, but the patient refused.

Systemic steroid treatment with methylprednisolone 40 mg once daily was then initiated for

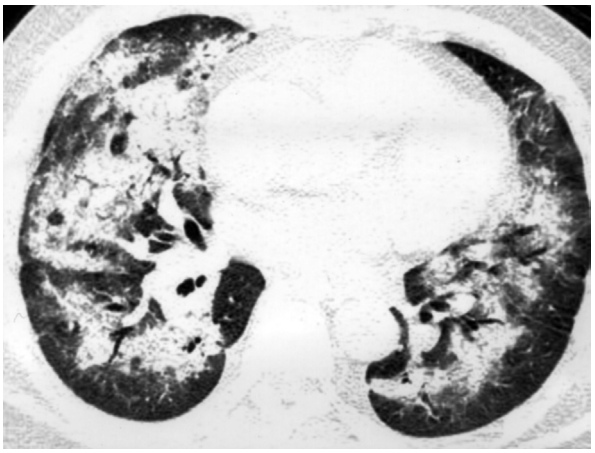

Fig. 2. Computed tomography of the chest revealed bilateral consolidations with peri-bronchovascular bundle distribution.

probable imatinib-related pneumonitis. Since limited adjuvant therapy for high-risk GIST was available, imatinib was not discontinued but was tapered from 400 mg per day to 300 mg per day, and watchful observation of the treatment response to the steroid was maintained instead. The patient experienced rapid improvement of his dyspnea within 3 days and was able to ambulate without oxygen supplement after 10 days of treatment. The chest radiograph confirmed the course of gradual improvement. After 12 days of steroid treatment in the hospital, he was discharged with oral prednisolone 10 mg 3 times daily. He was followed up in the clinic, and had an uneventful recovery with gradual resolution of the pulmonary lesions on the chest radiograph and gradual tapering of the dose of steroid.

Discussion

Chemotherapeutic agents are widely used to treat various malignant diseases and are also applied to some autoimmune or inflammatory diseases. New classes of drugs, including target therapy, are emerging and becoming available in clinical practice continuously. Pulmonary toxicity induced by chemotherapeutic agents has been recognized since the early 1960s. Since pulmonary toxicity associated with busulfan was first noticed, a lot of chemotherapeutic agents have also been reported to have a toxic effect on the lung, and drug-induced pneumonitis has become an important clinical issue recently. Although these adverse events caused by chemotherapeutic drugs have been well-described, standard diagnostic criteria or specific pathologic characteristics for the definite diagnosis are still lacking. The diagnosis is usually made with a complete history-taking, careful analysis of the clinical course, and, most importantly, exclusion of other diagnoses, such as infection, interstitial lung disease, and pulmonary involvement of the underlying malignancy.

Drug-induced pneumonitis may present with low-grade fever, non-productive cough, dyspnea, hypoxemia, and weight loss. Pulmonary infection should be considered if there are chills or copious sputum, which is less common in the presentation of drug-induced pneumonitis. The onset of drug-induced pneumonitis is uncertain and its evolution can be insidious or fulminant, with interstitial lung disease or diffuse alveolar damage. There is a poor correlation between the drugs and the related radiographic presentation, making it more difficult to confirm the diagnosis by chest radiograph.

Imatinib is a selective Bcr-Abl tyrosine kinase inhibitor that is used in the treatment of CML. It also potently inhibits c-kit, another tyrosine kinase receptor, and is therefore indicated as an adjuvant treatment following complete resection of GIST and for patients with unresectable and/or metastatic GIST. This “magic bullet” has now been approved for many other

diseases, such as Ph^+ acute lymphoblastic leukemia, myelodysplastic/myeloproliferative diseases (MDS/MPD) associated with *PDGFR* (platelet-derived growth factor receptor) gene rearrangements, aggressive systemic mastocytosis (ASM), hypereosinophilic syndrome (HES) and/or chronic eosinophilic leukemia (CEL), and unresectable, recurrent, and/or metastatic dermatofibrosarcoma protuberans (DFSP). Due to its ability to inhibit platelet-derived growth factor (PDGF) and stem cell factor (SCF), imatinib may alter the lung response to inflammation or infection and the subsequent cellular repair.

Imatinib is generally well-tolerated, and grades 3 and 4 non-hematological adverse effects have been reported in only 0.2% and 1.3% of cases with early-phase CML, respectively [1]. Significant respiratory adverse effects were first reported from Japan and raised the suspicion that imatinib may cause drug-related pneumonitis, similar to another tyrosine kinase inhibitor, gefitinib [1]. Since then, imatinib-related pneumonitis has been occasionally reported, but the case number is still limited. A trend toward an epidemiological difference in incidence between races, similar to gefitinib, has been observed, and may be attributed to complicated genetic mechanisms [2]. The high prevalence of baseline abnormal radiographic findings also implies the hypothesis that imatinib-related pneumonitis occurs more easily within previously damaged lung via its effects on the repairing processes of pulmonary tissue.

Previously reported imatinib-related pneumonitis occurred mostly in CML patients. Discontinuing imatinib or shifting to another novel target therapy drug with or without systemic steroid treatment is the mainstay of treatment for these patients [3-6].

To our knowledge, only 10 cases of imatinib-related pneumonitis developing in GIST patients have been reported in the medical literature to date, and the clinical courses, treatment approaches, and outcomes have varied (Table 1). The onset of imatinib-related pneumonitis may be within 10 days or delayed up to 282 days after the initiation of the drug. The development of respiratory symptoms and hypoxemia may be fulminant enough to cause acute respiratory failure and requires timely diagnosis and management [7]. These cases illustrated the complexities of the clinical presentation and management of imatinib-related pneumonitis in GIST patients.

Due to limited alternative treatment options for patients with unresectable and/or metastatic GIST, the decision to discontinue the offending drug, imatinib, remains a clinical dilemma. In all of the previously reported cases (Table 1), imatinib was discontinued for patients with pneumonitis, whereas imatinib was kept in our case. Our patient experienced substantial improvement of the pneumonitis with systemic steroid, even though imatinib was not discontinued. To our knowledge, this is the first case of probable imatinib-related pneumonitis in a GIST patient that was managed efficiently this way. This case demonstrates the possibility of successful management of probable imatinib-related pneumonitis without discontinuing the offending drug.

In conclusion, imatinib-related pneumonitis should be considered in any patient who develops unexplained fever, dyspnea, cough, or other pneumonitis symptoms during the treatment course of imatinib. Although cessation of imatinib was suggested in the literature as the mainstay of management for imatinib-related pneumonitis, systemic steroid treatment without

Table 1. Cases of imatinib-related pneumonitis in GIST patients*

Author, Year	Age	Sex	Radiologic Manifestation	Duration†	Treatment	Outcome
Our case, 2011	53 y/o	M	PBVB	9 months	No cessation of imatinib Steroid Antibiotics	Imatinib was maintained. Improved symptoms and imaging. GIST was under control.
Izumiyama, *et al*, 2009 [8]	Fifth decade	F		5 months	Cessation of imatinib	Improved symptoms and imaging. Imatinib was reintroduced with low-dose prednisolone. GIST was under control.
Izumiyama, *et al*, 2009 [8]	Fifth decade	F		5 months	Cessation of imatinib	Improved symptoms and imaging. Imatinib was reintroduced with low-dose prednisolone. GIST was under control.
Loong, *et al*, 2008 [2]	63 y/o	M	IP	1 month	Cessation of imatinib Steroid (high-dose)	Improved symptoms and imaging. Imatinib was substituted with sunitinib. GIST was controlled and was later complicated by an episode of intra-tumor hemorrhage, which was managed well by trans-arterial embolization.
Seki, *et al*, 2007 [9]	70 y/o	M	PBVB	3 months	Cessation of imatinib	The pulmonary findings were nearly improved after discontinuation of imatinib. Due to progression of GIST, imatinib was later re-administered with a transient interruption. The patient had progressive lung destruction, but died of progression of GIST without fatal pneumonitis 4 years later.
Iritani, *et al*, 2007 [10]	64 y/o	F	COP	3 months	Cessation of imatinib Steroid (oral prednisolone 30 mg/day)	Improved symptoms and imaging. Steroid was tapered gradually. GIST follow-up was not mentioned.
Ohnish, *et al*, 2006 [1]	82 y/o	M	HR	38 days	Cessation of imatinib Steroid (high-dose) Others	Recovered

Author, Year	Age	Sex	Radiologic Manifestation	Duration†	Treatment	Outcome
Ohnishi, *et al*, 2006 [1]	61 y/o	M	HR	14 days	Cessation of imatinib Steroid (high-dose)	Improved
Ohnishi, *et al*, 2006 [1]	66 y/o	M	IP	50 days	Cessation of imatinib Steroid (high-dose) Others	Not improved
Ohnishi, *et al*, 2006 [1]	57 y/o	M	IP	49 days	Cessation of imatinib Steroid (high-dose)	Recovered
Ma, *et al*, 2003 [11]	69 y/o	M	HR	2 weeks	Cessation of imatinib Steroid (prednisolone 100 mg/day for 12 days)	Imatinib was reintroduced but was stopped again due to recurrent pneumonitis. Later, imatinib was reintroduced again successfully with concurrent oral steroid for progressive GIST.

* Abbreviations: COP, cryptogenic-organizing pneumonia; GIST, gastrointestinal stromal tumor; HR, hypersensitivity reaction; ILD, interstitial lung disease; IP, interstitial pneumonia; PBVB, peri-bronchovascular bundle

† Duration of imatinib use before the development of pneumonitis

discontinuation of the offending drug may be an alternative management, especially for patients with limited substitute options for imatinib.

References

1. Ohnishi K, Sakai F, Kudoh S, *et al*. Twenty-seven cases of drug-induced interstitial lung disease associated with imatinib mesylate. Leukemia 2006; 20: 1162-4.
2. Loong HH, Yeo W. Imatinib-induced interstitial lung disease and sunitinib-associated intra-tumour haemorrhage. Hong Kong Med J 2008; 14: 495-8.
3. Rosado MF, Donna E, Ahn YS. Challenging problems in advanced malignancy: Case 3. Imatinib mesylate-induced interstitial pneumonitis. J Clin Oncol 2003; 21: 3171-3.
4. Yokoyama T, Miyazawa K, Kurakawa E, *et al*. Interstitial pneumonia induced by imatinib mesylate: pathologic study demonstrates alveolar destruction and fibrosis with eosinophilic infiltration. Leukemia 2004; 18: 645-6.
5. Isshiki I, Yamaguchi K, Okamoto S. Interstitial pneumonitis during imatinib therapy. Br J Haematol 2004; 125: 420.
6. Rajda J, Phatak PD. Reversible drug-induced interstitial pneumonitis following imatinib mesylate therapy. Am J Hematol 2005; 79: 80-1.
7. Lin JT, Yeh KT, Fang HY, *et al*. Fulminant, but reversible interstitial pneumonitis associated with imatinib mesylate. Leuk Lymphoma 2006; 47: 1693-5.
8. Izumiyama N, Noguchi K, Takahashi H, *et al*. Successful reintroduction of mesylate imatinib after pneumonitis in two patients with gastrointestinal stromal tumor (GIST). Nihon Kokyuki Gakkai Zasshi 2009; 47: 918-23. [In Japanese English abstract]
9. Seki N, Ito A, Watanabe K, *et al*. Irreversible imatinib-induced pneumonitis following long-term imatinib administration. Intern Med 2007; 46: 1941-2.
10. Iritani E, Kondo M, Kanemura T, *et al*. Drug-induced pneumonia that may have been caused by imatinib mesylate administered for gastrointestinal stromal tumor. Nihon Kokyuki Gakkai Zasshi 2007; 45: 577-81. [In Japanese English abstract]
11. Ma CX, Hobday TJ, Jett JR. Imatinib mesylate-induced interstitial pneumonitis. Mayo Clin Proc 2003; 78: 1578-9.

未停用 Imatinib 即成功治療一胃腸道間質腫瘤病患之疑似 Imatinib 相關肺炎——病例報告與文獻回顧

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Imatinib 是一種用於治療慢性骨髓性白血病及胃腸道間質腫瘤的酪胺酸激酶抑制劑。Imatinib 相關肺炎很少被報告，尤其在胃腸道間質腫瘤的病人中。我們報告一名五十三歲胃腸道間質腫瘤的男性病患因十天內漸進式之呼吸困難被轉至本院，他因低血氧的情形而需要氧氣治療。胸部 X 光及電腦斷層檢查顯示雙側沿支氣管血管束分布之肺實質化變化。在藥物相關肺炎的臆斷下，他接受了類固醇治療。雖然 imatinib 並未被停用，他呼吸困難的情形在類固醇治療下逐漸改善，在十天內即不需要氧氣供應，而胸部 X 光上也發現明顯的改善。據我們所知，這是文獻上第一次報告在胃腸道間質腫瘤病人的疑似 imatinib 相關肺炎未停用 imatinib 即成功治療之案例。這樣的案例顯示藥物相關肺炎有機會在沒有停用相關藥物的狀況下仍能治療成功。*(胸腔醫學 **2012; 27: 311-317**)*

關鍵詞：Imatinib，肺炎，類固醇

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