Clinical characteristics and related factors of fungal empyema thoracis

EnJian Zhong

First Affiliated Hospital of Soochow University

HuiWen Qian

First Affiliated Hospital of Soochow University

ChunQi Hou

First Affiliated Hospital of Soochow University

Juan Li

First Affiliated Hospital of Soochow University

XueFeng Qian

First Affiliated Hospital of Soochow University

LiRong Zou

First Affiliated Hospital of Soochow University

Jing Li

First Affiliated Hospital of Soochow University

YongHong Zhang

Soochow University

ChongKe Zhong

Soochow University

cheng ji (✉ jicheng_suda@163.com)

First Affiliated Hospital of Soochow University

Research

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Abstract

Object

Data on the characteristics and related factors of fungal empyema thoracis (FET) are limited. Our aim is to investigate the clinical characteristics and related factors of FET.

Methods

We conducted a retrospective study of patients with positive culture from pleural effusion who were admitted to the First Affiliated Hospital of Soochow University between January 2007 and January 2018. The clinical and laboratory characteristics of all study participants were collected. Logistic regression models were used to assess the related factors of FET.

Results

There were 30 patients diagnosed with FET. The median age of patients with FET was 62.7 years old and 24 (80.0%) were male. The most frequent pathogens of FET were *Candida albicans* (55.9%). Diabetes mellitus (23.3% vs. 7.9%, $P = 0.019$) and upper gastrointestinal tract perforation or rupture (20.0% vs. 2.1%, $P < 0.001$) were associated with increased risk of FET. The adjusted odds ratios (95% confident interval) were 3.11 (1.02–9.56) for diabetes mellitus and 12.71 (3.47–46.55) for upper gastrointestinal tract perforation or rupture. There were 10 deaths (33.3%) among FET patients after one-year of follow-up.

Conclusions

Diabetes mellitus and upper gastrointestinal tract perforation or rupture were associated with increased risk of FET.

Introduction

Empyema thoracis (ET) is defined as the accumulation of pus within pleural cavity [1]. It had been a life-threatening disease until thoracic drainage and antibiotic were recommended, although Hippocrates put forward the first hypothesis and experimental treatment of empyema thoracis in 500 BC [2]. It is reported that more than 18,000 patients were diagnosed as ET in the USA each year and mortality rate was up to 15%-75% in the history [3–5].

Fungal empyema thoracis (FET) is a rare ET subtype caused by fungus, and *Candida* species are the major kinds of pathogens [6]. A retrospective study conducted in Australia indicated that FET was commonly seen in postoperative immunosuppressed patients with the incidence of only 7.0% in the ET patients [7]. However, a high mortality was observed in patients with FET, for example, one study in American showed a 6-week mortality of 34%, and another two Taiwan studies reported the mortality was up to 61.9%-73.0% [8–10]. Pneumonia, surgery and gastrointestinal tract rupture were reported to be the

most common causes of FET [8]. Despite the high mortality rate of FET, there has been no large-scale study of FET describing the characteristics and related factors of FET in mainland China.

Therefore, we conducted this retrospective study to investigate the clinical characteristics, related factors and outcome of FET in a Chinese population with positive effusion culture, in order to provide references for clinicians to select a reasonable treatment strategy.

Materials And Methods

Patients

The diagnosis of empyema thoracis was suspected by the finding of a pleural effusion on chest imaging and/or ultrasound examination and confirmed by diagnostic pleural aspiration from which organisms were grown. All patients admitted at the First Affiliated Hospital of Soochow University from January 2007 to January 2018 with positive culture from pleural effusion were included except tuberculous empyema. This study was approved by the Ethics committee of the First Affiliated Hospital of Soochow University and written informed consent was waived as a retrospective study.

Data collection

The demographic data (sex, age), co-morbidity (hypertension, diabetes, chronic lung disease, cirrhosis, chronic renal disease, malignancy), pathogen and outcome were collected by means of hospital database. Infection and nutrition related laboratory examination, such as white blood cell (WBC), neutrophil count, lymphocyte count, hemoglobin and albumin were recorded.

Definitions

Charlson's Comorbidity Index (CCI) included 19 different medical conditions with variable scores based on severity: 1 point for chronic obstructive pulmonary disease (COPD), dementia, connective tissue disease (CTD), congestive heart insufficiency, cerebral or peripheral vascular disease, cardiac infarction, peptic ulcer and mild diabetes or hepatopathy; 2 points for hemiplegia, moderate/severe renal failure, end-stage diabetes, any neoplasm, leukemia or lymphoma; 3 points for moderate/severe hepatopathy and 6 points for acquired immune deficiency syndrome (AIDS), and metastatic parenchymal tumor[11]. Age-adjusted Charlson's Comorbidity Index (ACCI) was calculated by one point that added to the CCI for each decade from the beginning of 50 years old[11]. Possible factors that may lead to empyema thoracis were classified into 4 groups: pneumonia, surgery (including thoracic and upper abdominal operation), gastrointestinal tract injury (including esophageal leak, gastroduodenal perforation) and thoracic trauma. Hospital acquired empyema was regarded as patients who developed empyema after 48 hours of hospitalization except those complicated to previous infection on admission (such as community-acquired pneumonia)[12].

Statistical analysis

Continuous variables were expressed as median (Interquartile range, IQR) and were compared using the Mann-Whitney U-test. Categorical variables were expressed with proportions (%) and were compared using the chi-square test or Fisher's exact test if necessary. Logistic regression models were applied for multivariate analysis to determine the influence of the variables on FET. Odds ratio (OR) and corresponding 95% confidence interval (CI) were calculated. Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) for Windows (Version 22.0; SPSS, Inc., Chicago, IL, USA).

Results

Patient characteristics

Of the 202 cases with culture-positive pleural effusion from January 2007 to January 2018, 8 cases were excluded (4 were mediastinal infections and the others were contaminated samples). The remaining 194 cases were then classified into FET group (n = 30) and non-FET group (n = 164) according to their pathogen from pleural effusion (Fig. 1).

An average of 3 FET cases were seen each year (range, 1 to 5 per year), with no significant increase of the overall incidence during the 11 years. In FET group, there were 24 men (80.0%) and 6 women (20.0%), ranging in age from 19 to 83 years (average, 62.7 years), and 14 cases were older than 65 years old (46.7%). All cases had clinical signs of a pleural effusion: 18 on the right (60.0%), 9 on the left (30.0%) and 3 on the bilateral (10.0%). 21 cases (70.0%) were hospital-acquired empyema. Some form of comorbidities were detected in most patients (29/30, 96.7%): hypertension (11 cases, 36.7%), diabetes mellitus (7 cases, 23.3%), chronic lung disease (2 cases, 6.7%), cirrhosis (2 cases, 6.7%), chronic renal disease (2 cases, 6.7%) and cancer (16 cases, 53.3%, including 6 esophagus carcinomas, 4 lung cancers and 4 gastric carcinoma).

The possible primary causes of FET thoracis seen in this series were as follows: pneumonic, 11 cases (36.7%); surgery, 13 cases (43.3%); Upper gastrointestinal tract perforations or rupture, 6 cases (20.0%). All surgeries were chest approach, including 6 esophagectomies, 3 gastrectomies and 4 pulmonary lobectomies. Upper gastrointestinal tract perforation or rupture included 3 spontaneous esophagus ruptures and 3 gastroduodenal perforations. There were ten deaths and one-year mortality was 33.3% (Table 1).

Table 1
Summary clinical data for empyema thoracis

Variable	FET (n = 30)		Non-FET (n = 164)		P-value
Age(years)	62.67	(57–71)	62.45	(57–70)	0.538
> 65 years old	14	(46.7)	79	(48.2)	0.879
Male	24	(80.0)	119	(72.6)	0.395
ACCI	4.03	(3–5)	3.81	(3–5)	0.731
>4 points	15	(50.0)	50	(30.5)	0.037
Recorded diagnoses					
Hypertension	11	(36.7)	56	(34.1)	0.790
Diabetes mellitus	7	(23.3)	13	(7.9)	0.019 ^a
Chronic lung disease	2	(6.7)	16	(9.8)	0.612 ^a
Cirrhosis	2	(6.7)	11	(6.7)	1.000 ^a
Chronic renal disease	2	(6.7)	5	(3.1)	0.296 ^a
Cancer	16	(53.3)	100	(61.0)	0.432
Esophagus carcinoma	6	(20.0)	59	(35.9)	0.088
Lung cancer	4	(13.3)	16	(9.8)	0.521 ^a
Liver cancer	0	(0.0)	6	(3.7)	0.593 ^a
Gastric carcinoma	4	(13.3)	14	(8.5)	0.490

Continuous data are presented as median (Interquartile range, IQR) and categorical data as n (percentage, %)

a. Using Fisher's exact test.

b. Including one pancreatic cancer and one B-cell type lymphoma.

c. Including three colorectal cancers, one pancreatic cancer and one granulocytic sarcoma.

d. Causes for gastroduodenal perforation were portal hypertension with cirrhosis, gastric ulcer, iatrogenic perforation and duodenal trauma, respectively.

FET = Fungal Empyema Thoracis, ACCI = Age-Adjusted Charlson's Comorbidity Index, WBC = White Blood Cell.

Variable	FET (n = 30)		Non-FET (n = 164)		P-value
Others	2 ^b	(6.7)	5 ^c	(3.1)	0.435 ^a
Possible Etiology					
Pneumonia	11	(36.7)	61	(37.2)	0.956
Surgery	13	(43.3)	96	(58.5)	0.123
Upper gastrointestinal tract perforations, rupture or fistulas	6	(20.0)	4	(2.1)	0.001 ^a
Esophagus rupture	3	(10.0)	3	(1.6)	0.048 ^a
Gastroduodenal perforation ^d	3	(10.0)	1	(0.6)	0.012 ^a
Trauma	0	(0.0)	3	(1.8)	1.000 ^a
Hospital acquired infection	21	(70.0)	120	(73.2)	0.735
Laboratory examination					
WBC count (x10 ⁹ /L)	12.68	(8.37–14.97)	12.96	(8.81–15.24)	0.468
Neutrophil count (x10 ⁹ /L)	10.88	(6.52–13.62)	11.02	(7.04–13.72)	0.456
Lymphocyte count (x10 ⁹ /L)	1.06	(0.60–1.62)	0.96	(0.43–1.49)	0.834
Hemoglobin (g/L)	100.3	(87–109)	103.6	(92–114)	0.191
Albumin (g/L)	30.30	(25.5–33.0)	31.46	(27.4–34.9)	0.163
1-year mortality	10	(33.3)	38	(23.2)	0.236
Continuous data are presented as median (Interquartile range, IQR) and categorical data as n (percentage, %)					
a. Using Fisher's exact test.					
b. Including one pancreatic cancer and one B-cell type lymphoma.					
c. Including three colorectal cancers, one pancreatic cancer and one granulocytic sarcoma.					
d. Causes for gastroduodenal perforation were portal hypertension with cirrhosis, gastric ulcer, iatrogenic perforation and duodenal trauma, respectively.					
FET = Fungal Empyema Thoracis, ACCI = Age-Adjusted Charlson's Comorbidity Index, WBC = White Blood Cell.					

Microbiology

Among 34 fungal isolates from pleural effusion culture, 31 isolates (91.2%) in corresponded to yeasts (30 *Candida* and 1 *Cryptococcus neoformans*) and the remaining 3 isolates (8.82%) to molds (2 *Aspergillus* and 1 undifferentiated mold). 30 *Candida* included *Candida albicans* (19 isolates, 55.9%), *Candida tropicalis* (5 isolates, 14.7%), *Candida parapsilosis* (4 isolates, 11.7%) and *Candida glabrata* (2 isolates, 5.9%) (Table 2).

Table 2
Distribution of 34 fungal isolates from pleural fluid culture.

Organism	Cases	Proportion
Yeasts	31	91.2%
Candida	30	88.2%
<i>Candida albicans</i>	19	55.9%
<i>Candida tropicalis</i>	5	14.7%
<i>Candida parapsilosis</i>	4	11.7%
<i>Candida glabrata</i>	2	5.9%
Cryptococcus	1	2.9%
<i>Cryptococcus neoformans</i>	1	2.9%
Molds	3	8.8%
<i>Aspergillus</i>	2	5.9%
Undifferentiated mold	1	2.9%

Related factors of FET

Patients who were over 65 years old had a similar proportion in FET and non-FET (46.7% vs. 48.2%, $P=0.879$). 80.0% patients with FET were male, closed to that of non-FET patients (80.0% vs. 72.6%, $P=0.395$). There was no significant difference in hospital-acquired infection (70.0% vs. 73.2% $P=0.735$) or laboratory examination between FET group and non-FET group (Table 1). Patients whose ACCI were over 4 points had a higher risk for FET (50.0% vs. 30.5%, $P=0.037$). Among detected comorbidities, only diabetes mellitus was associated with higher risk for FET (23.3% vs. 7.9%, $P=0.019$). Furthermore, FET tended to occur in patients who experience upper gastrointestinal tract perforation or rupture (20.0% vs. 2.1%, $P=0.001$) (Table 1).

Multivariate analysis

All variants significantly associated with higher FET risk found in univariate analysis were included in multivariate model. The findings revealed that diabetes mellitus ($P = 0.047$), and upper gastrointestinal tract perforation or rupture ($P < 0.001$) were associated increased risk of FET (Table 3). The adjusted ORs were 3.11 (95% CI 1.02–9.56) for diabetes mellitus and 12.71 (95% CI 3.47–46.55) for upper gastrointestinal tract perforation or rupture, compared with those without diabetes mellitus or upper gastrointestinal tract perforation or rupture.

Table 3
Multivariate logistic regression analysis of risk factors

Variable	OR	95%CI	S.E.	P valve
Diabetes mellitus	3.11	1.02–9.56	1.78	0.047
Non-surgical related upper gastrointestinal tract damage	12.71	3.47–46.55	3.84	< 0.001
ACCI above 4 points	2.22	0.91–5.42	1.01	0.081
OR = Odds Ratio, CI = Confidence Interval, S.E.= Standard Error, ACCI = Age-Adjusted Charlson's Comorbidity Index.				

Discussion

FET remains as a rare but fatal disease and leads to a puzzling condition for clinicians. In our study, the proportion of FET case was 15.5% (30/194), which is significantly higher than prior reports of 7.0% conducted in Australia [7]. The growth in the rate of FET is likely related to the increasing application of broad-spectrum antibiotics, transthoracic surgery and the number of critical or immunocompromised patients, as well as better fungal detection techniques recently [8]. In addition, the one-year mortality was up to 33.3% (10/30) in our study, the rate was similar to the study in American, which showed the 6-week all-cause mortality of patients with FET due to *Candida* or *Aspergillus* spp. was 34%. However, Ko et al and Lin et al respectively conducted a study about FET in Taiwan, they reported that the mortality was 73.0% (49/67) from January 1990 to December 1997 and 61.9% (39/63) from October 2002 to September 2011[8, 10]. There were several possible explanations to the decrease in mortality: (1) Early administration of antifungal agents for patients with high risk for fungal infection; (2) Thoracic drainage measures were implemented in time for all of patients. Nevertheless, it is worth noting that FET still represents a very important cause of mortality.

Similar to previous studies, *Candida* was the most common fungal pathogens in our cohort (30/34, 91.2% vs. 47/73, 63.5%) [8]. *Candida albicans* remains the major causative agent while non-*Candida albicans* species such as *Candida glabrata*, *Candida tropicalis* and *Candida parapsilosis* were not rare as FET pathogens (11/33, 33.3%). *Candida tropicalis* was one of most commonly-detected fungi in human gut mycobiome and was detected in 67.0% of samples based on 17 gut mycobiome studies [13]. Notably, 4 of 5(80.0%) *Candida tropicalis* empyema thoracis in our study had gastrointestinal tract surgery or injury and it is believable that *Candida tropicalis* is commonly associated with digestive diseases. Apart from *Candida*, one *cryptococcosis* empyema thoracis case in our study was comorbid with malignancy B

cell lymphoma. *Cryptococcosis* infection has been reported in immunocompromised patients such as HIV infection, liver cirrhosis or Bruton's agammaglobulinemia and most *cryptococcosis* empyema thoracis has similarly been described in immunodeficiency patients [14].

A number of factors had been proved to predispose patients to fungal infection. Impaired T-cell function followed by high-dose glucocorticoid therapy, chemotherapy, or AIDS, as well as depressed neutrophil number or function were considered to increase the risk of fungal infection [8]. But researches about factors of predispose patients to FET were limited. Masayuki N et al. studied 97 FET patients complicated with malignant tumors and indicated that previous surgical operation was a risk factor for candida infection and the presence of uncommon mold species suggested as the contamination of pleural effusion specimens [15]. FET had been reported as a complication of operation or esophageal pleural fistula [16, 17]. Takashi I et al. found that all of candida empyema (5/5) were secondary to esophageal or gastric fistula and proposed a hypothesis that Candida species in the pleural effusion can be an important clue for suspecting gastrointestinal tract perforation [18]. From 194 cases of culture-positive empyema thoracis, our study identified 10 cases due to upper gastrointestinal tract perforations, rupture or fistulas including spontaneous esophagus ruptures (6 cases) and gastroduodenal perforations (4 cases), 6 of whom were diagnosed as FET and had confirmed statistical difference compared to non-FET. Those patients with gastroduodenal perforation had variable causes (portal hypertension with cirrhosis, gastric ulcer, iatrogenic perforation or duodenal trauma) and it was hard to assess the risk difference in gastroduodenal perforations with different causes due to limited samples in this study. Candida species is a kind of normal commensals of humans throughout the entire gastrointestinal tract and can be the pathogen causing empyema when they break out the gastrointestinal tract barrier and enter the pleural cavity through esophagus rupture directly or gastroduodenal perforation [13]. Thus, the damage of gastrointestinal tract barrier had potential risk for development of fungal infections.

Diabetes mellitus has become one of the leading chronic disease burden worldwide and the overall morbidity was estimated to be 11.6% in the China [19]. Patients with diabetes mellitus were proven to have increased respiratory infectious risk due to inadequate clearance or the disturbance of normal pulmonary immune function [20]. It has been reported that diabetic patients conferred a 1.71-fold increased risk of empyema thoracis without any comorbidity [21]. A series of retrospective studies showed that the hazard of developing empyema was higher for patient with diabetes mellitus than those with chronic obstructive lung disease or chronic liver disease and cirrhosis [20, 22]. Gosiewski T et al found the quantity of candida in the feces of patients with diabetes was significantly higher compared to non-diabetic controls[23]. However, the association between diabetes and FET has not yet been fully evaluated. Our study showed that patients with diabetes have an increased risk of FET, suggesting that diabetes mellitus could be an important risk factor for FET.

Conclusion

Our study firstly provided fundamental clinical characteristics and related factors about FET in mainland China. We demonstrated that upper gastrointestinal tract perforation or rupture and diabetes mellitus

were associated with higher risk of FET. Additionally, patients with FET still had a higher one-year mortality in China. Our findings provided evidences to get further insight into the mechanism of FET and references for clinicians to draft reasonable treatment strategy.

Abbreviations

FET: fungal empyema thoracis; ET: Empyema thoracis; WBC: white blood cell; CCI: Charlson's Comorbidity Index; COPD: chronic obstructive pulmonary disease; CTD: connective tissue disease; AIDS: acquired immune deficiency syndrome; ACCI: Age-adjusted Charlson's Comorbidity Index; IQR: Interquartile range; OR: Odds ratio; CI: confidence interval;

Declarations

Ethics approval and consent to participate:

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was approved by the ethics committee of the First Affiliated Hospital of Soochow University (2019-012). The informed consensus from each patient or the individual patient's family was waived because there were no new interventions for the patients and the information was anonymized.

Consent for publication:

Not applicable.

Availability of data and materials:

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests:

The authors declare that they have no competing interests.

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Authors' contributions:

(I) Conception and design: EJZ, HWQ, CJ; (II) Collection and assembly of data: EJZ, CQH, XFQ, LRZ, JL; (III) Data analysis and interpretation: EJZ, HWQ, CKZ, YHZ; (IV) Manuscript writing: All authors; (V) All authors read and approved the final manuscript.

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Figures

Figure 1

Flow chart representing case filter