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ORIGINAL ARTICLE

Report of a 63-case series of *Candida* empyema thoracis: 9-year experience of two medical centers in central Taiwan

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KEYWORDS
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Background: *Candida* empyema thoracis is a serious complication of invasive candidiasis with high mortality. However, the treatment for *Candida* empyema remains controversial. We conducted a 9-year retrospective study to analyze the treatments and factors associated with the mortality of patients with *Candida* empyema thoracis in two medical centers in central Taiwan.
Methods: The medical records of all patients with positive *Candida* culture from pleural effusion between October 2002 and September 2011 were reviewed. The demographic data, treatment regimens, and factors associated with mortality were analyzed.
Results: During the period of this study, 102 patients were identified. Sixty-three of these patients fulfilled the enrollment criteria, and their data were analyzed. Three-quarters of these patients were male, and the median age of these patients was 69. Thirty-five (55.6%) patients had contiguous infection. The crude mortality rate was 61.9%. *Candida albicans* was the most common isolate, and malignancy was the most common underlying disease. Patients with advanced age, a higher Charlson's score, shock status, respiratory failure, and noncontiguous infection had a higher mortality rate. Those who had received surgical intervention had a better outcome. In multivariate analysis, the shock status, respiratory failure, and noncontiguous infection source were associated with a higher mortality risk.

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Conclusion: Candida empyema thoracis is a severe invasive candidiasis with high mortality rate. Shock status, respiratory failure, and noncontiguous infection were factors associated with a higher mortality rate. Surgical intervention or drainage may improve the treatment outcome, especially in patients with contiguous infection.

Introduction

Invasive candidiasis has emerged as an important nosocomial infection, especially in critical patients. The most common invasive candidiasis is candidemia and the incidence of nosocomial candidemia has increased in the past few decades.[1,2] Fungal empyema thoracis is a rare but severe invasive candidiasis with high mortality, and *Candida* species are the most frequent isolates.[3] There are several mechanisms of empyema thoracis, including infection of the pleural cavity, thoracotomy, trauma, esophageal rupture, subdiaphragmatic spread, and hematogenous seeding.[3,4] Treatment options for *Candida* empyema thoracis, regardless of the mechanism, include antifungal therapy, tubal drainage, tubal irrigation, fibrinolytic therapy, and surgical intervention.[3,5,6] However, despite the high mortality rate of *Candida* empyema, the treatment for *Candida* empyema thoracis remains controversial.[3] There has been no large series of *Candida* empyema thoracis reports in the past 10 years. Therefore, we conducted this retrospective study in two medical centers in central Taiwan to analyze the treatments and factors associated with the mortality of patients with *Candida* empyema thoracis.

Materials and methods

Patients and settings

During the period from October 2002 to September 2011, all patients treated at the China Medical University Hospital (CMUH; a 2000-bed teaching hospital in Taichung City, central Taiwan) and Changhua Christian Hospital (CCH; a 1600-bed teaching hospital in Changhua City, central Taiwan) with a positive culture of *Candida* spp. from pleural effusion were included. The medical charts were thoroughly reviewed and the demographic data, predisposing factors, underlying disease (including malignancy, diabetes, uremia, heart failure, and cirrhosis), Charlson's score (used as a composite index of comorbidities), clinical features, laboratory data, treatments, and outcomes were collected. The association of variables with the mortality of patient with *Candida* empyema thoracis was analyzed.

Inclusion criteria

Only patients with conditions fitting the diagnostic criteria of *Candida* empyema thoracis during study period were included. The diagnostic criteria of *Candida* empyema thoracis was modified according to that proposed by Ko et al[3]: (1) isolation of a *Candida* species from an exudative pleural effusion; (2) significant signs of infection, such as fever (body temperature $>38.3^{\circ}C$ or $<36^{\circ}C$) and leukocytosis (white blood cells $>10{,}000/mL$) or leucopenia (white blood cells $<1000/mL$); and (3) isolation of the same *Candida* species from pleural effusion on more than one occasion, or from pleural effusion and blood. *Candida* isolated from prior tube thoracotomy for preexisting pneumothorax or bacterial empyema were assumed to be colonized within the chest tubes, unless the infection persisted without antifungal therapy.

Definitions

The definitions of an appropriate antibiotic treatment was defined as using antibiotics, to which the bacteria isolates were *in vitro* sensitive, within 72 hours after the diagnosis of empyema was made. All-cause in-hospital mortality was defined as all deaths that occurred during hospitalization after the onset of *Candida* empyema thoracis. The pathogenic mechanisms of *Candida* empyema thoracis were divided into two categories: contiguous infection for empyema in patients who had adjacent infection, such as esophageal rupture, pneumonia, mediastinitis, paraspinal abscess, or subdiaphragmatic liver abscess; and noncontiguous infection for empyema in patients who had a distant infection focus, such as intra-abdominal abscess, ischemic bowel, bowel perforation or fungemia, or an unidentified infection source.

Microbiology identification

The pleural fluid collected by thoracentesis or during tube thoracotomy were streaked over trypticase soy agar (TSA) with 5% sheep blood (TSA II/Levine eosin methylene blue agar; Becton Dickinson, Franklin Lakes, NJ, USA) and incubated at 35 °C. Blood culture was processed initially by the BACTEC 9000 system (Becton Dickinson). Positive bottles were subcultured onto TSA II/Levine eosin methylene blue agar and incubated at 35°C. Isolates were identified as various *Candida* spp. by Gram stain, CHROMagar™ culture (Becton Dickinson), and the ID 32 C (bioMerieux SA, Marcy l'Etoile, France) system for yeast. The sensitivity test was performed using the ATB™ FUNGUS 3 system. The sensitivity test, however, was not performed at CCH, which was the only difference between the methods employed for microbiological identification by the two hospitals.

Statistical analysis

Normally distributed continuous variables were reported as mean $\pm$ standard deviation (SD) and were compared using the independent Student's *t*-test. Medians with ranges were used

to describe non-normally distributed continuous variables and were compared using the Mann–Whitney *U*-test. Categorical variables were analyzed with proportions and were compared using the chi-square test. A p value of ≤ 0.05 was considered statistically significant, and all tests for significance were two-tailed. A logistic regression model was applied for multivariate analysis to determine the prognostic influence of the variables on mortality. Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) for Windows (Version 18.0; SPSS, Inc., Chicago, IL, USA).

Results

Clinical characteristics and manifestations

Between October 2002 and September 2011, 102 patients with *Candida* species isolated from pleural fluid were identified. Thirty-nine patients were excluded due to at least one of the following conditions: (1) the pleural effusion was transudate ($n = 8$); (2) the patient had no symptoms or signs of infection ($n = 5$); and (3) the *Candida* species was isolated from the existing tubal thoracotomy ($n = 26$), which was considered a colonizer using the criteria described above. The data of the remaining 63 patients were further analyzed.

The demographic data, clinical manifestation, treatment, and outcome are displayed in Table 1. Of these enrolled patients, more than half were over 65 years old, and they had a higher mortality than those younger than 65 years (68.4% vs. 52%, $p = 0.042$). Three-quarters of the patients with *Candida* empyema were male, but they had a similar mortality rate to that of the female patients (63% vs. 58.8%, $p = 0.78$). Patients who survived this infection had a longer hospital stay. Furthermore, three-quarters ($n = 47$) of the patients needed intensive care unit care. Patients with a higher Charlson's score had poorer outcomes ($p = 0.03$). Most patients presented respiratory symptoms including chest pain, dyspnea, and respiratory failure, and half of them had a shock status. Patients who presented respiratory failure ($p < 0.01$) or had a shock status ($p < 0.01$) bore higher risk for mortality. In laboratory tests, most patients had an abnormal blood cells count and a C-reactive protein level over 5 mg/dL (data not shown). The median white blood cell count of pleural effusion is 13,650 cells/μL, and the median red blood cell count is 18,500 cells/μL. About half of the enrolled patients had bacterial coinfection in empyema (46%). Malignancy was the most commonly encountered underlying disease (29 patients, 46%). The three most frequently encountered types of malignancy were esophageal cancer (12 patients), gastric cancer (4 patients), and breast cancer (3 patients). Only nine (14.3%) patients did not have an underlying comorbidity. *Candida* empyema thoracis due to contiguous infection was more common than those due to noncontiguous infection (55.6% vs. 44.4%). Patients with contiguous infection had a lower mortality rate than those with noncontiguous infection (45.7% vs. 82.1%, $p = 0.004$).

Table 1 Demographic data and clinical characteristics of patients with *Candida* empyema thoracis

	Survival (%)	Mortality (%)	*p*
Total patient number, *n* (%)	24 (38.1)	39 (61.9)	
Age (y), mean ± SD	59 ± 17	70 ± 13	0.042
Male, *n* (%)	17 (71)	29 (74.4)	0.78
Charlson's score, median (range)	3 (0–8)	4 (1–11)	0.03
Clinical manifestations			
Shock, *n* (%)	4 (16.7)	28 (71.8)	<0.01
Respiratory failure, *n* (%)	12 (50)	36 (92.3)	<0.01
Dyspnea, *n* (%)	18 (75)	35 (89.7)	0.16
Fever, *n* (%)	17 (71)	24 (61.5)	0.59
Chest pain, *n* (%)	10 (41.7)	8 (20.5)	0.09
Fungemia, *n* (%)	1 (4.2)	8 (20.5)	0.13
Concomitant bacterial infection, *n* (%)	11 (45.8)	20 (51.3)	0.80
Underlying disease			
Malignancy, *n* (%)	11 (45.8)	18 (46.2)	1.00
Diabetes mellitus, *n* (%)	6 (25)	10 (25.6)	1.00
Uremia, *n* (%)	3 (12.5)	7 (17.9)	0.73
Congestive heart failure, *n* (%)	2 (8.3)	7 (17.9)	0.46
Liver cirrhosis, *n* (%)	1 (4.2)	5 (12.8)	0.40
Chronic obstructive pulmonary disease	1 (4.2)	4 (10.2)	0.64
Pathogenic mechanism			
Contiguous infection, *n* (%)	19 (79.2)	16 (41)	0.004
Noncontiguous infection, *n* (%)	5 (20.8)	23 (59)	
Treatment			
With antifungal agents, *n* (%)	20 (83.3)	24 (61.5)	0.10
Duration of antifungal agents, median (range)	15 (7–26)	14 (1–39)	
With interventions, [a]*n* (%)	22 (91.7)	26 (66.7)	0.03
With appropriate antibacterial antibiotics	10(41.7)	15 (38.5)	0.37
Outcome			
From culture day to death, median (range)	–	11 (1–95)	

[a] Interventions include surgical treatment, tubal drainage, tubal irrigation, and fibrinolytic irrigation.
SD = standard deviation.

Microbiology

Candida albicans was the most common isolated species (49 isolates, 76.5%), followed by *C. tropicalis* (seven isolates, 10.9%), then *C. glabrata* (three isolates, 4.6%) (Table 2). The isolated strains whose sensitivity test was performed at the CMUH included 22 strains of *C. albicans*, three of *C. tropicalis*, one of *C. guilliemondii*, and one of *C. glabrata*. The sensitivity result revealed that all isolates were sensitive to fluconazole, apart from the *C. glabrata* isolate, whose fluconazole minimal inhibitory concentration (MIC) was 4.0 μg/mL. For bacteria concomitantly isolated from pleural effusion, *Pseudomonas aeruginosa* was the most common isolated pathogen (12 isolates), followed by *Klebsiella pneumoniae* (8 isolates), *Enterococcus faecalis* (5 isolates), *Escherichia coli* (4 isolates), *Enterobacter cloacae* (3 isolates), and *Acinetobacter baumannii* (2 isolates). *Streptococcus* species was cultured in eight specimens.

Table 2 *Candida* species isolated from pleural fluid

Candida isolates	Number of isolates[a] (%)
C. albicans	49 (76.5)
C. tropicalis	7 (10.93)
C. glabrata	3 (4.68)
C. famata	2 (3.12)
C. intermedia	1 (1.56)
C. guilliermondii	1 (1.56)
C. melibiosica	1 (1.56)

[a] Sixty-three patients with 64 isolates, one patient with two isolates of *C. tropicalis* and *C. glabrata* in pleural effusion.

Treatment and outcome

Forty-four patients received antifungal treatment ranging from 1 to 39 days, with a median duration of 15 days. One patient received anidulafungin as the initial treatment for *C. albicans* empyema, while 43 others received fluconazole initially. One of these 43 patients shifted regimen to amphotericin B plus flucytosine; another individual shifted to caspofungin; and yet another one shifted to voriconazole according to the clinician's judgment. Of the 44 patients who received antifungal agent treatment, 24 (54.5%) died ($p = 0.1$).

Regarding invasive procedures, 12 patients received surgical treatment, 48 patients received tubal drainage, and two patients received fibrinolytic therapy. Seven (11.1%) patients received no antifungal treatment, drainage, or surgical intervention. Patients who received surgical or drainage intervention had a lower mortality rate than those who did not (54.2% vs. 86.7%, $p = 0.03$). All seven patients who received no treatment for *Candida* empyema thoracis died. Among the total of 63 patients with *Candida* empyema, 39 died. The crude mortality rate was 61.9%. The median interval between the diagnosis of *Candida* empyema and death was 11 days. Of the three patients with *C. glabrata* isolated from their pleural fluid, two died. These three patients all received intravenous fluconazole for the treatment of *Candida* empyema thoracis. However, the one who survived had a contiguous infection and received surgical intervention, while the other two had a noncontiguous infection and did not receive invasive drainage procedure. Thirty-one patients had concomitant bacterial pleural infection. Twenty-five patients received appropriate antibiotics treatment and 15 of them (60%) died, and in the other six patients who did not receive appropriate antibiotics treatment, five (83.3%) died ($p = 0.37$).

Multivariate analysis

Multivariate logistic regression analysis was performed. All variants significantly associated with mortality found in univariate analysis were drawn into the analysis. The result of multivariate analysis revealed that shock status ($p = 0.03$), respiratory failure ($p = 0.01$), and noncontiguous infection ($p < 0.01$) were independent risk factors for the mortality of patients with *Candida* empyema thoracis (Table 3).

Table 3 Factors associated with mortality in patients with *Candida* empyema thoracis: multivariate analysis

	Mortality		
	Odds ratio	95% confidence interval	*p*
Age	1.03	0.97–1.09	0.30
Male	3.52	0.50–24.52	0.20
Charlson Comorbidity Index	1.29	0.91–1.81	0.14
Shock	6.43	1.19–34.69	0.03
Respiratory failure	26.00	1.99–339.16	0.01
Contiguous infection	0.03	0.003–0.41	0.008

Discussion

Male patients accounted for a higher proportion than female patients in *Candida* empyema. This may be due to the high percentage of patients with esophageal cancer or gastric cancer, which are male-dominant diseases in Taiwan. The median interval from the culture day to death is only 11 days, which may explain why those patients who survived this infection had a longer hospitalization period or intensive care unit stay.

The major causes of reported cases of fungal empyema thoracis include esophageal perforation, abdominal infection, bronchopulmonary infection, surgical intervention, and repeated thoracentesis.[3,6–9] More than half of our patients had *Candida* empyema thoracis with a gastrointestinal origin, which may explain why the most common fungal pathogen isolated from pleural effusion was *C. albicans*. This supports the finding that the isolation of *Candida* species can be an important clue for suspecting gastrointestinal tract perforation, as proposed by Ishiguro et al.[6] Furthermore, in this study, we discovered that the hematogenous spread of *Candida* into the pleural space may also be an important infection route in the noncontiguous infection group, and the patients with this route of infection had poorer outcomes.

Many factors have been reported to be associated with the mortality of patients with candidemia including advanced age, septic shock, non-albicans candidemia, and a high severity of the disease.[10–12] For patients with fungal empyema, immunocompromised status and respiratory failure were reported to be associated with mortality, and systemic antifungal therapy was associated with a lower risk of death.[3] In our study, patients with advanced age (>65 years), a higher Charlson's score, a noncontiguous infection, a shock status, respiratory failure, or no intervention had a higher risk of mortality according to the univariate analysis. In multivariate logistic regression analysis, only shock status, respiratory failure, and noncontiguous infection were significantly associated with the risk of mortality. Shock status and respiratory failure reflect the severity of the disease and their association with mortality is logically reasonable. However, the higher mortality rate of patients with noncontiguous infection has never been mentioned before. In our study, patients who received drainage (surgical or tubal) had a lower mortality

rate than those who did not (54.2% vs. 86.7%, $p = 0.03$), although it was not significant in the multivariate analysis. A similar difference was also highlighted in Ko et al's[3] study (66% vs. 87%, with and without drainage). In another previous study, patients who did not receive antifungal therapy were reported to have survived from *Candida* empyema thoracis due to GI tract rupture with only drainage and antibiotics.[6] Therefore, we believe that surgical intervention with adequate drainage could constitute an essential treatment for patients with *Candida* empyema thoracis. After comparing the clinical data, it was found that the patients' clinical conditions were similar in both contiguous and noncontiguous infection groups, except for the fact that more patients received surgical intervention or drainage in the contiguous infection group (88.6% vs. 60.7%). So the higher percentage of patients receiving surgical intervention in the contiguous infection group could lead to the lower mortality rate in this group, and this finding could also explain why, of the three patients with *C. glabrata* empyema, only the patient who had received surgical intervention survived.

A possible reason surgical intervention is more effective than a systemic antifungal agent is that the concentration of antifungal agents in pleural fluid is variable. Voriconazole and micafungin have been reported to provide good pleural penetration and successful treatment for *Aspergillus* empyema.[13,14] Anidulafungin and liposomal amphotericin B, in contrast, were reported to have poor pleural concentration and a low pleura/serum concentration ratio, and tubal drainage is warranted for successful treatment.[15–17] Data on the concentration of fluconazole, the agent used most frequently to treat *Candida* empyema thoracis in our study, in pleural effusion are lacking, and it remains uncertain whether the pleural effusion concentration of fluconazole influenced the success rate of the treatment of *Candida* empyema thoracis in this study. Further studies investigating the association between the concentration of antifungal agents in pleural fluid and the treatment outcome are warranted.

Another reason for the improved outcomes of the patients in contiguous infection group may be the localized infection in nature, which may respond to adequate debridement and drainage. In contrast, *Candida* empyema thoracis from a noncontiguous infection source was supposed to spread hematogenously, and an early systemic antifungal agent treatment is essential for treating systemic fungal infection. Because of the suspected hematogenous route of infection, we have tried to figure out if eradication of other infection focus, such as central catheter, would improve mortality rate. Removal of central venous catheter (CVC) was only performed in a few patients with candidemia in CMUH, however, and no removal was performed in all 29 CCH patients. For the nine patients with candidemia in this study, seven patients had CVC placement and three of them had removal of CVC. After analysis, the correlation between catheter removal and mortality was not significant ($p = 0.606$). However, the sample size might be too small to make this result meaningful.

There are several limitations to our study. First, our sample size is small, which may render some potentially influential parameters insignificant, such as antibacterial antibiotic therapy and interventions in multivariate analysis. Second, because this is a retrospective study, it was impossible to identify whether the improved outcome of the contiguous infection group was caused by the increased surgical intervention, the localized infection itself, or both. Third, because the sensitivity test for *Candida* species isolated from CCH is not routinely performed, and it was not performed for all *Candida* species isolated from CMUH, we could not totally exclude the possibility that strains resistant to antifungal agents existed and could not be sure if all antifungal agents were active to the isolates. This resistance might also contribute to the failure of treatment for *Candida* empyema thoracis. Fourth, also because this study is retrospective, other manifestations of systemic involvement, such as eye ground involvement or liver/spleen involvement, could not be evaluated if the examination was not performed when *Candida* empyema thoracis was diagnosed. Also, the effect of eradicating pathogens from infection sites other than pleural space, such as ophthalmic debridement or abscess drainage, could not be evaluated in this study.

In conclusion, *Candida* empyema thoracis is a severe invasive candidiasis with a mortality rate as high as 61.9%. Patients with shock status and respiratory failure were associated with a higher mortality rate, and those with empyema due to contiguous infection had better outcomes. As to antifungal therapy, micafungin and voriconazole were reported with good pleural fluid concentration and successful treatment, but data on the pleural concentration of fluconazole are lacking, and its treatment efficacy for *Candida* empyema thoracis remains undetermined. Finally, we conclude that surgical treatment and adequate drainage are essential for *Candida* empyema, especially in patients with contiguous infection.

Conflicts of interest

All contributing authors declare no conflicts of interest.

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