

[CASE REPORT]

Severe Fever with Thrombocytopenia Syndrome Complicated with Pseudomembranous *Aspergillus* Tracheobronchitis in a Patient without Apparent Risk Factors for Invasive Aspergillosis

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Abstract:

Severe fever with thrombocytopenia syndrome (SFTS) is a tick-borne infectious disease. A 91-year-old woman was admitted to our intensive-care unit with SFTS, and she developed dyspnea with wheezes 5 days after admission. Bronchoscopy showed scattered white mold in her central airway. An airway tissue biopsy and culture of bronchial lavage fluid revealed fungal hyphae in the necrotic tissue, confirmed as *Aspergillus fumigatus*. She was thus diagnosed with pseudomembranous aspergillus tracheobronchitis. She had no common risk factors for invasive aspergillosis (IA). Patients with SFTS, even those without apparent risk factors for IA, may be at risk of developing IA.

Key words: aspergillus tracheobronchitis, bronchoscopy, invasive aspergillosis, risk factor, severe fever with thrombocytopenia syndrome

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Introduction

Severe fever with thrombocytopenia syndrome (SFTS) is a tick-borne infectious disease that is associated with a high mortality rate due to multiorgan failure. In recent years, it has been suggested that the prevalence of mycosis, especially invasive aspergillosis (IA), is high in patients with SFTS (1, 2). However, all reported cases of SFTS-related IA had some common risk factors for IA (1-5). Therefore, it is unclear from these cases whether SFTS-related IA is due to SFTS itself or because of common, coexisting risk factors.

We herein report a patient who developed SFTS-related IA in the absence of common risk factors for IA.

Case Report

A 91-year-old woman with a recent history of farm work

and medical history of hypertension and dyslipidemia was admitted to a local hospital because of vomiting and diarrhea that had started the previous day. She experienced systemic muscle pain and fatigue seven days before admission and developed a low-grade fever three days before admission. On admission, laboratory data revealed leukocytopenia (white blood cell count: 2,100/ μ L; neutrophil count: 1,407/ μ L), thrombocytopenia (platelet count: 5.6×10^4 / μ L), and mild liver injury (aspartate aminotransferase level: 377 U/L; alanine aminotransferase level: 86 U/L). One day after admission, she developed disorientation and shock and was referred to our hospital.

On a physical examination at our hospital, her respiratory rate was 22 breaths per minute, oxygen saturation was 95% in room air, heart rate was 95 beats per minute, blood pressure was 85/45 mmHg, Glasgow Coma Scale was E4V2M5, and body temperature was 36.0°C. No abnormal breath sounds were heard on chest auscultation. An eschar, sugges-

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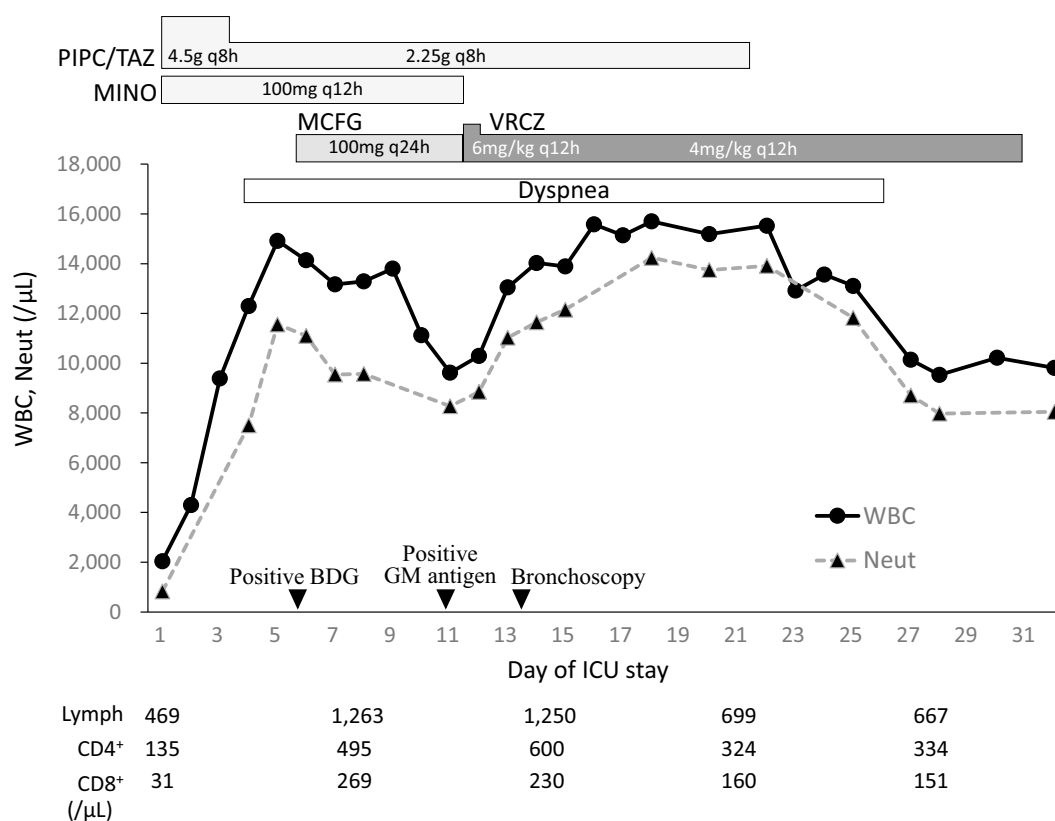


Figure 1. Clinical course of the patient. BDG: (1→3)- β -D-glucan, CD4⁺: CD4⁺ T cell, CD8⁺: CD8⁺ T cell, GM: galactomannan, Lymph: lymphocyte, MCFG: micafungin, MINO: minocycline, Neut: neutrophil, PIPC/TAZ: piperacillin-tazobactam, VRCZ: voriconazole, WBC: white blood cell

tive of a tick bite, was found on her right lower limb. She had multiorgan failure, including acute kidney injury and disseminated intravascular coagulation (DIC). Computed tomography (CT), including lung CT, on referral showed no significant findings except for swelling of her right inguinal lymph nodes. Reverse-transcription polymerase chain reaction of blood samples detected SFTS virus, confirming the diagnosis of SFTS.

She was prescribed antibiotics (minocycline and piperacillin-tazobactam) and recombinant thrombomodulin for the treatment of DIC in our intensive-care unit (ICU). On Day 2 of her ICU stay, gastrointestinal bleeding caused by an acute gastric mucosal lesion with coagulopathy was found. She developed severe anemia requiring blood transfusion. Her white blood cell count increased rapidly to 4,300/ μ L by day 2 of her ICU stay (Fig. 1). Her liver disorder and coagulopathy resolved by day 10 of her ICU stay. Systemic or inhaled steroids were never used during her clinical course.

She developed dyspnea on day 5 of her ICU stay, and chest auscultation revealed bilateral wheezes. An inhaled short-acting β_2 agonist did not relieve her respiratory symptoms. Because her dyspnea and hypercapnia progressed, high-flow nasal canula oxygen therapy was performed. Chest CT revealed bilateral patchy peribronchial consolidation, ground-glass opacity, and bronchial wall thickening (Fig. 2a). No pathogenic bacteria were isolated from her

sputum culture. At this time, her serum (1→3)- β -D-glucan level had increased to 61.4 pg/mL (normal range, 0-11.0 pg/mL), and a test for serum aspergillus galactomannan antigen was positive. Bronchoscopy revealed some erosion and scattered white mold in her trachea and central bronchi (Fig. 2b). A pathological examination of the airway tissue biopsy revealed eroded bronchial mucosa with fungal hyphae in necrotic tissue (Fig. 2c), and *Aspergillus fumigatus* was isolated from a culture of bronchial lavage fluid. Therefore, she was diagnosed with pseudomembranous aspergillus tracheobronchitis (ATB), a subtype of IA. She was treated with voriconazole, and her dyspnea and radiological findings improved after approximately three weeks. She was discharged from the ICU on day 32.

Discussion

To our knowledge, this is the first report of SFTS-related IA in a patient without other common risk factors for IA.

SFTS is a tick-borne infectious disease that is caused by the SFTS virus. SFTS is prevalent in East Asian countries, including Japan, and is characterized by a fever, thrombocytopenia, leukocytopenia, and gastrointestinal symptoms. In recent years, the number of reports of SFTS-related IA has increased (1-5), and the prevalence of IA (6.1-8.3%) was reported to be higher in patients with SFTS than in other critically ill patients (1.1-3.7%) (1, 2, 6, 7). We also previously

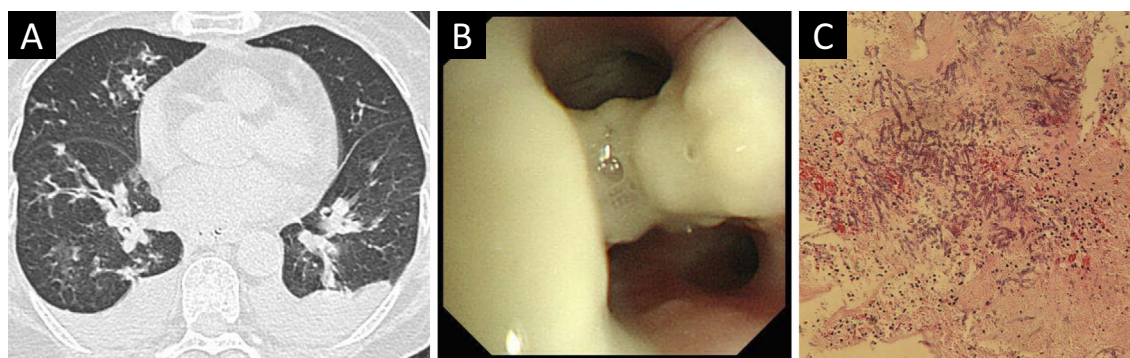


Figure 2. Clinical and pathological images. (A) Chest computed tomography on day 7 showing patchy peribronchial shadowing and bronchial wall thickening in both lungs. (B) Bronchoscopy on day 14. The right bronchus intermedius was covered by white mold and constricted. A tissue biopsy was performed at the bifurcation of the right middle and lower bronchus. (C) A pathological examination of the bronchoscopic biopsy specimen revealed fungal hyphae in the necrotic tissue (Hematoxylin and Eosin staining. Magnification $\times 100$).

Table. Summary of Published Cases of SFTS-related IA.

Case, ref.	Age	Sex	Lowest WBC count (μL)	Corticosteroid use prior to IA diagnosis	Other risk factors for IA	Diagnosis	Day of diagnosis	Chest CT findings	Major airway lesion	Antifungal treatment	Outcome
1 [1]	72	F	1,700	DEX 5 mg	None	Proven	13	Scattered nodular and peribronchial patchy shadowing	Pseudomembranous	VRCZ	Died
2 [1]	42	F	3,800	DEX 10 mg	None	Proven	19	Globular mass and peribronchial shadowing	Pseudomembranous	VRCZ, CPF, L-AMB	Died
3 [1]	58	F	1,290	DEX 10 mg	None	Probable	5	Consolidation in part of the left lung with infiltrative shadowing	NA	VRCZ	Died
4 [1]	65	M	1,700	None	COPD	Probable	8	Consolidation and emphysema	NA	None	Died
5 [2] ^a	NA	NA	NA	mPSL 125 mg	NA	Probable	NA	NA	NA	NA	Survived
6 [3]	57	F	1,140	mPSL 1 g	None	Probable	11	Bilateral ground-glass opacity, and cavity in right middle lobe	NA	L-AMB, CPF, VRCZ	Survived
7 [4]	83	F	2,200	mPSL 1 g	None	Proven	14 ^d	NA	Tracheal ulcer with aspergillus invasion	MCFG, L-AMB	Died
8 [5]	83	M	930	mPSL 1 g	None	Proven	12 ^d	NA	Tracheal ulcer with aspergillus invasion	None	Died
9 ^b	65	M	670	mPSL 1 g	None	Proven	27	Consolidation in the left lower lobe	Pseudomembranous	VRCZ, L-AMB	Died
10 ^c	91	F	2,040	None	None	Proven	14	Bilateral patchy peribronchial shadowing and bronchial wall thickening	Pseudomembranous	MCFG, VRCZ	Survived

^aTwo of three case of IA included in this study were documented in other case reports [3,4]. Information regarding corticosteroid use was provided by the author.

^bAnother patient treated at our institution.

^cPresent patient.

^dIA was diagnosed at autopsy.

COPD: chronic obstructive pulmonary disease, CPF: caspofungin, DEX: dexamethasone, L-AMB: liposomal amphotericin B, MCFG: micafungin, mPSL: methylprednisolone, NA: not available, IA: invasive aspergillosis, VRCZ: voriconazole, WBC: white blood cell

experienced another case of IA in patients with SFTS (Table), and SFTS-related IA occurred in two of three patients

with SFTS who were treated in our institution.

IA is a severe fungal infection caused by aspergillus inva-

sion. IA was originally thought to occur in severely immunosuppressed patients, especially those with severe and prolonged neutropenia. However, it was recently recognized that IA can also develop in critically ill patients with less-severe immunosuppression. Indeed, in a previous report, 60% of patients who developed IA in an ICU did not have traditional risk factors for IA (8). In addition, steroid administrations and chronic obstructive pulmonary disease (COPD) have been reported as risk factors for IA in critically ill patients (7).

Why patients with SFTS are susceptible to IA is unclear. Consistent with a previous report (9), our patient had relatively mild neutropenia, which seemed unlikely to be related to an increased risk of IA. In contrast, all of the previously reported cases of SFTS-related IA had other risk factors (e.g., steroid use and COPD; Table) that may be related to the development of IA. In particular, it was reported that corticosteroids were used in 58% of patients with SFTS (2). The frequent use of corticosteroids may partly explain the high prevalence of IA in patients with SFTS. However, corticosteroids were not administered to our patient. This suggests that SFTS itself can increase the risk of IA, and that SFTS-related lymphocytopenia may increase the risk of IA.

ATB is an uncommon clinical manifestation of IA that predominantly involves the major airway and was reported to occur in about 8% of patients with IA and common risk factors (10). Among patients without traditional risk factors, higher rates of ATB were reported in patients with severe COPD (18-36%) or influenza pneumonia (16%) (11-13). However, central airway lesions were found in all patients with proven SFTS-related IA, including our patient (Table). The estimated prevalence of ATB in SFTS-related IA may be as high as 60%, which is much greater than its prevalence in other populations. The diagnosis of ATB is often difficult and delayed because of its non-specific clinical presentation and radiological findings, particularly if the physician has not considered it. Indeed, the typical chest CT findings for invasive pulmonary aspergillosis, such as nodules with halo signs or cavities, are rarely seen in patients with SFTS-related IA, and in some patients, IA was diagnosed by an autopsy (Table). Therefore, diagnostic examinations for IA, including bronchoscopy, should be considered for patients with SFTS and refractory respiratory symptoms (e.g., cough or wheeze) or respiratory failure.

In conclusion, we encountered a patient with SFTS-related IA without any other common risk factors for IA. Because SFTS-related IA may have uncommon clinical

presentations, like ATB, physicians should consider the risk of IA in patients with SFTS, even in the absence of common risk factors for IA.

The authors state that they have no Conflict of Interest (COI).

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