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Proven invasive pulmonary aspergillosis in the early clinical course of severe fever with thrombocytopenia syndrome: Importance of an early diagnosis

KEYWORDS
Severe fever with thrombocytopenia syndrome;
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Invasive pulmonary aspergillosis;
Bronchoscopy

Dear Editor,

Severe fever with thrombocytopenia syndrome (SFTS) is an emerging tick-borne zoonosis in East Asia caused by SFTS virus (SFTSV). The case-fatality rate ranges from 16% to 32%.[1] Cytokine storms caused by viral infection are thought to be important in its pathogenesis, resulting in death from systemic inflammatory reactions, multi-organ failure, and coagulation abnormalities.

Superinfections, including invasive pulmonary aspergillosis (IPA), are well-known complications of severe viral pneumonia in critically ill patients.[2] SFTS-associated pulmonary aspergillosis (SAPA) has been reported in several small case series and is an important cause of morbidity and mortality.[3,4]

Here, we describe a case of proven IPA diagnosed without abnormal chest radiographic findings in the early clinical course of SFTS and introduce our screening and diagnostic protocol for SAPA.

A healthy 62-year-old woman was admitted to our hospital in summer because of fever and severe fatigue. Three days before admission, fever developed which was followed by severe fatigue, headache, abdominal pain, and non-bloody diarrhoea.

On admission, she was alert and her vital signs normal except the fever. Laboratory tests revealed the following: white-cell count 800/μL, platelet count 52,000/μL, C-reactive protein 4.62 mg/dL, lactate dehydrogenase 617 IU/L, aspartate aminotransferase 447 IU/L, alanine aminotransferase 100 IU/L, creatinine phosphokinase 749 IU/L, and ferritin 1675 ng/mL. On the second hospital day, the patient lost consciousness and developed multi-organ dysfunction (MODS score 3 at baseline to 9). Early management of septic shock was initiated, and she was transferred to the intensive care unit. SFTSV was detected that day by real-time reverse transcription-polymerase chain reaction. Cefepime and azithromycin were administered empirically, and therapeutic plasma exchange was performed daily for two days.

On the fourth hospital day, the chest x-ray was normal. However, serum *Aspergillus* galactomannan antigen (GM) level was 0.67 (0—0.49). Chest computed tomography (CT) revealed multifocal patchy mixed ground-glass attenuations in both upper lungs (Fig. 1A, B). Although the patient had no risk factor of IPA, voriconazole was started because of possible IPA. Bronchoscopy revealed a small ulcer covered by a white exudate in the proximal right upper lobe bronchus and this was biopsied (Fig. 1C). In bronchoalveolar lavage (BAL) fluid, lymphocytes were predominant (45%), and no bacteria were isolated. On the seventh hospital day,

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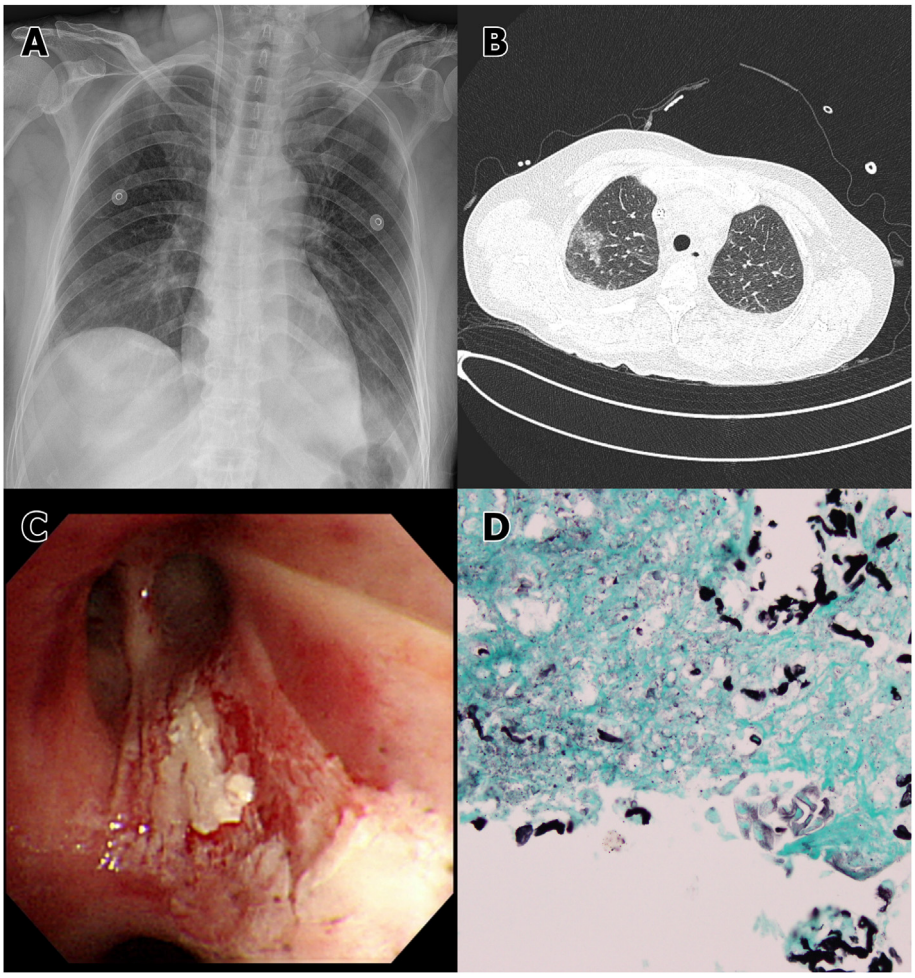

Figure 1. (A) A chest radiograph obtained on the fourth hospital day. (B) CT of the chest reveals multiple patchy mixed ground-glass opacities in both upper lungs without cavitation. (C) Bronchoscopy shows a small ulcerative lesion covered with exudate on the right upper lobe bronchus. (D) Gomori methenamine silver staining of biopsied specimen from the right upper bronchus at 400 × magnification shows many fungal hyphae, morphologically consistent with aspergillosis.

GM was 5.02 and SFTSV-RNA was detected on BAL fluid. The tissue specimen showed necro-inflammatory exudates admixed with fungal hyphae (Fig. 1D). Finally, *Aspergillus niger* was cultured from the BAL fluid. The SAPA was treated with voriconazole for 3 months and the patient recovered fully.

This case documents a proven SAPA in the early phase of severe SFTS in a previously healthy woman through appropriate screening. Clinicians are alert to the possibility of bacterial co-infection; however, the risk of fungal co-infection remains underappreciated.

Fatal SFTS patients might be heavily immunosuppressed relatively in the early course of infection. SFTSV has several mechanisms for damping the host defences. The mechanisms of virus-induced immunosuppression are explained by immune-suppressive interleukin-10 overproduction, and a reduction in lymphocyte, especially CD4+ T cells.[3]

In STFS, IPA occurs earlier than other common risk factors for fungal infection, and the median time until diagnosis is approximately 8 days. In severe patients with altered mental status, SAPA is more common and the mortality rate exceeds 60%.[3] As in our patient, SAPA may develop earlier than expected and, unlike other risk factors, it often manifests as Aspergillus tracheobronchitis.[5] Therefore, bronchoscopy is important to observe endobronchial lesion.

Our institution treats more than 10 SFTS cases annually and is implementing a strategic approach for the early diagnosis and subsequent management of SAPA. Initial screening for SAPA entails using a combination of chest x-ray and serum GM tests in patients with severe SFTS or a pulmonary infiltrate. If screening is positive, Chest CT and bronchoscopy are performed, and a pre-emptive antifungal drug is administered if indicated.

In conclusion, physicians should consider the risk of IPA in patients with SFTS. A strategic approach to diagnosing SAPA is important for early detection and appropriate treatment. In addition, aspergillosis tracheobronchitis may occur at an early stage, so it is important to consider

bronchoscopy. More prospective research on the epidemiology and diagnosis of SAPA is needed.

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Declaration of Competing Interest

The authors declare that they have no competing interests.

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