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BRIEF REPORT

Invasive Pulmonary Aspergillosis in Patients With Severe Fever With Thrombocytopenia Syndrome

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Sixteen of 45 patients with severe fever with thrombocytopenia (36%) were admitted to an intensive care unit; 9 (56%) developed invasive pulmonary aspergillosis (IPA) within a median of 8 days (range, 2–11). Mortality was higher in the IPA vs non-IPA patients and in those without vs with antifungal therapy.

Keywords. severe fever with thrombocytopenia syndrome; severe fever with thrombocytopenia syndrome virus; invasive pulmonary aspergillosis.

Severe fever with thrombocytopenia syndrome (SFTS) is an emerging tick-borne disease that has been reported in East Asia, including China, Korea, and Japan, for a decade [1]. The SFTS virus (SFTSV), which is a newly discovered phlebovirus of the family *Phenuiviridae*, is the causative agent of the disease [1]. The median length of hospitalization for SFTS patients was reported to be 16 days (interquartile range, 13–23 days), with approximately 33% being admitted to the intensive care unit (ICU) and a 20% case fatality rate [2, 3]. Although corticosteroids, ribavirin, and plasmapheresis were administered to SFTS patients in varying degrees, without proven therapeutic benefits, supportive care is the most important part of the treatment strategy [1–3]. However, the mechanisms of viral-induced immunosuppression, including initial immunosuppressive interleukin (IL)-10 production [4], reduction of $CD3^+$ and $CD4^+$ T cells [1], and cytokine storms [5], further complicate the hospital course for SFTS patients. Concern regarding complications such as invasive pulmonary aspergillosis (IPA) in critical SFTS patients has been growing, similar to the high IPA risk in patients admitted to the ICU with severe influenza [6]. Therefore, we investigated the incidence and clinical characteristics of IPA, including computed tomography (CT) findings, in patients with laboratory-confirmed SFTS.

METHODS

Study Population

All SFTS patients were retrospectively enrolled at the Asan Medical Center, which is a 2700-bed tertiary hospital in Seoul, South Korea, from January 2014 to October 2018. The SFTS diagnosis was confirmed by detection of the viral genome in patient sera using reverse-transcriptase polymerase chain reaction (RT-PCR) with the DiaStar 2X OneStep RT-PCR Pre-Mix kit (SolGent, Daejeon, South Korea), as described elsewhere [7]. The Asan Medical Center Institutional Review Board approved the study protocol.

Definition of Invasive Aspergillosis Among SFTS Patients

Because SFTS patients do not have classic host factors according to the European Organization for the Research and Treatment of Cancer/Mycosis Study Group (EORTC/MSG) criteria, we used a "putative" aspergillosis concept, which is a new diagnostic IPA category defined by the *Asp*ICU algorithm to encompass a broader range of patients at risk. This externally validated algorithm has been widely adopted to define putative IPA (PIPA) cases among critically ill patients without conventional risk factors [8]. We categorized putative aspergillosis using a modified *Asp*ICU algorithm as described previously [6]. Briefly, the putative aspergillosis definition was based on clinical, radiological, and mycological criteria as the presence of the following 3 criteria: compatible signs and symptoms of IPA, abnormal findings on either a chest X ray or CT scan of the lungs, and mycological criteria such as histopathologic evidence of hyphae with recovery of *Aspergillus* from tissue, positive culture from a bronchoalveolar lavage (BAL), galactomannan (GM) index in BAL ≥1, or GM index in serum ≥0.5. Two independent radiologists analyzed the radiological findings of patients classified with PIPA through review of chest X rays and CT images.

Statistical Analyses

Categorical variables were compared using the Fisher exact or Pearson χ^2 test, as appropriate. Continuous variables were compared using the Mann-Whitney *U* or Student *t* test, as appropriate. For the survival analysis, Kaplan-Meyer analysis was applied using the log-rank test to compare groups. All significance tests were 2-tailed, and differences were considered statistically significant at $P \leq .05$. The results were analyzed using SPSS for Windows, version 23.0 (IBM Corp, Armonk, NY).

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RESULTS

A total of 45 patients with laboratory-confirmed SFTS were analyzed. Of these patients, 36 (80%) had leukopenia (white blood cells, <4000/μL) and 43 (96%) had thrombocytopenia (platelet, $<150 \times 10^3$/μL). Sixteen (36%) critically ill patients were admitted to the ICU, of whom 9 (56%) developed PIPA during hospitalization. Therefore, 20% of all SFTS patients (9 of 45) and 56% of ICU-admitted patients (9 of 16) developed PIPA. The median time from admission to IPA diagnosis was 8 days (range, 2–11). No PIPA case met the EORTC criteria in terms of host and clinical factors. The demographic and laboratory characteristics are summarized in Supplementary Tables 1 and 2.

No significant difference in the underlying disease was found between the PIPA and non-PIPA patients. At the initial visit, an altered mental status was more frequently observed in the PIPA patients (Supplementary Table 1). The lactate dehydrogenase and procalcitonin levels were higher in the PIPA than in the non-PIPA group. Additionally, initial X-ray abnormalities and aggravated radiologic findings during the hospitalization period were more frequent, and the septic shock, ICU admission, and ventilator care rates were significantly higher in the PIPA than in the non-PIPA patients. The frequency of corticosteroid use was higher in the PIPA than in the non-PIPA patients, but no significant difference in antibiotic use was found between the groups (Supplementary Table 2). Of the 9 patients with PIPA, 6 received antifungal therapy and 3 were untreated. The PIPA group had higher mortality than the non-PIPA group (log rank, $P = .048$; Figure 1A). In the PIPA group, patients who received antifungal therapy had better survival than those who did not (log rank, $P = .002$; Figure 1B).

We also reviewed the radiological findings of PIPA cases (summarized in Supplementary Table 3). The most frequently observed finding was a dense circumscribed lesion as a consolidation. The typical radiological features are shown as a mixture of IPA-specific and nonspecific findings in Supplementary Figures 1 and 2. Details of the hospital course of the PIPA patients are summarized in Supplementary Table 4.

DISCUSSION

It has been reported that the SFTSV has several mechanisms for evading a host's innate and adaptive immune system. First, immunosuppressive IL-10 production, induced by an SFTSV nonstructural protein, has been proposed as a key mechanism that allows initial immune evasion and promotes viral replication [4]. Second, the reduction of $CD3^+$ and $CD4^+$ T cells due to extensive monocyte apoptosis by viral replication can lead to the attenuation of cellular and humoral immune responses [1]. Third, cytokine storms have been reported as a major pathophysiological mechanism that aggravates leukopenia and thrombocytopenia [5]. A dysregulated immune system with hypercytokinemia may cause leukopenia and thrombocytopenia due to peripheral destruction and/or bone marrow suppression, which subsequently might result in further immunosuppression. Eventually, the immunosuppression caused by these mechanisms may contribute to the development of IPA in critically ill SFTS patients. Leukopenia is a well-known risk factor for IPA [6]. In addition, a recent study revealed that patients with enhanced IL-10 expression due to single nucleotide polymorphisms showed higher susceptibility to IPA [9]. Given the ability of platelets to block *Aspergillus fumigatus* germination and hyphal elongation, a characteristic platelet deficiency in SFTS can make patients more vulnerable to IPA [10]. Taken together, we believe that leukopenia, thrombocytopenia, and IL-10 overexpression play important roles in IPA development in critically ill SFTS patients.

Most research on the clinical impact of IPA has been conducted in patients with hematologic malignancies or in transplant recipients [11]. Recently, several studies reported the burden of IPA in other categories of critically ill patients without classic EORTC host factors [8]. The *Asp*ICU algorithm enables clinicians and researchers to diagnose and identify invasive aspergillosis in patients with various underlying conditions, such as cirrhotic liver disease, chronic obstructive pulmonary disease, and severe influenza [6, 12, 13]. Because most patients cannot be classified according to the EORTC criteria due to a lack of classic EORTC host and clinical factors, diagnosis and appropriate antifungal therapy are often delayed. Notably, the use of antifungal agents in PIPA patients was significantly associated with improved survival. Therefore, early diagnosis of IPA and use of appropriate antifungal agents as supportive care will contribute to better outcomes of SFTS because no effective antiviral agents are available.

Our study has a few limitations. First, we included only SFTS patients from a tertiary referral hospital. Thus, selection bias toward more severe diseases could exist. Second, some may argue that the frequent use of corticosteroids in critically ill SFTS patients may play a major role in the development of IPA, instead of SFTS itself. However, most SFTS patients received corticosteroids for a relatively short period (median, 3 days), followed by the rapid development of IPA after admission (median, 8 days). In this context, the use of corticosteroids may contribute to the development of IPA in SFTS patients, but other factors associated with SFTS (ie, leukopenia, thrombocytopenia, IL-10 overexpression, and the use of broad-spectrum antibiotics) may also contribute to the development of IPA. Further studies are needed on this issue with larger numbers of SFTS patients with IPA. Third, because of the retrospective study design, we found a significant change in the early detection and treatment of IPA among SFTS patients in clinical practice (ie, that the learning effect over time changes).

In conclusion, approximately one-fifth of SFTS patients developed IPA during their hospital course. Cautious scrutiny for

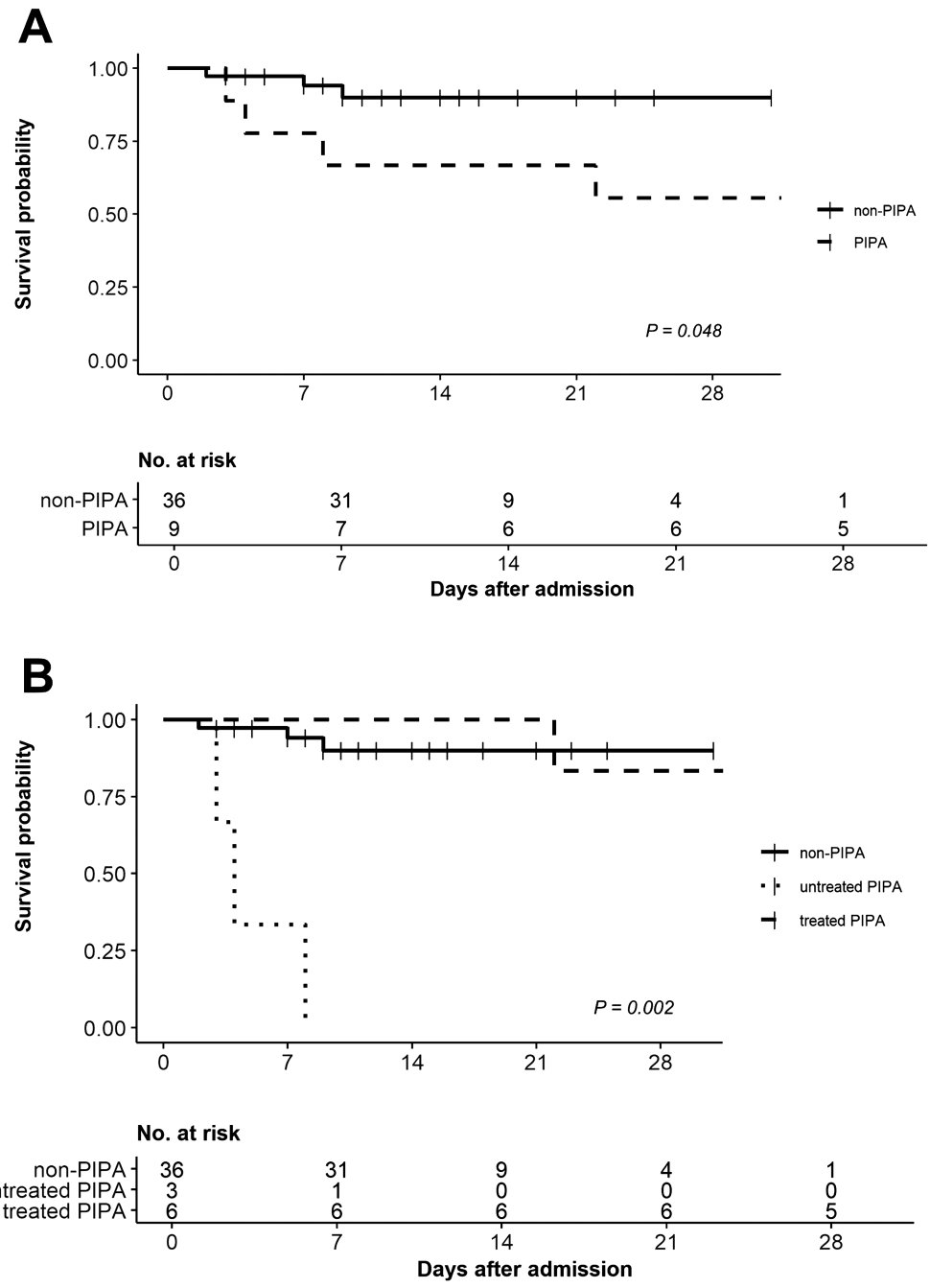

Figure 1. Kaplan–Meier curves for survival in the severe fever with thrombocytopenia syndrome (SFTS) patients. *A,* Survival curves for SFTS patients complicated with and without putative invasive pulmonary aspergillosis ($P = .048$ by log-rank test). *B,* Survival curves for SFTS patients classified into 3 groups (nonputative invasive pulmonary aspergillosis (PIPA), PIPA with antifungal treatment, and PIPA without antifungal treatment) in the same plot with the log-rank test. Abbreviation: PIPA, putative invasive pulmonary aspergillosis.

IPA in SFTS patients followed by early appropriate antifungal therapy for IPA are needed.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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