J Infect Chemother xxx (2018) 1–6

Contents lists available at ScienceDirect

Journal of Infection and Chemotherapy

journal homepage: http://www.elsevier.com/locate/jic

Original Article

Clinical features of fatal severe fever with thrombocytopenia syndrome that is complicated by invasive pulmonary aspergillosis

Xiancheng Chen [1], Zhuxi Yu [1], Yajun Qian, Danjiang Dong, Yingying Hao, Ning Liu, Qin Gu*

Department of Critical Care Medicine, Nanjing Drum Tower Hospital, The Affiliated Hospital of Nanjing University Medical School, No. 321 Zhongshan Road, Nanjing, Jiangsu Province, China

ARTICLE INFO

Article history:
Received 26 August 2017
Received in revised form
31 October 2017
Accepted 10 January 2018
Available online xxx

Keywords:
Severe fever with thrombocytopenia syndrome
Invasive pulmonary aspergillosis
Prognosis
Aspergillosis
Diagnostics

ABSTRACT

Introduction: Severe fever with thrombocytopenia syndrome (SFTS) has been prevalent in parts of Asia during recent years. However, SFTS with invasive pulmonary aspergillosis (IPA) is rare, and it is important to understand its clinical features.
Materials and methods: Total four cases of SFTS with IPA are reviewed and detailing the disease progression, treatment options, and prognosis were summarized and analyzed.
Results: The patients with SFTS-associated IPA first presented with fever, gastrointestinal symptoms, thrombocytopenia, leukopenia, and multiple organ failure. After 1–2 weeks, the patients developed mild polypnea and wheezing rales, and quickly developed dyspnea and respiratory failure. Tracheal intubation was usually performed, but did not relieve the intractable airway spasm and pulmonary ventilation failure. Bronchoscopy confirmed that the antifungal treatment was ineffective and the aspergillosis had worsened. All patients died of type 2 respiratory failure caused by continued airway obstruction and spasticity.
Conclusions: Given the high mortality rate in this series, there is a need for increased awareness of SFTS-associated IPA. Additional examinations should be performed in these cases, and early-stage antifungal treatment with organ support may be helpful.

1. Introduction

Severe fever with thrombocytopenia syndrome (SFTS) is an infection that is caused by a novel phlebovirus, characterized by unexplained fever, thrombocytopenia, leukopenia, gastrointestinal symptoms (e.g., nausea, celiodynia, and diarrhea), and multiple organ failures. This disease is mainly prevalent in the agricultural and mountainous regions of China, Japan, and South Korea [1]. A bunyavirus that is associated with the disease has been named the SFTS virus (SFTSV), and its RNA was isolated and identified in 2011 [2]. SFTS-related mortality is caused by multiple organ failures, which can involve significant thrombocytopenia, severe coagulopathy, central nervous system damage, and respiratory failure [3]. However, we are not aware of any reports that have examined the association of SFTS with invasive pulmonary aspergillosis (IPA).

IPA is the most common type of invasive aspergillosis, and usually develops in immunocompromised patients who have experienced neutropenia, hematological malignancy, transplantation, prolonged treatment with corticosteroids, or lung destruction [4]. The primary disease is usually masked by equivocal symptoms of IPA, such as fever, cough, chest pain, and hemoptysis [5].

We report the clinical characteristics and treatments from four cases of SFTS-associated IPA, in order to help improve the clinical outcomes among these critically ill patients.

2. Materials and methods

This retrospective study examined data from 48 patients with SFTS who were treated at the Nanjing Drum Tower Hospital between July 2010 and July 2017. Four patients were found to have SFTS with IPA. The study's retrospective protocol was approved by the Ethics Committee of the Nanjing Drum Tower Hospital, and all data were anonymized. The patients' medical records were searched to obtain clinical and demographic data, such as underlying medical conditions, clinical signs and symptoms, and laboratory test results, as well as any relevant follow-up data.

* Corresponding author. No. 321 Zhongshan Road, Nanjing, Jiangsu Province, 210008, China.
E-mail address: guqin_icu1@yeah.net (Q. Gu).
[1] Xiancheng Chen and Zhuxi Yu contributed equally to this work.

https://doi.org/10.1016/j.jiac.2018.01.005
1341-321X/

The SFTS diagnoses were confirmed based on (a) acute fever, (b) thrombocytopenia, (c) detection of SFTSV RNA using polymerase chain reaction, (d) detection of IgM to the SFTSV, or (e) seroconversion or a >4-fold increase in IgG to SFTSV when the acute and convalescent serum samples were compared [6]. The IPA diagnoses were based on the revised definitions of invasive fungal infections from the European Organization for the Research and Treatment of Cancer/Mycosis Study Group [7]. A diagnosis of IPA is considered probable if the patient has appropriate clinical manifestations, positive cultures, and a positive result from the serum galactomannan antigen test for aspergillosis. However, a diagnosis of proven IPA requires direct histopathological evidence.

3. Results

The initiation and progression of disease for four cases of SFTS with IPA are summarized as follows:

3.1. Case 1

A 72-year-old woman who performed agricultural work presented to a local hospital with a 3-day history of fever (>38.5 °C), nausea, and vomiting. Laboratory tests revealed leukopenia (white blood cell [WBC] count: 1700/μL, normal: 4000–10000/μL), thrombocytopenia (platelet [PLT] count: 0.36 × 10^4/μL, normal: 1–3 × 10^4/μL), acute liver injury (aspartate aminotransferase [AST] level: 93 U/L, normal: 8–40 U/L; alanine aminotransferase [ALT] level: 319 U/L, normal: 5–40 U/L), and acute renal injury (creatinine [Cr] level: 1.58 mg/dL, normal: 0.50–1.20 mg/dL; blood urea nitrogen (BUN) level: 44.23 mg/dL, normal: 8.12–21.01 mg/dL). She was treated using antibiotics (cephalosporin) and antipyretics, which included dexamethasone and nonsteroidal anti-inflammatory drugs. However, her fever did not improve and she gradually became somnolent before being referred to our hospital for additional treatment. The laboratory test results from her admission to our hospital were a PLT count of 0.38 × 10^4/μL, an activated partial thromboplastin time (APTT) of 57.1 s (normal: 20–40 s), and a thrombin time (TT) of 110 s (normal: 13–21 s). After she was admitted to our infectious disease ward, she received antiviral treatment (ribavirin and ganciclovir), an antibiotic (minocycline), plasma, cryoprecipitate, and a gamma globulin infusion based on a suspicion of SFTS. Fourteen days after the onset of disease, she slipped into a coma and developed dyspnea with acute left heart failure, and was subsequently transferred to our intensive care unit (ICU). The patient underwent endotracheal intubation with simultaneous intermittent mechanical ventilation and continuous renal replacement therapy (CRRT) to improve the acute renal injury and fluid overload.

During this period, the patient tested positive for bunyavirus RNA, which confirmed the diagnosis of SFTS. In addition, her sputum culture was positive for *Aspergillus flavus*, and she had a serum galactomannan (GM) level of 5.4 (normal cut-off index:0–0.5) and a (1 → 3)-β-D-glucan level of 617.4 pg/mL (normal: 0–100.5 pg/mL). Chest radiography revealed bilateral lung infiltration and computed tomography (CT) revealed scattered nodular or patchy shadows with obscure borders on both sides of the lungs. Bronchoscopy revealed that the right airway was obstructed by yellowish white mold, and the left airway had scattered yellowish-white mold. The airway mucosa was edematous and bled easily. Pathological examination of the airway tissue revealed necrotic fibrous tissue and fungal filaments, which confirmed an Aspergillus infection (Fig. 1). The patient received voriconazole (6 mg/kg every 12 h for first day, then 4 mg/kg every 12 h, intravenous) based on suspected IPA. But serious airway spasms persisted despite treatment using bronchial and muscle relaxants. Arterial blood gas analysis revealed a persistently increasing partial pressure of carbon dioxide (PCO_2), and the patient ultimately died because of pulmonary function failure and a severe coagulation disorder.

3.2. Case 2

A 42-year-old female farmer developed fever (>38 °C), fatigue, anorexia, and muscle pain. A community hospital treated her using antipyretics (acetaminophen and dexamethasone, 5 mg, twice) and an antibiotic (ceftriaxone), although these treatments did not improve her symptoms. On day 7, the patient experienced hyperspasmia with loss of consciousness for 1 min. On day 8, the patient experienced another episode of hyperspasmia and continued drowsiness, and was subsequently admitted to our hospital. After being admitted to an emergency ICU, she underwent endotracheal intubation and ventilator-assisted breathing. Laboratory testing revealed a WBC count of 3800/μL, a PLT count of 0.36 × 10^4/μL, an AST level of 3510 U/L, an ALT level of 745 U/L, and a Cr level of 5.03 mg/dL. The patient subsequently received antiviral treatment (ribavirin), an antibiotic (ceftizoxime), an immune globulin infusion, a transfusion, and CRRT. Bunyavirus RNA was detected, which supported a diagnosis of SFTS. Two weeks later, the patient developed progressively worsening shortness of breath, and multiple sputum cultures tested positive for *Aspergillus fumigatus*, with a serum GM level of 5.6 and a serum (1 → 3)-β-D-glucan level of 134.1 pg/mL. Radiography revealed bilateral lung infiltrations and CT revealed a globular shadow along the bronchi tree, which supported a probable diagnosis of IPA. The patient received caspofungin (70 mg/day for first day, then 50 mg/day, intravenous) and voriconazole (6 mg/kg every 12 h for first day, then 4 mg/kg every 12 h, intravenous), although her partial PCO_2 continued to rise (to 100 mmHg) and CT revealed multiple cavities with serious bilateral consolidation. Thus, she was transferred to our ICU (Fig. 2).

Bronchoscopy revealed yellowish-white mold that was partially obstructing the entire airway. The airway mucosa was edematous and bled easily. Pathological examination of the airway tissue revealed fungal filaments (Fig. 3). The patient's pulmonary function improve slightly after the ventilator parameters were adjusted and she received bronchial and muscle relaxants. In addition, the patient received intravenous antifungal treatment (voriconazole and caspofungin) with inhaled amphotericin B (10 mg, every 8 h, inhaled). However, the patient's asthma and dyspnea worsened on day 23, and her partial PCO_2 rose to 105 mmHg. Bronchoscopy revealed diffuse yellowish-white mold throughout the entire airway, which obstructed the subsegmental bronchi. Oxygenation could not be maintained using mechanical ventilation because of the patient's respiratory failure, and venovenous extracorporeal membrane oxygenation (ECMO) was used. The IPA had progressed despite 11 days of voriconazole and caspofungin treatment, the antifungal therapy was changed to intravenous voriconazole, intravenous amphotericin B liposome (3 mg/kg, every day) and inhaled amphotericin B. The 9-day ECMO treatment maintained oxygenation at a normal level, but the airway spasms and obstruction did not improve. Repeated bronchoscopy also confirmed that the mold was not controlled by the treatments. The patient subsequently slipped into a deep coma after developing serious coagulopathy, aggravated liver failure, and complete dependence on ECMO for oxygenation. She eventually died because of SFTS with IPA.

3.3. Case 3

A 58-year-old female farmer developed a fever (>39 °C), fatigue, anorexia, dizziness, and vomiting. She was initially treated using dexamethasone and intravenous fluids, although 3 days later she

Please cite this article in press as: Chen X, et al., Clinical features of fatal severe fever with thrombocytopenia syndrome that is complicated by invasive pulmonary aspergillosis, J Infect Chemother (2018), https://doi.org/10.1016/j.jiac.2018.01.005