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Communication

The First Case of Non-retrospective Clinical Identification of Severe Fever with Thrombocytopenia Syndrome Patient in 2013 in South Korea

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In this study, we report the first clinically identified case of severe fever with thrombocytopenia syndrome (SFTS) in a 73-year old man from Jeju Island, South Korea. Although his initial manifestation suggested tsutsugamushi disease with cutaneous lesion, later the patient presented with symptoms characteristic of SFTS. Despite intensive medical therapies upon the clinical diagnosis of SFTS, patient's condition rapidly deteriorated. SFTS is a fatal disease that requires early diagnosis and appropriate supportive treatment.

Key Words: Severe fever with thrombocytopenia syndrome, South Korea, Jeju Island

Severe fever with thrombocytopenia syndrome (SFTS) is an emerging infectious disease caused by severe fever with thrombocytopenia virus (SFTSV), the *Phelobovirus* species in the family Bunyaviridae (1, 2). A number of SFTS cases have been reported since the first identification of SFTSV as an etiologic agent of SFTS in 2009 in China (3), but most of them were diagnosed retrospectively (1~7). Although clinical symptoms and progression of SFTS vary individually, common symptoms and signs include fever, thrombocytopenia, neutropenia, hemorrhagic tendency, and multiple organ dysfunction involving gastrointestinal (GI), renal, and nervous systems (4). Because its mortality is approximately 12% on average in China, it is essential for clinicians to recognize characteristic symptoms of SFTS although guidelines for diagnosis and treatment have yet been established (5). Here, we describe the first clinically recognized case of SFTS in South Korea in 2013. Since the current case, more patients have been identified and diagnosed with SFTS in Korea. Kim *et al*. reported about the first case of SFTS in Korea. However, they did not consider SFTS when they saw the patient at first. That case was detected retrospectively after this patient was identified in Korea (7). This study protocol was reviewed and approved by the institutional review board of JNUH (2013-10-010).

A 73-year-old man, who is a farmer raising cattles, was admitted to a hospital in Jeju with worsening fever and lower back pain lasting for 5 days. The patient discovered a tick crawling on his abdomen and a crust round erythematous cutaneous lesion suspicious of tick-bite at his right axilla. Clinicians suspected of tsutsugamushi disease at first and

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initiated antibiotic treatment with doxycycline (200 mg every 12 h). The initial complete blood count revealed no abnormalities except for neutropenia (2,290/mm^3) and thrombocytopenia (106,000/mm^3). In addition, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were mildly increased with 100 IU/l and 60 IU/l, respectively. Diarrhea began on the 2nd day of admission, and on the 3rd day, the patient was transferred to our hospital with persistent fever, neutropenia, and thrombocytopenia.

At the time of admission to emergency department of our institution, the patient had a fever of 39℃, diarrhea, and petechiae on all of the extremities. Blood examination indicated white blood cell 1,500/mm^3, hemoglobin 15.6 g/dl, and platelet 30,000/mm^3 along with further elevated liver enzymes of AST 392 IU/l and ALT 136 IU/l. Based on the patient's clinical manifestations such as persistent high fever, GI symptoms, leukopenia, thrombocytopenia, and hepatic dysfunction, we were able to suspect of SFTS, performed blood culture, and initiated cefepime (1 g every 12 h), in accordance with treatment of neutropenic fever, in an isolation room. On 2nd hospital day, despite the broad spectrum antibiotic treatment, persistent fever continued, and progressive loss of consciousness and dyspnea newly appeared. The patient was transferred to intensive care unit and put on mechanical ventilator. On 3rd hospital day, continuous renal replacement therapy (CRRT) was initiated due to newly appeared oliguria and metabolic alkalosis. On 5th hospital day, hemorrhagic tendency was evident at insertion sites of nasogastric tube, intubation, and central catheter in addition to extensively prolonged activated partial thromboplastin time, suggesting disseminated intravascular coagulation. Blood culture carried out on the 1st day was negative, but following blood culture on 3rd day showed fungal infection, which was later identified as *Candida albicans* and treated with amphotericin B (1 mg/kg every 24 hr). In addition, reverse transcriptase-polymerase chain reaction (RT-PCR) was positive for S segment and L segment of SFTSV (Fig. 1) (8). Despite intensive medical treatment including continuous blood and platelet infusion, CRRT, mechanical ventilation, broad spectrum antibiotics, and antifungal agents, the patient was expired on the 9th day of hospitalization.

In previous reports of SFTS including the current case, it is difficult to expectantly treat the rapid progression of clinical manifestations and to predict the course of disease progression. Unlike previous reports, the current case was unusual with eschar-like cutaneous lesion as seen in tsutsugamushi disease (9). Lack of response to doxycycline and other initial clinical symptoms including persistent fever, thrombocytopenia, and multiple organ dysfunctions suggested clinically more toward diagnosis of SFTS in this case. Despite lack of established diagnostic guideline, clinical suspicion of SFTS should be made from high fever, thrombocytopenia, and leukopenia in a patient with a history of tick-bite; in addition, GI and neurologic manifestations are carefully evaluated. Differential diagnosis includes tsutsugamushi disease, lyme disease, anaplasmosis, Crimean-Congo hemorrhagic fever and hemorrhagic fever with renal syndrome (6). Furthermore, SFTSV infection can be identified by viral isolation, Real-time RT-PCR for viral RNA, and changes in serum anti-SFTSV immunoglobulin G (IgG) titers between acute and convalescent phase (3, 10). From whole-genome sequencing and analysis, SFTSV is confirmed to be a novel *Bunyavirus*, and the genome of SFTSV comprises of large (L), medium (M), and small (S) segments, each of which is responsible for specific genetic properties (11). Total RNA of SFTSV is extracted from patient's serum, which was kept at -80℃ and SFTSV were confirmed by real-time RT-PCR (8, 11, 12). The two primer sets used were: for S segments, forward primer (5'-ACCTCTTTGACCCTGAGTTWGACA-3') and reverse primer (5'-CTGAAGGAGACAGGTGGAGATGA-3') (8); for L segments, forward primer (5'-AGTCTAGGTCATCTGATCCGTTYAG-3') and reverse primer (5'-TGTAACTTCGCCCTTTGTCCAT-3') (12). The real-time RT-PCR mixture contained 8 microliter of One-step RT-PCR premix (Thermo Scientific, Made in EU Lithuania), 7 microliter of detection solution, and 5 microliter of RNA template in a total volume of 20 microliter. PCR was performed under the following conditions: 30 minutes at 45℃, 10 minutes at 90℃, 45 cycles of 15 seconds at 95℃ and 30 seconds at 48℃. As a result, 110-bp and 100-bp fragments were amplified for S

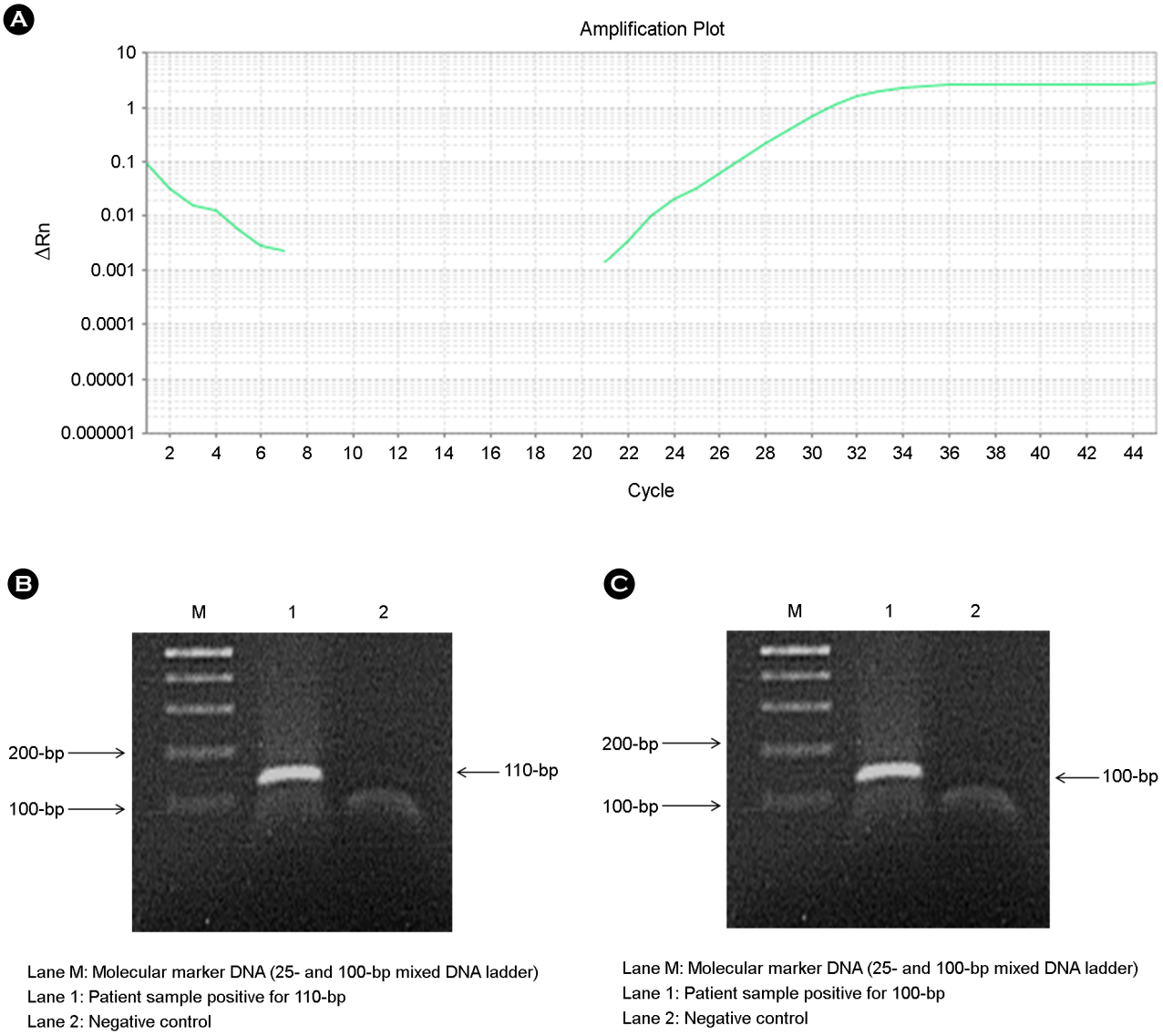

Figure 1. Amplification of S and L segment of SFTSV. (A) S segment of SFTSV was amplified from the SFTS patient's serum by real-time RT-PCR. 1.2% agarose gel electrophoresis demonstrates the 110-bp corresponding to the S segment (B) and the 100-bp corresponding to the L segment (C) of SFTSV.

and L segments, respectively (Fig. 1), which confirmed SFTS in our case finally.

Despite many reports on SFTS, effective treatment methods against SFTS have not been proven, and conservative therapy is currently the mainstream of treatment in SFTS. Based upon the treatment in Crimean-Congo hemorrhagic fever, another tick-born disease by a Bunyaviridae virus, high dose methylprednisolone, fresh frozen plasma, and intravenous immunoglobulin were found to be effective in macrophage suppression, disseminated intravascular coagulation, and thrombocytopenia, respectively, in addition to use of ribavirin for hematologic abnormalities (13, 14). From the most recent case of SFTS, the combination of plasma exchange and ribavirin was tried with a favorable outcome and recommended as a potential rescue therapy for rapidly progressing SFTS (15). However, their efficacies in

treatment of SFTS are still under investigation.

Because diagnosis of SFTS is difficult to be made solely based on clinical manifestations, virological tests such as culture and RT-PCR are necessary for accurate diagnosis. Due to difficulty in prediction of disease progression in SFTS, intensive medical therapies are required. Even though treatment of SFTS is limited to conservative therapies up to now, it has been reported that early diagnosis increases the survival rate in patients with SFTS (16). Therefore, primary care physicians need to be aware of increasing reports on the incidence of SFTS, in endemic regions especially, and further researches on diagnosis and treatment of SFTS are critical.

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