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Preface

Severe fever with thrombocytopenia syndrome (SFTS) was reported to be a novel bunyavirus infection by the Chinese scientists in 2011. SFTS is a tick-borne virus infection with high case fatality, and its vectors playing a role in transmitting the causative agent, SFTS virus (SFTSV), are *Haemaphysalis longicornis* and others. To tell the truth, I could not imagine that SFTS was endemic to Japan, when I received the information on the discovery of SFTS in China, even though I knew the evidence that *Haemaphysalis longicornis* was prevalent in Japan.

In autumn, 2012, a woman aged 50s died of multiorgan failure with unknown etiologies. She was retrospectively diagnosed as having SFTS by isolation of SFTSV from the serum specimen and identification of SFTSV antigen in the tissue specimens through the postmortem examination in Japan. The discovery of SFTS patient in Japan indicated that SFTS was also endemic not only to China but also to Japan. SFTS patient was also identified in South Korea as well.

SFTSV is circulating in nature in some regions of mainland China, Korean peninsula, and Japan through the lifecycle between mammals and some species of ticks. The evidence indicates that SFTS has occurred since the past and will continue to occur in the future. We cannot escape the risk being infected with SFTSV. We should study the epidemiology, pathology, and clinical aspects of SFTS more. Basic research on SFTSV and its associated areas is also important. Furthermore, specific antiviral therapies for and the vaccines against SFTS should be developed.

I have studied Crimean-Congo hemorrhagic fever (CCHF) in collaboration with the Chinese scientists in the Chinese Centers for Disease Control and Prevention (China CDC) for a long time. Based on the experience of studying CCHF, I have noticed that there might be many similarities in the disease characteristics between SFTS and CCHF. The studies on SFTS might contribute to those on CCHF, and vice versa.

I believe that we would be able to reduce the number of fatal SFTS patients through further studies including the development of specific antiviral therapies for and effective vaccine against SFTS.

Seven years only have passed since the first report on the discovery of SFTS in 2011. Although the time of the discovery of SFTS to date is short, the summarization of the recent knowledges on SFTS reported at this stage may help us to understand the entire nature of and our study direction for SFTS.

I deeply thank all the contributors of each chapter. I also deeply thank Ms. Kripa Guruprasad, Project Coordinator for Springer Nature.

I wish to dedicate this book to and hope to contribute for all patients with SFTS.

Tokyo, Japan Masayuki Saijo

Contents

Chapter 1
Introduction

Masayuki Saijo

Abstract Novel viral hemorrhagic fever named "severe fever with thrombocytopenia syndrome (SFTS) (N Engl J Med 364:1523–1532, 2011)" or "fever, thrombocytopenia and leukopenia syndrome (FTLS) (PLoS Pathog 7:e1002369, 2011)", both of which are an identical disease, was discovered in China. SFTS is a tick-borne and generalized infection caused by SFTS virus (SFTSV), which is classified in the genus of *Phlebovirus* of the *Bunyaviridae* family, with high morbidity and mortality. According the the recent International Committee on Taxonomy of Viruses, the name of the virus has been changed from SFTSV to Huaiyangshan bangyangvirus, *Banyangvirus* genus of the *Phenuiviridae* family. However, the names of the disease and the virus used in this textbook are SFTS and SFTSV, respectively, because the disease and virus names have been used and recognaized widely and internationally so far. It was later discovered that SFTS was endemic not only to China, but also to South Korea and Japan. The research on SFTSV and SFTS has been conducted by many researchers in terms of virology, pathophyisiology, pathogogy, entemology, epidemiology, veterinary science, developmet of specific treatments and preventive measures for SFTS. The discovery of SFTS might be one of the great achievements in infectious disease science history in a decade. SFTSV is maintained in nature in East Asia. It is desired to develop effective treatments for patients with SFTS and preventive measures for people at risk in the endemic regions. In this chaper, the author summarized the general features of SFTS obtained through the intensive studies on SFTS so far from the discovery of this novel virus infection to the development of specific treatments and preventive measures. It is evident that the studies on SFTSV and SFTS has just started and there are many issues to be addressed.

Keywords Severe fever with thrombocytopenia syndrome · Novel bunyavirus · Severe fever with thrombocytopenia syndrome virus

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1.1 Introduction

The author summarized the general features of severe fever with thrombocytopenia syndrome (SFTS) obtained through the intensive studies on SFTS so far in this introduction section: from the discovery of this novel virus infection to the development of specific treatments and preventive measures. All the contents described in this introduction section are the summary for each section that will appears in this book described by each contributor.

1.2 Discovery of a Novel Viral Hemorrhagic Fever-like Infection, SFTS, in Peoples' Republic of China

Two research papers, in which a novel *Phlebovirus* of the *Bunyaviridae* Family, were reported to be the causative agent of the severe disease with high case fatality rate (CFR) by two independent research groups in PR China (Xu et al. 2011; Yu et al. 2011). One study was led by the researchers of the Chinese Centers for Disease Control and Prevention (China CDC, Beijing, China) (Yu et al. 2011) and the other was led by the researchers of the CDC of Henan province, Zhengzhou, PR China (Xu et al. 2011). A novel phlebovirus in the *Bunyaviridae* Family was reported to be the causative virus of the severe disease. The symptoms of the disease includes sudden onset of fever, gastrointestinal symptoms (vomiting, diarrhea, etc.), unconsciousness and hemorrhage. The disease was reported to be a tick-borne virus infection and *Haemaphysalis longicornis* might be the vector playing a role in transmitting the virus to humans (Yu et al. 2011). In the former article, the authors proposed to name the disease and the causative virus severe fever with thrombocytopenia syndrome (SFTS) and SFTS virus (SFTSV), respectively (Yu et al. 2011). In the latter article, the authors called the disease and the causative agent as fever, thrombocytopenia and leukopenia syndrome (FTLS) and Henan virus, respectively (Xu et al. 2011). Both disease names and the virus names are used internationally, but the former disease and virus names, SFTS and SFTSV, are used in general internationally. In this book, the terms, SFTS and SFTSV, are used for the description of the disease and the causative virus, respectively.

According to the natures of the disease reported, it was speculated that the disease might be a viral hemorrhagic fever (VHF)-like disease. The nature of the virus and the symptoms of the disease seemed to be similar to those of Crimean-Congo hemorrhagic fever (CCHF), which is caused by CCHF virus (CCHFV) (Bente et al. 2013). CCHF is also a tick-borne virus infection (Hoogstraal 1979). Furthermore, CCHFV belongs to the *Bunyaviridae* Family, although the Genus of the virus is *Nairovirus*, while that of SFTSV is *Phlebovirus*.

The wonderful aspects of the studies were that both studies were conducted prospectively to identify the causative agents for the etiology-unknown disease, which had been observed in the residents, farmers and others living in mountainous regions of Henan, Hebei, Shandong, and Heilongjiang Provinces, with using the new technologies such as next generation sequencing as well as the classical techniques such as cell-based virus isolation.

According to the former article, the residents living in mountainous areas in Henan Province, Hubei Province, Shandong Province and Heilongjiang Province of China, were reported to have suffered from severe infection-like disease, whose CFR was 12% (Yu et al. 2011). SFTSV was isolated from the patients with the disease. It was also reported that 5.4% of ticks, *Haemaphysalis longicornis*, were positive for SFTSV genome with highly sensitive reverse-transcription polymerase chain reaction (RT-PCR), indicating that SFTS was a tick-borne infection (Yu et al. 2011).

In the latter article, it was written that since 2007, many cases of fever, thrombocytopenia and leukopenia syndrome (FTLS) have emerged in Henan Province, PR China (Xu et al. 2011). The patients with FTLS experienced tick-bite, suggesting the disease might be a tick-borne virus infection. Only 8% of the FTLS patients were diagnosed as having human granulocytic anaplasmosis (HGA), an ehrlichial disease, suggesting that the other pathogens might be the cause of the disease. The authors detected virus genome sequence by using metagenomic approach with whole-genome sequencing. BLASTx analysis of deduced protein sequences revealed that the virus was a novel Bunyavirus, which was closely related to Uukuniemi virus of the *Phlebovirus* Genus through phylogenetic analyses. Novel virus was isolated from the serum samples of the acute phase patients.

1.3 Discovery of SFTS Epidemics in Japan and South Korea

In January 2013, SFTS patient was discovered for the first time in Japan (Takahashi et al. 2014). A woman aged 50's, who lived in western Japan, died of multi-organ failure in November 2012 and she was examined for postmortem autopsy to determine the cause of the fatality. She was retrospectively diagnosed as having SFTS by isolation of SFTSV from serum sample using cell culture system and the detection of SFTSV antigen (nucleocapsid protein) in the regional lymph nodes with immunohistochemistry analysis. It became evident that SFTS was endemic to Japan.

An SFTS patient was also identified in South Korea (Yun et al. 2014). A previously healthy 63-year-old woman who lived in Chuncheon-si, Gangwon Province, South Korea, died of multi-organ failure 10 days later from the disease onset in August 2012. She was also retrospectively diagnosed as having SFTS by isolation of SFTSV from

the serum samples, which had been stored at −70 °C, indicating that SFTS was also endemic to South Korea, possibly to the entire areas of Korean Peninsula.

1.4 Causative Virus, SFTSV

The causative agent, SFTSV, is a negative sense, single-stranded RNA virus classified to the *Phlebovirus* Genus of the *Bunyaviridae* Family (Fig. 1.1). Viral particles contain three-segmented RNA (L-, M-, and S-genes in descending order according to size). L-, M-, and S-genes encode RNA-dependent polymerase synthase, membrane glycoprotein, and nucleoprotein and nonstructural protein, respectively.

According to the phylogenetic analyses based on the nucleotide sequence of SFTSV genes reported so far, most SFTSV Japanese strains form clusters independent from Chinese strains, indicating that the SFTS epidemic in Japan is due to the SFTSV, which has evolved independently in Japan from those in mainland China (Takahashi et al. 2014; Yoshikawa et al. 2015).

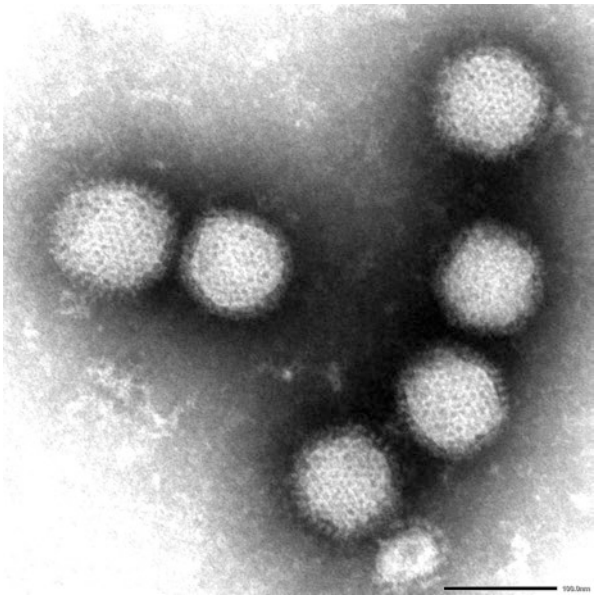

Fig. 1.1 Morphological feature of SFTSV isolated from a patient in Japan using Vero cells. SFTSV is a spherical virion with a diameter of 80–100 nm in length. Three segmented RNA, S-, M-, and L-segments are included in one virion particle. Glycoprotein encoded by M-segment can be seen on the entire virion surface

1.5 Similarity and Difference in the Characteristics Between Two Bunyavirus Infections SFTS and CCHF

There are some similarities and differences in the characteristics between SFTS and CCHF, which is also caused by CCHF virus (CCHFV) classified as *Bunyaviridae* (*Nairovirus* Geunus) (Saijo 2018). Both SFTS and CCHF are tick-borne virus infections. SFTSV and CCHFV are maintained in nature between some tick species ixodid (hard) ticks and mammals. *Haemaphysalis longicornis* and *Amblyomma testudinarium* play a role in transmitting SFTSV to humans, while some species of ticks (*Hyalomma* species) play a role of transmitting CCHFV to humans. CCHF has historically been classified as VHF. The clinical manifestations, pathophysiology, and the CFRs of both diseases seem to be similar. Most patients with SFTS showed fever, gastrointestinal tract symptoms such as diarrhea and vomiting, deterioration in consciousness and hemorrhage in severe cases, and total blood cell counts usually reveal the presence of leukopenia and thrombocytopnia. Serum chemistry analyses reveals the increase in liver associated enzymes (Cui et al. 2013; Deng et al. 2013; Kato et al. 2016; Takahashi et al. 2014; Xu et al. 2011; Yu et al. 2011). Coagulopathy with prolongation of prothrombin and partial thromboplasitin times (PT and aPTT) are also demonstrated in SFTS patients (Takahashi et al. 2014). Furthermore, hemophagocitic syndrome (HPS)-associated findings were demonstrated in all the severe SFTS patients, in whom bone marrow aspiration test was performed (Kaneko et al. 2017, 2018; Kim et al., 2016, 2018; Kitao et al. 2016; Lee et al. 2016; Nakano et al. 2017; Shin et al. 2016; Takahashi et al. 2014; Uehara et al. 2016). The symptoms of SFTS are similar to those summarized in patients with CCHF by Ergonul et al. (Ergonul 2007). HPS findings are also reported in some patients with CCHF as well (Erduran and Cakir 2010; Tasdelen Fisgin et al. 2008).

In order to understand SFTS more in detail, it is important to understand what are the similarities and the differences between the 2 diseases and to clarify the mechanisms of the similarities and differences.

1.6 Life Cycle of SFTSV and the Transmission Route of SFTSV to Humans

SFTSV is maintained in nature in a life cycle between some species of ticks and some species of mammals. The life cycle is composed of the 2 sub-cycles, tick-mammals cycle and tick-tick cycle. In the tick-tick cycle, SFTSV is transmitted from adult ticks to the offspring, larva, through the transovarian transmission of SFTSV. However, the ratio would be far less than 100%. Therefore, SFTSV cannot be maintained only in the tick-tick cycle. The tick-mammals cycle plays an important role in the SFTSV maintenance in nature. When naïve and susceptible mammals were infected with SFTSV through virus-positive tick bite, viremia would occur. Most of the animals are considered not to show severe SFTSV infection associated

symptoms. When SFTSV-negative tick bit the viremic animals, the tick would acquired SFTSV. Therefore, both cycles (tick-tick cycle and animal-tick cycle) are necessary for the maintenance of SFTSV in nature (Saijo 2018). Humans are mainly infected with SFTSV through the tick-bite with SFTSV. Humans are also be infected with SFTSV, if it comes into direct contact with body fluids such as blood of the animals including humans (patients) at the time of positive viremia. Tick species that play a role in the transmission of SFTSV to humans in Japan are considered to be *Haemaphysalis longicornis* and *Amblyomma testudinarium*, because the ticks found on the skin surface of SFTS patients in Japan are these two species.

We still do not know how the virus is maintained in nature in detail and what kind of animals and ticks play a major role in the maintenance of SFTSV in nature in East Asia.

1.7 Epidemiology

Currently, SFTS has been confirmed to be endemic to Japan, South Korea, and PR China. The number of SFTS patients increases in early summer and SFTS patients continue to occur until the end of fall. The epidemiology of SFTS in Japan, China and South Korea is written in detail in the other chapters of this book.

In Japan, SFTS patients have been reported from the western part of Japan (https://www.niid.go.jp/niid/ja/sfts/sfts-idwrs/7415-sfts-nesid.html). Since the discovery of SFTS in Japan in early 2013, 40–90 patients with SFTS have been reported to the National Epidemiological Surveillance of Infectious Diseases (NESID) in Japan. Although the accurate case fatality rate has not yet been reported, because there is no legal framework to report the outcome of the SFTS patients, the CFR of SFTS in Japan might be expected to exceed 25% (Kato et al. 2016). To obtain the accurate CFR of SFTS patients, further study is needed. In 2016, an SFTS patient occurred in Okinawa Prefecture, an most southern island prefecture of Japan, which is geographically close to Taiwan, in which no SFTS patients have been reported so far.

1.8 Clinical Manifestations

The major clinical manifestations of SFTS are rapid onset of high fever and gastrointestinal tract symptoms (diarrhea, vomiting, and nausea), headache, muscle ache, and unspecific symptoms in the early phase of the disease. Lymph node enlargement is sometimes detected (Takahashi et al. 2014). Hepatosplenomegaly is not common. The differentiation of SFTS is difficult from the other infectious diseases commonly seen such as viral respiratory infection including common cold and diarrheal diseases in the early disease phase. Altered consciousness and hemorrhagic tendency appear in the later stage of SFTS and those patients with hemorrhagic

symptoms due to intravascular coagulation (DIC) and/or deterioration in consciousness have a poor prognosis (Deng et al. 2013; Shin et al. 2015). A fatal patient with hematemesis, who was examined for the cause of hemorrhage by gastrointestinal endoscopy had multiple ulcerative gastric lesions from which oozing hemorrhage occurred (Kaneyuki et al. 2016).

Most patients show thrombocytopenia and leukopenia in their total blood cell counts. Serum chemistry analyses reveal the increase in the liver-associated enzymes, alanine aminotransaminase (ALT), aspartate aminotransaminase (AST), lactate dehydrogenase (LDH), and creatine kinase (CK). The level of amylase in serum is also demonstrated to increase in some patients (Takahashi et al. 2014). Most severe SFTS patients show the extreme increase in the ferritin level, which might be associated with a pathophysiological feature, hemophagocytic syndrome (HPS).

1.9 Laboratory Diagnosis

Patients should be diagnosed as having SFTS by detection of SFTSV in the acute phase of the disease and/or demonstration of the significant increase in the antibody IgG titers to SFTSV between the acute and convalescent phases. Detection of IgM antibody to SFTSV in patients is also available for the diagnosis of SFTS. SFTSV in the serum samples collected in acute phase is usually detected with using SFTSV genome amplification with reverse-transcription polymerase chain reaction (RT-PCR) including the quantitative real-time RT-PCR (Cui et al. 2012; Li et al. 2013; Xu et al. 2013; Yoshikawa et al. 2014). Virus isolation from the patients' acute phase serum using the susceptible cell-culture using Vero cells is also the efficient test methods for diagnosis, although it takes a longer time than the genome amplification methods. It is of note that SFTSV does not induce a significant cytopathic effect to the cells, in which SFTSV replicates. Therefore, identification of SFTSV replicated in the cells requires a careful observation. SFTSV replicated in the cells should be detected with indirect immunofluorescent assay using specific antibodies to SFTSV or the amplification of SFTSV genome with the above-mentioned virus genome amplification.

In the fatal cases of SFTS, SFTSV antigens can be detected with immunohistochemistry analyses in organs such as lymph nodes (especially the regional lymph nodes enlarged), spleen, and liver, making it possible to make diagnosis for the patients who died (Kaneko et al. 2018; Nakano et al. 2017; Saijo 2018; Takahashi et al. 2014).

Antibodies to SFTSV are detected in enzyme-linked immunosorbent assay (ELISA), indirect immunofluorescent assay (IIFA), and neutralization assay (Jiao et al. 2012; Liu et al. 2013a). Recombinant SFTSV protein-based antibody detection systems have also been developed, making it more convenient to prepare SFTSV antigens (Jiao et al. 2012; Moming et al. 2017; Yu et al. 2015), because SFTSV is usually designated as biosafety level-3 pathogen in most countries.