



A family cluster of pediatric cases of severe fever with thrombocytopenia syndrome following short-time exposure to a city park in China: case reports

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Abstract: In our study, we described a family cluster of pediatric cases of severe fever with thrombocytopenia syndrome (SFTS) that occurred in Lishui district of Nanjing City, Jiangsu Province of China. Clinical and epidemiological data for these two children indicated that they were infected in the city park in Baima Town, Lishui District, Nanjing, simultaneously. Phylogenetic analysis showed that the new strains isolated from genome sequence of two children was similar to that of the SFTS virus (SFTSV) strain from Lishui district. The symptoms of two children were mild and they all recovered and were discharged from hospital. Although Lishui district has been the epidemic focus of SFTS in Jiangsu Province, no SFTS case was reported by exposed to the city park. This cluster of SFTS was firstly revealed of pediatric cases with possible infection risk factor of exposure to the city park lawn in Lishui district, which suggests that the city park could become a new epidemic focus of SFTS. We also found the clinical symptoms of two pediatric SFTS cases were relatively mild compared with adult SFTS cases, presented with no exhibit dyspnea, consciousness disorder, dizziness, or gastrointestinal and hemorrhagic symptoms and the delayed onset of thrombocytopenia (about 7 days after disease onset compared to 1 to 2 days for adults). This is a rare cluster of SFTS occurred in the city park. Close attention and further study should be conducted to provide reference for the following prevention and treatment of SFTS.

Keywords: Case report; severe fever with thrombocytopenia syndrome (SFTS); Phlebovirus; family cluster; children

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Introduction

Severe fever with thrombocytopenia syndrome (SFTS), a new tick-borne zoonosis caused by severe fever with thrombocytopenia syndrome virus (SFTSV), is characterized by fever, thrombocytopenia, leukopenia and gastrointestinal symptoms (1,2). SFTSV is primarily transmitted to humans by exposure to or bitten by infected ticks (3-5), while the secondary cases can also be infected

by person-to-person transmission with possible inhalation of virus-containing aerosol (6), or direct contact with blood or bloody secretions carrying SFTSV (7,8). SFTS usually occurs as sporadic cases, and clustered cases occur less frequently (9). Meanwhile, elderly people in rural areas with hills and mountains have the greatest risk of acquiring SFTS (2,10-12). Here, we described a family cluster of two pediatric cases of SFTS following short-time exposure to a

city park in Jiangsu Province, and analyzed the clinical and epidemiological characteristics of these two cases.

We present the following article in accordance with the CARE reporting checklist (available at <https://jphe.amegroups.com/article/view/10.21037/jphe-21-41/rc>).

Case presentation

Case detection and investigation

Two children from the same family in Lishui District, Jiangsu Province, were diagnosed with suspected SFTS cases by a doctor of Nanjing Children's Hospital, since they had fever, leukopenia and thrombocytopenia. Then their serum specimens were collected and sent to the laboratory in Jiangsu Provincial Center for Disease Control and Prevention (CDC). Finally, SFTSV-specific RNA was detected from the serum specimens of them. After anti-virus and anti-infective therapy (use ribavirin and moxalactam respectively) and other supportive treatment, they all recovered well without sequelae being observed.

After receiving the case report, Lishui District CDC, Nanjing Municipal CDC, and Jiangsu Provincial CDC jointly conducted an epidemiological investigation into this family cluster of laboratory-confirmed SFTS cases, including inquiring about the cases' clinical and laboratory characteristics, living surroundings, history of tick bites and animal contacts, and the routes of possible exposure to risk factors. Their father and medical staff were also interviewed.

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Oral informed consent was obtained from the patients' parents.

Case description

Case 1

Case 1 was a 5-year-old boy who experienced sudden onset fever with the highest temperature of 39 °C at night on 10 July 2018. The boy was admitted to People's Hospital of Lishui District on 13 July 2018, where he received treatment for 3 days. On 16 July, the boy was transferred to Nanjing Children's Hospital because of persistent and high fever with the highest temperature of 40 °C and cough. He had leukopenia (white blood cell count, $2.25 \times 10^9/L$) and thrombocytopenia (platelet count, $92 \times 10^9/L$), elevated liver-associated enzyme levels (glutamic oxaloacetic

transaminase, 98 U/L) and positive urine protein. The boy was diagnosed with bronchitis according to his clinical symptoms and chest X-ray examination, no gastrointestinal and hemorrhagic symptoms were observed. He was diagnosed with SFTSV infection on 17 July 2018, then he was treated with moxalactam and other symptomatic and supportive treatment. His temperature began to drop to the normal range (around 36.5 °C) on the same day. On 18 July, the boy's white blood cell count raised to $4.76 \times 10^9/L$. On 24 July, his platelet count raised to $297 \times 10^9/L$, his glutamic oxaloacetic transaminase had declined to 25 U/L and urine protein turned negative. Finally, the boy was discharged on 25 July.

Case 2

Case 2 was a 15-year and 6-month-old girl who had experienced a sudden onset fever with the highest temperature of 40 °C on 10 July 2018. She was admitted to People's Hospital of Lishui District on 13 July. With persistent and high fever after 3 days of treatment, she was transferred to Nanjing Children's Hospital on 16 July. She had leukopenia (white blood cell count, $2.40 \times 10^9/L$) and thrombocytopenia (platelet count, $42 \times 10^9/L$), then she was diagnosed with SFTSV infection on 17 July and she was treated via moxalactam, ribavirin and other symptomatic and supportive treatment. The girl's illness was more serious than that of her brother, her white blood cell count and blood platelet count decreased rapidly to $1.18 \times 10^9/L$ on 17 July and $27 \times 10^9/L$ on 18 July, respectively. Her urine protein presented positive on 22 July. She did not exhibit any symptoms of dyspnea, consciousness disorder, dizziness, or hemorrhage. The girl's body temperature turned to normal (around 36.5 °C) on 20 July, her white blood cell and platelet finally returned to normal range with the white blood cell count of $4.46 \times 10^9/L$ on 24 July and platelet count of $122 \times 10^9/L$ on 22 July. Laboratory testing indicated that her urine protein presented negative on 26 July, but her liver enzyme was still above normal range (glutamic-pyruvic transaminase, 207 U/L; glutamic oxaloacetic transaminase, 109 U/L. Anti-virus and anti-infective therapy (use ribavirin and moxalactam respectively) were discontinued since 27 July. Then the doctor approved her parents' asking for leaving the hospital. Followed-up observation showed the girl got well recovered after a period of time.

Dynamic profiles of clinical indicators [peak temperature, white blood cell, platelet, alanine aminotransferase (ALT), aspartate aminotransferase (AST)] of two SFTS pediatric cases are shown in the *Tables 1,2* and *Figure 1*.

Table 1 Clinical characteristics and laboratory testing results of case 1 involved in the cluster

Clinical feature	10 July	16 July	17 July	18 July	19 July	20 July	21 July	22 July	23 July	24 July	25 July (discharge)
Peak temperature (°C)	39	40	36.5	36.5	36.5	36.5	36.5	36.5	36.5	36.5	36.5
Malaise	N	Y	Y	Y	Y	N	N	N	N	N	N
Cough	N	Mild	Mild	Mild	Mild	Mild	Mild	N	N	N	N
Pharyngeal swelling	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	N
Antiadoncus	N	N	N	N	N	I°	I°	I°	N	N	N
Astriction	N	N	N	N	Y	Y	Y	N	N	N	N
Laboratory variables											
White blood cells ($\times 10^9/L$)	-	2.25	-	4.76	-	-	4.79	-	-	5.59	-
Platelets ($\times 10^9/L$)	-	92	-	64	-	-	94	-	-	297	-
ALT (U/L)	-	-	31	-	-	-	-	-	-	30	-
AST (U/L)	-	-	98	-	-	-	-	-	-	25	-
Positive urine protein						+	+		-		

Y, yes; N, no; I°, the least severe grade of antiadoncus; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Table 2 Clinical characteristics and laboratory testing results of case 2 involved in the cluster

Clinical feature	10 July	16 July	17 July	18 July	19 July	20 July	21 July	22 July	24 July	26 July	27 July	29 July	30 July (discharge)
Peak temperature (°C)	40	-	-	-	36.8	36.5	36.5	36.5	36.5	36.5	36.5	36.5	36.5
Malaise	N	N	N	N	Y	Mild	N	N	N	N	N	N	N
Pharyngeal swelling	N	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N
Antiadoncus	N	N	I°	I°	I°	I°	I°	I°	N	N	N	N	I°
Nausea and vomiting	N	Y	Y	Y	Y	Y	N	N	N	N	N	N	N
Anepithymia	N	Y	Y	Y	Y	Y	N	N	N	N	N	N	N
Astriction	N	N	N	Y	Y	N	N	N	Y	N	N	N	N
Laboratory variables													
White blood cells ($\times 10^9/L$)	-	2.40	1.18	1.67	2.41	3.76	3.98	3.51	-	4.46	-	-	4.61
Platelets ($\times 10^9/L$)	-	42	32	27	29	40	40	122	-	301	-	-	361
ALT (U/L)	-	-	26	-	-	-	-	-	-	207	-	-	-
AST (U/L)	-	-	102	-	-	-	-	-	-	109	-	-	-
Positive urine protein					+			+		-			

Y, yes; N, no; I°, the least severe grade of antiadoncus; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Epidemiology

These two cases lived in the center of Baima town (with a population of 39,859 in 2017) in Lishui District of Nanjing

City, Jiangsu Province. This district has a high incidence of SFTS, where 46 SFTS confirmed cases were reported from 2010 to 2018, accounting for 18.78% of the total cases

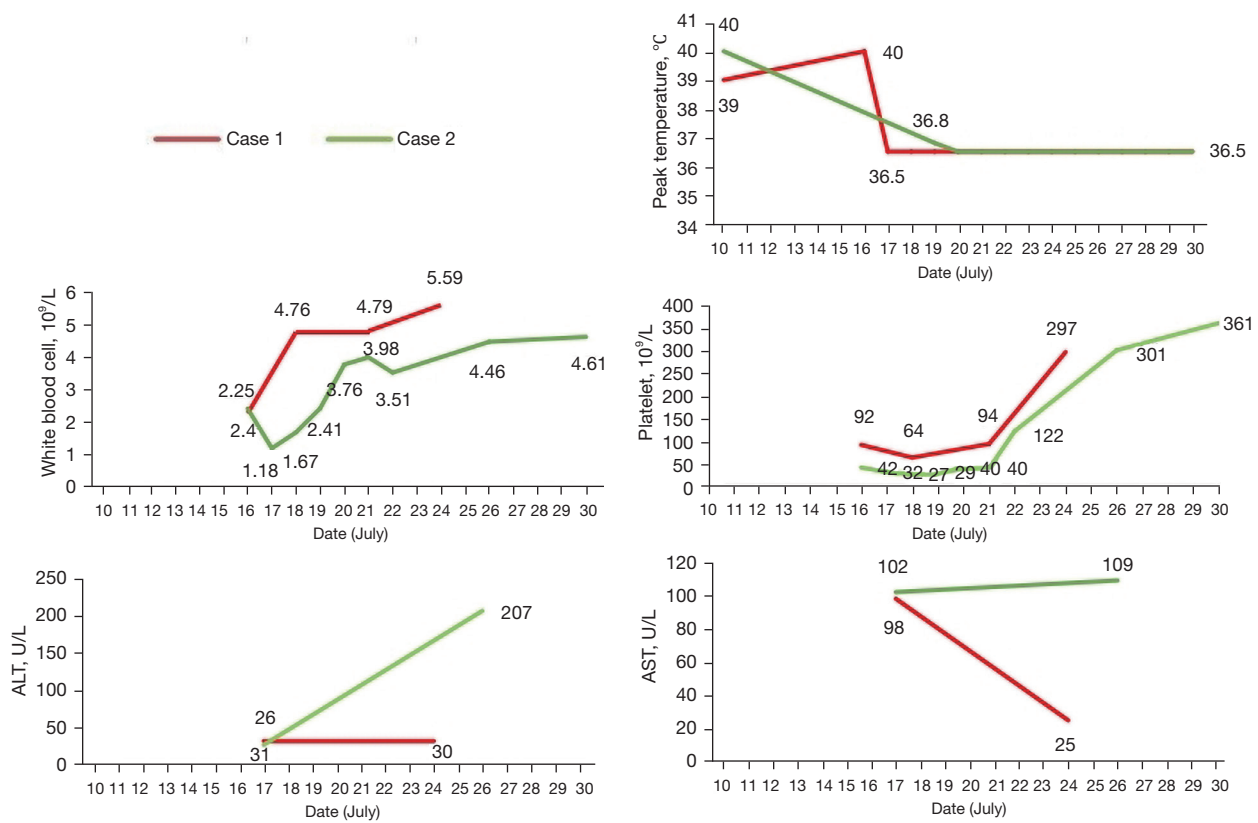


Figure 1 Dynamic profiles of clinical indicators in 2 SFTS pediatric patients. ALT, alanine aminotransferase; AST, aspartate aminotransferase; SFTS, severe fever with thrombocytopenia syndrome.

in Jiangsu Province according to surveillance data from Jiangsu Provincial CDC.

These two cases lived in a high-rise building with a green belt in the residential area. According to their parents, they had used to take exercise and play on the green belt. However, no similar cases were reported in their residential area, and they had no contact with a similar patient before illness onset. Epidemiological investigation showed that these two children had played in a city park. They complained about no clear history of insect bites, and no skin itching or redness and other discomfort symptoms during the play.

We collected questing ticks by using tick drags (1×1 m² white cotton flannel cloth) on the residential area's green belt of these two cases and the city park lawn. Three questing ticks were caught on the city park lawn, but no ticks were caught on the residential area's green belt. Although these ticks were identified as *Haemaphysalis longicornis*, the results were negative in SFTS-RNA

detection in these ticks.

Viral RNA extraction and detection

Acute phase blood samples were collected from the suspected SFTS patients. Sera were separated from the blood samples by centrifugation at 3,500 rpm for 5 min. RNA was extracted from 140 μL serum samples using QIAamp Viral RNA Mini kit (Qiagen, Hilden, Germany) according to the manufacturer's instructions. SFTSV RNA were detected with a real-time RT-PCR assay previously described using QuantiTect Probe RT-PCR Kit (Qiagen, Hilden, Germany) (13). The conditions for real-time RT-PCR reaction were as follows: 50 °C for 30 min, 95 °C for 10 min, 45 cycles of 95 °C for 15 s, 55 °C for 40 s. Data were analyzed using the software supplied by the manufacturer.

SFTSV genome sequencing and phylogenetic analysis

Complete sequencing of M segment of SFTSV strain was performed using primers as previously described (13). The

RT-PCR products were sent to Sangon Biotech (Shanghai, China) for Sanger DNA sequencing. The termini of viral RNA segments were determined with the First Choice RLM-RACE Kit (Invitrogen, USA). Phylogenetic analysis was conducted based on the M segments of SFTSV. Sequences were aligned using Clustal W. The phylogenetic trees were constructed using the Maximum Likelihood Method with the MEGA5.1 software based on M segments of SFTSV strains from different SFTS endemic areas. The reliability values indicated at the branch nodes were determined using 1,000 bootstrap replications. The red taxon names of the phylogenetic trees presented SFTSV strains isolated in this study.

Blast comparison showed that both of these two new strains (2019 child 1 and 2019 child 2) were close to SFTSV strains from Jiangsu province. The two M segments in this study shared high nucleotide similarity with strain Jiangsu/China/2011/JS2011-004 (99.2% and 99.1%), which was isolated from a local patient in Lishui in 2011. The boy's M segment wasn't exactly the same as his sister's. Phylogenetic analysis showed that both of the two new strains belonged to Clade D genotype based on the maximum likelihood tree of M segments (Figure 2). These results suggested that these two cases were infected with SFTSV from the local area.

Discussion

This report described a family cluster of pediatric cases of SFTS. We speculate that two cases' short-time exposure to the city park lawn was the main cause of this cluster. There are three reasons present as follows. Firstly, these two cases were exposed to the city park lawn at the same time and they got sick on the same day. The interval from exposure to illness onset was five days, which was consistent with the incubation period of SFTS (14). Secondly, the longhorned tick, namely *Haemaphysalis longicornis*, the most abundant human-biting tick species in most SFTS-endemic areas of China, is known as the major vector (8,9). We found *Haemaphysalis longicornis* ticks on the city park lawn, although the SFTS-RNA detection was negative in these ticks, maybe caused by small sample size. Last but not least, with no SFTS cases reported in the children's residential area and no ticks have been collected from the green belt where they used to play, the two children were less likely to be infected by exposure to the green belt of their residential area.

According to their clinical symptoms mentioned above, children's illnesses suffered from SFTS were relatively

mild compared with adult SFTS cases. They did not exhibit dyspnea, consciousness disorder, dizziness, or gastrointestinal and hemorrhagic symptoms. In addition, the onset of thrombocytopenia was also delayed for pediatric cases than in adults (about 7 days after disease onset *vs.* 1 to 2 days, respectively), which was consistent with the previously report of pediatric cases of SFTS (15-17). Besides, two children in this cluster all have the symptoms of elevated liver-associated enzyme level and positive urine protein, which were similar to adults who infected with SFTSV, these could be caused by virus infection and long-term antiviral treatment after admission (18).

The result of the genetic sequencing was something representation based on these two cases' common exposure history and pathogenesis. Phylogenetic analysis showed that both of the two new strains were belonged to Clade D genotype, although the boy's M segment wasn't exactly the same as his sister's. These results suggested that both of these two cases were infected with SFTSV from the local area, while there was no human-to-human transmission of infection between them. High nucleotide similarity (99.2% and 99.1%) between the M segments of the two cases and a local patient in Lishui in 2011 suggested that these children were infected with SFTSV from the local area and this sequence of SFTS may have already exist in the hills or mountains areas of Lishui in 2011 and then it transported to the other areas such as city park via human or animal migration later. The infection of this two SFTS pediatric cases suggests that the city park could become a new endemic area of SFTS, which was rarely mentioned by previous studies.

In our report, we revealed a family cluster of pediatric cases of SFTS in Lishui District of Nanjing City, Jiangsu Province. This cluster of SFTS was firstly revealed of pediatric cases with possible infection risk factor of exposure to the city park lawn which suggests that the city park could become a new endemic area of SFTS. Besides, we found the children's illness suffered from SFTS were relatively mild compared with adult SFTS cases. We also carried out propaganda and disseminated knowledge about SFTS among nearby residents. Close attention and further study should be conducted to provide reference for the following prevention and treatment of SFTS.

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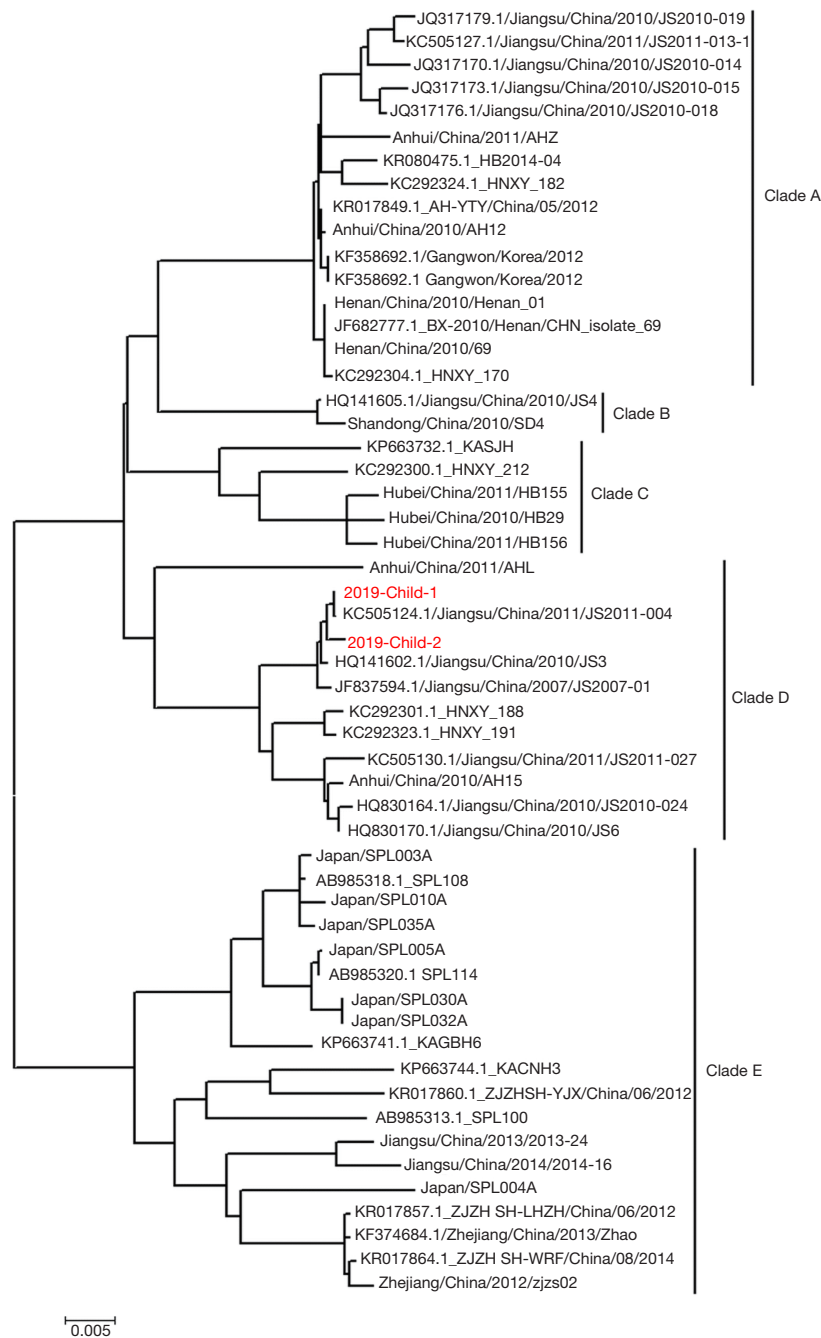


Figure 2 Evolutionary analysis of SFTSV genome system. SFTSV, severe fever with thrombocytopenia syndrome virus.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at <https://jphe.amegroups.com/article/view/10.21037/jphe-21-41/rc>

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://jphe.amegroups.com/article/view/10.21037/jphe-21-41/coif>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Oral informed consent was obtained from the patients' parents.

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