Epidemiological Characteristics and Clinical Features of Patients With Severe Fever With Thrombocytopenia Syndrome Bunyavirus Infection

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Research Article

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Abstract

Objectives

To investigate the epidemiological characteristics, clinical features and prognosis of patients with severe fever with thrombocytopenia syndrome bunyavirus (SFTSV) infection.

Methods

The data of 23 patients with SFTSV infection from June 2012 to July 2018 were analyzed retrospectively.

Results

Among the 23 patients, 10 (43.5%) were male and 13 (56.5%) were female. The mean age was 58.9 ± 12.1 years old. In total, 19 patients (82.6%) were farmers, and 21 cases (91.3%) occurred during the spring and summer season, especially in May and June. There were 5 cases (21.7%) with a clear history of tick bites and 2 cases (8.7%) with close contact with the patient who was feverish due to thrombocytopenia syndrome. Seventeen (73.9%) patients came from the mountainous area of southern Anhui Province. All patients had fever and thrombocytopenia. Most patients had leukocytopenia; proteinuria; urine occult blood; elevated liver enzymes; increased creatine kinase, lactate dehydrogenase and D-dimer levels; muscle soreness and clinical haemorrhage. One patient even displayed a local haematoma on the abdominal wall. Some patients had low albumin, elevated serum amylase and increased lipase. After active supportive treatment, 5 patients (21.7%) were cured, 14 patients (60.9%) were improved, 2 patients (8.7%) were discharged without recovery and 2 patients (8.7%) died of multiple organ failure.

Conclusions

SFTSV infection has specific epidemiological and clinical characteristics. The disease can involve multiple organs, and its mortality rate is relatively high. Therefore, we should pay more attention to the disease to promote the early detection, timely diagnosis and accurate treatment.

Introduction

In recent years, fever and thrombocytopenia syndrome have been one prominent infectious disease in 23 provinces in China, including Henan Province, Hubei Province, Anhui Province, Jiangsu Province, Zhejiang Province and Liaoning Province, mainly the central region of China [1]. Henan Province has the largest number of the reported cases [2]. The pathogen of the disease is severe fever with thrombocytopenia syndrome Bunyavirus (SFTSV), which belongs to the Bunyavirales family and is a new RNA virus discovered by Chinese Center For Disease Control And Prevention in 2010 [3]. With the advances in detection methods and the emergence of new diseases, the number of members of the Bunya virus family is increasing [4]. Molecular biological detection technology plays an important role in the discovery of pathogens and the identification of different genotypes of virus strains [3,5]. SFTSV infection is regional and seasonal. And the virus can lead to multiple organ dysfunction and endanger the life of

patients [2]. The aim of this study was to investigate the epidemiological characteristic, clinical feature and prognosis of SFTSV infection in hope of providing some referential ideas for the treatment of the disease.

Methods

Study participants and data collection The medical records of 23 patients with SFTSV infection admitted to Yijishan Hospital of Wannan Medical College from June 2012 to July 2018 were collected. All patients met the diagnostic criteria of confirmed cases. The diagnosis of the cases was in accordance with the "Guidelines for the Prevention and Treatment of Fever with Thrombocytopenia Syndrome" issued by Chinese Ministry of Health in October 2010[6]. In all the 23 cases, SFTSV nucleic acid was detected by RT-PCR in Wuhu Center for Disease Control and Prevention of Anhui province.

Epidemiological data The patients' sexes, ages, occupations, onset seasons, contact history and concomitant basic diseases were observed. Clinical manifestations Such manifestations as the body temperature, heat course, respiration, heart rate, blood pressure, chills, headache, muscle soreness, cough/expectorations, palpitation, nausea/vomiting, abdominal pain, abdominal tenderness, skin rash except for hematic eruption, clinical hemorrhage (such as blood stasis, ecchymosis, gingival bleeding, bloody stool, hematuria, local hematoma), oliguria, consciousness disorder, secondary infection, dialysis treatment, lower extremity edema and hospitalization days were observed.

Laboratory examination data The changes of laboratory data were observed and we collected the maximum or minimum values of such tests during hospitalization as white blood cell (WBC), platelet (PLT), prothrombin time (PT), activated partial thromboplastin time (APTT), D-dimer, glutamic-pyruvic transaminase (GPT), glutamic oxaloacetic aminotransferase (GOT), total bilirubin (TBIL), albumin, blood urea nitrogen (BUN), creatinine (CR), amylase (AMY), lipase (LIP), blood glucose (BG), creatine kinase (CK), creatine kinase isoenzyme-MB (CK-MB), lactate dehydrogenase (LDH), blood potassium (K⁺), blood sodium (Na⁺), blood chlorine (Cl⁻), blood calcium (Ca²⁺), carbon dioxide binding capacity (CO₂-CP) and urine protein, urine occult blood and fecal occult blood. The above indexes were detected by Sysmex XE-2100 automatic blood cell analyzer of Himori Mikang Company of Japan, Uritest 500B urine analyzer of Guilin Ultra Electronic Group Co., Ltd., Hitachi 7600 automatic biochemical analyzer of Japan and Sysmex CS-5100 Automatic Coagulation Analyzer of Himori Mikang Company of Japan.

Therapeutic measurement It was mainly symptomatic and supportive treatment. The patients were advised to stay in bed, eat liquid or semi liquid food, drink more water, were closely monitored vital signs and were maintained water, electrolyte and acid-base balance. High fever was treated mainly by physical cooling. Patients with significant hemorrhage or decreased platelet count ($<30 \times 10^9/L$) were treated with plasma and/or platelet transfusion. Recombinant human granulocyte colony-stimulating factor of 150 ug was performed in patients with severe neutropenia ($<1 \times 10^9/L$). The patients in early fever stage were given ribavirin 0.5g once a day. And secondary infections were treated by empirical medication or sensitive antibiotics. Also, At the same time, we paid attention to the treatment of basic primary diseases and related complications at the same time.

Prognosis Assessment of prognosis falls into category of cure, improvement, unhealed and death. Cure referred to the complete remission of clinical symptoms, and WBC, PLT and blood biochemical indicators

were returned to normal levels. Improvement referred to the improvement of clinical symptoms, but PLT was not completely restored to normal or blood biochemical indicators improved but not completely restored to normal. Unhealed referred to clinical symptoms did not improve and laboratory indicators did not improve. Death was referred to the patient who died during hospitalization. Statistical analysis SPSS22.0 statistical software was used to analyze the data. The counting data were expressed as percentage (%) and the measurement data were expressed as ($\bar{x} \pm s$).

Results

Epidemiological data

The epidemiological data of 23 patients were shown in Table 1. The average age of all the patients was 58.9 ± 12.1 years old. The range was 23-77 years old. There were 13 women (56.5%) and 10 men (43.5%), and the ratio of female to male was 1.3:1. Except for 19 farmers (82.6%), 1 unemployed person (4.3%), 2 retirees (8.7%) and 1 worker (4.3%) all had a history of going to mountainous or hilly areas before the onset of the disease. 21 cases (91.3%) occurred in spring and summer, mainly in May with 12 cases (52.2%) and in June with 6 cases (26.1%). There were 5 cases (21.7%) of tick bite history before onset. Two patients (8.7%) had participated in the nursing of one patient with fever and thrombocytopenia syndrome, who eventually died of disseminated intravascular coagulation and multiple organ failure. 17 patients (73.9%) came from the mountainous areas of southern Anhui Province, 2 patients (8.7%) came from the Dabie Mountains and 4 patients (17.4%) came from the hilly areas around the Yangtze River valley. There were 10 patients (43.5%) with chronic diseases, including 4 cases (17.4%) of type 2 diabetes, 2 cases (8.7%) of hypertension, 2 cases (8.7%) of cholelithiasis, 1 case (4.3%) of chronic bronchitis and 1 case of hypophysis.

Clinical symptoms

The related clinical data such as symptoms and signs were shown in Table 2. In all the patients, 23 cases (100%) had fever and the mean heat duration was (8.24 ± 3.6) days. 14 patients (60.9%) had clinical hemorrhage, including 4 cases (17.4%) of black stool, 4 cases (17.4%) of skin ecchymosis, 2 cases (8.7%) of gingival bleeding, 1 case (4.3%) of hemoptysis, 1 case (4.3%) of gross hematuria, 1 case (4.3%) of epistaxis and 1 case (4.3%) of abdominal hematoma. Secondary infection was found in 9 cases (39.1%), including 4 cases (17.4%) of pulmonary infection, 4 cases (17.4%) of abdominal infection and 1 case (4.3%) of urinary tract infection. All patients were not treated with dialysis and the average length of stay was (11.5 ± 4.1) days.

Laboratory results

Laboratory results were shown in Table 3. There were 23 cases (100%) of thrombocytopenia, 20 cases (87.0%) of leucocytopenia and 16 cases (69.6%) of low albumin. In addition, GPT, GOT, AMY, LIP, CK, CK-MB, LDH and D-dimer increased in some patients. Semi-quantitative urinary protein results showed 12 cases (52.2%) with +++, 5 cases (21.7%) with ++, 3 cases (13.0%) with +, 1 case (4.3%) with $\pm$ and 2

cases (8.7%) with -. Semi-quantitative urinary occult blood results showed 3 cases (13.0%) with +++, 4 cases (17.4%) with ++, 9 cases (40.1%) with + in, 3 cases (13.0%) with $\pm$ and 4 cases (17.4%) with -. Fecal occult blood results showed 4 cases (17.4%) with +, 4 cases (17.4%) with $\pm$ and 15 cases (65.2%) with -.

Prognosis

Five cases (21.7%) were cured, 14 cases (60.9%) were improved, 2 cases (8.7%) were unhealed and 2 cases (8.7%) died of multiple organ failure.

Case introduction

One patient, who was a 60-year-old female farmer with fever and general fatigue lasting 4 days from Guangde County, Anhui Province, was hospitalized on May 13, 2014. During the course of the disease, the patient had nausea, no vomiting and feeling of weakness and anorexia. On May 11, 2014, blood routine examination was conducted in local hospitals such as WBC of $5.0 \times 10^9/L$, haemoglobin (HGB) of 107g/L and PLT of $87.0 \times 10^9/L$. The infusion treatment was performed but the specific plan was unknown and the curative effect was not good. And then the patient was transferred to our hospital. The patient had a history of taken care of her sister, who was a patient with fever and thrombocytopenia syndrome and died of disseminated intravascular coagulation and multiple organ failure. in Zhejiang Province, 10 days before the onset of the disease. The patient was conscious with temperature of $38.7^\circ C$, a small amount of ecchymosis on the upper limb and purple ecchymosis on the upper abdomen. The conjunctiva was slightly edema. Her abdomen was soft and a mass about $3cm \times 4cm \times 4cm$ without fluctuation sense and no tenderness at the left lower abdomen could be touched. Laboratory data were WBC of $1.9 \times 10^9/L$, HGB of 97g/L, PLT of $40.0 \times 10^9/L$, PT of 9.2s, international standardized ratio of 0.75, D-dimer of 9.94 ug/ml, urine occult blood of +, urinary protein of ++, fecal occult blood of -, albumin of 28.7g/L, GPT of 71U/L, GOT of 128U/L, BUN of 1.87mmol/L, CR of 71.7umol/L, CK of 216U/L, CK-MB of 24U/L, LDH of 586U/L, AMY of 152.0 U/L and LIP of 160.0 U/L. The patient's abdominal CT (Fig. 1) showed that a mass was found at the left abdominal wall, which was considered the possibility of hematoma. The progressive decline of HGB was lowest to 57g/L. There were some treatment measurements such as ribavirin injection, recombinant human granulocyte colony stimulating factor, somatostatin, ordering fasting, liver protection, hemostasis, prevention and treatment of infection and symptomatic supporting treatment. At last, her temperature returned to normal and the left lower abdominal mass disappeared. WBC and PLT gradually returned to normal (Fig. 2 and Fig. 3), HGB increased significantly, liver function and myocardial enzymes returned to normal and pancreatic function improved. She was cured and discharged on June 13, 2014.

Discussion

SFTSV infection is mostly believed to be related to ticks. Studies have shown that effective measures have been taken to reduce the number of ticks in the local area, so as to reduce the incidence of diseases to a certain extent [7]. But many patients do not have a history of tick contact in clinical. In this study, patients with history of tick bite account for 21.7%. Studies have shown that the related diseases

transmitted by different ticks are different. The tick that transmits SFTSV are *Haemaphysalis longicornis* [8], which carries 4.17% to 18.75% of SFTSV [9, 10]. Mosquitoes do not transmit the virus [11]. In addition to tick bites, human-to-human transmission through blood or close contact has been reported [12]. In this study, two patients had the contact history with one patient with fever with thrombocytopenia syndrome. It is suggested that more attention be paid to cross infection when nursing and caring patients.

The average age of this study was 58.9 ± 12.1 years, and the ratio of female to male was 1.3:1, which was close to the median age of 61 and the ratio of 1.16:1 from previous studies [13,14]. We found that farmers accounted for 82.6% of all the patients, especially in mountainous areas in southern Anhui Province. We all understand that farmers are more likely to contact pathogens In our study, 91.3% of the cases occurred in spring and summer, especially in May and June. The data of reported cases in China show that the vast majority of cases occurred from March to November, and the main epidemic season is from May to July, which peaks in May [2], as is the breeding and active season for ticks.

Fever and thrombocytopenia are the most prominent features of all the patients. Leucocytopenia is common. Consciousness disorder and secondary infection could be found in some patients. Liver enzymes increase and GOT increases more markedly. Our results confirm that myocardial and pancreatic dysfunctions were found in some cases. The disease can affect the coagulation system and increase the D-dimer. It can also cause proteinuria, hematuria and even local hematoma. All of the above suggests that SFTSV can involve the patients' multiple organs. Some studies have shown that the spleen contains the highest density of SFTSV [15].

Form the perspective of therapeutic treatment, there is no specific anti-pathogenic drug for the pathogen of SFTSV. According to the "Guidelines for the Prevention and Treatment of Fever with Thrombocytopenia Syndrome" in China, ribavirin is recommended to treat the disease. Therefore, the patients in fever stage were treated with ribavirin in our study. But Liu reported that antiviral effect of ribavirin is not significant in SFTSV infection [16]. In addition to antiviral therapy, the main treatments are liver protection, myocardial nutrition, maintenance of water and electrolyte balance, symptomatic supporting treatment, platelet transfusion should be actively treated when platelet is significantly lower than $30 \times 10^9/L$. In our study, 2 cases died of multiple organ failure and the mortality rate was 8.7%. And All the two patients were all over 50 years old. Zhan reported that the average mortality rate in China from 2010 to 2016 was 5.3% [2]. Influencing factors of poor prognosis were mainly associated with viral load, cytokine function and T cell number [17]. Hu reported that the imbalance of inflammatory response in SFTSV infection was related to the mortality rate [18]. Some studies have shown that age, GOT levels, central nervous system involvement and bleeding tendency could affect the prognosis of the patients with SFTSV infection [19, 20]. Children would were also be reported infected by the virus, but their condition is relatively mild [21]. The mortality rate of elderly patients is significantly higher than that of young people because of the decline of immune function and the underlying primary diseases in elderly patients.

Conclusion

To sum up, SFTSV infection has regional specificity and seasonality and can cause multiple organ dysfunction. Its mortality is relatively high. Therefore, the disease should be paid more attention in order to make promote early detection, timely diagnosis and accurate treatment, which is of great significance for improving the prognosis of the patients with SFTSV infection.

Declarations

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Authors'Contributions

Jin-sun Yang and Gan Liu contributed to the study design, analysed, interpreted the data and wrote the first draft of the article. Ting-ting Hu contributed to data collection and interpretation. Gan Liu contributed to data collection. Ting-ting Hu and Gan Liu contributed to the study design and to data analysis and interpretation and to writing the article. All authors critically reviewed the article for important intellectual content and gave final approval for submitting the article.

Ethics approval and consent to participate

The ethics committee approved the study. Written informed consent has been obtained from the patient in accordance with the Declaration of Helsinki.

Consent for publication

Written informed consent for publication was obtained from the patients.

Availability of data and materials

The data used to support the findings of this study are available from the corresponding author upon request.

Competing interests

The authors declare that they have no competing interests

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Tables

TABLE 1 Epidemiological data for the 23 patients with SFTSV infection

Index	No. of patients (%)
Sex (male)	10 (43.5)
Occupation (farmer)	19 (82.6)
Season (spring and summer)	21 (91.3)
History of tick bite	5 (21.7)
History of contact with the patients with fever and thrombocytopenia syndrome	2 (8.7)
Distribution area (mountainous area of southern Anhui Province)	17 (73.9)
Affected by chronic disease	10 (43.5)

TABLE 2 Related symptoms and signs in the 23 patients with SFTSV infection.

Symptom/sign	No. of patients (%)
Fever	23 (100)
Respiratory rate $\geq$ 20/min	5 (21.70)
Heart rate $\geq$ 100 bpm	12 (52.2)
Systolic blood pressure $\geq$ 90 mm Hg	8 (34.8)
Chill	7 (30.4)
Headache	10 (43.5)
Muscular soreness	16 (69.6)
Cough/expectoration	2 (8.7)
Palpitation	14 (60.9)
Nausea/vomiting	6 (26.1)
Abdominal pain	3 (13.0)
Abdominal distention	4 (17.4)
Abdominal tenderness	5 (21.7)
Skin rash (except for haematic eruption)	2 (8.7)
Clinical haemorrhage	14 (60.9)
Oliguria	4 (17.4)
Lower extremity oedema	3 (13.0)
Mental disorder	8 (34.8)
Secondary infection	9 (39.1)
Dialysis treatment	0 (0)

TABLE 3 Laboratory results for the 23 patients with SFTSV infection

Test indexes	Abnormal No. of patients (%)	Admission value ()	Maximal/minimal value ()
WBC ($\times 10^9/L$)	20 (87.0)	3.44 $\pm$ 2.7	2.75 $\pm$ 1.12
PLT ($\times 10^9/L$)	23 (100)	54.31 $\pm$ 20.92	31.89 $\pm$ 15.03
BUN (mmol/L)	-	5.72 $\pm$ 2.34	-
Cr (μ mol/L)	-	81.25 $\pm$ 31.14	-
GPT (U/L)	20 (87.0)	51.35 $\pm$ 18.92	70.25 $\pm$ 25.81
GOT (U/L)	22 (95.7)	101.59 $\pm$ 32.48	197.41 $\pm$ 56.92
ALB (g/L)	16 (69.6)	34.86 $\pm$ 11.58	30.27 $\pm$ 13.12
TBIL (μ mol/L)	-	14.15 $\pm$ 8.23	-
BG (mmol/L)	-	5.45 $\pm$ 2.31	-
AMY (U/L)	13 (56.5)	112.72 $\pm$ 57.24	176.38 $\pm$ 76.28
LIP (U/L)	11 (47.8)	178.70 $\pm$ 49.81	303.93 $\pm$ 58.25
CK (U/L)	22 (95.7)	436.91 $\pm$ 118.32	842.31 $\pm$ 321.80
CK-MB (U/L)	20 (87.0)	32.76 $\pm$ 13.60	43.92 $\pm$ 25.86
LDH (U/L)	22 (95.7)	419.03 $\pm$ 185.38	845.71 $\pm$ 232.99
Na ⁺ (mmol/L)	-	133.82 $\pm$ 6.29	-
Cl ⁻ (mmol/L)	-	101.88 $\pm$ 5.92	-
K ⁺ (mmol/L)	-	3.67 $\pm$ 0.72	-
Ca ²⁺ (mmol/L)	-	1.92 $\pm$ 0.21	-
CO ₂ -CP (mmol/L)	-	22.75 $\pm$ 5.01	-
PT (s)	-	12.15 $\pm$ 1.73	-
APTT (s)	-	55.02 $\pm$ 18.01	-
D-dimer (ug/ml)	21 (91.3)	3.89 $\pm$ 1.24	5.23 $\pm$ 3.81
Urine protein (+~+++)	20 (87.0)	-	-
Urine occult blood (+~+++)	16 (69.6)	-	-
Faecal occult blood (+)	4 (17.4)	-	-

Figures

Figure 1

Abdominal CT showing a left abdominal wall haematoma in a patient with SFTSV infection.

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Abdominal CT showing a left abdominal wall haematoma in a patient with SFTSV infection.

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Figure 2

Change in the WBC count in a patient with SFTSV infection. Note: On the 5th and 10th days, the WBC count was $0.9 \times 10^9/L$ and the patient was subcutaneously injected with 150 μg recombinant human granulocyte colony-stimulating factor.

Figure 2

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Figure 3

Change in the PLT count of a patient with SFTSV infection.

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