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Case report

Ruxolitinib for severe fever with thrombocytopenia syndrome (SFTS)

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ABSTRACT

Severe fever with thrombocytopenia syndrome (SFTS) is an emerging infectious disease with high mortality. A 73-year-old woman presented to the hospital with fever after being bitten by ticks and was diagnosed with SFTS. Three days after treatment with high-flow oxygen and supportive therapy, her condition deteriorated to septic shock and multiple organ failure. Ruxolitinib, a JAK1/2 inhibitor, was used for the treatment of cytokine release syndrome, and the patient finally recovered. Ruxolitinib and other host-based immunomodulatory drugs may be potential treatments for fatal SFTS.

1. Case presentation

In May 2022,a previous healthy 73-year-old female farmer was admitted to the infectious diseases department of Qilu Hospital in Jinan, China, after 9 days of fever (the maximum temperature was 39 °C), nausea and vomiting. Her fever persisted and was accompanied by cough and an altered state of consciousness 7 days later. She had a history of a tick bite.

Physical examination of the patient on admission day confirmed a coma with a Glasgow Coma Scale of 8/15 (E2V2M4). She had a body temperature of 38.5 °C. There was a recent tick bite on her right upper abdomen (Figure 1) and ecchymosis on her trunk and limbs. A 2 cm swollen lymph node was palpable in her right inguinal region. Auscultation revealed moist crackles in her lower lung fields and dullness to percussion at the base.

Initial patient investigations revealed pancytopenia with a total white cell count (WBC) of 0.65×10^9/L (absolute neutrophil count of 0.34×10^9/L), hemoglobin level of 10.1 g/dl, and platelet count (PLT) of 42×10^9/L. There was significant instability of her coagulation function including a prothrombin time (PT) of 12 s, activated partial thromboplastin time (APTT) of 60.3 s, fibrinogen (Fib) level of 1.61 g/L, and D-dimer level of 4.73 ng/ml. There was a marked elevation of her serum cytokines including an Interleukin-6(IL-6) level of 55.54 pg/ml, Interleukin-8(IL-8) level of 126 pg/ml, Interleukin-10(IL-10) level of 79.36 pg/ml, and Interferon-α(INF-α) level of 2335 pg/ml. Her lactate dehydrogenase (LDH) level was elevated at 2646 U/L, and creatine kinase (CK) level was elevated at 850 U/L. There was also elevated serum galactomannan (GM) and (1–3)-β-D-glucan (Table 1). The nucleic acid of SFTS virus (SFTSV) was detected using a reverse-transcription polymerase chain reaction (12500 copies/ml). Her sputum culture was positive for *Aspergillus flavus*. Chest computed tomography (CT) showed patchy shadows on both sides of the lungs and bilateral pleural effusion (Figure 2A). The diagnosis of SFTS accompanied by invasive pulmonary aspergillosis (IPA) was confirmed.

On admission (Day 0), the patient was treated with high-flow oxygen (8 L/min), an expectorant (ambroxol 30 mg intravenous drip twice daily),

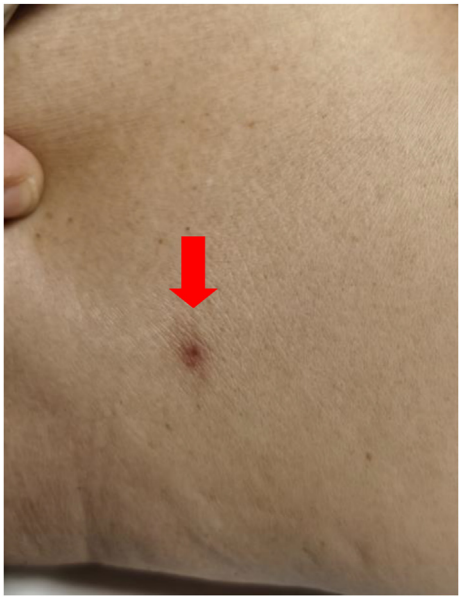

Figure 1. The tick bite lesion on the patient's right upper abdomen.

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Table 1. Laboratory and clinical findings of the patient.

	Hospital days										
	Reference Range	-3	-1	1	3	5	7	9	11	13	15	17
BT (°C)		39	38.7	38.5	38.9	37.6	37.8	37.2	36.8	37.1	36.9	37
BP (mmHg)		104/68	112/65	102/58	89/47	98/62	105/66	106/65				116/68
CRP (mg/L)	0–10	0.86		2.09								
Ferrinti (ng/ml)	13–400				33737		18060				1058	
WBC (10^9/L)	3.5–9.5	1.2	0.65	8.29	11.89	9.49	12.04	8.43	6.45	6.06	7.95	6.75
ANC (10^9/L)	1.8–6.3	0.96	0.34	7.26	8.73	7.99	10.37	7.23	4.64	4.69	6.43	5.42
ALC (10^9/L)	1.1–3.2	0.22	0.26	0.76	2.43	0.63	0.9	0.61	0.79	0.61	0.89	0.62
PLT (10^9/L)	125–350	73	42	176	37	19	26	16	55	108	220	303
PT (s)	11–14.5	14.2		12	14	9.3	11.7		10			
PT-INR	0.8–1.2	1.1		0.9	1.09	0.81	0.87		0.87			
APTT (s)	28–45	59		60.3	84.2	45.1	43		28.9			
Fib (g/L)	2–4 g/L	1.65		1.61	1.29	1.39	2.94		3.53			
D-Di (ug/ml)	< 0.5	2.92		4.73			6.48					
ALT (U/L)	9–50	35		91	130		95		55			20
AST (U/L)	15–40	107		768	929		310		108			34
TG (mmol/L)	0.3–1.7			23.86	14.08	4.48	2.53					
LDH (mmol/L)	120–230			2646					662			537
CK (U/L)	26–140			850					252			114
CK-MB (ng/ml)	0.3–4.0			11.2					2.3			4.3
hs-CTNI (ng/L)	<17.5	62.64		330.4					88.8			17.7
BUN (mmol/L)	2.3–7.8	6.9		3.3	4		7.9		4.3			3.3
Cr (umol/L)	53–97	76		59	65		55		58			44
NT-PROBNP (pg/ml)		712.9		4385	17110				1502			
PaO2 (mmHg)	80–100		61		89	80		69				91
PaO2/FiO2 (mmHg)	400–500		149		88	132		269				433
Lac (mmol/L)	0.5–2.2		2.4		2.7	2.2		2.1				1.3
GM	<0.5				7.15							
(1–3)-β-D-glucan (pg/ml)	70–95				113.2							
CD4+Tcell (/ul)	441–2156			49						463		
CD8+Tcell (/ul)	125–1312			54						190		
B cell (/ul)	107–698			75						127		
NK cell (/ul)	95–640			50						40		
IL-6 (pg/ml)	≤5.30			55.54	327.8					53.9		34
IL-8 (pg/ml)	≤53.09			126						14.5		
IL-10 (pg/ml)	≤4.91			79.36						<2.5		
IFN-α (pg/ml)	≤8.50			2335						<2.5		
IFN-γ (pg/ml)	≤7.42			12.09						<2.5		
SFTS virus load (copies/ml)				12500						2360		

Abbreviations: BT: body temperature; BP: blood pressure; CRP: C-reactive protein; WBC: white blood cell; ANC: absolute neutrophil count; ANC: absolute lymphocyte count; PLT: blood platelet; PT: prothrombin time; APTT: activated partial thromboplastin time; Fib: fibrinogen; D-Di: D-dimer; AST: aspartate aminotransferase; ALT: alanine aminotransferase; TG: triglyceride; LDH: lactate dehydrogenase; CK: creatine kinase; CK-MB: creatine kinase myocardial band; hs-CTNI: high-sensitivity cardiac troponin; BUN: blood urea nitrogen; Cr: creatinine; NT-PROBNP: N-terminal brain natriuretic peptide; PaO2: oxygen pressure; Lac: lactic acid; GM: galactomannan; Interleukin-6:IL-6; Interleukin-8:IL-8; Interleukin-10:IL-10; Interferon-α:INF-α; Interferon-γ:INF-γ.

antipyretic drugs (ibuprofen 200 mg once, when necessary), and fluid rehydration. We started infusion of voriconazole (200 mg twice a day) for the treatment of IPA. After 3 days of admission, her condition worsened, with a low blood pressure of 89/47 mmHg, hypoxemia (oxygen arterial partial pressure and fraction of inspired oxygen ratio (PaO_2/FiO_2) of 88 mmHg), elevated lactate levels (2.7 mmol/L) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels (17110 pg/ml), and a decrease in PLT (37×10^9/L). The chest CT showed significantly worse than before (Figure 2B). Her disease deteriorated with sepsis shock and multiple organ failure, requiring high flow nasal cannula and positive vasoactive agents. On day 3, ruxolitinib (10mg twice daily nasal administration first 5 days, 5mg twice daily orally for the next 5 days)was administrated to inhibit hyperinflammation. Two days (Day 5) after administering oral ruxolitinib, her dyspnea and coma improved to a Glasgow Coma Scale of 13/15 (E3V5M5). On Day 9, her temperature gradually dropped to a normal one. The laboratory test results gradually improved, and the chest CT results also improved (Figure 2C). The SFTSV load decreased to 2360 copies/ml on day 13. After a duration of 18 days of hospitalization, she finally recovered. Her clinical course is summarized in Figure 3 and Table 1.

The patient received follow-up 2 weeks after discharge in the clinic, where the laboratory tests showed normal WBC and PLT.

The study of this case was approved by the institutional review board of Qilu Hospital of Shandong University (KYLL-202206-011-1). The patient provided written informed consent.

2. Case discussion

SFTS was first reported in China in 2011, it is an emerging hemorrhagic fever-like disease caused by *Dabie bandavirus*, also named SFTS virus (SFTSV) [1]. The fatality rate of SFTS varies, ranging from 16.2% to

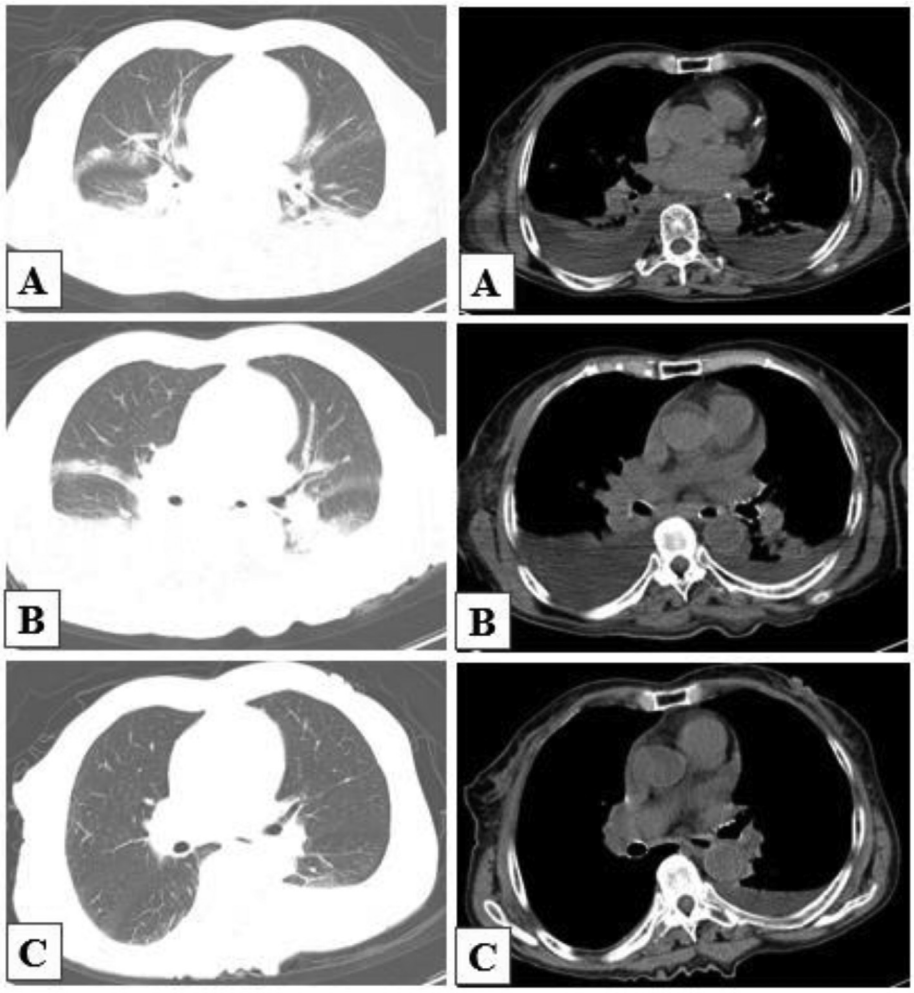

Figure 2. Unenhanced chest CT results on Day 1(A), Day 3 (B) and Day 16(C). The left panel shows the lung window, and the right panel shows the mediastinal window.

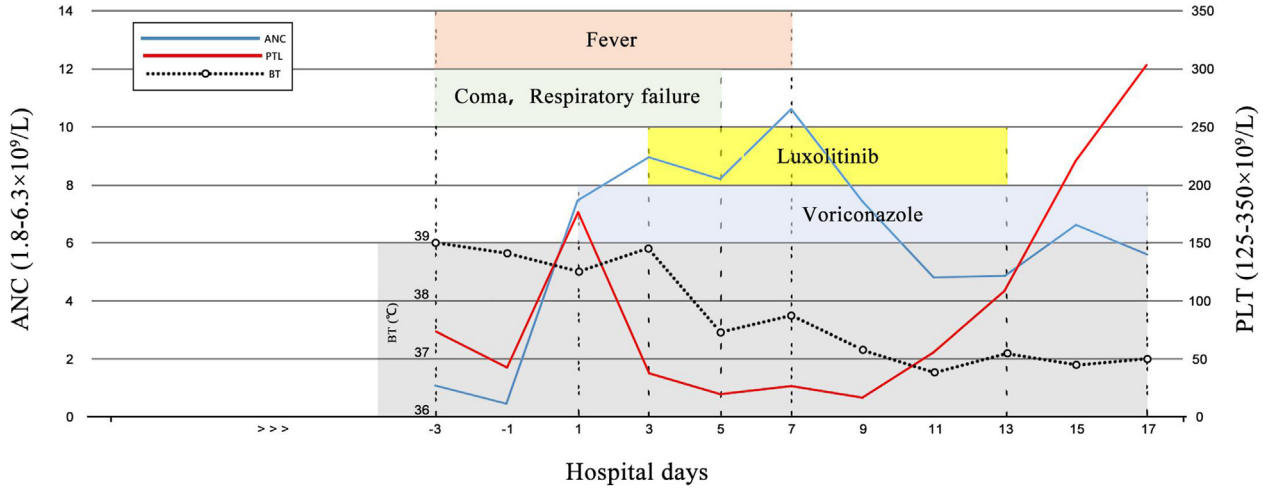

Figure 3. Clinical course of this patient with SFTS. Abbreviations: BT: body temperature; ANC: absolute lymphocyte count; PLT: blood platelet.

40%, depending on different regions and populations [2, 3, 4]. Patients who were older than 60 years, suffer neurological symptoms, accompanied by IPA and cytokine storm are higher risks of death. According to the clinical scoring model [2], this patient has a higher risk of a fatal outcome. There is no effective antiviral therapy for SFTS [5]. Several treatments have been applied to fulminant patients with SFTS (e.g., corticosteroids, intravenous immunoglobulin, and therapeutic plasma exchange), however, none has definitive efficacy [5].

Dysregulated host immunity and an exacerbated Interferon-I response are related to hyperinflammation and fatal outcomes in SFTS [2, 6]. In infection-induced hyperinflammation syndromes (e.g., severe COVID-19), immunomodulatory therapies, such as IL-6 inhibition and

Janus kinase (JAK) inhibition, decrease mortality in these patients even without antiviral therapies [7]. Ruxolitinib is a JAK1/2 inhibitor with potent anti-inflammatory properties that inhibits inflammatory cytokines and the activation of immunocompetent cells [8]. The pathogenesis of COVID-19 involves not only viral replication but also an overexuberant inflammatory reaction. The use of ruxolitinib is safe and associated with the improvement of systemic hyperinflammation in severe COVID-19 [9, 10]. In the case presented here, the patient was an elderly fulminant SFTS patient in whom hyperinflammation syndrome, IPA, multiorgan dysfunction, and pancytopenia had developed. Ruxolitinib, which is used for the treatment of hyperinflammation, is efficacious and safe which does not inhibit the clearance of SFTS virus or patient recovery from pulmonary infections. To our knowledge, no similar studies have been reported. There is one limitation of our report. This is a single case, and further research is needed to prove the effectiveness and safety of ruxolitinib for fatal SFTS in a large sample size.

3. Teaching point

Ruxolitinib and other host-based immunomodulatory drugs may be potential treatments for fatal SFTS.

Declarations

Author contribution statement

All authors listed have significantly contributed to the investigation, development and writing of this article.

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Data included in article/supp. material/referenced in article.

Declaration of interest's statement

The authors declare no competing interests.

Additional information

No additional information is available for this paper.

References

[1] X.J. Yu, et al., Fever with thrombocytopenia associated with a novel bunyavirus in China, N. Engl. J. Med. 364 (2011) 1523–1532.
[2] H. Li, Q.B. Lu, B. Xing, et al., Epidemiological and clinical features of laboratory-diagnosed severe fever with thrombocytopenia syndrome in China, 2011-17: a prospective observational study, Lancet Infect. Dis. 18 (10) (2018) 1127–1137.
[3] X.C. Tran, Y. Yun, L. Van An, et al., Endemic severe fever with thrombocytopenia syndrome, Vietnam, Emerg. Infect. Dis. 25 (5) (2019) 1029–1031.
[4] A.M. Win, Y.T.H. Nguyen, Y. Kim, et al., Genotypic heterogeneity of orientia tsutsugamushi in scrub typhus patients and thrombocytopenia syndrome coinfection, Myanmar, Emerg. Infect. Dis. 26 (8) (2020) 1878–1881.
[5] J.W. Seo, D. Kim, N. Yun, D.M. Kim, Clinical update of severe fever with thrombocytopenia syndrome, Viruses 13 (7) (2021) 1213. Published 2021 Jun 23.
[6] H. Li, X. Li, S. Lv, et al., Single-cell landscape of peripheral immune responses to fatal SFTS, Cell Rep. 37 (8) (2021), 110039.
[7] A. Agarwal, B. Rochwerg, F. Lamontagne, et al., A living WHO guideline on drugs for covid-19, BMJ 370 (2020 Sep 4) m3379.
[8] A. Ahmed, S.A. Merrill, F. Alsawah, et al., Ruxolitinib in adult patients with secondary hemophagocytic lymphohistiocytosis: an open-label, single-center, pilot trial, Lancet Hematol 6 (12) (2019) e630–e637.
[9] A.M. Vannucchi, B. Sordi, A. Morettini, et al., Compassionate use of JAK1/2 inhibitor ruxolitinib for severe COVID-19: a prospective observational study, Leukemia 35 (4) (2021) 1121–1133.
[10] F. La Rosée, H.C. Bremer, I. Gehrke, et al., The Janus kinase 1/2 inhibitor ruxolitinib in COVID-19 with severe systemic hyperinflammation, Leukemia 34 (7) (2020) 1805–1815.