J Vector Borne Dis 50, December 2013, pp. 314–317

Case Reports

Mutiple organ damage caused by a novel tick-borne Bunyavirus: A case report

Qin-xiu Xie, Xu Li, Jun Cheng & Yibo Shao

Department of Infectious Diseases, Affiliated Hospital of Anhui Medical University, Anhui, China PR

Key words Novel bunyavirus; multiple organ damage; severe fever with thrombocytopenia syndrome; sepsis

There were some patients who had the same symptoms of severe fever with thrombocytopenia successively or simultaneously in rural areas of central and northeast China in 2009. Infection with *Anaplasma phagocytophilum* or a virus has been suggested as a cause, but the pathogen has not been detected in most of the patients on laboratory testing. Instead, a novel virus, a member of the family *Bunyaviridae* was isolated from some patients' blood in 2010[1]. The major clinical symptoms of severe fever with thrombocytopenia syndrome (SFTS) included fever, thrombocytopenia, leukocytopenia, gastrointestinal symptoms, hemorrhagic tendency, liver and kidney dysfunction, and even a few severe patients died with multiple organ failure[2]. Several patients with disturbance of consciousness may mimic other infections like human anaplasmosis, viral meningoencephalitis, dengue fever and severe sepsis of obscure origin[3–4]. Here, we report a case of SFTS with multiple organ damage caused by the novel Bunyavirus, involving high-grade fever, thrombocytopenia, leukocytopenia, coma, gastrointestinal symptoms, hemorrhagic tendency, and liver and kidney dysfunction, initially diagnosed as a severe sepsis of obscure origin in Anhui, a province in central China in 2009.

Case report

A 62-yr old woman lived in a hilly area with a fever, unconsciousness and balderdash on 7th July 2009 was admitted to our hospital. Before admission, she had a history of continuous high-grade fever (temperatures of 39.2 to 39.7°C) with watery diarrhoea (about 5–6 episodes per day, 100–150 ml each, without foul smell, blood or mucus), fatigue, headache, myalgias, arthralgias for 5 days and with disturbance of consciousness for one day. She was suspected as central nervous system infection to our hospital. Physical examination on admission revealed a temperature of 38.2°C, pulse of 82 beats/min, blood pressure 110/75 mmHg, unconsciousness, petechiae around injection site and abdominal pain and tenderness without guarding and rigidity. She had lacunar infarction by cephalic CT and a moderately abnormal electroencephalogram. The laboratory data obtained on admission included: white blood cell (WBC) 1.8l ($\times 10^9$/l), with 83.3% polymorphonuclear elements, eosinophilic granulocyte (EOS) 0, platelets (PLT) 33 ($\times 10^9$/l), aspartate aminotransferase (AST) 238 (U/L), alanine aminotransferase (ALT) 781 (U/L), blood urea nitrogen 14.5 (mmol), creatinine 162 (μmol/l), urine protein (+++), urine for occult blood test (+++), hemodiastase 172 μ/l, serum potassium 3.29 mmol/l and serum sodium 124 mmol/l. Cerebrospinal fluid analysis was normal. The other examinations, such as chest X-ray, abdominal ultraphonic, autoimmune, blood culture and other workup of infective etiology were negative. She was diagnosed as severe sepsis of obscure origin complicated with multiple organ damage. Meropenem, Vancomycin and other symptomatic treatment includ-ing highly active hemostasis and fluid infusion therapy (using granulocyte-macrophage colony stimulating factor (GM-CSF) 300 μg/day, intramuscular injection; moreover, ribavirin 0.5 g/day, intravenous injection; levofloxacin 0.4 g/day, intravenous injection and Mino-cycline 100 mg every 12 h at a time) had been gradually administrated to her for seven days. Her condition showed marked clinical improvement after three days treatment, she became afebrile and conscious. Therefore, further evaluations were conducted. There was no evidence to show that with severe sepsis, Meropenem and Vancomycin discontinued. Fortunately, she recovered and discharged from hospital on 21st July 2009 with consciousness, normal temperature and normal laboratory findings. The pathogen isolated from the blood sample of this case in 2010 was identified as a new novel Bunyavirus.

Literature review

Including the case reported here, a total of 11 hospitalized patients with culture confirmed a novel Bunyavirus

infections have been reported from Anhui province in China in 2009. All patients were farmers and healthy previously, aged 36 to 67 yr (mean 54 yr), and the male to female ratio was 7 : 4. They came from different hilly or rural areas in the southwest of Anhui province. Domestic animal cultivation, tea collection and other agricultural activities before the disease were investigated. Ticks were commonly found in the cattles, goats and dogs in those areas. All the 11 confirmed patients were bitten by them more than one time before, but they didn't always have symptoms. Out of 11, five patients were confirmed bitten by ticks 3–14 days before falling ill. The clinical symptoms of the patients were non-specific, including fever (100%, they were all having continuous fever, lasting 6 to 20 days), chill (100%), headache (100%), severe malaise (100%), and so on (Table 1). Laboratory abnormalities included leukopenia (81.8%), thrombocytopenia (100%), eosinopenia (100%), increased prothrombin times (PT), activated partial thromboplastin times (APTT), lactate dehydrogenase (LDH), creatine kinase (CK), blood urea nitrogen (BUN), blood creatine (CR), and alkaline phosphatase (AKP). Hepatic transaminase levels such as aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were observed to be increased in all the patients (Table 2). All the patients were diagnosed as infectious disease caused by a bacteria,

Table 1. Individual clinical symptoms and signs in novel Bunyavirus infected patients in Anhui province, China in 2009

Patient number	Sex	Age	Temp. (°C)	Headache	Chill	Myalgia/ Arthralgia	Nausea	Vomiting	Diarrhoea	Cough	Hemorrhage complications	Lympha-denectasis	Psychotic symptoms
1	F	47	40	+	+	+	+	–	+	–	+	+	+
2	M	36	39.6	+	+	+	–	–	+	–	–	–	–
3	M	61	39.6	+	+	+	+	+	+	–	+	–	+
4	F	48	40	+	+	+	–	+	–	–	–	–	–
5	M	56	40	+	+	+	–	+	–	+	+	–	+
6	M	67	39.3	+	+	+	–	+	+	+	+	+	+
7	M	60	39	+	+	+	+	–	–	+	–	+	–
8	F	62	38.2	+	+	+	+	+	+	–	+	–	+
9	M	52	40	+	+	+	–	–	–	–	+	–	+
10	F	62	40.1	+	+	+	+	–	+	–	–	–	+
11	M	45	39	+	+	+	–	–	–	–	–	–	–

Table 2. Individual laboratory findings in novel Bunyavirus infected patients in Anhui province, China in 2009

Patient number	WBC ($\times10^9$/l)	LYMPH ($\times10^9$/l)	NEU ($\times10^9$/l)	HGB (g/l)	PLT ($\times10^9$/l)	ALT (U/L)	AST (U/L)	PT (s)	APTT (s)	LDH (μ/l)	CK (μ/l)	AKP (μ/l)	BUN (mmol/l)	Cr (μmol/l)
1	3.3	1.27	0.97	111	31	122	435	10.7	33.1	2085	323	201	5.2	67
2	2.2	1.05	0.71	111	65	100	435	11.7	33.6	–	37	26	6.1	79
3	2.9	0.43	1.68	128	13	118	221	19.3	129.2	29655	973	–	14	235
4	1.9	1.08	0.64	112	26	79	343	13.1	76.3	1495	–	95	3.6	61
5	3.3	0.93	2.18	157	15	61	182	15.4	180	–	–	–	13.8	191
6	8.1	0.97	6.89	121	63	52	62	25.6	76.1	2250	172	30	15.7	85
7	7	1.02	5.74	120	77	99	110	12.1	35.1	–	–	–	5.7	75
8	1.8	0.24	1.5	110	33	781	238	10.1	32.3	–	–	–	14.5	162
9	1.3	0.61	0.3	125	16	2514	2712	11.5	33.2	394	–	133	1.9	54
10	1.04	0.09	0.8	99	33	709	628	18.6	35.2	2384	–	455	9	67
11	1.95	0.36	1.39	147	41	268	637	11.3	45.6	2250	1506	103	5.8	86
Normal	4–10	0.8–4	2–7.5	110–160	100–300	0–40	0–40	11–14	28–42	109–245	53–106	40–150	3.2–7.1	53–106

(–) Not done; WBC: White blood cell; LYMPH: Lymphocyte; NEU: Neutrophil; HGB: Hemoglobin; PLT: Platelet; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; PT: Prothrombin times; APTT: Activated partial thromboplastin times; LDH: Lactate dehydrogenase; CK: Creatinine kinase; AKP: Alkaline phosphatase; BUN: Blood urea nitrogen; Cr: Creatinine.

virus or *Anaplasma phagocytophilum* at that time. They were administrated by the Meropenem, Vancomycin, Ribavirin, Minocycline, and other symptomatic treatment including injection granulocyte colony stimulating factor (GCSF), fluid replacement therapy, blood transfusion, hemostasis, and so on. Out of 11, nine patients were cured, but two died with multiple organ failure.

SFTS is a serious infectious disease with 12% case-fatality rate that has been documented in six rural provinces in northeast and central China. SFTS is caused by a novel Bunyavirus, SFTS virus (SFTSV)[1]. SFTSV is classified in the family *Bunyaviridae*, genus *Phlebovirus*, and is believed to be transmitted by ticks because the virus has been detected in *Haemaphysalis longicornis* ticks . However, the disease can also be transmitted from person to person through contact with infected patient's blood or mucous[5–6]. Mostly, the cases occurred from May to September. This was consistent with the feature of tick activity. Most of the farmers were bitten by ticks more than once in our investigation, but few of them had clinical symptoms in endemic areas. Sub-clinical SFTSV infections or a relatively mild form of SFTS illness may occur in humans in an endemic area[7]. Patients with SFTS had non-specific clinical symptoms. People with Bunyavirus are similar to the flu, dengue fever, hemorrhagic fever (rift valley fever, the Crimean-Congo hemorrhagic fever, etc), human granulocytic anaplasmosis (HGA) and encephalitis (California encephalitis).

Patients with HGA have fever and a decreased number of peripheral white cells and platelets, but gastrointestinal symptoms are not common[8]. In the initial febrile phase, patients with hemorrhagic fever with renal syndrome may have gastrointestinal symptoms and abdominal pain resembling symptoms of SFTS, but the characteristic flushing of the face and V-area of the neck and thorax, conjunctival suffusion, and periorbital edema, hypotension, oliguria, polyuria, and bleeding disorders have not been observed in patients with SFTS[9]. Patients with severe sepsis with fever, chill, myalgia, hemorrhagic tendency, mental confusion, decreased number of peripheral white cells and platelets may accompanied by circulatory failure and disseminated intravascular coagulation (DIC). Multiple organ damage, mental confusion and hemorrhagic tendency were often observed at the end-stage of severe sepsis as well as at the early stage of the SFTS. Patients with severe sepsis with multiple organ dysfunction would improve gradually after administering antibiotics, but not in a short time as observed in this case. Symptomatic treatment may improve the prognosis at the early stage of illness, although there is no effective therapy for SFTS caused by novel Bunyavirus. It was often difficult to differentiate severe sepsis and SFTS without pathogen. We can isolate the pathogen by inoculation of cell culture and detection of viral RNA on polymerase-chain reaction assay from their blood specimens, feces, urine and throat swabs. However, some physicians could not obtained the pathogen due to the limited laboratory conditions. It is important to note that the patient's epidemiological features including endemic area, season, occupation, tick sting history, may differentiate the two diseases. Virus replication and host immune responses may play an important role in determining the severity and clinical outcome in patients with infection by SFTSV[10]. The pathogenesis of SFTSV infection in humans needs more research.

To conclude, patients with multiorgan dysfunction with SFTS, the physician should be aware of the causes of SFTSV based on their epidemiological features.

ACKNOWLEDGEMENTS

We are grateful to Yan Liu (from the Department of Pathology, University of Texas Medical Branch, USA) for contributing to isolate and identify the virus.

REFERENCES

1. Yu XJ, Liang MF, Zhang SY, Liu Y, Li JD, Sun YL, *et al*. Fever with thrombocytopenia associated with a novel bunyavirus in China. *N Engl J Med* 2011; *364:* 1523–32.
2. Zhang YZ, Zhou DJ, Xiong Y, Chen XP, He YW, Sun Q, *et al*. Hemorrhagic fever caused by a novel tick-borne Bunyavirus in Huaiyangshan, China. *Zhonghua Liu Xing Bing Xue Za Zhi* 2011; *32:* 209–20.
3. Zhang YZ, Zou Y, Fu ZF, Plyusnin A. Hantavirus infection in humans and animals, China. *Emerg Infect Dis* 2010; *16:* 1195–1203.
4. Gao X, Nasci R, Liang G. The neglected arboviral infections in mainland China. *Plos Negl Trop Dis* 2010; *4:* 624.
5. Liu Y, Li Q, Hu W, Wu J, Wang Y, Mei L, *et al*. Person-to-person transmission of severe fever with thrombocytopenia syndrome virus. *Vector Borne Zoonotic Dis* 2012; *12:* 156–60.
6. Bao CJ, Guo XL, Qi X, Hu JL, Zhou MH, Varma JK, *et al*. A family cluster of infections by a newly recognized bunyavirus in eastern China, 2007: Further evidence of person-to-person transmission. *Clin Infect Dis* 2011; *53:* 1208–14.
7. Zhao L, Zhai SY, Wen HL, Cui F, Chi YY, Wang L, *et al*. Severe fever with thrombocytopenia syndrome virus, China. *Emerg Infect Dis* 2012 June; *18*(6): 963–5.
8. Dumler JS, Choi KS, Garcia-Garcia JC, Barat NS, Scorpio DG, Garyu JW, *et al*. Human granulocytic anaplasmosis and *Anaplasma phagocytophilum*. *Emerg Infect Dis* 2005; *11:* 1828–34.
9. Peters CJ, Simpson GL, Levy H. Spectrum of hantavirus

infection: Hemorrhagic fever with renal syndrome and hantavirus pulmonary syndrome. *Annu Rev Med* 1999; *50:* 531–45.
10. Zhang YZ, He YW, Dai YA, Xiong Y, Zheng H, Zhou DJ, *et al*. Hemorrhagic fever caused by a novel Bunyavirus in China: Pathogenesis and correlates of fatal outcome. *Clin Infect Dis* 2012; *54*(4): 527–33.

Correspondence to: Qin-xiu Xie, Department of Infectious Diseases, Affiliated Hospital of Anhui Medical University, 230022, Hefei, Anhui, China PR.
E-mail: xqx1977@163.com

Received: 27 January 2013 *Accepted in revised form:* 12 June 2013