View Point on Severe Fever with Thrombocytopenia Syndrome

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Severe fever with thrombocytopenia syndrome (SFTS), a new disease of zoonotic natural foci has been increasing in recent years. In this review, the disease of human granulocytic anaplasmosis infection due to tick-borne and new Bunia virus infection, have similar clinical symptoms. Total of 11 articles were retrieved. The emergence, etiology, nomenclature and pathogenic mechanisms, clinical diagnosis and genotyping of SFTS were summarized, and the current situation of treatment was also evaluated. In conclusion, early detection, identification and treatment are the key points to SFTS, but how to reduce the mortality of critically ill patients is still the focus in the future.

Key words: Severe fever with thrombocytopenia syndrome; New Bunia virus; Clinical classification

The symposium of severe fever with thrombocytopenia syndrome (SFTS) on national emerging infectious diseases and re-emerging infectious diseases was held in Zhengzhou from June 29 to July 1, 2012. The discussion was mainly focused on SFTS caused by new Bunia virus infection, severe hand/foot and mouth disease, influenza etiological study of chronic viral hepatitis, *Yarrowia Pneumocystis* pneumonia, disease by Hantaviruses, new infections diarrhea, advances in diagnosis and treatment of AIDS, new-onset recurrent parasite diseases, imported malaria and other issues. Totally, 11 reports on SFTS were obtained, and current research progress and main points on SFTS are summarized as following.

THE EMERGENCE, ETIOLOGY AND NOMENCLATURE OF SFTS

It was proposed by Professor Bianli Xu from CDC of Henan Province that several patients of Guangshan County died in May 2007, including three patients who were initially diagnosed as “acute gastroenteritis” with the characterization of abdominal pain, diarrhea, nausea, vomiting, anorexia, fatigue, unexplained

fever and multiple organs damage. The Chinese Ministry of Health, the Chinese Center for Disease Control and Prevention (CDC), Health Department of Henan Province and CDC of Henan Province organized the experts to go to five epidemic counties in Xinyang City, from April 1 to June 26, 2009, and investigated 49 clinical cases, 8 of which died. This disease was highly sporadic, mainly distributed in the hilly areas, most patients were farmer with a history of tick bites, mainly were females aged 50-70 years old. Ten serum samples randomly selected were sent to laboratory and antibody to *Chlamydia pneumoniae*, *Mycoplasma pneumoniae*, *Legionella*, adenovirus, cytomegalovirus, Coxsackie virus, EB virus, respiratory syncytial virus, Hantaan virus, Dengue virus, *Ehrlichia chaffeensis* etc were tested and the results were negative. Two throat swabs were tested for human-avian influenza by nucleic acid test, and the results were negative; 22 samples were tested for anaplasma by PCR, and anaplasma-specific amplification products were found in 5 sera and 2 throat swab. Antibody of human granulocytic anaplasmosis (HGA) in 20 serum sample were tested with indirect immunofluorescence assay, and the results showed that 12 were positive, the antibody titers of 5 sera were 1:256.¹ According to the case report by Yijishan Hospital in 2006, the outbreak was initially described as “anaplasma infection”, and it was identified preliminary as emerging infectious diseases caused by tick bites. The treatment with doxycycline or rifamycin recommended by “The

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Guideline of Prevention and Treatment on Human Infection with Anaplasmosis” (published by Health Department of Henan Province in 2007 and by the Ministry of Health in 2008 and 2010)²⁻³ has showed significant effect in some cases.

The infectious diseases emerged in south of Henan Province, China, caused widespread concern by experts who engaged in infectious diseases at home and abroad. With the progress of the study on SFTS, it gradually had a consensus, however the name of this disease was still uncertain. The name of this disease was firstly proposed in “The Guideline of Prevention and Treatment on Granulocytic Anaplasmosis Disease what people are infected” (which was published by the Health Department of Henan Province in 2007 and by Health Ministry of the People’s Republic of China in 2008). In May 2010, the Henan CDC, the team by Professor Bianli Xu found the new virus (SFTSV) using advanced “macro-technology” and proposed broader naming of this disease: “fever and neutropenia thrombocytopenia syndrome”. Severe fever with thrombocytopenia syndrome virus (SFTSV) is a newly identified pathogenic member of the *Phlebovirus* species in the *Bunyaviridae* family, spherical, the diameter is 80-100 nm, coated with spinous process, the genome contains three single-stranded negative RNA fragments (L, M and S). The amino acid homology is about 30% between SFTSV and Rift Valley fever virus of the *Phlebovirus* species in the *Bunyaviridae* family.¹

The similar virus was also found in Hubei Province and Henan Province. Professor Yongzhen Zhang proposed that the outbreak of SFTS was mainly in the rural areas with mountains in Suizhou, Macheng City of Hebei Province, which belongs to Tongbaishan, and Xinyang City of Henan Province, which belongs to Dabieshan area. Tongbaishan, Dabieshan, Zhang Baling were called the Huaiyang mountains in geology. According to the clinical features, China CDC, Wuhan Union Hospital, Zhongnan Hospital, Wuhan CDC all believed the disease was tick-borne hemorrhagic fever-like illness caused by SFTSV. According to the international practice—naming a disease or a virus after its first discovering geographical names—it was named as, “Huaiyangshan hemorrhagic fever, HYSHF; Huaiyangshan virus, HYSV” and “Henan fever, HNF; Henan fever virus, HNFV”.⁵

In the meeting it was revealed that according to the geographical distribution of the disease, no one

in Henan, Hubei and Anhui Provinces was infected, but Shandong, Liaoning and Jiangsu Provinces had similar cases. Professor Shibo Li of Wenzhou Medical College reported that there was 94% - 96% in the homology of virus sequence between virus found in Zhoushan Island and the new Bunia virus.⁷ So the definition of “Huaiyang Hill virus” was not accurate.

There were also arguments about the naming of Dabieshan virus. Although the first case and most of the cases were in foothills of Dabieshan, Southern Henan, the naming still need the confirmation and demonstration of the international and domestic experts.

According to the results of 76 serum samples collected from SFTSV-endemic areas, “severe fever with thrombocytopenia syndrome virus, SFTSV” was proposed by China CDC in May 2010. Then “severe fever with thrombocytopenia syndrome prevention guide (2010 Edition)” was issued by the Ministry of Health of the People’s Republic of China in September 2010.

Now, it is assumed that it may be ticks that caused the outbreak of the new Bunia virus (SFTSV), because ticks were considered as carriers responsible for 10% of the cases.

In my opinion, in the treatment of the disease, I suggested we should combine symptomatic treatment with the doxycycline-based treatment, this combined treatment was effective. Ribavirin treatment showed no efficacy, and mortality of critical illness still did not decline.

THE PATHOGENESIS OF SFTS

Professor Yongzhen Zhang of China CDC proposed that the viral load and the severity of the disease were positively correlated, and presented the results of their research on viral load, cytokines, and biochemical changes. They also carried out animal experiments including the sensitivity of small rodents to the virus (SFTSV), how the new Bunia virus affected the weight and survival rate of mice, the pathological changes of brain and liver tissue in Kunming mice after SFTSV infection.⁹

Professor Yaping Han, from First Affiliated Hospital of Nanjing Medical University, reported the characteristics of lymphocyte subsets in peripheral blood of 12 patients with SFTS by quantitative flow cytometry. They also detected the expression of peripheral blood T-lymphocyte cells (CD3⁺, CD4⁺,

CD8⁺), NKT cells (CD3⁺CD16⁺CD56⁺) by in SFTS patients. Then they got the conclusion: obvious immune injury existed in patients infected with SFTSV, and changes in lymphocyte subsets were related to clinical classification and prognosis; total of T cells of peripheral blood were significantly decreased than before, accompanied by significant increase of NK cells. These may be important indicators of poor prognosis of SFTS patients and important tips for the development of appropriate rescuing program in clinical.¹⁰

THE FIRST CASE OF RENAL INJURY

Huazhong Chen et al of Taizhou City Hospital in Zhejiang Province reported three cases of SFTS characterized by renal dysfunction. The epidemiological characteristics were renal dysfunction on the 2-6 day after the onset of the disease: decrease in urine, light edema of lower extremity, upper urinary protein, blood creatinine and urea nitrogen, leukopenia, thrombocytopenia, different degrees of myocardial damage and mild liver dysfunction. The renal dysfunction reached a peak within 6-8 days. After supported treatment of ribavirin, diuretic and symptomatic for 2-3 days, blood creatinine and urea nitrogen began to decline. Three to six days later, the renal function returned to normal¹¹.

CLINICAL DIAGNOSIS AND TYPING

According to “severe fever with thrombocytopenia syndrome prevention guide (2010 Edition)” issued by the Ministry of Health of the People’s Republic of China,¹² Jibin Ye et al first proposed the clinical classification of “human granulocytic anaplasmosis” in 2010,¹³ and that also could be applied in the “severe fever with thrombocytopenia syndrome (SFTS)”, “new Bunia virus infected disease”.¹⁴

1. The ordinary type (multi-system damage, light):

- (1) Treated promptly, good spirit ;
- (2) The age <60 years old;
- (3) Body temperature <38 °C, or duration of fever is short;
- (4) Loss of appetite, nausea, vomiting and other gastrointestinal symptoms are mild;
- (5) Platelets $30-60 \times 10^9 / L$, no bleeding;
- (6) Peripheral blood leukocytes $> 2.0 \times 10^9 / L$, granulocytes $> 1.0 \times 10^9 / L$, blood biochemical ALT, AST, CK, CK-Mb and LDH are within 2 times of the

upper limit of normal value.

2. The critical type (multi-system failure, critical):

- (1) Body temperature >about 39 °C for 48-72 hours or more, relative bradycardia;
- (2) Apathetic or tremors;
- (3) Extreme fatigue, loss of appetite;
- (4) Over 60 years old;
- (5) Diabetes, hypertension, or heart, liver, lung underlying disease;
- (6) Platelets count $< 30 \times 10^9 / L$, or a variety of bleeding;
- (7) White blood cell count decreased, white blood cells $< 2.0 \times 10^9 / L$, granulocytes $< 1.0 \times 10^9 / L$;
- (8) Blood biochemical: the level of ALT, AST, CK, CK-Mb, LDH were 2 times higher than normal.

If there were three or more than three symptoms mentioned above, it should be given the critical type treatment as soon as possible.

CURRENT MANAGEMENT OF SFTS

The recommendation of “doxycycline plus symptomatic and supportive treatment” for human granulocytic anaplasmosis (HGA) and “symptomatic and supportive treatment combined with ribavirin” for SFTS by Ministry of Health of the People's Republic of China has been applied in clinical.

It has been demonstrated that patients of critical type who had early infusion of same type plasma, platelet, or gamma globulin impact therapy had good treatment effects, and the mortality rate was significantly declined. It is necessary not to lose the best opportunity of treatment for higher cost, and there's no need to wait until all standards of critical type existed.

The combined therapy of doxycycline with small dose interferon or thymosin was applied in the treatment of recovered patients with various types of SFTS. Currently it was under observation in clinical.

In the meeting, experts of hand, foot and mouth disease (HFMD) from Beijing Ditan Hospital, Capital Medical University, believed that for children who were infected with EV71, treatment made according to different clinical stage could significantly reduce the mortality rate, it also could make a good balance between the cost and efficacy. It was put forward in the meeting that based on treatment made according to different clinical stage, whether or not special treatment such as gamma globulin could be used in advance to stop the progression of SFTS and reduce

the mortality rate.

Since the birth of the earth, microbes have existed in nature for billions of years. The history of human was just hundreds of thousands of years so far, the struggle with infectious diseases that emerging in nature will be long-term. The development of our society can not prevent the emergence of new infectious diseases. In recent years, severe fever with thrombocytopenia syndrome emerged as a new infectious diseases. A lot of manpower, material and financial support have been put in it. China CDC has carried out the epidemiological investigation, specimen collection, etiology detection, and cooperative research of new Bunia virus reagent development with foreign counterparts, which have reached a very high level. However, the clinical research on the pathogenesis of the disease, infringement of organs and the system were still uncertain. There were also defects of clinical study such as small sample, poor project, no substantial progress and insufficient investment of public health resources. Now the mechanism of doxycycline was unclear, treatment of critical type need to be improved, how to reduce mortality still needs to be explored in the future, clinical pathway of the disease and the emergency response plan were in the blank. So we got a consensus that severe fever with thrombocytopenia syndrome was not only a disaster for people in the disaster area, but also opportunity and resource which history has given us. To strengthen the research on emerging infectious diseases is not only the responsibility of our front-line medical workers, but also the obligations of governments and the health authorities.¹⁵

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