

A Case Report of Scrub Typhus: Secondary Acute Arrest of Hemopoiesis with Multiple Organ Dysfunction Syndromes

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Abstract

Scrub typhus is a zoonotic disease caused by *Orientia tsutsugamushi* (*O. tsutsugamushi*) in which humans are accidental hosts. Acute arrest of hemopoiesis (AAH) always manifests in pancytopenia and with supportive treatment or inducement removal, the AAH patients would show significant improvement in blood routine for about a week. As a rapidly progressive and potentially life-threatening organ function disorder syndrome, multiple organ dysfunction syndrome (MODS) is often induced by many factors including infection, illness and injury. We received a rare case of scrub typhus rapidly presenting with AAH and MODS 2 weeks ago. The clinical data of a 32-year-old female with *O. tsutsugamushi*-induced AAH and MODS was summarized retrospectively and analyzed with a literature review. In this case, we selected tigecycline and moxifloxacin as treatment regimens for scrub typhus. When the potential infection was controlled, her pancytopenia and hepatic function rapidly improved in a few days.

Keywords

Scrub Typhus, *Orientia tsutsugamushi*, Acute Arrest of Hemopoiesis, Multiple Organ Dysfunction Syndrome

1. Introduction

Scrub typhus, also known as tsutsugamushi disease, is a natural focal disease caused by infection with *O. tsutsugamushi*, with rodents as the main source of infection and Chigger mite larvae as the vector. *Orientia tsutsugamushi* (from Japanese *tsutsuga* meaning “illness”, and *mushi* meaning “insect”) is a mite-borne bacterium belonging to the family Rickettsiaceae and is responsible for a disease

called scrub typhus in humans [1]. Patients mostly have a history of field work, and an incubation period of 5 - 20 days. They are characterized by complex and diverse clinical manifestations, and numerous complications, often leading to multiple organ damage, and a high rate of early misdiagnosis [2]. In some cases, the pathogens form eschar-like inflammatory lesions when they enter the body site. Various antibiotics, such as chloramphenicol, tetracycline, doxycycline, macrolides, quinolones, and rifampicin, have been used to treat scrub typhus [3]. The failure of two or more vital organ systems is termed multi-organ dysfunction syndrome (MODS) and resembles a very critical condition associated with high morbidity and mortality [4]. Scrub typhus is a serious disease that can result in multiple organ dysfunctions in some individuals, with a maximum mortality rate of 30% if left untreated [2]. Nevertheless, cases of aplastic crisis due to scrub typhus have been rarely reported. A case of acute arrest of hemopoiesis with multiple organ dysfunction syndrome secondary to scrub typhus was admitted to the Department of Hematology, the Second Affiliated Hospital of Chongqing Medical University, which was diagnosed promptly and successfully cured with tigecycline, was presented here for analysis and review of the literature.

2. Case Presentation

A 32-year-old female was admitted to our hospital with recurrent fever for 2 weeks and abnormal hemogram for 2 days. Two weeks before, she had fever of unknown origin at the highest temperature of 40.0°C with fatigue, dizziness and muscle soreness. The first blood routine in the local hospital showed: hemoglobin, 141 g/L; white blood cell count, $3.74 \times 10^9/L$ and platelet count, $72 \times 10^9/L$. Thirteen days after this examination, she rechecked the blood routine and other imaging examinations: hemoglobin, 45 g/L; white blood cell count, $2.50 \times 10^9/L$; platelet count, $18 \times 10^9/L$; chest computed tomography (CT) suggested a fibrous cord lesion in the middle lobe of the right lung, a small amount of effusion in bilateral pleura and pericardium; abdominal CT showed a significantly enlarged spleen. At this time, pancytopenia appeared on her body and she was treated with andrographolide, dexamethasone and blood component transfusion without any response. There were still many symptoms on her body: fever at a highest temperature of 40.3°C, chills, cough, expectoration, tired out of breath, polypnea, dizziness, headache and leg muscle soreness. Therefore, she was brought to emergency department of our hospital and rapidly screened by professional doctors to send to the hematology department.

On physical examination, the temperature was 40.3°C, the pulse rate was 125 beats/min, the respiratory rate was 35 breaths/min, and the blood pressure was 99/62mmHg. The patient presented an acutely ill face with mild yellow staining of the bilateral scleral icterus, pale palpebral conjunctiva, slightly swollen left submaxillary lymph nodes touched soft without pain, coarse breath sounds in both lungs with little moist rales, soft abdomen that pressed mild pain and spleen could be touched 2 cm below the ribs, mild pitting edema in both lower

limbs.

Laboratory testing and imaging examinations showed the following (**Table 1**): hemoglobin, 114 g/L; white blood cell count, $8.77 \times 10^9/L$; platelet count, $41 \times 10^9/L$; neutrophilic granulocyte percentage of 76%; absolute reticulocyte count, $0.049 \times 10^9/L$; procalcitonin level, 0.87 ng/ml; prothrombin activity (PTA), 85%; prothrombin time (PT), 14.3 s; activated partial thromboplastin time (APTT), 51.8 s; fibrinogen (FIB), 1.98 g/L; fibrinogen degradation products (FDPs), 11.18 ug/L; total protein (TP), 53 g/L; albumin (ALB), 27.9 g/L, alanine aminotransferase (ALT), 258 U/L; aspartate aminotransferase (AST), 298 U/L; alkaline phosphatase (ALP), 172 U/L; γ -glutamyltransferase (GGT), 122 U/L; prealbumin (PAB), 39 mg/L; β 2-microglobulin, 5.71 mg/L; lactic dehydrogenase (LDH), 590 U/L; plasma D-dimer, 3202 ng/ml; immunoglobulin G (IgG), 10.5 g/L; immunoglobulin A (IgA), 2.97 g/L; immunoglobulin M (IgM), 3.59 g/L; light chain κ , 10.9 g/L; light chain λ , 5.94 g/L; complement C3, 0.64 g/L; complement C4, 0.24 g/L; anti-mitochondrial M2 antibody, 36.2 RU/ml; interleukin-2 receptor (IL-2R), 1126 U/ml; interleukin-1 β (IL-1 β), 8.24 pg/ml; ferritin, 1321 ng/ml. The examination of HIV, syphilis, hepatitis A, B, C, D and E testing showed negative results. Similarly, the results of blood culture, fungal G and GM test, Epstein-Barr virus DNA, human cytomegalovirus DNA, antinuclear antibody testing and vasculitis-associated antibodies didn't show obvious abnormalities. TORCH examination was positive for herpes simplex virus IgM. Bone marrow morphology test showed: hyperplasia of bone marrow was obviously active, mainly granular cell hyperplasia; hyperplasia of erythroid cell was severely reduced; atypical lymphocytes were seen, and plasma cells were more active. PNH examination in peripheral blood (CD55 and CD59) and flow cytometry in bone marrow: no abnormality was found in flow cytometry of lymphocytes and plasma cells.

Table 1. A part of laboratory examinations during hospitalization.

Title	Reference range	Day 1	Day 2	Day 5	Day 6	Day 7	Day 9
WBC ($\times 10^9/L$)	3.5 - 9.5	8.7	5.5	6.6		6.6	4.0
HB (g/L)	130 - 175	114	51	112		112	115
PLT ($\times 10^9/L$)	100 - 300	41	42	130		156	187
ALB (g/L)	40 - 55	27.9	24.8	24.5		31	34.7
ALT (U/L)	7 - 40	258	203	74		40	38
AST (U/L)	13 - 35	298	256	48		48	32
PT (s)	11 - 14.5	14	15.7	13.8	17.5	16.4	14.4
APTT (s)	31.5 - 43.5	51.8	74.5	55.7	67.2	61.2	48.9
FIB (g/L)	2 - 4	1.98	1.21	1.3	0.71	0.82	1.08
D-D (ng/ml)	0 - 550	3202	1665			1672	

On the first day of hospitalization, she had recurrent fever, chills and her state of illness rapidly progressed on the next day: the intensity of polypnea, dizziness and headache increased and new symptoms like nausea, emesis, abdominal pain, diarrhea and dyspnea, occurred. Therefore, we repeated the physical examination: the blood pressure was 87/54mmHg, the pulse rate was 125 beats/min, the respiratory rate was 35 breaths/min, and the body temperature was 40.0°C. The upper and left lower harder abdomen pressed moderate pain without rebound pain. The circumstance of edema worsened and the limbs started to become cold. A signature eschar was observed in the sacrococcygeal region (**Figure 1**). The results of emergency examinations showed the following (**Table 1**): hemoglobin, 51 g/L; white blood cell count, $5.50 \times 10^9/L$; platelet count, $42 \times 10^9/L$; PT, 15.7 s; APTT, 74.5 s; FIB, 1.21 g/L; ALB, 24.8 g/L; ALT, 203 U/L; AST, 256 U/L; plasma D-dimer, 1665 ng/ml; CT of the chest and abdomen indicated bilateral lung scattered inflammation and bilateral chest cavity filled with little to medium amount of effusion, pulmonary edema, splenomegaly. On further questioning, more medical history details revealed that the patient lived in Fengqing County, Lincang City, Yunnan Province which is a major agricultural province and there were similar patients with recurrent fever like her in the surrounding area. They all had a history of farming or getting unknown insect bites before the initiation of the disease. Based on the clinical, laboratory and even medical history findings, we highly suspected that this patient had scrub typhus. Until then, she had secondary septic shock, pulmonary infection, liver damage, multiple organ dysfunction syndrome (MODS), coagulation dysfunction and aplastic crisis. Empirical intravenous administration of tigecycline and moxifloxacin was initiated immediately. Human immunoglobulin 20 g per day was given for 4 consecutive days to enhance immunity and resist potential virus infection. Human serum albumin (HSA) and plasma were infused for edema remission and coagulation factors complement. Glutathione was administered for liver protection. In addition, quantity fluid resuscitation, oxygen inhalation and other support treatments were added to the regimen. On day 5 of hospitalization, after 3 days of treatment with tigecycline and moxifloxacin, the clinical manifestations, liver function, coagulation function and aplastic crisis improved greatly (**Table 1**). At the same time, the result of the high throughput DNA test of blood pathogens was back: *O. tsutsugamushi* as sequence number 447 was discovered. Until day 9 of hospitalization, we reexamined some indicators: blood biochemical indexes basically recovered (**Table 1**); bone marrow smear and biopsy showed the hyperplasia of hematopoietic cells; CT of chest and abdomen suggested that the pulmonary infection and chest cavity fluid were obviously fade away, meanwhile, the size of spleen reduced. She spent 12 days during hospitalization, and she was discharged with basic recovery. After discharge, she was continued with a course of oral minocycline. During nearly 9 months of follow-up, she was left with sequelae of lung infection that she felt out of breath after moderate-intensity physical activity. Beyond that, she didn't feel any discomfort.



Figure 1. Eschar in the sacrococcygeal region.

3. Discussion

Scrub typhus is a zoonosis caused by the pathogen *O. tsutsugamushi* which is classified as a separate genus in the Rickettsiaceae family. It is described as an acute febrile illness and is confined to a definite geographic region. The “tsutsugamushi triangle” extends from northern Japan and far eastern Russia in the north, to northern Australia in the south, and to Pakistan and Afghanistan in the west [5]. Scrub typhus is a serious public health problem in the Asia-Pacific area. There is an estimated one million new scrub typhus infections each year, and over one billion people around the world are at risk. Without appropriate treatment, the case fatality rate of scrub typhus can reach 30% or even higher [6]. Based on previous studies, rickettsiae are located in endothelial cells in all the organs evaluated, namely heart, lung, brain, kidney, pancreas, appendix, and skin, and within cardiac muscle cells and in macrophages located in lymph node, liver and spleen [7] [8]. The manifestation of disease varies from mild to severe, some just have fever and some cases get fatal syndromes like MODS. According to previous studies, liver dysfunction accounted for 89%, lung involvement accounted for 65%, splenomegaly accounted for 47%, gastro-intestinal haemorrhage accounted for 25% and there were variant reports on the injury of other organ systems [9]. Typical symptoms include eschar, fever, gastrointestinal disturbance, malaise, cough, myalgia, and headache. Diagnosis is often missed in the early stage of the disease, as it presented as an acute febrile illness which is similar to other tropical febrile infections. However, the characteristic eschar-like rash, endemic area, and history of mite bites can assist doctors in rapid diagnosis. In most cases, the timely administration of antibiotics brought out a good outcome [2] [10].

Splenomegaly is a common hematological manifestation in typhus, seen in up to 47% of patients [9], furthermore, disseminated intravascular coagulopathy (DIC) [11] [12], hemophagocytic lymphohistiocytosis (HLH) [13] [14], thrombopenia [15], monoclonal gamma-globulinemia [16] and thrombosis [17], all of which have been reported in some cases. AAH, also known as aplastic crisis, is a sharp decline in hematopoietic function of bone marrow under the interaction of infection, drugs, immune disorders and other inducement, manifested as

erythropenia, hyperplasia of bone marrow and erythroid hematopoietic cells differentiation disorder. Scrub typhus can be secondary to various infectious diseases containing virus infection, which is the most common, especially the B19 virus infection. Specifically, hemoglobin of this case progressive declined in the short term and the bone marrow suggested hypoplasia of erythroid hematopoietic cells. During the hospitalization, after treatment of anti-infection and symptomatic treatment, her symptoms, signs, blood parameters and hypoplasia of erythroid hematopoietic cells recovered rapidly. After case analysis, we considered AAH in scrub typhus was secondary to infection and immune disorders.

As previous articles indicated, there are many literatures summarizing the manifestations of scrub typhus secondary multiple organs involvement. It usually presents as an acute febrile illness, with high fever, malaise, headache and cough. The most characteristic clinical feature of scrub typhus is the presence of an eschar at the site of the bite of the mite [9]. In this case, the transaminase level increased 5 times over than standard values which showed the liver dysfunction. Besides, the level of WBC and PLT decreased sharply and weak erythroid hematopoiesis in bone marrow reflected the further impairment of hematologic system. This specific case, scrub typhus involving AAH and MODS progressed promptly. With medical history details and typical eschar found, correctly diagnosis was given by our experienced doctors. Thanks to timely therapy, this patient rapidly recovered and the expected treatment outcome was achieved.

4. Conclusion

Scrub typhus involving AAH and MODS is not frequently seen in clinical. Apart from careful medical history questioning, witness of eschar is the critical evidence. As shown in our case, people with common febrile illnesses in the tsutsugamushi triangle must be carefully evaluated by the screening of eschar and after treatment of antibiotics, the symptoms and laboratory indicators improved promptly.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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