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CASE REPORT: A RARE CASE OF SCRUB TYPHUS ASSOCIATED WITH HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS

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ABSTRACT

Scrub typhus is a bacterial infection caused by the *Orientia tsutsugamushi* bacteria. The illness can cause anything from a fever to serious multi-organ malfunction. Clinical symptoms and antibody serological testing, which have low sensitivity and specificity, are used to make the diagnosis. Multiple organ dysfunction syndrome (MODS) and hemophagocytic lymphohistiocytosis (HLH) are only infrequently linked to scrub typhus. In this study, we describe a 62 year old female who had a prolonged fever without eschar.

Following the negative results of normal tests, she was identified as having scrub typhus. After receiving dexamethasone, enhanced life support, and anti-rickettsial medication, the patient, who had progressed to HLH and MODS, made a successful

recovery. Furthermore, we provide a brief review of the literature on scrub typhus and its complications.

Introduction

The bacteria *Orientia tsutsugamushi* causes the natural foci illness scrub typhus. The illness can cause anything from a minor fever to many system dysfunctions. The most pathognomonic symptom is an eschar. Despite their poor sensitivity and specificity, clinical symptoms and serological tests (such as the Weil-Felix test) are employed to diagnose scrub typhus. Alternative testing include enzyme-linked immunosorbent assays (ELISA), polymerase chain reactions (PCR), serum immunoglobulinM (IgM) and immunoglobulinG (IgG) antibodies. mNGS, or metagenomic next

generation sequencing, is a cutting-edge approach for locating unique pathogenic diseases. Scrub typhus cases have only seldom been confirmed by mNGS up to this point.

Scrub typhus cases have been recorded more frequently in recent years. Multiple organ dysfunction syndrome (MODS) and haemophagocytic lymphohistiocytosis (HLH) linked with scrub typhus have only been described in a small number of investigations. In the rare and fatal hyperinflammatory disease known as HLH, T lymphocytes and macrophages are overactive, while natural killer (NK) cells and cytotoxic T lymphocytes are depleted. This leads to various organ dysfunction caused by cytokine-mediated multiple histiocytic phagocytosis of blood cells. Genetic mutations are the root cause of primary HLH. Immunodeficiency, autoimmune disorders, infections, and malignancies are the primary causes of secondary HLH. In this case report, scrub typhus without eschar was determined by immunoglobulins. The patient developed HLH and MODS but showed clinical improvement. We also analysed the clinical characteristics, diagnostic approaches, therapeutic approaches, and clinical results of scrub typhus and associated HLH.

CASE REPORT

The case history started with the patient having history of sudden onset of high-grade fever 4 days ago, which was intermittent and accompanied with chills, rigors and was taken to an outside hospital for management of the above symptoms, for which she was managed symptomatically. She developed breathlessness which was sudden in onset for the past two days. Thus the Patient was relieved to the casualty from the outside hospital with chief complaints of breathlessness for the last 2 days. Breathlessness aggravated on exertion and hence is grade 2 according to MMRC classification.

She neither had any history of cough, cold, or any cardiac symptoms such as chest pain, palpitations and syncope, nor any gastrointestinal symptoms such as abdominal pain, vomiting, loose stools and constipation. No history of burning micturition or reduced urine output was present in the patient. She was also not a known case of any comorbidities such as type 2 diabetes mellitus, hypertension, etc and had no history of similar complaints in the past.

On examination, the patient was conscious, oriented and afebrile, but also had Bilateral pitting pedal oedema. Her vitals were stable, with a blood pressure of 130/80 mmHg, spO₂ of 97%, though she had tachycardia due to her pulse rate being

126bpm. Systemic examination of cardiovascular and neurological examination revealed no abnormalities. Per abdomen examination indicated that the abdomen was soft though with diffuse tenderness. On auscultating the abdomen, bowel sounds heard whereas lung auscultation revealed bilateral basal crepitations along with normal vesicular breath sounds.

All necessary investigations were done and the patient was started on the IV fluids, diuretics, antibiotic, and other supportive medications. CBC report revealed a hemoglobin, packed cell volume, erythrocyte and total leukocyte counts within normal limits and a decreased platelet count of 20000/mm³. Urine routine examination revealed albuminuria and glucosuria of 2+ and 3+ respectively. Liver function test confirmed hypoalbuminemia with the serum albumin levels of 2.0 and globulin and alkaline transaminase and alanine transaminase, alkaline phosphatase and gamma glutamyl transferase all being elevated with values of 316, 78, 246 and 117 respectively. Further, fasting and post prandial blood sugar and HbA1C tests showed values of 131, 151 and 8.81mg/dl respectively which lead to the patient being newly diagnosed with type 2 diabetes Mellitus.

Also, ultrasound abdomen and hrct chest were done to rule out gastrointestinal and lung abnormalities respectively. Though the ultrasound abdomen indicated nil significant abnormalities, HRCT chest report pointed towards subpleural thickening with fibroatelectatic changes in the posterior segment of right upper lobe, lingual segments of the left upper lobe, superior basal and posterior basal segments and bilateral lower lobes. Renal function test was also done which showed elevated mildly serum creatinine and Uric acid levels of 1.3mg/dl and 7.1mg/dl, and increased serum urea levels of 90mg/dl. And serum electrolyte levels were borderline normal. Widal test, RT PCR, viral serology, dengue serology, leptospira IgM test were all negative.

Scrub typhus was suspected and serum igM levels for the same were investigated and resulted in a positive value. By this time, the patients platelets have gradually dropped to 15000 and hence 4 units of single donor platelets and 1 unit of packed red blood cells have been transfused. IV doxycycline 100mg BD, which was prophylactically added previously was continued. Meanwhile, serum creatinine levels were fluctuating between 2.1 to 3.7 indicating an unstable kidney function and thus nephrologist added intravenous diuretic. 2decho, done as per the cardiologist suggestion, revealed aortic valve sclerosis, grade 1 diastolic dysfunction,

normal LV systolic function. Pulmonologist noted the ABG parameters of PH, PCO₂, pO₂ and HCO₃-values of 7.3, 35, 52 and 17.2 respectively.

Serum procalcitonin, PT, APTT and INR have been investigated due to d-dimer levels being 3900 and intravenous hydrocortisone added according to the pulmonologist's advice. Serum procalcitonin values returned 4.90, and that coupled with elevated leukocyte count indicated that the patient was in sepsis and blood culture ad sensitivity also showed enterococcus fecium in the sample and hence intravenous azithromycin, meropenem and Teicoplanin were included in her Antibiotic regimen. **HLH** As the patient's condition improved, she was taken off mechanical ventilation support and put on nasal oxygen support with 2 litres and slowly weaned to room air. Vasopressin support had also been tapered as her blood pressure improved and the patient was moved from intensive care unit to the premium ward. **HLH**

Keywords

Orientia tsutsugamushi, hemophagocytic lymphohistiocytosis disease, scrub typhus

Discussion

In endemic locations, scrub typhus is an acute fever illness brought on by chiggers. Eschars are unique signs. Clinical symptoms and serological tests were used to determine the diagnosis of scrub typhus. Scrub typhus serological testing are often available 5–10 days after the commencement of the illness. The most widely used serological test is the Weil-Felix test, but it has low specificity and sensitivity. According to one study, the Weil-Felix test and IgM enzyme-linked immunosorbent assay (ELISA) had sensitivity and specificity of 47%, 96%, 91%, and 100%, respectively. According to studies, PCR-based tests provide superior predictive value in the diagnosis of scrub typhus than IgM ELISA and IgM capture ELISA approaches. High-throughput sequencing, also referred to as mNGS, is a more recent technique for assessing infections. For a few hours, mNGS uses a massively parallel sequencing device to sequence millions of DNA fragments concurrently. DNA fragments from a clinical specimen can be sequenced using this technology. However, mNGS has only sometimes been used to confirm cases of scrub typhus up to this point. According to Li et al., a 51-year-old patient who had no eschar and an inexplicable fever was detected using mNGS on blood and sputum samples. After receiving minocycline, the patient was released from the hospital without any issues. To diagnose scrub typhus, Liu et al. used mNGS, Weil-Felix reaction, indirect immunofluorescence test (IIFT), respiratory tract profile IgM, and

routine bacteria culture. Nine of the 10 patients were finally diagnosed as scrub typhus. All patients were positive of mNGS. For other methods, only Weil–Felix reaction of one patient detected the pathogen. From these results, we considered that mNGS as a better diagnostic method than conventional clinical methods in early diagnose of scrub typhus.

The ultimate diagnosis for nine of the ten patients was scrub typhus. Every patient tested mNGS-positive. Only one patient's Weil-Felix reaction was able to identify the infection using other methods. Based on these findings, we concluded that mNGS is a more accurate diagnostic tool than traditional clinical techniques for detecting scrub typhus early on.

HLH is a condition of immune system activation that results in blood cell phagocytosis and histiocyte growth in solid tissues. When scrub typhus infects macrophages and endothelial cells, it activates many chemokine genes. In patients with severe infections, these inflammatory cytokines cause HLH and MODS. For the purpose of identifying HLH, the HLH-2004 criteria are listed in It has been previously documented that scrub typhus is associated with a high frequency of HLH. One study of scrub typhus in children included information on about 3% of related HLH cases. However, isolated instances of linked HLH have been noted in a different newborn study. However, adult scrub typhus and HLH and MODS are rarely linked. Five patients exhibited HLH and MODS related to scrub typhus, according to Basheer et al. All of the patients were adults, including an 81-year-old woman who passed away after receiving supportive care and antibiotics. One patient had DIC, and three other patients had sepsis. No patients suffered a rash or eschar. Additionally, no one underwent immunosuppressive or immunomodulatory medication. During infection, *Orientia tsutsugamushi* invades smooth muscle cells, perivascular macrophages, and monocytes in addition to the vascular endothelial cells of small to medium-sized blood arteries. Widespread vasculitis/perivasculitis is the typical pathophysiologic mechanism in MODS in patients with severe infections. In a few reports, we speculated that advanced age, the absence of eschar or rash, delayed diagnosis, and additional comorbidities could be risk factors for the progression of HLH and MODS in patients with Scrub Typhus. In these severe individuals, immunosuppressive and immunomodulatory medication needs to be thoroughly evaluated.

The management of HLH and scrub typhus is summarised in Doxycycline, azithromycin, and clarithromycin have a therapeutic response rate for scrub typhus that ranges from 64% to 100%. Doxycycline has been recommended as an empirical treatment for patients with a central nervous system (CNS) infection in endemic areas. Chloramphenicol is only occasionally used to inhibit bone marrow. In every instance, intravenous azithromycin was the preferable course of action. In the pathogenesis of HLH, profound hypercytokinaemia has a significant role, as was previously mentioned. The first and most crucial step in treating HLH is controlling hypercytokinemia. Initial therapies include dexamethasone, cyclosporin A (CSA), and etoposide. Broad-spectrum antibiotics and proper supportive care are advised. These studies showed that anti-rickettsial treatment and immunoregulatory therapy may be effective in patients with scrub typhus-associated HLH. It may be hard to utilize cytotoxic agents in patients with severe diseases (such as sepsis or multiple organ dysfunction). For anti-inflammatory effects, immunosuppression remains as the basis of early management.

Previous studies suggest that infection-associated HLH may have a poor clinical prognosis. Additionally, patients with a delay in anti-rickettsial therapy had a higher risk of complications. Early diagnosis and therapy are important for disease management. The mortality rate of scrub typhus varies widely. In one study, the mortality was up to 10% in patients with significant risk factors, including shock, renal failure, thrombocytopenia, MODS, and CNS involvement. In another study, up to 30% mortality was reported in patients with severe complications without proper treatment. A recent study from Japan showed that old age is an independent risk factor for mortality in scrub typhus cases.

The patient in our study was unusual for diagnosing by mNGS and recovering under treatment of anti-rickettsial, immunoregulatory and supportive therapy, without chemotherapy and HSCT. From our case report, we may highlight the following: (1) mNGS may be a good choice when routine serological tests cannot be obtained; (2) eschar or bites are important for diagnosis, but patients with negative results cannot be ruled out from being diagnosed with scrub typhus; (3) anti-rickettsial therapy, anti-inflammatory therapy, and advanced life support are key therapies for scrub typhus and associated HLH and MODS; and (4) chemotherapy and HSCT may be not necessary in the management of secondary HLH.

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