Introduction

Scrub typhus may not be recognized, especially in non-endemic area such as western Taiwan. Delayed diagnosis and treatment may lead to severe complications such as multi-organ dysfunction and failure\(^{(1)}\) with a high mortality rate\(^{(2,3)}\). Serological analysis might be negative in the first two weeks of the disease. Early diagnosis relies on a high index of suspicion, a detailed travel history and familiarity with the typical primary skin lesion in a febrile patient. Herein we report a case of scrub typhus imported from Ma-Tzu. It was initially diagnosed as acute tonsillitis, leading to delayed treatment and multi-organ dysfunction.
Case Report

A 21-year-old Taiwanese man who served as a soldier with the army in Ma-Tzu developed general malaise, muscle pain and fever in 2006 when he was on leave in Taiwan. These symptoms were followed by a headache and sore throat.

Because of persistent symptoms, he visited a district hospital in Chang-Hua county, where he was admitted under the impression of acute tonsillitis and acute hepatitis. Physical examination showed enlarged palatine tonsils and a general skin rash. Laboratory examination showed leukocytosis with neutrophils predominant, thrombocytopenia, and elevated glutamic oxaloacetic transaminase (GOT 204 U/L) and glutamic pyruvic transaminase (GPT 225 U/L). The results of anti-mycoplasma pneumoniae immunoglobulin G (IgG) and immunoglobulin M (IgM) tests were negative. Chest radiographic and sonographic findings were unremarkable. On the fourth day of hospitalization, following the development of a general maculopapular skin rash, an eschar on his left anterior chest wall developed but was ignored. In spite of treatment with aqueous penicillin-G (3 million units, intravenous, every 6 hours), the fever, leukocytosis, and thrombocytopenia worsened, the liver function impairment persisted, and the patient developed shortness of breath, jaundice, and oliguria. On his sixth day of hospitalization, he was transferred to our hospital due to the uncertain diagnosis and uncontrolled complications.

In the emergency room, the patient appeared acutely ill-looking, was alert (glascow coma scale: E4M6V5), and had a pupil size of 3 mm with normal light reflexes bilaterally. His blood pressure was 100/70 mmHg, pulse rate 110/min, respiratory rate 30/min, and body temperature 36.9 °C. Physical examination revealed icteric sclera bilaterally with subconjunctival hemorrhage (Fig. 1A), a 1.5 cm eschar on his left chest wall (Fig. 1B), tenderness and enlargement of the left axillary lymph nodes with limitation in lifting his left arm due to pain, and rhonchi with basal rales bilaterally.

Laboratory data revealed acute inflammation with a high C-reactive protein level (CRP 20.5 mg/dl), leukocytosis, thrombocytopenia, elevation of GOT, GPT, direct (6.9 mg/dl) and total bilirubin (7.9 mg/dl), blood urea nitrogen (BUN 65 mg/dl), creatinine (2.2 mg/dl), and alkaline phosphatase (Alk-p 644 U/L), hypoalbuminemia (1.9 mg/dl), proteinuria, and hyperbilirubinuria. Arterial blood gas analysis showed the PO$_2$ was 59.8 mmHg, PCO$_2$ 31.6 mmHg, HCO$_3^-$ 19.6 mmol/L and SaO$_2$ 90.6% with a pH of 7.411. Chest radiography showed cardiomegaly and increased interstitial infiltrations in the bilateral lower lobes (Fig. 2). Abdominal sonography revealed hepatomegaly and splenomegaly with coarsening of the hepatic echo pattern and a minimal amount of pleural effusion bilaterally. Scrub typhus with multi-organ dysfunction was diagnosed clinically by a senior physician who had experience in military service in Kin-Men island, one of the endemic areas for scrub typhus.

Gram stain and bacterial culture were negative for both aerobic and anaerobic bacteria. The titers of HBsAg and Anti-HCV antibodies were within the normal ranges. Serum titers of S. typh-O and S. typh-H were negative.

Tetracycline (Minocycline HCL, 100 mg, every 12 hours) was administered intravenously and the fever subsided from the second day of medication. The white blood cell count (WBC 29190/μL-11100/μL) decreased and the platelet count (65×10$^3$/μL-108×10$^3$/μL) rose gradually. However, anemia with a gradual decrease in the red blood cell (RBC) count and hemoglobin level (14.7 g/dL-11.9 g/dL) occurred. We reported the case to the Center for Disease Control and asked for confirmation of the diagnosis. A series of chest radiographs showed persistent...
Fig. 1 (A) Photographs show subconjunctival hemorrhage (B) and a 1.5 cm eschar on the left anterior chest wall demonstrating erythematous plaque with central erosion.

Fig. 2 Chest radiography shows cardiomegaly and acute pulmonary edema.
cardiomegaly with acute pulmonary edema and pleural effusion. An electrocardiogram showed sinus tachycardia with an elevated ST segment on lead I, V2 and V3, suggestive of cardiomyopathy. Echocardiography disclosed impaired motion of the anteroseptal and apical areas of the left ventricle, dilatation of the left atrium, and a small amount of pericardial effusion.

The laboratory data on the third and sixth days of hospitalization showed a trend toward recovery, including a lower WBC count and CRP level, elevated platelet count, lower direct and indirect bilirubin, and lower GOP and GPT (although still abnormal). The serum albumin, BUN, creatinine and potassium returned to the normal level. He was discharged after eight days in the hospital with improvement in cardiac, hepatic and renal function. Results of serum indirect immunofluorescent staining analysis from a blood sample taken on the fifth hospital day showed positive results for both IgG (>1:640) and IgM (>1:160), confirming the clinical diagnosis of scrub typhus.

Discussion

Scrub typhus, an acute febrile disease caused by infection with Orientia tsutsugamushi transmitted by the bite of larval trombiculid mites (chiggers), is a self-limited or curable disease most of the time. However, it can be a life-threatening disease that can cause multi-organ dysfunction or failure when it is not diagnosed and treated properly. Mortality rates of 0% to 30% have been reported. It is well characterized by a typical primary lesion (eschar), lymphadenopathy, skin rash and some other nonspecific symptoms such as fever, headache, general malaise, cough, and sore throat. Epidemiologically, scrub typhus commonly occurs in the Asian countries bounded by Pakistan, Afghanistan, Japan and Australia. This is the so-called “tsutsugamushi triangle” where the disease is endemic. In Taiwan, it occurs most commonly in northern Taiwan, such as on Yang-Ming Mountain, in eastern Taiwan, such as in Taitung and Hualien, in southern Taiwan, such as in Chiayi, Tainan, Kaohsiung, and Pingtung, and on offshore islands including the Pescadores, Kin-Men, and Ma-Tzu. Although sporadic cases have been reported in nearly all counties, physicians on the west coast of Taiwan might be unfamiliar with scrub typhus, leading to delayed diagnosis, as was encountered in our case. Our patient was bitten while in Ma-Tzu, and developed a typical eschar on his chest wall after the fever. This important sign, however, was ignored in his first hospitalization.

Humans are accidental hosts in this zoonotic disease and acquire the disease when an infected chigger, the larval stage of the trombiculid mite, bites them while feeding and inoculates Orientia tsutsugamushi pathogens. The bacteria multiply at the inoculation site with the formation of a papule that ulcerates and becomes necrotic, evolving into an eschar. However, an eschar is not specific to scrub typhus. Other possible causes include warfarin necrosis, cutaneous anthrax, aspergillus, ecthyma gangrenosum and plague. In our patient, the cause of the eschar lesion was more likely to be scrub typhus rather than other diseases, judging from the history and clinical course. Orientia tsutsugamushi is an obligate intracellular gram-negative bacterium that invades the endothelium of affected organs when patients are rickettsemic. Perivasculitis of the small blood vessels occurs and results in multi-organ impairment. This explains the multi-organ dysfunction which occurred in our patient.

Without proper treatment, scrub typhus may lead to severe complications such as multi-organ dysfunction or failure, including myocarditis, cardiomegaly and cardiac dysfunction, hypoalbuminemia, interstitial pneumonitis, acute pulmonary edema, acute hepatic and renal failure and bone marrow suppression, shown as
thrombocytopenia, disseminated intravascular coagulation, and anemia(1).

Although scrub typhus can be diagnosed based on serological tests such as enzyme immunoassay, enzyme-linked immunosorbent assay, the Weil-Felix test, polymerase chain reaction, and indirect immunofluorescent antibody assay(8,11), our patient initially showed negative serological results sampled within two weeks after infection. The definite diagnosis was made on the 26th day of disease, an unacceptably long time in the critical treatment of scrub typhus. Our experience highlights the paramount importance of a high index of suspicion for scrub typhus when there are symptoms such as the typical primary skin lesion, eschar, lymphadenopathy, fever and a detailed travel history showing the patient has been in an endemic area, not only for the correct diagnosis but also for timely treatment of this curable disease and prevention of severe complications.

In summary, we reported a case of initially unrecognized scrub typhus with multi-organ dysfunction. The patient recovered well with administration of tetracycline under a correct clinical and serological diagnosis(12). Physicians should be aware of scrub typhus in treating patients with fever, rash, eschar and systemic organ dysfunction.

References

初期誤判為急性扁桃腺炎之恙蟲病
併發多器官功能障礙

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恙蟲病是因立克次體感染所引起的一種急性病，多見於南美洲、東南亞、東南亞、
非洲等地區。恙蟲病的典型症狀包括發燒、頭痛、皮膚紅斑、淋巴結腫大等。

恙蟲病的診斷根據臨床症狀及實驗室檢查結果進行，治療則以抗生素為主。

本研究報告一例恙蟲病患者病例。該患者因出現高燒、頭痛、皮膚紅斑等症狀於
縣立醫院就診，經治療後病情有所好轉。恙蟲病的治療需要及時有效的抗生素治療。

關鍵詞：恙蟲病、恙蟲立克次體、恙蟲病