

Case Report

Scrub Typhus: An Alert for Physicians: 2 Case Reports

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Abstract

Scrub typhus is an acute febrile illness caused by *Orientia tsutsugamushi*. This is a vector borne zoonotic disease that spreads through blood and lymphatics in humans. All patients present with fever. Some of them show poor localizing features while some develop features of multi-organ involvement. Fatal outcomes can occur if not treated. However, many cases remain undiagnosed due to not only lack of diagnostic aids but also not considering it as a diagnosis.

We report here a series of two scrub typhus cases admitted in the medicine inpatient of a tertiary care teaching hospital in Sylhet, Bangladesh. Of them, one is a 44 year old poultry farmer presenting with features of meningo-encephalitis and the other is a 45 year old housewife having a 14 day high fever not responding to multiple antibiotics. Diagnosis of both the cases are based on the presence of acute fever, black eschars, raised Weil-Felix test titers and prompt clinical response to doxycycline.

Keywords: Scrub typhus, meningitis, meningo-encephalitis, black eschar, zoonosis, tsutsugamushi disease.

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Introduction

Scrub typhus (ST) is a vector-borne zoonotic disease caused by a Gram-negative obligatory intracellular bacterium, *Orientia tsutsugamushi* manifested by acute febrile illness. The larval stage of mites ('chiggers') of Trombiculidae family are the vectors of the disease.¹

ST is endemic in the Asia-Pacific that includes Korea, Japan, China, Taiwan, India, Indonesia, Thailand, Sri Lanka, and the Philippines.

However, re-emergence has made it a global disease affecting one million people of the world each year. It accounts for up to 23% of hospital admitted febrile patients. In uncomplicated cases, mortality is reduced from 0.6% to 1.4% with treatment. However, mortality can be as high as 70% in severe cases.² The WHO (World Health Organization) has categorized this complex tropical disease as world's one of the most under diagnosed and under reported diseases of the world.³ There has been a global rise in the outbreaks of this disease over the last decade. It has not only extended beyond the so called 'tsusugamushi triangle'⁴ to new areas of Africa and South America, but also from older time military areas to civil population and from rural to urban localities at large. Furthermore, newer species of *Orientia*, *Candidatus Orientia Chuto* and others have been identified as causatives.⁵

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ST patients present with high fever with headache and malaise that does not respond to beta lactam antibiotics. Some may have rash, eschar, lymphadenopathy and dry cough.⁶ A few percentage of patients may develop serious problems like multi organ dysfunction, acute kidney injury, acute respiratory distress syndrome and acute meningitis/encephalitis syndrome.⁷ Diagnosis remains evasive and challenging due to non-specific nature of clinical and routine blood test findings. A diagnosis may be suggested by a history of occupational or recreational exposure to vegetation or vector bite.⁸ However, the most important cause of a missed diagnosis is lack of consideration of ST as a differential of fever. Prompt recognition leads to specific treatment and hereby improves outcome.

The knowledge gaps in understanding the biology, life-cycle and effect of the organism on the vector, geographical variation of the vector, dynamics of high risk areas, human risk factors are barriers of developing diagnostics and vaccines of ST.¹

CASE 1

A 44 year old poultry farmer presented with high grade fever with chills and rigors for 10 days. He had cough, scanty mucopurulent sputum, headache and malaise. His blood pressure was 100/60 mmHg, pulse 100 /minute and highest recorded core temperature was 105°F. Two non-tender skin lesions were found one on the left side of umbilicus and the other on the medial surface of right arm (Fig 1 and 2). They had black necrotic centers with red margin (black eschar). There was no regional lymphadenopathy, hepatosplenomegaly or precordial murmur. He had stiff neck and positive Kernig's sign but had normal mentation. A few crepitation was audible over the lung bases but breath sound was vesicular. On the 13th day of fever, he became disoriented with

bizarre behavior and. However, no sign of focal neurological deficit was there. His blood reports showed neutrophilic leukocytosis (total WBC count 21900/ cu-mm, neutrophil 85%), thrombocytopenia (82,000/cu-mm) but normal hemoglobin and ESR. Peripheral blood film (PBF) showed toxic granulation within neutrophils suggestive of septicemia. Both PBF and immune-chromatographic test (ICT) for malaria were negative for this parasite. Weil Felix test was positive (OX-K 1: 320). His blood urine cultures were unyielding. Chest X-ray showed bilateral inflammatory shadows. CSF study revealed leucocytes 8-10/ cu-mm with 42mg/dl protein level. Considering the raised titers of Weil Felix test and poor response of the patient to Ceftriaxone, Meropenem injections along with oral Doxycycline were started. The patient became afebrile after 24 hours with gradual resolution of other features.



Fig 1: Black eschar in arm, case 1

CASE 2

A 45 years old female patient presented with high fever and malaise for 14 days with no other systemic complaints (unlike case 1). Her highest

recorded temperature was 104°F with normal vitals. A non-tender skin lesion with black necrotic center and reddish margin (black eschar) was found on the left side of her neck (Fig 3). Patient had already taken trials of antibiotic therapy with Quinolone and Cephalosporin with no remission of fever. With a high index of clinical suspicion, Weil Felix test was advised which turned out to be positive (OX-K 1:320). Other routine investigations were within normal limits. Patient became afebrile within 48 hours of treatment with Doxycycline.



Fig 2: Black eschar around umbilicus, case 1



Fig 3: Black eschar in neck, case 2

Discussion

Rickettsial diseases are important febrile illness not only in Bangladesh, but also throughout the globe. It is often difficult to distinguish this disease entity from other etiologies of febrile illness.⁹ We have reported here a series of two cases from the same institute having different clinical presentations. Fever is the key feature in all cases of ST but other features vary according to systemic involvement. Variable degrees of involvement of lungs, kidneys, liver and meninges can occur. Headache, body ache, arthralgia, isolated splenomegaly, hepato-splenomegaly, lymphadenopathy, epistaxis, cough, palpitation, chest pain and unconsciousness, are the different clinical features other than fever, according to a large Bangladeshi series of 40 Rickettsia cases.¹⁰ Black eschar and maculopapular rash are important clues for diagnosis at presentation.¹¹ Black eschars are painless, itchy and are usually found around swollen lymph nodes.¹² Both of our cases were diagnosed on the basis of presence of acute fever, black eschar and raised Weil-Felix test titers. However prompt clinical response to doxycycline was an authentic feature of one of them. Black eschar shows difference as a clinical feature in different parts of Asia and also between males (predominantly in axilla, groin and genitalia) and females (predominantly in chest and abdomen). Absence of black eschar and rash does not rule out ST.¹³ Our female case had eschar in the neck but the male had multiple eschar in the arm and around umbilicus. Apart from uncomplicated febrile illness some of the patients may develop life threatening complications like septic shock, multi-organ failure (MOF), acute respiratory distress syndrome (ARDS), meningo-encephalitis, myocarditis and disseminated intravascular coagulation (DIC), that can lead to fatal outcomes.² Of the different body systems involved,

lungs are the most frequently affected organs in ST infection.¹⁴

Weil Felix (WF) test that uses the OX-K strain *Proteus mirabilis*, is the widely available serological test for diagnosis of ST, with poor sensitivity but good specificity. A fourfold rise of titer is considered significant.¹⁵ Due to the diverse nature of clinical presentation and lack of wide availability of specific laboratory tests, diagnosis of ST remains challenging in many parts of the world.¹² A high degree of clinical suspicion is the key to diagnosis. Immunofluorescence (IFA), though expensive and requires bio containment facilities, is the gold standard serological method for detection of ST IgG. Enzyme linked immunosorbent assay (ELISA), immunochromatographic test (ICT), Indirect immunoperoxidase assay (IIP) are other serological tests for ST. There are a number of molecular tests which are appropriate for rapid diagnosis. Of them, rapid flow assay uses recombinant 56 kDa protein as antigen. This test can be positive on the first day and is considered as a confirmatory test due to its high sensitivity and specificity. Loop-mediated isothermal amplification assays (LAMP) and polymerase chain reaction (PCR) are other molecular and rapid point of care tests for ST.⁵ However, these tests are not widely used and WF test is still the most frequently used diagnostic test. Most of the reported cases used it for diagnosis of ST.⁴ Both of our cases had raised titers of this test. Chest X-rays may reveal non-specific infiltrates as is found in many of the reports.⁹ In a study by Varghese *et al.* showed that a trio of findings - elevated hepatic transaminases, thrombocytopenia and leucocytosis can diagnose ST with 80% specificity and 80% positive predictive value.¹⁶ Laboratory findings reveal abnormalities according to extent of different organ involvement.¹² Diagnosis of ST meningitis or meningo-encephalitis is made on the

basis of clinical features of meningeal irritation, like neck stiffness and Kernig's sign. CSF analysis in ST meningo-encephalitis usually shows mild to moderate elevation of protein, low to normal glucose and presence of a few lymphocytes. CSF adenosine deaminase (ADA) helps in differentiating ST meningitis from tubercular meningitis. A retrospective case control study on 22 cases of ST meningo-encephalitis demonstrated these CSF findings and it also found out presence of interstitial pneumonitis along with clinical features of meningeal affection in these patients.¹⁷

Most of the previous case reports showed good therapeutic outcome in less severe cases of ST with a 7 day treatment with oral doxycycline.^{5, 18} However, in patients who are critically ill intravenous azithromycin is chosen either singly or in combination with oral doxycycline. Azithromycin is also chosen for treating pregnant women with ST.¹⁹ Besides, rifampicin has shown efficacy and can be used for treating ST in areas non endemic for tuberculosis. No vaccine is available so far and mite or chigger control remains the mainstay of prevention of ST.⁵

Most of the early case reports in the sixties and seventies are from armed forces facilities,²⁰ but the disease shows remarkable resurgence among civil people in the recent years not only in Asian countries but across the globe.¹ The disease still remains underdiagnosed, not due to difficulty in testing, rather due to lack of considering it as a differential.^{2,5} A study conducted to identify Rickettsias among febrile patients presenting to six different hospitals in Bangladesh, revealed ST is an under diagnosed illness in this country. It demonstrated a 37% prevalence of rickettsial fever in this country with a 5% mortality, which is alarming.¹⁵ Though there is a significant serosurveillance reporting in Bangladesh, not many cases are reported in literature from this country. One of the largest series published in

2007, showed how frequently clinical presentation and routine laboratory tests of ST cases can be misdiagnosed as enteric fever.¹⁰ All these facts warrant further research in order to figure out the actual situation and also revised clinical guidelines for medical practitioners in Bangladesh.

Conclusion

Scrub typhus infections are under-recognized causes of febrile illness across the tropics including Bangladesh. There is no specific geographical distribution within the country. Therefore, determining whether or not rickettsial fever is widespread in this country with economic constraints, is of urgent public health interest.

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