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Review Article

Scrub typhus: as it stands today

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ABSTRACT

Scrub typhus is one of the three most common causes of prolonged fever in Southeast Asia and Pacific affecting almost 1 million people annually worldwide out of 1 billion exposed. Scrub typhus is a rickettsial infection caused by *Orientia Tsutsugamushi* transmitted through bite of Chiggers (larval stage of trombiculid mite). It is an acute febrile illness which generally causes non-specific symptoms and signs. The clinical manifestations of this disease range from sub-clinical disease to organ failure and death. Deaths are attributable to late presentation, delayed diagnosis, and drug resistance. Scrub typhus, though endemic in India; yet is under reported. It should be considered as an important differential diagnosis in a febrile patient with thrombocytopenia, deranged liver or renal functions, and B/L chest opacities. Relapse is not uncommon. Presumptive treatment with Doxycycline can be a suitable option in febrile patients from *Typhus pockets.* Alert physician should keep an eye on deviation from usual presentation to changing spectrum of the disease. Early diagnosis and appropriate treatment is rewarding and prevents morbidity and mortality.

Keywords: Scrub typhus, Thrombocytopenia, Tsutsugamushi Triangle, Typhus pockets

INTRODUCTION

Scrub typhus is one of the 3 most common causes of prolonged fever in Southeast Asia and Pacific affecting almost 1 million people annually worldwide out of 1 billion exposed. Its distribution is limited to a triangle the so called" Tsutsugamushi triangle" extending between Northern Japan, Western Australia, and Central Russia that includes the Indian subcontinent, eastern Russia, China, and the Far East. Scrub typhus is a mite-borne infectious disease caused by *Orientia tsutsugamushi*, distinct from other rickettsial infections.[1] The disease has been known since ancient times and was first described by the Chinese in the third century (313 A.D.), but the first description of its classic features came to surface when it showed a dramatic emergence in soldiers fighting on both sides in the Pacific theatre during World War II.

ETIOLOGY

O. tsutsugamushi is a rickettsial (Gram -ve intracellular Cocobacillus) organism, formerly (until 1995) named Rickettsia tsutsugamushi which multiplies freely in the cytoplasm of the host cells. The target cells in humans are endothelial cells or monocytes and vasculitis is the most prominent clinical manifestation. This bacterium exhibits a wide heterogeneity which explains several species in this genus. It lacks both lipopolysaccharide and peptidoglycan in its cell wall. There are three variants or strains of O. tsutsugamushi (Karp, Gilliam and Kato). Infection with one strain does not preclude reinfection with a different strain. Seasonality of the disease is determined by the appearance of larvae. In Southeast Asia, scrub typhus season is observed mainly in summer and autumn (July to November) after growth of scrub vegetation particularly after rains.

Epidemiology and transmission

Scrub typhus is a common disease in endemic areas. Although most cases of scrub typhus occur in rural areas, a number of cases have been acquired in settings such as suburban Bangkok, where the sero-prevalence exceeds 20 percent, as well as urban areas, such as Beijing and Seoul. It is also common in India but is apparently grossly underreported. Hotspots of Scrub typhus (termed 'Mite Island') are associated with secondary vegetation and an abundance of Trombiculid mites. It is transmitted by the bite of trombiculid mite (genus- Leptotrombidium) larvae (chiggers), infected by O. tsutsugamushi which serves as both vector and reservoir. The larvae typically bite humans on the lower extremities or in the genital region. Transmission of O. tsutsugamushi may occur in sharply delineated "mite islands" that consist of focal locations of scrub vegetation as small as a few square meters. The ease of air travel and relatively long incubation period of scrub typhus (up to two weeks) allow the disease to occur in tourists returning to regions where it is not endemic.[2]

Clinical manifestations

The disease occurs in patients exposed to rural or urban foci of scrub typhus which usually occurs 7 to 10 days after the bite of an infected chigger (range 6 to 19 days)[1].Scrub typhus may begin insidiously with headache, anorexia, and malaise, or start abruptly with chills and fever. Respiratory complaints are often present; cough occurs in about 45 percent of patients.

Approximately one-half of all patients develop a characteristic non pruritic, macular or maculo- papular, pale, transient rash. The rash typically begins on the abdomen and spreads to the extremities. The face is also often involved. Rarely, petechiae may develop.[3]

Attentive examination may reveal an inoculation eschar at the site of the chigger bite and if present is pathognomic, the common sites of which are axilla, groin, back and breast. Tender draining lymph nodes are sometimes present and limited to the site proximal to the mite bite. A painless papule often appears at the site of the infecting chigger bite. Subsequent central necrosis then occurs, which in turn leads to the formation of a characteristic eschar with a black crust (Figures 1& 2 from author's series).[4] The frequency of eschars in patients with scrub typhus is highly variable (7-68%). One or multiple eschars may develop before the onset of systemic symptoms. Hepatomegaly and splenomegaly can be observed. Neuro meningeal symptoms are relatively common and range from slight intellectual blunting to coma or delirium.

The symptoms also vary according to organ involvement. Gastrointestinal symptoms, including abdominal pain, vomiting, and diarrhoea, occur in up to 40% of children at presentation. Severe forms can be manifested as septic shock. Abortion commonly occurs in pregnant women. In severe cases, evolution to a multi organ dysfunction syndrome with haemorrhage can be observed.

Figure 1: A tough black scab surrounded by elevated red areola neither painful nor pruritic.

Figure 2: A tough black healing scab mimicking a cigarette burn mark.

Elderly patients are more likely to have severe illness and complications compared with younger patients. Acute kidney injury (AKI), mental confusion and dyspnea are more common in older patients, whereas the frequency of fever, rash and eschars is similar in both groups. A delay in therapy is associated with a higher risk of complications.

Complications of scrub typhus include interstitial pneumonia (20-35%), pulmonary edema, myocardial dysfunction, reversible complete heart block, congestive heart failure, circulatory collapse, CNS dysfunctions (delirium, confusion or seizures), cerebellitis, meningoencephalitis (15%), ADEM (Acute Disseminated Encephalomyelitis), AKI, transverse myelitis, opisthotonus, tetanic spasms and reversible pancytopenia.

Gupta N. et al, in North India studied 33 cases of scrub typhus in which 18.2% (6/33) cases progressed to Acute Respiratory Distress syndrome (ARDS).[5] Acute kidney

injury evidenced by increased urea and creatinine was seen in 18.2% (6/33) cases. Features of encephalitis were seen in 21.2% cases (7/33). Myocarditis was seen in 15.15% (5/33) of cases while a single case of pericardial effusion was observed.

A systematic review, which included a total of 19,644 patients with untreated scrub typhus, reported a median mortality rate of 6 percent (range: 0-70 percent).[6] Mortality rate varies widely by location and is more in older patients. In addition, the presence of myocarditis, delirium, and pneumonitis is associated with a fatal outcome.

Varghese et al, in South India studied 623 cases of scrub, in which MODS occurred in (34%) and the overall case fatality rate was 9%. Sharma R. et al, in North India studied 125 cases with MODS occurring in 28.86% and a mortality rate of 10.4% (Table 1).[3,4]

Table 1: Scrub Typhus: Prevalence of Signs and Symptoms.[3-5]

	Varghese et al[3]	Sharma R et al[4]	Gupta N et al[5]
Year of study	2005-2010	2012-2013	2013-2015
Number of cases	623	125	33
Location	South India	North India	North India
Population	Local residents	Local residents	Local residents
Signs and symptoms (%)			
Fever	100	100	100
Headache	46	81.6	---
Cough and dyspnoea	38	58.4	54.5
Myalgias	---	48	---
Nausea/vomiting	54	46.5	---
Altered sensorium	26	20.8	21.2
Adenopathy	---	29	18.2
Hepatosplenomegaly	---	59.4	48.5
Eschar	43.5	17.6	18.2
MODS (Multiorgan Dysfunction)	34	28.86	---
Case-fatality rate %	9	10.4	---

Paradoxically, scrub infection has been reported to lead to a diminution of viral load in human immunodeficiency virus (HIV)-1-infected patients and to help restore the immune status of infected patients.[7]

Diagnosis

As with all rickettsial diseases, no laboratory test is diagnostically reliable in the early phases of scrub typhus. The disease is usually recognized when clinicians correlate the presence of compatible clinical signs, symptoms and laboratory features with epidemiologic clues.

Patients with scrub typhus may develop the following laboratory abnormalities- The lymphocyte count is decreased and the T4: T8 ratio is diminished; lymphocytosis can also occur; Liver enzyme levels, serum bilirubin and creatinine are increased in 60% of cases and thrombocytopenia may be present which is sufficient to cause bleeding.

As these laboratory findings are relatively nonspecific, to confirm the presence of O. tsutsugamushi infection four methods can be used more definitively: serology, biopsy, culture, and polymerase chain reaction. Serology is the most used diagnostic tool. Immunofluorescence and immuno peroxidase studies are the most reliable. The Weil-Felix test detects cross-reacting antibodies to Proteus mirabilis OX-K and is still in use because of its low cost but it lacks sensitivity and specificity and should be replaced by IFA or ELISA.[8] Polymerase chain reaction assay carried out on blood, eschar material, or lymph node samples are very useful. Histopathology of eschar or generalized rash reveals intense vasculitis with perivascular collection of lymphocytes and macrophages.

Differential diagnosis

The differential diagnosis includes fever of unknown origin, enteric fever, dengue, dengue hemorrhagic fever, malaria, other rickettsioses, tularemia, anthrax, leptospirosis and infectious mononucleosis.

Treatment

Owing to the potential for severe complications, diagnosis and decision to initiate early treatment should be based on clinical suspicion or after confirmation by serological testing.

The recommended treatment regimen for scrub typhus is doxycycline (4 mg/kg/day PO or IV divided every 12 hr, 100 mg BD; maximum 200 mg/day for 7 days).[9] Alternative regimens include tetracycline (25-50 mg/kg/day PO divided every 6 hr, 500 mg QID; maximum 2 g/day) or chloramphenicol (50-100 mg/kg/day divided every 6 hr IV or PO, 500 mg QID; maximum 4 g/24 hr) or Azithromycin (500 mg OD for 7 days).[10] Azithromycin is the drug of choice in pregnancy and children. Cases resistant to doxycycline have been reported, and rifampin (600-900 mg orally daily) is a reasonable alternative often in combination with doxycycline in such cases. Quinolones are not effective and should be avoided.

Duration of treatment should be at least 5-7 days or until the patient has been afebrile for ≥3 days to avoid relapse. Scrub Typhus is so responsive to treatment that if patient does not become afebrile within 48 hrs, diagnosis of Scrub Typhus is unlikely or presence of other concomitant infection should be thought of[11].After apparent recovery, relapses frequently occur and may also follow short treatment courses. Relapse is usually less severe than the first attack.

Prevention

Prevention is based on avoidance of the chiggers that transmit O. tsutsugamushi. Protective clothing is the next most useful mode of prevention. No vaccine is available till date.

Mite control the use of insect repellants and miticides such as N, N-diethyl-3-methyl benzamide (DEET) are highly effective when applied to both clothing and skin. Permethrin and benzyl benzoate are also useful agents when applied to clothing and bedding.

DISCUSSION

Scrub typhus is a common cause of prolonged fever amongst hospitalized individuals in Southeast Asia and Pacific areas where it is endemic. It has gained significance lately as cause of fever amongst travellers returning from the Tsutsugamushi triangle. Globalization of trade and travel has led to spread of typhus fever far and wide, leading to its paradigm shift from rural to urban areas.

Scrub can have varied clinical spectrum ranging from insidious onset headache, malaise and anorexia to sudden onset fever with chills with respiratory system involvement or multi organ dysfunction. The pathognomic eschar is evident only on keen examination of breast, axilla, groin and back. Since the symptoms are similar to other prevalent arboviral infections such as dengue in the endemic zones, a vigilant physician has to remain alert for both clinical and epidemiological clues to suspect scrub and confirm it with help of serological and PCR assays. Apart from the typical presentation seen with scrub typhus fever various atypical manifestations too have been documented in the form of cerebellitis, myocarditis, interstitial pneumonia, reversible complete heart block, CNS dysfunctions (delirium, confusion or seizures), ADEM (Acute Disseminated Encephalomyelitis), transverse myelitis, opisthotonus, tetanic spasms and reversible pancytopenia. This was found both in studies from South India and North India by Varghese et al, and Sharma et al respectively. The various atypical manifestations and complications of scrub are attributable to its pathogenic mechanism of intercellular dissemination leading to cellular damage and vasculitis.

The three antigenic prototypes of O. tsutsugamushi (Karp, Kato and Gilliam) and several other antigenic variants due to immunodominant 56-kDa type specific antigen located on its surface are responsible for re infection in individuals from endemic areas. The knowledge of these variants is a matter of future research to develop region specific diagnostic assays and vaccines.

CONCLUSION

Scrub typhus is a potentially serious but easily treatable infection. It should be considered as an important differential diagnosis in febrile patients with thrombocytopenia and MODS. ß-Lactam that are used for undifferentiated febrile illnesses are ineffective. Relapse is not uncommon. Presumptive treatment with Doxycycline can be a suitable option in febrile patients from *Typhus pockets.* Alert physician should keep an eye on deviation from usual presentation to changing spectrum of the disease.

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