



COMMON CLINICAL PRESENTATION OF AN UNCOMMON INFECTION

Nephrology

Dr Rimi Som Sengupta

Associate Professor, Department of Medicine

Dr Sudeshna Ghosh*

Senior Resident, Department of Medicine *Corresponding Author

Dr Upal Sengupta

Assistant Professor, Department Of Nephrology, KPC Medical College

Dr Anirban Ghosh

Associate Professor, Department of Medicine

Dr Anirban Sarkar

Assistant Professor, Department Of Medicine

Dr Samir

Chakraborty

Assistant Professor, Department Of Medicine

Dr Avishek Naskar

Assistant Professor, Department Of Medicine

Dr Tapas Kumar Mondal

Professor & Head, Department Of Medicine

ABSTRACT

Scrub typhus is the most important re-emerging causes of acute febrile illnesses in India. Caused by *Orientia tsutsugamushi* transmitted to humans by an arthropod vector. It presents like any other acute febrile illness, however if left untreated it progresses to involve multiple systems and can be fatal. We are presenting a cohort of 16 serologically proven Scrub typhus patients admitted at our institution during the months of April to November. Although it has been common knowledge that scrub is prevalent in hilly areas and forests, the recent trend has challenged that belief, wherein most of our patients belonged to sub urban Kolkata.

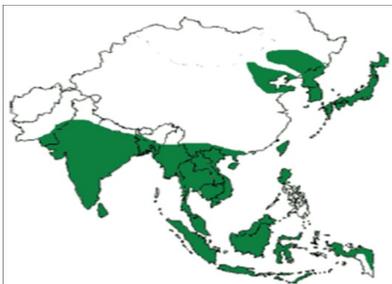
KEYWORDS

INTRODUCTION :

Scrub typhus is an acute febrile infectious illness caused by *Orientia* (formerly *Rickettsia*) *tsutsugamushi*. It is also known as *tsutsugamushi* disease. Scrub typhus was first described by the Chinese in the third century, but however in modern medical literature it was reported from Japan only in 1899. Humans are accidental hosts in this zoonotic disease. The term scrub is used because of the type of geographical area (terrain between woods and clearings) that harbours the vector.

The infection is found in wide range of ecological conditions, however jungles, semi-desert, mountain desert, alpine meadows predominate. The disease has been reported from various parts of the world however it is endemic in the geographical area termed as the *Tsutsugamushi Triangle*, which includes South and East Asia and South West Pacific. In India, the first reported cases were from Himachal Pradesh back in 1960s. However thereafter the disease saw a decline in prevalence probably due to widespread use of pesticides and use of Tetracycline and Chloramphenicol in treating acute febrile episodes. Unfortunately this disease has shown resurgence in recent years, has become more urbanised and is causing significant mortality and morbidity.

EPIDEMIOLOGY :



Tsutsugamushi triangle⁽⁴⁾

Scrub typhus is known to be prevalent in foot hills of Himalayas viz. Jammu & Kashmir, Sikkim, Manipur, Nagaland, Meghalaya,

Himachal Pradesh etc. The disease has also been reported from Tamilnadu and Kerala. However, seropositive patients from Delhi, Haryana, Rajasthan, Maharashtra, Uttarakhand and Chhattisgarh are also being reported in recent years. During 2012, outbreaks of scrub typhus were reported from many states in India. Over the years, the numbers of samples and areas which detected scrub typhus have also increased.^(2,3)

O. tsutsugamushi is distributed through out the Asia Pacific rim. Scrub typhus is endemic in Korea, China, Japan, Taiwan, India, Pakistan, Thailand and Malaysia. Accurate data on the incidence of scrub typhus is not available to us because the diagnosis is often missed, unconfirmed and confused with other febrile illnesses due to common presentation. According to the World Health Organization, "Scrub typhus is probably one of the most underdiagnosed and under-reported febrile illnesses requiring hospitalization"

The clinical spectrum of Scrub typhus is quite variable but is usually fatal if left untreated, hence high degree of suspicion, prompt diagnosis and early initiation of antibiotics before multiorgan failure sets in, is of paramount importance. Patients with scrub typhus often present with fever, headache, myalgias, which are common to many other acute febrile illnesses as well. An eschar may develop at the site of chigger bite, which is highly suggestive of scrub typhus but is reported to occur in a variable proportion of patients (from 7% to 97%). Eschar may be inconspicuous and may go unnoticed unless looked for carefully. In the absence of an eschar, presenting features are often indistinguishable from those of other acute febrile illnesses like malaria, dengue, typhoid, leptospirosis, and viral hemorrhagic fevers.

MATERIALS AND METHODS:

We conducted a cross sectional descriptive study among patients admitted in our hospital in the month of April to November with acute febrile illness. During this period of time a total of 16 patients admitted in medicine department, presenting with acute febrile illness were recruited in the study. 6 patients were admitted during the months of April and May, with another cluster of 10 patients presenting in the months August to November. Patients with only serologically proven scrub typhus have been described here.

RESULTS:

Clinical Characteristics Seen In Scrub Typhus N= 16

Symptoms

CLINICAL CHARACTERISTICS	NUMBER
FEVER	16
HEADACHE	16
BODYACHE	16
SORE THROAT	10
COUGH	12
SPUTUM	4
CHEST PAIN	12
SHORTNESS OF BREATH	12
NAUSEA	6
VOMITING	2
ABDOMINAL PAIN	2
SEIZURES	NIL
COGNITIVE IMPAIRMENT	7

Signs

ESCHAR	7
HYPOTENSION	12
TACHYCARDIA	16
TACHYPNEA	16
JAUNDICE	NIL
LYMPHADENOPATHY	3
PALPABLE LIVER	3
PALPABLE SPLEEN	7
ENCEPHALOPATHY	7
AKI	14
ARDS	
MYOCARDITIS	4
VENTILATION SUPPORT	3
ICU ADMISSION	4



ESCHAR ON BACK



ESCHAR ON LEG

A total no of 16 cases of serologically proven scrub typhus were documented. 14 of them were male patients, 2 females. The mean age at presentation was 34.33 years. The oldest patient was 50 years while youngest was of 15 years. Majority of the patients were from sub-urban areas of Kolkata.

Fever was the most predominant symptom, present in all patients with an average duration of 9.16 days. Constitutional symptoms like

malaise, bodyache, myalgias were present in all the patients with varying severity. Other symptoms like headache, sore throat, non productive cough was present in most of the patients. The second most common presentation was shortness of breath, usually abrupt in onset, developing after the first week of fever, attributed to either pneumonitis or ARDS or myocarditis associated heart failure. Chest pain was uncommon. Clinically, all patients had blood pressure on the lower side, inotrope support was required in 4 of the patients. Marked tachycardia with shortness of breath and features of heart failure was found in 4 patients who had elevated cardiac enzymes. Two patients amongst them developed Atrial fibrillation which reverted to normal rhythm after treatment. Two of the patients developed ARDS heralded by tachypnea and rapid desaturation. Gastrointestinal manifestations like abdominal pain, nausea and vomiting was present in few patients but clinical jaundice was present only in 1 patient. Mild hepatosplenomegaly was common but lymphadenopathy was rare. Cognitive impairment was relatively common occurring in 7 patients however seizures or other neurological impairment were relatively uncommon. Eschar was present 7 out of 16 patients, the common sites being axilla, flank, medial thigh. Oliguria was more predominant in patients with clinical HF, otherwise most of the patients had non oliguric AKI. Three of them required ICU admission, with need of mechanical ventilation in one of the patients.

Laboratory characteristics : Neutrophilic leucocytosis was the most common laboratory characteristic seen, however anemia or thrombocytopenia was absent. The next most common finding was transaminitis without significant hyperbilirubinemia or alteration in alkaline phosphatase. SGOT was more elevated than SGPT in all. AKI was an universal finding, usually rapidly reversible with therapy and without any pyuria or hematuria or oliguria. Electrolyte imbalance was absent.

DISCUSSION:

Scrub Typhus an endemic zoonosis of South East Asia ⁽¹⁾ is an important cause of acute undifferentiated fever, with high mortality and morbidity. Although it's endemic, but most cases might go unnoticed due to non specific initial presentation or unawareness among internists.

Scrub Typhus, predominant in various other parts of India, specially in the forests and hilly areas, was a rare entity in urban and sub-urban areas of West Bengal. This study aims to draw attention towards this emerging change in the epidemiology of Scrub Typhus over the last few years.

Changing epidemiology of Scrub?

Even though it has been increasingly appreciated that there has been a recent re-emergence of scrub typhus in the traditionally endemic areas and worldwide, scrub typhus is still a neglected infectious disease. The geographical distribution of scrub typhus is determined by the distribution of its vector and reservoir—mites, primarily of the genus *Leptotrombidium*. Humans are accidental hosts [1]

Outdoor workers, especially field workers in rural areas, have a higher risk of acquiring the disease since they are more exposed to the biting of mites and transmission of *O. tsutsugamushi* while working in the endemic areas. Tropical weather in India provides stable and ideal conditions for transmission of the disease. High temperature and high humidity are optimal for mite activity. In more temperate climates, the transmission of scrub typhus is more seasonal due to the temporal activity of chiggers.

In our study it was noted that the population affected belonged to a more sub-urban area with most of them not working at fields, which is contrary to our understanding of the disease.

Globally, Scrub typhus was originally associated with the Asian-Pacific "Tsutsugamushi triangle," until recently studies show scrub typhus effecting people from the Arabian Peninsula, Chile and possibly Kenya suggesting a wider global distribution in tropical and subtropical regions.

The use of improved diagnostic methods and increased awareness have recently contributed to greater recognition of scrub typhus in some countries, such as in Laos, India, southern China, South Korea, and Japan. There is also evidence suggesting that a combination of climate change and expansion of humans into previously uninhabited

areas, ease of air travel and long incubation period may play a role in both re-emergence and apparent rising incidence of scrub typhus.

There are no licensed vaccines for scrub typhus, and no systematic vector control efforts in place. Despite increasing awareness in endemic regions, the public health burden and global distribution of scrub typhus remains poorly known.

PATHOPHYSIOLOGY :

The reservoir and vector of scrub typhus is larval trombiculid mites. Human beings contract the disease when an infected chigger, that is the larval stage of trombiculid mites (*Leptotrombidium deliense* and others), bites them while feeding and inoculates *Orientia tsutsugamushi* pathogens.

Transmission of scrub typhus disease occurs throughout the year in the tropical areas, whereas in the temperate zones, transmission is seasonal. Occurrence might be influenced by rainfall, with more chiggers attached to the rodents in the wetter months of the year, which may be the reason for clustering of cases during the rainy season as shown by Gurung *et al.*^[8] However, outbreaks have been reported during the cooler season in southern parts of India.^[9]

The bacteria then multiply at the inoculation site with the formation of a papule initially that ulcerates and becomes necrotic, evolving into an 'eschar', with regional lymphadenopathy that progress to generalized lymphadenopathy within a few days. Before symptoms develop, patients are rickettsemic⁽¹⁾

Recent advances from histopathological studies on specimens collected from scrub typhus patients have revealed, that disseminated vasculitis with perivasculitis is the hallmark of scrub typhus, wherein involvement of the brain and lungs are the most important factors in any fatal outcome. Vascular damage usually manifests as a hemorrhagic phenomena rather than thromboembolic event.

Several cytokines are induced such as granulocyte-colony-stimulating factor (CSF), macrophage-CSF, interferon γ , and tumor necrosis factor- α . The cytotoxic T-lymphocytes and the NK T-cells play an important role in destroying the infected host cells. The bacteria downregulates the host defense mechanism by downregulating the GP-96 on the macrophages and the endothelial cells, which plays a prime role in antigen presentation, functioning of the dendritic cells, antibody production, and cross-priming of the immune system. The immune response against *O. tsutsugamushi* is both humoral and cellular.^[10] T-lymphocytes are involved in cell-mediated immunity against *Orientia*, producing interferon γ by mononuclear cells in the peripheral blood.

The recent discovery that *Orientia tsutsugamushi* infects principally the endothelial cells in all of the organs with infected macrophages and cardiac myocytes explains the findings of our study, in which patients had features of heart failure with raised cardiac enzymes and even a reversible atrial fibrillation in two cases. (6). In another study, which focused on microscopic examination of the heart in 31 cases, found that six were perfectly normal, and 13 with inflammatory infiltrates showed intact heart muscle fibers (7) whereas 12 cases showed injury to cardiac myocytes, including several with frank focal necrosis that was rarely severe.

CLINICAL FEATURES :

Scrub typhus presents as an acute undifferentiated fever. The incubation period for symptoms is between six and twenty-one days from exposure. The clinical picture is characterized by sudden onset fever with chills, headache, backache and myalgia, profuse sweating, vomiting and enlarged lymph nodes. In some patients, an eschar may develop at the site of chigger feeding, usually at sites where the skin surfaces meet, such as axilla, groin and inguinal areas. Although the eschar is reported to be less frequently observed in South Asian patients than in East Asian or Caucasians, 55% of patients had an eschar in a recent study from South India.

Five to eight days after the onset of fever, a macular or maculopapular rash may appear on the trunk and later extend to the arms and the legs in a small proportion of patients. If untreated the disease might be fatal as various complications set in, usually in the late second week of the illness. Complications of scrub typhus infection include pneumonia, acute respiratory distress syndrome (ARDS), myocarditis,

encephalitis, hepatitis, acute kidney injury, DIC, hemophagocytic syndrome, acute pancreatitis, adrenal insufficiency, subacute painful thyroiditis.

A variable range of neurological manifestations have been observed in scrub typhus infection. The most common neurological presentation in scrub typhus is as meningitis, meningoencephalitis or encephalitis. Others include albeit rarely cerebral venous thrombosis, Guillain-Barre Syndrome, transient Parkinsonism and myoclonus, opsoclonus, cerebellitis, transverse myelitis, polyneuropathy, facial palsy, abducens nerve palsy and bilateral optic neuritis.

DIAGNOSIS :

In view of frequent outbreaks witnessed in different parts of the country in the recent past, scrub typhus is being described as a re-emerging infectious disease in India. Differentiating scrub typhus from other endemic diseases like malaria, leptospirosis, dengue fever, typhoid, etc. is difficult due to overlapping clinical features and a lower positivity for eschars in Asian populations. Hence, the diagnosis heavily relies on laboratory tests.

Serology is the mainstay of diagnosis. In primary infection with *O. tsutsugamushi*, a significant antibody titer is observed at the end of the 1st week, which are mainly IgM antibodies, whereas IgG antibodies appear at the end of the 2nd week. In the case of re-infection with *O. tsutsugamushi*, IgG antibodies are detectable by day 6, with IgM antibody titers being variable.

The cheapest and most easily available serological test is the Weil-Felix (WF) test. It has a high specificity but a low sensitivity and is based on the detection of antibodies to various *Proteus* species which contain cross-reacting antigenic epitopes to antigens from members of the genus *Rickettsia* with the exception of *Rickettsia akari*. The test is said to be positive when there is a titer of 1:320 or greater or a 4-fold rise in titer starting from 1:50.

The gold standard is indirect immunofluorescence antibody (IFA). This detects the presence of scrub typhus-specific antibody bound to smears of scrub typhus antigen. This can confirm infection before their seroconversion.

The widespread use is limited by the fact that it is expensive, requires specialized laboratories and considerable training.

The immunochromatographic test (ICT) to detect antibodies against *O. tsutsugamushi* also serves as a rapid diagnostic test which is available in some of the commercial laboratories in India. In our study this method was used.

Indirect immunoperoxidase technique is a good alternative the expense of a fluorescent microscope is reduced by substituting peroxidase for fluorescein. Results are interpreted by an ordinary microscope. Hence, it can serve as a useful tool in an even resource-poor setup, which is important in a country like India. Western immunoblot assay with sodium dodecyl sulfate-gel electrophoresed and electroblotted antigens, useful for large-scale screening, is a powerful and specific diagnostic tool for epidemiology and confirmation of diagnoses. It also helps in identifying the cross-reactive strain.

A recombinant protein-based enzyme-linked immunosorbent assay using the most abundant and immunodominant protein for the detection of *Orientia*-specific antibodies in serum has been developed. Cell culture is time consuming, taking a minimum of 4 weeks and hence not a good choice for quick diagnosis in what can be a fatal infection.

Molecular detection using polymerase chain reaction (PCR) is possible from skin rash biopsies, lymph node biopsies, or EDTA blood. GroEL-based real-time PCR assays are more sensitive and give a more quantitative assay.

Nested PCR technique can detect it as early as day 3 of the fever phase which is even before the appearance of antibody. Some studies suggest that nested PCR in conjunction with IFA may serve as a rapid and reliable method for diagnosing scrub typhus^(11,12,13,14,15,16)

TREATMENT :

Chloramphenicol was the first drug shown to be effective against Scrub

Typhus, at a dose of 250 or 500 mg orally or intravenously every 6 hours. Today, we have a better alternative in the form of Doxycycline. A dose of 100mg twice daily, for atleast 7 days is recommended to avoid relapse. Azithromycin is an alternative agent for consideration.⁽¹⁷⁾

PREVENTION :

Presently no vaccine is available to prevent Scrub typhus, the antigenic heterogeneity of the bacteria is a significant obstacle to vaccine development. Till we have a vaccine, chemoprophylaxis and mite control are our weapons of prevention.

Chemoprophylaxis with a long acting tetracycline is an effective choice in non immune individuals living or working in endemic areas. The recommended drug is Doxycycline, 200 mg weekly dose.

Insect repellants and miticides, such as DEET (N,N-diethyl-3-methylbenzamide), Permethrin, Benzyl Benzoate are effective when applied to skin or clothings. Focal arease of high prevalence may be treated with chlorinated hydrocarbons like Lindane.

Intensive efforts at rodent control might paradoxically increase human infection.

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