

CLINICAL SPECTRUM OF SCRUB TYPHUS IN A TERTIARY CARE HOSPITAL AT EASTERN INDIA

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ABSTRACT

Objective: Our hospital, tertiary care hospital in the capital of the state of Odisha, had been witnessing pyrexia of unknown origin, associated with breathlessness, renal, and liver impairment, which did not respond to high antibiotics but to doxycycline; therefore, the present study was undertaken to identify whether scrub typhus is the etiological agent, and thereafter, their characteristic features were further evaluated as an effort in supporting its diagnoses and treating patients accordingly.

Methods: A total of 65 adult patients (age >15 years) admitted with pyrexia between April 2015 and October 2017 were evaluated. Immunoglobulin M (IgM) scrub typhus test was done in all these patients. IgM scrub typhus test positive samples were included in the study and various clinical parameters analyzed.

Results: Of the 65 patients included in the study, all were found to be positive for IgM antibodies against *Orientia tsutsugamushi*. The cases were seen mainly in the months between September and November. The common symptoms found were fever, myalgia, breathlessness, rash, and abdominal pain and rarely altered sensorium. The diagnostic features like eschar were found in 23% patients. Nearly, two-thirds of patients had fever more than 7 days and myalgia (76.92%), headache (58.46%). The most common complications were renal failure (20%) followed by pneumonia (10.76%). Laboratory findings of high C-reacting protein (89.23%) and leukocytosis are found in 35.38%.

Conclusion: Our results showed that scrub typhus should be considered in the differential diagnosis of pyrexia of unknown origin associated with breathlessness, myalgia, rash, gastrointestinal symptoms, hepatorenal syndrome, or acute respiratory distress syndrome. Empirical treatment with doxycycline may be given in the cases with strong suspicion of scrub typhus.

Keywords: Immunoglobulin M scrub typhus, *Orientia tsutsugamushi*, Eschar, Scrub typhus, Doxycycline.

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INTRODUCTION

Scrub typhus (or tsutsugamushi disease) is an acute, febrile, and infectious illness caused by *Orientia tsutsugamushi* and transmitted by chiggers. The disease is endemic in South Asia, with reports of reemergence from various regions in India. Clinically, it presents as non-specific febrile illness with constitutional symptoms of fever, rash, myalgias, headache or gastrointestinal symptoms, regional lymphadenopathy, and maculopapular rash. Life-threatening complications may develop with multiorgan dysfunction. This study was done in IMS and SUM Hospital, Bhubaneswar, over a period of 2 years (2015-2017) with the aim of establishing the clinical spectrum of presentation in hospitalized patients.

Scrub typhus, caused by *Orientia* (formerly *Rickettsia*) *tsutsugamushi*, is an acute infectious disease of variable severity that is transmitted to humans by an arthropod vector of the Trombiculidae family. "Tsutsuga" means small and dangerous and "mushi" means insect or mite. It affects people of all ages including children. Humans are accidental hosts in this zoonotic disease. While scrub typhus is confined geographically to the Asia-Pacific region, a billion people are at risk, and nearly, a million cases are reported every year [1]. Scrub typhus was first described from Japan in 1899. It was a myriad disease in drug-resistant era and an important disease that affected nearly thousands of soldiers in the Far East during the Second World War [2].

The rickettsia is transmitted by bite from an infected mite to human, after which it grows at the location of the bite and a characteristic

skin lesion known as an eschar is formed. The rickettsia then spreads systemically through the hematogenous and lymphatogenous routes. The infected human then develops various systemic symptoms and reactions including fever, rash, lymphadenopathy, elevations of C-reacting protein (CRP), and liver enzymes [3]. In India, scrub typhus broke out in an epidemic form in Assam and West Bengal during the Second World War. Later, the presence of this disease was found throughout India in humans, trombiculid mites, and rodents [4]. The term "scrub" is used because of the type of vegetation (terrain between woods and clearings) that harbors the vector; however, the name is not entirely correct because certain rare areas including mountain deserts. The word "typhus" is derived from the Greek word "typhus," which means "fever with stupor" or smoke [5]. Scrub typhus is a diagnostic dilemma because it has non-specific presentations, limited awareness, low index of suspicion among clinicians, and lack of diagnostic facilities [6]. *O. tsutsugamushi* is an obligatory intracellular Gram-negative bacterium and is a zoonotic disease. Man is accidentally infected when he encroaches the mite infected areas, known as the mite islands. It is noted that these regions are showing with secondary scrub growth, which grows after the clearance of primary forest, and hence, the term scrub typhus. However, the infection can occur in disease habitats such as seashore, rice fields, and even semideserts [7]. If the diagnosis is delayed or patient is not treated with appropriate antibiotics, the scrub typhus can present with serious complications such as renal failure, myocarditis, septic shock, and meningitis. Scrub typhus broke out in an epidemic form in Assam and West Bengal during

World War II. Outbreak of scrub typhus in southern India has been reported in 2003 [8]. This study was conducted to analyze different clinical presentation as well as organ dysfunction in adults in scrub typhus in Odisha presenting to a tertiary care hospital.

METHODS

This study was conducted in IMS and SUM Hospital a 700 bedded tertiary care and a medical college catering patients from most districts of Odisha and nearby states too, situated in Bhubaneswar, Odisha, India, over a period of 2 years from 2015 to 2017. This study is approved by the institutional ethics committee of our esteemed institute.

Hospitalized cases admitted to the department of medicine for the evaluation of fevers who were suspected clinically undergone initial Weil-Felix test followed by immunoglobulin M (IgM) scrub typhus if positive. Some cases had IgM scrub typhus only. Cases who were IgM for scrub typhus positive were included in the study. Fever diagnosed with other causes such as malaria, enteric fever was excluded. Their clinical presentation and investigations were taken into account. Spectrum of clinical manifestations analyzed.

RESULTS

A total of 65 cases who are IgM positive for scrub typhus were analyzed with their age, sex, and epidemiological variation. Different clinical manifestations and complications were accounted. Of 65 cases, most of the cases 18 (27%) belong to age group 31–40 years followed by 15 (22%) in age group of 21–30 years. The two-tailed T test revealed $p=0.0458$ By conventional criteria, this difference is considered to be statistically significant, so males are predominate with respect to the age group (Table 1). Less number of patients found in 15–20 as well as 61–70 years of age. Males (44, 67%) outnumbered females in our study. In all age groups, males are more than females. Patients admitted from different districts of Orissa most of the cases 22 (%) belongs to Khurda district with male predominance followed by Nayagarh district 9 cases (%). Other districts have fewer number of cases (Table 2). The two-tailed T test revealed $p=0.1817$ By conventional criteria, this difference is considered to be not statistically significant with respect to gender.

Fever is the most common mode of presentation (100%). Of 65 cases, all (100%) patients presented with fever, 22 (33.8%) with fever <7 days, and rest 43 (66.15%) with more than 7 days of fever. Total 6 (9.26%) cases had clinically detectable jaundice; malaise is also a common symptom in 76% cases (Table 3). Cough is found in 35% cases. Headache was a common symptom found in 58% of cases. Other clinical presentations included nausea and vomiting in 47.6%, pain abdomen in 41%, cough in 35.3%, respiratory difficult in 9.2%, central nervous system (CNS) symptoms and confusion in 9.2%, and rash in 12.3% patients. Rash is an uncommon finding mostly maculopapular found in limbs followed by abdomen and thorax. Eschar, which is the most diagnostic clinical presentation, is found in 15 (23%) cases (Table 4 and Fig. 1). Most of eschars found in extremities followed by abdomen and thorax. Groin and axilla are the next site of affection and single case was found in genitalia in male patient. Clinical presenting signs such as hepatomegaly in 40%, splenomegaly in 27.6%, anemia in 29.2%, clinically detectable icterus in 15%, ascites in 3%, edema in 4.6%, and conjunctival chemosis in 12.3%. Lymphadenopathy (local or generalized) found in 9 (13.85%) cases.

Renal failure is most common 13 (20%) complication in our study followed by pneumonia 7 (10.76%), acute respiratory distress syndrome (ARDS) in 7.6%, multiple organ dysfunction syndrome (MODS) in 7.6%, meningoenephalitis in 6.1%, shock in 4.6%, myocarditis in 1.5%, and among them, mortality in 2 (3%) patients (Table 5). Laboratory findings suggested high CRP in 58 (89.23%) patients followed by leukocytosis (>11,000) in 23 (35.38%) cases, hepatopathy in the form of raised liver enzymes 3 times above normal range in 33.8%, nephropathy in 20%, proteinuria in 27%, anemia in 29.2%, and pulmonary infiltrates in chest X-ray in 10.7% cases. Thrombocytopenia found in 17 (26.15%) cases (Table 6).

Table 1: Age and sex variation

Age group	Male	Female
15–20	4	1
21–30	11	4
31–40	13	5
41–50	7	5
51–60	5	3
61–70	4	3
Total (%)	44 (67)	21 (32)

Table 2: Number of the patients with respect to regional distribution

District	Male	Female
Balasore	4	2
Mayurbhanj	0	1
Khurda	14	8
Balangir	0	1
Bhadrak	1	0
Boudh	1	0
Cuttack	4	1
Ganjam	1	1
Kalahandi	1	1
Kandhamal	0	1
Kendujhar	1	0
Malkangiri	1	0
Nayagarh	6	3
Phulbani	1	0
Puri	7	1
Rayagada	1	1
Sundergarh	1	0
Total	44	21

Table 3: Clinical presenting symptoms

Symptoms	Number of cases n=65 (%)
Fever >7 days	43 (66.15)
Fever <7 days	22 (33.84)
Rash	8 (12.3)
Pain abdomen	27 (41.53)
Nausea/vomiting	31 (47.69)
Respiratory difficulty	6 (9.23)
CNS symptoms/confusion	6 (9.23)
Headache	38 (58.46)
Cough	23 (35.38)
Malaise	50 (76.92)
Jaundice	6 (9.26)

CNS: Central nervous system

DISCUSSION

Scrub typhus is an emerging disease of clinical importance and is increasingly noticed in India. Scrub typhus is an acute febrile illness presenting mostly with non-specific constitutional symptoms making it difficult to suspect unless an eschar is detected which is most pathognomonic. The diagnosis of scrub typhus is usually made by the history and clinical presentation. The vast variability and common clinical manifestations of the disease which is similar to other febrile illnesses make the clinical diagnosis a challenge. It is reported indoor admissions as high as 12% [9-16].

The total burden of the disease, however, may be grossly underreported as most of the studies are hospital based. Furthermore, the serological tests, other than Weil-Felix, are not freely available in most of the endemic areas. The infection presents as a non-specific febrile illness with rash, lymphadenopathy, gastrointestinal, respiratory, or central nervous symptoms, which if not diagnosed and treated early can lead to complications such as myocarditis, pneumonia,

Table 4: Presenting signs

Signs	Number of cases n=65 (%)
Fever	65 (100)
Eschar	15 (23.7)
Hepatomegaly	26 (40)
Splenomegaly	18 (27.69)
Rash	8 (12.32)
Lymphadenopathy	9 (13.84)
Anemia	19 (29.23)
Icterus	10 (15.38)
Ascites	2 (3.07)
Edema	3 (4.61)
Conjunctival chemosis	8 (12.3)



Fig. 1: Eschar on the skin of scrub typhus patients

Table 5: Complications of the patients during the study periods

Complication	Number of cases n=65 (%)
Renal failure	13 (20)
Pneumonia	7 (10.76)
ARDS	5 (7.69)
MODS	5 (7.69)
Meningoencephalitis	4 (6.15)
Shock	3 (4.61)
Pancreatitis	1 (1.53)
Myocarditis	1 (1.53)
Death	2 (3.07)

ARDS: Acute respiratory distress syndrome, MODS: Multiple organ dysfunction syndrome

Table 6: Investigation findings of the study populations

Investigation	Number of cases n=65 (%)
IgM scrub	65 (100)
CRP	58 (89.23)
Leukocytosis (TLC >11000)	23 (35.38)
Hepatopathy	22 (33.84)
Nephropathy	13 (20)
Proteinuria	18 (27.69)
Pulmonary infiltrate	7 (10.76)
Thrombocytopenia	17 (26.15)
Anemia	19 (29.23)

CRP: C-reacting protein, IgM: Immunoglobulin M, TLC: Total leukocyte count

meningoencephalitis, gastrointestinal bleeding, acute renal failure, and ARDS like picture [17,18]. Our study constituting 65 subjects of adult population of above 15 years had male predominant in all of age groups with more than 2:1 proportion in age groups 21–30 and 31–40 years of age. Kumar *et al.* [16] had similar results of male preponderance in their study; however, Wei *et al.* [12] and Trowbridge *et al.* [15] found female prevalence in their studies above 50 years of age. Our study group has more patients in 31–40 years of age followed by 21–30 years of age combinedly constituting around 50% of patients in comparison to Wei *et al.* [1] who has demonstrated 71% cases above 40 years of age. In the present study, out of total 65 adults, most prevalent age group was 31–40 years (24.6%). The male and female ratio of 2:1 was found in our study. Similar results were observed in a study conducted by Bhat *et al.* [13] in which the male-to-female ratio was 1.44:1 [10]. In all age groups, males are more than females. Patients admitted from different districts of Orissa, most of the cases 22 (33.8%) belongs to Khurda district with male predominance followed by Nayagarh district 9 cases (13.8%). Other districts have fewer number of cases. This may be due to location of hospital in Khurda district. Most of the cases hospitalized during July–November implicating the seasonal variation of presentation.

In our study, fever was the most presenting complaints (100%), out of them 66.15% had fever for more than 7 days and rest 33.84% had fever for <7 days, other symptoms were malaise (76.92%), headache (58.46%), vomiting (47.6%), abdominal pain (41.53%),

cough (35.38%), rashes (12.3%), jaundice (9.26%), respiratory difficulty (9.23%), and CNS symptoms and confusion (9.23%). On examination, eschar which is most diagnostic finding was present only in 23.7%, anemia 29.23%, generalized or local lymphadenopathy 13.84%, hepatomegaly 40% and splenomegaly 27.69%, icterus 15.38%, ascites 3.07%, and edema in 4.61% cases. Superficial ophthalmic manifestation like conjunctival chemosis detected in 8 (12.3%) cases. Our observation can be comparable to the earlier studies on scrub typhus patients. Sirisantha *et al.* [11] observed common physical signs as fever (100%), lymphadenopathy (93%), hepatomegaly (73%), eschar (68%), conjunctival hyperemia (33%), maculopapular rash (30%), and splenomegaly (23%) [10]. Pattnaik *et al.* [14] studied in same region also had similar result of fever in 100% cases also other studies in different regions of India [3,2]. Jim *et al.* [17] reported the clinical manifestations with scrub typhus as fever (100%), cough (72%), anorexia (72%), eschar (69%), and lymphadenopathy (64%) [11]. Similar findings were observed by Varghese *et al.* [18] However, they found eschar 56% in their study. The clinical manifestations vary from mild febrile illness to a severe potentially fatal disease with (MODS). In our study group had some complications, acute renal failure was the most common (20%) followed by pneumonia (10.76%). Other complications such as multiorgan dysfunction (7.69%), ARDS (7.69%), shock (4.61%), meningoencephalitis (6.15%), and myocarditis (1.53%) were also found. In our study, only two persons died, mortality rate was 3.07% which is lower than the previous studies. Mortality might depend on early introduction of specific antibiotics such as doxycycline and degree of organ involvement. Bhat *et al.* [13] also reported that mortality rate was 7.5% in their study. However, Palanivel *et al.* [19] showed mortality 11.94% in their study.

In our study, 89.23% patients had high CRP, leukocytosis in 35.38%, anemia 29.3%, thrombocytopenia 26.15%, elevated liver enzyme 33.84%, and impaired renal function test 20%. These findings can be comparable with the previous studies. The previous study by Palanivel *et al.* [19] reported 49% leukocytosis, 55% anemia, 77% thrombocytopenia, and 64% elevated liver enzyme in their study group.

Digra *et al.* [20] reported renal functions were deranged 4.7% of their patients. In our study group, all cases with positive for IgM scrub were included in the study. The most widely performed laboratory test in India is Weil–Felix test which has low sensitivity and specificity. The test shows false-negative results in the early stage of disease as the agglutinating antibodies can be detected only in the 2nd week of illness [21]. The IgM ELISA with good sensitivity and specificity, ease to perform, swift results, and also suitable for testing large number of specimens may be considered as good replacement for Weil–Felix test and IFA test in diagnosis of scrub typhus. In a study by Prakash *et al.* [22], sensitivity of 44% and 87% was observed with Weil–Felix test and IgM ELISA, respectively [13]. Weil–Felix has a poor sensitivity but still serves as a useful and cheap test for laboratory diagnosis of rickettsial diseases. Prakash *et al.* [22] evaluated two specific serological tests, dot enzyme immunoassay and IgM ELISA and the Weil–Felix test and found a sensitivity of 100%, 86.5%, and

43.5%, respectively [13]. Without proper diagnosis, antibiotics are mostly used indiscriminately in fever of unknown origin, which leads to multidrug-resistant to most of the organisms. In scrub typhus, doxycycline is the most effective antibiotic and also cost-effective. Hence, with proper diagnosis of scrub typhus, doxycycline should be prescribed. However, empirical therapy in suspected case of scrub typhus should be doxycycline [23,24].

CONCLUSION

Scrub typhus is an important differential diagnosis of pyrexia of unknown origin and clinical features mimic with most of the common infective diseases such as malaria and typhoid with or without organ dysfunction. However, it is grossly underdiagnosed due to low index of suspicion and due to non-specific clinical manifestation and also due to lack of diagnostic procedures in most of clinical settings. Eschar, which is the most diagnostic clinical sign, is not detected in most of the cases. Patients presenting with fever and gastrointestinal manifestation, hepatopathy, shortness of breath, and generalized myalgia should be considered to exclude scrub typhus. If diagnosed at early stages, treatment is easy cost-effective due to good response of drugs such as doxycycline and also azithromycin.

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