

Review Article

Chiggerosis: an emerging disease

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Received: 06 August 2016

Accepted: 06 September 2016

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ABSTRACT

Scrub typhus is a zoonotic disease caused by *orientia tsutsugamushi*, is a very less known cause of fever of unknown origin (FUO). It was first observed in Japan where it was found to be transmitted by mites. The disease was called as *tsutsugamushi* (*tsutsu* means dangerous and *mushi* means insect or mite). This disease is endemic to a geographically distinct region, so called *tsutsugamushi* triangle, which includes northern Japan and eastern Russia in the North to northern Australia in the South and to Pakistan and Afghanistan in the West. Clinical picture consist of high grade fever, severe headache, myalgia, lymphadenopathy and maculopapular rash on the trunk and then on extremities. A necrotic eschar at the inoculating site of the mite is pathognomic of scrub typhus. Incubation period is 1-3 week. Patients may develop complication like interstitial pneumonia, meningoencephalitis and myocarditis. Diagnosis is often missed because clinical manifestations are similar with other febrile tropical infection. It is diagnosed clinically based on sign and symptoms, serologically molecular methods can be used for their rapid identification as well as for epidemiological purposes. However public health importance of this disease is underestimated because of difficulty in clinical diagnosis and lack of laboratory methods in many geographical areas. Drugs like chloromphenicol and tetracycline effectively treat scrub typhus. No vaccine is available for Scrub typhus but many vaccines using Sta47 and Sta56 antigens are under trial as a recombinant vaccine.

Keywords: Eschar, Mite islands, Scrub triangle, Scrub vegetation, Zoonotic tetrad

INTRODUCTION

Scrub typhus is an acute, febrile, infectious illness that is caused by *Orientia tsutsugamushi* (a gram negative intracellular bacterium). The name derives from the type of vegetation that harbors the vector. The disease is also known as *Tsutsugamushi* disease, Mite borne typhus fever, Chiggerosis or Tropical typhus. It is an important military disease which caused thousands of cases in the Far East during Second World War. This disease is endemic in many countries in eastern and south-east Asia and in northern Australia.¹

Scrub typhus was first described from Japan in 1899. Now it has been reclassified as *Orientia tsutsugamushi*. As *O. tsutsugamushi* has a different cell wall structure (it

lacks lipopolysaccharide layer) and genetic composition than that of the rickettsiae. There are numerous serotypes of which five distinct serological strains (Gilliam, Karp, Kato and Kawazaki, Boryon) are helpful in serologic diagnosis. About half of isolate are seroreactive to Karp antisera and approximately one quarter of isolates are sero-reactive to Gilliam antisera.²⁻⁴

It is transmitted to the human by an arthropod vector of trombiculidae family. No man to man transmission occurs. Man is accidentally infected, usually during rainy season. On encroaching a zone of mite-infested areas, known as mite islands. These zone are often made up of secondary 'scrub' growth, which grows after clearance of primary forest.⁵ The term 'scrub' is used because of the type of vegetation (terrain between woods and clearings) that harbours the vector.

However the name is not entirely correct because certain endemic area can be sandy, semi-arid and mountain desert. Thus infection is found in wide range of ecological climate.⁶ There are multiple cause of FUO but infection such as enteric fever, malaria, dengue, tuberculosis, brucellosis are among most common cause. Scrub typhus caused by *O. tsutsugamushi*, is a very less common cause of FUO.

Scrub typhus is known to occur all over India. However, the public health importance of this disease is underestimated because of difficulty in clinical diagnosis due to nonspecific clinical manifestations, low index of suspicion amongst clinicians, limited awareness and limited diagnostic facilities in many geographic area.⁷

PATHOGENESIS

Scrub typhus is transmitted to humans and rodents by some species of trombiculid mites of genus *Leptotrombidium* (*L. akamushi* in Japan and *L. deliensis* in India). *O. tutsugambushi* belongs to the typhus group and there is a high degree of antigenic heterogeneity among the different strains. Rodents are the natural host of the pathogen.

The vector is infected larval stage of the mite (chiggers) that inoculate the human, while feeding. The adult mites have a four-stage lifecycle: egg, larva, nymph and adult. The larva is the only stage (chigger) that can transmit the disease to humans and other vertebrates, since the other life stages (nymph and adult) do not feed on vertebrate animals. Both the nymph and the adult are free-living in the soil. Mites can maintain the organism through transovarian transmission.⁸

The pathogen multiply at the site of entry which later develops into an eschar and this is followed by febrile illness and many clinical manifestations. It is now established that it multiplies and disseminates within the human host, its principal target site is endothelial cells. This pathogen produces phospholipase A that lyses the vacuoles; thus, it grows freely in the cytoplasm of infected cells.⁸ Because they are intracellular parasites, they can live only within the cells of other animals. The organism proliferate on the endothelium of small blood vessels releasing cytokines which damage endothelial integrity, causing fluid leakage.

Platelet aggregation, polymorphs and monocyte proliferation, leading to focal occlusive end-angitis causing microinfarcts. This process especially affects skeletal muscles. This can also cause venous thrombosis and peripheral gangrene.⁹

CLINICAL MANIFESTATION

Scrub typhus is an acute febrile illness which generally causes nonspecific sign and symptoms. The classic presentation of scrub typhus consists of triad of an eschar

(at the site of bite), regional lymphadenopathy and maculopapular rash. However, it is seen only in 40-50% of cases. Nonspecific manifestation may appear early like fever, headache, myalgia, cough and gastrointestinal symptoms.⁸

Incubation period is 1-3week. chigger bite is painless and may become noticed as a transient localized itch. Bites are often found on the groin, axillae, genitalia or neck. A necrotic eschar is often seen in humans at the site of the chigger bite. Eschars are rare in patients in countries of South-East Asia and indigenous persons of typhus-endemic areas commonly have less severe illness, often without rash or eschar. Fever is the most common feature of scrub typhus and in endemic areas it is the one of the causes of "fever of unknown origin."⁶

Complications of scrub typhus are not uncommon and may be fatal: they include atypical pneumonia, pneumonia with adult respiratory distress syndrome (ARDS)-like presentation, myocarditis, and disseminated intravascular coagulation and meningoencephalitis, acute renal failure and gastrointestinal bleeding.

Early diagnosis is important because there is excellent response to treatment and timely anti-microbial therapy may prevent complications. In developing countries with limited diagnostic facilities, it is prudent to recommend empiric therapy in patients with undifferentiated febrile illness having evidence of multiple system involvement.¹⁰

With appropriate antibiotic treatment, mortality from scrub typhus is quite rare and the recovery period is short and usually without complications. However, mortality is still approximately 15% in some areas as a consequence of missed or delayed diagnosis. If there is severe complication like ARDS mortality may still be high.^{11,1}

EPIDEMIOLOGY

Scrub typhus is often acquired during occupational or agricultural exposures. Because rice fields are an important reservoir for transmission.² In tropical regions, scrub typhus may be acquired year round. In Japan, the chigger of *L. akamushi* is only active between July and September, when the temperature is above 25°C. In contrast, *L. pallidum*, which is found over a wide range, is active at temperature of 18-20°C, from spring into early summer and autumn.¹³

Zoonotic tetrad

Four elements are essential to maintain *O. tutsugambushi* in nature.⁸

- Trombiculid mites.
- Small mammals like field, mice, rats.
- Secondary scrub vegetations.
- Wet season (when mite lays eggs)

Global scenario

Currently, it is estimated that about one billion people are at risk for scrub typhus and one million cases occur annually. Geographic distribution of the disease occurs within Afghanistan and Pakistan to the west; Russia to the north; Korea and Japan to the northeast; Indonesia, Papua

New Guinea, and northern Australia to the south; and some smaller islands in the western Pacific. This is found only in areas with a suitable climate, plenty of moisture and scrub vegetation. Recently, rickettsiosis has been an emerging disease along the Thai Myanmar border. There are reports of emergence of scrub typhus in Maldives Islands and Micronesia.¹⁴

Indian scenario

In India, the disease had occurred among troops during Second World War in Assam and West Bengal, and in the 1965 Indo-Pak war.¹⁵ There was a resurgence of the disease in 1990 in a unit of an army deployed at the Pakistan border of India. It was known to occur all over India, including Southern and Northern India. However, in the later years, the disease virtually disappeared, probably because of widespread use of insecticides to control other vector born disease, empiric treatment of febrile illness with tetracyclines and chloramphenicol by practitioners and changes in life style.¹⁶

Recent reports from India and other neighboring countries suggest that there is a resurgence of scrub typhus infection in the some parts of the World and that the resurgence is associated with considerable morbidity and mortality.^{15,16} In India, scrub typhus has been reported from Rajasthan, Jammu and Kashmir and Vellore. In addition, few cases have been reported for scrub typhus in Sikkim, Darjeeling, and Nagaland and Manipur.¹⁴

DIFFERENTIAL DIAGNOSIS

It should be differentiated from malaria, dengue, leptospirosis, meningococcal disease, typhoid, infectious mononucleosis and HIV. The macular rash of dengue is much finer. Malaria can be ruled out by obtaining peripheral smear. Leptospirosis, typhoid and meningococcal disease can be diagnosed by culturing blood, CSF or bone marrow. Serology can diagnose leptospirosis, infectious mononucleosis and HIV.¹⁷

GUIDELINE FOR MANAGEMENT

Case definition

Suspected/clinical case: Acute undifferentiated febrile illness of 5 days or more with or without eschar should be suspected as a case of Rickettsial infection. (If eschar is present, fever of less than 5 days duration should be

considered as scrub typhus.) Other presenting features may be headache and rash (rash more often seen in fair person lymphadenopathy, multi-organ involvement like liver, lung and kidney involvement.

The differential diagnosis of dengue, malaria, pneumonia, leptospirosis and typhoid should be kept in mind.

- *Probable case:* A suspected clinical case showing titres of 1:80 or above in OX2, OX19 and OXK antigens by Weil Felix test and an optical density (OD) > 0.5 for IgM by ELISA are considered positive for typhus and spotted fever groups of Rickettsiae.
- *Confirmed case:* A Confirmed case is the one in which: Rickettsial DNA is detected in eschar samples or whole blood by PCR or Rising antibody titers on acute and convalescent sera detected by Indirect Immune Fluorescence Assay (IFA) or Indirect Immunoperoxidase Assay (IPA).

Laboratory criteria

There are various laboratory tests available for diagnosis of rickettsial diseases. Indirect immunoperoxidase assay (IPA) and immunofluorescence assay (IFA) are considered

Serological gold standards but are available at laboratories with higher level of facilities and expertise. Molecular diagnosis by PCR is available only at few centres in India. However, ELISA based tests, particularly immunoglobulin M (IgM) capture assays can be made available at secondary and tertiary levels of health care like District hospitals and medical colleges.¹⁸

A. Specific investigations

Weil Felix: The sharing of the antigens between rickettsia and proteus is the basis of this heterophile antibody test. It demonstrates agglutinins to Proteus vulgaris strain OX19, OX2 and Proteus mirabilis OXK. Though this test lacks high sensitivity and specificity but still serves as a useful and inexpensive diagnostic tool for laboratory diagnosis of rickettsial disease. This test should be carried out only after 5-7 days of onset of fever. Titre of 1:80 is to be considered possible infection. However, baseline titres need to be standardized for each region.

IgM and IgG ELISA: ELISA techniques, particularly immunoglobulin M (IgM) capture assays for serum, are probably the most of sensitive tests available for rickettsial diagnosis and the presence of IgM antibodies, indicate comparatively recent infection with rickettsial disease.

Cases of infection with *O. tsutsugamushi*, a significant IgM antibody titre is observed at the end of 1st week, whereas IgG antibodies appear at the end of 2nd week. The cut off value is optical density of 0.5. Baseline titres

need to be established keeping in view the regional variations.

Polymerase chain reaction (PCR): It is a rapid and specific test for diagnosis. It can be used to detect rickettsial DNA in whole blood and eschar samples. The PCR is targeted at the gene encoding the major 56 Kda and/or 47 Kda surface antigen gene. The results are best within first week for blood samples because of presence of rickettsemia (*O. tsutsugamushi*, *R. rickettsii*, *R. typhi* and *R. prowazekii*) in first 7-10 days.

Immunofluorescence assay (IFA): This is a reference serological method for diagnosis of Rickettsial Diseases and is considered serological 'gold standard'; however, cost and requirement of technical expertise limit its wide use. Therefore, it is recommended only for research and in areas where sero-prevalence of rickettsial diseases has been established.

Indirect immunoperoxidase assay (IPA): It gives comparable result as IFA but requires special instrument and experienced personnel for interpretation of the test. We do not recommend any rapid test for diagnosis of scrub typhus at the present stage of development of these tests as they need further evaluation.

B. Supportive laboratory investigations

These are required as additional diagnostic clues and sometimes can indicate severity and development of complications. These investigations can assist in deciding upon appropriate management of patients.

Hematology total leucocytes count during early course of the disease may be normal but later in the course of the disease; WBC count may become elevated to more than 11,000 / cu. mm., Thrombocytopenia (i.e. <1,00,000/cu.mm) is seen in majority of patients. Biochemistry raised transaminase levels are commonly observed. And Imaging Chest X-Ray showing infiltrates, mostly bilateral.

C. Isolation of the organism

As rickettsiae are highly infectious and have caused several serious and fatal infections among laboratory workers, it is risk group 3 organisms. Isolation should be done in laboratories equipped with appropriate safety provisions preferably biosafety level-3 laboratory following strict biosafety precautions. Rickettsia may be isolated in male guinea pigs or mice; yolk sac of chick embryos; vero cell line or MRC 5 cell lines from patients in early phase of the disease.

TREATMENT

In fever cases of duration of 5 days or more where malaria, dengue and typhoid have been ruled out;

following drugs should be administered when scrub typhus is considered likely

Doxycycline 200 mg/day in b.d. for individuals above 45 kg for duration of 7 days. Or Azithromycin 500 mg in a single oral dose for 5 days in adults.

Doxycycline in the dose of 4.5 mg/kg body weight/day in two divided doses for children below 45 kg or Azithromycin in the single dose of 10mg/kg body weight for 5 days in children.

Azithromycin 500 mg in a single dose for 5 days, (drug of choice in pregnant women).In complicated cases the following treatment is to be initiated–

Prevention and control

- The control of mite vectors of scrub typhus by treating the ground and vegetation with residual insecticides, reducing rodent populations, and destroying limited amounts of local vegetation.
- Persons who cannot avoid infested terrain should wear protective clothing, impregnate their bedding with a miticide (e.g. benzyl benzoate) and apply a mite repellent, diethyltoluamide, to exposed skin.
- Chemoprophylaxis by a single dose of doxycycline given weekly started before exposure and continued for 6 weeks after exposure.¹⁹

CONCLUSION

Scrub typhus is prevalent but under diagnosed in india due to its nonspecific, clinical presentations, low index of suspicion amongst clinicians, limited awareness and limited diagnostic facilities. The possibility of Scrub typhus should be born in mind whenever a patient of fever presents with varying degree of renal failure particularly if an eschar exists along with history of environmental exposure. However, the eschar may not be present in a large number of cases. Rapid and specific diagnostic methods using ELISA can be carried out timely in patients with FUO in developing countries like India. Empirical therapy, with doxycycline may be lifesaving when clinical suspicion is high. Vaccines are under trial. At present there is no vaccine against rickettsial diseases.

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: Not required

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Cite this article as: Meena M, Meena S. Chiggerosis: an emerging disease. *Int J Res Med Sci* 2016;4:4236-40.