



Diagnosis and Treatment of Scrub Typhus – The Indian Scenario

AR Chogle

Scrub Typhus, or tsutsugamushi disease is a febrile illness caused by bacteria of the family Rickettsiaceae and named *Orientia tsutsugamushi*. Scrub typhus is endemic to a geographically distinct region, the so-called tsutsugamushi triangle, which includes Japan, Taiwan, China, and South Korea.¹ It also occurs in Nepal, Northern Pakistan, Papua New Guinea, and the Australian states of Queensland and Northern New South Wales.² In India, the disease had occurred among troops during World War II in Assam and West Bengal, and in the 1965 Indo-Pak war. There was a resurgence of the disease in 1990 in a unit of an army deployed at the Pakistan border of India.³ It is known to occur all over India, including Southern India⁴ and Northern India.⁵ However, the reported number of cases of Scrub typhus from different parts of the country particularly from large tertiary care hospitals do not give a true picture of prevalence of scrub typhus in the country. As yet there are not many community based studies in our country. One such community based study involving several districts in Tamil Nadu showed that scrub typhus and rickettsial diseases were widely distributed in the state.⁶

In this context the report of outbreak of scrub typhus in Pondicherry and in the current issue of the Journal⁷ is meaningful. In this report the diverse clinical and laboratory manifestations of scrub typhus are described. The diagnosis was based on the presence of eschar and/or positive Weil Felix test with a titre of $> 1:80$.

In scrub typhus, an eschar approximately 5 to 20 mm in diameter is formed at the site bitten by trombiculid mites, and this may be considered the most important clinical finding for the diagnosis of scrub typhus. The site bitten by chiggers is initially a papule followed by a blistered ulcer, and this is then covered with a black crust; the border of the eschar is surrounded by reddish erythema. Such a typical eschar is formed at the time when symptoms are manifested.⁸

In the past, the clinical diagnosis of scrub typhus was dependent on detecting eschar and rash and on the history of outdoor activity.⁸⁻¹⁰ Nevertheless, under actual clinical conditions, only eschar without rash may be seen in some cases. As was shown in one previous case report, for febrile patients showing a lesion similar to eschar, distinguishing whether such an eschar-like lesion is actually a simple crust or eschar is required.¹¹ Furthermore, eschars are also detected in rickettsial pox, cutaneous anthrax, and other diseases, and travel and other population migrations are currently often occurring. Scrub typhus has been reported in Western countries.^{12,13} Recently it has been shown that patients' eschars can be used for detection and genetic characterization of *Orientia tsutsugamushi* during the convalescent phase.¹⁴ Immunohistochemical staining of skin biopsy specimens, particularly that of eschars, is sensitive and

specific, and this technique can be reliable for confirming the diagnosis of scrub typhus. Also immunohistochemical staining performed on skin lesions within 3 or 4 days of administration of antibiotics that are effective for *Rickettsia*, did not greatly influence diagnostic sensitivity.¹⁵

The diagnosis of a rickettsial illness has most often been confirmed by serologic testing. The specific gold standard techniques like the immunofluorescence antibody test (IFA), the indirect immunoperoxidase (IP) test, ELISA are not available in our country and the isolation of the organisms in animals or cell culture is limited by the lack of containment facility as well as the lack of expertise in handling these high risk group pathogens.¹⁶ Many report of scrub typhus and other rickettsial diseases from the Indian sub-continent are based on clinical findings and the relatively non-specific Weil-Felix test including the study by Vivekanandan M and co-workers.⁷

Weil-Felix test has shown reasonably high specificity but a low sensitivity for the diagnosis of Rocky mountain spotted fever, Mediterranean boutonneuse fever, murine typhus, epidemic typhus and scrub typhus.¹⁶ Although a good correlation between the results of the Weil-Felix test and detection of IgM antibodies by an IFA is often observed, with the development of techniques that are used to grow rickettsiae, this test should be used only as a first line of testing in rudimentary hospital laboratories. In spite of all the drawbacks associated with it, the Weil Felix test still serves as a useful and cheapest available tool for the laboratory diagnosis of rickettsial diseases. A four-fold rise in agglutinin titres in paired sera is diagnostic for infection with these febrile agents. However, with a single serum sample available, the test is suggestive of infection only at a high cut-off titre ($> 1 : 320$) at which the positive predictive value and the specificity is reliable.¹⁶ Recently, commercial rapid detection kits like Dip-S-Ticks, scrub typhus RCT and scrub typhus IgM and IgG Rapid Immunochromatographic Assay (PanBio, Brisbane, Australia) and Multies Dip-S-Ticks Scrub Recombinant Assay (Integrated Diagnostics, Baltimore, Maryland, USA) have appeared in the market but are still far from the reach of most of the developing countries due to their high cost.¹⁶

Serious complications of scrub typhus are not uncommon and may be fatal; they include pneumonia, myocarditis, meningoencephalitis, acute renal failure and gastrointestinal bleeding. Early diagnosis is important because there is usually an excellent response to treatment and timely anti-microbial therapy may help 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. A clinical algorithm has been proposed for diagnosis of scrub typhus among patients hospitalized with febrile illness and to determine predictors of bad prognosis. If a combination of elevated transamines, thrombocytopenia and leukocytosis is used, the specificity and positive predictive value for diagnosis of scrub typhus are

Hon.Physician, Kasturba Hospital for Infectious Diseases, Mumbai 400 008; Consultant Physician, Sir H.N.Hospital & Research Centre, Mumbai 400 004.

about 80%.¹⁷ Regarding ancillary investigations in scrub typhus patients with multiorgan involvement, CT Scan findings of both chest and abdomen have been described in detail. Although these findings are non-specific they may facilitate accurate diagnosis.¹⁸

A recent Cochrane review, on antibiotics for scrub typhus prepared and published in Cochrane library¹⁹ has made the following observations :

1. At present there is insufficient evidence from trials of comparative effects of different broad spectrum antibiotics in scrub typhus.
2. Doxycycline and tetracycline are similar drugs, both have been used to treat this condition and both appeared to cure the small number of patients studied.
3. Rifampicin is seen to be more effective than doxycycline in areas where scrub typhus appears to respond poorly to standard anti rickettsial drugs.
4. Clinicians should monitor the progress of patients in the light of reports of drug resistance.
5. Further research is required to evaluate antibiotics usage in scrub typhus. Trials would be more easily interpreted if reliable diagnostic tests were available. Such research could examine whether a single dose of doxycycline is as effective as a three to five days course of treatment.
6. Regimens for severe disease need to be evaluated for example, comparing intravenous chloramphenicol with intravenous tetracycline.
7. Studies are also needed to evaluate alternative antibiotics (e.g. Azithromycin and Ciprofloxacin) particularly in areas where scrub typhus appears to respond poorly to standard anti-rickettsial drugs.

Clearly more research on scrub typhus in the Indian context is required, particularly regarding epidemiology, pathogenesis, diagnosis and treatment of this condition.

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