Outbreak of Scrub Typhus in Southern India during the Cooler Months

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ABSTRACT: ***Orientia tsutsugamushi*, the agent of scrub typhus, is a strict intracellular bacterium which is found in many parts of Asia including India. During the past few years, the number of patients with rickettsial infection and scrub typhus has increased, especially during the cooler months. We report in this study a recent outbreak of scrub typhus recorded during the cooler months (October 2001 to February 2002) in patients admitted to our hospital with acute febrile illness associated with diverse signs and symptoms. Overall, 28 patients were clinically and serologically confirmed to have scrub typhus. Fever for more than one week was the only common manifestation. Myalgias was the next most common feature (52%), and rash was observed in only 22% of the cases. Seventeen patients treated with doxycycline recovered in 1 to 3 days, as well as two patients who received chloramphenicol. In five patients who received ciprofloxacin, fever subsided only after five days. Finally three patients (10.7%) died, including one patient treated with doxycycline. These data indicate that scrub typhus is a reemerging infectious disease in India with a possibility of drug resistance. This reemergence emphasizes the need for further prospective studies to design effective control measures.**

KEYWORDS: **scrub typhus; outbreak; fever; India; *Orientia tsutsugamushi***

INTRODUCTION

Scrub typhus caused by *Orientia tsutsugamushi* is an acute febrile rural zoonosis endemic in the Asia Pacific region, Australia, Japan, and India.[1] In India, the presence of scrub typhus and other types of rickettsial infections has been documented for several decades. It is recorded that during World War II and early Indo-Pakistan conflicts, more people died of scrub typhus in some areas than from war.[2] However, the incidence declined considerably due to widespread use of pesticides, effective antibiotics, and changes in life style.[3] All the same, this disease has not disappeared from the Indian subcontinent.[1] A recent report based on serology suggests that, at least in southern India, human rickettsioses and scrub typhus continue to occur and that the magnitude of the problem is not recognized.[1]

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Symptoms occur usually 2 to 10 days after the bite and may be associated with an eschar, fever, lymphadenopathy, rash, headache, and myalgia. The severity of the disease varies from asymptomatic to fatal. In untreated cases, mortality may be as high as 30%. Vasculitis, the main pathology in scrub typhus, can affect any part or organ in the body and cause varied clinical manifestations. This causes problems with diagnosis.

From October 2001 to February 2002, several patients presented to our hospital with acute febrile illness associated with diverse signs and symptoms and were found to have positive scrub typhus serology. This manuscript describes our experience with this recent outbreak.

MATERIALS AND METHODS

Adult patients admitted to Christian Medical College Hospital—an 1800-bed teaching hospital situated 140 km interior from the east coast in South India at an altitude of 240 meters—with acute febrile illness are routinely evaluated for common causes of fever, like leptospirosis, dengue fever, malaria, typhoid fever, urinary tract infection, and pneumonia. This teaching hospital has a catchment area with a population of about 5.5 million. However, several other government and private health care providers also function in this area. During October 2001 to February 2002, approximately 300 patients had fever and other associated features requiring admission to our hospital. Etiological diagnosis was established for about 50% of these patients. Clinical and laboratory data were collected from the case records.

In the initial part of the outbreak, serum samples were tested for rickettsial illnesses only after excluding other febrile illnesses. Sera were tested using the Weil-Felix (WF) test with OX-19, OX-2, and OX-K antigens with a positive cut off of 1:80.[1] Positive and a few negative serum samples were then sent to Unité des Rickettsies Marseille, France, for specific microiimunofluorescence assay (MIF) using whole-cell antigens of *O. tsutsugamushi* serotypes Karp, Kato, Gilliam, and Kawasaki.[4] Sera were also tested with a large panel of other antigens including *Bartonella henselae*, *Rickettsia typhi*, *Francisella tularensis*, *Coxiella burnetii*, *R. felis*, *R. japonica*, *R. helvetica*, *R. conorii*, *R. honei*, and "*R. heilongjangii*." This MIF assay was conducted as previously described for other rickettsiae.[5] Positive cut off values were greater than or equal to 1:128 for IgG and greater than or equal to 1:64 for IgM.

RESULTS

During the period October 2001 to February 2002, which are the cooler months in this region, a total of 28 patients were diagnosed with scrub typhus on the basis of serology (see TABLE 1). These patients were residents of either Vellore or neighboring districts. Most were young adults with a mean age of 38.9 years (range: 16–65) and 60% were farmers belonging to low income groups. Clinical and laboratory data for 27 of these patients are presented in TABLE 2. For one patient we received

TABLE 1. Results of Weil Felix test and the microimmunofluorescence assay performed on 28 patients

			Weil Felix	Microimmunofluorescence assay			
Case	Sex	Age	OX-K	Karp	Gillian	Kato	Kawazaki
1	F	17	320	0/0	256/512	1024/512	0/0
2	F	31	160	0/0	512/512	0/64	0/0
3	M	26	80	0/0	128/64	128/64	0/0
4	F	58	80	0/0	256/256	128/32	0/0
5	M	45	neg	0/0	128/0	128/0	0/0
6	M	45	320	0/0	1024/256	1024/256	0/0
7	M	34	NA	64/1024	64/1024	0/0	64/1024
8	M	24	NA	256/1024	128/1024	0/0	0/1024
9	F	28	160	2048/1024	512/1024	256/0	1024/0
10	F	32	neg	0/64	0/256	0/0	128/64
11	M	65	80	128/0	128/0	0/0	0/0
12	F	24	640	64/1024	64/1024	0/0	64/1024
13	M	35	neg	128/0	128/0	0/0	0/0
14	F	19	80	64/1024	64/1024	0/0	64/1024
15	M	55	1024	128/1024	64/1024	0/0	128/1024
16	M	30	320	512/1024	64/1024	0/0	64/1024
17	F	20	1280	2048/1024	2048/1024	0/0	1024/1024
18	29	29	320	NA	NA	NA	NA
19	M	54	neg	0/0	0/64	0/0	0/0
20	M	52	320	256/512	512/512	0/0	64/512
21	M	56	320	256/512	512/512	0/0	64/512
22	M	55	neg	1024/0	2048/0	0/0	1024/0
23	F	54	neg	64/0	512/0	0/0	0/0
24	M	16	320	2048/128	2048/128	0/0	512/128
25	F	42	320	128/64	128/64	0/0	128/64
26	M	64	320	256/64	256/64	0/0	0/0
27	F	21	5120	0/0	128/32	32/32	0/0
28	F	58	160	64/128	512/512	0/0	0/0

ABBREVIATIONS: neg, negative; N.A., not available.

TABLE 2. Clinical and laboratory data for the 28 patients suffering from scrub typhus

Clinical data	
Fever duration < 7 days	1 (4%)
Fever duration 7–14 days	20 (74%)
Fever duration 15–21 days	6 (22%)
Myalgias	14 (52%)
Headache	9 (33%)
Nausea or vomiting	13 (48%)
Altered sensorium	5 (19%)
Cough	12 (44%)
Jaundice	7 (26%)
Rash	6 (22%)
Eschar	1 (4%)
Laboratory data	
Leukocyte count >11,000/mm^3	14 (54%); $n = 26$
Platelet count <100,000/mm^3	9 (43%); $n = 21$
Transaminase level > twice normal	22 (88%); $n = 25$
Bilirubin level > 25μmol/L	7 (29%); $n = 24$
Creatinine > 120μmol/L	8 (37%); $n = 24$
Abnormal chest X-ray	9 (37%); $n = 24$

only the serum with the patient's age and sex without clinical or therapeutic data. Fever was the only common manifestation with the majority having temperatures above 101°F for more than one week. Myalgia was the next most common feature (52%). Only 22% had rash, which was either maculopapular or purpuric. Laboratory tests showed evidence of abnormal liver function in 88% and abnormal renal function in 38%. Three or more systems were involved in 12 patients (44%) and 3 patients (11%) required intensive care. One patient each required ionotropic support and ventilatory support. Of the five women who were pregnant, four had perinatal deaths and one had a preterm baby.

Seventeen patients who received doxycycline showed fever defervesence in 1–3 days. Two patients who received chloramphenicol also improved clinically. In five patients who received ciprofloxacin, fever subsided only after an average of five days. Two patients were brought late with severe jaundice and died within 48 hours of admission. A third patient on admission had fever, cough, and rash suggestive of rickettsial infection, all of 10 days duration. His fever subsided with doxycycline, but the vasculitic rash progressed to multiple ulcers and digital gangrene. He was given steroids to suppress inflammation. He later developed features of septic shock and succumbed. The overall mortality was therefore 3 (11.1%).

DISCUSSION

Our data shows that scrub typhus continues to occur in India and has the potential to cause outbreaks and deaths. Scrub typhus has protean manifestations making clinical diagnosis difficult.[1] Access to specific laboratory tests is a problem in developing countries like India.[1] These factors are likely to lead to under diagnosis of this infection in these areas.

This probably accounts for the absence of reports from most parts of India. Our limited experience and previous literature from India show that there is an upsurge in cases during winter months. Scrub, optimum amount of monthly rainfall, and soil-bound moisture are important for disease transmission. Consequently, an increase in incidence of cases is seen in the cooler months of the year. Clinical diagnosis of scrub typhus is difficult since the pathognomonic rash and eschar are seen in less than 50% of cases.[6,7] This is confirmed in this series. Moreover, skin manifestations may go unnoticed especially in dark skinned people. Therefore laboratory tests are required to make a diagnosis. Specific serology remains the main method for diagnosis of rickettsial infection. All except one (serum not available for the MIF assay) of our cases were confirmed by MIF assay. Our data show that testing four different serotypes (namely, Gilliam, Karp, Kato, and Kawasaki; TABLE 1) is necessary since these strains are antigenically distinct.[8] Weil Felix test,[1] the only commercially available assay in India, is grossly insensitive to anti-*O. tsutsugamushi* antibodies, as 6/26 (23.1%) of our cases were negative by this test, and so it is not useful for screening cases.

Empirical therapy may be used in areas where no specific testing facilities exist, especially in the seriously ill. Useful clinical features we observed in such patients in addition to rash were, multisystem involvement, elevated transaminases, and thrombocytopenia. Rapid defervescence after antibiotic therapy is so characteristic that in itself can be considered as a diagnostic test. Scrub typhus is potentially treatable and therefore the morbidity and mortality associated with it can be reduced if diagnosed early. Doxycycline remains the antibiotic of choice for scrub typhus, but chloramphenicol is still commonly used in many endemic areas. In our series, patients treated either with doxycycline or chloramphenicol were cured except one patient who died after he was given doxycycline. *O. tsutsugamushi* resistant to doxycycline and chloramphenicol has been reported in northern Thailand,[7] and thus there is a need to have alternative drugs especially those which are safe during pregnancy. Based on preliminary published *in vitro* and clinical studies, azithromycin (500 mg on the first day followed by 250 mg daily for 2 to 4 days),[9] and rifampin (one-week 600–900 mg/day oral treatment)[10] are proposed as alternatives to doxycycline and chloramphenicol.

Our observations confirm that scrub typhus is a cause of concern in India. Systematic surveillance over the next few years will be required to ascertain the magnitude of the problem and its association with seasons in different geographic areas. The reemergence of the disease after a period of rarity along with a possibility of drug resistance emphasizes the need for further prospective studies to design effective control measures.

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