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Scrub typhus in rural areas & suburbs of Vidarbha region of Maharashtra

Sir,

In 2018, between August and October, 490 serum samples from patients with acute undifferentiated febrile illness of more than four days and varied symptoms with or without eschar were collected at various primary health centres and rural and district hospitals of Vidarbha region of Maharashtra State, India, through the Directorate of Health Services (DHS), Maharashtra, under the Integrated Disease Surveillance Programme (IDSP). The samples were maintained in cold chain and received in the State Surveillance Laboratory, department of Microbiology, Government Medical College and Hospital, Nagpur, for the laboratory diagnosis of scrub typhus. In 2017, only 29 samples were received during the same period, from the same region and under the same programme with immunoglobulin (Ig) IgM enzyme-linked immunosorbent assay (ELISA) positivity in two samples. We report here the clinicoepidemiological findings and laboratory investigations of the seropositive cases. The study was approved by the Ethics Committee of Government Medical College, Nagpur.

Information on demographic, clinical and available supportive laboratory investigations (haemoglobin percentage, complete blood count, liver function tests and kidney function tests) of the patients was collected. Scrub typhus was diagnosed using InBios Scrub Typhus Detect IgM ELISA test as per manufacturer's instructions (InBios International Inc., USA). The test detected IgM antibodies against a recombinant 56 kDa antigen.

Ten randomly selected samples, proven positive by IgM ELISA, were sent for confirmation to the Indian Council for Agricultural Research (ICAR) Center for Zoonosis, Nagpur Veterinary College, Nagpur, where samples were processed for DNA isolation. Nested polymerase chain reaction (N-PCR) targeting the 56 and 47 kDa surface antigen genes was performed in two rounds[1] each using primers synthesized by Eurofins Genomics, Ebersberg, Germany. The first round of N-PCR for the 56 kDa antigen was performed using primers, P34 and P55; while the second round was performed using the first-round PCR product as the template DNA and primers, P10 and P11. The first round of N-PCR for amplification of the 47 kDa antigen was performed using primers, OtsuFP555 and OtsuRP771; and the second round was performed using first PCR product as the template DNA and primers, OtsuFP630 and OtsuRP747. In addition, quantification of bacterial load was done by qPCR targeting the 47 kDa surface antigen[1]. The cloned plasmid was quantified using DU 530 Life Science UV/visible spectrometer (Beckman Coulter, USA). Quantification and analysis were carried out by Insta 96 software (HiMedia, Mumbai).

IgM ELISA was positive in 158 (76 female, 82 male) of 490 (32.24%) samples. Ten of these randomly selected samples were tested positive by qPCR. The age of the seropositive patients ranged from 5 to 80 yr, with 18 (11.39%) patients being ≤10 yr. The age group most commonly affected was 21-30 yr. Agricultural workers constituted 65 per cent (n=103) and those not associated with field work constituted about 35 per cent (n=55). As the catchment area was predominantly rural, houses surrounded by scrub vegetation might have predisposed non-field workers to infection.

All patients presented with fever (Table). Duration of fever was 4-20 days, and the mean duration of fever was 12 days. The DHR-ICMR guidelines define a suspected/clinical case as having acute undifferentiated febrile illness of five days or more with or without eschar[2]. In this study, IgM ELISA was positive in patients with fever duration as short as four days. Sites of eschar in 46 (29.11%) patients were upper and lower extremities, thorax, thigh, chest and neck. It is pathognomonic but detected with a varying frequency

Table. Clinical presentation in IgM ELISA-positive patients (n=158)

System	Symptoms	Number of patients (%)
Non-specific	Fever (4-20 days)	158 (100)
	Eschar	46 (29.11)
	Headache	98 (62.03)
	Myalgia	96 (60.76)
	Generalized weakness	20 (12.66)
Respiratory	Cough with breathlessness	15 (9.49)
	Sore throat	12 (7.59)
Central nervous system	Altered sensorium	4 (2.53)
	Seizures	2 (1.27)
	Meningitis	3 (1.90)
Gastrointestinal	Vomiting	5 (3.16)
	Diarrhoea	7 (4.43)
Multiple organ involvement	MODS	30 (18.99)

MODS, multiple organ dysfunction syndrome

of 7-97 per cent[2]. Reasons cited for the absence of eschar were identification difficulty in dark-skinned individuals, difference in eschar-producing capacity of different strains, presence in atypical sites such as skin folds or moist skin or an eschar going unnoticed being painless and antipruritic[3].

Symptoms were non-specific and organ specific (Table). Non-specific symptoms have been reported in patients of scrub typhus and have resolved after specific treatment[4,5]. This reaffirms that in a febrile patient with non-specific symptoms, scrub typhus must be ruled out. Organ-specific symptoms were mainly respiratory in 27 (17.09%) patients although respiratory symptoms as high as 76.9 per cent have been reported[6]. Neurological symptoms were found in nine (5.70%) patients, while similar symptoms ranging from 9.5 to 23.3 per cent have been reported[6-8]. In six out of seven patients with raised serum creatinine and in two patients with raised serum bilirubin, there were no renal and hepatic complications, respectively.

Twelve (7.59%) of the 158 patients died. Of these, seven patients died due to acute respiratory distress syndrome (ARDS) with respiratory failure along with cardiorespiratory arrest, two due to ARDS with meningoencephalitis, another two due to ARDS with respiratory failure and one due to acute renal failure. Haemorrhagic complications were not observed. Respiratory failure was predominantly the cause of death.

Based on the information available in 96 patients, leucocytosis was observed in 61 (63.54%), thrombocytopenia in 29 (30.21%) and increased transaminases in 72 (75%) patients. The least platelet count was 57,000/µl. There were 15 patients with leucocytosis, thrombocytopenia and increased serum transaminases in combination. When used in combination, these three findings can predict specificity and positive predictive value in 80 per cent of patients with scrub typhus[9]. Scrub typhus can coexist with viral infection, malaria or typhoid[10]. Coexisting infection was ruled out with dengue NS1 and IgM in 10 patients, malaria HRP-II antigen in 79 patients by rapid card test and typhoid in 30 patients by slide agglutination test. Lymphocytosis observed in cererbrospinal fluid in two of the three patients with meningitis may not have contributed to the diagnosis of scrub typhus as raised lymphocytes can be found in other rickettsial infections, chronic bacterial infections and viral infections[11]. Abnormal chest radiograph was seen in 18 (85.71%) of 21 referrals to higher centres, all with a history of untreated fever of long duration at the time of admission. This reiterates the importance of early diagnosis.

Treatment was effective with doxycycline in adults at a dose of 100 mg twice a day for seven days and in children at 2.25 mg/kg body weight twice a day for seven days. As the incident cases continued to increase, the policy of empirical use of doxycycline in all cases of acute undifferentiated febrile illness was adopted by the district health administrators of the Government of Maharashtra in early September 2018 and the response was good. As the diagnosis of scrub typhus is difficult clinically, a heightened surveillance will facilitate early case identification, early laboratory-based specific diagnosis and early initiation of antimicrobial therapy, thereby preventing complications and mortality.

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***Conflicts of Interest*:** None.

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