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Case Report

Paediatrics Section

Doxycycline-resistant Scrub Typhus in a Syndromic Child

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BY-NC-ND

ABSTRACT

Scrub Typhus, a human febrile illness caused by *Orientia tsutsugamushi*, is common in Asia and infects persons those visiting the endemic areas. Scrub typhus is a zoonotic infection. It is transmitted by a trombiculid mite which introduces the bacteria by its bite. Scrub typhus is associated with maculopapular rashes and local and/or generalised lymphadenopathy.It is characterised by eschar at the site of the bite. A child with doxycycline-resistant scrub typhus is being presented here. A 10-year-old female child was brought to the hospital with complaints of fever for six days, cough for three days, loose stools for two days, and vomiting for one day duration. S1 and S2 sounds were heard while bilateral vesicular breath sounds were normal. There was no hepatosplenomegaly and Central Nervous System (CNS) examination showed no focal neurologic deficits. Investigations showed a normal leukocyte count and Differential Leucocyte Count (DLC), microcytic hypochromic anaemia, thrombocytopenia, hyponatraemia, and elevated liver enzymes. Scrub Immunoglobulin M (IgM) was positive. Chest radiograph showed a bell-shaped chest with vertical straightening of ribs. The child was started on intravenous (i.v.) fluids, Doxycycline 4 mg/kg, and paracetamol. The child continued to spike fever at day six of Doxycycline and hence was started on Azithromycin 10 mg/kg, following which the fever subsided and the child was discharged.

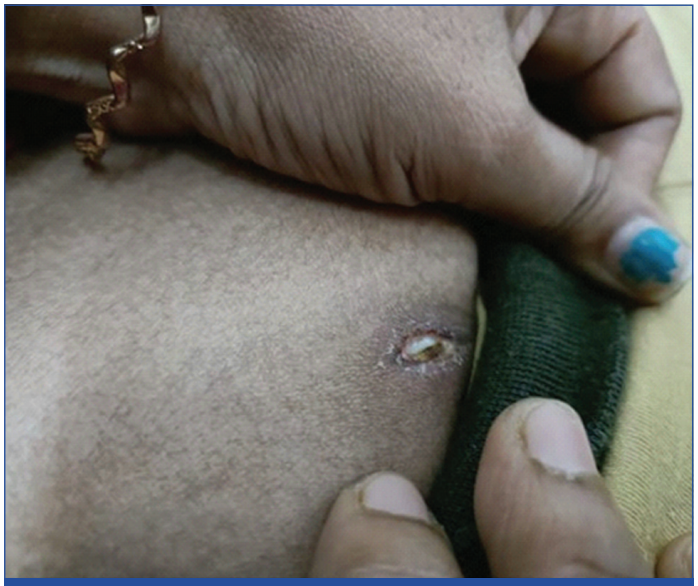
Keywords: Azithromycin, Hyponatraemia, Immunoglobulin M

CASE REPORT

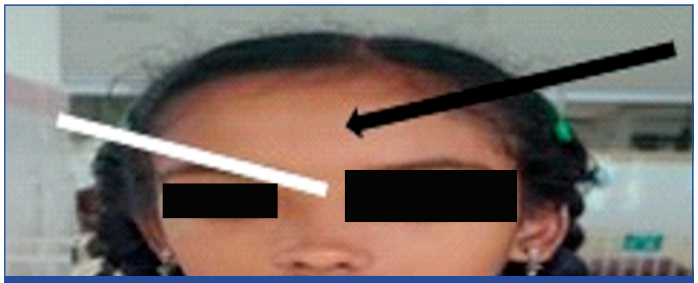
A 10-year-old female child was bought to the hospital with complaints of fever for six days, cough for three days, loose stools for two days, and vomiting for one day duration. The fever was low grade, intermittent, relieved by medications, and not associated with chills and rigors lasting for six days. The child had a productive cough, sputum was mucoid in consistency, not associated with any nocturnal or diurnal variations and non blood stained sputum. The child had loose stools, watery in consistency, not foul smelling and not blood stained.

She had a history of one episode of vomiting which was non projectile, consisted of food particles with no haematemesis. There was no history of rash, sore throat, dysuria, ear pain or ear discharge. The child was operated for inguinal hernia at 45 days of age. The antenatal history was uneventful. The child was born of full term normal delivery, did not cry immediately after birth and was kept in the Neonatal Intensive Care Unit (NICU) for an hour. There was history of a mild developmental delay. She was immunised to date and was on a normal diet. She was born of second-degree consanguineous marriage. There was no history of contact with open tuberculosis. There was no history of travel. There was history of infestation of rodents and ticks in the locality of residence but there was no known history of bites. She was on Doxycycline 100 mg 1-0-1/2 for one day which was started by a private practitioner, suspecting scrub typhus due to the presence of the eschar.

On examination, she weighed 35 kg (75th percentile for age and sex), and her height was 147cm (95th percentile), her head circumference was 57 cm and chest circumference was 64 cm. She had a bell-shaped chest, with frontal bossing, depressed bridge of nose, hypertelorism, and squint. She had Marphanoid features. Her body temperature was 101.7°C, Pulse Rate (PR) was 104 beats per minute, Respiratory Rate (RR) 29/breaths per minute, Blood Pressure (BP) was 100/80 mm Hg. She was anaemic. No jaundice, cyanosis, clubbing, pedal oedema and lymphadenopathy were observed. There was an eschar 2 cm by 1.5 cm in the right inguinal region [Table/Fig-1,2].



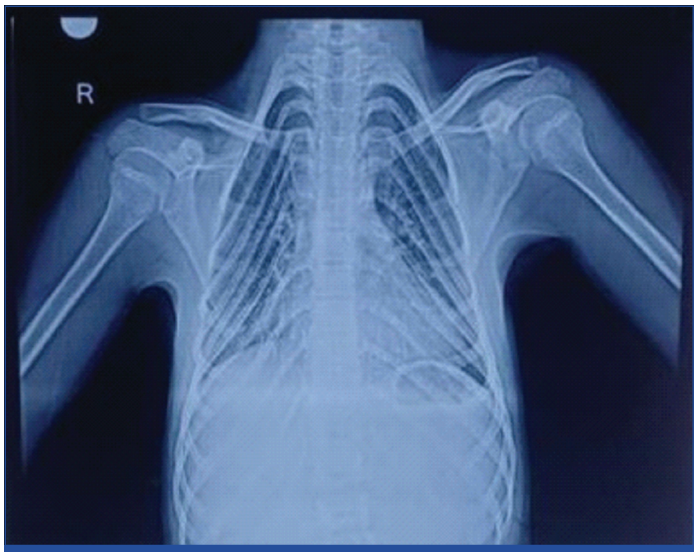
[Table/Fig-1]: Eschar.



[Table/Fig-2]: Hypertelorism (line), frontal bossing (arrow).

On systemic examination, S1 S2 and bilateral normal vesicular breath sounds heard. Abdomen showed no hepatosplenomegaly and CNS examination showed no focal neurologic deficits. Investigations showed a normal leukocyte count and DLC, microcytic hypochromic anaemia, thrombocytopenia, hyponatraemia. Liver enzymes were elevated and other liver function tests were normal. Urine routine examination was normal and culture/sensitivity showed

no growth. Stool examination was normal and it showed no growth. Widal test, done on the eighth day of fever, was negative. Blood culture, done by the automated method, showed no growth probably because the child was already on Doxycycline. The C-Reactive Protein (CRP) was 91 mg/L and ultrasound abdomen showed no hepatosplenomegaly. Hepatitis markers were negative. Dengue serology was done and it was negative. Scrub IgM Enzyme Linked Immunosorbent Assay (ELISA) was positive- 76.19 Clorprenaline (CLO) units. Chest radiograph showed a bell-shaped chest with vertical straightening of ribs [Table/Fig-3].



[Table/Fig-3]: Chest radiograph- bell-shaped chest.

The heart and the lungs were normal. The child was started on i.v. fluids, doxycycline was continued at 4 mg/kg, and paracetamol. But she continued to spike fever at day six of Doxycycline inspite of compliance and dosage. Hence, she was started on Azithromycin 10 mg/kg, following which the fever subsided. The child was finally discharged when she remained afebrile for 48 hours. On follow-up, after one week, she was afebrile with no symptoms.

DISCUSSION

Scrub typhus is caused by organisms of the family Rickettsiaceae. These organisms are obligate intracellular, Gram-negative, non flagellate, small pleomorphic coccobacilli. Scrub typhus is an acute, febrile, infectious illness that is caused by *Orientia tsutsugamushi*. Hashimoto described the illness in 1810. Heterophile antibody agglutination of (O-specific polysaccharide O-specific chain of outer membrane lipopolysaccharid)-2 and OX-19 strains of proteus mirabilis by typhus sera was described by Weil and Felix in 1916. Ogata in 1931 isolated the organism and named it *Rickettsia tsutsugamushi*. Later, it was renamed *Orientia tsutsugamushi* [1]. The vector is the larva of a trombiculid mite. These larvae enter small rodents particularly wild rats. During rainy season when man encroaches a zone of infected mites he gets accidentally infected. The name 'scrub typhus' is derived from the type of vegetation (i.e., terrain between woods and clearings) that harbours the vector. Thus, it is also known as bush typhus [2]. When infected chiggers (larval mites) bite people, they get the infection. The chigger phase is the only stage that is parasitic on animals or humans.

The rural areas of Southeast Asia, Indonesia [3], China, Japan, India, and northern Australia are endemic for scrub typhus [4]. People get infected when they live in or travel to endemic areas. Symptoms include fever and chills, headache, myalgia, rash, enlarged lymph nodes, mental changes, ranging from confusion to coma, and a distinct eschar, which is a dark scab-like lesion at the site of the chigger bite [5]. Fever is one of the most common features of scrub typhus. In endemic areas, one of the causes of "fever of unknown origin" is Scrub typhus. In a hospital-based study in Western Himalayas by Mahajan SK et al., noted fever (100%), cough (24%) chills (39%), diarrhoea (18%), headache (21%), adenopathy (33%) eschar (60%) and rash (21%) in 33 patients of scrub typhus [6].

Serological tests still remain the mainstay in the diagnosis. Micro immunoflourescence is considered the test of choice. Indirect haemagglutination, Latex agglutination, immunoperoxidase assay, Polymerase Chain Reaction (PCR) and ELISA are other tests that are available. The disease has to be treated early for better outcomes than delayed treatment [7]. Doxycycline 4 mg/kg for seven days is the treatment of choice [8]. Azithromycin 10 mg/kg on day 1 and 5 mg/kg on day 2 to day 5 is used as a second line of treatment [9].Preventive measures in endemic areas include short-term vector reduction using environmental insecticides and vegetation control, protective clothing and insect repellents [9,10].

Scrub typhus can be easily treated with tetracycline, chloramphenicol and azithromycin but other antibiotics like penicillins and cephalosporins are not efficacious in treating Scrub typhus [8-10]. As of now, no vaccine is available. Over the recent years, Doxycycline-resistant scrub typhus is emerging. Diminished susceptibility to doxycycline is proved by an attenuated clinical response of scrub typhus to doxycycline [11]. As the case fatality ratio in the preantibiotic era was 50% the emergence of resistant strains of scrub typhus is concerning [12]. Smadel reported recovering isolates of chloramphenicol-resistant scrub typhus some months to years from the patients who had initially become afebrile [13]. In 1953 tetracyclines were introduced to treat scrub typhus and they proved to be superior to chloramphenicol. Tetracyclines produced a rapid resolution of fever and the complication of blood dyscrasias were not there [14]. Doxycycline was patented in 1957 and was Food and Drug Administration (FDA) approved in 1967 [15]. Response to treatment with Doxycycline in the form of defervescence within 24-36 hours was obtained. When defervescence was not produced in 48 hours, alternate diagnosis or co-infections or resistance to doxycycline was considered [16]. Response to doxycycline was so good that in regions where there was a lack of diagnostic tools response to therapy was considered to confirm scrub typhus [17].

For a long time, scrub typhus was very susceptible to doxycycline. But the authors now have entered the post-antibiotic era or the era of the super bug. Reports of antibiotic resistance to doxycycline have been emanating from Thailand in 1990 and from other regions also. *Oriental tsutsugamushi* is resistant to penicillins, gentamycin, cephalosporin, and fluroquinolones [18]. It is extremely susceptible to tetracycline, chloramphenicol and azithromycin until recently when strains of resistance to several of these drugs have been reported. As *O.tsutsugamushi* is an obligate intracellular organism it is very difficult to find its antibiotic sensitivity. Patient relapse and persistence of rickettsial infection have been reported in patients treated with chloramphenicol and tetracycline [19,20].

Earliest reports of antibiotic resistance to doxycycline were reported by Chanta C and Phloenchaiwanit P, Watt G et al., a United States Army clinical researcher assigned to the Armed Forces Research Institute of the Medical Sciences, Bangkok (AFRIMS) [19,21]. They observed that the patients were not recovering with tetracyclines or chloramphenicol and the mortality rate was as high as 15%. Following this a clinical trial was conducted in Thailand to find out the susceptibility of *O.tsutsumugashi* to doxycycline and azithromycin. It was found that the strains that were resistant to doxycycline were susceptible to azithromycin. Also, azithromycin is safe to use in pregnant women and in children compared to tetracycline or chloramphenicol [21]. Later a prospective trial was conducted in Korea which proved the efficacy of azithromycin in scrub typhus patients resistant to doxycycline [22]. Liu Q and Panpanich R also studied the efficacy of rifampicin in the treatment of scrub typhus. In that trial more than 12000 febrile patients were screened and 126 patients had scrub typhus infections. The investigators found that fever clearance times were significantly lower in the rifampicin group as compared to the doxycycline group [22]. Doxycycline resistance was reported out of Thailand also [23].

Corwin reported doxycycline resistance in US military personnel [24,25]. The personnel received doxycycline prophylaxis for malaria and yet 3 out of 14 of them developed symptoms of scrub typhus. This proved the existence of doxycycline-resistant scrub typhus as the doxycycline prophylaxis failed to prevent the scrub typhus infections. There was a report of doxycycline-resistant scrub typhus from South Korea. A farmer had meningoencephalitis with scrub typhus and he failed to improve with doxycycline but improved immediately after starting Azithromycin [24].

Varghese GM et al., report a death from South India due to doxycycline resistance patient died of septic shock in spite of being on doxycycline. This shows doxycycline resistance in *O.tsutsumugashi* [25]. A diminished response in mild cases could translate to severe morbidity and mortality in severe cases. Antibiotic exposure through animal feeds could drive resistance [26].

Infantry soldiers deployed in the Cowley beach training area in Australia were affected with scrub typhus despite being provided doxycycline prophylaxis. The chemoprophylaxis consisted of oral doxycycline 200 mg on entering the training area, 200 mg weekly thereafter, and 200 mg on exit from the area. A soldier was declared as a case if he displayed symptoms of fever, maculopapular rash, arthralgia and headache. Immunoglobulin G (IgG) titres were measured between acute and convalescent serology and if there was more than four-fold titre rise in IgG titres of *O.tsutsumugashi* the person was taken as a case. If there was a positive Polymerase Chain Reaction (PCR) on blood or tissue or a positive culture from clinical specimens the person was considered a case. A punch biopsy of the eschar tissue was done. A vero cell culture of severe combined immunodeficient mice was taken and the samples were inoculated.The presence of *O.tsutsumugashi* was confirmed by a PCR of the mice spleens and an immunofluorescence of the Vero cells. Scrub typhus developed in the infantry soldiers despite the doxycycline prophylaxis taken by them hence the possibility of *O.tsutsumugashi* resistant to doxycycline was proved [27].

In Taiwan, Lai CH et al., reported cases of scrub typhus showing delayed defervescence to doxycycline. The fever persisted in these patients three days despite starting doxycycline therapy. Infections by resistant strains or virulent strains may result in a poor response to Doxycycline [28]. If there is inadequate concentration of Doxycycline in infections sites this may lead to a poor response to Doxycycline. A severe disease and some factors of the infected hosts may also lead to a poor response to Doxycycline [29,30]. There is a report of an occurrence of meningoencephalitis in a patient with scrub typhus who was being treated with doxycycline [29].

In Northern, eastern and southern India, scrub typhus is rampantly present. In scrub typhus resistant to doxycycline central nervous system involvement like meningitis and meningoencephalitis is common [30,31]. There is a re-emergence of scrub typhus in the present days. In endemic areas, the magnitude of this problem is underestimated. Doxycycline-resistant scrub typhus is becoming a cause of meningitis in India [32].

Wangrangsimakul T reported a patient from Korea with doxycycline-resistant scrub typhus. Even after 96 hours of doxycycline treatment, he continued to have fever and myalgia. When clarithromycin was added he promptly responded to treatment. Either virulent strains or resistant strains of *O.tsutsumugashi* could have caused the delay in response [33].

The macrolide Azithromycin has certain advantages over chloramphenicol and tetracyclines. Like chloramphenicol, it does not cause marrow suppression and like tetracycline it does not affect the growing bones and teeth [34]. It can be readily given in children and in pregnant women. Doxycycline-resistant *O.tsutsumugashi* is emerging. So, it is vital to suspect infection with resistant strains in cases of scrub typhus. A sustained fever after administration of doxycycline points out to a resistant infection and alternate antibiotics should be tried [34].

CONCLUSION(S)

Scrub typhus is an acute febrile illness. Non specific signs and symptoms occur in scrub typhus. It is a zoonosis. Scrub typhus is endemic in Asia and Pacific islands. It was a dreaded disease of the preantibiotic era which caused many deaths in the far eastduring the second world war. Subclinical disease, or organ failure or even death can occur in scrub typhus. A late presentation or a delayed diagnosis or resistance can cause a patient to die of scrub typhus. Clinicians should be aware that scrub typhus can be resistant to Doxycycline. In such cases the organism responds to macrolides like Azithromycin.

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