

(CASE REPORT)



The silent killer: ARDS in scrub typhus patients

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Abstract

Rickettsial diseases are an important cause of fever of acute onset and short duration. Transmitted by mites, rickettsial infections are an important differential when treating patients with fever exposed to such an environment. The common clinical manifestations include apart from fever, a viral rash, presence of eschar, evidence of loss of fluid in third spaces like pleural effusion and ascites. Laboratory investigations that favour rickettsial infections include presence of thrombocytopenia, leukopenia, hyponatremia, hypoalbuminemia. These findings on investigations should prompt a clinician to investigate for rickettsial infections particularly scrub typhus. Although the classical clinical picture is as described above, children can present with unusual presentation due to multiorgan failure resulting in a myriad of clinical presentations like respiratory distress, encephalitis etc. A high index of suspicion should be kept in such cases of multiorgan involvement for investigation and treatment of scrub typhus which is an easily treatable cause of multiorgan failure. **METHODOLOGY:** after taking informed consent from parents, we reviewed four cases of children between 7 to 10 years who presented in a tertiary care hospital with the complaint of fever of acute onset and subsequently developed acute respiratory distress syndrome (ARDS). They were subsequently diagnosed as scrub typhus and showed good response to doxycycline. **CONCLUSION:** scrub typhus as a cause of acute respiratory distress must be kept in mind in children presenting with acute onset fever. Although pathognomic, presence of an eschar does not predict the severity of disease. Definitive tests for scrub typhus may be negative in the initial phase of illness and must be interpreted with caution when dealing with such cases.

Keywords: Scrub Typhus; Acute Respiratory Distress Syndrome; Eschar; Hyponatremia

1. Introduction

Rickettsial diseases are zoonotic infections with acute fever. Scrub typhus, caused by the bacteria *Orientia tsutsugamushi* transmitted by *leptotrombidium* mites, is responsible for a potentially fatal tropical infection which is a grossly under recognised public health problem in India. (1) Despite being easily treatable with early diagnosis, rickettsial diseases can cause severe illness and death if left untreated. An estimated one million cases occur annually with a high case fatality rate. The incidence rate in India below or at 15yrs of age is 20.3%. (2) Some areas of country, scrub typhus accounts for up to 35-50% of acute undifferentiated febrile illnesses requiring hospital admissions. (3). While fever, nausea, and vomiting are common symptoms of scrub typhus, recent reports indicate an increasing incidence of multi-organ damage associated with this infection. We present four cases of patients admitted to a tertiary care hospital with undifferentiated febrile illnesses and subsequently diagnosed with scrub typhus. Two of these patients developed acute respiratory distress syndrome (ARDS) and other due to immediate management ARDS was averted. All patients were successfully treated with doxycycline and supportive care, including non-invasive ventilation. This case series highlights the importance of considering scrub typhus in the differential diagnosis of

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patients presenting with fever and respiratory symptoms, especially in endemic regions. Early diagnosis and prompt treatment are crucial to prevent severe complications such as ARDS. (4)

2. Case presentation

2.1. Case 1

7-year-old girl was brought to the hospital with severe fever and difficulty breathing. Upon examination, the child had severe respiratory distress (retractions and hypoxia) and systemic examination findings showed splenomegaly. Initial tests revealed normal except for anemia with thrombocytopenia. (Table 1) Chest Xray imaging reticulonodular opacities, air space consolidation, peribronchial infiltration. (Figure 1) The child was initially started on a high-flow nasal cannula, but her condition worsened, requiring escalation of respiratory support with continuous positive airway pressure (CPAP). Initial treatment was started with antibiotics (ceftriaxone). She continued to deteriorate and developed distributive shock (warm shock); non responsive to fluids and her condition remained critical, necessitating additional medication (noradrenaline) was added. Noradrenaline, a powerful vasoconstrictor was used to treat shock, was administered for 48 hours, resulting in improved blood circulation but her fever was still persisted. ELISA (IgM) for scrub was found positive and was started on doxycycline. Within 24 hours of beginning doxycycline, the fever subsided and in next 72-84 hours, her respiratory support was gradually reduced as her condition stabilized.

2.2. Case 2

A 8-year-old girl was brought to the hospital with a high fever. Upon examination, she was found to have significantly enlarged liver and spleen (hepatosplenomegaly) and initial tests for tropical infections including scrub typhus were negative, (Table1). She was started on an antibiotic ceftriaxone. Within 24 hours of admission, her breathing worsened with tachypnea and hypoxia with increased work of breathing, requiring immediate placement on continuous positive airway pressure (CPAP). Chest Xray was suggestive of reticulonodular opacities, air space consolidation, peribronchial infiltration, and pleural effusion (Figure2) , lung ultrasound revealed pulmonary edema and ultrasound abdomen revealed mild ascites. During the course in hospital, the child developed a dark, crusty lesion (eschar) on her inner thigh. ELISA (IgM) for scrub typhus was found positive along with eschar and other symptoms, the child was treated with doxycycline. Her fever subsided within 24 hours, indicating a positive response to the treatment. However, she remained on respiratory support for three days.

2.3. Case 3

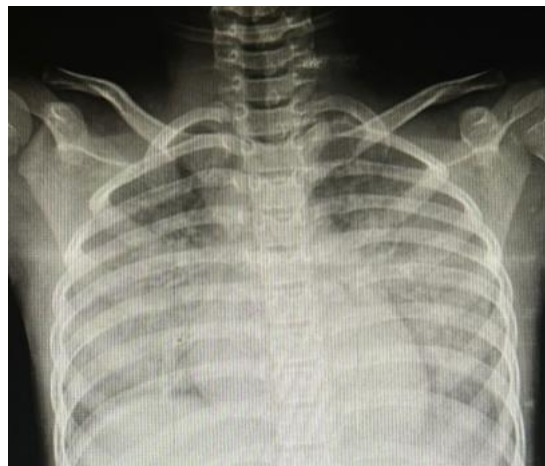
A 10-year-old girl was brought to the hospital with a high fever. Upon examination, she was found to have significantly enlarged liver and spleen (hepatosplenomegaly) and two dark, crusty lesion (eschar) on her inner thigh (figure 4). Initial investigations for tropical infections were negative (Table1), and Xray revealed reticulonodular opacities, air space consolidation, peribronchial infiltration, and pleural effusion and lung ultrasound revealed pulmonary edema. The child had minimal respiratory distress with tachypnoea and hypoxia. Low flow nasal prong oxygen therapy was given for 24 hours. Suspecting scrub typhus based on the eschar and other symptoms, the child was sampled for ELISA (IgM) for scrub typhus and immediately started with doxycycline. Her fever subsided within 48 hours, indicating a positive response to the treatment. Since prompt management was given at arrival, the child did not have any further worsening of respiratory difficulties. Overall, her condition improved significantly after receiving treatment for scrub typhus.

2.4. Case 4

A 9-year-old girl was brought to the hospital with a high fever. Upon examination, she was found to have significantly enlarged spleen. Initial tests for tropical infections including scrub typhus were negative, (Table1) and she was started on antibiotic ceftriaxone. The peripheral smear suggested of falciparum infection and was started on artesunate combined therapy but despite which the child developed respiratory worsening with tachypnoea and hypoxia with increased work of breathing, requiring immediate placement on continuous positive airway pressure (CPAP). Chest Xray revealed reticulonodular opacities, air space consolidation, peribronchial infiltration, and lung ultrasound revealed pulmonary edema and ultrasound abdomen revealed mild ascites. During the course in hospital, the child developed a dark, crusty lesion (eschar) on her inner thigh. ELISA (IgM) for scrub typhus was found positive along with eschar and other symptoms, the child was treated with doxycycline. Her fever subsided within 24 hours, indicating a positive response to the treatment. She required respiratory support for five days.

Table 1 Lab Investigations

Date	CASE 1	CASE 2	CASE 3	CASE 4
HB	8.6	8.7	8.4	7.2
HCT	26.7	27.1	26.3	23.1
TLC	12,000	5600	11100	7800
DLC	N-77 L-18.6 M-3	N-64 L-27 E-1 M-3	N-77 L-18.6 M-3	N-74 L-21 E-1 M-3
PLT	63000	79000	109000	53000
T.BIL/D.BIL	3.2, 0.2	0.4/0.2	0.5/0.2	0.6/0.3
SGOT/SGPT	78/98	133/75	115/67	100/95
TP/ALB	3.5/2.1	5.9/3.4	4.9/2.6	5.5/2.4
BUN/Cr	35/0.7	31.8/0.9	45/0.8	56/0.7
Na/K/Ca	131/4.2/9.1	134/4.1	129/3.6/8.7	140/4.0/7.5
IGM DENGUE	NEGATIVE	NEGATIVE	NEGATIVE	NEGATIVE
IGM TYPHIOD	NEGATIVE	NEGATIVE	NEGATIVE	NEGATIVE
BLOOD C/S	No growth	No growth	No growth	No growth
MALARIA	NEGATIVE	NEGATIVE	NEGATIVE	POSITIVE
ELISA IGM SCRUB	POSITIVE	POSITIVE	POSITIVE	POSITIVE
RFA IGM SCRUB	NEGATIVE	NEGATIVE	NEGATIVE	NEGATIVE
OSI (OXYGEN SATURATION INDEX)	8	7.5	-	9
SETTINGS (CPAP)	Max-80/9	Max-70/9	Nasal prongs	Max-80/9
2D Echo	Normal EF	Normal EF	Normal EF	Normal EF

**Figure 1** Chest Xray showing Reticulonodular opacities

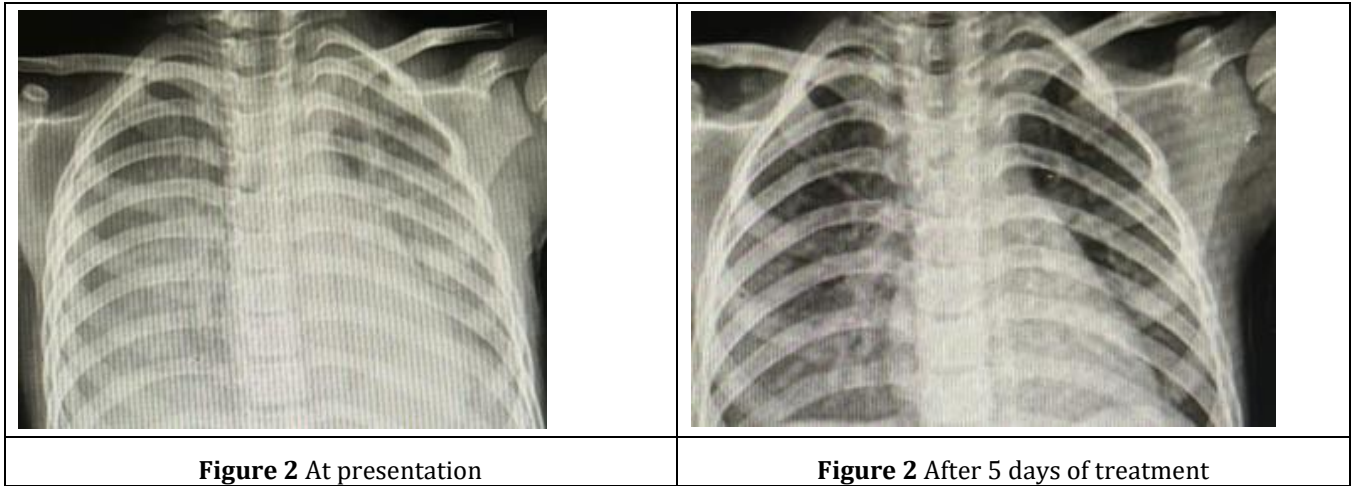


Figure 3 Eschar

3. Discussion

Scrub typhus, one of the commonest rickettsial infections, is endemic to “tsutsugamushi triangle” and has been reported from the various parts of the Indian subcontinent. (2) Scrub typhus, a potentially fatal rickettsial infection, is often associated with nonspecific symptoms. (5) The infection is caused by bacteria called *Orientia tsutsugamushi* spreads from person to another by the bite of a mite infected with the bacteria. The pathogenesis includes initial multiplication at inoculation site and forms a papule. It later ulcerates and becomes necrotic, evolving into an eschar, with regional lymphadenopathy. (6) The bacteria are further carried by the immune cells and escapes phagosome, replicates in cytoplasm of immune cells and endothelial cells. The bacteria are then disseminated to multiple organs through endothelial cells and macrophages resulting in multiple clinical presentations.

The clinical symptoms include

- Papule followed by an eschar at the site of chigger feeding (67%)
- Fever
- Headache
- Myalgia
- Diarrhoea, abdominal pain, nausea and vomiting (6)
- Regional lymphadenopathy
- Maculopapular rash
- Severe cases- encephalitis and interstitial pneumonia.

This presentation of ARDS in pediatric age group within short period of illness has been highly noted recently. Severe scrub typhus is associated with the involvement of various organs. Pulmonary manifestations include bronchitis and interstitial pneumonia which may progress to ARDS. (7)

3.1. Development of ARD

Vascular Damage: The bacteria can damage endothelial cells, leading to increased vascular permeability. This causes fluid leakage from blood vessels into the surrounding tissues, including the lungs.

Pulmonary Edema: The increased vascular permeability can result in pulmonary edema, where excess fluid accumulates in the alveolar space. This can interfere with ventilation and perfusion mismatch and oxygen exchange, making it difficult to breathe.

Inflammation: The body's immune response to the infection can also contribute to ARDS. Inflammation can cause damage to the lungs and further impair their function.

It was observed in 20.5% of cases by Devasagayam *et al.* while 19.1% required mechanical ventilation. Varghese *et al.* observed respiratory system dysfunction as a part of multiple organ dysfunction syndrome (MODS) in 76.9% of cases. The diagnosis was classically established earlier by the Weil–Felix reaction. Serologic tests like indirect immunofluorescence or enzyme-linked immunosorbent assay to detect IgM *O. tsutsugamushi* antibodies are used nowadays, with molecular tests such as quantitative polymerase chain reaction being restricted to high-resource settings. The mainstay of treatment of severe scrub typhus is doxycycline 2.2mg/kg twice daily for 7days orally or intravenously. Azithromycin can also be used as an alternative. While the response to treatment is often dramatic, failure of defervescence within 48 h should raise the suspicion of an alternative diagnosis. Treatment should be initiated while awaiting lab confirmation as delay in treatment might prove to be fatal. In our case, timely initiation of specific treatment halted the need for ventilation. The initial clinical symptoms of scrub typhus are non-specific like other viral illnesses or malaria. There is a good chance of misdiagnosis due to lack of awareness of the disease and non-availability of the specific serological test. The diagnosis may be missed in the absence of rash or a typical eschar, or if the eschar is present in hidden areas of the body, such as the axilla or scrotum. (2)

4. Conclusion

Scrub typhus, a neglected tropical disease, is often overlooked as a potential cause of acute undifferentiated febrile illness. Despite its significant morbidity and mortality, its nonspecific symptoms can lead to delayed diagnosis. A thorough clinical evaluation is essential for identifying scrub typhus, especially in patients presenting with acute respiratory distress syndrome (ARDS). Recognizing the disease's atypical presentations and potential complications is crucial for timely diagnosis and treatment. By increasing awareness and improving diagnostic capabilities, healthcare providers can reduce the burden of scrub typhus and improve patient outcomes.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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