

Case Report

Typhus pneumonitis – A rare and life-threatening complication of scrub typhus

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Introduction

Scrub typhus is a disease caused by a proteobacterium named *Orientia tsutsugamushi* (OT). Majority of cases occur in rural areas of south and southeast Asia including India and Indonesia, far eastern countries such as China and Japan and northern Australia. Scrub typhus is transmitted through the bite of infected larval mites called chiggers. The most common symptoms of scrub typhus are fever, headache, body aches and, sometimes, rash [1]. Multi organ dysfunction is not uncommon in severe infection. Involvement of the respiratory system, the cardiovascular system and liver with significant mortality is well documented [2]. Typhus is also implicated as a causative agent of acute encephalitis syndrome in Bihar, India [3].

Case presentation

A 31-year-old lady from northern Sri Lanka presented to Teaching Hospital, Jaffna with high grade fever accompanied by headache and generalised body ache of 03 days duration. She had intractable nausea and vomiting since the onset of fever along with oliguria and loose stools.

On examination, she was febrile and hypovolaemic. She had a painless eschar in the right inguinal region (Figure 1) with associated right inguinal lymphadenopathy. She was tachypnoeic, tachycardic and had a blood pressure of 100/80 mmHg. Auscultation of the lungs revealed bilateral lower zone fine crepitations. Her oxygen saturation (SpO₂) on room air was 96% at the time of admission. She did not have any other evidence of cardiac failure.

A clinical diagnosis of scrub typhus was made, and she was started on oral doxycycline 100 mg 12 hourly along with antiemetics and paracetamol.

On the next day, her respiratory symptoms worsened, and she was prescribed supplementary oxygen by scale 1, targeting a saturation of (92- 96%). Full blood count (FBC) showed a normal leucocyte count with mild anaemia and thrombocytopenia. C-reactive Protein (CRP) was

elevated. Aspartate transaminase (AST), alanine transaminase (ALT) and alkaline phosphatase (ALP) levels and a serum creatinine (S.cr) that was near the upper limit of normal (Table 1). Chest -X Ray showed bilateral multi lobar airspace shadowing (Figure 2) 12-lead ECG was normal. Two-dimensional echocardiogram (2D Echo) showed normal wall movements with preserved biventricular functions. Sonography of the abdomen was unremarkable except thin pericholecystic oedema and left sided mild pleural effusion. Arterial blood gas (ABG) analysis showed evidence of hypoxaemic (type 1) respiratory failure.



Figure 1: Eschar found at the inguinal region in the patient

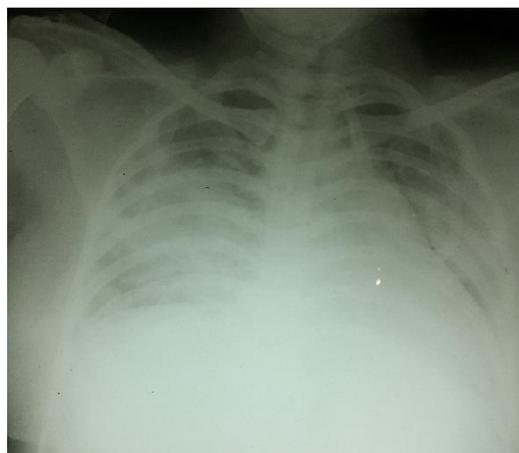


Figure 2: CXR (Posteroanterior view) shows diffuse inflammatory shadows

She was started on oral azithromycin 500 mg daily in addition to oral doxycycline. As her respiratory symptoms worsened, intravenous (IV) dexamethasone 8 mg t.i.d was started. A high-resolution computed tomography (HRCT) of the chest was taken which showed bilateral multi-lobar air space consolidation with a predilection for the peribronchovascular areas. There were no centrilobular nodules or interlobular septal thickening in the HRCT (Figure 3).

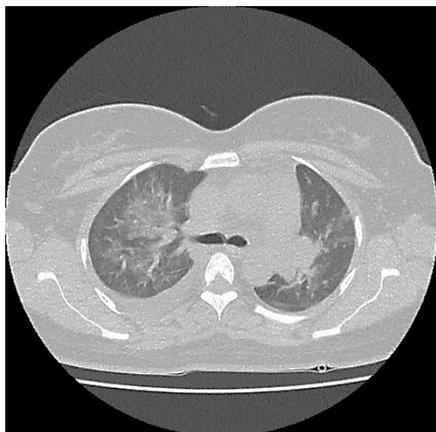


Figure 3: HRCT/Chest shows bilateral airspace consolidation predominantly in the upper lobes

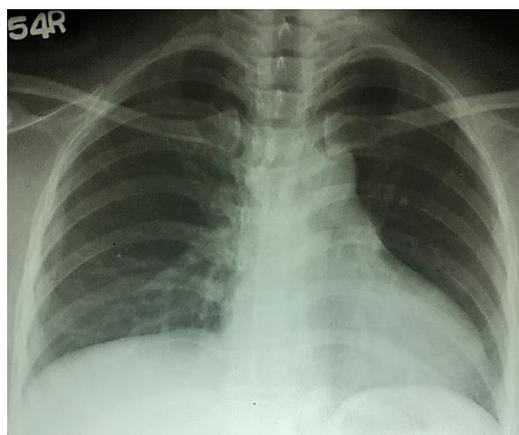


Figure 4. Repeat CXR on Day 13 after discharge shows complete resolution of pulmonary shadows

Blood culture was negative and test for typhus antibodies were positive by the SD BIOLINE® Tsutsugamushi immunochromatographic assay.

Over the following days, she showed remarkable improvement. Her oxygen support was tailed off while antibiotics were continued. Repeat chest radiography showed partial resolution. She was mobilized from the bed on day 5. Subsequently she was discharged on day 7 of admission on oral doxycycline for a total of fourteen days.

She was reviewed eight days after discharge and reported feeling progressively better. Follow up blood investigations showed resolution of haematological and biochemical abnormalities. (Table 1). Follow up CXR showed complete resolution of the pulmonary infiltrate (Figure 4).

Table 1: Summary of investigations

Investigations	Days since onset of fever							
	D ₃	D ₄	D ₅	D ₆	D ₇	D ₈	D ₁₀ (D)	D ₁₆ (R/V)
FBC								
WBC ($\times 10^3/\mu\text{L}$)	9.67	10.22	8.93	9.17	5.71	-	10.45	6.89
N (%)	78.8	79.7	71.5	64.8	52.2	-	57.2	23.7
L (%)	17.0	17.7	23.7	31.8	40.8	-	36.5	62.0
E (%)	0	0	0.1	0.1	0	-	0.4	0.4
Hb (g/dL)	10.2	10.6	10.2	9.6	8.2	-	9.5	10.2
Plt ($\times 10^9/\mu\text{L}$)	117	110	96	105	156	-	259	315
ALT (U/L)	-	135	132	189	477	536	464	128
AST (U/L)	-	176	206	357	631	505	150	53
ALP (U/L)	-	278	300	442	435		303	220
SCr ($\mu\text{mol/L}$)	95	95	91	59	52	63	55	58
SE								
Na (mmol/L)	137	137	140	146	141	140	138	137
K (mmol/L)	4.6	3.4	3.4	4.0	3.9	3.7	3.7	4.1
CRP (mg/L)	313	307	265	157	51	31	12	2.8
ESR (mm/1 st hour)	-	75	-	-	-	-	-	-
Typhus antibody	-	-	Positive	-	-	-	-	-
Blood culture	-	-	Negative	-	-	-	-	-
Troponin I	Negative	-	-	-	-	-	-	-

FBC, full blood count; WBC, white blood cells; N, neutrophils; L, lymphocytes; E, eosinophils; Hb, haemoglobin; Plt, platelets; ALT, alanine transaminase; AST, aspartate transaminase; ALP, alkaline phosphatase; S.cr, serum creatinine; SE, serum electrolyte; Na, sodium; K, potassium; CRP, c-reactive protein; ESR, erythrocyte sedimentation rate; (D), day of discharge; (R/V), day of review

Discussion

Scrub typhus usually presents as an acute febrile illness around 7 to 10 days after the bite of an infected larval mite. Intense headache, generalized myalgias, non-pruritic, macular or maculopapular rash and eschar are common symptoms. Eschar, a painless lesion with a black crust, is characteristic of scrub typhus but could be easily missed [4]. Prevalence of an eschar in typhus patients is highly variable (7-97%) [5]. Eschars are rare among patients in countries of South-East Asia and, indigenous persons in typhus-endemic areas are likely to have less severe illness, often without rash or eschar [6]. Localized or generalized lymphadenopathy, acute kidney injury, respiratory symptoms, gastrointestinal symptoms, encephalitis and meningitis are also known to occur in scrub typhus. Acute respiratory distress syndrome (ARDS), pericarditis and myocarditis are rare but potentially lethal complications [4]. Scrub typhus can lead to multiorgan failure and death with a reported median mortality rate of 6 percent. Mortality rates are higher in older patients and in the presence of myocarditis, delirium, and pneumonitis. Delays in therapy is also associated with a higher risk of complications [4].

Abnormalities in laboratory investigations include thrombocytopenia and a rise in liver transaminases, bilirubin, and creatinine. Most patients have a normal white blood cell count. Leukopenia or leucocytosis can also occur [4]. CRP and ESR are usually elevated [7]. In this case, white cell counts were persistently within the normal range. Liver enzymes (AST > ALT) and ALP were elevated. Both ESR and CRP were significantly high. Serum creatinine was elevated from her baseline. (Table 1)

A diagnosis of scrub typhus may be established by serology, tissue biopsy, culture or polymerase chain reaction (PCR). The indirect fluorescent antibody (IFA) test is the mainstay of serologic diagnosis. A panel of antigens from common strains of OT should be used to detect convalescent antibodies because of the organism's antigenic heterogeneity [4]. In Sri Lanka, all three main OT genotypes have been implicated in scrub typhus, and the majority fell into the Karp related clade [8]. In endemic areas, the serologic diagnosis of acute infection must be differentiated from background immunity against scrub typhus. A conclusive diagnosis of acute scrub typhus infection using the IFA assay should be based upon at least a fourfold rise in titres in paired samples drawn at least 14 days apart. A single measurement may be informative when there are locally validated criteria for a positive test. An enzyme-linked immunosorbent assay and a passive hemagglutination assay are also used in the diagnosis. The Weil Felix test is no longer used due to low specificity and sensitivity [4]. In this case, a rapid immunochromatographic assay (SD BIOLINE[®] Tsutsugamushi rapid kit), that uses strains of Karp, Kato and Gilliam, was used. According to the manufacturers, this test demonstrated a sensitivity of 99% and specificity of 96% and serological agreement of 97.5% with IFA [9]. Another study showed the sensitivity and specificity to be 98.4% and 66.7% respectively, and it was found to be more sensitive than the standard IFA in acute specimens [10]. Although culture of OT or detection of nucleic acid in blood and eschar tissue by polymerase chain reaction (PCR) technology definitively establish the diagnosis, these tests are not widely available [4].

Biopsy of the eschar or skin rash is also useful and may show histologic changes such as focal areas of cutaneous necrosis encircled by an area of intense vasculitis, with perivascular lymphocytes and macrophages. Thrombosis of small blood vessels may occur. Observation of

these typical histologic changes is of diagnostic value even in the absence of serological evidence.

Pulmonary involvement in scrub typhus is significantly associated with morbidity and disease severity [11]. According to studies, around 58% of patients with scrub typhus show symptoms of pulmonary involvement [5] and around 78% have chest radiographic abnormalities [11] but the exact incidence of clinically significant typhus pneumonitis is not clear. The pathogenesis of scrub typhus pneumonitis is explained as an immunological reaction due to vasculitis secondary to direct endothelial injury or direct injury by the organism itself.

Based on the analysis of chest radiographs interstitial pneumonia (IP) is the commonly observed lung abnormality in patients with scrub typhus, followed by pleural effusion, air space consolidation, increased cardio thoracic ratio, hilar prominence and segmental atelectasis. Commonly observed CXR features of IP are reticular opacities and septal lines. Patients with CXR changes compatible with IP were found to have a higher incidence of hypoxia, hypotension, severe thrombocytopenia and hypoalbuminemia [12].

Specific HRCT findings in patients with scrub typhus IP include thickening of the bronchial wall, nodules in a centrilobular pattern and interlobular septal thickening. Involvement of the lung parenchyma is usually bilateral with lower zone predilection [12]. But in our case bilateral upper lobes were involved, bilaterally.

Doxycycline (100mg/12hourly, orally/IV) for 5-7 days is the preferred treatment. Chloramphenicol also could also be used (250 to 500 mg orally or IV /six hourly). Azithromycin may be an alternative in case of doxycycline-resistant strains and in pregnancy. Combination therapy with doxycycline and rifampin appeared to be more effective in some studies [13]. Antibiotic treatment is similar for typhus pneumonitis as with uncomplicated typhus fever. Studies on the use of corticosteroids in complicated severe typhus infections showed that adjuvant use of corticosteroids in anti-inflammatory or immunosuppressive doses, in addition to antibiotics, may not have detrimental effects on the disease course. But their role as a treatment to alter the clinical course or improve mortality is still not established [14].

This patient was treated with a combination of oral doxycycline and oral azithromycin. IV dexamethasone was given in this patient based on the safety profile observed in previous studies despite the lack of evidence in terms of benefit. A vaccine against OT is not available. Chemoprophylaxis with doxycycline is effective. Mite control is also useful but over-keen efforts may paradoxically pave the way for an increase in the disease [13].

Conclusions

Typhus pneumonitis is a life-threatening complication of scrub typhus. The treating physician should be aware of it as early detection will help in proper management. Trial of steroids, despite lack of evidence on efficacy, was not found to be detrimental.

Acknowledgements

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