Leukocytoclastic Vasculitis

A peculiar presentation of Scrub typhus

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Abstract
Scrub typhus is a disease endemic to the Indian subcontinent caused by the obligate intracellular pleomorphic organism, Orientia tsutsugamushi. Scrub typhus among other acute febrile illnesses present with prodromal symptoms of fever, malaise, myalgia, anorexia followed by a distinct maculopapular rash, hepatosplenomegaly, and lymphadenopathy. In this case report, we present a patient who developed a rare cutaneous vasculitis secondary to infection with Orientia tsutsugamushi. After performing the Weil Felix test, a diagnostic titer of 1:640 against OX-K was obtained. Furthermore, a skin biopsy was carried out which confirmed the diagnosis of leukocytoclastic vasculitis. The patient was treated with Doxycycline and showed a drastic improvement in his symptoms.

Keywords: Scrub Typhus, Rickettsia; Vasculitis; Doxycycline.

Introduction
Scrub typhus is a disease endemic to the Indian subcontinent caused by the obligate intracellular pleomorphic organism, Orientia tsutsugamushi. This organism is transmitted naturally through
the Leptotrombidium mite population and is accidentally acquired in humans via the bite of a mite as a dead-end host. Scrub typhus among other acute febrile illnesses present with prodromal symptoms of fever, malaise, myalgia, anorexia followed by a distinct maculopapular rash, hepatosplenomegaly, and lymphadenopathy. Rarely, it can even progress to septic shock/multi-organ failure. As in every disease, scrub typhus can have some peculiar manifestations. There have been previous case studies reporting features of hemophagocytic syndrome,\(^1\) epididymo-orchitis,\(^2\) acute severe monoarthritis,\(^3\) and Guillain Barre syndrome.\(^4\) In this case report, we present a patient who developed a rare cutaneous vasculitis in setting of Orientia tsutsugamushi infection with good response to doxycycline.

**Case Report**

A 28-year-old man farmer presented with high grade, intermittent fever (102°F), vomiting and generalized muscle pain to a local primary center and was treated with antipyretics. Four days later, the patient developed multiple palpable purpuric eruptions predominantly affecting the lower limbs. Thereafter, the patient was subsequently transferred to our tertiary care hospital in 2021.

On examination, the patient’s vital signs were stable and he was afebrile when he presented to our hospital. Skin examination revealed multiple palpable purpuric eruptions arranged in a retiform pattern with a dusky necrotic center and peripheral rim of erythema distributed symmetrically over bilateral lower limbs [Figure 1A-1C]. The mucosa, palms and soles were spared. The rest of the systemic examination was deemed to be normal.

A panel of laboratory investigations were carried out to determine the etiology [Table 1]. A routine urinalysis was unremarkable, confirming no renal involvement. Antinuclear antibody (ANA) and antineutrophil cytoplasmic antibodies (ANCA), serum C3 and C4 complement levels were negative, making vasculitis due to autoimmune inflammatory disorders less likely.

This constellation of findings is unique to acute febrile illnesses. Therefore, a panel of serum studies were performed to determine the organism. Subsequently, leptospirosis, dengue (NS1 Ag & anti-dengue IgM), malaria, and Hepatitis B & C were ruled out.
However, a Weil Felix test (WFT: tube agglutination) was performed and a diagnostic titer of \( >1:640 \) against OX-K was obtained. The skin biopsy done from the lesion revealed necrotizing vasculitis [Figure 2]. In most cases, a skin biopsy is not routinely performed if clinical and serological criteria for scrub typhus are met. However, due to the rare manifestation of this disease, a skin biopsy was done in order to rule out other etiologies of vasculitis in the patient.

Hence, the patient was treated with doxycycline 100 mg twice daily. On day 3, improvement of the vasculitis and other symptoms were noticeable [Figure 1B] and the patient was discharged on Day 7 with an additional week of Doxycycline 100 mg twice daily. The patient followed up three weeks later with a significant improvement in his lesions [Figure 1D]. The patient provided informed consent to the publication of this case.

Discussion

Scrub typhus is a common cause of pyrexia of unknown origin in India due to its nonspecific clinical features. It is caused by the organism *O. tsutsugamushi* which was previously classified under the genus Rickettsia. However, due to different phenotypic and genotypic features, the organism has its own separate genus. In fact, it is a component of the Tsutsugamushi triangle formed by Northern Japan/East Russia (North), Afghanistan/Pakistan (West), and Northern Australia (South). There are three strains of *Orientia tsutsugamushi* namely Karp, Gilliam, and Kato strains. Infection with one particular strain does not confer immunity to infection with another strain.

The organism enters the human body via the bite of a chigger (trombuculid mite) where it multiplies and then disseminates through the blood and lymph. At the site of inoculation, necrosis of the skin occurs forming a black eschar, which is typical of scrub typhus. However, in the Indian subcontinent, a necrotic eschar can only be detected 10% of the time due to darker skin complexions of the majority of the population and bites located in hidden areas. Hence, serology or a high degree of clinical suspicion based on epidemiological data must be used to guide the diagnosis.

Scrub typhus usually targets a specific population encompassing rural populations predominantly involved in agriculture and those who engage in poor protective personal habits. Moreover,
overcrowding plays a huge role in dissemination of the disease as rodents often act as amplifiers of infection.

*O. tsutsugamushi* breaches the endothelial cell barrier creating vascular and perivascular lesions that ultimately cause vascular leakage and end-organ damage to multiple organs in the body. Once the organism successfully evades the innate human host defenses, various cytokines such as TNF-α, IFN-γ, and M-CSF are produced that results in the multitude of symptoms experienced by the patient. Both humoral and cellular immunity play a role in combating this organism. It involves the production of antibodies against *O. tsutsugamushi* which can be detected by the WFT and activation of macrophages and helper T cells (Th1) which secrete IFN-γ.

The pathophysiology of *O. tsutsugamushi* causing widespread endothelial damage involves disruption of the adherens junction of the endothelial cells. This results in increased vascular permeability, formation of inter-endothelial gaps, development of actin stress fibers, and change in the shape of the endothelial cells from polygonal to a spindle form. Furthermore, there is also increased vascular expression of nitric oxide and COX-2 expression by the endothelial cells, resulting in the production of prostaglandins. In addition, *O. tsutsugamushi* multiplies within the endothelial cells and via oxidative stress, destroys the integrity of the blood vessels. This can be established by immunohistochemical staining of endothelial cells which demonstrates rich deposits of the *O. tsutsugamushi* antigens.

Scrub typhus can present with a few dermatological manifestations that can overlap with other acute febrile diseases. The typical erythematous maculopapular rash and necrotic eschar can point to a diagnosis of scrub typhus, especially in an area of high endemicity. Moreover, the site of the rash can help differentiate between rickettsial diseases. A maculopapular rash distributed across the trunk, sparing the face, palms and soles makes rickettsial spotted fevers an unlikely diagnosis. Other tropical diseases with a similar dermatological presentation include dengue, leptospirosis, enteric fever, malaria, and melioidosis.
Infectious causes of leukocytoclastic vasculitis are most commonly viral in origin such as hepatitis B (polyarteritis nodosa), hepatitis C (mixed cryoglobulinemia), cytomegalovirus, or parvovirus B19. Parasites, bacteria, rickettsia are lesser known culprits of systemic vasculitis. It is paramount to determine the underlying cause of the vasculitis, as this governs the treatment regimen.

The organism is mainly confined to the reticuloendothelial system resulting in hepatosplenomegaly and generalized lymphadenopathy along with other features like fever, myalgia, and a centripetally-distributed maculopapular rash. Complications include acute respiratory distress syndrome, acute renal failure, disseminated intravascular coagulation, meningoencephalitis, myocarditis, pericarditis, and acute hearing loss. It is imperative that serology be done in order to ascertain proper treatment. WFT is a heterophile agglutination test that can be used to diagnose scrub typhus infection. This test relies on the principle that an antibody triggered by a particular antigen can cross-react with antigens of other species. In this test, antibodies produced by *O. tsutsugamushi* cross-react with the antigen OX-K of *Proteus mirabilis*. In our patient, we received a titer of 1:640 which is above the diagnostic titer of 1:320. WFT only tests positive during the 2nd week of illness and has a low sensitivity and specificity as compared to the indirect fluorescent antibody (IFA) test and indirect immunoperoxidase (IIP) test. Even though IFA/IIP are more accurate and precise, WFT is used because of its cost-effective and swift results. A recent case report was published linking a case of Henoch-Schönlein purpura to scrub typhus which used indirect immunofluorescence to confirm the diagnosis (IgM antibody: 1:1024). This is an accurate and precise tool to corroborate the etiology. The current guidelines for the treatment of scrub typhus include doxycycline 100 mg twice daily. Alternatives such as chloramphenicol, azithromycin, tetracycline, and rifampicin can be used as second-line options. Treatment with doxycycline renders the patient afebrile within 48 hours. Due to the rarity of the necrotic eschar in the Indian population and nonspecific clinical features, a delay in the start of treatment increases the risk of developing complications and causing
irreversible damage. As a result, empirical therapy with doxycycline should be started without delay if there is a high degree of clinical suspicion.\textsuperscript{11}

**Conclusion**

Scrub typhus remains to be a common zoonotic disease in the Indian subcontinent which is often misdiagnosed or underdiagnosed. This may be due to overlapping clinical features of other tropical diseases, lack of highly sensitive and specific equipment for diagnosis in endemic areas, or delay in presentation. Cutaneous vasculitis secondary to \textit{O. tsutsugamushi} is an unusual manifestation of this disease and should be considered in endemic areas to avoid delay in treatment.

**Authors’ Contribution**

AV, RVA and SMP conceptualized the report. KP provided the pathology report of the skin biopsy. VMS analysed the skin findings and performed the skin biopsy. AV drafted the manuscript writing. RVA, RK, AD and SMP reviewed the manuscript and provided intellectual input. All authors approved the final version of the manuscript.

**References**


**Table 1: Laboratory investigations.**

<table>
<thead>
<tr>
<th>Lab Investigation</th>
<th>Value</th>
<th>Normal range</th>
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<tr>
<td>Haemoglobin (g/dL)</td>
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<td>13–17</td>
</tr>
<tr>
<td>Platelet count (cells/µL)</td>
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<td>1,50,000–4,00,000</td>
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<td>White blood cell count (cells/µL)</td>
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<td>Aspartate transaminase (IU/L)</td>
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<tr>
<td>Alanine transaminase (IU/L)</td>
<td>274</td>
<td>5–40</td>
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<tr>
<td>Alkaline Phosphatase (U/L)</td>
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<td>40 – 130</td>
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<td>Erythrocyte Sedimentation Rate (mm/hr)</td>
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<tr>
<td>C-Reactive Protein (mg/L)</td>
<td>40.92</td>
<td>0–5</td>
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**Figure 1:** Clinical image showing multiple, palpable purpuric lesions arranged in a retiform pattern with a dusky necrotic center and peripheral rim of erythema distributed symmetrically over bilateral lower limbs on day 1 (A) and day 3 (B). A close-up view of skin lesion over the left leg on day 1 (C) and a significant improvement in his lesions on day 21 (D).
Figure 2: Photomicrograph (H&E), (A: X 100) shows dermis with prominent vasculo-centric infiltrate. (B: X 200) shows vessels showing fibrinoid necrosis of vessel walls, dense infiltration of vessel walls by neutrophils with leukocytoclasis.