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Case Report

A rare presentation of common tropical fever, scrub typhus-purpura fulminans, lower limb arterial thrombosis and pulmonary artery thrombosis

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ABSTRACT

Purpura fulminans (PF) is an acute emergency condition manifested as purpuric rash secondary to thrombosis of microvasculature. It is rapidly progressive, can cause thrombosis in large as well as small vessels and tissue infarction. Although it is commonly associated with *Meningococcal* and *Streptococcal* infections, here we report this case of PF associated with scrub typhus infection. Our patient presented with generalised body rash and progressed to multiorgan dysfunction. On evaluation, common causes of PF were ruled out and eventually patient came out to be IgM scrub typhus serology kit test positive. Lower limb angiography and pulmonary artery angiography revealed vascular thrombosis. The patient started on IV antibiotics, other supportive managements , anticoagulation. Later the patient improved clinically, skin rash resolved with excoriations but developed gangrenous changes in both lower limbs. Hence the uncommon presentation of scrub typhus infection as purpura fulminans needs early identification and effective treatment to achieve mortality and morbidity benefit.

Keywords: Purpura fulminans, Scrub typhus, Pulmonary artery thrombosis, DIC, MODS, Arterial thrombosis

INTRODUCTION

Purpura fulminans (PF) is an acute emergency condition manifested as purpuric rash secondary to thrombosis of microvasculature, leading to acute and progressive hemorrhagic infarction of skin and disseminated intravascular coagulation (DIC).[1] It is a rapidly progressing fatal syndrome of intravascular thrombosis, circulatory collapse, and cutaneous infarction. Infectious PF is most often caused by *Meningococcal* and *Streptococcal* infections.[2] Other infectious causes are VZV, *Staphylococci*, leptospira, and malaria.[3,4] Amongst Ricketssial fevers, Rocky Mountain fever itself presents with PF as an intrinsic complication of disease pathophysiology whereas few case reports of PF with Indian tick typhus are published, but the same as a complication of scrub typhus is rare to find.

Scrub typhus is caused by gram-negative intracellular rickettsial bacteria *Orientia Tsutsugamushi*, spread by the bite of an infected trombiculid mite("chiggers", particularly leptotrombidium delicense).[5] It is endemic in part of the world known as the "Tsutsugamushi triangle", which extends from northern Japan and far-eastern Russia in the north, to the territories around the Solomon Sea into northern Australia in the south, and to Pakistan and Afghanistan in the west, having an incubation period of 9-18 days.[6] In around 50% of patients with scrub typhus, we get skin rash, about 35% of patients have characteristic skin lesions known as Eschar, and regional lymphadenopathy is also usually present. But the presence of extensive purpura, along with multiple site arterial thrombosis is an uncommon complication in cases of scrub typhus.

Here, we present a life-threatening, but relatively common case of tropical fever, scrub typhus presenting with atypical skin manifestations in form of PF with bullous eruptions and bilateral lower limb arterial thrombosis leading to bilateral multiple toe tip gangrene with pulmonary arterial thrombosis. This patient also had manifestations of severe sepsis, DIC, and multiorgan dysfunction syndrome (MODS).

CASE REPORT

Our patient was a 30-year-old male patient, resident of Seoni, MP, sales executive by occupation admitted to intensive care unit (ICU) with complaints of fever for 6 days, abdominal pain for 5 days, bilateral lower limb painful swelling for 4 days, and rash predominantly over the distal part of all 4 limbs since 2 days. The rash appeared first on bilateral lower limb distally that progressed proximally up to the third of the thigh then gradually progressed to the upper limb, abdomen and chest.

On examination, he was conscious, oriented, responding to oral commands, and vitally stable. Icterus was present. Bilateral gross edema feet were present extending up to the middle third of the leg. Calf tenderness was present. A reticular Rash was visible involving both lower limbs up to the thigh, both upper limbs up to the shoulders and abdomen.

Gangrenous changes were visible over toes of both lower limbs. Eschar was present over the left thigh of the patient. No signs of meningeal irritation were present. On auscultation patient had coarse crepitations in bilateral lung fields.

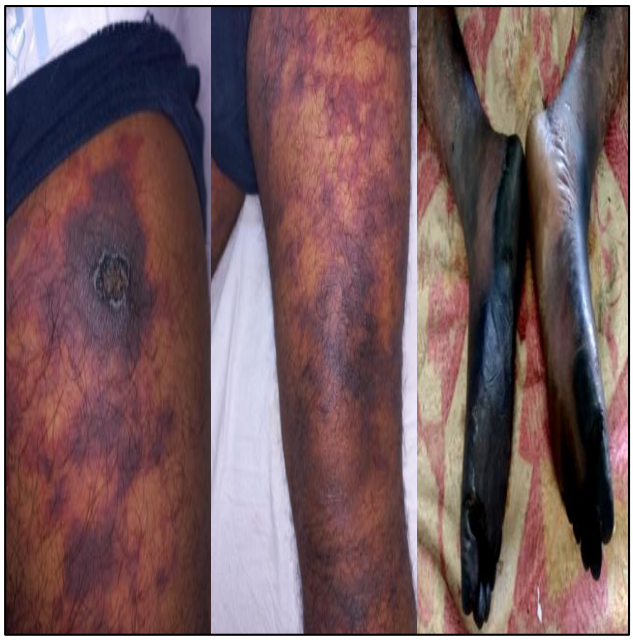

Figure 1: Reticular rash over lower limbs associated with eschar and gangrenous changes over b/l feets.

There was no significant travel history. He had no co-morbidities. History of occasional alcohol intake was present.

Routine laboratory investigations revealed hemoglobin-13.2, leucocytosis (TLC-33000/ cumm, 72% granulocytes, 21% lymphocytes), severe thrombo-cytopenia (19,000/ cumm, raised urea (89 mg/dl) and creatinine (1.7 mg/dl), raised liver enzymes with increased serum bilirubin (SGPT-144 IU; SGOT-122 IU, total bilirubin 8.6 mg/dl, direct 7.8 mg/dl, indirect 0.8), INR-1.56, ApTT-37.5 sec, D-dimer-8900. serum procalcitonin-2.12. Arterial blood gas analysis revealed compensated metabolic acidosis, which improved with fluid resuscitation. Pt's urine output was adequate. The patient was started on broad-spectrum antibiotics [IV meropenem and IV metronidazole] in view of sepsis and multiorgan dysfunction. On 2nd day of admission, pt had an episode of mild epistaxis and INR was also marginally deranged. Thus, pt was also transfused with fresh frozen plasma (FFP). Serology was negative for malarial parasite; dengue and Leptospira. Acute hepatitis profile (IgM hepatitis A virus, IgM hepatitis E virus, hepatitis B surface antigen, hepatitis C virus antibodies) negative. Vasculitis workup (antinuclear antibody profile, perinuclear antineutrophil cytoplasmic antibody, cytoplasmic anti-neutrophil cytoplasmic antibody), didn't reveal any abnormality. Blood culture and urine culture were sterile. Serology to *Orientia tsutsugamushi* (IgM scrub typhus) done with rapid kit test (sensitivity 98.03%, specificity 97.60% as per details provided by kit manufacturer) was positive.

The patient was immediately started on IV doxycycline 100 mg BD. In view of lower limb gangrenous changes, CT lower limb angio-venography was done, which was suggestive of thrombosis of distal 1/3rd of the right anterior and posterior tibial artery, faint contrast opacification in bilateral dorsalis pedis artery. The patient subsequently developed bullous eruptions on the purpuric lesions. The patient developed hemoptysis in due course of hospitalization, CT pulmonary angiography was done, which revealed a focal eccentric filling defect in the segmental branch from the right descending lobar artery along the medial basal segment of the right lower lobe suggestive of thrombosis. Hence the patient was started on anticoagulation (initially injectable then oral) in view of pulmonary artery thrombosis, and antiplatelet drugs in view of lower limb arterial thrombosis. The patient's Skin biopsy revealed epidermal necrosis and diffuse basal cell vacuolation along with a dermal focus of microthrombi and hemorrhages. PCR for scrub antigen from serum and skin scraping samples were also sent, which turned out to be negative but the samples were sent on the 10th day of admission due to the non-availability of the test at the institution.

The patient improved clinically after 8 days of doxycycline treatment and was shifted to the general ward. The serum creatinine declined, though the liver

enzymes were still elevated, and serum bilirubin decreased from 8.6 to 2.5 mg/dl. The retiform rash started to fade with excoriations and scab formation. As the patient improved clinically, he was discharged after a total of 14 days of hospital stay.

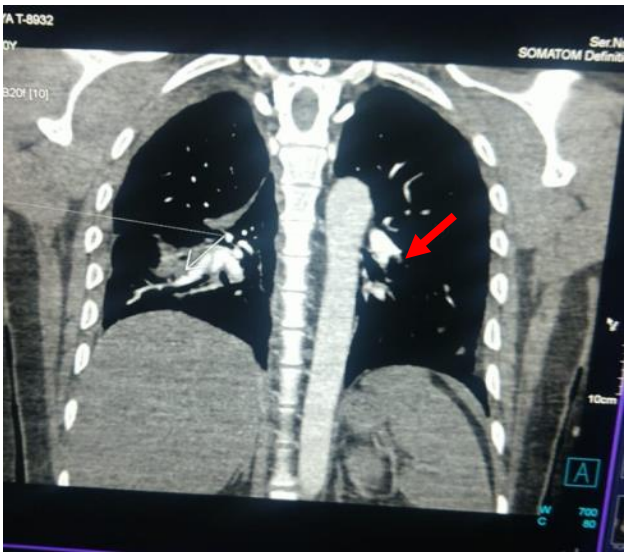

Figure 2: CTPA coronal section showing eccentric filling defect.

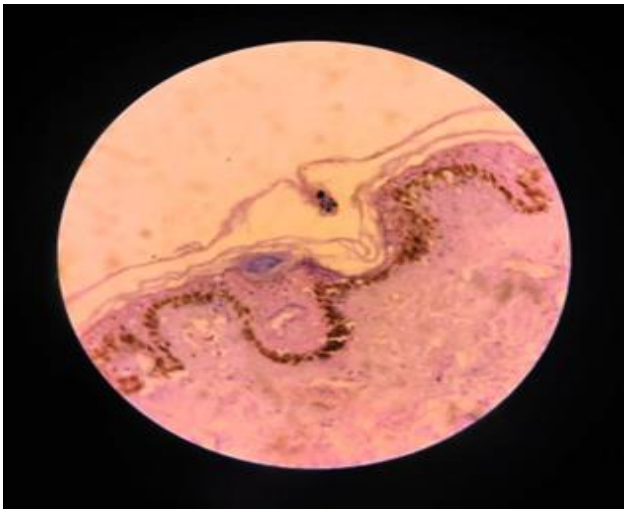

Figure 3: Skin biopsy microscopy.

DISCUSSION

Scrub typhus caused by *Orientia Tsutsugamushi* is a disease under Rickettsial infections spread by the bite of an infected mite, leptotrombidium-deliense.

The disease is usually characterized by Eschar and regional lymphadenopathy. But the presence of PF, and multiple site arterial thromboses as in our case is a very uncommon complication in cases of scrub typhus.

Weil Felix test based on detection of antibodies to various proteus antigens with cross-reacting epitopes of genus *Rickettsiae* (except *Rickettsia Akari*) has low sensitivity and specificity for the diagnosis of these infections.7 Thus major limitation of the WF test is the cross-reactivity among several Rickettsial species.

Specific investigations like immunofluorescence, Western blot, or polymerase chain reaction-based tests, which help make accurate diagnosis of Rickettsial diseases expensive and not readily available.[7]

PF progresses rapidly and can herald multi-organ failure or large vessel thrombosis.

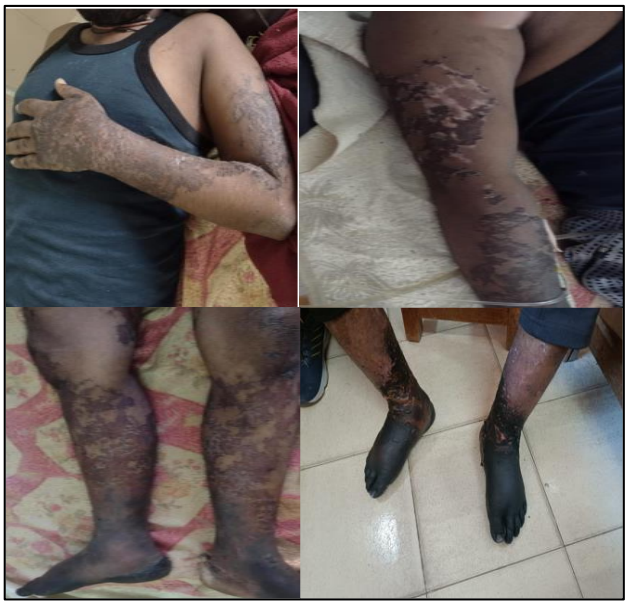

Figure 4: resolving rash with excoriations and scab formation and persistent gangrenous changes.

Initially, PF appears as well-demarcated erythematous macules and progresses rapidly to develop irregular central areas of blue-black hemorrhagic necrosis, surrounded by a thin border of erythema that fades into adjacent uninvolved skin. Hemorrhage into the necrotic dermis results in painful, dark, and raised lesions, sometimes with vesicle or bulla formation.[8] Our patient also had painful vesicle and bulla formation which developed 2-3 days after the appearance of rash.

Early PF lesions may be reversible with therapeutic intervention but established lesions often progress within 24 to 48 h to full-thickness skin necrosis or more extensive soft tissue necrosis that may require surgical debridement, fasciotomies, or amputation.[9] Our patient also presented 2-3 days after the appearance of rash, and the lesions already had gangrenous involvement of multiple toes bilaterally on presentation. On discharge also, the patient had these persistent cutaneous gangrenous changes.

Despite the devastating clinical course associated with PF, the mechanism of PF remains poorly understood. In

severe sepsis, PF follows the acute inflammatory response, due to systemic activation of the coagulation and complement pathways along with endothelial dysfunction causing DIC.[10] Very often in DIC complicating sepsis, there is also a local defect in the activation of Protein-C on endothelium in small vessels leading to further loss of local anticoagulant and anti-inflammatory protein-C (PC) activity. This initiates micro-vascular thrombosis in the dermis causing PF.[11]

Severe acquired deficiency of protein C and dysfunction of the protein C-thrombomodulin pathway as well as other systems that exert a negative regulatory effect on coagulation have also been implicated.

As PF is most commonly associated with sepsis, accordingly, most patients who present with PF are initially assumed to have a septic cause and are managed with full supportive care, and urgent broad-spectrum antimicrobial and adjunctive therapies. PF with DIC also requires urgent FFP (10-20 ml/ kg every 8-12 h) to replace pro-coagulant and anticoagulant plasma proteins that are consumed in the DIC process.

Anticoagulation should be used with caution in the treatment of acute PF because of the increased bleeding risk caused by the depletion of pro-coagulant clotting factors caused by DIC. However, when PF is accompanied by large vessel venous thrombosis or central venous catheter thrombosis, weight-adjusted unfractionated heparin is usually necessary but should be given concurrently with FFP replacement therapy. This helps reduce bleeding risk and avoids heparin resistance caused by acquired antithrombin deficiency which commonly accompanies severe sepsis.[12] Anticoagulation with vit K antagonists might also be required when large vessel thrombosis is present. Vitamin K antagonists should be used with extreme caution since these agents cause further depletion of PC and PS and may therefore precipitate further micro-vascular thrombosis and PF.[13] Vitamin K antagonists should therefore be started at a low dose while unfractionated heparin treatment is continued for at least 48 h after a therapeutic INR is reached.

Our patient had no occupational history but belonged to the tropical belt, where scrub typhus is prevalent. He had leukocytosis, thrombocytopenia, deranged liver and kidney function tests, pneumonitis suggestive of sepsis and MODS. The PF rash all over the body predominantly over limbs along with high-grade fever led to initial suspicion of meningococcemia, but it was ruled out as no signs of meningeal irritation were there and CSF analysis was also normal. Positive serology to *Orientia Tsutsugamushi* (IgM scrub) clinched the diagnosis. Our patient came 2-3 days after the rash appearance when the gangrenous changes had already appeared on toes of both lowe limbs. He was successfully treated with doxycycline. Broadspectrum antibiotics were also continued in view of sepsis. Antiplatelet and anticoagulation were started in view of lower limb arterial thrombosis and segmental pulmonary artery thrombosis.

Considerable clinical improvements were noted within 5 days of doxycycline. He was given a total of 14 days of IV doxycycline treatment. During the later course of in-hospital stay, the PF rash too started resolving with the formation of scabs and excoriations. Only gangrenous changes over feet were persistent on discharge.

CONCLUSION

Though the appearance of PF rash is not common in scrub typhus, its early identification and timely causal treatment can result in significant morbidity and mortality benefit. At the same time, one should also actively search for complications of the same and manage likewise.

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