



Case Report

Purpura fulminans in probable scrub typhus group of rickettsioses from hilly region in Nepal - A case report

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ABSTRACT

Introduction: Purpura fulminans is an acute and fatal condition presenting with acute progressive hemorrhagic infarction of the skin and disseminated intravascular coagulation. Scrub typhus, is an emerging disease of Nepal, despite being a rickettsioses has been rarely associated with Purpura fulminans. The non-specific clinical presentation and limited diagnostic facility make it difficult for clinicians to diagnose the disease. Knowing the prevalence of the disease, suspecting the disease early and treatment with appropriate antibiotics can limit the course of the disease.

Case presentation: A 46-year-old female with no comorbidity presented with febrile illness and generalized weakness in the emergency department. During the course in hospital, she developed purpura followed by painful hemorrhagic bullae in bilateral lower limb with bluish discoloration in bilateral feet. IgM antibodies against the Orientia Tsutsugamushi antigen came out to be positive making diagnosis of purpura fulminans secondary to scrub typhus. She recovered with anti rickettsial therapy.

Discussion: Purpura fulminans is an emergency condition. Scrub typhus, one of the rare cause, is diagnosed with Rickettsial DNA by PCR or by Indirect Immunofluorescence Assay (IFA) or Indirect Immunoperoxidase Assay (IPA). Medical management includes Doxycycline, fluid therapy, antipyretics and surgical management includes escharotomies and fasciotomies if required.

Conclusion: We feel that clinicians should be aware of rickettsia as a differential of acute febrile illness, especially when the patient presents from endemic areas. In addition to it, they should be aware of rare presentations such as purpura fulminans which can help with early suspicion of the disease and appropriate antibiotic therapy.

Introduction

Purpura fulminans is a descriptive term for an acute emergency condition manifesting with acute and progressive hemorrhagic infarction of skin and disseminated intravascular coagulation [1].

There are three types of purpura fulminans, namely idiopathic, neonatal and acute infectious. Amongst all these types, acute infectious purpura fulminans is considered to be the commonest form. Mostly acute infectious purpura fulminans occur secondary to meningococemia and Streptococcus pneumonia [2]. Scrub typhus, caused by Orientia tsutsugamushi, a common rickettsiosis of Nepal, endemic in Chitwan,

Kailali, Nawalparasi, Gorkha with outbreaks occurring mostly in the month of August and September [3]; however, is rarely associated with purpura fulminans.

We present a case of purpura fulminans secondary to probable Scrub Typhus. The non-specific clinical presentation and limited diagnostic facility make it difficult for clinicians to diagnose the disease. Knowing the prevalence of the disease, early suspicion of the disease and treatment with appropriate antibiotics may limit the disease course and prevent complications.

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Case presentation

A 46-year-old female with no comorbidity presented to the emergency department at Bir Hospital, Kathmandu as a referral from a primary health care center, Gorkha with continuous fever (max of 102.2 F) for a week and generalized weakness for 4 days. Her fever had not subsided with antibiotics: cefixime, azithromycin, paracetamol for the past 1 week. There were no history of animal and insect bites, chigger exposure and no relevant travel history. She had no similar history in the past. She had regular menstruation.

At the time of presentation, she was oriented to time, place and person but irritated and febrile (101.2 F), her BP was 74/56 mmHg, respiratory rate of 25 breaths/min and pulse of 120 beats/min. No yellowish discoloration of sclera, skin rashes and lymphadenopathy were present. No meningeal signs were appreciated.

While awaiting for the results of the lab investigations, she was treated on line of shock with fluid therapy (Normal Saline), antipyretic (IV paracetamol 500mg 6 hourly), and vasopressor (IV adrenaline). Blood and urine were sent for culture.

The patient hemogram showed leukocytosis (12,200/mcL) with predominance of neutrophils (69%) and thrombocytopenia (21,000/mcL). Her urine routine examination revealed 15–20 RBC and 10–12 pus cells. Lab findings showed ALT 134 (<45u/L), AST 524 (<50u/L), Urea 92 and creatinine of 1.6. Chest X ray revealed normal findings. Arterial blood gas analysis revealed metabolic acidosis (pH 7.12, HCO₃ 11.7mmol/L) and increased lactate (6.45 mmol/L). Serology for Hep B, Hep C and HIV were negative. USG abdomen/pelvis and electrocardiogram were unremarkable. Her PT 21.2 sec (12–16 sec), INR (1.92), aPTT was (50.5 sec 25–36), D-dimer 4.25 mg/dl (0.0–0.5 mg/dl) suggested finding of disseminated intravascular coagulation (DIC).

With presumptive diagnosis of sepsis, she was admitted to ICU where broad spectrum antibiotics meropenem (1 gm IV 8 hourly), IV doxycycline (100 mg BD) were commenced empirically, platelet rich plasma (PRP) and fresh frozen plasma (FFP) were given to treat thrombocytopenia.

On the 2nd day of admission to ICU, purpuric rashes were seen on bilateral legs. In addition, she developed altered sensorium with Glasgow Coma Scale of 8 with eye opening 2, best verbal response 2, best motor response 4. Her BP showed no improvement, so vasopressin was added with titrating escalating dosage. Blood and urine culture revealed no growth.

On the 4th day of admission, there were multiple tense, painful bullous lesions of various size in bilateral lower legs (Fig. 1) with ecchymotic patches and bluish discoloration present over toes in bilateral feet (Fig. 2) and few ecchymotic patches were present over bilateral upper limb. Thus, we diagnosed the condition to be 'purpura fulminans'.

We made the differentials of different zoonotic diseases like scrub typhus, brucellosis, leptospirosis, malaria and vasculitis. Antigen testing

for Scrub typhus (Rapid IgM antibody) was positive while Brucella melitensis/abortus antibody, Leptospira antibody, Malaria antigen, came out to be negative. ANA and anti dsDNA was above normal range while c-ANCA and p-ANCA were within normal range. Although dsDNA was above normal range but insufficient to meet diagnostic criteria for systemic lupus erythematosus.

We made the probable diagnosis of purpura fulminans secondary to Scrub typhus (*Orientia Tsutsugamushi*).

Her clinical findings, biochemical and hematological parameters progressively came back to normal. She was shifted to the medical ward after a week in ICU. The assessment of gold standard diagnosis of Scrub typhus, Indirect Immunofluorescence Assay, Protein C, Protein S and Antithrombin III could not be done due to financial constraints as well as lack of these test availability in the hospital. Excision of necrotic tissue, graft placement and wound closure was done after she was stable. At the time of discharge, other lesions had started to desiccate. She was discharged from hospital after 14 days of admission. She was advised for follow up every 15 days with LFT, RFT reports. At follow up after 1 month, the rashes had partially resolved with some scar. Her ALT and AST had come back to normal. She was in good health.

Discussion

A 46 year old patient from Gorkha, an endemic region of Scrub typhus, presented with febrile illness which later was complicated with DIC and further by symmetric hemorrhagic skin necrosis on bilateral lower limb. The IgM antibody test for scrub typhus came to be positive which led to the probable diagnosis of Scrub typhus with purpura fulminans. She recovered with administration of doxycycline.

At presentation, she had a continuous fever which was not subsiding despite use of antibiotics (cefixime and azithromycin) and antipyretic for four days. We suspected 'probable sepsis' due to the patient's fluctuating BP, increased pulse rate, respiration rate and leukocytosis. Elevated lactate level despite use of normal saline and inotropic drugs suggested the patient to be in shock.

On the second day of admission, the patient developed rash and laboratory investigations showing increased PT, aPTT and decreased platelets guided towards disseminated intravascular coagulation.

One retrospective review of 28 patients, reported skin discoloration, disseminated intravascular coagulation, fever and septic shock to be the most common manifestation of acute infectious purpura fulminans [4]. Purpura fulminans usually occurs after 1 week to 3 weeks after an infective episode and typical cutaneous lesion of Rickettsia manifests as discrete maculopapular rash at trunks, limbs, palms and soles sparing the face [5,6]. Severe forms such as purpura fulminans present with digital gangrene and extensive skin necrosis with blackish discoloration [6]. Like in our case, blackish discoloration may desiccate and peel off with complete recovery or hypertrophic scar formation after healing



Fig. 1. Multiple tense bullae and eschar measuring about 5*6 cm and 10*11 cm each in the bilateral lower leg.



Fig. 2. Ecchymotic patches and bluish discoloration present over toes in the bilateral feet.

[7].

The mechanism of acute infectious purpura fulminans is considered to be due to bacterial endotoxin triggering consumption of proteins C and S and antithrombin III [2]. Different organisms like *Neisseria meningitidis*, *Streptococcus pneumoniae*, *varicella*, *leptospira*, *malaria* have been reported to be associated with purpura fulminans [2,6,8]. However, clinical presentation, normal blood and urine culture, no antibody against *leptospira*, negative antigen test for *malaria*, ruled out the potential cause of acute infectious purpura fulminans. In addition to this, the above features ruled out potential causes of thrombocytopenia.

Different strains of rickettsia have been associated with purpura fulminans but only few have reported on scrub typhus [9]. Epidemiology and Disease Control Division defines 'probable case' of Scrub typhus as a case with acute undifferentiated febrile illness for 5 or more days with or without eschar (fever can be less than 5 days if eschar is present) along with IgM titer >1:32. In addition to this, elevated leukocyte count, low platelet count, elevated liver transaminases (ALT, AST) supports the diagnosis. While confirmatory diagnosis requires Rickettsial DNA which is detected in eschar samples or whole blood by PCR or rising antibody titers on acute and convalescent sera detected by Indirect Immunofluorescence Assay (IFA) or Indirect Immunoperoxidase Assay (IPA), these are expensive and not readily available [10].

Antinuclear antibody (ANA) was positive in our patient, and study shows that there can be transient rise in ANA in infection due to scrub typhus [11]. Also, cANCA and pANCA were in normal range which ruled out other forms of vasculitis including scrub typhus induced vasculitis [12]. Management of purpura fulminans needs collective involvement of various specialities like medicine, dermatology, surgery, physiotherapy. Any case of purpura fulminans requires adequate hydration and supportive care, and empiric broad spectrum antibiotics should be used in acute infectious situations [2]. The recommended treatment of any type of rickettsioses is doxycycline [10]. Alternatively, azithromycin, chloramphenicol, rifampicin can be used. However, in any case, the combination of doxycycline and chloramphenicol resulted in a good response [13]. Consumption of procoagulants and anticoagulants which occurs in presence of DIC in Purpura fulminans are replaced by urgent FFP. Similarly, to delay the progression of the disease processes, protein C, S and antithrombin C are added. Significant thrombocytopenia and

hypofibrinogenemia resulting in pathological bleeding requires transfusion with platelet or cryoprecipitates [14]. Surgical management includes: escharotomies, fasciotomies, amputation if indicated [15].

There were some limitations in our study as we could not confirm the diagnosis with PCR DNA due to the limitation in hospital's resources and financial constraints from the patient's side.

Conclusion

We believe that clinician should suspect scrub typhus as one of the differentials of acute febrile illness which also present as purpura fulminans similar to our case. This needs emergency treatment with anti rickettsial agent like doxycycline for earlier recovery.

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Ethical approval

This is a case report, therefore, it did not require ethical approval from ethics committee.

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Author contribution

We the undersigned declare that this manuscript is original, has not been published before and is not currently being considered for publication elsewhere.

We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us.

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Registration of research studies

Not applicable.

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Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editor-in-chief of this journal on request.

Declaration of competing interest

The authors report no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.amsu.2022.104701>.

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