Purpura Fulminans and Spotted Fever: A Case Series from South India

Karthik Gunasekaran, Divyaa Elangovan[1], Susmitha Perumalla[1], Kundavaram Paul Prabhakar Abhilash[2], John Antony Jude Prakash[1]

Departments of Internal Medicine, [1]Clinical Microbiology and [2]Emergency Medicine, Christian Medical College, Vellore, Tamil Nadu, India

Abstract

Purpura fulminans (PF) is associated with acute infections such as meningococcal, staphylococcal, streptococcal, and rickettsial infections. However, there are only a few reports of association of PF with rickettsial fever from India. In this case series of seven adults with PF, four were definitive cases of spotted fever as the ompA real-time polymerase chain reaction was positive. The other three adults were probable cases of spotted fever, as they were positive by immunoglobulin M enzyme-linked immunosorbent assay, and their fever subsided within 72 h of rickettsia-specific therapy. Three of the seven patients had peripheral gangrene. These patients, despite presenting with severe spotted fever, had a favorable outcome. This is attributed to the high index of suspicion and early treatment supported by diagnostic assays.

Keywords: Febrile rash, gangrene, purpura fulminans, rickettsia, spotted fever

Introduction

Purpura fulminans (PF) is a rare syndrome of intravascular thrombosis and infarction of the skin resulting in hemorrhagic purpura that is often accompanied by vascular collapse and disseminated intravascular coagulation (DIC).[1] PF is usually described with meningococcemia, staphylococcal sepsis, scrub typhus, and spotted fever.[2] Spotted fever is caused by members of the genus Rickettsia *(*obligate intracellular parasites), having a predilection for vascular endothelium.[3-5] Rickettsiae causing spotted fever reported from India include *Rickettsia conorii, Rickettsia felis,* and *Candidatus Rickettsia kellyi*.[3-6] In severe cases, vascular damage can result in the purpuric or petechial rash that can progress to PF and is generally indicative of a bad prognosis.[2,7-11] Here, we describe seven cases of PF, four of which were definitive cases (polymerase chain reaction [PCR] confirmed) and three cases where the clinical picture and serology were strongly suggestive of spotted fever. The laboratory methodology used for the confirmation of spotted fever and exclusion of other differentials is as described below.

Case Report

From December 2017 to May 2019, a total of 48 cases of spotted fever were diagnosed. Our case series describes seven cases of spotted fever with PF [Figures 1-3]. In our case series of seven cases, four were confirmed by ompA *quantitative* PCR (qPCR), which is specific for spotted fever. Three patients were considered probable cases based on serology (immunoglobulin M (IgM) enzyme-linked immunosorbent assay [ELISA]). As other etiologies of fever with rash were ruled out, they are most likely to be the cases of spotted fever. All seven patients had automated blood culture (BacT/Alert 3D, bioMerieux, Marcy l'Etoile, France) to rule out enteric fever and septicemia. ELISA was performed to detect IgM antibodies to spotted fever (*R. conorii* IgM ELISA, Vircell, Granada, Spain) and scrub typhus (Scrub typhus Detect IgM ELISA, InBios International Inc., Seattle, WA, USA). Malaria was ruled out by performing peripheral blood smears (thick and thin smears). Detection of NS1 antigen, IgM and IgG antibodies to dengue was by ELISA (J Mitra and Co. Pvt. Ltd, New Delhi, India). Real-time PCR assays (TaqMan) were performed for detecting scrub typhus

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Address for correspondence: Dr. Kundavaram Paul Prabhakar Abhilash, Department of Emergency Medicine, Christian Medical College, Vellore, Tamil Nadu, India.
E-mail: kppabhilash@gmail.com

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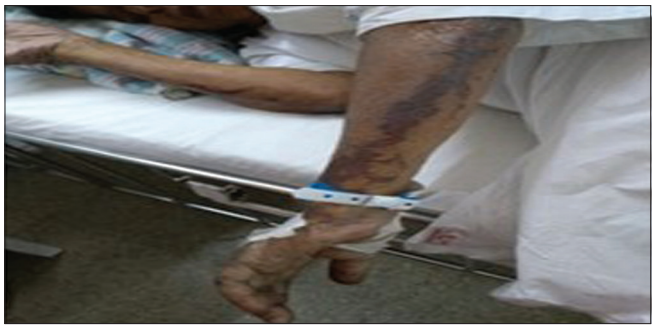

Figure 1: A 28-year-old male with purpura in the upper extremity (Case 1)

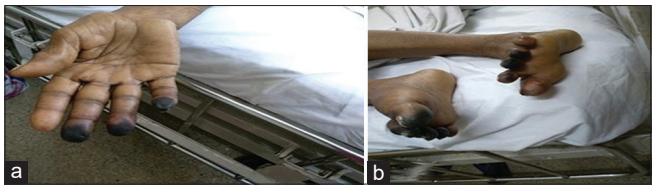

Figure 2: (a and b) Gangrene in peripheries without rash in a 66-year-old female (Case 2)

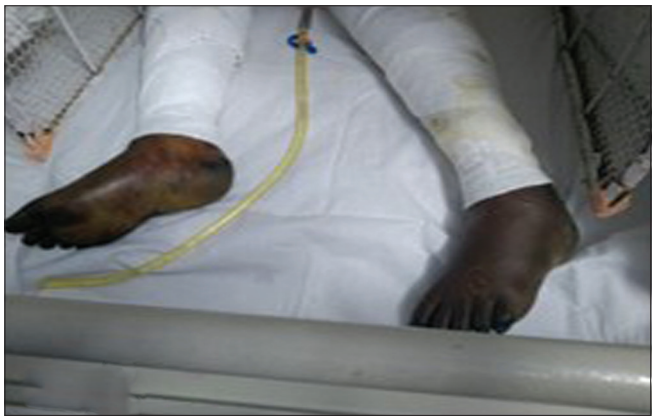

Figure 3: Purpura fulminans and gangrene in lower limb in a 36-year-old female (Case 3)

and spotted fever DNA. DNA was extracted from skin biopsy and the whole blood specimens (where available) using the QIAamp Mini Kit (Qiagen Valencia, CA, USA). We tested samples for SFG rickettsia by an ompA (outer membrane protein A gene) real-time PCR using primers derived from consensus sequences of the spotted fever rickettsia.[4,12] Amplification was confirmed by sequencing the gltA (citrate synthase gene) nPCR product as described previously.[6] To verify the DNA extraction and ruling out the inhibitors for PCR, a qPCR targeting a house-keeping gene, RNAse P,[4] was performed on all samples. Genomic DNA of *R. conorii* was used as control (Courtesy: Dr. Chao CC, NMRC, Silver Spring MD, USA). The sample was considered qPCR-positive if a Ct value was ≤38 cycles; positive and negative controls were included for all PCR runs. One of the gltA nPCR (Case 4) amplified products (citrate synthase gene) was subjected to a sequencing reaction to determine the fidelity of the amplification by nested PCR.

All patients were managed as per standard of care, with doxycycline 100 mg twice daily for 7 days; two pregnant women (case 4 and case 7) were given a course of azithromycin, as doxycycline is contraindicated in pregnancy. In case 3, myocarditis was considered based on elevated cardiac enzymes (creatine kinase – MB 18.6 ng/ml and troponin T 4031 pg/ml), and bedside echocardiogram revealed global hypokinesia with a 30% ejection fraction. She had cardiogenic shock requiring inotropic and ventilator support. All patients were discharged in a stable condition, and none had septic shock or features of DIC. Table 1 summarizes the clinical features, laboratory investigations, and outcomes in these seven cases.

Discussion

Acute infectious PF, a potentially fatal condition, is commonly caused by bacteria, including rickettsia.[2,13] PF (fern-leaf pattern purpura) has been reported commonly with *R. rickettsii*, *R. australis,* and *R. conorii*.[2,7-11]Among the various species of rickettsiae causing spotted fever, the types known to be associated with mortality are *R. rickettsii*, *R. conorii* (subtypes *conorii*, *israelensis*, and *indica)*, and rarely *R. australis*.[14,15] Mortality is due to associated vasculitis and multiorgan failure. In contrast to other reports, there was no mortality in our case group. This is likely due to a better awareness among our clinicians, which led to early recognition of a rickettsial illness and treatment with subsequent confirmation by available diagnostic methods.

Peripheral gangrene, though uncommon in spotted fever, has been reported from India;[16] three of our cases had this manifestation. Noninvolvement of palm and soles has been described,[5,17] and in this series of spotted fever with severe rash, two did not have palmoplantar rash. All the cases were positive for spotted fever IgM ELISA except for the second-trimester pregnant woman (Case 4). This patient's serology was negative though serum was collected on the 10th day of illness. This could be due to altered immunological responses to infections observed in pregnancy.[18] PCR performed on the buffy coat was positive for spotted fever rickettsial DNA. As dengue NS1 antigen was also positive in the same patient, this could be a coinfection. However, the clinical picture showed leukocytosis with normal platelets responding to antirickettsial therapy favoring the diagnosis of spotted fever.

All of these patients, who acquired the disease in south India, were treated and discharged from our facility. It is probable that the rickettsial species infecting our spotted fever patients is "*Candidatus Rickettsia kellyi"* as reported previously.[6,19] Moreover, this species may induce a life-threatening rash in some individuals, but have extremely low mortality. In addition, to other causes of PF like *Neisseria meningitides,*[20] the clinician should also be considered a spotted fever.

To conclude, a high index of suspicion and prompt initiation of therapy are keys to favorable outcomes. Availability of

Table 1: Clinical features, treatment, and outcome of spotted fever cases with purpura fulminans

Cases	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7
Age/sex	28/male	66/female	36/female	23/female	48/male	58/female	22/female
Fever (days)*	10	10	12	10	9	14	10
Type of rash	PF	Acral PF	PF	Purpuric	PF	PF	Purpuric
Day of rash onset#	4	3	6	4	5	7	4
Palmoplantar rash	Yes	No	Yes	No	Yes	Yes	Yes
Pedal edema	Yes	Yes	Yes	Yes	Yes	Yes	No
Gangrene	Yes	Yes	Yes	No	No	No	No
SF PCR (buffy coat)	Negative	Negative	Positive	Positive	Negative	Negative	Negative
SF PCR (skin rash)	Positive	ND	Positive	ND	Negative	ND	Positive
SF IgM ELISA	Positive	Positive	Positive	Negative	Positive	Positive	Positive
Fever subsided (h)	<48	<72	<96	<48**	<72	<72	<72**
Hospitalization (days)	7	10	56	5	7	9	9
SF case	Yes	Probable	Yes	Yes	Probable	Probable	Yes

*Duration of fever (days) at the time of testing for SF, **Treated with azithromycin, others with doxycycline, #On which day of fever rash appeared.
PF: Purpura fulminans, SF: Spotted fever, PCR: Polymerase chain reaction, ND: Not done

rickettsial diagnostics enables a more accurate diagnosis and provides useful feedback to reinforce clinician practices.

Declaration of patient consent

The authors declare that they have obtained consent from patients. Patients have given their consent for their images and other clinical information to be reported in the journal. Patients understand that their names will not be published and due efforts will be made to conceal their identity but anonymity cannot be guaranteed.

Research quality and ethics statement

The authors followed applicable EQUATOR Network (http://www.equator-network.org/) guidelines, notably the CARE guideline, during the conduct of this report.

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Conflicts of interest

There are no conflicts of interest.

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