Gangrene in cases of spotted fever: a report of three cases

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SUMMARY

Gangrene is an uncommon complication in cases of rickettsial spotted fever. We report three cases of spotted fever from south India, presumably caused by *Rickettsia conorii* subspecies *indica*. Along with gangrene, these cases had severe manifestations of sepsis and multiorgan dysfunction syndrome (MODS) like acute kidney injury, liver dysfunction, delirium and seizure. One patient died while the other two recovered well. This case series is being reported to highlight the occurrence of gangrene in spotted fever rickettsiosis and the importance of appropriate management at the earliest.

BACKGROUND

Rickettsial diseases are prevalent in all parts of the world except Antarctica. Rickettsial diseases have been described from India quite long ago. However, the reported incidence and prevalence are an underestimation of the true problem because of lack of awareness among physicians, lack of reliable community-based data and diagnostic tests. Rickettsial diseases have been described from various parts of India.^{1–3} This case series is being reported to highlight the occurrence of gangrene in rickettsial spotted fever and the importance of appropriate management at the earliest.

CASE PRESENTATION

Case 1

A 35-year-old man, known to have hypothyroidism and type 2 diabetes mellitus was referred to our hospital with a history of fever and myalgias of one week duration in January 2011. He was drowsy for the last 24 h. On arrival in our hospital he had a generalised seizure (no past history of seizures). On admission to the ICU, he was in post-ictal state. Physical examination revealed pulse rate of 110 bpm, blood pressure (BP) 110/70 mm Hg, respiratory rate (RR) 32 breaths/min, temperature 99°F, pallor, icterus, tender hepatomegaly (span 19 cm) and crepitations all over the chest. He had pitting oedema of all the limbs along with discrete, palpable, purpuric rash (figure 1, panel A) all over the body including palms. He was intubated and ventilated due to acute respiratory distress syndrome (ARDS) and metabolic acidosis.

Case 2

A 69-year-old lady, hypertensive, on treatment, was referred to us in March 2011, with fever and myalgias of one-week duration, generalised rash since 3 days and being drowsy since 24 h. Owing to oliguric acute kidney injury, she had one session of haemodialysis before coming to our hospital. On arrival, she had a generalised seizure. Decision of

mechanical ventilation was taken prior to the seizure and accordingly she was intubated and ventilated.

Physical examination revealed pulse rate of 116 bpm, BP 130/80 mm Hg, fever (104°F) and RR 45/min.

She had purpuric and echymotic rash all over the body. She did not need further haemodialysis or inotropic support.

Case 3

A 70-year-old man, recently diagnosed diabetic, presented, in August 2011, with fever and body-ache since 5 days, swelling of both upper and lower limbs since 3 days and generalised rash since 2 days. He was a heavy smoker and abused alcohol. Physical exam revealed a pulse rate of 106 bpm, BP 120/76 mm Hg, RR 24/min and temperature 98°F. He had pitting oedema of all limbs and purpuric rash with blebs all over the body sparing the palms and soles. He had hepatomegaly but no splenomegaly or lymphadenopathy and had bilateral chest crepitations.

Case 1 was from the state of Kerala while cases 2 and 3 were from Tamilnadu. Both are in the southern part of India. Owing to thrombocytopaenia, cerebrospinal fluid (CSF) study was not conducted in all the patients at presentation. CSF study in case 1 was conducted in due course as he continued to be in altered sensorium and septic shock. It was unremarkable. Eschars, lymphadenopathy or splenomegaly were not identified in any of the three patients.

INVESTIGATIONS

Investigations

Case 1: Investigations were suggestive of severe sepsis with MODS (table 1). Blood and urine cultures were sterile.

Case 2: Initial investigations were suggestive of severe sepsis with MODS (table 1). EEG was suggestive of diffuse brain dysfunction. CSF study was not conducted due to thrombocytopenia.

Case 3: Investigations revealed a picture of sepsis with MODS. Cardiac biomarkers were elevated and 2DEcho showed global hypokinesia suggestive of myocarditis.

Other important investigations and relevant features of the cases are depicted in the table. Diagnosis in all cases was made by immunofluorescence assay (IFA) (FOCUS Diagnostics, Cypress, California, USA) showing a fourfold rise in IgM antibody titre, in paired sera about 7–10 days apart, against the spotted fever group rickettsia (which includes *R. conorii*, *Rickettsial akari*, *Rickettsial sibirica* and *Rickettsial australis*).

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Figure 1 (A) Typical rash of spotted fever (case 1). (B) Gangrene of the ear lobe (case 1). (C) Gangrene of both feet (case 1).

TREATMENT

Case 1: He was treated with broad spectrum antibiotics including doxycycline in view of severe sepsis, purpura fulminans and multiorgan dysfunction. Parenteral doxycycline was not available, hence doxycycline was changed to intravenous clarithromycin. He needed daily haemodialysis, due to oliguric acute renal failure, along with inotropes from day 2 of hospitalisation. Mechanical ventilation was needed from day one onwards till he died.

Cases 2 and 3: Broad spectrum antibiotics including doxycycline. Mechanical ventilation.

OUTCOME AND FOLLOW-UP

Case 1: On day 9 of hospitalisation, gangrene of ear lobe was noted (figure 1, panel B). Over the next 5 days he developed dry gangrene of both the lower limbs (figure 1, panel C) and multiple fingers of both hands extending upto the wrists. Amputation was not performed as his family members did not

Table 1 Characteristic features of the three cases

Parameter	Normal range	Case 1	Case 2	Case 3
Total leucocyte count (per litre)	4.0–11.0×10 ⁹	11.7×10 ⁹	14.4×10 ⁹	9.1×10 ⁹
Neutrophil (%)	40–70	92	82	91
Platelet count (per litre)	150–400×10 ⁹	12×10 ⁹	22×10 ⁹	32×10 ⁹
Total bilirubin (μmol/l)	3.4–17.1	56.4	76.9	23.9
ALT* (IU/l)	0–41	226	79	54
AST† (IU/l)	0–38	241	211	127
ALP‡ (IU/l)	40–129	195	214	226
Serum albumin (g/l)	35–52	26	27	29
Serum sodium (mmol/l)	136–145	147	144	134
BUN§ (mmol/l)	2.2–7.1	9.9	33.3	6.06
Serum creatinine (μmol/l)	53–114.9	114.9	291.7	79.5
Procalcitonin (ng/ml)	<0.1	13.4	21.3	4.15
CPK¶ (IU/l)	38–174	94 300	1269	1470
ARDS		+	+	+
Duration of symptoms before doxycycline therapy, in days		7	7	5
Seizures		+	+	–
Mechanical ventilation		+	+	+
IFA		Positive	Positive	Positive
Outcome		Died	Recovered	Recovered

* Alanine aminotransferase.

† Aspartate aminotransferase.

‡ Alkaline phosphatase.

§ Blood urea nitrogen.

¶ Creatine phosphokinase.

consent for the same. He developed nosocomial sepsis in the form of pneumonia. He continued to be critical and finally succumbed on day 40 of hospitalisation.

Case 2: On day 2 of hospitalisation, dry gangrene of the left second toe was noted (figure 2). Surgical intervention was not considered essential. She was extubated on day 4. She gradually improved and was discharged in stable condition on day 15.

Case 3: He needed intubation and ventilation along with inotrope support from day 3 due to respiratory distress, severe metabolic acidosis and septic shock, respectively. Dry gangrene of the tip of right index finger was noticed on day 5 of hospitalisation (figure 3). He was gradually weaned off inotrope and ventilator and was discharged in a stable condition on day 15.

Figure 2 Gangrene of left second toe (case 2).

Figure 3 Gangrene of right index finger (case 3).

DISCUSSION

Early clinical features are common in all rickettsial diseases and include, fever, headache, myalgia, arthralgia, cough, nausea and vomiting. Rash appears 5–7 days after onset of symptoms. Rash can be macular, maculopapular, petechial or haemorrhagic. Palpable purpura is sometimes seen. Rash may not appear in 9–16% cases of spotted fever.⁴ Eschar can be single or multiple or may not be seen in some cases. Tick bite being painless, the site may not be identified by the patient (Indian tick typhus) ITT differs from (Mediterranean spotted fever) MSF in that the rash is frequently purpuric and an inoculation eschar at the bite site is rarely identified.⁵ Haepatosplenomegaly and generalised lymphadenopathy may be seen.⁶ Hepatic injury manifests as increased aminotransferase levels. Respiratory system involvement may manifest as interstitial pneumonitis, non-cardiogenic pulmonary oedema, radiographic infiltrates and respiratory failure.⁴ Neurological symptoms may include encephalitis, meningoencephalitis and various other focal neurological deficits. Acute renal failure complicating rickettsial diseases is associated with a bad prognosis.⁷ Cardiac involvement may manifest as dysrhythmia in 7–16% of cases.⁴ One of our patients has features of myocarditis. Myositis can occur in some cases. It manifests as elevated levels of serum creatine kinase and areas of rhabdomyolysis.⁴

Gangrene of digits or limbs is an uncommon but serious complication. It may need amputation of the digits or the limb. A few case reports of digital gangrene complicating rickettsial diseases are available in the literature.^{8–11} The acral distribution of gangrenous lesions may be due to selective or enhanced proliferation of spotted fever-group rickettsiae in cooler body regions.⁸ Pathophysiologically, gangrene is related, most likely, to small-vessel occlusion. Vasculitis, disseminated intravascular coagulation and hypotension may play a role.⁸

Other serious complications of rickettsial infections include thrombosis of major blood vessels,¹² severe sepsis syndrome and death.

Diagnosis

Immunofluorescence assay is the recommended diagnostic test. Weil-Felix test has low sensitivity and hence is not recommended as a diagnostic test. Polymerase chain reaction, immunohistochemistry and isolation of the organism in cell culture, are other useful investigations. Clinical clue to the diagnosis depends on epidemiology, characteristic rash, eschar and

investigations showing normal or low leucocyte count, thrombocytopenia, hyponatraemia and elevated transaminase levels.⁴

Treatment

Doxycycline is the drug of choice for all tick-transmitted rickettsioses unless the patient is pregnant or allergic to doxycycline. Josamycin or chloramphenicol is recommended in pregnancy. Doxycycline is recommended even in children of any age. Other useful drugs include azithromycin, clarithromycin and ciprofloxacin. Beta-lactum antibiotics, aminoglycosides and sulfa drugs are not useful. pH drugs may even be harmful. Treatment should be initiated as early as possible, on clinical suspicion alone, to prevent a bad outcome, because confirmed diagnosis is made in routine clinical practice by IFA which is positive in the second week of illness.^{4 13}

Case 1, which was treated with intravenous clarithromycin did not do well and died. Hence, we consider that even if parenteral doxycycline is not available, oral preparation should be continued via the nasogastric tube.

Learning points

- ▶ Rickettsial infection should be considered in any unexplained fever.
- ▶ Clinical suspicion is necessary to start treatment since serology becomes positive late in the course of the disease.
- ▶ Doxycycline is the drug of choice except in pregnancy or patients allergic to the drug.
- ▶ Josamycin or chloramphenicol is recommended in pregnancy.
- ▶ Other useful drugs include azithromycin, clarithromycin and ciprofloxacin.
- ▶ Renal failure in spotted fever carries a bad prognosis.

Competing interests None.

Patient consent Obtained.

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