Case Report

A confirmed case of macrophage activation syndrome secondary to spotted fever rickettsiosis: Response to immunomodulation in a pediatric patient in northeastern, Mexico

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ABSTRACT

An 8-year-old girl with a rash and high-grade fever for 6 days arrived at the emergency room. She had an erythematous macular rash on the face, trunk, arms, and legs. Further interrogation called attention to the presence of close contact with stray dogs. Her town had been recognized as a site of a rickettsiosis outbreak in the past year. Spotted fever rickettsiosis was suspected, and doxycycline treatment was initiated. Macrophage activation syndrome (MAS) secondary to *Rickettsia rickettsii* infection was diagnosed according to the Hemophagocytic lymphohistiocytosis and EULAR/PRINTO/PRES 2016 criteria. As there are no clear guidelines on the treatment of MAS secondary to *R. rickettsii.* the course of action taken by the pediatric intensive care unit team was to avoid disseminated intravascular coagulopathy and treat MAS, both life-threatening conditions. Directed therapy with high doses of methylprednisolone and intravenous immunoglobulin therapy was initiated. The patient recovered, regaining her functional state before the illness. Few articles have described the association between MAS and rickettsiosis, an illness with high mortality, which makes it paramount to detect and treat promptly.

Key words: Immunomodulation, Macrophage activation syndrome, Rickettsia infections

Spotted fever rickettsiosis is a group of tick-borne diseases caused by different species of Rickettsia. *Rickettsial* infections are known to cause macrophage activation syndrome (MAS).

The data concerning the epidemiologic status of spotted fever rickettsiosis in Mexico are limited. The few available reports describe it as being more prevalent in states with deserts, such as Sonora, Coahuila, Durango, and Baja California, all of them located in northern Mexico [1-4]. The latest epidemiologic report described a total of 220 cases of rickettsiosis [5]. The more prevalent species reported are *Rickettsia typhi* (66%) and *Rickettsia rickettsii* (21%). In Nuevo Leon, there is an epidemiologic report, already accepted by the state committee but still not published, about an outbreak of cases since January 2022. The preliminary count to date is 41 confirmed cases of rickettsiosis [6].

Since this is a disease with high mortality, the researchers consider it valuable to describe how a patient with MAS secondary to rickettsiosis was treated successfully, with targeted immunomodulatory therapy treatment.

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CASE PRESENTATION

An 8-year-old girl originating from Escobedo, Nuevo Leon, with no relevant background presented at our emergency department with an erythematous macular petechial rash, non-pruritic, in the face, trunk, arms, and legs, with a centripetal distribution, involving the soles of hands and feet. The rash began 6 days before admission accompanied by a high-grade fever (39–40°C). Two days later, the rash progressed to a petechial generalized rash (Fig. 1) accompanied by myalgia and arthralgia.

At arrival at the emergency room, the patient was febrile, tachycardic, with prolonged capillary filling, weak peripheral pulses, and hypotensive. A quick interview draws attention to the presence of close contact with stray dogs. Furthermore, the patient's town was identified as a site of a rickettsiosis outbreak in the last year.

Laboratory examinations were performed finding severe metabolic acidosis (pH<7), thrombocytopenia

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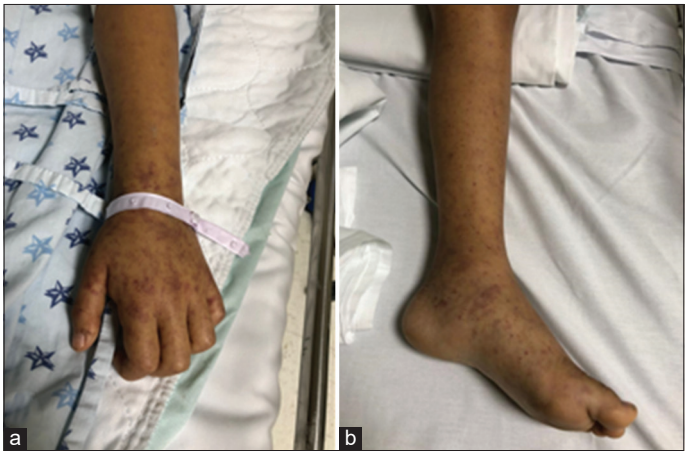

Figure 1: (a and b) Generalized erythematous-macular petechial rash

(22,000/mm^3), elevation of Creatine phosphokinase (2501 U/L), hypertriglyceridemia (247 mg/dL), hyperbilirubinemia (TB: 8.6 mg/dL), transaminasemia (AST: 440 U/L, ALT: 110U/L), and elevated inflammatory markers: D-dimer (8,435 ng/mL), hyperferritinemia (4,240 ng/mL) and C-reactive protein (19.73 mg/dL) with hyponatremia (125 mmol/L) and hypoalbuminemia (2.8 g/dL). Spotted fever rickettsiosis was suspected, and doxycycline was started immediately. A transthoracic echocardiogram reported a 2 mm pericardial effusion and an abdominal ultrasound showed splenomegaly. The patient's neurological state deteriorated, presenting impaired alertness with an 8-point Glasgow coma scale, a brain computed tomography showed mild edema. Intubation and mechanical ventilation were performed to protect the airway; subsequently, she was transferred to the pediatric intensive care unit (PICU).

On the 2nd day of hospitalization, the patient presented clinical data of severe vasculitis and plasma leakage, characterized by hypotension, interstitial pneumonia (Fig. 2), pleural effusion, edema, and oliguria. Inflammatory markers, complete blood count (CBC), and coagulation factors were taken periodically (Table 1). A polymerase chain reaction assay confirmed *R. rickettsii.*

The worsening of the cardiovascular and neurological state, the bicytopenia, and the rising of the inflammatory markers (Table 1) made the clinicians consider MAS. The patient met the hemophagocytic lymphohistiocytosis (HLH) and EULAR/PRINTO/PRES 2016 criteria and therefore the diagnosis was confirmed.

Due to the worsening of her clinical state, immunomodulatory therapy with high doses of methylprednisolone 30 mg/kg/day for 5 days and intravenous immunoglobulin (IVIG) therapy 2 g/kg/dose were initiated. She also required management with vasopressor, albumin, and diuretics. Management with blood products was initiated to prevent and treat disseminated intravascular coagulopathy (DIC) and consisted of platelet apheresis, fresh frozen plasma, and cryoprecipitates. Enoxaparin 0.5 mg/kg/dose BID was initiated to prevent thrombosis. Clinically, the patient developed data of cutaneous vasculitis with livedo racemose (Fig. 3). Due to clinically moderate response to the initial immunomodulatory therapy, and the persistence

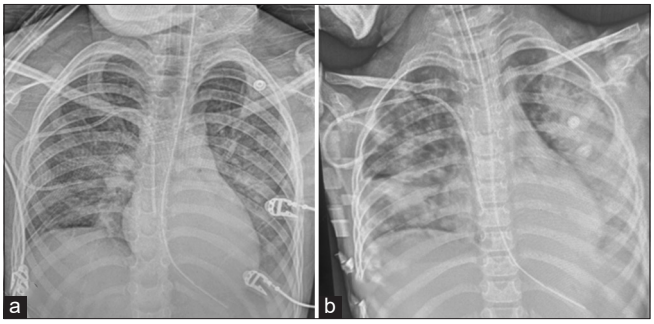

Figure 2: (a and b) Chest X-ray diffuse interstitial infiltrates and pleural effusion

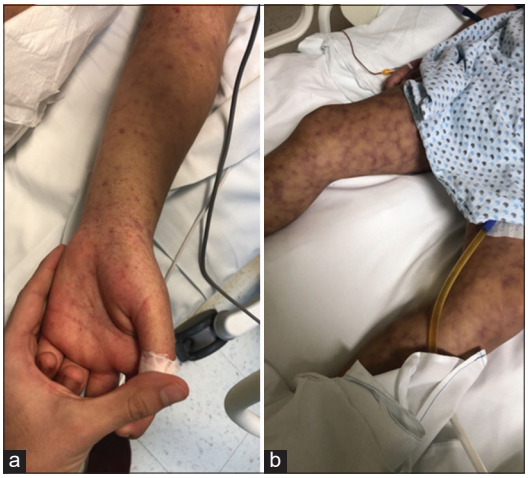

Figure 3: (a and b) Livedo racemosa

of elevation of inflammatory markers after 5 days of the first IVIG dose, it was decided to administer a second dose of IVIG 2 g/kg/dose, with the aim of potentiating the immunomodulation effect. A response was documented when inflammatory markers showed a significant decrease, as well as improvement of the neurological, kidney, and liver function. The patient underwent a total of 9 days of mechanical ventilation and 2 days of high-flow nasal cannulas. A course of 10 days of doxycycline was given. The blood culture taken at admission was reported as negative. Enteral feeding was initiated within 72 h of admission. Other illnesses the patient developed at PICU were rhabdomyolysis, critical illness myopathy, and cerebral vasculitis (Fig. 4). Her symptoms, blood count, and inflammatory markers fully resolved after 5 weeks of hospitalization.

DISCUSSION

The patient had a classic clinical picture of rickettsiosis. Her city was already identified as a site of a rickettsiosis outbreak in 2022. It is highly important to detect areas of rickettsiosis outbreak, to be able to identify those patients at risk and start antibiotic-directed therapy as soon as possible. The mortality of this illness can be as high as 80% when delayed therapy after the 5th day of symptoms [7,8]. The start of doxycycline must be the first treatment to initiate when rickettsiosis is suspected since it is the most significant intervention in the reduction of mortality.

Table 1: Laborateory investigations of the patient

Test	Results	Reference range*
Complete blood picture	Hemoglobin-12.7 g/dL (day 1), 8.8 mg/dL (day 2). 8.6 g/dL (day 10)	11.8–14.7 g/dl
	White blood count- 14.9×10³/uL 3 (day 1), 22.5×10³/uL (day 2), 12, 900 ×10³/uL (day 4), 16.3 ×10³/uL (day 10)	3.8–10.4 ×10³/uL
	Platelets- 45.6 ×10³/uL (day 1), 48.1 ×10³/uL (day 2), 69 ×10³/uL (day 4). 193 ×10³/uL (day 10)	186.7–400.4×10³/uL
Renal function tests	Blood urea nitrogen- 45 mg/dL (day 1), 36 mg/dL (day 2), 39 mg/dL (day 3), 21 mg/dL (day10)	5.1–16.8 mg/dL
	Creatinine- 0.28 mg/dL (day 1), 0.59 mg/dL (day 2), 0.74 mg/dL (day 3), 0.16 mg/dL (day 10)	0.31–0.61 mg/dL
	Sodium-125 mmol/L (day 1), 128 mmol/L (day 2), 131 mmol/L (day 10)	132–141 mmol/L
Liver function tests	Aspartate aminotransferase- 110 U/L (day 1), 89 U/L (day 3), 34 U/L (day 10)	14–36 U/L
	Alanine transaminase- 440 U/L (day 1), 362 U/L (day 3), 66 U/L (day 10)	13–69 U/L
	Total bilirubin-8.6 mg/dL (day 1), 11.5 mg/dL (day 3), 4.5 mg/dL (day 10)	<0.8 mg/dL
	Direct Bilirubin-6.5 mg/dL (day 1), 8.4 mg/dL (day 3), 2.7 mg/dL (day 10)	<0.2 mg/dL
	Albumin- 2.6 g/dL (day 1), 2.2 g/dL (day 3), 4 g/dL (day 10)	3.5–5 g/dL
Inflammatory markers	C-reactive protein- 19.73 mg/dL (day 1), 15.2 mg/dL (day 2), 6.27 mg/dL (day 10)	0–0.5 mg/dL
	Serum ferritin- 4,240 ng/mL (day 1), 2, 492 ng/mL (day 2), 1520 ng/mL (day 3), 658 ng/mL (day 6), 467 ng/mL (day 10)	6–67 ng/mL
	D-dimer- 8,435 ng/mL (day 1), 7,107 ng/mL (day 2), 23, 895 ng/mL (day 3), 17, 669 ng/mL (day 6)	<220 ng/mL
	Creatine phosphokinase- 226 U/L (day 1), 2501 U/L (day 3)	30–200 U/L
	CK-MB- 58 U/L (day 1), 115 U/L (day 3)	0–20 U/L
Coagulation tests	Prothrombin time- 13 s (day 1), 13.3 s (day 4), 12.1 s (day 10)	10.2–12.1
	International Normalized ratio-1.32 (day 1), 1.46 (day 4), 1.16 (day 10)	0.91–1.11
	Partial thromboplastin time-43.2 s (day 1), 30.6 s (day 4), 24.9 s (day 10)	26–36
	Fibrinogen- 385 mg/dL (day 1), 91 mg/dL (day 4), 567 mg/dL (day 10)	169–515 mg/dL

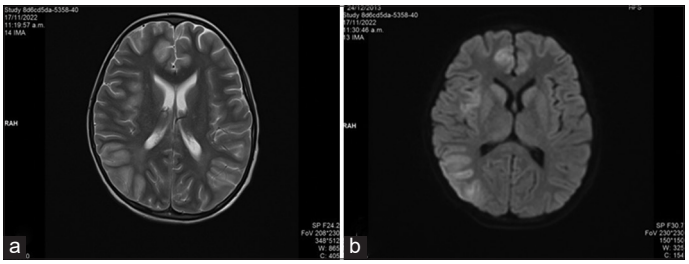

Figure 4: (a and b) Brain magnetic resonance imaging right frontoparietal cortico-subcortical hyperintensity in T2 and fluid-attenuated inversion recovery

Vasculitis is a fundamental part of the physiopathology of rickettsiosis due to damage to the endothelial cells by R. rickettsii. Early detection of hyperinflammatory status is fundamental to start directed therapy. Once the cytokine storm initiates, it progresses into multiorgan failure, causing hypotension, perpetuating acidosis, and eventually death. The use of immunomodulatory doses similar to the therapy directed to medium and small vessel vasculitis demonstrates the reduction of IL-1 in macrophages and IL-6 production by monocytes. A case report showed a successfully treated case of HLH secondary to rickettsiosis with anakinra, an IL-1 receptor antagonist [9]. The mechanism of modulation of immune response mediated by IVIG also demonstrates effects in the inhibition of phagocytosis by inhibiting FCR. The latter is the basis of its anti-proliferative effects, it modulates apoptosis and activation of specific cell adhesion and immunoregulatory molecules such as T-cell receptors, CD4, and CD5, which mediates cytokine levels and therefore the activation of complement [10,11]. In addition, IVIG influences glucocorticoid receptor binding affinity, which makes it ideal as synergic therapy to treat a hyperinflammatory status.

Avoiding DIC by monitoring platelets, fibrinogen, coagulation factors, D-dimer, and treating with blood products as necessary, should have an impact on mortality in this context [9,12].

CONCLUSION

This case is relevant since an outbreak of fever-spotted rickettsiosis has been identified in the northeastern region of Mexico. The high mortality of the disease when it is not treated promptly motivates researchers to alert the local and global community of its clinical manifestations so that this disease is suspected, diagnosed, and treated on time.

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