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Complications and cause of death in Mexican children with Rocky Mountain spotted fever

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Abstract

Background: *Rocky Mountain spotted fever is a life threatening disease caused by Rickettsia rickettsia, characterized by multisystem involvement.* **Methods:** *We studied 19 dead children with Rocky Mountain spotted fever. All children who were suspected of having rickettsial infections were defined as having Rocky Mountain spotted fever by serology test and clinical features. Through the analysis of each case, we identified the clinical profile and complications associated to the death of a patient.* **Results:** *In nine (69.2%) of 13 cases that died in the first three days of admission, the associated condition was septic shock. Others complications included respiratory distress causes by non-cardiogenic pulmonary edema, renal impairment, and multiple organ damage.* **Conclusions:** *The main cause of death in this study was septic shock. The fatality rate from Rocky Mountain spotted fever can be related to the severity of the infection, delay in diagnosis, and delay in initiation of antibiotic therapy. Pulmonary edema and cerebral edema can be usually precipitated by administration of excess intravenous fluids.* (Gac Med Mex. 2016;152:704-10)

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Introduction

Rocky Mountain spotted fever (RMSF) is an acute infectious disease caused by the intracellular bacteria *Rickettsia rickettsia* (RR), which is considered the most pathogenic species[1]. In the State of Sonora, RMSF is assumed to be transmitted by the brown dog tick (*Rhipicephalus sanguineus*)[2].

Since its reemergence, RMSF has become a health problem of difficult prevention, diagnosis and treatment in Sonora. The real frequency of this condition is unknown, since only isolated references on the disease are made. The first cases were confirmed in children residents of the State of Sonora in 2003[3], and clinical serious forms have been reported ever since and a high mortality risk has been established in this age group.

In two case reports studied at the Children's Hospital of the State of Sonora (HIES – *Hospital Infantil del Estado de Sonora*)[4,5], lethality associated with this condition ranged from 22 to 43%, which are rates much higher than those published for areas of the USA where RMSF is also endemic, where the condition is estimated to cause the death of 1-3% of infected patients[6]. The reasons for this discordance are multifactorial, and

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the causes proposed for its explanation include: belittling of the disease by primary care health personnel due to its initial unspecific clinical presentation; limited availability of early diagnostic tests, in particular polymerase chain reaction; delay in diagnosis and late initiation of doxycycline as first line antibiotic, and belonging to low and highly marginalized socioeconomic groups, which hinders early assistance to health units[7,8].

Most RMSF-related deaths occur during the second week of evolution and usually are due to septic shock or pulmonary complications (edema, pneumonia, or both). At late stages, or in very serious cases, patient death is caused by circulatory overload and pulmonary edema secondary to myocardial or renal damage[9].

Vasculitis is the cardinal finding in RMSF, and this phenomenon has been confirmed to constitute the most important event in multisystemic tissue damage. Blood vessel endothelial cell damage favors capillary permeability increase, extravascular volume depletion and interstitial fluid increase and tissue hypoxia, which promotes the complications of the disease[10,11].

Treatment of this infectious disease is essentially based on effective and opportune antibiotic administration, although supportive medical care including adequate management of endovenous fluids contributes to maintain vital signs and the life of patients with the most serious clinical forms[12].

In view of all the above, knowing the way children with RMSF get worse and die is considered to be important. The purpose of the present work is to know the clinical complications and, where appropriate, to identify the presence of clinical and laboratory signs that allow for this condition's fatal evolution to be modified.

Methods

The present investigation is a retrospective clinical study of 19 children younger than 18 years with a RMSF diagnosis who died at the HIES during the period of July 2006 to August 2011.

Every child younger than 18 years who had had fever ≥ 38.5 °C, headache, myalgias and exanthema with palm and sole involvement during the previous 15 days, with or without contact with ticks, and with laboratory report of thrombocytopenia < 150,000 mm^3 and liver aminotransferases ≥ 2-fold the normal values, was considered to be a RMSF probable case. All probable patients who had anti-RR immunoglobulin M-immunoglobulin G antibodies by indirect fluorescence were defined as RMSF confirmed cases[13]. Fulminating RMSF was defined as any RR infection that led to death in less than 5 days of disease onset[14].

The sepsis criterion was regarded as systemic inflammatory response secondary to RMSF, whereas serious sepsis was defined as the presence of sepsis in combination with organ dysfunction, and septic shock was characterized by serious sepsis with persistent hypotension in spite of adequate resuscitation with fluids and inotropic or vasopressor agents' use[15].

By means of analysis of each case's daily and hourly evolution recorded in hospital files, the clinical-humoral dysfunction the patient's death was associated with was identified according to Goldstein et al.[15] criteria. Cardiovascular dysfunction was diagnosed when systolic blood pressure (SBP) was below the 5th age-specific percentile, with the need to administer amines to maintain blood pressure, accompanied by oliguria and hypoperfusion. Acute renal failure was characterized by creatinine levels > 2-fold the age-specific upper level of normal, while neurological dysfunction was detected by a Glasgow score < 11. Mechanical ventilator support and blood gas parameters irregularities defined the respiratory function. The criterion to identify hepatic damage was based on transaminase elevation up to double the age-specific normal limit, and platelets < 80,000 mm^3 with international normalized relation (INR) > 2 characterized hematological dysfunction. On the other hand, histopathological analyses performed in 10 cases were reviewed.

Demographic, clinical and laboratory data were obtained from the patients' medical files, using a case report form. Endovenous fluids rapid load or bolus was specified as the infusion of ≥ 10 ml/kg crystalloid saline solution at 0.9% or Hartman solution. The results of the following tests were recorded: first blood count, blood chemistry, liver function tests, blood gas, serum electrolytes and coagulation tests obtained after patient admission.

Data were presented using the elements of descriptive statistics.

Results

Table 1 shows some demographic aspects and previous history of the 19 studied cases. In 11 patients (57.8%), the diagnosis was confirmed by serologic

Table 1. Demographic aspects and previous history of 19 children deceased due to RMSF

Characteristic	Value*
Disease:	
Confirmed	11 (58)
Probable	8 (42)
Gender:	
Male	10 (52)
Age:	
Years	6 (1-15)
Evolution, days:	
Prior to admission	6 (3-10)
From admission to death	1.5 (0.5-3)
Death < 3 days	12 (63)
Antibiotics:	
Prior to admission†	18 (94.7)
During hospitalization	17 (89.5)

*Median (variation) or number of patients (%).
†Non-anti-rickettsial agents.

Table 2. Complications in 19 children deceased due to RMSF

Dysfunction	No.	%
Hematological	17	89.4
Neurological	14	73.7
Cardiovascular	12	63.1
Pulmonary	12	63.1
Hepatic	9	47.4
Renal	8	42.1
Peripheral gangrene	5	26.3

Table 3. Children deceased due to RMSF according to decease-associated condition and hospitalization days

Condition	Hospitalization days			
	1	2	3	4 or more
Shock	4	4	1	
Respiratory dysfunction		2		1
Neurological dysfunction	1	1		1
Renal dysfunction				2
Co-infection				2

study. Patients younger than 7 years accounted for 47.4% of total deaths.

The largest number of cases (63.1%) was observed between the months of May and September. Median evolution of the condition prior to admission was 6 days, and 7 patients (37.0%) were admitted within the five first days of disease onset.

All studied patients presented with fever and exanthema (100%). Facial and limb edema was appreciated 84.2% of cases. Presence of abdominal pain (73.7%) and vomiting and somnolence (57.9%) was less frequently reported. Ten of the 19 patients (52.6%) met the criteria for serious sepsis, and the rest, for septic shock: one patient was classified as fulminating RMSF carrier.

Except in the case of two patients, 9 (53.0%) were treated with an antibiotic scheme of doxycycline (2.2 mg/kg every 12 h) plus ceftriaxone (75 mg/kg/day), whereas the remaining 8 received management with triple antimicrobial scheme (doxycycline, chloramphenicol at doses of 75 mg to 1 g/kg/day and ceftriaxone). Endovenous solutions administration in the form of rapid loads was indicated in 17 patients (89.5%), 12 (70.5%) of whom received an average of 2.5 (2-5) crystalloid loads.

Table 2 describes complications or organic dysfunctions identified in the patients. Hematological dysfunction was the most common (89.4%); in little more than 60% of cases, neurological, cardiovascular and pulmonary dysfunctions were observed. All patients required mechanical ventilation.

Thirteen cases (68.4%) died within the first 72 h of admission and, in 9 of them (69.2%), septic shock was considered the RMSF complication that directly had caused the decease; in the remaining 4, most important death-associated conditions were acute respiratory distress syndrome (2 cases) and neurological dysfunction (2 cases). Other clinical entities that were present, considered not to be directly causative of the decease, were neurological dysfunction, acute renal failure, respiratory distress and massive bleeding (Table 3).

When death occurred after the first 72 hospitalization hours, death-associated conditions included renal dysfunction (2 cases) and co-infection with pulmonary focus (2 cases); 2 more patients died owing to respiratory dysfunction (one case) and neurological dysfunction (one case). Other associated clinical manifestations included: gastrointestinal tract and pulmonary

hemorrhage in 6 patients, and pulmonary and neurological dysfunction and peripheral gangrene in 4 cases.

In 9 out of 10 patients, skin histological analysis reported the presence of necrotizing vasculitis with lymphocytic infiltrate by Pinkerton staining. On the other hand, different histopathological findings corresponding to the two serology-confirmed cases where a necropsy study was practiced are presented in figures 1 and 2.

Discussion

The present investigation shows two important points on RMSF clinical course. In the first place, it emphasizes the seriousness of the disease even when early diagnosed and in spite of anti-rickettsial antimicrobials administration and life support procedures. And, in second place, the infection dissemination to almost every tissue causes a disease with characteristics of multiple organ failure that ultimately leads to patient death.

It is important mentioning that 37% of cases were hospitalized prior to the fifth day of evolution and 68% of deaths occurred within the first 3 days of admission. Such conditions may be secondary to the patients' critical state and a reflection of RR virulence[16]. Although the design of the present studio does not allow for an adequate treatment assessment to explain early death in these patients, the omission of antibiotic management in two cases constitutes a factor of poor prognosis, as well as the dismissal of RMSF diagnosis, even in reference hospitals. Under these circumstances, it is possible to explain these findings from four points of view: doxycycline insufficient doses during the first 72 h of treatment[17]; parenteral fluid overload by rapid crystalloid loads[18]; inotropic amine administration[18], and elevated numbers of high-risk population (children younger than 9 years)[19].

Microvascular permeability increase and massive plasma extravasation, as well as water and electrolyte losses associated with fever, vomiting, diarrhea and hyporexia, determine for shock in RMSF to be primarily hypovolemic. Subsequently, other factors contributing to the establishment of the septic component are added, including myocardial dysfunction, peripheral vaso-regulation irregularities and the presence of cytokines[9,16,20].

Rickettsia species do not produce exotoxins that explain the pathophysiological changes observed in RMSF. However, endothelial cell proliferation and infection by bacteria induce cell oxidative stress, injury and necrosis, which trigger an acute phase inflammatory response with macrophage activation and proinflammatory cytokines (tumor necrosis factor α, interferon γ and interleukin 1β) release. Elimination of infected apoptotic cells by cytotoxic T-lymphocytes (CD8+) and activation of mediators such as selectin E, cyclo-oxygenase 2, prostaglandins and leukotrienes also favor greater endothelial damage and osmotic and immune dysfunction, with a decrease in CD4+ lymphocytes[11,21]. Finally, macrophage and lymphocyte accumulation contributes to the development of lymphohistiocytic vasculitis, which is characteristic of the disease (Fig. 1)[14].

The acute respiratory dysfunction observed in patients with RMSF originates in the development of pulmonary edema and hemorrhage[22], which generally is secondary to non-cardiogenic pulmonary edema. In the series under discussion, such complication was identified in 66% of the patients who died within the first 72 h of management; hypoxemia, pulmonary infiltrates and Kirby index alterations were the most important features of its clinical presentation. Based on these findings and on experimental data demonstrating extracellular and plasmatic space expansion with pulmonary tissue intracellular over-hydration[23], fluid and electrolyte cautious management should be emphasized to prevent further hypervolemia and, in consequence, higher risk of pulmonary complications, which occurs frequently in small children with serious RMSF.

Myocarditis is not an unusual complication in RMSF; in fact, it is regarded as one of the most important causes of death[17,24,25]. It should be suspected at the presence of the following conditions: heart failure or cardiomegaly, hemodynamical involvement requiring amines, ventricular dysfunction and elevation of CPK-MB or troponin blood levels. Incidence of this complication is difficult to establish, but a recently published study of cases has reported having found myocarditis in 34% of children with scrub typhus[26]. The present analysis indicates that this entity was overlooked by treating physicians, in spite of the elevated lethality attributed to refractory shock and cardiovascular dysfunction[27]. Therefore, the challenge is to consider myocarditis as a serious and common complication of RMSF; an echocardiogram can confirm myocardial damage and guide therapeutic interventions.

Brain dysfunction clinical manifestations in RMSF have been attributed to the presence of edema, thrombovasculitic lesions that are proliferative or destructive of different areas of the encephalon and meninges.

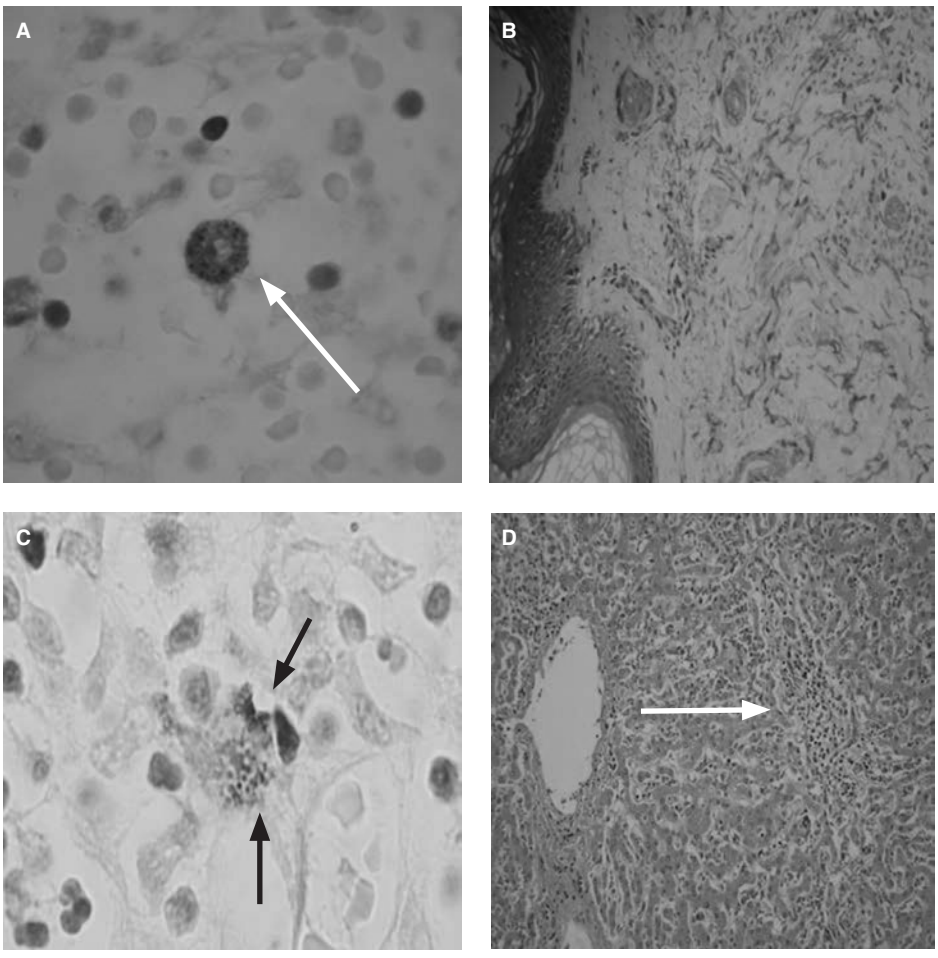

Figure 1. ***A:*** *rickettsia-positive Pinkerton staining (arrow) in skin biopsy.* ***B:*** *view of skin with vasculitis.* ***C:*** *rickettsia-positive Pinkerton staining in the liver (arrows).* ***D:*** *mononuclear infiltrate in portal spaces (arrow).*

Experimental studies carried out by Liu et al.[23] have revealed also a high content of water at the level of the encephalon, with a significant increase at the level of the medulla oblongata. These authors conclude that medulla oblongata over-hydration and edema may contribute to death as a result of cardiovascular and respiratory centers depression.

Similarly, Walker et al.[22] have established that the main causes of RMSF-related death are due to respiratory tract dysfunction and its association with acute respiratory distress syndrome, owing to pulmonary microcirculation infection and non-cardiogenic pulmonary edema. Furthermore, the study by Buckingham et al[18]. revealed that coma, inotropic support and the use of rapid fluid loads in seriously-ill children were associated with adverse results in the studied cases. Owing to an already existing hemodynamical overload and over-hydration in the lung and encephalon, extreme caution is recommended in water and electrolyte administration when treating this disease, especially when it affects small children[23].

In spite of RMSF seriousness, in none of the analyzed patients was the presence of disseminated intravascular coagulation (DIC) confirmed. During disease evolution, a procoagulant state is originated, which is secondary to the endothelial lesion and is accompanied by thrombin release, platelet destruction and activation, fibrinolytic factors increase and anticoagulant

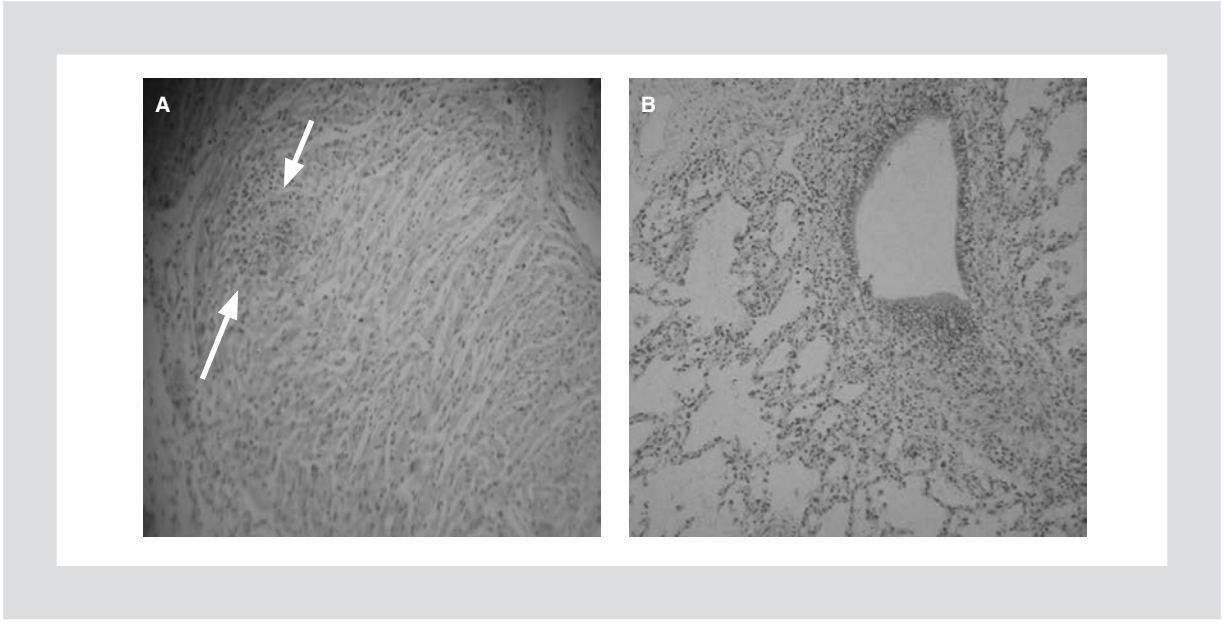

Figure 2. A: *heart microphotograph with signs of myocarditis; mononuclear infiltrate is observed.* ***B:*** *lung microphotograph with lymphocytic infiltrate, edema and peribronchial hemorrhage.*

consumption. The result is a homeostasis state that manifests itself by hemorrhages and thrombotic lesions. Hemostasis dysfunction and thrombin generation are considered poor prognosis factors in RMSF. Abnormality in coagulation tests is variable, but the D-dimer assay, which is accessible in our setting, has sufficient sensitivity and specificity to establish a correct DIC diagnosis[16].

The present study also shows that RMSF produces renal damage, which is observed in serious cases and represents by itself a sign of poor prognosis. Conlon et al.[28], when studying a series of clinical cases, reported that creatinine elevation above 2 mg/dl at patient admission increased 17 fold the disease lethality.

Several factors are implicated in the development of renal failure, including low blood pressure, prerenal failure, thrombosis and renal endothelial cell infection by RR. Renal dysfunction is another manifestation of multiple organ failure, and clearly contributes to patient death by producing important limitations in the management of shock.

Bacterial co-infection with pneumonic focus was the cause associated with death in 33% of children with four or more hospitalization days. Clinical characteristics of the disease, and the intensive and invasive care underwent by the patients partly explain the elevated risk for contracting this type of nosocomial infections. However, damage to both humoral and cellular immunity should be considered, as well as negative nitrogen balance in patients[29].

With no doubt, one of the greatest difficulties found in the management of RMSF is the correction of the shock status, without precipitating over-hydration or contributing to the patients' risk of death.

This work has several limitations. First, the study was carried out in a reference hospital and, therefore, the cases do not represent rickettsiosis true incidence. Second, only data recorded on files were analyzed and, therefore, some data might have been excluded. A third limitation is the possibility of probable cases being due to other etiologies. Nevertheless, the present report may provide better understanding of RMSF complications in children and adolescents and, consequently, improve their treatment.

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