

Fatal case of spotted fever in a patient from Northeastern Brazil

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ABSTRACT

Spotted fevers are diseases caused by bacterial agents belonging to the spotted-fever (SF) group of the genus *Rickettsia*. The first documented case of SF in Pernambuco State, Northeast Brazil, was reported here. Also, it is the first case described of fatal SF in Northeast region of Brazil. The patient was a resident of Arcoverde municipality and the probable site of infection lies in Sertania municipality, both in Pernambuco State, a semi-arid region of Brazil. The patient had not visited other areas where SF is endemic. The patient showed clinical manifestations and epidemiological exposure compatible with SF, and the infection was confirmed by molecular biology techniques.

KEYWORDS: *Rickettsia*. Differential diagnosis. Tick-borne diseases. Brazilian semi-arid, Caatinga biome.

INTRODUCTION

Spotted fever (SF) is an infectious, acute, febrile disease of varying severity, mainly transmitted by ticks^{1,2}. It has a non-specific symptomatology, during which early clinical-epidemiological diagnosis is a great challenge³. The rash, considered the only clinical marker, is not always present, which delays diagnosis and hinders appropriate medical action⁴.

In Brazil, the occurrence of other diseases of epidemic nature and more incidents (with similar symptomatology) add to the diagnostic difficulty, since it is necessary to consider the occurrence of other acute febrile diseases during assessment of cases⁵.

SF is widespread, with the highest incidence rate in the South and Southeast⁶. Classically, severe cases were associated with *Rickettsia rickettsii*, which have been recorded in anthropized areas of the Cerrado and Atlantic Rainforest biomes. The lethality rate of *R. rickettsii* infection in Brazil exceeds 50%, and may even reach 100%⁷⁻¹⁰.

In the Atlantic Rainforest, SF is also caused by *Rickettsia* sp. Atlantic Rainforest strain, a species genetically close to *Rickettsia parkeri*, *Rickettsia sibirica* and *Rickettsia africae*. In these area, both milder clinical forms were observed, having as common characteristics the presence of inoculation eschars (lesion at the tick attachment site) and lymphadenopathy^{2,11-17}. In the Northeast of Brazil, *Rickettsia* sp. Atlantic Rainforest strain has been recorded from fragments of Atlantic Rainforest in the States of Bahia and Ceara, though there were no reports of associated deaths^{6,15-17}. Here we described the first fatal case of spotted fever in the Northeast Brazil.

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Case presentation

A 78-year-old male patient with Alzheimer's disease, resident of Arcoverde municipality, State of Pernambuco, was admitted to hospital on November 14, 2015, with fever, oliguria and palmar and plantar rash. Symptom onset was reported to have begun approximately seven days before, accompanied by a progressive decline in general conditions. After admission, there was worsening of the clinical state, with tachypnea and decline in renal function. The patient was hospitalized, and management for pulmonary sepsis and renal dysfunction were initiated.

After 24 hours, a seizures occurred (there was no history of epilepsy). The patient was sedated (dormonid [midazolam] + fentanyl), intubated and transferred to the State referral hospital in Recife, Pernambuco (PE), where he was admitted to the intensive care unit. There, the following were observed: bilateral pleural effusion, leukocytosis with left upper shift; distended abdomen; Miotic pupils, GOT/AST - 188 U/L; GPT/ALT - 76 U/L; Total Bilirubin - 2.10 mg/dL, Direct - 2.00 mg/dL, Indirect - 0.10 mg/dL; CK MB - 12 U/L; CK Total - 438 U/L. The diagnostic hypotheses were severe viral meningoencephalitis; metabolic encephalopathy; acute respiratory failure or metabolic ileus. Treatment with intramuscular ceftriaxone and acyclovir was initiated.

On November 21st, 2015, the patient's condition got worsened, secretions were accumulating in the respiratory tract in moderate quantity. Teicoplanin was included in the treatment.

On November 24th, suspicion of rickettsiosis was raised as a result of the family information about the patient's routine visit to a rural property, located in Sertania municipality, State of Pernambuco, where he had direct and indirect contact with animals (dogs, horses, goats, armadillos, cows). Doxycycline treatment administered twice a day was initiated. The patient did not improve during treatment and died on January 16th, 2016.

A blood sample collected on November 24th, 2015 and kept at -20°C, was sent for analysis of *Rickettsia* sp. using the Polymerase Chain Reaction (PCR). We used gene-specific primers CS-78 (forward [5'-GCAAGTATCGGT GAGGATGTAAT-3']), CS-323 (reverse [5'-GCTTCCT TAAAATTCAATAAATCAGGAT'-3']) - which amplify a 401-bp fragment of the Citrate Synthase gene (gltA). Ultrapure milli-Q water was used, free of DNA, as the negative control, and *Rickettsia parkeri* genomic DNA as the positive control. PCR temperature conditions included an initial cycle at 95 °C for 3 min; 40 cycles of 15 s at 95 °C, 30 s at 48 °C and 30 s at 72 °C and one final cycle at 72 °C for 7 min^{18,19}.

The blood sample tested positive. However, the obtained sequence did not allow the construction of a phylogenogram to determine the identity of the detected rickettsia.

DISCUSSION

Although the indirect immunofluorescence test is considered the gold standard for SF diagnosis, there was initially no clinical suspicion. Thus, the sampling procedure did not follow the protocol established by the Brazilian Ministry of Health¹⁹ and, thus, it was not possible to evaluate the serological conversion by using paired samples collected with a minimum interval of 14 days. However, case confirmation can be made by other laboratory criteria, including molecular methods¹⁹. The performed molecular assays detected a genomic-specific gene fragment, confirming the patient's infection by *Rickettsia* sp.

The absence of initial clinical and epidemiological indicators, coupled with the rapid evolution of SF, has resulted in rickettsial deaths in several Brazilian States^{3,5,6}. *Rickettsia rickettsii* shows the strongest pathological alterations associated with the most severe and lethal clinical conditions. The effects of this pathogenic mechanism result in localized inflammation and procoagulant processes, causing increased vascular permeability, edema, hypovolemia and hypotension with vascular insufficiency associated with the subsequent leukocyte mononuclear response of the host²⁰. However, even if the patient's clinical evolution is compatible with *R. rickettsii* infections¹⁹, existing data are insufficient to infer which rickettsia species was responsible for the infection. Also, it is not possible to evaluate whether the infection got worsened due to comorbidity/patient's advanced age, or whether the use of different antimicrobials during treatment could have interfered in the disease progression, which had a morbidity period distinct from that known for *R. rickettsii*⁸.

During the epidemiological investigation of the case, it was considered that the patient had no history of travel to any area where SF is known to be endemic, and that the probable site of infection (PSI) (in Sertania municipality, PE) was the only environment frequented by the patient possessing favorable conditions for development of the rickettsial enzootic and epidemic cycle. The rural property, about 60 km from the patient's home, was frequently visited, primarily serving as a recreation area, as well as for the rearing of a few wild animals (armadillos), kept in captivity as a food source, and a variety of domestic animals (cows, goats etc.). An environmental investigation

in the PSI, conducted during the patient's hospitalization period, did not detect any of the ticks known in Brazil for transmitting rickettsia².

This result indicates the possibility of a still unknown transmission scenario in the country. The SF foci closer to the Caatinga biome have been detected only in the State of Ceara so far. However, these areas were located in Atlantic forest fragments and, like other foci in Brazilian Atlantic forests, involved dogs, *Amblyomma ovale* ticks and *Rickettsia* sp. strain Atlantic Rainforest, and mild to moderate disease associated with inoculation swelling and lymphadenopathy^{15,17}. In contrast, both Sertania municipality and Arcoverde municipality (where the patient resided) lie within the Caatinga biome, in a typical area of the Brazilian semi-arid region²¹. This area lacks any previous known epidemiological context for SF establishment. *R. rickettsii* was recently detected in *Rhipicephalus sanguineus* in areas of spotted fever transmission in Northeastern Brazil²², indicating the presence of this tick in areas where the ecoepidemiological profile is still unknown. However, this tick has a wide geographic distribution and is responsible for SF transmission in other parts of the world¹. This potential vector was found during the PSI investigation, but a PCR for *Rickettsia* was negative for the analyzed samples²³.

Considering that this is the first SF case in this region, to confirm identification of the transmission site and increase the robustness of the existing laboratory results, blood collection of contact people, area residents and animals (dogs and horses), as well as a seasonal monitoring of vector fauna, could reinforce the identity of the probable site of infection and support characterization of this new transmission scenario.

CONCLUSIONS

The first SF case is reported from Pernambuco State, in the Brazilian semiarid area, Caatinga biome, as the first death in the Northeast of Brazil associated with *Rickettsia* sp.

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CONFLICT OF INTERESTS

The authors declare that they have no competing interests.

AUTHORS' CONTRIBUTIONS

SVO and GSG participated in the study planning; MFM and LCA were responsible for the molecular diagnosis. RMFC, GF, SVCP and MA were involved in discussion of results and the drafting/ reviewing of the manuscript. All authors have read and approved the final manuscript.

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