



Case Report/Relato de Caso

Fatal Brazilian *spotless* fever caused by *Rickettsia rickettsii* in a dark-skinned patient

Febre maculosa brasileira sem exantema causada por *Rickettsia rickettsii* em um paciente de cor negra

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ABSTRACT

Brazilian spotted fever (BSF) is the most important and frequent rickettsial disease in Brazil. A fatal case of BSF is reported in a 32-year-old black man, who died of irreversible shock after five days of fever, severe headache and abdominal pain with no rash. Spleen, kidney and heart samples collected at autopsy were positive for *Rickettsia rickettsii* by PCR and sequencing. The authors emphasize the need for a high index of diagnostic suspicion for spotted fever in black patients. Absence of a skin rash should not dissuade clinicians from considering the possibility of BSF and initiating empirical therapy.

Keywords: Fatal Brazilian *spotless* fever. Black patient. PCR.

RESUMO

Febre maculosa brasileira (FMB) é a mais importante e frequente doença *rickettsial* no Brasil. Relatamos um caso fatal de FMB em um homem negro de 32 anos de idade que morreu de choque irreversível após cinco dias de febre, cefaléia intensa, dor abdominal, e sem evidência de exantema. Amostras de baço, rim e coração coletadas na necropsia foram positivas para *Rickettsia rickettsii* por PCR e sequenciamento. Os autores ressaltam a necessidade de um alto índice de suspeita diagnóstica para febre maculosa em pacientes negros. Ausência de exantema não deve dissuadir os clínicos de considerar a possibilidade de FMB e iniciar a terapêutica empírica.

Palavras-chaves: Febre maculosa brasileira sem exantema. Paciente negro. PCR.

INTRODUCTION

Described for the first time in 1929, Brazilian spotted fever (BSF) is caused by *Rickettsia rickettsii* and is considered the most important spotted fever group rickettsiosis (SFGR) in Brazil¹⁻⁶. Since 2001, when national compulsory notification was implemented, the number of notified BSF cases has increased and in the last 10 years, more than 735 confirmed cases have been reported, with a mean

mortality of 28% (Brazilian Ministry of Health, 2009). Although the clinical triad of fever, headache and rash is considered the classical description of BSF, which is similar to Rocky Mountain spotted fever (RMSF), this infection has a broader spectrum of manifestations, ranging from asymptomatic and mild disease to the severe form with fatal outcome²⁻¹⁰. Differential diagnosis is often difficult and includes SFGR caused by *Rickettsia felis*, dengue, leptospiroses and meningococemia, among others known diseases in Brazil. The classic red-spotted rash usually develops 3-5 days after the onset of other symptoms on the patient's extremities (ankles, feet, wrists, and hands) and spreads to the body. After six or more days of the illness, the rash can become petechial and can subsequently coalesce to form ecchymoses or gangrene. In Brazil, as well as other places of world, spotted fever cases without rash or with fleeting or atypical skin eruptions (evanescent, localized to a particular region of the body, papulovesicular or ulcerative lesions), have been confirmed. Although in some cases the absence of rash may be due to the prompt institution of therapy with doxycycline/tetracycline or chloramphenicol, in other confirmed cases, in which long delays in the diagnosis and treatment occurred, the characteristic rash does not develop or is not detected, particularly in black patients⁸⁻¹⁰.

The serological diagnosis, more specifically indirect immunofluorescence assay (IFA), is the most frequently used method for confirming spotted fever worldwide, but its use is limited during the first 10 days of disease and polymerase chain reaction assay (PCR) should be considered for the diagnosis at this acute onset of illness^{5,10}.

Herein, the authors report a case of fatal BSF diagnosed at autopsy by molecular methods in a black man with absence of cutaneous lesions.

CASE REPORT

On November 25th 2006, a 32-year-old, previously healthy black man, sought medical attention by a primary care physician with complaints of high fever, headache, nausea, myalgia and asthenia. He was treated with oral amoxicillin, but his symptoms persisted. Two days later, he was admitted to hospital in Itambacuri County, in the State of Minas Gerais, Southeast Brazil, with the presumptive diagnosis of dengue fever. Examination showed fever to 38.8°C, mild dehydration and hypotension. The laboratory findings showed a hematocrit of 47%, white blood cell count of 4,700/mm³, neutrophils 50%, a platelet count of 60,000/mm³, creatinine of 4.2mg/dl, ureia of 139mg/dl, and total bilirubin level of 6.2mg/dl. After symptomatic

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treatment, the patient developed neurological manifestations, lethargy, mental confusion, agitation and a generalized seizure. Empiric treatment with chloramphenicol was initiated, but the patient's condition worsened and he died from multiple organ failure 24h after admission. Although there was no history of tick bites or exposure to tick-infested habitats, the patient lived in a rural area where two other cases of unexplained deaths in young adults had been notified within the preceding months. An autopsy was performed and serum and tissue samples from various organs were analyzed at the Laboratory of Hantaviruses and Rickettsioses, Oswaldo Cruz Foundation.

Indirect immunofluorescence assays for immunoglobulin M (IgM) and IgG antibodies reactive to *R. rickettsii* (Panbio™, Australia) were performed on serum and were nonreactive. DNA extraction from liver, heart and lung tissue autopsy samples was performed using the QIAamp DNA Blood Mini kit (QIAGEN®, Hilden, Germany), in accordance with the manufacturer's instructions. PCR assay was performed as described previously⁵. Segments of several rickettsial genes, including the 17kDa antigen gene [*htrA*], *ompA*, *ompB* and citrate synthase [*gltA*] were amplified from liver, heart and lung tissue DNA. The PCR products were purified using QIAquick PCR Purification Kit (QIAGEN) and sequenced using the ABI Prism 377 DNA Sequencer (Applied Biosystems, CA, USA). All sequences were edited with the BioEdit software, identified with the BLAST software (<http://blast.ncbi.nlm.nih.gov/Blast.cgi>), and the partial sequence *ompA* from the tissue samples generated in this study (GenBank accession n° FJ959382) showed 99% identity to the corresponding sequence of *R. rickettsii ompA* gene available at the GenBank.

DISCUSSION

The clinical severity of BSF, like RMSF, varies from mild to severe or fatal presentations¹⁻¹⁰. Nonspecific clinical symptoms, such as fever, headache and muscle pain, occur in the first 10 days after the tick bite of the genus *Amblyomma*, particularly *A. cajennense*. The typical rash usually occurs on days 3 to 5 of the disease. In its early stages, this tick-borne disease can resemble many other infectious diseases, such as dengue and leptospirosis, which are endemic in Brazil, making diagnosis difficult, especially in patients with gastrointestinal and severe systemic manifestations with no presentation of a rash or a known history of tick bites²⁻⁵.

In the case reported here, a diagnosis of BSF was not considered due to the absence of cutaneous lesions. This probably made a correct diagnosis even more difficult. Although the rash may be completely absent or atypical in up to 15-20% of RMSF cases, *spotless* rickettsiosis caused by *R. rickettsii* in black patients has rarely been reported^{8,9}. One review of 43 cases of Rocky Mountain *spotless* or *almost spotless* fever was published in 1992 and the authors demonstrated 61% of these patients had been men and two-thirds of them were black⁹.

The only serum sample collected on day 5 of disease was IFA negative for antibodies to SFGR. Indirect immunofluorescence assays remains the most commonly used serological technique for diagnosis; however, serological evidence of infection occurs no earlier than 7 to 10 days after the onset of illness^{8,10}. Thus, the diagnosis must be based on clinical and epidemiological grounds, because the delay of specific treatment with doxycycline or chloramphenicol increases the risk of severe or fatal outcomes.

In the present case, death occurred five days following the onset of illness, an acute fulminant presentation. Although at least half of all deaths occur within 7 to 9 days of disease, accelerated clinical courses may occur and other variables, such as chronic alcoholism, cardiac problems and glucose-6-phosphate dehydrogenase deficiency (G6PD), associated with absence of early antibiotic treatment, can explain the severity of these cases¹⁰. None of the conditions previously mentioned were identified, except for delayed treatment, though G6PD deficiency is not routinely performed. PCR is a useful diagnostic method in the early phase of illness when antibodies are undetectable^{5,10}. In this case report, *ompA* sequences by PCR amplification detected in tissue fragments of liver, heart and lung were sequenced and *R. rickettsii* was identified as the etiologic agent.

The present case illustrates well the diversity of clinical presentations of BSF and the difficulty of detecting the rash on dark-skinned individuals, emphasizing the importance of the earliest possible antibiotic empiric therapy in severe *spotless* fever, during the period of May to November, when peak *Amblyomma* reproductive activity is observed.

Finally, although the detection of antibodies against SFGR remains the best recognized and most used laboratory method to confirm BSF, PCR should be considered the gold standard early in the course of disease and an important diagnostic tool to help identify missed, unconfirmed, or unreported deaths which may be caused by *R. rickettsii* in Brazil.

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