

Tick bite fever in South Africa

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Abstract

Tick bite fever has been a constant feature of the South African medical landscape. While it was recognised many years ago that there was a wide spectrum of clinical severity of infection, only recently has it been established that there are two aetiological agents, with different epidemiologies and clinical presentations. *Rickettsia conorii* infections resemble the classical Mediterranean spotted fever (*fièvre boutonneuse*), and patients are sometimes at risk of severe or even fatal complications. On the other hand, African tick bite fever is a separate entity caused by *Rickettsia africae* and tends to be a milder illness, with less prominent rash and little tendency to progress to complicated disease. Irrespective of the agent, the treatment of choice for tick bite fever in South Africa remains doxycycline or tetracycline, and the role of macrolide and quinolone antibiotics is still unclear, or at least restricted.

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Introduction

The rickettsiae comprise a diverse group of bacterial organisms responsible for various clinical entities globally. With a couple of exceptions, all are vector-borne. In South Africa the most common rickettsial disease is tick bite fever (TBF). Two typical clinical scenarios are presented for consideration.

Case 1

A 60-year-old farmer in North-West Province complains of fever and severe headache a few days after removing ticks from his dogs. Four days later he becomes confused and is admitted to hospital. He is found to be hypotensive, with a generalised maculopapular rash that rapidly becomes confluent and haemorrhagic in places. The leukocyte count is $2 \times 10^9/L$ with an absolute neutrophilia; there is profound thrombocytopenia, hepatic transaminases are four times normal and there is evidence of renal failure. The Weil-Felix test is negative, and smears for malaria are repeatedly negative. He is started on ceftriaxone for a possible bacterial septicaemia. Blood cultures are negative. Tests for Crimean-Congo fever are negative. No ticks or tick bites are found. Two days after admission the patient dies of multi-organ failure. What diseases would you include in your differential diagnosis?

Case 2

A three-year-old child complains of a headache seven days after visiting a farm in Mpumalanga Province. She is febrile (39°C), with a painful cervical lymph node, and an eschar is found on the scalp. Three days later she develops a sparse maculopapular rash on the trunk and palms and soles. How would you manage the patient?

Discussion

The earliest description of the disease resembling boutonneuse or Mediterranean spotted fever in southern Africa dates back to 1911. In 1931 Troup and Pijper published their classic description of South African TBF, which distinguished between mild and severe forms of the disease.¹ Unfortunately, laboratory correlates of this distinction were subsequently lost, and the result was that *Rickettsia conorii* var *pijperi* became accepted as the sole agent of South African TBF. In 1992, however, a different rickettsial species responsible for some cases of TBF was identified by molecular techniques, and was named *Rickettsia africae*.² There are therefore at least two TBF diseases of southern Africa: boutonneuse fever-like TBF (caused by *R. conorii*) and African TBF (caused by *R. africae*).

The former is usually transmitted by dog ticks in a peri-urban or peri-domestic setting, with dogs, rodents and ticks themselves forming the reservoir. In contrast, African TBF is typically transmitted by specific cattle and game ticks (*Amblyomma hebraeum*) in rural settings of southern Africa (see Figure 1). Surveys have shown up to 70% seroprevalence in sub-Saharan areas where *Amblyomma* ticks and cattle farming coincide.³ Notwithstanding this, there are very few clinical case reports of TBF in indigenous populations,⁴ presumably because of mild or inapparent disease and consequent lack of clinical recognition. In Zimbabwe annual case incidence rates of African TBF have been estimated as 60 to 80 per 10 000 patients.⁵ TBF is commonly recognised in non-African patients in South Africa but the incidence is not known. The incidence rates of infection have been estimated to be in the region of 4–5% in visitors from Europe, which are higher than those for other febrile illnesses such as malaria and typhoid fever. There is a large population at risk, e.g. game reserve visitors, hunters, soldiers and farmers.⁶

Figure 1: *Amblyomma hebreum*, adult male (Photo: Dr P Jupp, A Kemp)

Clinical features

As indicated above, TBF is common in South Africa, although recognised cases are probably far outnumbered by subclinical ones. Larval- and nymph-stage ticks typically transmit the diseases; larvae ('pepper ticks') are often unnoticed on the body because they are so small. *R conorii* infections (boutonneuse fever-type TBF) begin after an incubation period of five to seven days, with a consistent prodrome of malaise, fever, headache, nightmares and myalgia. The eschar is the primary lesion and marks the site of attachment of the infected tick; it consists of a central necrotic area surrounded by inflamed skin (see Figure 2). The eschar is not always apparent; it may be under scalp hair, behind the ear, in the anogenital area or on other cryptic body sites. Dog owners who crush engorged ticks are at risk for acquiring infection via conjunctival splashes (see Case 1). About three days after the onset of symptoms, the rash appears. It is usually a coarse maculopapular eruption involving the palms and soles (see Figure 3).

Figure 2: Tick bite fever eschar (Photo: Dr J Hyslop)

Clinical presentation varies from very mild to severe and even fatal disease; the latter occurs particularly in elderly or debilitated people but is not limited to this group.⁷ Complications include encephalitis, confusion or coma, pneumonia, pulmonary embolism following deep vein thrombosis, consumptive coagulopathy, bleeding, gangrene, hepatorenal failure and myocarditis. Rarely, but particularly when treatment is delayed, TBF cases can present with multi-organ involvement and mimic meningococcal septicaemia, other fulminant

Figure 3: Typical coarse maculopapular rash of tick bite fever (Photo: Dr B Miller)

Gram-negative septicaemia or even a viral haemorrhagic fever, most commonly being confused with Crimean-Congo haemorrhagic fever (CCHF) (as in Case 1). The incubation period from tick bite to clinical disease differs in the two diseases; one to three days following tick-transmitted CCHF and usually five to seven days in TBF. African TBF (*R africae*) tends to be a milder disease in general, and life-threatening complications have not been described,³ although significant acute neuropsychiatric features⁸ as well as prolonged sub-acute neuropathy⁹ have been described. The African TBF prodrome is similar to that of *R conorii* infection; characteristic, but not consistent, distinguishing features are multiple eschars, tender regional lymphadenopathy, rashless illness or only scattered and/or vesicular rash elements. Aphthous stomatitis was noted in 11% of a series of 38 patients.⁶

Diagnostic issues

The classical clinical triad of *fever, eschar and rash* occurs in 50–75% of cases of TBF, but there are less typical presentations. The eschar may resemble an infected insect bite or other skin trauma or an early anthrax lesion. The rash may suggest rubella, measles, secondary syphilis, disseminated gonococcal disease, enterovirus or arbovirus infections, leptospirosis, typhoid, immune complex vasculitis or drug reactions (see Figure 4). Meningococcal rashes can look similar, but the onset and progression of illness is much faster than in TBF. During the non-specific prodromal period, malaria is an important differential diagnosis in travellers. Serological tests are often negative early in the disease and repeat testing is required; treatment should not be delayed solely because of negative serology. Specific micro-immunofluorescence is the serological method of choice; the two species share antigens and are not routinely distinguishable, but this does not affect treatment. The Weil-Felix agglutination test is now regarded as obsolete as it is neither sensitive nor specific. In most patients the white blood cell count remains within the normal range with neutrophilia being typical. In complicated disease neutropenia and thrombocytopenia may be noted.

Figure 4: Purpuric rash in severe tick bite fever (Photo: Dr B Miller)

Treatment

Large-scale clinical trials of treatment for TBF have not been done. Some infections may be mild, but TBF can be very severe and therapeutic delay should be avoided. Tetracycline-group antibiotics, particularly doxycycline, are the treatment of choice. For adults, doxycycline 100 mg bd for five to seven days is recommended although shorter courses may be adequate.¹⁰ Doxycycline is highly effective and a clinical response with symptom relief and defervescence can be expected within 48 hours. Failure of response within this period should suggest the possibility of another diagnosis.

Chloramphenicol and the 4-fluorinated quinolones show in-vitro activity, but clinical data on efficacy is limited.¹¹ However, a 4-fluorinated quinolone such as ciprofloxacin, or chloramphenicol, may be the only available option in critically ill patients unable to tolerate oral medication, as parenteral tetracycline is unavailable in South Africa. Erythromycin has poor efficacy and there is insufficient clinical data to recommend the new macrolides such as clarithromycin and azithromycin,^{11,12} although they may have a place in supplementing initial doxycycline treatment. As TBF can be life-threatening in patients of any age group, treatment with the most effective agent, doxycycline, is the recommended therapy for all patients. Therefore, doxycycline

should be strongly considered at least for initial therapy even in children under eight years of age and pregnant women (see Case 2). An initial treatment of two days of doxycycline should be given followed by three to five days of a macrolide to complete the therapeutic course. Limited data supports the use of steroids in patients with fulminant TBF, or disease complicated by acute respiratory distress. Most of the experience of steroids in rickettsial disease can be extrapolated from their use in patients with complicated Rocky Mountain spotted fever.¹²

Conclusion

The diagnosis of TBF is usually readily made if the classic triad of fever, rash and eschar is apparent. Less typical forms of TBF present with a wide range of clinical features and severity. The treatment of choice is doxycycline or tetracycline. 🙏

Conflict of interest

No conflict of interest exists.

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