

ZOONOTIC AND VECTOR-BORNE DISEASES

Severe tick bite fever

Tick bite fever must be considered as part of the differential diagnosis in patients with acute febrile illness, particularly when there is a supportive epidemiological history, negative laboratory tests for malaria, no response to the usual empiric antibiotics for 'septicaemia' and evidence of multisystem pathology, with or without bleeding. Two fatal cases of tick bite fever were recently referred to the NICD for consideration as possible Crimean-Congo haemorrhagic fever (CCHF).

The first patient was a 57-year-old male who lived on a smallholding (with no animals) in North West Province. Due to the COVID-19-related restriction on visitors, important history about possible tick exposures and a bite mark on the neck was not elicited. He was admitted to hospital with a history of a stiff neck for 10 days with headache, diarrhoea and a maculopapular rash. The patient appeared to have a thick neck and the tick bite was not noted. Encephalitis was considered due to the history, clinical findings of confusion and disorientation, and CSF findings (polymorphonuclear cells 3/mm³, lymphocytes 17/mm³, protein 655 mg/dL; culture negative; PCR for viral pathogens negative). He was treated with ceftriaxone and acyclovir, but his condition deteriorated rapidly and he required ventilator support and renal dialysis. Laboratory results: Hb 12.4 g/dL, WCC 7.07 ×10⁹/L, neutrophils 88%, lymphocytes 6.2%, eosinophils 0%; platelets 52 ×10⁹/L, CRP 201 mg/L, bilirubin 88 µmol/L, AST 210 U/L, ALT 124 U/L, creatinine 341 µmol/L, urea 13.6 mmol/L, SARS-CoV-2 negative by PCR. A history of tick exposures and bite on the back of the neck was obtained from family members later in the admission. Tick bite fever was considered but the patient demised despite the introduction of ciprofloxacin and doxycycline treatment. PCR for *R. conorii* on blood was positive.

The second patient was an adult male who lived in a Free State Province town and worked in recycling. A week before the onset of his illness, he underwent ablative treatment for refractory atrial fibrillation, complicated by a minor tear in the oesophagus. He was admitted to hospital with an acute febrile illness and multi-organ failure, and was intubated, ventilated and dialysed. A very astute physician noted a lesion highly suggestive of an eschar on the chest wall in between the multiple and extensive

ecchymotic lesions. Doxycycline and ciprofloxacin were started but his condition deteriorated and he demised.

While the majority of cases of tick bite fever (TBF) are mild and uncomplicated, a number of severe cases with multi-organ pathology have been referred previously. Severe tick bite fever may be misdiagnosed as bacterial sepsis and even Crimean-Congo haemorrhagic fever (CCHF). In very ill patients, especially those requiring admission to the intensive care unit, the history of a possible tick exposure may be missed and the finding of an eschar may be particularly difficult, given that ticks frequently attach in unusual places not easily visible in a critically-ill patient. Haematological abnormalities including low white cell and platelet counts, raised transaminases, and a rash that may be petechial or maculopapular, are often reported. *Rickettsia conorii* infections are more likely to evolve to serious and complicated disease, compared with *R. africae* infections.

Routine serological tests do not distinguish between the two rickettsial species, and antibodies are often undetectable at the onset of illness. In any case, the diagnosis of TBF is primarily clinical, based on presence of fever, intense headache and an eschar, often accompanied by tender local lymphadenopathy. PCR for rickettsiae in blood has low sensitivity; however, when applied to a dry cotton wool swab from an eschar, PCR can be a useful confirmatory investigation.

If TBF is considered based on the clinical findings or as part of the differential diagnosis of a patient with 'sepsis', particularly if tick exposure is likely as a result of occupation (e.g. farmers, vets), animal contact or geographic exposure, empiric treatment should be commenced with doxycycline, the treatment of choice. In patients unable to tolerate oral treatment, particularly those who are critically ill, intravenous ciprofloxacin should be used. Experience with tigecycline is very limited with only one clinical case report of its use in severe murine typhus, although in vitro and animal studies suggest it is likely to be effective in other rickettsial infections. CCHF must be considered in critically-ill patients with no obvious eschar, on the basis of clinical and epidemiological findings (tick exposure, occupational risk, incubation period).