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CASE REPORT

Coxiella burnetii causing haemophagocytic syndrome: a rare complication of an unusual pathogen

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Abstract We describe an unusual presentation of Q fever with associated haemophagocytic syndrome, confirmed by bone marrow aspirate, Q fever polymerase chain reaction (PCR) and serological testing. Clinical recovery was observed after the commencement of doxycycline with normalisation of the patient's full blood count and serum biochemistry. Serial monitoring of the Q fever serology revealed the subsequent development of sustained high phase 1 IgG antibodies, suggestive of chronic Q fever. Although many infectious aetiologies have been associated with haemophagocytosis, Q fever has only rarely been described in this context. The diagnosis of Q fever is often overlooked, especially when the presentation is atypical. We describe how the use of PCR testing significantly shortened the interval to definitive diagnosis and helped elucidate the underlying cause of the patient's haematological disorder.

Keywords *Coxiella burnetii* · Q fever · Haemophagocytosis · Haemophagocytic lymphohistiocytosis

Consent: written permission to publish was obtained from the patient.

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Introduction

Q fever is a zoonosis caused by the obligate intracellular γ-proteobacterium *Coxiella burnetii*. It represents a significant public health problem in many areas of the world, particularly where there is close contact with farm animals or meat products. It was originally described in Queensland, Australia, by Edward Derrick in 1937 amongst abattoir workers, and termed Q (for query) fever "until fuller knowledge should allow a better name" [1]. Australia has high rates of notification for Q fever, averaging 3 notifications per 100,000 annually between 1991 and 2004 [2]. Recent large outbreaks in the Netherlands have infected more than 3,000 individuals and refocused attention upon this often neglected disease [3]. Clinical manifestations can range from asymptomatic seroconversion to non-specific febrile reactions, with varying degrees of pneumonia or hepatitis. Many other organ systems may be affected, with neurological, osteoarticular, genitourinary, gastrointestinal, endocrine and cutaneous complications described [2, 4–6]. A small proportion of cases will develop chronic disease with life-threatening complications, such as endocarditis [7]. Given the wide variation in presenting features, it can be hard to recognise and is frequently overlooked. Here, we present an unusual case of acute Q fever presenting with associated haemophagocytic syndrome.

Case report

A 58-year-old farmer from rural north Queensland, Australia, presented with a week-long history of high fevers, chills, arthralgias, fatigue and anorexia. He was found to be febrile, hypotensive and delirious. Physical

examination revealed hepatosplenomegaly with moderate ascites and bibasal crackles on chest auscultation. Relevant haematology and biochemistry results are shown in Table 1. He was admitted to the intensive care unit and treated with broad-spectrum antibiotics. His progress was complicated by significant cytopaenia. His platelet count and haemoglobin reached a nadir of 5 $\times$ 10^9/L and 75 g/L, respectively, despite the transfusion of blood products. A bone marrow aspirate at that time was suggestive of haemophagocytic syndrome, otherwise known as haemophagocytic lymphohistiocytosis (HLH) (see Fig. 1).

The underlying diagnosis was suggested by a history of occupational exposure to cattle. An enzyme immunoassay (EIA) showed a reactive IgM against *C. burnetii* phase 2 antigens (Panbio, Queensland, Australia). This was subsequently confirmed by immunofluorescence (IF), with convalescent sera demonstrating a rise in phase 2 IgG IF from <10 to 1,280 (Pathology Queensland, in-house assay). Phase 1 IgG IF was initially <10. *C. burnetii* real-time polymerase chain reaction (RT-PCR) testing was also positive on both serum taken at presentation and the bone marrow aspirate (Pathology Queensland, in-house assay). The RT-PCR assay was performed using TaqMan primers and probes based on the sequence of bases 1–1,061 of the 27-kDa outer-membrane protein gene (*com1*) of *C. burnetii* (GenBank accession number AB004712), which has previously been shown to be a useful target for detecting *C. burnetii* in serum samples [8].

The patient was treated with oral doxycycline and also received five doses of intravenous immunoglobulin.

Table 1 Admission blood test results

Value	Result	Normal range
Sodium	127 mmol/L	135–145 mmol/L
Potassium	2.7 mmol/L	3.5–4.5 mmol/L
Creatinine	203 μmol/L	73–108 μmol/L
Bilirubin (total)	22 μmol/L	<20 μmol/L
ALP	147 U/L	53–128 U/L
γ-GT	61 U/L	<55 U/L
ALT	128 U/L	<45 U/L
AST	372 U/L	<35 U/L
Albumin	26 g/L	35–50 g/L
Haemoglobin	125 g/L	120–180 g/L
White cells	8.0 $\times$ 10^9/L	3.5–11 $\times$ 10^9/L
Platelets	25 $\times$ 10^9/L	140-400 $\times$ 10^9/L
Ferritin	4,630 μg/L	30–300 μg/L
Fibrinogen	1.2 g/L	1.7–4.5 g/L
INR	1.5	0.9–1.2

ALP alkaline phosphatase, *γ-GT* gamma-glutamyltransferase, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *INR* International normalized ratio

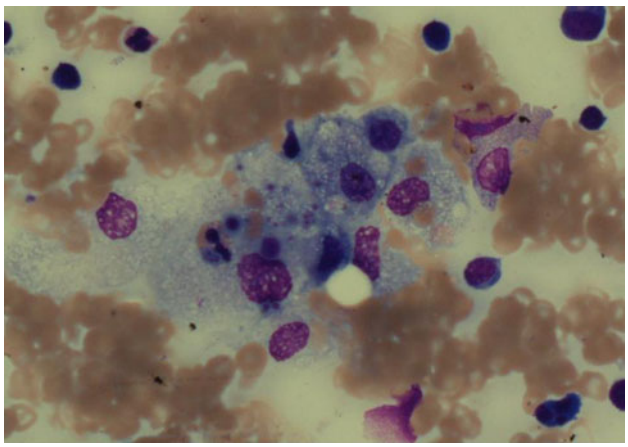

Fig. 1 Bone marrow aspirate showing activated macrophages engulfing red cells and platelets

Within 2 weeks, his symptoms improved with near normalisation of his blood counts and biochemistry. Subsequent serial measurement of his Q fever serology revealed a sustained rise in his phase 1 IgG and IgA titres to ≥1,280 after 6 months. Phase 1 IgG titres >800 are commonly used as a serological marker for the development of chronic Q fever [6]. Transoesophageal echocardiography showed no evidence of endocarditis, although it did reveal mild mitral valve prolapse. As such, he was restarted on doxycycline and hydroxychloroquine for the treatment of chronic Q fever with a planned minimum duration of 18 months.

Discussion

Haemophagocytosis has only rarely been described in the context of Q fever [9–11]. The disorder is characterised by activated macrophages engulfing erythrocytes, leukocytes, platelets and precursor cells in bone marrow, liver or lymph nodes with associated fever, pancytopaenia and splenomegaly [12]. Very high ferritin levels, deranged liver biochemistry and coagulopathy may also be observed. An elevated plasma concentration of the alpha chain of the interleukin-2 receptor (soluble CD25) and impaired or absent natural killer cell activity may also be diagnostic [13]. Haemophagocytic syndrome is often a familial disorder of children, but has been described in relation to a wide variety of infectious agents, as well as collagen-vascular disorders and malignancies [12, 14, 15]. It is thought to reflect inappropriate macrophage activation in relation to subtle genetic and immunological defects. Management should include the identification of any potentially treatable infectious cause, as effective antimicrobial therapy can result in the recovery of haematological parameters, especially when bacterial triggers are identified.

The diagnosis of Q fever is often difficult given its protean manifestations, its inability to be cultured on standard media and the reliance on serology for confirmation. The PCR on serum in this case was positive before diagnostic levels of antibody could be detected. Q fever serology is often non-reactive or difficult to confirm on specific IF testing within the first 10–14 days of illness. As such, a positive PCR in cases where there is a high index of suspicion and significant complications can be of value [16–19]. The sensitivity of PCR from blood specimens diminishes once seroconversion occurs and, therefore, has lesser utility beyond the acute phase of illness [20]. It may also be useful in the detection of *C. burnetii* from tissue (e.g. heart valves) or from blood in the context of Q fever endovascular infections [16]. The presence of *C. burnetii* DNA in bone marrow, as detected by PCR, could represent contamination by peripheral blood. However, immature cells in the monocyte–macrophage lineage are thought to support the replication of *C. burnetii*, and may be less able to clear the infection than fully differentiated macrophages [21]. Various patterns of bone marrow involvement have been described in Q fever, including granuloma formation, marrow necrosis and angiitis [22–24]. Although a low platelet count is a common finding in acute Q fever [25], profound thrombocytopaenia or unexplained pancytopaenia should prompt the consideration of haemophagocytosis in the differential diagnosis.

The patient in this case developed elevated titres of phase 1 IgG antibodies 6 months after recovery from his presenting illness. Whether the slow evolution of this serological profile reflected the nature and severity of his original infection is unclear. It is possible that the persistence of *C. burnetii* in infected bone marrow precursor cells may have provided a focus for the subsequent development of chronic disease [21]. However, the diagnosis of chronic Q fever on serological criteria alone is controversial. Immunofluorescence, despite remaining the reference method for confirming the diagnosis by serology, is not well standardised across laboratories. Wide variations in reported antibody titres are known from studies that have compared sera tested in different countries [26]. As such, doubt exists as to whether a high phase 1 IgG titre alone is sufficient evidence for the diagnosis of chronic Q fever. The cut-off value of >800 is based upon the experience from a single centre using an in-house assay. This group have recently suggested that this value should be increased to ≥1,600 to improve specificity [27]. Some commercial assays may demonstrate phase 1 IgG titres ≥1,280 several months after acute presentation without evidence of chronic disease, and subsequent decline without therapy [28]. However, subtle endovascular lesions can be easily missed on echocardiography and patients may have few, if any, overt symptoms. As such, treatment is often commenced once sustained elevated phase 1 IgG levels are found, given the potential risks of missing the opportunity for early therapy.

In conclusion, HLH is a rare but recognised complication of Q fever. In the context of acute Q fever, profound and persistent haematological abnormalities should prompt the consideration of HLH as a diagnosis. Conversely, if a diagnosis of HLH is made, infectious causes such as Q fever should be investigated using serology and PCR, especially in endemic areas.

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