Q Fever with Isolated Bone Marrow Involvement

Febre Q com Envolvimento Isolado da Medula Óssea

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Abstract:

A 71-year-old man presented to the emergency department with 3 weeks of fever, asthenia and night sweats. The initial laboratory results showed mild anaemia, thrombocytopenia and elevated C-reactive protein, with normal liver enzymes. The remaining initial study was unremarkable. Due to haematologic abnormalities, a bone marrow biopsy was performed, revealing multiple ring epithelioid granulomas, consisting of a central lipid vacuole surrounded by epithelioid cells and some neutrophils. These findings, although not pathognomonic, favoured the diagnosis of Q fever with isolated bone marrow involvement. The diagnosis was later confirmed by seroconversion and exclusion of other causes for this histopathologic finding. The patient was treated with doxycycline for fourteen days with a good response and no evidence of the disease after six months.

Keywords: Bone Marrow; Coxiella burnetii; Q Fever/complications.

Resumo:

Homem de 71 anos recorreu ao serviço de urgência com 3 semanas de febre, astenia e suores nocturnos. Os resultados laboratoriais iniciais mostraram anemia ligeira, trombocitopenia e elevação da proteína C reativa, com enzimas hepáticas normais. O restante estudo inicial foi inconclusivo. Devido às anomalias hematológicas, foi realizada biópsia da medula óssea que revelou múltiplos granulomas epitelioides em anel, que consistiam num vacúolo lipídico central rodeado por células epitelioides e alguns neutrófilos. Estes achados, embora não patognomónicos, favoreceram o diagnóstico de febre Q com envolvimento isolado da medula óssea. O diagnóstico foi posteriormente confirmado com seroconversão e exclusão de outras causas para este achado histopatológico. O paciente foi tratado com doxiciclina durante catorze dias, com boa resposta e sem evidência da doença ao fim de seis meses.

Palavras-chave: Coxiella burnetii; Febre Q/complicações; Medula Óssea

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https://doi.org/10.24950/rspmi.2616

Introduction

Q fever is a zoonosis caused by *Coxiella burnetii*, a strictly intracellular bacteria with a worldwide distribution and high infectivity. Humans are typically infected after contact with farm animals, including cattle, goats and sheep, mainly through inhalation of contaminated aerosols.[1] The acute form of the disease can have a wide range of clinical manifestations, from asymptomatic seroconversion or a self-limited flu-like syndrome to severe disease with different organ involvement, most commonly pneumonia and hepatitis.[1,2] The diagnosis is usually confirmed by serology.[1,3] This requires a high degree of suspicion, as the epidemiological information, physical exam and routine laboratory results are non-specific. Some patients may develop a chronic or persistent localized infection.

We report a case of acute Q fever with isolated bone marrow involvement, which is a rare manifestation of an infrequent disease. This case highlights the difficulties that can arise in its diagnosis, the benefits of following small diagnostic clues and the histopathologic features of bone marrow involvement in Q fever.

Case Report

A 71-year-old man, working as a manager, presented to the emergency department with a high fever of 38.8ºC for 3 weeks, asthenia and night sweats. He did not report myalgias, headache or other symptoms. He had previously received 7 days of prulifloxacin without clinical improvement.

He had a history of high blood pressure, type 2 diabetes mellitus, both controlled with medication, and had been recently diagnosed with atrial fibrillation, taking rivaroxaban. He lived in an urban area, consumed bottled water and had no pets or contact with animals, including cats, dogs and cattle. The symptoms started one week after a leisure trip to Madeira, but he also had a business trip to Cairo three months before, having stayed in the city and mostly at the hotel. During these trips, he denied having had contact with animals or consuming dairy products.

On physical examination, he was febrile, with low blood pressure (80/60 mmHg), heart rate 75 bpm and peripheral oxygen saturation of 96%. The physical exam was otherwise unremarkable.

His initial blood tests revealed anaemia (hemoglobin 11.5 g/dL), thrombocytopenia (platelets 39.000/µL), total white blood cell 16.280/µL, 59% neutrophils and 32% lymphocytes,

international normalized ratio (INR) 1.87, C-reactive protein (CRP) 30.25 mg/dL (normal < 0.5 mg/dL) and ferritin 2956 µg/L (normal 21.8-274.7 µg/L). There was mild elevation of creatinine (1.31 mg/dL, normal 0.6-1.3 mg/dL) and urea (81 mg/dL, normal 22-52 mg/dL), with a normal urinalysis. Total and direct bilirubin were slightly elevated (1.68/0.76 mg/dL, normal 0.2-1.2/<0.5 mg/dL), with normal liver enzymes. Computed tomography (CT) of the chest, abdomen and pelvis was unremarkable. Transthoracic and transoesophageal echocardiograms were negative for endocarditis and valvular disease. Blood cultures and serologies for human immunodeficiency virus (HIV), cytomegalovirus (CMV), Epstein-Barr virus (EBV), hepatitis B and C virus, *Salmonella*, syphilis, malaria, dengue, *Rickettsia* spp., *Borrelia* spp. and *Leptospira* spp. were negative. Initial *Coxiella burnetii* serologies (indirect immunofluorescence technique) were: phase I IgG 20, phase I IgM 80, phase II IgG 40 and phase II IgM 40 (Table 1).

Table 1: Titter evolution during the follow-up. Reference cut-off < 20. Note the 4-fold increase of phase II IgG, which supports the diagnosis of acute infection.

Serology	3 weeks after symptoms	5 weeks after symptoms
IgG Phase I	<20	<20
IgG Phase II	40	200
IgM Phase I	80	320
IgM Phase II	40	40

While awaiting laboratory results, and considering the haematological abnormalities the sole discriminator of the fever, a bone marrow myelogram and biopsy were performed which revealed erythroid and myeloid hyperplasia and multiple ring epithelioid granulomas, consisting of a central lipid vacuole surrounded by epithelioid histiocytes and some neutrophils (Fig. 1). Periodic acid-Schiff and Giemsa stains were negative. Peripheral blood and bone marrow immunophenotyping by flow cytometry showed no abnormal populations.

The histopathological findings supported the diagnosis of Q fever, which was later confirmed by repeating the *Coxiella burnetii* serology, which showed seroconversion to the phase II antigen (Table 1). Polymerase chain reaction (PCR) in a blood sample to detect *Coxiella burnetii* after treatment was negative.

Treatment with doxycycline 100 mg two times daily was initiated. After starting treatment, the fever resolved and the patient showed an improvement on well-being and activity level.

After completing 14 days of treatment, without reporting any side effects, he remained asymptomatic, anaemia and thrombocytopenia had resolved, and CPR levels were normal. Follow-up at two, four and six months after treatment showed no signs of persistent infection. *Coxiella burnetii* serologies six months after the initial treatment were negative.

Discussion

Q fever is an acute febrile and occasionally persistent infection that occurs worldwide. Humans are infected mostly by contaminated aerosol inhalation and, after an incubation

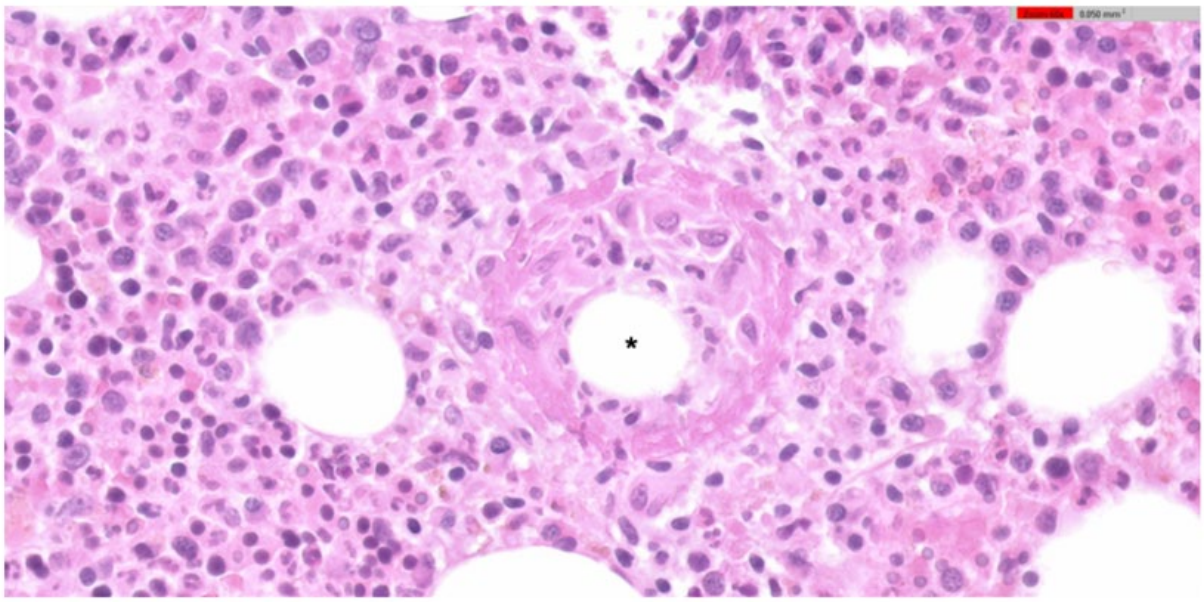

Figure 1: Haematoxylin and eosin staining of bone marrow biopsy. Ring granuloma of epithelioid histiocytes and some neutrophils around a central clear space composed of fat (*).

period of 1 to 39 days, about 40% of individuals develop acute febrile disease, with severe headache, chills, fatigue and myalgia, sometimes with pneumonia and/or hepatitis.[1] Hepatitis is a frequent presentation of acute Q fever in countries where the disease is endemic, like Portugal.[4,5] Bone marrow involvement is rarely mentioned in the literature.[6,7]

Primary (acute) *C. burnetii* infection is defined by the association of acute clinical symptoms with the following serologic criteria: phase II IgG titers≥ 200 and phase II IgM titers≥ 50[8] or a fourfold rise in anti-phase II IgG from two serum samples taken apart.[3]

In recent years, studies have shown the usefulness of PCR to detect *C. burnetii* in blood.[1,3] These techniques can overcome the delay in diagnosis based on serology, as it has high sensitivity and specificity for acute Q fever if collected during the acute phase (optimally during the first 2 weeks of symptoms) and either before or shortly (24-48 hours) after antibiotic administration.[3]

In our case, the distinct feature that helped the diagnosis was the ring granulomas, also sometimes called "doughnut" granulomas, found in the bone marrow biopsy. Historically described as pathognomonic of Q fever, these granulomas can appear in different organs, being more frequent in the liver, and are known to appear in different infections, including EBV, CMV, Hepatitis A virus, *Brucella melitensis*, *Salmonella* spp. and other intracellular bacteria such as mycobacterial infections,[6,9] as well as secondary to Hodgkin and non-Hodgkin lymphomas,[9,10] autoimmune disorders and drugs such as allopurinol.[9] The ring epithelioid granulomas in the Q fever consist of histiocytes, lymphocytes and eosinophils surrounding a central lipid vacuole with a fibrinoid outer ring. The pathophysiology is not well understood, but it has been suggested that these lesions are related to focal vasculitis with endothelial injury and deposition of immune complexes.[11,12]

When adequate treatment is initiated, prognosis is usually good. One to five per cent of the infected patients can develop a persistent focalized infection, mainly as endocarditis, osteoarticular infection or persistent lymphadenitis.[2,13] Patients with prosthetic valves, valvular abnormalities like aortic bicuspid or mitral prolapse, vascular graft, prosthetic joint, pregnant women or immunocompromised hosts have a higher risk of persistent infection.[1] Long-term studies show that patients with acute Q fever are at risk of developing post-Q fever fatigue syndrome.[14] Although there are some concerns about a link between Q fever, especially if affecting the bone marrow or lymph nodes, and non-Hodgkin lymphoma,[7] more studies are needed.[15]

To our knowledge, this is the only case in the literature that describes an isolated bone marrow involvement of Q fever, especially without elevated liver enzymes or pneumonia, making the diagnosis of this rare entity even more challenging. ■

Contributorship Statement

JRA – Data collection, manuscript drafting, and literature review
JAG, AM – Manuscript drafting and revision, literature review
LM – Data collection, manuscript drafting and revision, literature review
All authors approved the final version to be published.

Declaração de Contribuição

JRA – Recolha de dados, redação do manuscrito, revisão bibliográfica
JAG, AM – Redação e revisão do manuscrito, revisão bibliográfica
LM – Recolha de dados, redação e revisão do manuscrito, revisão bibliográfica
Todos os autores aprovaram a versão final a ser publicada.

Ethical Disclosures

Conflicts of Interest: The authors have no conflicts of interest to declare.
Financing Support: This work has not received any contribution, grant or scholarship.
Confidentiality of Data: The authors declare that they have followed the protocols of their work center on the publication of patient data.
Patient Consent: Consent for publication was obtained.
Provenance and Peer Review: Not commissioned; externally peer-reviewed.

Responsabilidades Éticas

Conflitos de Interesse: Os autores declaram a inexistência de conflitos de interesse na realização do presente trabalho.
Fontes de Financiamento: Não existiram fontes externas de financiamento para a realização deste artigo.
Confidencialidade dos Dados: Os autores declaram ter seguido os protocolos da sua instituição acerca da publicação dos dados de doentes.
Consentimento: Consentimento do doente para publicação obtido.
Proveniência e Revisão por Pares: Não comissionado; revisão externa por pares.

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Received / Recebido: 2024/08/05
Accepted / Aceite: 2024/11/05
Published Online / Publicado Online: 2026/02/27
Published / Publicado: 2026/02/27

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