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Case report

Q fever presenting as splenic infarct without endocarditis

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ABSTRACT

Q fever is frequently associated with the development of antiphospholipid antibodies though rarely causes thromboses. A 44-year-old man presented with diarrhea and fevers and was found to have a splenic infarct. Infectious work-up revealed acute Q fever as well as high anticardiolipin antibody titers. He was treated with doxycycline and hydroxychloroquine and suffered no further thromboembolic complications. The optimal management of thromboembolic complications is uncertain given the rarity of documented cases. However, the presence of these antibodies has been associated with increased risk of complications. Further investigation into the management of patients with Q fever associated hypercoagulability is needed.

Objective

We present a case of a 44-year-old man presenting with fever and splenic infarct caused by acute *Coxiella burnetii* infection (Q fever) to highlight the association between thromboembolic events and development of antiphospholipid antibodies in *Coxiella* infection. We review the data underlying current management guidelines.

Introduction

Coxiella burnetii is the causative agent of Q fever and has protean manifestations, including development of antiphospholipid antibodies leading to thromboses. About one-third to one-half of patients develop antiphospholipid antibodies though the rate of thromboses and diagnosis of antiphospholipid syndrome remain low [1,2]. Nevertheless, the presence of these antibodies is associated with an increased risk of complications of *Coxiella* infection, particularly the development of endocarditis [2,3]. The thromboembolic events commonly associated with Q fever are deep vein thromboses and pulmonary emboli [1]. Optimal management of hypercoagulability in Q fever is uncertain; some experts suggest the use of hydroxychloroquine in patients who develop anticardiolipin antibodies although there is a paucity of data supporting this practice. Here we describe a case of a previously healthy man diagnosed with Q fever with high anticardiolipin titers, found to have a splenic infarct as his sole thrombotic manifestation. Splenic infarction is a rare thrombotic complication of Q fever and has been infrequently reported in the literature [4–6]. Awareness of atypical presentations of Q fever is essential for medical professionals because specialized testing is required for diagnosis. Moreover, identification of these atypical cases will be helpful to determine best practices for management of Q fever complications.

Case

A 44-year-old man with no known past medical history presented with one week of fatigue, abdominal pain, diarrhea, and fevers. He reported non-bloody watery diarrhea after every meal that progressively worsened and prompted presentation to the hospital. He denied recent travel, sick contacts, animal exposures, and water exposures. Social history was notable for childhood and early adulthood spent in rural Mexico and current employment as a landscaper.

On presentation to the hospital, he was tachycardic and febrile to 38.9 °C, but had normal blood pressure and respiratory status. Exam revealed diffuse abdominal tenderness without organomegaly. Laboratory investigations were significant for a white blood cell count of 4.0×10^9/L with 75 % neutrophils, 17 % lymphocytes, and 0.3 % monocytes. Platelet count was 171×10^9/L. Creatinine was within normal limits, and liver function tests were mildly elevated with alanine aminotransferase of 97 units/L and aspartate aminotransferase 92 units/L, and alkaline phosphatase of 146 IU/L. Hemoglobin A1C was 10.1 % on

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admission, with no prior value on record. Multiple sets of blood cultures were negative.

The patient underwent computed tomography (CT) of his chest, abdomen, and pelvis. CT revealed mild transverse colon thickening, as well as a wedge-shaped hypo-enhancing splenic lesion consistent with a splenic infarct (Fig. 1). Transthoracic and transesophageal echocardiograms were within normal limits without valvular pathology. Despite antimicrobial therapy with ceftriaxone and metronidazole, the patient continued to have fevers and abdominal pain.

A thorough infectious work-up was undertaken including testing for *Mycobacterium tuberculosis* via sputum induction, stool ova and parasite screening, polymerase chain reaction testing for infectious causes of gastroenteritis, and Epstein-Barr Virus serology. As part of this evaluation, *Coxiella* serology was obtained. The patient's Q fever Phase I IgM was 1:64, Phase I IgG was negative, Phase II IgG was 1:4096, and Phage II IgM was 1:16,384 (Table 1). Based on these results, the patient was diagnosed with acute Q fever and started on doxycycline 100 mg twice daily with resolution of his fevers after about 48 h of treatment (Tables 1 and 2).

Antiphospholipid syndrome testing was obtained due to suspicion for endovascular involvement given his splenic infarct (Table 2). His anticardiolipin antibodies were all above the upper limit of normal; IgM was greater than 150 MPL U/mL (reference range 0–12 MPL U/mL), anticardiolipin IgG was greater than 150 GPL U/mL (reference range 0–14 GPL U/mL), and IgA was 104 APL U/mL (reference range 0–11 APL U/mL). Other antiphospholipid antibody testing, such as β2-glycoprotein, was not performed. At the time of diagnosis, the patient's prothrombin time was 15.9 s (reference range: 11.9–14.5 s), partial thromboplastin time was 42 s (reference range: 22–32 s), and international normalized ratio was 1.2 s (reference range 0.8–1.1 s). Subsequent coagulation studies after initial diagnosis are not available.

Hydroxychloroquine (200 mg three times daily) was added to doxycycline soon after diagnosis based on expert opinion that it may reduce the risk of further thrombotic and endovascular complications [1]. Anticoagulation was deferred as the risks of anticoagulation were thought to outweigh the benefits. The patient experienced headaches attributed to hydroxychloroquine and completed only five weeks of the planned 12-month hydroxychloroquine course. Doxycycline was discontinued after 11 weeks of treatment due to suspected medication-induced hearing loss and tinnitus. Fortunately, after treatment with 11 weeks of doxycycline, anticardiolipin IgG and IgA normalized, and IgM decreased to 14 MPL U/mL. At seven months after treatment initiation, Phase I IgG was elevated to 1:8912. Attempts were made to have the patient obtain a repeat transthoracic echo, however he was lost to follow up.

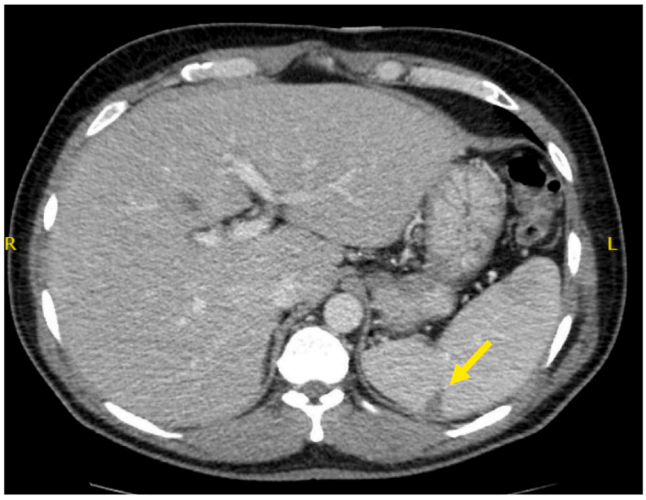

Fig. 1. Splenic infarct in Q fever. Computed tomography of the abdomen and pelvis with intravenous iodinated contrast demonstrating wedge-shaped hypoenhancing lesion in the spleen (indicated by the yellow arrow).

Table 1
Change in Q fever titers over time. Reference range: negative < 1:16.

	At diagnosis	6 weeks	12 weeks	7 months
Q fever Phase I IgM titer	1:64	1:256	1:128	1:256
Q fever Phase I IgG titer	Negative	1:16	1:64	1:8912
Q fever Phase II IgM titer	1:16,384	1:4096	1:1024	Negative
Q fever Phase II IgG titer	1:4096	> 1:131,072	1:32,768	1:32,768

Table 2
Change in anticardiolipin titers over time. GPL: IgG phospholipid; MPL: IgM phospholipid; APL: IgA phospholipid; U: Units; mL: milliliter.

	At diagnosis	6 weeks	12 weeks
Anticardiolipin IgG (reference range: 0–14 GPL U/mL)	> 150	39	12
Anticardiolipin IgM (reference range: 0–12 MPL U/mL)	> 150	57	14
Anticardiolipin IgA (reference range: 0–11 APL U/mL)	104	< 10	< 10
Prothrombin time (reference range: 11.9–14.5 s)	15.9		
Partial thromboplastin time*(reference range: 22–32 s)	42		
International normalized ratio (reference range: 0.8–1.1 s)	1.2		

Discussion

During acute Q fever, anticardiolipin antibodies are associated with thrombocytopenia, valvular heart disease, and progression to chronic endocarditis, along with hemophagocytic syndrome, meningitis and acalculous cholecystitis [1,3]. Interestingly, the presence of these antibodies is only associated with development of thrombotic complications in a small fraction of cases. In an observational study in France ranging from 2007 to 2015, 1.9 % patients with acute Q fever developed arterial and venous thromboses. Most cases with thromboses (12/13) were associated with positive anticardiolipin antibodies, and three of these patients developed persistently positive anticardiolipin antibodies beyond 12 weeks, meeting criteria for antiphospholipid syndrome [1,7]. Thrombotic complications of acute fever associated with antiphospholipid antibodies include pulmonary emboli, deep vein thromboses, cerebral vein thrombosis, splenic infarcts, myocardial infarction, and limb ischemia [1]. Given these thrombotic complications in association with elevated anticardiolipin levels, practitioners should be aware that Q fever can present with thromboses and elevated antiphospholipid antibodies. Some experts suggest routine antiphospholipid antibody screening in acute Q fever to guide additional workup and early detection of complications, such as acute endocarditis or thromboses [8].

Doxycycline 100 mg twice daily for 14 days is the standard regimen for management of acute uncomplicated Q fever [9]. For chronic or complicated disease, such as endocarditis or infected bone, the addition of hydroxychloroquine 200 mg three times per day is recommended [9]. Clinical data regarding use of hydroxychloroquine in Q fever is primarily limited to endocarditis [7]. The addition of hydroxychloroquine to treatment with doxycycline in acute Q fever is thought to prevent development of chronic Q fever [10]. However, due to limited studies on treatment of Q fever in noncardiac organ disease, duration of treatment is poorly defined in these cases and is often based on serological response [9]. Similarly, due to the rarity of thromboses in Q-fever

associated with positive anticardiolipin levels, there are no clear practice guidelines. Although no clinical trial exists, some experts suggest that high IgG anticardiolipin levels ($\geq$ 75 GPL U/mL) benefit from use of hydroxychloroquine until IgG decreases to below this value [11].

Our case report describes a splenic infarct as a rare manifestation of acute Q fever in a patient with positive anticardiolipin antibodies successfully managed with doxycycline and hydroxychloroquine. This case may raise awareness regarding thrombotic complications in Q fever. Further studies are needed to evaluate the utility of adding hydroxychloroquine to doxycycline in cases with elevated antiphospholipid antibodies to reduce the risk of complications, including disease progression and thrombosis, while balancing this with the risk of medication related side effects and toxicities.

Ethical approval

Not applicable.

Consent

Written informed consent was obtained from the patient for publication of this casereport and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

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None.

CRediT authorship contribution statement

Caitlin A Contag: Writing – review & editing, Writing – original draft, Investigation, Data curation, Conceptualization. **Lucy Studemeister:** Writing – review & editing, Writing – original draft, Data curation, Conceptualization. **Yael Bogler:** Writing – review & editing, Data curation, Conceptualization. **Joseph D. Cooper:** Writing – review & editing, Writing – original draft, Supervision, Data curation, Conceptualization.

Conflict of Interest Statement

The authors state that they have no competing interests that are directly or indirectly related to the submitted work.

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