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BRIEF REPORT

Coxiella burnetii Infection Associated With Thromboangiitis Obliterans–like Phenomena With Digital Autoamputation: A Case Report and Review of Q Fever–Associated Autoimmunity

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We present a case of a patient with chronic Q fever who presented with digital necrosis, autoamputations, and positive anticentromere antibody, mimicking a scleroderma vasculopathy or thromboangiitis obliterans. *Coxiella burnetii* infection has long been associated with the presence of autoantibodies and autoimmune phenomena including vasculitis. Clinicians should consider Q fever testing in patients with new-onset autoimmune diseases or autoantibodies and appropriate exposure histories.

Keywords. anticentromere antibody; autoimmunity; *Coxiella burnetii*; Q fever; thromboangiitis obliterans.

CASE REPORT

A 51-year-old man with a past medical history of polysubstance abuse presented with progression of chronic wounds on multiple digits of his left hand. Three years prior to admission, the patient was incarcerated in a state penitentiary wherein the inmates worked on the prison farm with duties that included feeding, milking, and birthing goats. The patient described suffering from a self-limited febrile and diarrheal illness that was common among new inmates that was colloquially referred to as "goat fever." It was during this time that he began experiencing Raynaud phenomenon and ulceration and necrosis of the digits of his right hand. He reported that he was told he might have thromboangiitis obliterans (TAO) or other autoimmune process, but he did not undergo formal workup. He ultimately experienced autoamputation of all 5 right-sided digits. While he had been sober during his period of incarceration, he relapsed onto cocaine and methamphetamine use following his release roughly 2 years prior to his presentation.

In the emergency department he was noted to have a temperature of 36.7°C, heart rate of 94 beats per minute, blood pressure 138/104 mm Hg, and respiratory rate 18 breaths per minute with an oxygen saturation 99% on room air. Examination was notable for prior amputations to the digits of the right hand and dry gangrene of multiple fingertips of the left hand with tenderness and purulent discharge (Figure 1). Laboratory values were notable for total white blood cell count of 15 300 cells/μL (reference range, 4000–11 100 cells/μL); absolute lymphocyte count, 2400 cells/μL (reference range, 1000–4800 cells/μL); absolute neutrophil count, 11 200 cells/μL (reference range, 1800–6600 cells/μL); C-reactive protein, 117.1 mg/L (reference, 0.0–10.0 mg/L); erythrocyte sedimentation rate, 54 mm/hour (reference range, 0–10 mm/hour); and antinuclear antibody >1:320 in a speckled pattern with anticentromere antibody >1:2560. Antineutrophilic cytoplasmic antibodies were negative. Magnetic resonance imaging showed osteomyelitis of multiple left-sided digits and extensive cellulitis and myositis. Computed tomographic (CT) angiography of the chest and upper extremities did not reveal evidence of vasculitis.

He underwent amputation of the left second and fourth digits with operative cultures growing *Streptococcus dysgalactiae*, methicillin-susceptible *Staphylococcus aureus*, *Staphylococcus lugdunensis*, and mixed anaerobic organisms, and he was started on cefazolin and metronidazole.

On day 11 of hospitalization, *Coxiella burnetii* serologies returned with phase I immunoglobulin G (IgG) positive at 1:2048, phase I immunoglobulin M (IgM) negative, phase II IgG positive at 1:2048, and phase II IgM negative, which was thought to represent chronic Q fever. Doxycycline and hydroxychloroquine were added to his antimicrobial treatment regimen. Transthoracic echocardiography did not reveal any abnormalities on the mitral, tricuspid, aortic, or pulmonic valves, and serum *C burnetii* polymerase chain reaction (PCR) was negative.

Positron emission tomography (PET)–CT to look for additional foci of *C burnetii* infection showed mild fluorodeoxyglucose (FDG) uptake in multiple cervical, left axillary, and right pelvic lymph nodes most consistent with reactive changes and diffusely increased FDG uptake in the spleen (Figure 2).

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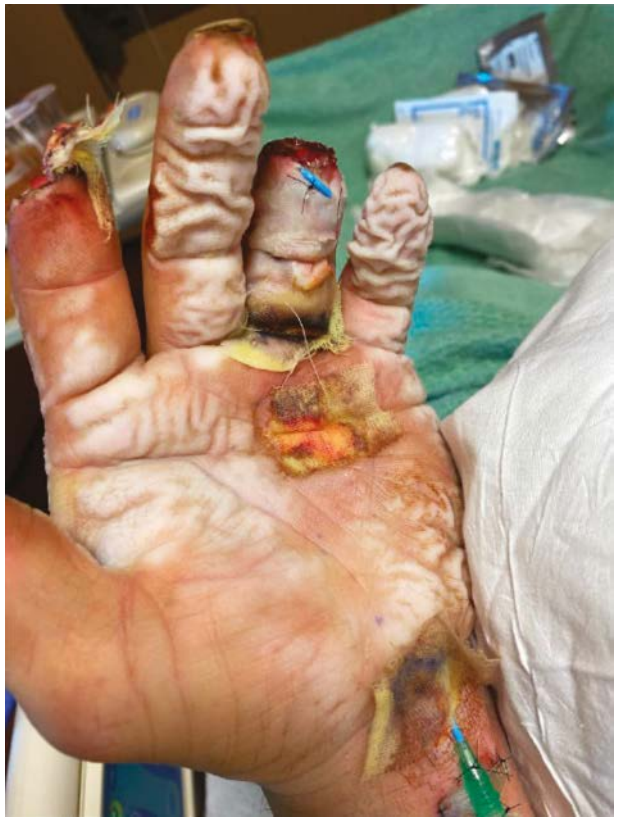

Figure 1. Photograph of left hand taken 6 days after admission.

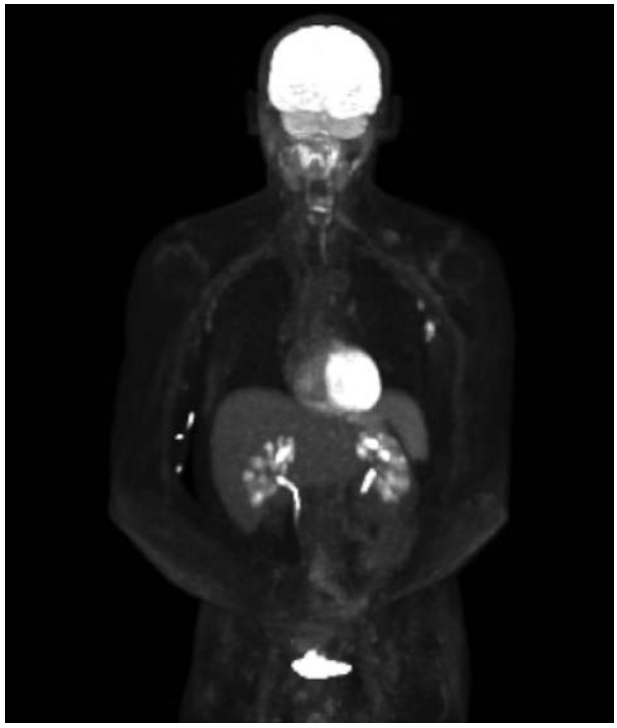

Figure 2. Positron emission tomography–computed tomography demonstrating cervical, left axillary, and right pelvic lymph nodes most consistent with reactive changes and diffusely increased fluorodeoxyglucose uptake in the spleen.

Despite abstinence from tobacco or methamphetamines for many weeks, his clinical course was complicated by ongoing ischemia of the left second and fourth fingers requiring 2 additional debridements and revision of his prior amputation. Subsequent pathologic evaluation of digital arteries was notable for small fibrosed vessels without evidence of vasculitis.

The patient remained hospitalized for the duration of his treatment for acute osteomyelitis and had complete healing of his wounds (Figure 3). Laboratory work after 8 weeks of hospitalization showed normalization of his white blood cell count and C-reactive protein. *Coxiella burnetii* phase I IgG decreased to 1:1024, phase II IgG positive at 1:1024, and phase I and II IgM remained negative. Repeat antinuclear antibody titer declined to 1:320 and anticentromere antibody remained positive.

The patient failed to attend scheduled follow-up with primary care and infectious disease.

Patient Consent Statement

Verbal consent was obtained during the patient's hospitalization; however, written consent could not be obtained as the patient did not attend follow-up appointments and did not provide valid contact information. All identifying details of the patient have been removed in accordance with our institutional policy and *Open Forum Infectious Diseases* publishing policy. Ethical board approval was not believed to be indicated because this did not involve human subjects research.

DISCUSSION

Coxiella burnetii is a obligate intracellular gram-negative organism that is responsible for both acute illness and a chronic infection known as Q fever [1]. It is a zoonotic pathogen with worldwide distribution and has animal reservoirs that include goats, sheep, and cattle [2, 3]. Infection typically occurs via inhalation of contaminated aerosols, and the infectious inoculum can be as low as a single organism [1–3]. After inhalation, *C burnetii* organisms are engulfed by alveolar macrophages, subsequently resist phagosomal killing, and are then transported throughout the host with predilection epithelium, endothelium, and atherosclerotic plaques [1].

Typical presentation of acute illness is a self-limited flulike syndrome that can be punctuated by high-grade fevers, headaches, myalgias, fatigue, pneumonia, and hepatitis [2, 4]. The presentation of chronic Q fever can be varied, with infective endocarditis, vascular infections, native and prosthetic joint infections, osteomyelitis, and lymphadenitis all being described [2, 3]. The Centers for Disease Control and Prevention define chronic Q fever as an elevated phase I IgG of ≥1:1024 with an identifiable focus of ongoing infection [5]. The 2011 Dutch consensus guideline on chronic Q fever diagnostics defines proven chronic Q fever as positive *C burnetii* PCR from blood or tissue

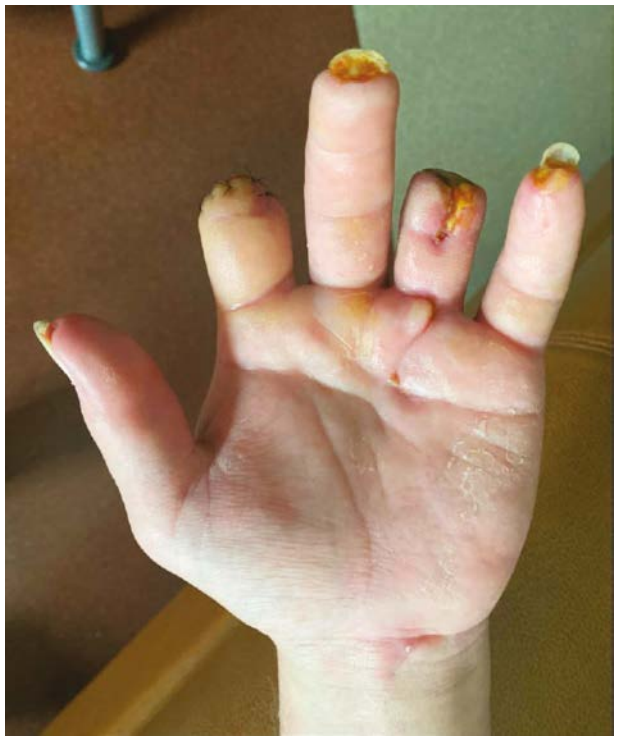

Figure 3. Photograph of left hand taken on hospital day 54.

or phase I IgG titer ≥1:1024 and either definite infective endocarditis by Duke criteria or proven large-vessel or prosthetic infection by imaging [6]. Probable chronic Q fever is defined as having a *C burnetii* phase I IgG titer ≥1:1024 and 1 additional finding including valvulopathy not meeting Duke criteria, known aneurysm or vascular prosthesis without signs of infection, suspected osteomyelitis or hepatitis due to chronic Q fever, pregnancy or immunocompromised state, signs and symptoms of chronic infection, or histologically proven granulomatous tissue inflammation [6]. The same consensus guideline defines possible chronic Q fever as the presence of *C burnetii* phase I IgG titer ≥1:1024 without meeting criteria for proven or probable infection [6]. Serum *Coxiella* PCR is specific, but has a sensitivity of only 22.9% in chronic Q fever [6]. While the patient in this case had a *Coxiella* phase I IgG positive at 1:2048; reactive cervical, axillary, and pelvic lymphadenopathy; splenic FDG uptake on PET scan; and signs and symptoms of infection that could all contribute to a diagnosis of probable chronic Q fever, the polymicrobial infection of his hand precluded attributing those signs and symptoms to chronic Q fever. In light of this uncertainty, the patient in this case was believed to have a diagnosis of possible chronic Q fever.

Prior studies have demonstrated the presence of autoantibodies in patients infected with *C burnetii* that include antinuclear antibodies, anti-double-stranded DNA antibodies, antineutrophilic cytoplasmic antibodies, antiparietal cell antibodies, lupus anticoagulant, and anticardiolipin, which can be present in up to 81% of patients with Q fever [7–9]. Despite a well-described association between *C burnetii* and the formation of other autoantibodies, presence of anticentromere antibodies, as seen in this patient, has been less frequently described [10]. Anticentromere antibodies can be seen in limited cutaneous systemic sclerosis, though this patient did not have clinical or radiographic evidence of systemic sclerosis aside from his history of Raynaud phenomenon with gangrene [11]. The improvement in this patient's antinuclear antibody titer following treatment of *C burnetii* infection is consistent with other reports of improvement in autoantibody titers following Q fever treatment [7, 12].

In addition to the frequent presence of autoantibodies, Q fever has long been known to mimic autoimmune diseases such as systemic lupus erythematosus, Crohn disease, and vasculitides such as Kawasaki disease, polyarteritis nodosa, giant-cell arteritis, and antineutrophil cytoplasmic antibody–associated vasculitis [9, 12–20]. The exact mechanism of the effect is not well described. In many of these cases, disease improvement occurred with a combination of doxycycline with or without immunosuppressive therapy [12, 14, 18–20].

Prior to his admission, it had been suggested that this patient carried a diagnosis of TAO, also known as Buerger disease, a small- and medium-vessel vasculitis predominantly affecting males aged 40–45 years and associated with tobacco smoking [21, 22]. Pathologic findings of vessels in TAO include highly cellular and inflammatory thrombi with the vessel walls being relatively spared, which contrasted with pathologic evaluation of this patient's digital arteries, which were notable for fibrosis with the absence of inflammation [22].

The patient's tobacco and methamphetamine use predated his symptoms by many years, and while both are associated with exacerbation of TAO, the digital ulcerations and necrosis only developed after his presumed *Coxiella* exposure and during the time of his incarceration when he did not have access to either substance. While the combination of possible preexisting vasculitis, chronic Q fever infection, and bacterial superinfection of his digital wounds makes the definitive diagnosis of *Coxiella*-related vasculitis difficult, the coincidence of his high-risk zoonotic exposure with initial symptom onset are highly supportive of this diagnosis.

CONCLUSIONS

Whether *Coxiella* is a mimicker or inducer of autoimmune disease remains unclear, but the association is nonetheless well described. This case is important as it demonstrates a unique coincidence of *C burnetii* infection and a TAO-like disease with digital necrosis and autoamputation. As has been seen with other cases of Q fever with autoimmune phenomena, this patient improved with a combination of surgery, wound care, antibiotics directed at his superinfecting organisms, and doxycycline and hydroxychloroquine to treat chronic *C burnetii* infection.

Notes

Author contributions. Z. S. drafted the manuscript. T. S. drafted and revised the manuscript. L. E., L. D., and K. E. revised the manuscript.

Potential conflicts of interest. All authors: No reported conflicts of interest.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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