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Case report

Venous thrombosis, peripheral aneurysm formation, and fever in a feral pig hunter with Brucellosis

Ivan Gowe[a,*], Christopher Parsons[b], Stephen Vickery[c], Michael Best[d], Scott Prechter[e], Marilyn Goss Haskell[f], Eveline Parsons[g]

[a] Infection Prevention and Control Department, Margaret R Pardee Hospital, 800 North Justice Street, Hendersonville, NC 28791, USA
[b] Pardee Hospital Center for Infectious Diseases, 705 6th Avenue West, Suite D, Hendersonville, NC 28739, USA
[c] Wingate University School of Pharmacy, 805 6th Avenue West, Suite 200, Hendersonville, NC 28739, USA
[d] Department of Microbiology, Margaret R. Pardee Memorial Hospital, 800 North Justice Street, Hendersonville, NC 28791, USA
[e] Department of Radiology, Margaret R. Pardee Memorial Hospital, 800 North Justice Street, Hendersonville, NC 28791, USA
[f] MGH Innovative One Health Solutions, Raleigh, NC, USA
[g] Department of Animal Science, Berry College, P.O. Box 493259, Mount Berry, GA 30149, USA

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ABSTRACT

Brucellosis is a systemic bacterial zoonotic disease with potential endovascular complications including endocarditis, although multifocal vasculopathy is rare. Moreover, swine-associated human infections are less common since brucellosis was eradicated in commercial swine in U.S. states and territories. However, feral swine continue to serve as a reservoir for *Brucella suis*. We describe the case of a feral swine hunter who presented with fever and respiratory symptoms and was diagnosed with pulmonary embolus. Blood cultures revealed growth of *Brucella*, later confirmed as *Brucella suis*. Despite initial appropriate antimicrobial therapy, he maintained fever with worsening knee pain, and magnetic resonance imaging and two-dimensional echocardiography subsequently confirmed the presence of a thrombosed popliteal artery aneurysm and mitral valve vegetation, respectively. To our knowledge, this is the first report of contemporaneous venous and arterial thromboembolism attributable to *B. suis* infection.

Introduction

Infection with *B. suis* is potentially fatal, and occupational or recreational exposure to animals poses a risk of transmission. It is important for health care providers to take thorough exposure histories relating to other modes of exposure (including travel, and consumption of unpasteurized dairy products or raw meat), and to recognize the myriad clinical presentations of brucellosis in order to avoid delays in initiation of appropriate antimicrobial therapy. This case highlights one such unusual presentation – endovascular disease marked by concurrent pulmonary embolism and arterial aneurysm formation – caused by *Brucella suis* infection. Additionally, the case highlights the need to consider brucellosis and blood culture collection in patients with appropriate exposure histories with fever and venous thromboembolism. The case also reinforces the potential for exposure to *B. suis* associated with hunting and handling of feral swine in the United States, as well as the need to educate the public about the risks and prevention measures associated with hunting, dressing, and preparation of feral swine.

Case report

A 74-year-old, Caucasian male with a history of well-controlled diabetes mellitus and chronic obstructive pulmonary disease was seen in the emergency department of a rural hospital in western North Carolina reporting the onset of fever, dyspnea and cough over several days. Based on results of a chest CT angiogram, he was diagnosed with pulmonary embolism, started on rivaroxaban, and discharged from the emergency department. He returned to the same emergency department two days later reporting a fever of 103 °F at home, although denying cardiopulmonary, gastrointestinal, or other focal symptoms other than some mild knee pain. He reported being compliant with anticoagulation. Chest imaging

* Corresponding author.
E-mail addresses: ivan.gowe@unchealth.unc.edu (I. Gowe), chris.parsons@unchealth.unc.edu (C. Parsons), s.b.vickery@wingate.edu (S. Vickery), michael.best@unchealth.unc.edu (M. Best), scottx@protonmail.com (S. Prechter), mghaskell@gmail.com, m.gosshaskell.dvm@gmail.com (M.G. Haskell), eparsons@tusculum.edu (E. Parsons).

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revealed no new findings, routine labs were unrevealing, and blood cultures were drawn. He was discharged once again with plans to follow-up with his primary care physician under the assumption that his fever was related to pulmonary embolization.

Within 48 h following discharge, blood cultures exhibited growth of an organism resembling *Brucella species.* The hospital's microbiology laboratory contacted the North Carolina State Laboratory of Public Health Bioterrorism and Emerging Pathogens Branch (NC SLPH BTEP), where identification of *Brucella* was confirmed by PCR. The isolate was subsequently sent to the U.S. Centers for Disease Control and Prevention where additional testing confirmed its identification as *B. suis.* This result was reported to the local county health department, and the patient was seen by his primary care provider. Based on CDC guidance and clinician judgment, he was prescribed oral trimethoprim-sulfamethoxazole 160–800 mg twice daily and doxycycline 100 mg twice daily. Rifampin was considered but not used due to concern for drug-drug interactions with rivaroxaban.

He reported improvement in his cough and dyspnea thereafter, but 17 days after initiation of antimicrobial therapy, he noted recurrence of fevers and was instructed to return to the outpatient clinic. On arrival, he reported additional symptoms of anorexia, fatigue, night sweats, chills, and worsening right knee pain for the preceding several days. He denied dyspnea, chest pain, back or flank pain, diarrhea, or urinary symptoms at that time. Chest radiography and repeat blood cultures were unrevealing, and he was referred to an Infectious Disease specialist. On further questioning, he denied consumption of unpasteurized dairy products, recent homelessness, commercial food handling, recent travel outside of North Carolina, ownership of pets, exposure to livestock, or past military service. However, he did report been hired to trap wild feral pigs on a local farm about 3 months prior to presentation. He had performed this service for local farmers annually for the past several years, and his custom was to take several pig carcasses back to a meat-processing warehouse on his property where he and his son butchered the animals and provided meat to their friends and family. In addition, they would take part in a ritual that involved tasting a small portion of raw meat prior to its freezing. On physical examination, he exhibited intense pain near the popliteal fossa extending to both distal thigh and proximal calf, as well as swelling and pain with flexion or extension of his right knee. Laboratory evaluation revealed a peripheral white blood cell count of 5200/μL. He was urgently referred for an MRI of his right knee which revealed a lobular, well-circumscribed lesion in the popliteal fossa measuring 4.6 cm in largest dimension and which exhibited lack of internal contrast signal as well as adjacent soft tissue enhancement, consistent with a thrombosed popliteal artery aneurysm (Fig. 1). There was no evidence of joint effusion or synovitis. Subsequent arterial ultrasound confirmed this result, revealing a popliteal artery aneurysm measuring 7.1 cm in length and 5.3 cm in diameter, with blunted distal waveforms consistent with some degree of thrombosis.

Given his fevers and confirmation of a peripheral arterial aneurysm, he was referred for two-dimensional echocardiography, which revealed a small vegetation on the anterior leaflet of the mitral valve, consistent with endocarditis. He was admitted to the hospital where he underwent popliteal aneurysm resection with saphenous vein grafting. Repeat blood cultures and operative samples collected from the resected aneurysm revealed no bacterial growth, and pathology from the operative sample revealed thrombosed aneurysmal tissue without inflammation. He was started on combination antimicrobial therapy with oral doxycycline 100 mg twice daily, which was continued for 8 weeks, as well as intramuscular streptomycin, which was continued for 2 weeks. He made a full recovery with resolution of dyspnea, leg pain, swelling, and fevers over a two-week period following surgery, and he remained on rivaroxaban. Also of note, several individuals were given portions of meat from the same feral swine-trapping event, launching a local public health contact investigation. None of these individuals developed clinical or laboratory evidence of *B. suis* infection over one year of follow-up based on surveillance by local and state health departments.

Discussion

B. suis is a gram-negative, facultative coccobacillus which proliferates in host phagocytic cells. This potentially results in chronic infections due in part to evasion of host defenses [1]. There are five biovars of *B. suis*, although only two cause human infection [2]. *B. suis* has been eradicated from commercial swine in the United States [3], yet remains a concern due to its prevalence within feral swine (*Sus scrofa*), particularly in the southeastern United States [4]. One surveillance effort in North Carolina found that nearly 4% of feral swine exhibited serologic evidence of *B. suis* infection [5]. However, this is probably an underestimate, as more recent studies indicate that 18–53% of feral swine nationwide are carriers of *B. suis* [6]. Biovars 1 and 3 are found within feral swine throughout North America [7,8] and infection may lead to abortion, infertility, orchitis, or spondylitis in these animals. Swine infection may be subclinical, with animals appearing healthy and hunters and trappers unaware of the risk [9,10]. Although infected sows often abort, infections in the live offspring of *B. suis* seropositive sows may not be readily apparent until sexual maturity; it is common for infections to resolve by the time piglets reach 6 months of age [5,11]. These features lead to frequent human exposure to *B. suis* among those with feral swine contact. Most human infections arise after incidental exposure from direct contact with infected meat during processing or through dietary exposure (consumption of raw meat or unpasteurized dairy products), although those in proximity to infected swine or aborted fetuses may become infected with *Brucella* through contact of open wounds with blood or other infected fluids, or through inhalation of aerosolized bacteria [12–14].

Symptoms of *Brucella* infection tend to be non-specific and include flu-like symptoms of headache and muscles aches, along with relapsing fever, night sweats, polyarthralgias, weight loss and even depression [15]. Dyspnea on exertion and cough may occur with pulmonary involvement [16]. Physical examination may reveal hepatosplenomegaly, and basic laboratory studies may reveal anemia, leukocytosis, thrombocytopenia and hepatic enzyme elevation [15,17,18]. However, many patients lack significant laboratory abnormalities, with only 30–50% exhibiting anemia, less than 30% exhibiting either leukocytosis or leukopenia, less than 15% exhibiting thrombocytopenia, and less than 40% exhibiting elevation of hepatic enzymes, sedimentation rate or C-reactive protein [15]. Peripheral leukocytosis was not observed in our patient, and this is not unusual in patients with endovascular involvement, with 40–50% of these patients exhibiting no leukocytosis or even fever [19]. Arthritis, especially involving the knee, is a well-documented "focal" complication of brucellosis [20,21]. Other focal complications include spondylitis, epididymitis, hepatitis, pneumonia and endocarditis [16,19]. Vascular complications of *Brucella* infection are the result of direct infection of endothelial cells, causing a sustained pro-inflammatory response and vasculitis [22,23]. Peripheral artery aneurysms are seen in 5–10% of cases [19] and venous thromboembolism has been reported as well [24]. But to our knowledge, this is the first case report involving both venous and arterial vasculopathy with *B. suis* bacteremia.

Independent predictors of relapse with brucellosis include fever, a short duration of symptoms prior to diagnosis (< 10 days), and bacteremia [25], all of which were present in this case. Recognition of arthritis or endovascular involvement in patients with brucellosis is critical, as this influences both choice and duration of therapy. In addition, relapse or treatment failure occurs in 15–25% of patients with arthritis [20,21], and mortality in cases with endovascular

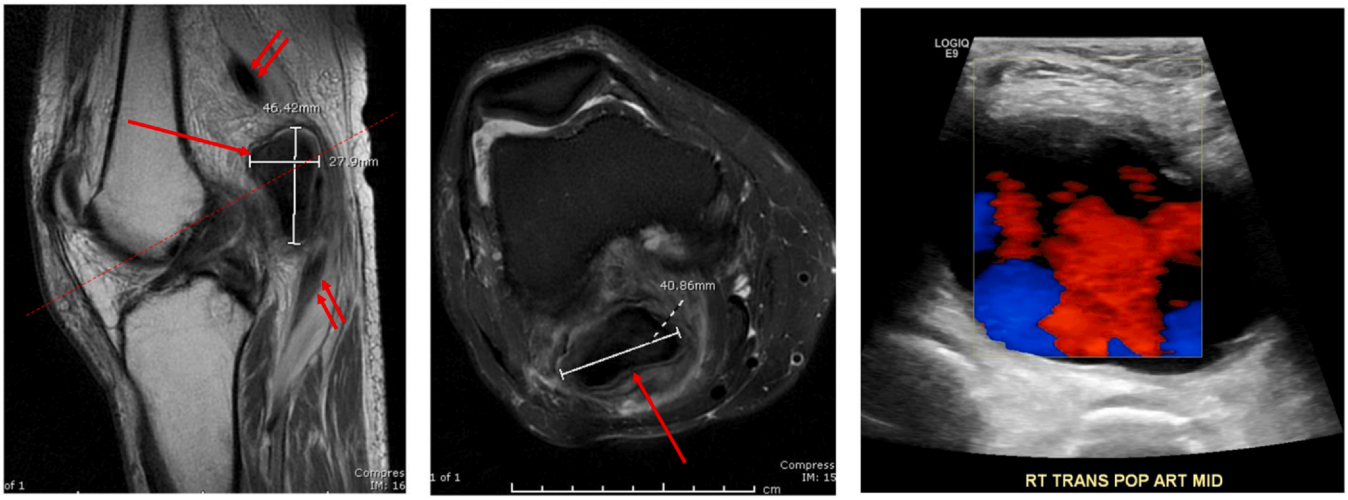

Fig. 1. Magnetic resonance imaging and sagittal PD (left panel) and axial T2 fat saturated images (middle panel) demonstrated a flow void within a popliteal artery aneurysm (single arrows) measuring 4.6 × 2.8 × 4.1 cm. Normal popliteal artery flow void is highlighted for reference (double arrows). The dashed line through the sagittal image denotes level of the axial image. Transverse sonographic imaging of the popliteal fossa (right panel) demonstrated an anechoic aneurysmal dilatation of the popliteal artery, with Doppler imaging demonstrating turbulent flow (red color) within consistent with turbulent aneurysmal flow.

involvement may be as high as 20% despite recommended therapies [19]. Doxycycline monotherapy has demonstrated equivalence to combination antibiotic therapy in cases without focal disease [26–28] and 6-week regimens with doxycycline are generally advisable to reduce early relapse [29]. But for focal infections, especially those involving osteomyelitis, arthritis, or arteritis, clinical trial data support use of combination therapy. The combination of doxycycline and rifampin for 6 weeks may be as effective as streptomycin-containing regimens in many cases of brucellosis [30]. However, for spondylitis or any form of endovascular involvement (including bacteremia), the combination of doxycycline and streptomycin may be optimal. Use of streptomycin for a total of 2 weeks and doxycycline for a total of 2–3 months may reduce relapse rates from over 25% to 4–8% compared to rifampin-containing regimens [19,31–37]. Notable adverse events associated with streptomycin include neurotoxicity (vestibular, cochlear, and ocular function), hearing impairment (especially in patients with pre-existing vertigo or hearing loss), renal impairment and bone marrow suppression which are important considerations in these cases [33–37].

Modern genotyping, including use of multilocus sequence typing, has been used to identify *B. suis* biovars and their relationship to human disease, as well as to elicit a better understanding of how transmission of *B. suis* can be prevented [4]. The USDA instituted regulations to eradicate *B. suis* from commercial domestic swine through swine herd cleanup which initially reduced the frequency of human infection [38]. *B. suis* has not been detected within commercial swine in the U.S. according to a 2017 USDA report [39]. However, sporadic detection of *B. suis* has been noted in feral and/or non-commercial production swine [39] and there are ongoing challenges for state and national agricultural and wildlife agencies in controlling the feral swine population. This case highlights the need for ongoing collaboration between public health agencies, healthcare providers, and agricultural and wildlife authorities to educate those with feral swine contact about risk, clinical signs, and prevention of infection by *B. suis*. Careful evaluation of a patient's exposure history (occupation, travel, recreation, and animal exposures) remains critical for early recognition of risk and diagnosis of brucellosis.

Ethical approval

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Consent

Given.

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Ivan Gowe: Formal analysis, Writing – original draft, Writing – review & editing. **Christopher Parsons:** Conceptualization, Methodology, Formal analysis, Investigation, Writing – original draft, Resources, Writing – review & editing, Visualization, Supervision. **Stephen Vickery:** Investigation, Formal analysis, Writing – original draft, Writing – review & editing, Visualization, Supervision, Project administration. **Michael Best, Scott Prechter, Marilyn Goss Haskell:** Methodology, Formal analysis, Investigation, Resources. **Eveline Parsons:** Investigation, Resources, Writing – original draft.

Conflicts of interest

The authors report no financial conflicts.

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