Falsely elevated immunologic markers with erythema nodosum and arrythmias in the setting of Q Fever

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Abstract

This work describes a case of a young adult male who presented with a fever of unknown origin of several weeks' duration and a painful, palpable rash. Initial workup suggested a viral or immunologic cause of his symptoms, as both rheumatoid factor and CMV antibodies (IgM and IgG) were positive. Repeat testing one week later was negative for CMV antibodies, and send-off testing eventually confirmed a diagnosis of Q fever. Biopsy of a skin lesion showed panniculitis consistent with erythema nodosum, an exceedingly rare manifestation of Q fever. The patient also experienced cardiac arrythmias during his hospital stay, although no structural heart disease was noted on imaging. The severity and duration of this patient's symptoms were unusual for Q fever, particularly as they presented in an otherwise healthy young male. His positive rheumatoid factor and CMV antibodies were likely a result of immunologic activation in response to the Q fever infection. Falsely elevated immunologic markers may delay the diagnosis and treatment of Q fever—especially when combined with signs such as erythema nodosum that are more commonly associated with other immunologic or infectious etiologies. As a result, this case serves as an important reminder to consider immunologic overlap when test results are inconsistent and when the patient may have experienced direct or indirect animal exposure.

Keywords: Q Fever, *Coxiella burnetii*, erythema nodosum, myocarditis, endocarditis, immunologic overlap, immunologic arousal, immunologic activation

Introduction

Q Fever, or "query fever," is the term commonly used to describe the illness resulting from infection with *Coxiella burnetii*, an obligate intracellular zoonotic bacterium. This report describes a case of a young adult patient diagnosed with Q Fever after his diagnostic workup was initially suggestive of another infectious or inflammatory etiology.

Case Report

A man in his late twenties presented to the emergency department of our tertiary care center in West Texas complaining of three weeks of high fevers (up to 103° F) with chills and malaise, a fifteen-pound weight loss, headaches, diarrhea, and a rash. Recent workup at an outside hospital was remarkable only for mild transaminitis.

Computed tomography (CT) head, chest X-ray, and CT abdomen/pelvis were largely unremarkable, although abdominal ultrasound did note hepatomegaly. Complete blood count (CBC) was significant only for a mildly elevated white blood count (WBC), and complete metabolic panel (CMP) was unremarkable other than persistent transaminitis (with alanine aminotransferase (ALT) and aspartate aminotransferase (AST) being greater than eight and three times the upper limit of normal, respectively). Routine point-of-care tests for influenza A/B, Group A *streptococcus*, and SARS-CoV-2 were all negative.

Inflammatory markers of procalcitonin, erythrocyte sedimentation rate (ESR), and C-reactive protein

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(CRP) were elevated. Further workup showed negative antinuclear antibodies (ANA) with positive rheumatoid factor (RF) but negative cyclic citrullinated peptide (CCP). The Infectious Diseases team was consulted. Initial differential diagnoses included viral meningitis, West Nile virus (WNV), other arboviruses, and less likely bacterial meningitis or measles virus.

Upon questioning, the patient denied recent travel, sick contacts, cave exposure, animal bites, or direct livestock exposure. He did report owning two dogs and stated that he worked at a dairy plant that produced butter. He denied alcohol use, drug use, or allergies. He also denied nausea, vomiting, neck stiffness, photophobia, or altered mental status.

On physical exam, he was afebrile with normal vital signs. No lymphadenopathy was noted. A tender, mildly erythematous rash involving the bilateral upper and lower extremities, as well as the area around the anus, was observed. All other physical exam findings were within normal limits, including a cardiac exam demonstrating regular rate and rhythm and a soft, non-tender abdomen.

Given his persistent mild transaminitis as well as the hepatomegaly noted on ultrasound, further workup was performed to rule out infectious agents known to affect the hepatobiliary system. Anti-Hepatitis A IgG was positive, while all other hepatitis antibodies and antigens were negative. Epstein-Barr virus (EBV) Nuclear Antigen IgG and viral capsid antigen (VCA) IgG were positive, while EBV VCA IgM was negative.

Sepsis polymerase chain reaction (PCR) was performed to rule out disseminated infection. Results were positive only for "Streptococcal species," and no specific species was detected. An initial blood culture and Gram stain were positive for alpha-hemolytic Streptococcal species not *Streptococcus pneumoniae*, while another sample was negative with no growth. Together, these findings suggested a likely contaminant, and no antibiotics were administered.

The patient's work at a dairy plant put him at increased risk for infection with brucellosis, a zoonotic infection caused by *Brucella spp.* that presents with flu-like symptoms in humans, including undulating fever, weight loss, and hepatomegaly.[1] While his symptoms were consistent with the illness, both IgM and IgG antibodies to *Brucella spp.* were negative.

A lumbar puncture was performed to evaluate further for the suspicion of meningitis in this patient with a headache and non-specific symptoms in the setting of an otherwise unremarkable infectious workup. Cerebrospinal fluid (CSF) showed a cell count of zero RBCs and fifteen WBCs with normal glucose and protein. CSF gram stain and cultures were negative, as was a bacterial meningitis antigen panel and Cryptococcal and Coccidiomycosis antigens. A non-Herpes simplex virus (HSV) viral meningitis was suspected, and the patient was discharged with return precautions.

Three days after discharge, the patient presented back to the emergency department with continuing complaints of fever, headache, malaise, and a worsening painful, palpable, non-pruritic rash on his upper and lower extremities. His CBC was notable for mildly elevated WBC and platelets (each approximately 1.5x upper limit of normal) and mildly decreased RBC (hemoglobin 13.3). ESR and procalcitonin levels approximated those from his prior admission. His CRP had doubled and was now twenty times the upper limit of normal, but his ANA remained negative. His liver enzymes remained mildly elevated but improved.

Since discharge, results from various send-out testing performed during his prior admission were now final, effectively ruling out WNV, HSV 1 and 2, lymphocytic choriomeningitis virus, measles, mumps, Varicella Zoster virus (VZV), and enterovirus. Notably, results were positive for IgM and IgG antibodies to cytomegalovirus (CMV).

Considering the patient's worsening rash and persistently elevated inflammatory markers, differential diagnoses included inflammatory disorders such as Sweet syndrome (acute febrile neutrophilic dermatosis), erythema nodosum, adult-onset Still's disease, and urticarial vasculitis in addition to infectious causes including acute CMV infection, Q Fever, and streptococcal bacteremia. Additional workup included repeat blood cultures (negative), tests for ASO (within normal range), repeat testing for CMV

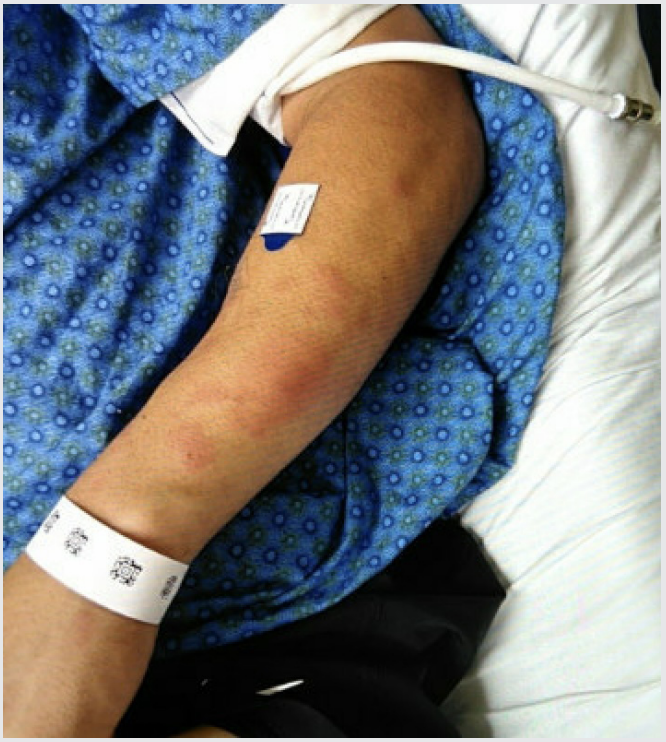

Figure 1. Multiple 2–3 cm erythematous, palpable papules (some coalescing into a plaque) on the distal left upper extremity.

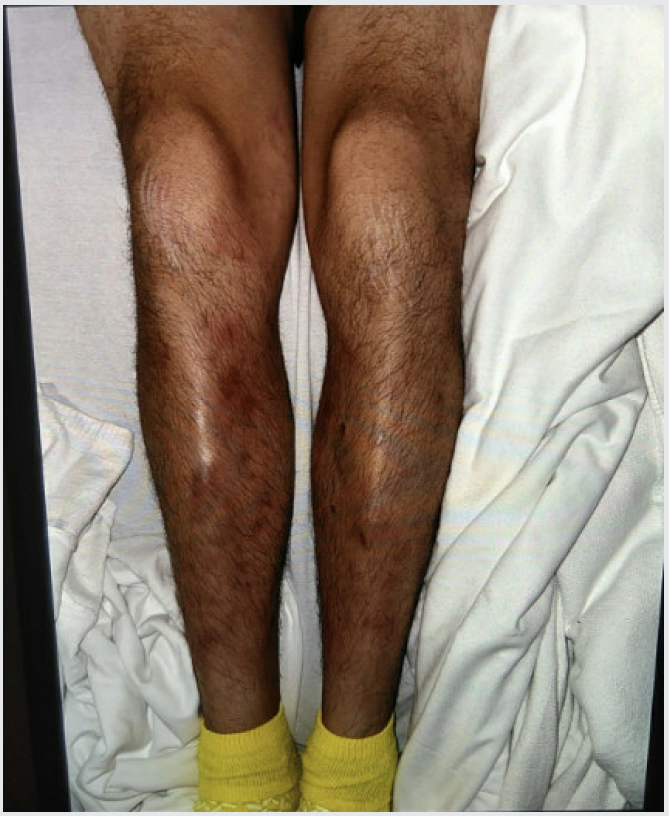

Figure 2. Multiple 1–2 cm violaceus, palpable papules on the distal lower extremities.

IgG and IgM (both now negative), and Phase I and Phase II antibodies to Q Fever, an infection caused by *Coxiella burnetii*.

Due to reported worsening of the patient's rash, Dermatology was consulted. Lesional biopsy showed panniculitis consistent with erythema nodosum and no evidence of vasculitis. Rheumatology was consulted and determined the symptoms were most consistent with erythema nodosum, likely secondary to a post-infectious process (see Figures 1 and 2).

During the patient's second admission, telemetry recorded non-sustained, asymptomatic ventricular tachycardia. Electrocardiogram (EKG) showed sinus rhythm with incomplete right bundle branch block and nonspecific ST elevations. The patient's calcium score was zero, and testing was negative for troponins. Telemetry later recorded atrial flutter, and he was converted back to normal sinus rhythm with amiodarone. A cardiac magnetic resonance imaging (MRI) showed no evidence of endocarditis or myocarditis.

Send-out labs for *C. burnetii* returned positive for IgM antibodies to Phase I and II antigens as well as IgG antibodies to Phase I (1:16) and II (1:1024) antigens, suggesting Q Fever as the likely cause of the patient's signs and symptoms. Qualitative PCR testing failed to detect *C. burnetti* DNA, but follow-up testing two months after discharge confirmed continued positivity of IgM Phase I and II antibodies and elevated IgG Phase I and II titers.

The patient was discharged with a prescription for a two-week course of doxycycline 100 mg twice daily for two weeks as well as amiodarone, metoprolol, and apixaban for his arrythmia. He reported no further symptoms at the time of his follow-up appointments.

Discussion

C. burnetii is an obligate intracellular zoonotic bacterium that may be transmitted to humans via inhalation of aerosolized animal feces or through fluids such as urine, genital secretions, or milk.[2] Domestic ruminants (i.e., animals like cattle, sheep, and goats that chew their cud) are the primary reservoirs leading to human exposure, and *C. burnetti* infections may be under-detected in dairy cattle.[3] Infection with *C. burnetii* results in an illness known as Q Fever, which is asymptomatic in approximately 60% of patients but may, in 4–5% of patients, present with systemic illness affecting organ systems including the lungs, liver, and heart.[4] Cutaneous manifestations are uncommon, and erythema nodosum is an especially rare manifestation with fewer than ten cases reported as of 2018.[2]

As evidenced by its name, the most prevalent manifestation of symptomatic Q fever is fever, which is often accompanied by headache, myalgia, rigors, cough, nausea, and vomiting. This varied presentation, coupled with nonspecific laboratory findings and precarious culturing methodology, requires a reliance on serological markers for diagnosis. IgM antibodies to *C. burnetii* rise 7–10 days after the first signs and symptoms of illness, and anti-IgG antibodies peak at 6 weeks. Diagnosis requires detection of IgM antibodies or four-fold rise in IgG titers in two consecutive tests. The strong immune response in acute Q fever infection may cause falsely elevated RF, ANA, and smooth muscle antibody (SMA), leading to delays in diagnosis and treatment. Similarly, antibodies to EBV, CMV, parvovirus, *Bordetella pertussis*, and *Mycoplasma pneumoniae* may also be falsely elevated in patients with acute Q fever.[5]

Traditionally, acute Q Fever has been diagnosed primarily by serology to detect phase II *C. burnetii* antibodies.[6] Sensitivity of PCR may be as high as 100% when obtained between days 3 and 7 of illness,[7] but it begins to decline once the serological response develops and antibodies to IgG phase II (IgG-II), IgM phase I (IgM-I), and IgG phase I (IgG-I) appear.[8] A positive blood culture or PCR can also be a strong indicator for the presence of chronic Q Fever, but sensitivity of these tests is only 50–60%, highlighting the importance of serological testing. Increasing IgG-I antibodies are more specific for chronic Q Fever, especially when signs or symptoms of endocarditis, large vessel infection, or other systemic illness are present.[2]

In the present case, our patient presented with fever, malaise, rigors, headaches, diarrhea, and a rash. Early lab findings showed elevated liver enzymes, and abdominal ultrasound noted hepatomegaly. Skin biopsy of the rash was consistent with erythema nodosum, and the patient experienced cardiac arrythmias, although MRI showed no evidence of structural abnormalities. Rheumatoid factor was elevated, and anti-CMV IgG and IgM went from positive to negative. IgM-I and IgM-II antibodies to *C. burnetii* were positive, and IgG-I and IgG-II antibodies were significantly elevated. Qualitative DNA PCR was negative, but this test was obtained more than 30 days after the patient's first symptoms, a time when the test has a lower sensitivity. Follow-up testing after discharge noted continued positivity of IgM-I and IgM-II as well as increasing IgG-I titers and decreasing IgG-II titers, a pattern suggestive of possible chronic Q Fever.[2]

Acute Q Fever is typically treated with two weeks of doxycycline, while persistent, focalized infections may require the addition of an additional antibiotic such as hydroxychloroquine or ciprofloxacin.[2] While the patient's IgG-I titers were elevated at follow-up, he demonstrated no signs of endocarditis, large vessel infection, or other clinical manifestations of disease. The patient will continue to be monitored closely to ensure no further complications.

Conclusion

The varied presentation of Q fever, coupled with its nonspecific laboratory findings and routinely negative culture results, make it difficult to diagnose. Couple these factors with a propensity to cause falsely elevated immunologic markers, and the diagnosis becomes even more challenging. While often asymptomatic or causing only mild disease, Q fever can cause systemic illness with pneumonia, endocarditis, or hepatitis in a small subset of patients. Clinicians should consider Q fever when a patient presents with a variety of nonspecific findings and contradictory immunological and infectious findings, particularly in

instances with known direct or indirect exposure to farm animals.

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