

Why did fever persist after metagenomic next-generation sequencing confirmed *Coxiella burnetii* infection? A hidden co-infection beneath a single “positive” report

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Case Report

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Abstract

A 43-year-old man presented with recurrent fever for one week, unresponsive to initial antibiotics. Blood mNGS detected *Coxiella burnetii*, confirming Q fever. After partial improvement with moxifloxacin-doxycycline and discharge, follow-up Brucella tube agglutination test (SAT) at 10 days post-discharge rose to 1:100 (++++). Combined with a slaughterhouse exposure history, concurrent brucellosis was diagnosed. Doxycycline plus trimethoprim-sulfamethoxazole for 6 weeks achieved complete recovery. Initial SAT was equivocal (1:50) with negative IgM/IgG, risking missed diagnosis. mNGS only identified *C. burnetii*, not *Brucella*, demonstrating false negatives from low nucleic acid load. Doxycycline-based therapy without a second agent was insufficient, necessitating regimen adjustment. Our patient, who purchased beef at a slaughterhouse and personally cut and packaged it one month before onset, represents a classic, easily overlooked urban exposure route.

Conclusions: A single mNGS-detected pathogen does not exclude co-infection in exposed patients. Dynamic serology is essential to avoid missed diagnoses of concurrent Q fever and brucellosis.

Introduction

Brucellosis and Q fever are major intracellular zoonoses that cause prolonged fever, fatigue, and potential chronic sequelae[1]. Shared transmission routes, via infected livestock, raw milk, or contaminated aerosols, place abattoir workers and livestock handlers at markedly elevated risk[2]. Both infections are frequently missed clinically due to nonspecific manifestations. Although co-infection with *Coxiella burnetii* and *Brucella spp.* is rarely reported, it is epidemiologically plausible. We describe a 43-year-old man with recurrent fever and right-sided pulsatile headache who failed initial empirical therapy. Blood mNGS detected *C. burnetii*, confirming Q fever; however, after partial improvement with moxifloxacin-doxycycline, relapsed symptoms prompted serial *Brucella* tube agglutination test (SAT) rise from equivocal to 1:100 and established a final diagnosis of Q fever with concurrent brucellosis.

Case presentation

A 43-year-old man was admitted on April 9, 2026, with recurrent fever (max 39°C) for one week, right parietal pulsatile headache, weakness, anorexia, and night sweats. Vital signs included 37.2°C, pulse 83, BP 118/66 mmHg, and SpO₂ 98%(room air). Baseline investigations showed mild fatty liver on ultrasound and pulmonary bullae with fibrocalcific lesions on chest CT; tests for common respiratory viruses, EBV, CMV, and tuberculosis were negative. The main laboratory findings are summarized in **Table 1**.

He was initially treated with ceftriaxone 2 g/day for presumed infectious fever, but after 3 days of persistent high fever and unchanged inflammatory markers, moxifloxacin 0.4 g/day plus doxycycline 0.1 g/12 h was initiated for atypical pathogens. Blood mNGS identified *Coxiella burnetii*, confirming Q fever. SAT was 1:50 (equivocal), with negative Brucella Rose Bengal plate agglutination test (RBPT) and IgM/IgG. Symptoms partially improved, and he was discharged on day 11.

Post-discharge, the patient adhered strictly to the regimen. However, at nearly two weeks, fatigue and night sweats persisted, and inflammatory markers had decreased only marginally, failing to meet the expected therapeutic response. The following conditions required differentiation: *Coxiella burnetii* resistance; chronic Q fever; drug fever; and co-infection with other pathogens.

Notably, the initial equivocal Brucella SAT titer prompted further investigation. Further epidemiological investigation revealed that the patient had bought beef from a slaughterhouse and butchered it himself one month before illness onset, confirming exposure to cattle/sheep and their derived products. Follow-up SAT for brucellosis at 10 days post-discharge showed a titer of 1:100 (++++), fulfilling the diagnostic standard for brucellosis, while RBPT and Brucella IgM/IgG remained negative. Integrating the epidemiological history and clinical symptoms, the patient was definitively diagnosed with Q fever and concomitant brucellosis. Treatment was escalated to oral doxycycline plus trimethoprim-sulfamethoxazole for 6 weeks. Symptoms completely resolved, inflammatory markers normalized, and the patient achieved full clinical recovery upon follow-up. The timeline of disease onset and treatment is presented in **Table 2**.

Discussion

Background and rarity of co-infection. Although *Coxiella burnetii* and *Brucella spp.* share reservoirs (cattle, sheep, goats) and transmission routes (aerosol inhalation, direct contact with animal products), human co-infection remains exceptionally rare. Most previously reported cases involved occupationally exposed individuals such as farmers, abattoir workers, or livestock handlers [3–6]. Our patient is distinctive in that he had no formal occupational exposure; instead, he acquired infection through an urban, non-traditional route, purchasing beef at a slaughterhouse and personally butchering, cutting, and packaging it at home. This highlights a frequently overlooked zoonotic risk in urban settings and reinforces the need to inquire about detailed animal-product exposure in patients presenting with prolonged fever.

Diagnostic pitfalls: mNGS and static serology. This case illustrates two critical diagnostic limitations. First, metagenomic next-generation sequencing (mNGS), while highly sensitive for pathogen detection, is not infallible. The initial mNGS result identified *C. burnetii* but failed to detect Brucella, most likely due to a low bacterial nucleic acid load below the assay's detection threshold[7]. Thus, a single positive mNGS result should not be interpreted as excluding co-infection, particularly in patients with clear zoonotic exposure. Second, static serology can be misleading. The initial Brucella tube agglutination test (SAT) was equivocal (1:50), with a negative Rose Bengal plate test (RBPT) and IgM/IgG results, which could easily lead to a missed diagnosis. Only through dynamic serial testing did a fourfold SAT titer rise to 1:100 (++++), becoming evident, fulfilling the diagnostic criteria for brucellosis. This underscores that, in intracellular zoonoses, serological interpretation must consider kinetics rather than isolated values.

Treatment response as a diagnostic guide. The patient's incomplete clinical and laboratory response after 10 days of moxifloxacin–doxycycline therapy was a key trigger for re-evaluation. While this regimen

is appropriate for acute Q fever, it is insufficient for brucellosis, which requires a two-drug combination to prevent relapse and complications. The differential diagnosis of persistent fever, including antimicrobial resistance, chronic Q fever, drug fever, and occult co-infection, followed standard clinical reasoning. The decision to switch to doxycycline plus trimethoprim–sulfamethoxazole (TMP-SMX) for six weeks was consistent with established brucellosis treatment guidelines[6,8]. The subsequent complete resolution of symptoms and normalization of inflammatory markers retrospectively validated the co-infection diagnosis and the necessity of regimen escalation.

Clinical implications: This case offers three practical lessons for infectious diseases practice. First, in patients with zoonotic exposure and persistent fever, a single mNGS-detected pathogen should not preclude consideration of co-infection. Second, dynamic serology is essential; serial SAT titers can uncover occult brucellosis even when initial serology and mNGS are non-diagnostic. Third, doxycycline-based therapy must be tailored to the full spectrum of suspected intracellular pathogens; doxycycline plus moxifloxacin does not reliably eradicate *Brucella*. More broadly, the case reinforces that fever of unknown origin is a dynamic diagnostic and therapeutic process: treatment response is itself a valuable diagnostic signal.

Limitations: As a single case report, these observations cannot establish definitive prevalence or treatment algorithms. In addition, *Brucella* was not confirmed by blood culture or molecular detection, likely due to low bacteremia levels and prior doxycycline exposure; the diagnosis therefore rested on serial serology and clinical response. Nevertheless, the case aligns with existing literature on brucellosis serodiagnosis and co-infection epidemiology.

Conclusion

This case highlights the diagnostic challenge of persistent fever and systemic symptoms when initial therapy yields a suboptimal response. It underscores the critical importance of integrating epidemiological history (e.g., livestock exposure) with serological kinetics to identify co-infections such as Q fever and brucellosis. Furthermore, it demonstrates that a tailored regimen of doxycycline combined with trimethoprim-sulfamethoxazole can achieve excellent clinical outcomes, emphasizing the need for vigilant monitoring and timely therapeutic escalation in complex infectious disease management.

Declarations

Ethics approval and consent to participate

This study was conducted in accordance with the ethical standards of the Declaration of Helsinki and was approved by the Institutional Review Board (IRB) of The People's Hospital of Longhua, Shenzhen (approval number:2026 (14)).

Consent for publication

Written informed consent was obtained from the patient for the publication of this case report and any accompanying data. A copy of the written consent is available for review by the Editor of this journal.

Availability of data and materials

All relevant clinical and laboratory data generated or analysed during this case are included in this published article and its supplementary information (Tables 1 and 2). The blood mNGS raw sequencing data are not publicly available because they contain potentially identifying patient information, but are available from the corresponding authors upon reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

KH and CJ managed the patient and conceived the study. GJ, TC, HZ, and QZ collected the clinical data and participated in patient care. XC performed the laboratory and microbiological investigations, including blood mNGS and serological testing. KH drafted the manuscript. CJ and XC supervised the study and revised the manuscript critically for important intellectual content. All authors read and approved the final manuscript.

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Tables

Table 1. Baseline laboratory findings on admission

Parameter	Results	Parameter	Results
Routine blood test		Inflammatory markers	
WBC (3.5–9.5×10 ⁹ /L)	8.57	Hs-CRP (0-8mg/L)	75.7
Neutrophil (40-75%)	61.9	PCT (0-0.1ng/mL)	0.17
Lymphocyte (20-50%)	26.5	IL-6 (0-7pg/mL)	22.7
Monocyte (3-10%)	10.9	SAA (0-10mg/L)	116
Hb (130-175g/L)	140	ESR (0-10mm/h)	28
PLT (125-350×10 ⁹ /L)	239	Ferritin (23.9-366.2ng/mL)	568.4
Liver function		Electrolytes	
TBIL (0-26μmol/L)	15.9	K ⁺ (3.5-5.3mmol/L)	4.14
ALT (7-40U/L)	70.0	Na ⁺ (137-147mmol/L)	133.5
AST (13-40U/L)	46	Cl ⁻ (96-108mmol/L)	100.8
GGT (11-50U/L)	209	Ca ²⁺ (2.10-2.69mmol/L)	2.01

Table 2. Timeline of Diagnosis and Treatment: Q Fever with Concurrent Brucellosis

2026-04-09	Admission: recurrent fever for 1 week; no response to broad-spectrum antimicrobials
Day 0	Empirical ceftriaxone initiated + symptomatic support
Day 3	Persistent high fever; inflammatory markers did not decline
Day 3	Switch to moxifloxacin + doxycycline for empirical intracellular coverage.
Day 4	Blood mNGS: <i>Coxiella burnetii</i> detected; Q fever confirmed
Day 10	Brucellosis screening: SAT 1:50 (equivocal); RBPT/IgM/IgG negative
Day 11	Discharge on moxifloxacin + doxycycline
Day 24	Fatigue/night sweats persisted; minimal inflammatory decline.
Day 34	Follow-up SAT: 1:100 (++++); co-infection with brucellosis confirmed
Day 34	Switch to doxycycline + TMP-SMX for a 6-week brucellosis regimen.
Day 76	Symptoms fully resolved; clinical recovery confirmed.