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Diagnosis of Acute Q Fever in an Elderly Patient Using Metagenomic Next-Generation Sequencing: A Case Report

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Abstract: Query fever (Q fever) is a globally spread zoonotic disease caused by *Coxiella burnetii*, commonly found in natural foci but rarely seen in Hebei Province. The clinical manifestations of Q fever are diverse and nonspecific, which often leads to missed or incorrect diagnoses in clinical practice. This article reports a case of acute Q fever diagnosed in an elderly patient using metagenomic next-generation sequencing.

Keywords: Elderly patient; Acute Q fever; Metagenomic next-generation sequencing (mNGS)

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1. Medical history information

The patient is an 85-year-old elderly male admitted to the hospital at 19:59 on August 5, 2022, due to cognitive impairment and sluggish responses lasting for one day and fever for five hours. One day prior, the patient experienced a decline in cognitive function without an obvious cause, manifested by incontinence and holding a spoon incorrectly while eating. On the way to the hospital (five hours before admission), the patient developed a fever. The patient had no history of diabetes, hypertension, or heart disease.

Upon admission, a complete blood count was performed, revealing the following: white blood cells (WBC) 3.62×10^9/L, red blood cells (RBC) 4.00×10^{12}/L, hemoglobin (Hb) 130g/L, platelets (PLT) 83×10^9/L, and neutrophil percentage of 64.5%. Tests for novel coronavirus nucleic acid and antibodies were negative. The following values were elevated: serum amyloid protein (160.7 mg/L), C-reactive protein (35.01 mg/L), and procalcitonin (0.60 ng/mL). Chest CT findings included: (1) chronic changes in the apical segment of the right upper lobe, (2) a small nodule in the apical segment of the left upper lobe (follow-up recommended), and (3) fibrous strands in the left lower lobe. Magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA) of the head revealed: (1) softening lesions in the left parietal lobe, (2) multiple lacunar infarcts and

degenerative lesions in the bilateral basal ganglia, bilateral corona radiata, and centrum semiovale, (3) brain atrophy and white matter rarefaction, (4) cerebral arteriosclerosis with multiple stenoses, and (5) C3/4 disc herniation and spinal canal stenosis. Abdominal and pelvic computed tomography (CT) showed: (1) calcification in the right hepatic lobe, (2) multiple liver cysts, (3) possible right kidney stones, (4) prostate enlargement, and (5) suspected left inguinal hernia (ultrasound recommended for confirmation). Echocardiography indicated segmental wall motion abnormalities, aortic valve degeneration with mild regurgitation, and mild regurgitation of the mitral and tricuspid valves, along with reduced left ventricular diastolic function.

The patient presented with cognitive decline and fever, with infectious encephalopathy and autoimmune encephalopathy both being considered. Initial treatment with ceftriaxone sodium (2 g daily intravenous) was administered for infection, and a lumbar puncture was planned for cerebrospinal fluid analysis. However, the family declined the lumbar puncture initially and decided to reconsider after further discussion. During hospitalization, the patient continued to have recurrent fever, with temperatures ranging from 37.7°C to 39°C. Viral encephalitis was suspected, and acyclovir (0.25 g intravenously every 12 hours) was added for antiviral treatment, but the patient's fever persisted. Procalcitonin levels were rechecked and increased to 1.33 ng/mL.

Further testing, including endotoxin levels, eight respiratory infection markers, the Widal-Weil-Felix test, TORCH screening, and the EB virus capsid antigen IgG and nuclear antigen IgG antibodies were positive. The tuberculosis T-cell test was positive, while the PPD skin test was negative. Complement C3, complement C4, antinuclear antibody panel, ANCA, and other rheumatological markers were negative. Hepatitis B, C, syphilis, and HIV tests were all negative. Blood cultures were performed twice, both yielding negative results. Follow-up echocardiography revealed a slightly enlarged left atrium, a slightly thickened basal septum, segmental wall motion abnormalities, aortic valve degeneration with mild regurgitation, mild regurgitation of the mitral and tricuspid valves, slightly elevated pulmonary artery pressure, and reduced left ventricular diastolic function, but no vegetations were observed on the valves.

Given that the patient regularly bought vegetables and fresh beef and lamb from the local market and was not attentive to hand hygiene, the possibility of an infection with an uncommon pathogen was considered. After a discussion with the patient's family, blood was sent for metagenomic next-generation sequencing (mNGS) for further diagnostic support. The results returned 2,486 sequences of *Coxiella burnetii*, leading to a diagnosis of acute Q fever. Doxycycline (0.1 g orally twice daily) was started, and the patient's body temperature returned to normal that day. His cognitive state gradually improved, and no further fever episodes occurred.

To confirm the diagnosis of acute Q fever, blood was again sent for *Coxiella* IgM antibody testing, which returned negative. This was attributed to the short disease duration and the patient's weakened immune response. After four days of oral doxycycline, a follow-up complete blood count showed a platelet count of 156×10^9/L, and the neutrophil percentage was 56.1%, indicating normalization of platelet levels. Procalcitonin decreased to 0.64 ng/mL. Liver and kidney function tests remained normal, and no doxycycline-induced liver or kidney damage was observed. The patient's condition improved, and he was discharged after nine days of hospitalization.

2. Discussion

Q fever is an important zoonotic disease caused by *Coxiella burnetii*, a pathogen with highly infectious potential, as inhalation of only a few organisms can lead to infection. Ticks are the primary vectors, and the

pathogen in tick feces can enter the human body through skin lesions after a tick bite [1]. The acute phase of Q fever typically lasts for 2–14 days, with some cases experiencing fever for more than 14 days. Common complications include endocarditis, hepatitis, meningitis, cholecystitis, lymphadenitis, rhabdomyolysis, and hemophagocytic syndrome. Some patients may develop chronic Q fever, primarily manifesting as endocarditis [2]. There have been reports of blood-related complications of Q fever, including hemolytic anemia caused by cold agglutinins and thrombocytopenia associated with Q fever endocarditis. This elderly patient's clinical presentation was consistent with acute Q fever, including fever, cognitive decline, and lethargy. Due to cognitive impairment, the patient was unable to report whether symptoms such as headache, muscle pain, or joint pain were present. Laboratory findings indicated elevated inflammatory markers, including PCT and CRP, along with a reduction in platelet count.

During daily physical examinations, no heart murmurs were detected, and two blood cultures returned negative results. Echocardiography was performed twice after admission, and no valvular vegetations were found, suggesting that a diagnosis of endocarditis could not be confirmed. Whether the patient's thrombocytopenia was related to the systemic inflammatory response remains to be further studied.

Patients with an initial Q fever infection primarily produce phase II antibodies, which are detectable 7–15 days after the onset of clinical symptoms, with antibody concentrations decreasing over 3–6 months. Serum phase II IgG antibody titers ≥ 200 and/or IgM titers ≥ 50 are diagnostic for primary Q fever infection [3]. Studies have shown that antibodies are typically detectable 5–10 days after the onset of Q fever, making serology unsuitable for early diagnosis. Moreover, early use of antibiotics and immunosuppression can lead to false-negative serological results [4]. This patient tested negative for *Coxiella* IgM antibodies, likely due to a false-negative result associated with the short duration of illness, immunosuppression, and the use of cephalosporin antibiotics. The patient was ultimately diagnosed with acute Q fever based on the detection of high sequences of *Coxiella burnetii* through metagenomic next-generation sequencing (mNGS).

mNGS is based on metagenomics and high-throughput sequencing technology, which allows unbiased sequencing of all nucleic acids in a sample. This method, combined with a pathogen microorganism database, can detect possible pathogen sequences (including bacteria, viruses, fungi, mycoplasma, chlamydia, parasites, etc.) in the sample. Clinically, many pathogens are difficult to culture due to various external factors, but mNGS resolves this issue by directly detecting pathogen nucleic acids. Therefore, mNGS has a significant reference value for detecting new, complex, and unknown infections. However, its limitations include high costs, and patient and family consent is required. In this case, mNGS helped expedite the patient's treatment.

In terms of treatment, guidelines such as "ABX – Diagnosis and Treatment of Infectious Diseases" and the "Sanford Guide to Antimicrobial Therapy" recommend tetracyclines, chloramphenicol, erythromycin, roxithromycin, and fluoroquinolones for treating Q fever. Therefore, the patient was treated with doxycycline 0.1 g orally every 12 hours. The patient's body temperature normalized on the first day of treatment, and no further fevers occurred. Follow-up testing showed normalization of platelet count, and significant decreases in PCT and CRP levels were observed. The patient was advised to continue medication for two weeks. The patient improved, was discharged, and fully recovered by the two-week follow-up.

This report presents the case of an elderly patient with recurrent fever, cognitive decline, elevated inflammatory markers, and thrombocytopenia. Acute Q fever was diagnosed based on high *Coxiella burnetii* sequence detection by mNGS, despite a negative serological IgM antibody result. This case highlights the clinical importance of mNGS for diagnosing challenging cases. Additionally, since the patient regularly bought

vegetables and fresh beef and lamb from the local market, it is essential to implement controls in markets, slaughterhouses, meat processing plants, livestock farms, and research laboratories working with cattle, sheep, and similar animals. Regular antibody screening for high-risk occupational groups exposed to *Coxiella burnetii* is necessary to prevent and control the spread of Q fever.

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Disclosure statement

The authors declare no conflict of interest.

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