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CASE REPORT

Crescentic Glomerulonephritis and Portal Hypertension with Chronic Q Fever: A Case Report and Comprehensive Literature Review

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Abstract: Q fever, an infectious zoonotic disease caused by *Coxiella burnetii*, remains prevalent in China. Systemic infections can result in renal or hepatic complications; however, it is rare for both the kidneys and liver to be simultaneously affected. We present a case of a patient who exhibited fever, rapid deterioration in renal function, thrombocytopenia, and severe ascites. Renal biopsy revealed crescentic glomerulonephritis, while liver biopsy demonstrated non-cirrhotic portal hypertension. Metagenomic next-generation sequencing (mNGS) identified the presence of *Coxiella burnetii* in both venous blood and liver tissue samples. Notably, the patient's renal insufficiency and ascites showed a positive response to treatment for chronic Q fever. These findings provide valuable insights into the limited understanding of kidney and liver diseases associated with Q fever. Advanced diagnostic technologies, including mNGS and positron emission tomography/computed tomography (PET/CT), have been employed to identify *Coxiella burnetii* infection.

Keywords: *Coxiella burnetii*, acute kidney injury, non-cirrhotic portal hypertension, biopsies

Introduction

Q fever, an infectious zoonotic disease caused by the Gram-negative bacterium *Coxiella burnetii*, was once considered a rare and regionally restricted disease. However, recent years have seen significant advances in our understanding of this disease, which has spread widely in China and developing regions worldwide. People typically become infected by inhaling contaminated aerosols that can be generated from products of infected animals, mainly cattle, goats and sheep.[1] The clinical manifestations of Q fever can present as either an acute, self-limiting febrile illness or as a chronic disease, which may lead to complications such as vasculitis and endocarditis.[2]

However, there are only a limited number of reports addressing renal injury[3–7] or hepatic complications[8] associated with the progression of the disease to its chronic stage. To our knowledge, this is the first case report documenting chronic Q fever with concurrent renal and hepatic involvement.

Case Presentation

A 70-year-old female patient who underwent bioprosthetic mitral and aortic valvular replacement because of degenerative heart valvular disease at the age of 68, presented with a six-month history of nightly low-grade fever. During the second month

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following the onset of fever, she experienced proteinuria and significant hematuria. Blood tests revealed significant pancytopenia. In the fourth month of fever duration, she exhibited oliguria, lower-leg edema and abdominal distension, accompanied by an elevation in serum creatinine up to 829μmol/L. She refrained from interacting with domesticated animals such as cattle, horses, sheep, and donkeys. Hemodialysis and renal biopsy were performed in the local hospital. Immunofluorescence revealed linear staining of IgG (2+), C3 (2+), IgG1 (2+) and IgG2 (2+) deposits along the glomerular capillary walls. In light microscopy, 13 out of 25 glomeruli exhibited cellular or cellular fibrous crescents. The glomeruli displayed with mesangial and endocapillary hypercellularity. Partial destruction of the Bowman capsule wall was accompanied by the formation of periglomerular granuloma. Electron microscopy demonstrated evidence consistent with tubular-interstitial nephropathy (Figure 1).

She received a course of glucocorticoid pulse therapy (250mg × 3d), followed by 30 mg of oral prednisolone daily, and underwent four sessions of plasma exchange. Despite this intensive treatment, the patient showed no response and was subsequently referred to a higher-level hospital for further management.

Examination of her distended abdomen revealed non-tender splenomegaly, with positive shifting dullness noted upon observation. Blood testing shows a white blood cell count of 3.1×10^9/L, hemoglobin level of 82 g/L and platelet count of 59×10^9/L. The patient tested negative for various autoantibodies, including anti–double-stranded DNA antibodies, ANCA, anti GBM antibodies including anti-α1-5, anti-Laminin-521 and anti-heparan sulfate proteoglycan 2 (HSPG2) antibodies, autoimmune liver disease antibodies, antiphospholipid antibodies and platelet antibodies. A comprehensive screening for the infection source and pathogens was conducted, including blood cultures, CMV/EBV-DNA and antibody tests, as well as G and GM tests for fungal infections. The results did not reveal a clear pathogen or infection source. Testing for EBV-DNA (serum), brucellosis, as well as viral hepatitis was negative. And she did test positive for cryoglobulins and human heparin-associated antibody. Additionally, C3 and C4 levels were found to be decreased (Table 1).

The abdominal ultrasound revealed dilatation of the portal vein, splenomegaly, and extensive accumulation of ascitic fluid. Echocardiography showed a slightly elevated pulmonary artery systolic pressure (38.8mmHg) and a mass on the surface of the left ventricular papillary muscle with potential vegetations, Positron emission tomography/computed tomography (PET/CT) demonstrated localized nodular wall thickening on the right side of the ascending aorta and increased glucose metabolism,

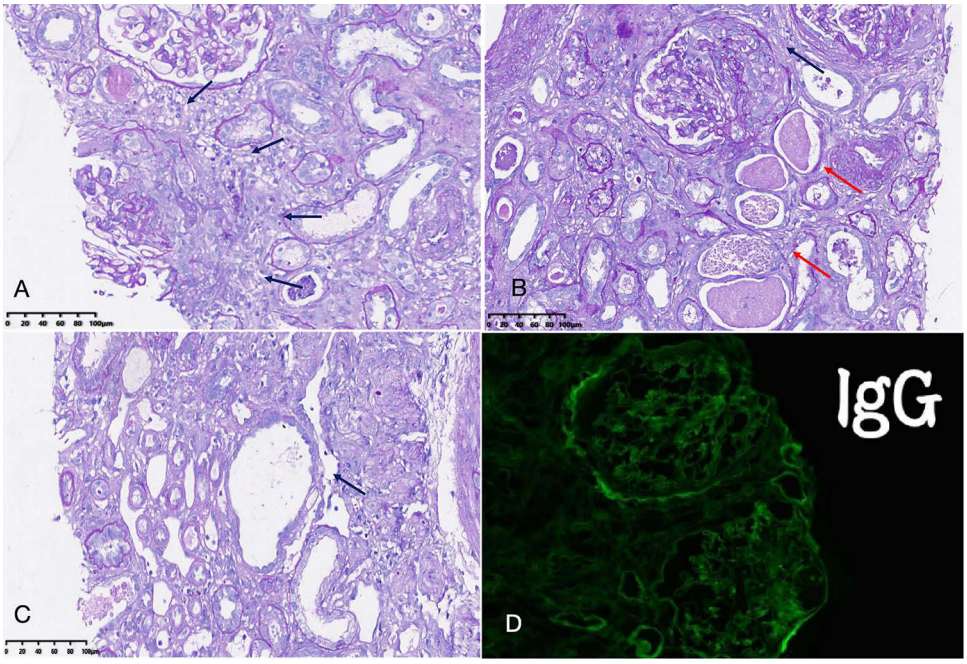

Figure 1 Kidney biopsy findings. (**A**) Periodic acid–Schiff (PAS) staining shows cellular crescent and periglomerular granuloma formation. (**B**) PAS, Black arrow shows a glomerulus with cellular crescent (involving above 50% of the glomerular circumference). Red arrow indicates protein and red cell cast in the renal tubules. (**C**) PAS, Acute tubular injury with cells vacuolar and granular degeneration in renal tubular epithelial, along with dilated renal tubules and diffuse exfoliation of the brush border. (**D**) Immunofluorescence revealed linear staining of IgG (2+) deposits along the glomerular capillary walls. Original magnification, ×400.

Table 1 Baseline and Follow-Up Manifestation of the Case

Laboratory Parameters	Normal Reference Range	Baseline	2 weeks After Treatment	2 Months After Treatment
White Blood Cell, $\times10^9$/L	3.5–9.5	3.1	5.7	4.19
Neutrophil, $\times10^9$/L	1.8–6.3	2.3	5.0	2.97
Lymphocyte, $\times10^9$/L	1.1–3.2	0.6	0.4	0.81
Hemoglobin, g/L	115–150	82	76	98
Platelets, $\times10^9$/L	125–350	59	52	117
Proteinuria, g/24h	0–0.15	0.9	NA	NA
Hematuria, /HPF	0–3	>100	>100	50–60
Creatinine, μmol/L	44–133	829	350	345
eGFR, mL/min/1.73m^2	N/A	4.130	10.806	11.827
Hemodialysis frequencies	0	3/w	3/w	1/w
ALT, IU/L	7–40	27	29	21
AST, IU/L	13–35	28	25	25
TBIL, μmol/L	1.7–20	13.2	14.1	8.2
DBIL, μmol/L	0–6	4.9	5.4	4.6
BNP, ng/mL	<100	568	602	NA
C-reactive proteinuria, mg/L	0–3.0	7.06	8.87	4.32
Immunoglobulins				
IgA, g/L	0.69–3.82	2.49	2.40	2.5
IgG, g/L	7.23–16.85	25.73	13.30	10.84
IgM, g/L	0.63–2.77	3.12	1.28	1.49
C3, g/L	0.6–1.5	0.338	0.439	0.623
C4, g/L	0.12–0.36	0.088	0.117	0.114

Abbreviations: HPF, High power field; eGFR, estimated glomerular filtration rate; BNP, Brain natriuretic peptide.

indicative of a localized infection (Supplementary Figure 1). Furthermore, metagenomic next-generation sequencing (mNGS) detected *Coxiella burnetii* (12,570 reads, 896 reads per million [RPM]) and human herpesvirus 4 (Epstein-Barr virus, 31 reads, 2.1 RPM) in the venous blood sample.

The interventional percutaneous liver biopsy revealed the presence of nodular regenerative hyperplasia of hepatocytes, indistinct branches of the portal vein, dilated sinusoids, and focal hepatic plate atrophy and disappearance in certain areas collectively contributing to the development of non-cirrhotic portal hypertension. Additionally, chronic intrahepatic cholestasis was observed in the liver (Figure 2). *Coxiella burnetii* (78 RPM) was also found in liver tissue but not observed in renal tissue.

Finally, the patient was diagnosed with chronic Q fever, ascending aorta infection leading to crescentic glomerulonephritis and non-cirrhotic portal hypertension resulting in splenomegaly and hypersplenism.

She was initiated on a treatment regimen of doxycycline and hydroxychloroquine, with a reduction in prednisolone to 15 mg. This led to a significant reduction in ascites. After two months of treatment, the frequency of hemodialysis was successfully reduced to once a week. The serum creatinine level decreased to 345 μmol/L before each dialysis session. Her platelet count remained stable at 65×10^9/L (Table 1).

Discussion

Despite the global prevalence of Q fever, the rarity of both acute and chronic cases with negative blood cultures in China results in a notably high rate of clinical misdiagnosis and missed diagnoses.[9] Traditionally, the diagnosis of Q fever is confirmed through serological testing, which detects elevated levels of Phase I and Phase II antibodies against Coxiella burnetii. It is generally believed that the titer of antiphase II IgG ≥220 and/or IgM ≥50 is of great significance for diagnosing primary Q fever infection. While the elevated IgG titers of ≥1:800 of antiphase I antibodies are related to chronic Q fever.[10] However, they were not widely used in clinical practice in China. We conducted a comprehensive literature review on previous cases of chronic Q fever with renal or hepatic involvement (Table 2,

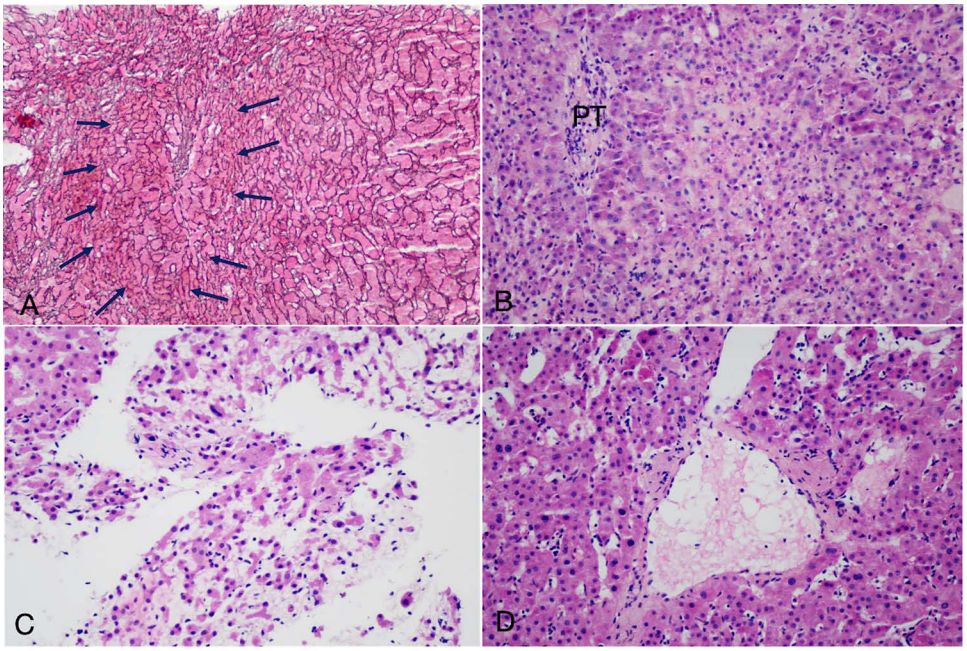

Figure 2 Liver biopsy of patient shows non-cirrhotic portal hypertension. (**A**) Reticulin ×200, Nodular regenerative hyperplasia of hepatocytes. (**B**) H&E ×400, No corresponding branches of the portal vein in the portal triads (PT); dilatation and congestion of the hepatic sinuses, accompanied by atrophy and disappearance of the hepatic plates in zones 2–3. (**C**) H&E ×200, Significant dilation of hepatic sinuses and atrophy of hepatic plates in some regions. (**D**) H&E ×400, Hepatic plates remain intact in some regions, with mild thickening and inflammation of the central venous wall, accompanied by inflammatory cell infiltration within the surrounding hepatic sinuses.

Supplementary Tables 1,2 and Supplementary literature review methods). To the best of our knowledge, the present study on chronic Q fever represents the first reported case of crescentic glomerulonephritis with periglomerular granuloma observed in renal biopsy, along with noncirrhotic portal hypertension.

A summary of previously reported cases of renal biopsy-proven renal disease in chronic Q fever is presented in Table 2 and Supplementary Table 1. Most (11 out of 13) patients had a history of cardiac disease or cardiac surgery and presented with an ill-defined fever. Serology was used for diagnostic purposes in all patients, with one patient in 2018 additionally confirmed through real-time polymerase chain reaction (PCR). The most common histopathological pattern observed was proliferative glomerulonephritis with or without crescents. Six patients succumbed to their illness, primarily during the 1960s or 1970s. Regarding specific kidney biopsy results, mesangial and endocapillary proliferation was identified as the predominant renal change in light microscopy. Positive staining was primarily detected for IgM and C3. Granulomas, a distinctive pathological alteration resulting from infection, were absent in renal tissues of all cases but were detected in our patient, further suggesting that the lesion in our patient may have originated from an infection. The pathogenesis of crescentic nephritis associated with *Coxiella burnetii* remains elusive. Nevertheless, even in the absence of detected *Coxiella burnetii* sequences in renal tissue using mNGS or observations under light microscopy, the pathological findings in the kidneys strongly imply that infection may significantly contribute to the renal damage in this patient. This, in turn, likely triggers immune-mediated inflammatory responses in the kidneys.

Liver involvement is relatively common in acute Q fever. Although we detected *Coxiella burnetii* in the liver specimen using mNGS, granulomas were not identified in the liver tissue. This may be attributed to the chronic nature of the liver changes, with a reduction in granulomas and an increase in fibrosis. This point is supported by a case reported in 1988, wherein the patient underwent four liver biopsies within an 11-month period. Granulomatous lesions gradually diminished over time, resulting in minimal fibrotic changes.[8] However, the mechanism underlying non-cirrhotic portal hypertension caused by Q fever remains unclear. In this case, the discovery of hepatic portal vein reflux obstruction, subsequent disappearance, along with a positive mNGS for *Coxiella burnetii* support the point that non-sclerotic portal hypertension in the liver could be attributed to *Coxiella*-induced venous inflammation. However, the absence of I/II phase antibody in China precludes obtaining definitive evidence from antibody titration levels.

Table 2 Chronic Q Fever Associated with Glomerulonephritis Confirmed by Kidney Biopsy

No	Author	Year	Age/ sex	Fever	Presentation	Cardiac Disease	Urine	HD	Test Method	Kidney Biopsy	Treatment	Outcome
1	Marmion	1960	48/M	Rare	Endocarditis Hemiparesis	No	Proteinuria	No	Serology	Chronic lobular GN	Penicillin, prednisone	Death
2	Ferguson	1962	48/M	Yes, 3 mo	Endocarditis Cardiac failure	Rheumatic fever	Proteinuria hematuria	No	Serology	Membranous glomerulonephritis.	Tetracycline	Death
3	Dathan	1975	58/M	Yes	Endocarditis Purpura Splenomegaly	Rheumatic fever, Cardiac Surgery	Hematuria Oliguria	Yes	Serology	GN probably caused by immune	Cotrimoxazole	Death
4	Uff	1977	43/F	No	Endocarditis Nephrotic syndrome	Mitral regurgitation	Proteinuria	No	Serology	Diffuse lobular GN	Tetracycline, lincomycin	Death
5	Rosman	1978	28/F	Yes	Endocarditis Hepatosplenomegaly	Valvular heart disease	Proteinuria Hematuria	No	Serology	Diffuse proliferative GN	Lincomycin, tetracycline	Persistent hematuria, clinically well
6	Perez-Fontan	1988	33/M	Yes	Endocarditis Hepatitis Splenomegaly	Rheumatic aortic valvular disease	Proteinuria Hematuria	No	Serology	Focal and segmental proliferative GN	Doxycycline, lincomycin	Persistent kidney dysfunction Hepatitis
7	Perez-Fontan	1988	38/M	Yes	Endocarditis Myocardial abscesses Hepatosplenomegaly	Rheumatic aortic valvular disease	Proteinuria Hematuria	Yes	Serology	Segmental proliferative and necrotizing GN	Doxycycline	Death
8	Perez-Fontan	1988	37/F	Yes	Endocarditis	Cardiac surgery	Proteinuria Hematuria	No	Serology	Focal and segmental proliferative GN	Doxycycline, cotrimoxazole, Valve surgery	Renal function improved
9	Gerlis	1994	27/M	Yes, 5mo	Endocarditis Purpura Myocarditis	Fallot Cardiac surgery	Unknown	Yes	Serology	Focal and segmental proliferative GN with cellular crescents; (autopsy) acute crescentic GN	None	Death
10	Vacher-Coponat	1996	69/M	No	Endocarditis	Mitral valve replacement	Proteinuria	No	Serology	Focal and segmental proliferative GN	Doxycycline, chloroquine	Renal function improved
11	Jandhyala	2018	59/M	Yes	Renal dysfunction	Heart-kidney transplantation	Proteinuria	No	Real-time PCR, Serology	Diffuse endocapillary proliferative GN	Doxycycline, hydroxychloroquine	PET/CT improved
12	Leclerc	2020	64/M	Yes, 1 year	Renal insufficiency	Fallot Cardiac surgery	Proteinuria Hematuria	No	Serology	Membranoproliferative glomerulonephritis	Doxycycline, hydroxychloroquine	Resolved
13	Thanamayooran	2022	52/F	Yes, 2 years	Rash Knee pain swelling	No	Proteinuria Hematuria	No	Serology	Immune complex mesangial proliferative glomerulonephritis.	Doxycycline, hydroxychloroquine	Resolved

Abbreviations: HD, hemodialysis; GN, glomerulonephritis; PCR, polymerase chain reaction.

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And the comprehensive diagnostic testing methods such as microbial culture, serological assays, and PCR-based nucleic acid detection are not widely available in most medical institutions including tertiary hospitals in China. In contrast, mNGS, a revolutionary technology that is more sensitive than PCR technology, has successfully diagnosed a number of acute and chronic Q fever patients in China,[11–13] as well as identified the first confirmed epidemic of Q fever in a contemporary city in China.[14]

Organ damage caused by Q fever is not uncommon; however, due to disparities in healthcare standards across different countries and regions, many clinical experts remain unfamiliar with this disease.[15] To mitigate the risk of kidney, liver, and cardiovascular complications associated with Q fever, it is essential to promote the widespread use of Q fever antibody testing kits and molecular diagnostics. These measures are crucial for preventing severe Q fever-related illnesses and ensuring that patients receive timely treatment.

Conclusions

We report a patient diagnosed with chronic Q fever and highlights a rare etiology of non-cirrhotic portal hypertension combined with crescentic glomerulonephritis contributing valuable insights to the limited understanding of kidney and liver diseases related to Q fever. Technologies including mNGS and PET/CT have been employed to identifying the *Coxiella burnetii* infection. And a prompt and appropriate treatment prevented further deterioration of renal and hepatic function.

Data Sharing Statement

The data generated and analyzed in this case are presented within the paper.

Research Ethics and Consent

The need for approval was waived by the Ethics Committee of Peking University First Hospital as this was a retrospective case report. Written informed consent to publish individual details and images were obtained from the subject.

Author Contributions

All authors made significant contributions to the work reported, in terms of the conception, study design, execution, acquisition of data, analysis and interpretation, or all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; agreed to submission to the journal; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests.

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