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Membranoproliferative Glomerulonephritis in a Patient With Chronic Q Fever

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INTRODUCTION

Chronic Q fever (or persistent focalized infection) is an infection caused by *Coxiella burnetii*, and patients can present with multisystemic manifestations including endocarditis. Membranoproliferative glomerulonephritis can result from various infectious or autoimmune diseases and has been described in cases of bacterial endocarditis. There are only a few reported cases of Q fever in which patients presented with glomerulonephritis and none of them with a clear description of membranoproliferative glomerulonephritis.

We report a case of a 64-year-old man with gradual decline in kidney function with significant proteinuria and hematuria. His kidney biopsy revealed membranoproliferative glomerulonephritis and an extensive infectious workup unmasked a chronic Q fever. His proteinuria and renal insufficiency responded to treatment of his underlying Q fever.

CASE PRESENTATION

A 64-year-old man presented with severe hyperkalemia and kidney failure. He was mainly known for a tetralogy of Fallot with complete surgical repair during childhood and bicuspid aortic valve. His disease course was complicated with a *Staphylococcus aureus* endocarditis at the age of 53 years. He underwent bioprosthetic aortic valvular replacement, ascending aorta aneurysm replacement with a Dacron graft, coronary bypass, residual ventricular septal defect closure, and septal myomectomy surgery at the age of 58 years. At that time, he developed a perioperative complete atrioventricular block necessitating dual-chamber pacemaker installation. His medical profile otherwise included peripheral artery disease, hypertension controlled with three agents, dyslipidemia, past apical thrombus, and nonsustained ventricular tachycardia.

Upon presentation, his medical questionnaire was notable for a 1-year history of cyclic subjective nocturnal fever and lower-leg edema. At the time of initial nephrology evaluation, urine analysis revealed 3 g of protein in 24 hours and significant hematuria. His serum albumin and creatinine levels were 3.1 g/dl and 1.80 mg/dl (estimated glomerular filtration rate 39 ml/min per 1.73 m^2 using the Chronic Kidney Disease Epidemiology Collaboration equation), respectively. He also had decreased complement factors C3 and C4. Urinary and serum laboratory studies are summarized in Table 1. A year before these laboratory results, the creatinine level was 1.08 mg/dl. An extensive workup was performed to exclude bacterial endocarditis (transesophageal echocardiography, fluorodeoxyglucose positron-emission tomography with computed tomography, and blood cultures) and was negative. He was also negative for antinuclear and anti–double-stranded DNA antibodies, antineutrophil cytoplasmic autoantibodies, antistreptolysin antibody, rheumatoid factor, and antiphospholipid antibodies. Testing for human immunodeficiency virus, brucellosis, as well as viral hepatitis B and C was negative. He was positive for cryoglobulins.

Given this absence of etiology, an infectious diseases specialist was consulted before initiating immunosuppressive treatment. Additional tests for culture-negative endocarditis were ordered and a targeted epidemiologic questionnaire was conducted which

Table 1. Laboratory investigations before and after kidney biopsy

Laboratory parameters	Within 6 months before biopsy	Biopsy time	6 months after treatment	12 months after treatment
Proteinuria	>5.0 g/l on dipstick	654 mg/mmol	15 mg/mmol	7 mg/mmol
Hematuria (RBC per HPF)	21–50	11–100	0	<5
Creatinine, mg/dl	1.1	1.8	1.9	1.6
eGFR,[a] ml/min per 1.73 m^2	71	38	37	46
Albumin, g/dl	2.5	3.2	4.1	4.5
Potassium, mmol/l	4.7	5.0	4.0	3.8
C-reactive protein, mg/l	—	5.8	—	—
ALT, UI/l	38	34	36	52
Total bilirubin, mg/dl	0.35	0.54	0.48	0.63
Complement factor C3, g/l	—	0.58 (0.82–1.85)	1.57 (0.82–1.85)	1.27 (0.81–1.57)
Complement factor C4, g/l	—	0.14 (0.15–0.53)	0.40 (0.15–0.53)	0.29 (0.13–0.39)
Q fever phase I IgG titer	—	1:16384	1:4096	1:4096
Q fever phase II IgG titer	—	1:16384	1:2048	1:2048
Q fever phase I IgM titer	—	Positive	Negative	Negative
Q fever phase II IgM titer	—	Positive	Negative	Negative
Hemoglobin, g/dl	11.0	7.8	13.0	14.1
Platelets ($\times 10^9$)	103	242	181	162

ALT, alanine aminotransferase; eGFR, estimated glomerular filtration rate; HPF, high power field; RBC, red blood cells.
[a]The eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration formula.

revealed the patient had experienced close encounters with goat herds while trekking in Morocco a year before presentation. Of note, the patient also reported having experienced a short self-limited febrile illness a few days after the contact with goats. Upon his return in Canada, a routine pacemaker monitoring revealed that nonsustained ventricular tachycardia had occurred concomitantly with the febrile episode. Four weeks after the initial presentation, *C burnetii* serology came back highly positive for both anti–phase I and II IgG antibodies (1:16384 for both). Anti–phase I and II IgM antibodies were also positive.

Two cores of renal parenchyma were received for light microscopy. There were 57 glomeruli, including 5 globally sclerotic. Glomeruli showed diffuse increase in cellularity with global mesangial and endocapillary hypercellularity. Glomerular capillary walls were thickened with segmental duplication on the silver stain. Interstitial fibrosis and tubular atrophy were mild, with mild mononuclear interstitial infiltrate. Arteriolar hyalinosis was mild to moderate, and arterial sclerosis was mild (Figure 1).

Routine immunofluorescence on frozen tissue showed positive staining for IgG (2+, on a 0 to 3 scale), IgA (2+), IgM (1+), C3 (3+), C1Q (2+), and both kappa (2+) and lambda (2+) with a segmental pseudolinear pattern along the capillary walls. There were no extraglomerular deposits.

Electron microscopy showed discrete subendothelial electron-dense immune-type deposits, without organization. The podocyte foot processes were extensively effaced (60% to 70%). Tubuloreticular inclusions were not seen.

The patient was thus diagnosed with immune-complex mediated membranoproliferative glomerulonephritis secondary to chronic *C burnetii* infection, with presumed endocarditis and/or vascular graft infection as the most likely source of infection.

The patient was started on doxycycline and hydroxychloroquine to treat his *C burnetii* infection. In addition, he received initially a short course of oral glucocorticoids and mycophenolate mofetil. This led to a complete resolution of fever along with a significant decrease in his Q fever antibody titers, as well as an improvement in renal function and complete remission in proteinuria (Table 1).

DISCUSSION

We presented the case of a 64-year-old male known for a surgically corrected tetralogy of Fallot and an aortic valve bioprosthesis associated to ascending aorta aneurysm repair with a Dacron graft who presented with hyperkalemia and kidney failure after one year of cyclic nocturnal fever. We diagnosed an immune-complex mediated membranoproliferative glomerulonephritis secondary to a chronic *C burnetii* infection. Although this complication of chronic Q fever infection is already known, this case is unique because it is rarely described in the recent literature. Furthermore, most published cases reported partial clinical and pathologic data and were diagnosed at times where membranoproliferative glomerulonephritis was classified and described differently.

C burnetii is a pleomorphic Gram-negative coccobacillus. The disease is a zoonosis and its main reservoir consists of various farm animals including sheep, cattle, and goats. People in direct contact with these animals, such as farm or abattoir workers, are at higher risk for infection, but even people with limited contact or living downwind from contaminated areas are at risk.[1] Infections tend to be more severe in older adults and in men. Acute infection is characterized in most cases by an influenza-like illness, with or without pneumonia or hepatitis, that often goes unnoticed or misdiagnosed. Approximately 5% of individuals go on to develop

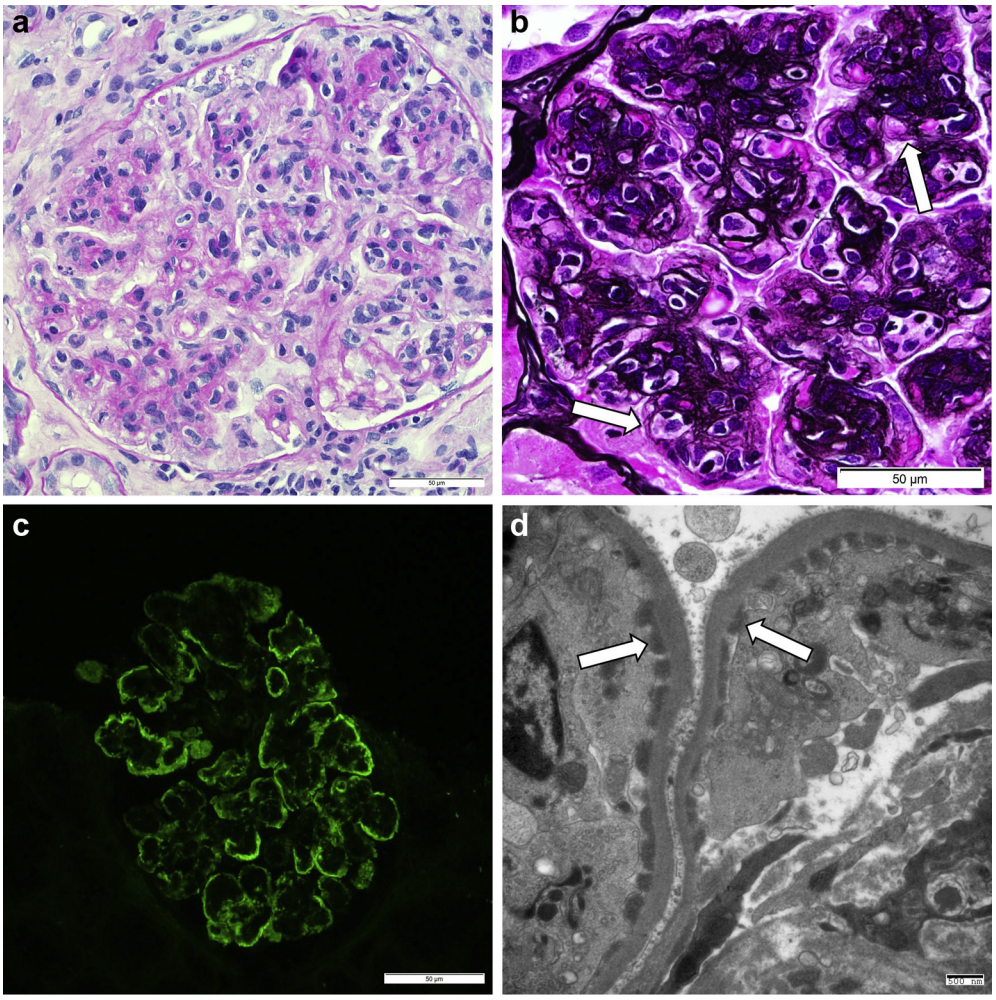

Figure 1. Kidney biopsy findings. (a) A light microscopic image showing a glomerulus with global endocapillary and mesangial hypercellularity (periodic acid–Schiff, original magnification ×400). (b) Thickening of capillary walls with segmental duplication (arrows) on the silver stain (Jones stain, original magnification ×600). (c) Immunofluorescence staining for anti-IgG showing pseudolinear pattern along the capillary walls (original magnification ×400). (d) Electron microscopy exhibiting subendothelial, nonorganized electron-dense immune-type deposits (arrows) (original magnification ×20,000).

chronic Q fever infection, especially in pregnant women or in people with cardiac anomalies and prosthetic material.[1] The most frequent manifestation of chronic Q fever infection is endocarditis. It is often difficult to diagnose as less than 40% of cases have vegetation and traditional blood cultures are negative.[2] Thus, patients often have a long course of disease at the time of diagnosis. Recommended treatment for Q fever prosthetic valve endocarditis is doxycycline and hydroxychloroquine for 24 months minimum or until there is a 4-fold decrease in phase I antibody titers.[3]

Membranoproliferative glomerulonephritis is a pattern of injury on kidney biopsy characterized by hypercellularity of the glomerular tuft and capillary wall thickening with double contour formation. It is a histologic lesion and not a specific disease entity. The classification of this type of kidney lesion greatly evolved over time, and an approach based on the pathophysiologic process and immunofluorescence results is now favored, distinguishing between immune-complex disease and complement-mediated disease. Among immune-complex membranoproliferative glomerulonephritis, common cases include viral infections, autoimmune disease and monoclonal gammopathy. A rarer entity is immune-complex membranoproliferative glomerulonephritis classically associated with bacterial endocarditis, and it has been associated with *C burnetii* in acute Q fever infection.[4,5]

A summary of previous reported cases of renal disease in chronic Q fever is shown in Tables 2 and 3. Only 14 detailed cases were found in the English literature, all but 1 of them reported before 1996. Most patients were adult males with previous heart condition presenting with long lasting ill-defined febrile illnesses. Upon further testing, all patients were diagnosed with *C burnetii* endocarditis. A minority presented with hepatosplenomegaly or purpura. One patient tested positive for cryoglobulins. Serum

Table 2. Clinical presentations of chronic Q fever cases in the literature

Case number	Author	Year	Age	Sex	Q fever manifestations	Dialysis	Proteinuria	Urine sediment	Outcome
1	Marmion[S1]	1960	48	M	Endocarditis	No	Yes	Hematuria	Death
2	Ferguson[S2]	1962	48	M	Endocarditis Pneumonia	No	Yes	Hematuria	Death
3	Dathan[S3]	1975	58	M	Purpura Endocarditis Splenomegaly	Yes	Unknown	Hematuria Granular casts	Death
4	Turck[S4]	1976	63	M	Endocarditis	Unknown	Unknown	Unknown	Unknown
5	Uff[S5]	1977	43	F	Endocarditis	No	4.0 g/d	Unknown	Death
6	Rosman[S6]	1978	28	F	Endocarditis	Unknown	Unknown	Hematuria	Persistent hematuria
7	Perez-Fontan[S7]	1988	33	M	Endocarditis Hepatitis Splenomegaly	No	1.0 g/d	Hematuria	Persistent kidney dysfunction
8	Perez-Fontan[S7]	1988	38	M	Endocarditis Hepatosplenomegaly	Yes	1.5 g/d	Hematuria Red cells casts	Death
9	Perez-Fontan[S7]	1988	37	F	Endocarditis	No	0.7 g/d	Hematuria	Renal function improved
10	Enzenauer[S8]	1991	41	F	Endocarditis Mixed cryoglobulinemia	Unknown	Unknown	Unknown	Renal function improved
12	Gerlis[S9]	1994	27	M	Purpura Endocarditis Myocarditis	Yes	Unknown	Unknown	Death
13	Vacher-Coponat[S10]	1996	69	M	Endocarditis	No	Yes	No	Renal function improved
14	Rafailidis[2]	2006	65	M	Purpura Endocarditis	No	Yes (1+)	Hematuria Red cells casts	Renal function improved

F, female; M, male.

creatinine levels upon presentation ranged from 0.4 mg/dl to 11.0 mg/dl. In all cases where a urinalysis was reported, proteinuria (ranging from 0.7 to 4.0 g/d) and hematuria (with or without red blood cells casts) were present. Three patients were started on dialysis; they all died from cardiac failure complications. The outcome of the 11 remaining patients was also known: 3 died, 3 had persistent chronic kidney disease after treatment, and 5 returned to their baseline kidney function.

These cases seem to highlight that *C burnetii* endocarditis with glomerulonephritis has a poor prognosis with a 43% mortality rate. However, it seems that this mortality is more related to the endocarditis and cardiac damage occurring before targeted therapy initiation. In those reported cases, the average time between presentation and diagnosis was 11 months, consistent with what was noted by Parker *et al*.[6] Furthermore, by opposition to a recent review of endocarditis-associated renal disease by Boils *et al*.[7] which showed that 94% of patients presented with acute kidney injury or rapidly progressive glomerulonephritis, patients with *C burnetii* seem to have a slightly milder renal presentation. In reported cases, only 21% needed dialysis. Our patient presented with nephrotic range proteinuria and progressive kidney disease after 1 year of cyclic nocturnal fever.

With respect to the kidney biopsy results, reported cases in the literature are heterogenous and incomplete. First, case reports were written in different eras ranging from 1960 to 2006, making comparison difficult in description and diagnosis. Second, only two case reports described comprehensive kidney biopsy results that include light microscopy, immunofluorescence, and electron microscopy. A further five case reports described kidney biopsy reports with light microscopy and immunofluorescence (without electron microscopy). Other reports contained information only about light microscopy or no information at all. Despite those serious limitations, one can realize that mesangial expansion and glomerular hypercellularity, either mesangial or endocapillary, seems to be a prominent feature of chronic Q fever related glomerulonephritis. Only two cases described diffuse basement membrane thickening, one evoking membranous nephropathy and one double contour characterizing membranoproliferative glomerulonephritis. When available, immunofluorescence seemed to be positive mainly for IgM and C3. No cases reported a full house pattern. Two cases with electron microscopy showed diffuse foot process effacement; deposits were seen in mesangial location in one and subendothelial location in the other.

Our case is unique in comparison to the cases mentioned above and raises interesting points about Q fever-related kidney diseases, as seen in Table 4. Detailed pathology results were available and described with contemporary terms and classification. Furthermore, as opposed to most described cases, light microscopy is clearly evoking a membranoproliferative glomerulonephritis pattern of injury, with mesangial and endocapillary hypercellularity and double contours of the capillary walls. In addition, this is to our

Table 3. Kidney biopsy results of chronic Q fever cases in the literature

Case number	Authors	Year	Light microscopy	Immunofluorescence	Electron microscopy	Diagnosis
1	Marmion[S1]	1960	Unknown	Unknown	Unknown	Chronic lobular GN
2	Ferguson[S2]	1962	Endothelial cell proliferation Diffuse basement membrane thickening	Unknown	Unknown	Chronic lobular GN
3	Dathan[S3]	1975	Glomerular hypercellularity Mesangial proliferation Mesangial expansion Endocapillary proliferation	Granular IgA, IgG, and C3 deposits	Granular mesangial deposits Diffuse foot process effacement	GN probably caused by immune complex
4	Turck[S4]	1976	Unknown	Unknown	Unknown	Diffuse GN
5	Uff[S5]	1977	Mesangial proliferation Mesangial interposition Capillary thickening	Granular IgM and C3 deposits	Unknown	Diffuse lobular GN
6	Rosman[S6]	1978	Mesangial hypercellularity Capillary loop leukocytes	Granular IgM and C3 deposits	Subendothelial deposits Foot process fusion	Diffuse proliferative GN
7	Perez-Fontan[S7]	1988	Mesangial expansion Mesangial hypercellularity Bowman capsule adhesion Interstitial infiltrate	Granular mesangial IgM and C3 deposits Capillary loops IgG deposits	Unknown	Focal and segmental proliferative GN
8	Perez-Fontan[S7]	1988	Endocapillary proliferation Focal necrosis Fibrocellular crescents Interstitial infiltrate	Granular mesangial IgM and C3 deposits Capillary loops IgG deposits	Unknown	Focal and segmental proliferative GN
9	Perez-Fontan[S7]	1988	Mesangial expansion Mesangial hypercellularity Endocapillary hypercellularity Endothelial swelling	Granular mesangial IgM, C1q, C3, and C4 deposits	Unknown	Diffuse proliferative GN
10	Enzenauer[S8]	1991	Unknown	Unknown	Unknown	Unknown
12	Gerlis[S9]	1994	Focal and segmental proliferation Crescents	Unknown	Unknown	Focal and segmental proliferative GN
13	Vacher-Coponat[S10]	1996	Mesangial proliferation Deposits within double contour of basement membrane	Diffuse IgG, IgM, C1q, and C3 deposits	Unknown	Focal and segmental proliferative GN
14	Rafailidis[2]	2006	Unknown	Unknown	Unknown	Unknown

GN, glomerulonephritis.

knowledge the first time that a full house pattern on immunofluorescence with positivity for IgA, IgM, IgG, C3, C1q, kappa, and lambda is described in a Q fever–related glomerulonephritis. Electron microscopy showed immune-type subendothelial deposits with no organization, despite the presence of circulating cryoglobulins.

The full house pattern usually evokes a diagnosis of systemic lupus erythematosus. This patient had negative tests for antinuclear antibodies and antiphospholipid antibodies. Also, there were no extraglomerular deposits and tubuloreticular inclusions. A case of acute Q fever with membranoproliferative glomerulonephritis and antiphospholipid antibodies has been described. However, the details of the kidney biopsy were not described in the article. Both kidney disease and the antiphospholipid antibodies disappeared with treatment.

Table 4. Teaching points

Coxiella burnetii infection is difficult to diagnose as only a minority of cases have vegetation or positive blood cultures.
Although glomerulonephritis is frequently associated with *C burnetii* endocarditis, membranoproliferative glomerulonephritis is rarely described.
Patients can present with rapidly progressive glomerulonephritis needing hemodialysis or with slowly progressive chronic kidney disease.
A full house pattern on immunofluorescence staining combined with a membranoproliferative glomerulonephritis and negative tests for systemic lupus erythematosus should encourage the search for *C burnetii* or other occult infections.
Although the prognosis of *C burnetii* endocarditis with kidney disease is poor, a timely diagnosis and treatment can help restore kidney function at least partially.

CONCLUSION

We report a case of a 64-year-old male known for congenital heart disease with aortic bioprosthesis, ascending aorta aneurysm repair with a Dacron graft, and a pacemaker, presenting after 1 year of cyclic nocturnal fever with hyperkalemia and kidney failure. He was found to have chronic *C burnetii* infection associated with membranoproliferative glomerulonephritis. This case adds to the short and heterogeneous list of chronic Q fever–related kidney diseases. To our knowledge, it is the second to show a membranoproliferative glomerulonephritis in this context, and the first to present with a full house pattern on immunofluorescence. This case highlights a rare cause of membranoproliferative glomerulonephritis and the importance of a thorough etiologic investigation that could lead to an appropriate treatment to prevent loss of kidney function.

DISCLOSURE

LPL is a Fonds de recherche du Québec-Santé Junior 1 Scholar. All the other authors declared no competing interests.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary References.

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