Cat-Scratch Disease Masquerading as C3 Glomerulonephritis

Benjamin Sutu[1], Shio Yen Tio[2], Lucy C. Fox[3,4], Joseph Sasadeusz[2,4], Piers Blombery[3,4], Moira J. Finlay[4,5] and Thomas D. Barbour[1,4]

[1]Department of Nephrology, Royal Melbourne Hospital, Parkville, Victoria, Australia; [2]Department of Infectious Diseases, Royal Melbourne Hospital, Parkville, Victoria, Australia; [3]Department of Hematology, Peter MacCallum Cancer Centre, Parkville, Victoria, Australia; [4]Department of Medicine, University of Melbourne, Melbourne, Victoria, Australia; and [5]Department of Anatomical Pathology, Royal Melbourne Hospital, Parkville, Victoria, Australia

Correspondence: Benjamin Sutu, Department of Nephrology, Royal Melbourne Hospital, Parkville, Victoria 3050, Australia. E-mail: benjamin.sutu@mh.org.au

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INTRODUCTION

C3 glomerulonephritis (C3GN) is a rare form of glomerulonephritis characterized by dominant staining for complement C3 within the glomerulus, with dense deposits on electron microscopy.[1] C3GN is associated with acquired or genetic factors that lead to impaired regulation of the complement alternative pathway (AP). Differentiating C3GN from "post-infectious" glomerulonephritis (PIGN) can be challenging because of overlap in pathogenesis and clinical and histologic characteristics.[2] Thus, C3-dominant glomerular staining is 1 of 5 classic clinicopathologic features described in PIGN,[3] and of the remaining features, preceding infection is also frequently observed in C3GN, low plasma C3 levels are found in over two-thirds of C3GN cases, diffuse endocapillary proliferation on light microscopy has been reported in 19% of C3GN cases, and subepithelial humps on electron microscopy have been reported in 35% of C3GN cases.[4]

In the modern era, the term "infection-related" glomerulonephritis has replaced PIGN because infection may be ongoing at the time of active renal disease.[5] In all such cases, there is real clinical urgency to investigating potential loci of infection, including occult ones. The ability to distinguish between infection-related glomerulonephritis and C3GN also is important for the appropriate treatment of C3GN, because retrospective studies indicate that mycophenolate mofetil and steroids,[S1,S2] or the complement C5 inhibitor eculizumab,[1,S3] may be beneficial in some patients. In this regard, previous reports have suggested that transient low serum C3 levels and the nephritic syndrome should be considered typical of acute PIGN, whereas hypocomplementemia and/or renal clinical abnormalities persisting beyond 8 to 12 weeks could increase the relative likelihood of C3GN.[6]

In 1 report, a child diagnosed clinically with acute poststreptococcal glomerulonephritis later underwent renal biopsies because of recurrent macroscopic hematuria with concurrent low plasma C3 levels.[7] Renal histology revealed a C3-dominant membranoproliferative glomerulonephritis, with detection of a heterozygous gene sequence variant in complement factor H–related protein 5.[7] In a series of 11 mostly adult patients with "atypical" (i.e., slow to resolve) PIGN, 4 were found to have complement sequence variants.[8] One possible explanation in such cases is that infection may trigger complement AP activation, which then becomes excessive in patients with an underlying disorder of AP regulation and consequent susceptibility to C3GN.[1] By contrast, we report a patient originally diagnosed with a relapsing form of C3GN in whom no genetic or acquired complement abnormalities could be detected. After 18 months of immunosuppressive treatment, *Bartonella henselae* endocarditis was diagnosed.

CASE PRESENTATION

A previously healthy 63-year-old white man presented with a 2-month history of lethargy, fatigue, and painless macroscopic hematuria without recent infection. He had no history of diabetes, immune compromise, heart disease, alcohol dependence, or intravenous drug use. On examination, he was afebrile, normotensive, and euvolemic, with no cardiac murmur, splenomegaly, lymphadenopathy, or fundoscopic changes. Initial

Table 1. Baseline laboratory data

Investigation	Result	Reference range
Hemoglobin, g/L	103	130–170
White blood cell count, $\times 10^9$ /L	4.6	4.0–11.0
Lymphocytes, $\times 10^9$ /L	1.2	1.2–4.0
Platelets, $\times 10^9$ /L	132	140-400
Blood film	Normocytic, normochromic anemia, no fragments	
Creatinine, μmol/L	345	70–114
Albumin, g/L	29	35–50
Calcium, mmol/L	2.45	2.1–2.6
Ferritin, μg/L	567	200–300
C-reactive protein, mg/L	13.9	<5.0
Erythrocyte sedimentation rate, mm in 1 h	92	2–14
ANA, dsDNA, ENA, anti-GBM, cANCA, pANCA, myeloperoxidase, proteinase-3	Negative	
Atypical ANCA	Weakly positive	
C3, g/dl	124	82–185
C4, g/dl	20	15–53
C3 nephritic factor	Negative	
α1-Globulins, g/L	2.2	0.8–2.0
α2-Globulins, g/L	5.3	5.4–8.9
β1-Globulins, g/L	4.2	4.2–6.8
β2-Globulins, g/L	3.5	1.7–4.3
γ-Globulins, g/L	21.4	4.7–11.6
IgG, g/L	9.7	5.4–18.2
IgA, g/L	0.6	0.6–4.8
IgM, g/L	0.2	0.2–2.4
Serum and urine PEP/IFE	No paraprotein	
Cryoglobulins	Negative	
Rheumatoid factor, IU/ml	15.0	<15
HbsAg, HBs, HBc, hepatitis C virus, HIV	Negative	
Midstream urine, cells $\times 10^6$/L	>1000 red blood cells <2 white blood cells Mixed red blood cell morphology, granular casts	<13
UPCR, mg/mmol	23	15–35
UACR, mg/mmol	9	<2.5

ANCA, antineutrophil cytoplasmic antibodies; ANA, antinuclear antibodies; dsDNA, (antibodies to) double-stranded DNA; ENA, extractable nuclear antigen antibodies; anti-GBM, anti-glomerular basement membrane antibodies; cANCA, cytoplasmic antineutrophil cytoplasmic antibodies; pANCA, perinuclear anti-neutrophil cytoplasmic antibodies; PEP/IFE, protein electrophoresis/immunofixation; UPCR, urine protein to creatinine ratio; UACR, urinary albumin to creatinine ratio.

blood tests showed acute kidney injury with a serum creatinine of 345 μmol/L and mild normocytic anemia and thrombocytopenia with no intravascular hemolysis (Table 1). There was hypergammaglobulinemia, elevated C-reactive protein and erythrocyte sedimentation rate, and weakly positive atypical antineutrophil cytoplasmic antibodies (ANCA) on indirect immunofluorescence with negative proteinase-3 and myeloperoxidase antibodies on ELISA. Autoimmune and viral serologies were otherwise unremarkable, and complement studies including serum C3 and C4 levels and C3 nephritic factor were negative. Blood cultures were negative. Urinalysis confirmed hematuria with glomerular red blood cell morphology, and albuminuria. Renal tract ultrasound showed normal kidneys and collecting system.

Renal biopsy (Figure 1a–e) demonstrated mild endocapillary proliferative glomerulonephritis involving mononuclear cells with early double-contour formation but no significant increase in mesangial cellularity. Of 21 glomeruli, all were viable, with no crescents or necrotizing lesions but with prominent red blood cell casts in renal tubules. There was no significant interstitial fibrosis or tubular atrophy, and arterioles were unremarkable. Immunoperoxidase staining showed capillary loop C3+++ and C1q+, mesangial and loop IgM++, and negative IgG, IgG_4, IgA, fibrin, and C4d. Immunofluorescent staining of paraffin-embedded renal tissue after proteinase digestion showed no light chain restriction (background staining only for kappa and lambda).[S4] Electron microscopy showed discontinuous, moderately dense, unstructured deposits located subendothelially and in the mesangium, without subepithelial humps.

The patient was treated with oral prednisolone at an initial dose of 70 mg once daily (patient weight, 73 kg), which was weaned and then ceased 3 months after a complete clinical remission (serum creatinine, 114 μmol/L). Two months later, recurrent macroscopic hematuria and acute kidney injury (serum creatinine, 241 μmol/L) prompted a second biopsy demonstrating membranoproliferative glomerulonephritis, now with more intense C3 staining but an otherwise identical pattern. Additional investigations included optical coherence tomography, showing normal macular anatomy without any drusen, and next-generation sequencing using a hybridization-based capture panel on a peripheral blood sample, which did not reveal any pathogenic variants in CD46, factor B, factor H, factor H–related proteins 1 and 5, factor I, or diacylglycerol kinase ε. A transient elevation in serum kappa free light chains associated with the acute kidney injury led to investigations for monoclonal gammopathy including computed tomography of the neck, chest, abdomen and pelvis, and bone marrow aspirate and trephine, which were normal. Oral prednisolone 50 mg daily was again effective in achieving clinical remission with a serum creatinine of 83 μmol/L, and at 2 months the dose had been reduced to 5 mg once daily. In the meantime, mycophenolate mofetil was added as an ongoing therapy at an initial dose of 1 g twice daily, which was then reduced to 500 mg twice daily at 4 months and 250 mg twice daily at 9 months.

Eighteen months after his second biopsy, the patient presented for routine review with unintentional weight loss of 8 kg (11%) over a 2-month period, fatigue, and night sweats. He was found to have splenomegaly, microscopic hematuria, acute kidney injury (serum

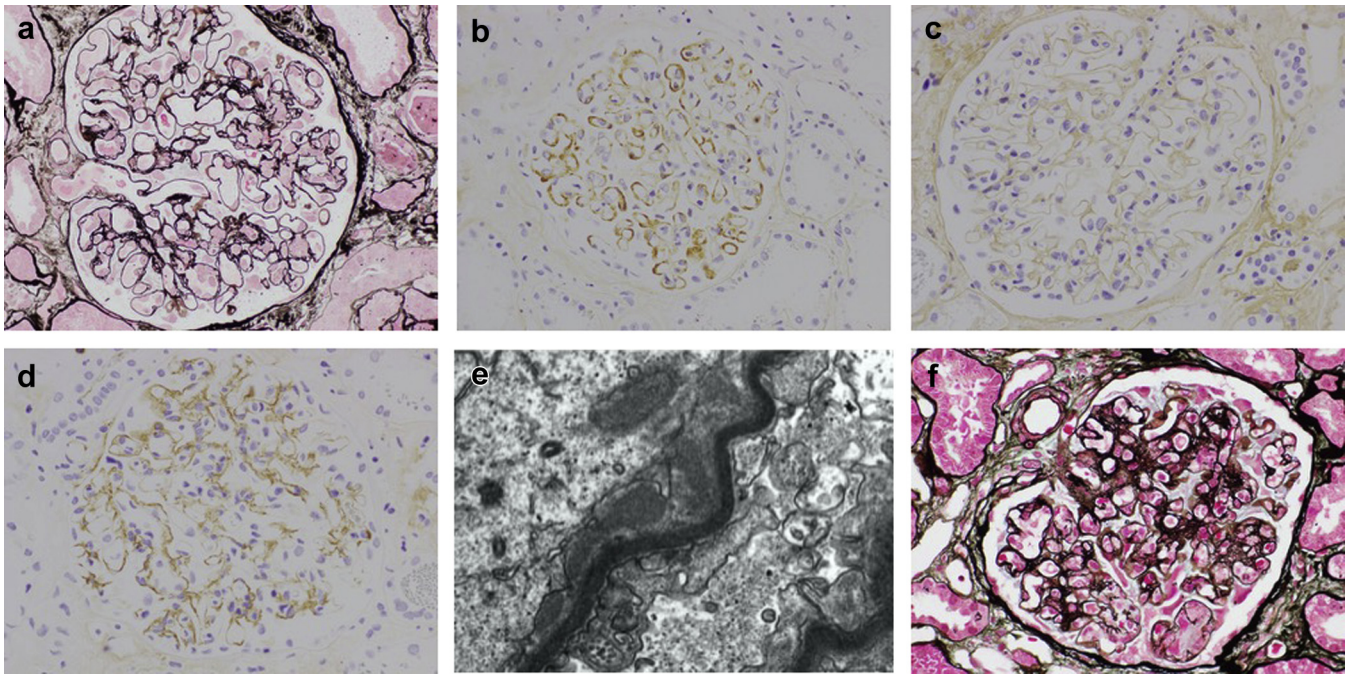

Figure 1. Renal histology. (a) First biopsy with silver Masson trichrome stain showing endocapillary proliferative glomerulonephritis with early double-contour formation. Immunoperoxidase stains for (b) C3, (c) IgG, and (d) IgM. (e) Electron microscopy showing mainly subendothelial deposits. (f) Third biopsy silver Masson trichrome stain showing membranoproliferative glomerulonephritis. Original magnification ×40.

creatinine, 185 μmol/L), and a cardiac murmur. Autoimmune hemolytic anemia and mild pancytopenia were evident with raised erythrocyte sedimentation rate and C-reactive protein, persisting hypergammaglobulinemia, and weakly positive antineutrophil cytoplasmic antibodies (now in a cytoplasmic pattern, with negative proteinase-3 and myeloperoxidase antibodies). Serologies were also now positive for cardiolipin IgG (25 GPU; reference range, <20), a type 3 cryoglobulin (0.1 g/L), and rheumatoid factor (35 IU/ml), with borderline low serum complement C3 (0.81 g/L) and C4 (0.14 g/L) levels and a normal serum sC5b-9 level (208 ng/mL; reference range, <300). Skin biopsy of a lower limb petechial rash was in keeping with thromboembolism, with immunostaining for C3+ and IgM++ suggestive of some damage to vessel walls but without frank vasculitis or features of cryoglobulinemia.

Serial blood cultures were now performed (before antibiotic therapy) and remained negative even after extended incubation. However, transthoracic followed by transesophageal echocardiography showed a 1.3 cm × 0.4 cm vegetation on the aortic valve with moderate aortic regurgitation and moderate left ventricular dilatation and systolic dysfunction. Decompensated heart failure led to urgent bioprosthetic aortic valve replacement, with eventual diagnosis of *Bartonella henselae* endocarditis based on positive polymerase chain reaction (PCR) and pathologic examination of the excised valvular tissue and an elevated serologic titer of 192 (IgM) and 66,536 (IgG). Serologies for other fastidious organisms including *Coxiella burnetii*, Q fever, and *Brucella* species were negative. A third renal biopsy (Figure 1f) showed more advanced membranoproliferative glomerulonephritis with lobular accentuation and many double contours and persisting strong immunoperoxidase and immunofluorescent staining for C3 in capillary loops, with moderate IgM and C1q, and new, light IgA and IgG staining. Electron microscopy showed mesangial, paramesangial, and subendothelial deposits. PCR of renal biopsy tissue was negative for *B henselae*.

Mycophenolate mofetil was ceased, and combination antimicrobial therapy consisting of doxycycline 100 mg twice daily and rifampicin 300 mg twice daily was commenced. Rifampicin was later switched to gentamicin 1 mg/kg per day once renal function had improved. At 2 years the patient remains well with a serum creatinine of 95 μmol/L, urinary red blood cells 1×10^6/L, and urine protein to creatinine ratio of 17 mg/mmol. On further questioning, he had kept several rescue cats at home before and after developing glomerulonephritis but could not specifically recall being scratched or bitten.

DISCUSSION

We report a case of relapsing C3-dominant glomerulonephritis in which an apparently durable response to immunosuppressive treatment was later overwhelmed by systemic illness associated with *B henselae*

Table 2. Teaching points

Bacterial endocarditis can lead to immune-mediated glomerulonephritis, with activation of the complement system.
Dominant complement C3 staining in "C3 glomerulonephritis" is the result of acquired or genetic defects in alternative pathway regulation.
Distinguishing C3 glomerulonephritis from infection-related glomerulonephritis may be challenging in clinical practice but is important for treatment decisions.
An evolving clinical picture that comes to include atypical features should prompt consideration of revised diagnoses, with appropriately targeted investigations.

endocarditis. Occult endocarditis appears likely to have been present in our patient from the onset of his renal disease (Table 2). Raised inflammatory markers and nonspecific serologic abnormalities may even have provided early clues. On the other hand, no clinical features at presentation were strongly indicative of either localized or systemic infection, and endocarditis was only confirmed 2 years later when echocardiography and specific serologic and DNA testing for *B henselae* were performed. Subsequent resolution of the renal clinical abnormalities after effective antimicrobial therapy further suggests that a primary diagnosis of C3GN is less likely, and no genetic defect of AP regulation could be demonstrated.

An important aspect of microbiology is that whereas infection due to certain microorganisms might be uncommon (in this case, *B henselae*), it can nevertheless account for a disproportionately large proportion of cases of a given clinical disease. Thus, *Bartonella* species, 11 of which have been described as human pathogens,[S5] are said to be responsible for up to 28% of blood culture–negative endocarditis cases.[S6] *B henselae* is a fastidious, intracellular, gram-negative bacillus for which cats are a natural reservoir. Cat-scratch disease occurs due to exposure of a human host's broken skin to cat saliva containing *B henselae* and usually takes the form of a self-limiting illness with localized lymphadenopathy. However, in susceptible individuals, including those with immune compromise or structural heart disease, hematogenous spread of bacteria from the lymph nodes can manifest as an insidious, systemic illness with end-organ dysfunction because of infection and/or the host immune response.[S6]

Glomerulonephritis has been extensively reported in association with *B henselae* endocarditis,[9] although to our knowledge this is the first report of a C3-dominant glomerulonephritis in the absence of congenital or structural cardiac disease.[S7-S11] C3-dominant staining implies uncontrolled C3 activation via the AP.[1] Whereas in many cases of endocarditis-associated glomerulonephritis, including those due to *B hensalae*, low plasma C3 levels reflect systemic AP activation, the persisting normal plasma C3 levels in our patient imply local C3 activation within the glomerulus, potentially as a result of deposition of bacterial AP-triggering antigens.[9] Direct AP activation due to *B henselae* has been demonstrated *in vitro*.[S12] On the other hand, the positive immunoperoxidase staining for IgM and C1q (albeit less intense than for C3) could have been related to deposition of immune complexes, triggering both the classic and alternative complement pathways.[5] Regardless, bacterial antigen could not be demonstrated on PCR of renal tissue, and systemic complement activation cannot be ruled out and may even have been augmented by circulating autoantibodies. The latter included antineutrophil cytoplasmic antibodies[S7–S9] and cryoglobulins,[S7,S8,S11] as described in previous reports of endocarditis-associated glomerulonephritis involving *B henselae*.

In conclusion, this unique case of C3-dominant glomerulonephritis in a patient with *B henselae* endocarditis highlights the potential for occult infection as the underlying cause of complement activation.

DISCLOSURE

All the authors declared no competing interests.

ETHICS AND CONSENT

The study was conducted under Melbourne Health research ethics approval (HREC2016.176), and written consent to participate and for publication was obtained from the patient.

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SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary References.

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