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Clinical Report

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Borrelia and nephropathy: cryoglobulinaemic membranoproliferative glomerulonephritis responsive to doxycyclin in active Lyme disease

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Abstract
The association of membranoproliferative glomerulonephritis (MPGN) with Lyme borreliosis has only been reported for the C1q-negative subtype. A 64-year-old male presenting with rising creatinine, nephrotic syndrome and monoarthritis few months after a tick bite was noted to have mixed cryoglobulinaemia, a positive borrelia western blot and 'full-house' pattern MPGN with interstitial granuloma. Findings resolved with prednisolone and doxycyclin therapy. The histology is consistent with MPGN secondary to cryoglobulinaemia, which has most likely been caused by borrelia infection. 'Full-house' pattern MPGN may result from Lyme borreliosis through cryoglobulinaemia and may be treated successfully with the appropriate antibiotic therapy.

Keywords: full-house pattern; Lyme borreliosis; membranoproliferative glomerulonephritis; mixed cryoglobulinaemia

Background

In the sparse literature regarding putative renal involvement of Lyme disease, the suggested pathologic mechanism is predominantly membranoproliferative glomerulonephritis (MPGN) with deposition of polyclonal immunoglobulins and complement components [1]. However, the association with Lyme borreliosis has only been described for the C1q-negative immunohistological subtype of MPGN, which is typically attributable to chronic infection [2]. The C1q-positive form characteristically results from autoimmune disorders, including cryoglobulinaemia [3, 4]. We present a case of c1q-positive MPGN in the setting of active Lyme disease and the subsequent treatment options.

Case report

A 64-year-old Bavarian farmer presented with a rise in serum creatinine to 239 µmol/L (2.7 mg/dL) from a baseline level of 115 µmol/L (1.3 mg/dL) and severe nephrotic syndrome. He reported monoarthritis and neuropathic pain with onset few months after a tick bite the year before. Urine sediments contained dysmorphic red cells and red cell casts. Laboratory tests showed depression of the C4 complement component with a slightly lowered C3 level, and mixed cryoglobulinaemia type II. Strong bands against p100, VisE, p41 and *Borrelia afzelii* OspC were found on borrelia IgM western blot, and against p100, VisE, p58, p41, p39 and *B. afzelii* P18 on borrelia IgG western blot. C3 nephritic factor, anti-nuclear antibodies (ANA), anti-neutrophil cytoplasmatic antibody and viral serology were negative (Table 1). Microscopic studies of a renal tissue specimen revealed MPGN I, immunohistological 'full-house' pattern with deposits of IgG, IgM, C1q, C3c and IgA, accompanied by tubular dilatation and mild interstitial nephritis with granuloma (Figures 1 and 2). After oral prednisolone therapy and an 8-week course of 100 mg doxycyclin bi-daily, urine sediment was bland and cryoglobulinaemia, complement consumption, and oedema had resolved. Serum creatinine had fallen to its baseline value and proteinuria was markedly reduced (Table 2).

Discussion

MPGN is traditionally categorized according to electron microscopic changes. For evaluating this case, we used the immunofluorescence-based classification of MPGN, which has been suggested to be more appropriate to direct the clinical evaluation [5].

McCausland *et al.* reported a case of a 57-year-old female presenting with rash, volume overload and decreased complement C3, who was diagnosed with active Lyme disease. The patient responded well to steroids and an oral course of doxycyclin, followed by intravenous ceftriaxone. Immunohistological findings were consistent with immune complex-mediated MPGN, but did not

Table 1. Laboratory tests on admission

Creatinine [µmol/L (mg/dL)]	239 (2.7)	Hepatitis B serology	Negative
GFR MDRD [mL/s (mL/min)]	0.38 (23)	Hepatitis C serology	Negative
Urea [mmol/L (mg/dL)]	35 (99)	HIV serology	Negative
Albumin [g/L (g/dL)]	22 (2.2)	Serum protein electrophoresis	Unremarkable
Sodium [mmol/L (mEq/L)]	139 (139)	Immunofixation	Unremarkable
Potassium [mmol/L (mEq/L)]	5.4 (5.4)	Cryoglobulin precipitation	Positive
Bicarbonate [mmol/L (mEq/L)]	25.4 (25.4)	Anti-nuclear antibody	Negative
pH	7.358	Anti-neutrophil cytoplasmatic antibody	Negative
pCO2 (40–50 mmHg)	40.8	Anti-ds-DNS-antibody	Negative
Base excess [mmol/L (mEq/L)]	−2.8	Anti-glomerular basement antibody	Negative
Complement C3 [g/L(mg/dL)]	0.61 (61)	Rheumatoid factor [U/mL (E/mL)]	29 (29)
Complement C4 [g/L(mg/dL)]	0.08 (8)	Anti-citrullin antibody [U/mL (E/mL)]	<25 (<25)
C3 nephritic factor	Negative	Urine protein-to-creatinine ratio [mg/mmol (mg/mg)]	648 (5.7)
LYME IgM titer (ELISA)	Positive	Urine Albumin [mg/mmol (mg/mg)]	418 (3.7)
LYME IgM titer (western blot)	Positive	Urine IgG [mg/mmol (mg/mg)]	89 (0.8)
LYME IgG titer [ELISA (U/L)]	>346 000	α1Microglobulin [mg/mmol (mg/mg)]	13 (0.12)
LYME IgG titer (estern blot)	Positive	α2Macroglobulin [mg/mmol (mg/mg)]	4.6 (0.04)

include deposition of C1q. Serum C4 was persistently within the normal range [1].

A 65-year-old male with MPGN and neurologic manifestation of Lyme disease was successfully treated with steroids and ceftriaxone. His serum complement values were normal [6]. In a further case report of MPGN related to active Lyme disease with neurological involvement and response to steroids and ceftriaxone, hypocomplementaemia or glomerular complement deposition was not mentioned [7]. To our knowledge, the case presented here is the first description of C1q-positive 'full-house' pattern MPGN in association with active Lyme disease. Rawal *et al.* reported acute renal failure, nephrotic syndrome and hypocomplementaemia in a patient who had been diagnosed with Lyme disease 12 years earlier [8]. However, the immunohistological pattern was not described and the result of testing for cryoglobulins was inconclusive. In contrast, serum cryoglobulin precipitation and glomerular C1q immunofluorescence were strongly positive in our case.

C1q is found in glomerular immune deposits attributable to systemic lupus erythematosus in most instances [3]. Upregulation and dysregulated shedding of the globular domain of C1q protein (gC1q-R) contributing to cryoglobulin-induced damage via the classic complement pathway was observed in both hepatitis C virus positive and -negative patients with mixed cryoglobulinaemia [4]. Consistent with this model, therapy was followed by an increase in the low baseline serum C4 level in our patient, indicating initial activation and treatment-induced inhibition of the C1 pathway. As commonly observed in the complement profile of patients with cryoglubulinaemia type II, the C3 component was only modestly altered, which might be explained by impaired C3 convertase formation and C3 fixation on cryoprecipitable IgM–IgG complexes [9] (Figure 3). In regard to the negative ANA and anti-ds-DNS-serology, the classic complement pathway was most likely triggered by the presence of antibodies with cryoglobulin activity in our patient, confirmed by the simultaneous normalization of renal parameters and resolution of cryoglobulinaemia under therapy.

Mixed cryoglobulinaemia type II is classically caused by chronic infections including Lyme borreliosis [10]. Consequently, strong specific bands on borrelia western blot in combination with clinical Lyme arthritis and peripheral neuropathy and the fast response to antibiotic treatment are highly suggestive of borrelia-induced cryoglobulinaemia.

Table 2. Laboratory data before and after treatment

Laboratory tests	On admission	After treatment
Creatinine [µmol/L (mg/dL)]	239 (2.7)	150 (1.4)
GFR MDRD [mL/s (mL/min)]	0.38 (23)	0.85 (51)
Urea [mmol/L (mg/dL)]	35 (99)	32 (92)
Albumin [g/L (g/dL)]	22 (2.2)	41 (4.1)
Complement C3 [g/L(mg/dL)]	0.61 (61)	1.16 (116)
Complement C4 [g/L (mg/dL)]	0.08 (8)	0.23 (23)
Cryoglobulin precipitation	Strongly positive	<1%
Urine protein/creatinine ratio [mg/mmol (mg/mg)]	648 (5.7)	79 (0.7)
Urine albumin [mg/mmol (mg/mg)]	418 (3.7)	56 (0.5)
Urine IgG [mg/mmol (mg/mg)]	89 (0.8)	1.1 (0.01)
α1Microglobulin [mg/mmol (mg/mg)]	13(0.12)	2.2 (0.02)
Urine sediment	Active	Bland

The triad of MPGN, tubular dilatation and interstitial nephritis was observed unrelated to spirochaete presence in 43 dogs with positive borrelia serology from Lyme disease-endemic areas [11]. Similarly, histopathology of our patient revealed tubulointerstitial lesions in addition to glomerulonephritis. Non-caseating granulomas were found in the interstitial tissue, as previously described in the liver, brain and skin of Lyme borreliosis patients [12–14]. The regression of the tubular component of proteinuria with doxycyclin therapy indicates that the tubulointerstitial changes were responsive to the treatment of borrelia infection. While MPGN is to be seen as indirectly borrelia-related through cryoglobulin-mediated complement activation in our case, the tubulointerstitial changes may be a direct manifestation of Lyme disease, which again outlines the association of borrelia and nephropathy.

Whereas most authors administered ceftriaxone or a combination of ceftriaxone and doxycyclin, Papineni *et al.* achieved regression in a patient with Lyme-associated membranous nephropathy after doxycyclin monotherapy [15]. An 8-week course of doxycyclin as recommended for advanced Lyme disease combined with steroids was sufficient for successful treatment in our case.

Conclusions

In the absence of additional autoimmune disorders, the immunohistological findings and complement profile in

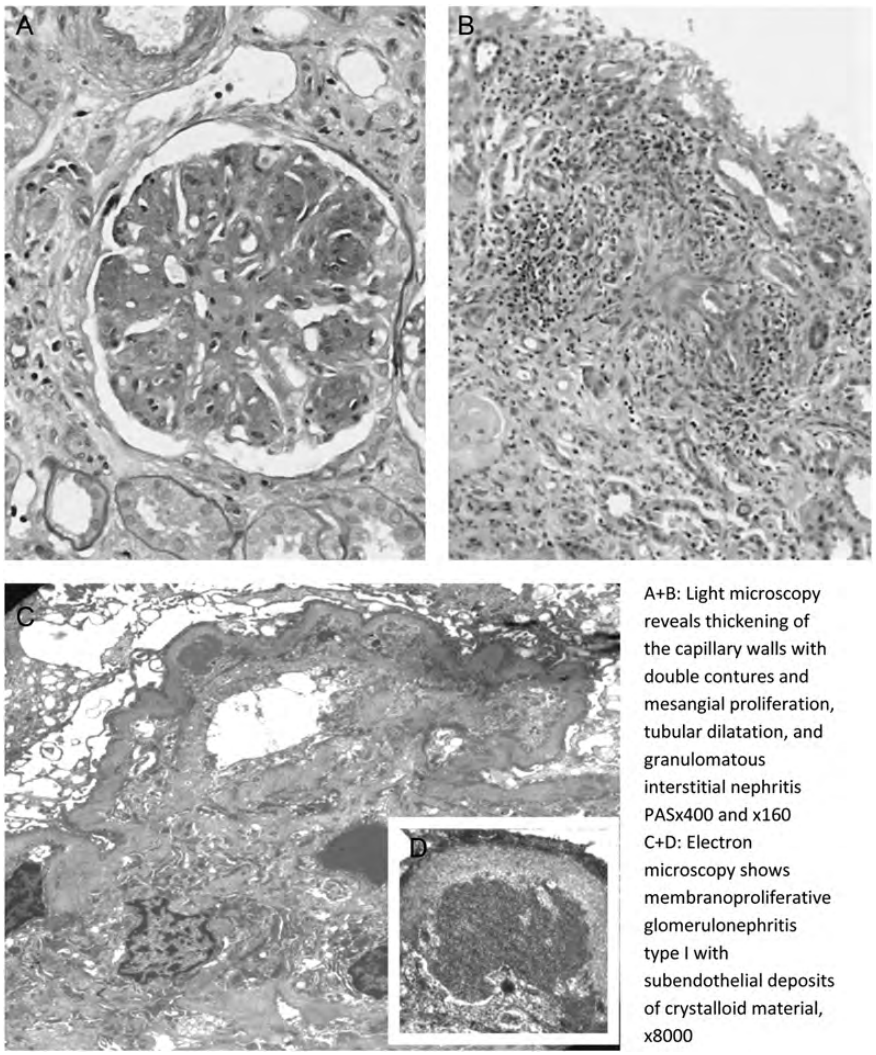

Fig. 1. Histopathology.

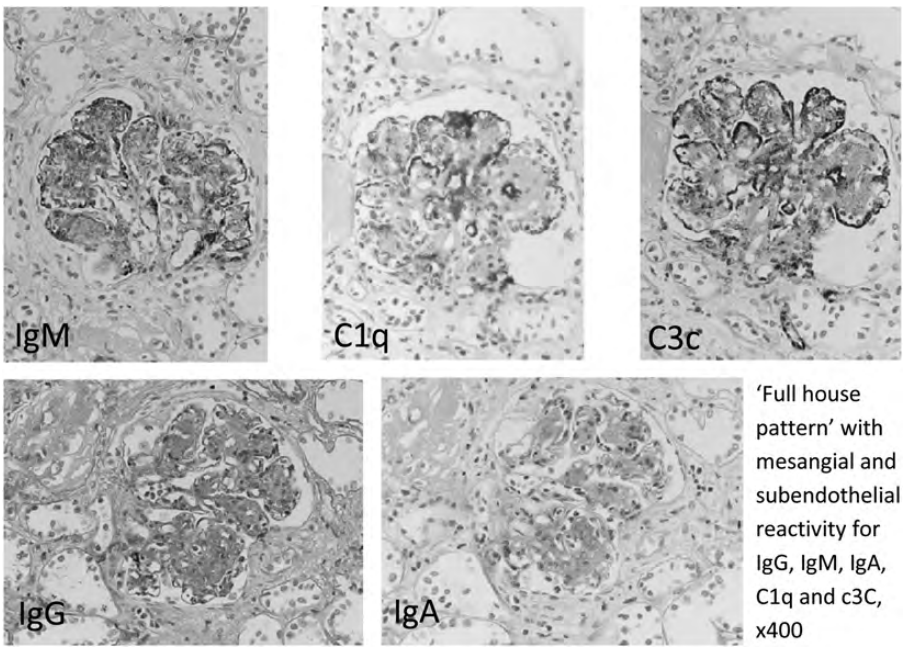

Fig. 2. Immunohistology.

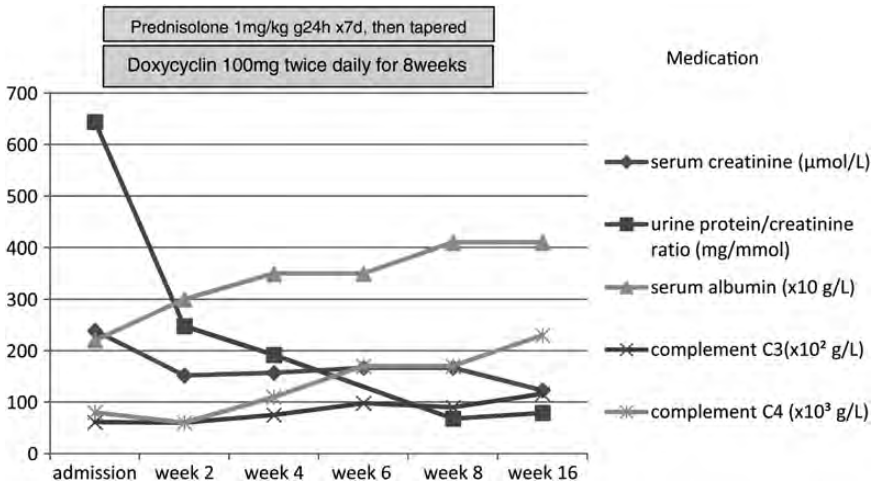

Fig. 3. Treatment monitoring: Treatment was monitored by routine parameters including cryoglobulin precipitation, C3, C4 and urine protein excretion pattern.

this case are consistent with cryoglobulinaemia-induced MPGN. Given the history of a tick bite a year before, followed by Lyme disease with classical joint involvement and tubulointerstitial lesions previously reported in Lyme borreliosis, the strongly positive borrelia serology and regression after administration of doxycyclin, para-infectious type II cryoglobulinaemia has most likely been caused by borrelia burgdorferi sensu latu infection in this patient. Our case suggests that C1q-positive MPGN may indirectly result from Lyme borreliosis through cryoglobulinaemic activation of the classic complement pathway and may successfully be treated with the appropriate antibiotic therapy of this underlying infection. Consequently, in cases with MPGN, careful examination for possible borrelia infection and subsequent antibiotic therapy are mandatory, even if immunohistological evaluation reveals the commonly not directly infection-induced C1q-positive 'full-house' pattern subtype. The interaction of gC1q-R and borrelia proteins should be subject to further investigation.

Conflict of interest statement. None declared.

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