Clinical Report

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

Christine A. Schneider¹, Jörg Wiemer¹, Sabine Seibt-Meisch¹, Werner Brückner¹, Kerstin Amann² and Jürgen E. Scherberich¹

¹Department of Nephrology, Hypertension, and Clinical Immunology, Harlaching Hospital, Ludwig-Maximilians-University, Munich, Germany and ²Department of Nephropathology, Erlangen University Hospital, Friedrich-Alexander-University, Erlangen-Nürnberg, Germany

Correspondence and offprint requests to: Christine A. Schneider; E-mail: tineannaschneider@gmx.de

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, p58, p41, p39 and B. afzelii P18 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
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, hypocomplementemia 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 hypocomplementemia 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 dyeregulated 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 cryoglobulinemia [4]. Consistent with this model, therapy 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 cryoglobulinemia 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-DNA-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 cryoglobulinemia under therapy.

Mixed cryoglobulinemia 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 cryoglobulinemia.

Table 1. Laboratory tests on admission

| Test                        | On admission       | After treatment  |
|-----------------------------|--------------------|------------------|
| Creatinine [µmol, (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)         |
| Sodium [mmol/L, (mEq/L)]    | 139 (139)          | 116 (116)        |
| Potassium [mmol/L, (mEq/L)] | 5.4 (2.4)          | 2.3 (23)         |
| Bicarbonate [mmol/L, (mEq/L)] | 25.4 (25.4)     | 4.6 (0.04)       |
| pH                          | 7.358              | <1%              |
| pCO2 (40–50 mmHg)           | 40.8               | Positive         |
| Base excess [mmol/L, (mEq/L)] | –2.8              | Positive         |
| Complement C3 [g/L, (mg/dL)] | 0.61 (61)        | 1.16 (116)       |
| Complement C4 [g/L, (mg/dL)] | 0.08 (8)          | 0.23 (23)        |
| LYME IgM titer (ELISA)      | Positive           | Positive         |
| LYME IgM titer (western blot) | >346 000         | Positive         |
| LYME IgG titer (ELISA)      | Positive           | Positive         |
| LYME IgG titer (urine)      | Positive           | Positive         |

Table 2. Laboratory data before and after treatment

| Test                        | On admission       | After treatment  |
|-----------------------------|--------------------|------------------|
| Creatinine [µmol, (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  | Positive           | Positive         |
| 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 | Blond |

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 doxycycline 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 doxycycline, Papineni et al. achieved regression in a patient with Lyme-associated membranous nephropathy after doxycycline monotherapy [15]. An 8-week course of doxycycline 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.

A+B: Light microscopy reveals thickening of the capillary walls with double contours and mesangial proliferation, tubular dilatation, and granulomatous interstitial nephritis. PAS x400 and x160
C+D: Electron microscopy shows membranoproliferative glomerulonephritis type I with subendothelial deposits of crystalloid material, x8000

Fig. 2. Immunohistology.

'I full house pattern' with mesangial and subendothelial reactivity for IgG, IgM, IgA, C1q and C3C, x400
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.

**References**

1. McCausland FR, Bijol V, Rennke H et al. Lyme disease-associated glomerulonephritis. *Nephrol Dial Transplant* 2011; 26: 3054–3056
2. Rennke H. Secondary membranoproliferative glomerulonephritis. *Kidney Int* 1995; 47: 643–56
3. Weening JJ, D’Agati VD, Schwartz MM et al. The classification of glomerulonephritis in systemic lupus erythematosus revisited. *J Am Soc Nephrol* 2004; 15: 241–250
4. Sansonno D, Tucci FA, Ghebrehiwet B et al. Role of the receptor for the globular domain of C1q protein in the pathogenesis of hepatitis C virus-related cryoglobulin vascular damage. *J Immunol* 2009; 183: 6013–6020
5. Sethi S, Fervenza FC. Membranoproliferative glomerulonephritis: pathogenetic heterogeneity and proposal for a new classification. *Semin Nephrol* 2011; 31: 341
6. Kelly B, Finnegan P, Cormican M et al. Lyme disease and glomerulonephritis. *Ir Med J* 1999; 92: 372
7. Kirmizis D, Efstratiadis G, Economidou D et al. MPGN secondary to Lyme disease. *Am J Kidney Dis* 2004; 43: 544–551
8. Rawal B, Rovner L, Thakar C et al. MPGN and nephrotic syndrome (NS) secondary to Lyme disease (LD). *Am J Kidney Dis* 2008; 51: A83
9. Ng YC, Peters DK, Walport MJ. Monoclonal rheumatoid factor-IgG immune complexes. Poor fixation of opsonic C4 and C3 despite efficient complement activation. *Arthritis Rheum* 1988; 31: 99–107
10. Steere AC, Hardin JA, Malawista SE. Erythema chronicum migrans and Lyme arthritis: cryoimmunoglobulins and clinical activity of skin and joints. *Science* 1977; 196: 1121–1122
11. Dambach D, Smith CA, Lewis RM et al. Morphologic, immunohistochemical, and ultrastructural characterization of a distinct renal lesion in dogs putatively associated with Borrelia burgdorferi infection: 49 cases (1987–1992). *Vet Pathol* 1997; 34: 85–96
12. Zanchi AC, Gindol AR, Neil D et al. Necrotising granulomatous hepatitis as an unusual manifestation of Lyme disease. *Dig Dis Sci* 2007; 52: 2629–2632
13. Mokry M, Flaschka G, Kleinert G et al. Chronic Lyme disease with an expansive granulomatous lesion in the cerebellopontine angle. *Neurosurgery* 1990; 27: 446–451
14. Moreno C, Kutzner H, Palmedo G et al. Interstitial granulomatous dermatitis with histiocytic pseudorosettes: a new histopathologic pattern in cutaneous borreliosis. Detection of Borrelia burgdorferi DNA sequences by a highly sensitive PCR-ELISA. *J Am Acad Dermatol* 2003; 48: 376–384
15. Papineni P, Doherty T, Pickett T et al. Membranous glomerulonephritis secondary to Borrelia burgdorferi infection presenting as nephrotic syndrome. *NDT Plus* 2010; 3: 105–106

Received for publication: 21.8.12; Accepted in revised form: 24.9.12