A paraneoplastic membranoproliferative glomerulonephritis with isolated C3 deposits associated with hairy cell leukaemia

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Abstract
We describe a 35-year-old woman who presented with proteinuria and microscopic haematuria. Blood tests revealed a low C3 complement level, with no evidence of cryoglobulin. Renal biopsy showed a Type 1 membranoproliferative glomerulonephritis (MPGN) with isolated C3 deposits on immunofluorescence study. Bone marrow aspirate, done for monocytopenia, was consistent with a diagnosis of hairy cell leukaemia (HCL). Both haematological and nephrological diseases completely responded to treatment with cladribine, strongly suggesting that the renal disease was a paraneoplastic syndrome. To our knowledge, this is the first report of a non-cryoglobulinaemic MPGN associated to HCL.

Keywords: hairy cell leukaemia; membranoproliferative glomerulonephritis; paraneoplastic; pentostatin

Background
Hairy cell leukaemia (HCL) is a rare chronic mature B cell lymphoproliferative disease that accounts for between 2 and 3% of all leukaemia cases. The characteristic ‘hairy cells’ are small clonal B lymphoid cells that possess abundant cytoplasm with micro-filamentous (‘hairy’) projections. These cells typically infiltrate the bone marrow, the spleen and, to a lesser extent, the liver, lymph nodes and skin. Patients usually present with splenomegaly, pancytopenia and recurrent infections. We report here the first case of non-cryoglobulinaemic membranoproliferative glomerulonephritis (MPGN) associated to HCL.

Case report
A 35-year-old woman was referred to the nephrology department for persistent albuminuria (around 1 g/day) and microscopic haematuria discovered by her general practitioner. This followed a transient episode of gross haematuria 3 months earlier, without any abnormality on imaging studies (renal and bladder ultrasonography, spiral CT scan).

The patient also complained of recent mild symptoms: aching of the elbows, wrists and hands in the morning, bilateral leg swelling in the evening and photosensitivity. Medical history was unremarkable besides one uncomplicated pregnancy (5 years earlier), occasional smoking and allergic rhinitis. Medications comprised only a contraceptive pill. Regular biochemistries showed a subnormal renal function (creatinine 81 µmol/L; estimated GFR 84 mL/min/m² by the MDRD formula), an abundant glomerular proteinuria (urinary protein/creatinine ratio of 4.5 g/g; albuminuria 1.19 g/L) and microscopic haematuria (4770/mm³) and leucocyturia (190/mm³). Complete blood count showed a mild normocellular anaemia and monocytopenia. Serum protein analysis revealed a mild hypoalbuminaemia (32 g/L; normal range, 39–48 g/L) and a hypogammaglobulinaemia (4.2 g/L; normal range, 7–15 g/L), without a monoclonal protein. Urinary Bence–Jones proteins were negative. Anti-nuclear antibodies (ANA) and double-stranded DNA antibodies were negative. C3 complement was moderately decreased (0.65 g/L; normal range, 0.75–1.50 g/L) and C4 complement was normal (0.19 g/L; normal range,
0.16–0.38 g/L). The following analyses were negative: anti-cardiolipin antibody, lupus anticoagulant, rheumatoid factor, extractable nuclear antigens, anti-neutrophil cytoplasmic antibodies, cryoglobulins, HIV serology, hepatitis B and C studies and glycated haemoglobin. The levels of complement alternative pathway proteins were normal when assessed by immunological analyses. Factor B (FB), factor I (FI) and factor H (FH) antigen plasma concentrations were 156 mg/L (normal range, 90–320 mg/L), 108% (normal range, 70–130%) and 117% (normal range, 70–130%), respectively. Plasma concentration of FB antigen was measured by nephelometry. FI and FH antigen concentrations were measured by a sensitive ELISA method. Membrane expression of membrane cofactor protein (CD46) was analysed on granulocytes using a FACS Calibur flow cytometer. Fluorescence intensity was 993 MFI (normal range 600–1400 MFI). C3 nephritic factor (C3NeF) activity was quantitated by assessing the ability of purified IgG from plasma to stabilize the cell-bound C3bBb convertase. No C3NeF activity was detected in our patient. Abdominal ultrasound study was normal (in particular, kidneys and spleen).

A renal biopsy was performed. Light microscopic examination revealed a focal Type 1 MPGN with mesangial proliferation and abundant subendothelial deposits (Figure 1). Proliferating/infiltrating elements in glomerular capillary lumens were mainly PMN and mononucleated cells. Mild interstitial fibrosis and tubular atrophy were noted with focal inflammation infiltrates. Arteries showed a mild intimal fibrosis and arterioles were unremarkable. Immunofluorescence study showed intense mesangial and subendothelial C3 complement deposits. Bowman’s capsules, peripheral capillary walls and tubular basement membranes did not contain C3 deposits. C1q stained very weakly on some subendothelial deposits. No staining was noted with light (κ and λ) and heavy (α, μ and γ) chains of immunoglobulins. Unfortunately, no specimen was available for electronic microscopy.

Because of unexplained anaemia and monocytopenia, a bone marrow aspirate was performed and revealed a HCL (14% of all aspirate cells; Figure 2) with a monoclonal B lymphocytes population staining for CD19, FMC7, CD11c, CD25, CD25, CD103 and kappa.

In light of this result, a complementary immunohistochemistry study was performed on renal biopsy specimen. This study showed no CD20 cell in glomerular and peritubular capillaries and some CD3(+) and CD163(+) cells infiltrating the interstitium.

The patient was treated with a purine analogue, pentostatin (Nipent™, SuperGen, San Ramon, CA), intravenously administered as 4 mg/m² every other week until complete remission followed by two additional infusions for consolidation (i.e. a total of eight doses over 4 months). Pentostatin acts in a pseudo-irreversible manner as a tight-binding inhibitor of adenosine deaminase leading to intracellular accumulation of deoxyadenosine and deoxyadenosine triphosphate. It is a strong lymphocytotoxic drug in both proliferating and resting lymphocytes. Adjuvant therapy comprised cotrimoxazole and valacyclovir for infections prophylaxis and an angiotensin receptor blocker (ARB) for hypertension and proteinuria.

Over the 6 months after the beginning of treatment, haematological and nephrological parameters improved dramatically with normalization of anaemia and monocytes count, normalization of blood pressure (despite discontinuing ARB therapy) and strictly normal urinalysis (no haematuria, no leucocyturia, albuminuria dosage <30 mg/day). Bone marrow aspirate and biopsy showed no residual tumoral infiltrate.

Discussion

HCL has been associated with a number of vasculitides [1] and other disorders of the immune system including cryoglobulinaemia [2,3], Behcet’s disease [4] and polyarteritis nodosa [5,6]. Herman et al. [7] previously reported a case of MPGN in a patient with HCL treated with alpha-II interferon, but our patient is, to our knowledge, the first reported case of a non-cryoglobulinaemic MPGN in a treatment-naïve patient.
Primary glomerulonephritis with isolated C3 deposits [8] is a rare entity, of which the general clinical picture is consistent with our patient presentation, i.e. episodes of gross haematuria and/or persistent or recurrent micro-haematuria and/or proteinuria and/or hypertension.

Initial presentation of the glomerular disease was somehow misleading because of atypical features suggesting systemic lupus erythematosus which was invalidated on renal biopsy. On the other hand, several lines of evidence strongly suggested that MPGN was a paraneoplastic syndrome of HCL in our patient: ANA were negative; the two diseases are very rare; they were discovered concomitantly and responded both completely and simultaneously to HCL therapy. Although cladribine seems to have some activity in autoimmune disorders including systemic lupus erythematosus [9], there is, to our knowledge, no published data on cladribine in other glomerular diseases.

Glomerulonephritis may predate the diagnosis of a lymphoproliferative disease, and patients with suspicious glomerular disease should be screened and monitored for possible lymphoproliferative diseases.

Conflict of interest statement. None declared.

References

Myocardial infarction is a complication of factor H-associated atypical HUS

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Abstract
Cardiac complications are frequently seen in thrombotic thrombocytopenic purpura related to ADAMTS13 deﬁciency. We describe the case of a 43-year-old woman who was diagnosed with an atypical haemolytic–uraemic syndrome (aHUS) associated with a pathogenic mutation in the factor H gene (C623S). After 15 days of treatment, she suffered a sudden cardiac arrest and died despite intensive resuscitation attempts. She showed only one cardiovascular risk factor, hypercholesterolaemia. Her sudden death was secondary to cardiac infarction related to a coronary thrombotic microangiopathy. This is the first case of aHUS related to a mutation in the factor H gene associated with cardiac microangiopathy. This case emphasizes the need to screen for cardiac complication during the treatment of aHUS.

Keywords: atypical haemolytic–uraemic syndrome; coronary thrombotic microangiopathy; factor H mutation; sudden death

Background
Thrombotic microangiopathy (TMA) is characterized by haemolytic anaemia, thrombocytopenia and microvascu-