Proliferative glomerulonephritis with monoclonal IgG deposits secondary to chronic lymphocytic leukemia. Report of two cases

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Abstract
Proliferative glomerulonephritis with monoclonal IgG deposits (PGNMID) is a recently described entity that is only rarely associated with a hematological or lymphoproliferative malignancy. We describe the cases of two men with preexisting chronic lymphocytic leukemia (CLL) who developed endocapillary proliferative glomerulonephritis with nonorganized monoclonal IgG deposits. One biopsy also showed CLL infiltration of the cortex. Both patients were treated with rituximab in addition to cyclophosphamide in one case and fludarabine in the other with significant improvement of their renal disease and CLL. This report provides additional evidence to support the use of rituximab in the therapy of CLL-associated PGNMID.

Keywords: chronic lymphocytic leukemia; glomerulonephritis; monoclonal IgG; rituximab

Background
Proliferative glomerulonephritis with monoclonal IgG deposits (PGNMID) is a rare entity characterized by monoclonal IgG in glomerular deposits which are not organized (nonfibrillar or nonmicrotubular) [1]. The disease presents clinically with proteinuria (often in the nephrotic range), hematuria and frequent renal insufficiency [1]. About 30% of patients have a serum monoclonal protein with the same heavy and light chain isotypes as those in the glomeruli [1]. In this report, we describe PGNMID with IgG subtyping in two patients with chronic lymphocytic leukemia (CLL) and their response to rituximab therapy.

Case reports

Case 1
The patient is a 73-year-old Caucasian male with a 1-year history of low-grade CLL being followed conservatively by a hematologist. Over 6 months, he developed progressive leg and periorbital edema and new onset hypertension. His creatinine was increased to 191 μmol/L estimated GFR (eGFR) 30 mL/min/1.73m2 by MDRD formula. His urine showed 11–30 RBC/hpf, but no dysmorphic cells or casts. His 24 h urine protein excretion was 6.9 g. His serum protein electrophoresis (PEP) revealed a trace band of monoclonal IgG kappa with reduction in the other gamma globulins. His urine PEP showed one faint IgG kappa band. No monoclonal free light chains were seen with immunofixation. Serum free light chain assay was not performed. He had a lymphocytosis of 243109/L with his other hematologic cell lines being normal. The rest of his investigations were normal (albumin, cryoglobulins, hepatitis B and C, anti-nuclear antibody (ANA), anti-neutrophil cytoplasmic antibody and rheumatoid factor). His serum C3 was 0.66 g/L (normal 0.85–1.86 g/L) and C4 was 0.05 g/L (normal 0.15–0.47 g/L). His creatinine increased over the next month to 259 μmol/L. A renal biopsy was performed.

His creatinine continued to rise to 368 μmol/L (eGFR 14 mL/min/1.73m2). His CLL was treated with 6 months of rituximab (375 mg/m2 once monthly) and cyclophosphamide (100 mg/m2/day orally for 14 days on, 7 days off, decreased at 3 months to 75 mg/m2/day due to neutropenia). Four months after completing his chemotherapy, his lymphocyte count had normalized to 0.6 × 109/L, his creatinine had improved to 158 μmol/L (eGFR 37 mL/min/1.73m2) and his urine albumin-to-creatinine ratio decreased to 128 mg/mmol.

Case 2
The patient is a 60-year-old Caucasian male with a 3-year history of CLL being managed conservatively by his hematologist. Six months prior, he developed new onset hypertension with peripheral and periorbital edema. At presentation, his creatinine was elevated at 181 μmol/L (eGFR 14 mL/min/1.73m2). His CLL was treated with 6 months of rituximab (375 mg/m2 once monthly) and cyclophosphamide (100 mg/m2/day orally for 14 days on, 7 days off, decreased at 3 months to 75 mg/m2/day due to neutropenia). Four months after completing his chemotherapy, his lymphocyte count had normalized to 0.6 × 109/L, his creatinine had improved to 158 μmol/L (eGFR 37 mL/min/1.73m2) and his urine albumin-to-creatinine ratio decreased to 128 mg/mmol.
his gamma globulins. No light chains were detected on urine PEP. His serum free light chain assay showed normal levels of kappa and lambda light chains but an increased kappa:lambda ratio of 1.92. The following investigations were normal: albumin, cryoglobulins, hepatitis B and C, ANA, C3 and C4. A renal biopsy was performed.

His renal function and proteinuria were stable over the subsequent 5 months, at which point he was started on fludarabine (90 mg daily for 5 days every 4 weeks, reduced to 70 mg after the first cycle due to anemia) and rituximab (875 mg every 4 weeks). After completing his sixth and final cycle of chemotherapy, his renal disease had improved with a creatinine of 148 μmol/L (eGFR 42 mL/min/1.73 m²) and proteinuria of 150 mg/day, and his lymphocyte count had decreased to 0.5 × 10⁹/L.

The renal biopsies from both patients demonstrated similar changes. Both contained at least 20 viable glomeruli which showed diffuse endocapillary proliferation (Figure 1) and focal mesangiocapillary change. In Case 1, the interstitium contained dense aggregates of CD20+ small lymphocytes. Glomeruli showed granular capillary staining for IgG, C1q and C3 with light chain restriction (limited to kappa in Case 1 and lambda in Case 2) by direct immunofluorescence (IF). Indirect IF for IgG subtypes demonstrated IgG1 only in both cases (Figure 1). Granular electron dense deposits were present focally along glomerular basement membranes (sub-endothelial in Case 1 and subepithelial in Case 2) (Figure 1).

**Discussion**

PGNMID is a rare entity with only 58 cases reported in the literature that meet the criteria proposed by Nasr et al. [1] (including monoclonal IgG deposition with only one IgG subtype, granular electron dense deposits without substructure and absence of cryoglobulins). Of these cases, only one is associated with a hematologic malignancy (multiple myeloma) [1]. Review of older literature identifies an additional four cases that may qualify as PGNMID, all associated with CLL, but only one case documented the IgG subtype (IgG1) [2–5]. To this small number of cases of CLL with PGNMID can be added the two patients described herein, both of which had deposition of IgG1.

Although IgG1 is the most common IgG subtype overall in PGNMID (occurring in 66% of cases), IgG1 is more common in patients with PGNMID and paraproteinemia [1]. IgG1 has been shown to be the most common subtype in glomerular deposits in patients with CLL and glomerulonephritis (GN) of any type [2, 4, 6, 7]. These observations are consistent with our findings and those of Touchard et al. [4], in which IgG1 is the exclusive IgG subtype documented in cases of PGNMID with CLL.

The pathogenesis of PGNMID proposed by Nasr et al. justifies the use of rituximab therapy. PGNMID is thought to be due to a clonal proliferation of B lymphocytes or plasma cells that hypersecrete abnormal IgG capable of self-aggregation and deposition in the glomerulus as electron dense deposits [1]. Because a minority of PGNMID cases have a documented paraprotein or hematologic malignancy, it is possible that the abnormal clone arises secondary to normal immune responses [1]. IgG3, the most common IgG subtype in PGNMID, is thought to be particularly nephritogenic because of its ability to self-aggregate and fix complement, resulting in the influx of inflammatory cells and subsequent proliferative GN [1, 8, 9]. Therefore, it is likely that the deposited monoclonal IgG in PGNMID are directly pathogenic, and therapy targeting IgG production may result in decreased deposition and improvement in the renal disease.

CLL is a malignancy characterized by clonal proliferation of B lymphocytes that are often CD20 positive [10]. Abnormal IgG produced by the malignant clone are thought to be responsible for the IgG deposition and subsequent proliferation observed in PGNMID [2]. Rituximab is a monoclonal antibody to CD20 that results in depletion of B lymphocytes, is a recommended therapy for CLL [10], and would be expected to reduce the production and deposition of pathogenic IgG [2]. The previously reported case of CLL and PGNMID treated with rituximab resulted in a limited renal response.
with subsequent progression to end-stage renal disease [2]. In our two cases, treatment with rituximab in addition to other agents resulted in a significant reduction of proteinuria and improvement in renal function with parallel control of the underlying CLL. This provides additional evidence that rituximab-based chemotherapy regimens can be effective in treating the renal disease of PGNMID secondary to CLL.

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References

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