Exceptional Cases

Rapidly progressive glomerulonephritis complicating primary AL amyloidosis and multiple myeloma

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Abstract

Crescentic glomerulonephritis is a rare complication of AA amyloidosis. There are no clinical case reports of this complicating AL amyloidosis. A 67-year-old man developed rapidly progressive glomerulonephritis (RPGN) on a background of primary AL amyloidosis and IgGκ multiple myeloma. Investigations for causes of glomerulonephritis were negative, and a renal biopsy confirmed crescentic glomerulonephritis and amyloid deposition. He progressed to end stage kidney disease (ESKD) requiring dialysis after 2 months and died 7 months after diagnosis after further treatment of multiple myeloma failed to arrest progression. We believe this to be the first clinical case report of RPGN complicating primary (AL) renal amyloidosis and multiple myeloma.

Keywords: acute renal failure; amyloidosis; crescentic glomerulonephritis; multiple myeloma

Background

Paraproteinaemias and plasma cell dyscrasias are associated with various forms of renal disease [1,2]. The most common manifestations are cast nephropathy due to multiple myeloma and the nephrotic syndrome secondary to glomerular amyloid deposition [2]. Less common manifestations include light-chain deposition disease, type I cryoglobulinemia and renal vein thrombosis due to hyperviscosity [1]. Acute renal failure due to crescentic glomerulonephritis is a rare but recognized complication of AA (secondary) amyloidosis [3]. This usually occurs in the setting of chronic inflammatory disease, particularly longstanding rheumatoid arthritis [3,4]. Although described in a retrospective pathology series [4], there are no clinical case reports of this occurring in AL (primary) amyloidosis. Rapidly progressive glomerulonephritis is an uncommon presentation of renal disease in patients with plasma cell malignancy.

Case report

A 67-year-old man with a 4-year history of primary AL systemic amyloidosis with renal and cardiac involvement and a 2-month history of superimposed IgGκ multiple myeloma was admitted to the haematology unit for investigation of deteriorating renal function and was found to have glomerular haematuria.

The 5-year time course of his illness is shown in Table 1. His initial presentation was with nephrotic syndrome and paraproteinaemia (16 g/L IgGκ). Renal biopsy at that time showed normal light microscopy and electron microscopy consistent with minimal change disease, and a bone marrow biopsy was non-diagnostic. He was treated with prednisolone followed by the addition of cyclophosphamide with minimal response. The following year, an echocardiogram demonstrated left ventricular hypertrophy and diastolic dysfunction, and on a repeat renal biopsy, he was diagnosed with primary (AL) amyloidosis. Bone marrow biopsy at that time showed a plasmacytosis (6%) but was not consistent with multiple myeloma. He received melphelan and prednisolone with improvement in end-organ function and proceeded the following year to consolidation treatment with a melphelan autograft. One year prior to the presentation described in this report, he developed evidence of relapse with paraproteinaemia and proteinuria that was treated with thalidomide. That episode of acute renal failure resolved with correction of hypercalcaemia. He received melphelan and prednisolone with improvement in end-organ function and proceeded the following year to consolidation treatment with a melphelan autograft. One year prior to the presentation described in this report, he developed evidence of relapse with paraproteinaemia and proteinuria that was treated with thalidomide resulting in a partial response. Two months prior to the current presentation, he presented with hypercalcaemia, acute renal failure and rising paraproteinaemia, and a bone marrow biopsy showed multiple myeloma. That episode of acute renal failure resolved with correction of hypercalcaemia. Treatment with bortezomib and dexamethasone was commenced with improvement in his paraproteinaemia.

One month after commencing bortezomib and dexamethasone, he was admitted to hospital with a rising serum creatinine (220 μmol/L on admission) and increasing haematuria of glomerular morphology (500/μL on admission) consistent with a clinical diagnosis of rapidly progressive glomerulonephritis. On review, lower levels of glomerular
<table>
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<th>Time Period</th>
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<tr>
<td>2003</td>
<td>Presented with: nephrotic syndrome, normal renal function monoclonal gammopathy of uncertain significance (MGUS) (16 g/L IgGκ)</td>
<td>EM consistent with minimal change disease. Nil evidence of light chain nephropathy or amyloid</td>
<td>Normocellular marrow aspirate. Moderate increase in plasma cells, not diagnostic of myeloma.</td>
<td>Cyclophosphamide and prednisolone with minimal response.</td>
</tr>
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<td>December 2004</td>
<td>trans-thoracic echocardiogram (TTE) changes consistent with cardiac amyloid deposition, aortic regurgitation and mitral regurgitation (AR/MR) moderate pulmonary HTN with diastolic dysfunction.</td>
<td>LM—suggestive of glomerular amyloidosis, Congo red positive. EM—moderate amounts electron dense material in mesangium with focal fibrillary appearance. Patchy foot process effacement in some peripheral capillary loops.</td>
<td>Mild plasma cell prominence (6%), nil other features of myeloma. Evidence of amyloid deposition involving vascular structures and perivascular tissue.</td>
<td>Thalidomide and warfarin resulted in partial response.</td>
</tr>
<tr>
<td>May 2007</td>
<td>Presented with hypercalcaemia (cCa 3.35 mmol/L) and acute renal failure (Cr peak 269 μmol/L) in March 2008. Rising monoclonal band (peak 34 g/L).</td>
<td></td>
<td></td>
<td>Monoclonal band falls to 19 g/L.</td>
</tr>
<tr>
<td>April 2008</td>
<td>Glomerular haematuria &gt;500 red cells/μL. Nephrotic range proteinuria 12 g/day. Progressive renal impairment: Cr &gt;100, &gt;180 and &gt;220 μmol/L over 1 month.</td>
<td></td>
<td></td>
<td>Pulse methylprednisolone</td>
</tr>
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</table>
haematuria had been present and increasing over the preceding 6 months (Figure 1). Serological tests for underlying causes of glomerulonephritis were all normal. A renal biopsy was performed. The major finding was crescentic glomerulonephritis with segmental necrotizing lesions and cellular crescents in 23% of glomeruli (Figure 2). In addition, Congo red staining and electron microscopy confirmed the presence of renal amyloidosis.

Fig. 1. Biochemical and clinical parameters in the months preceding diagnostic renal biopsy. The onset of glomerular haematuria is observed to follow the rising M-band but precedes the rise in serum creatinine and treatment with bortezomib. A reversible episode of acute renal failure in the context of hypercalcaemia occurred 2 months prior to a second and irreversible rise in serum creatinine. Abbreviations: RBCs—red blood cells, Cr—creatinine, M-band—monoclonal band.

Fig. 2. Renal biopsy finding in a 67-year-old man with a clinical presentation of rapidly progressive glomerulonephritis on a background of previously diagnosed renal amyloidosis and multiple myeloma. Several glomeruli (23%) contained segmental necrotising lesions and cellular crescents (arrows, A, B). Congo red staining confirmed the presence of amyloid (C). Electron microscopy (D) also showed amyloid deposition, with expansion of mesangium and capillary walls by randomly arranged fibrils with average diameter of 10 nm. Original magnification ×200 (A), ×400 (B, C) and ×26 700 (D).
The patient was refractory to subsequent treatment for multiple myeloma, his renal function deteriorated further and he became dialysis dependent. Six months after commencing haemodialysis, he died in the context of progressive complications of multiple myeloma.

Discussion

This patient presented clinically with rapidly progressive glomerulonephritis on a background of longstanding renal amyloidosis and recently diagnosed IgGκ multiple myeloma. Renal biopsy showed superimposed crescentic glomerulonephritis on a background of chronic changes consistent with renal amyloidosis. At the time of the presentation, the differential diagnosis was broad and included a new renal manifestation of underlying paraproteinaemia, a reaction to bortezomib or a de novo glomerulonephritis of unrelated aetiology.

Review of the clinical and biochemical parameters (Figure 1) illustrated that the diagnosis of crescentic glomerulonephritis was preceded first by an increase in the monoclonal band, followed by the onset of glomerular haematuria and then by a rising serum creatinine. Importantly, the onset of glomerular haematuria preceded treatment with bortezomib, indicating that bortezomib was highly unlikely to be the cause of the glomerular lesion. Taken together, the clinical picture and temporal sequence suggest that the crescentic glomerulonephritis was a complication of the underlying plasma cell malignancy. The renal biopsy appearance and negative autoimmune serology made a diagnosis of primary glomerulonephritis or vasculitis unlikely.

The most common renal manifestation of primary systemic AL amyloidosis is nephrotic syndrome due to glomerular amyloid deposition [5]. Vascular amyloid deposition causing luminal narrowing and tubular deposition with tubular dysfunction are less common but confer a better prognosis. Crescentic glomerulonephritis is a very rare complication of amyloidosis and usually occurs in the context of underlying renal amyloidosis [3,4]. The incidence is not known.

Schafernak et al. has summarised 12 previous case reports of crescentic rapidly progressive glomerulonephritis associated with amyloidosis, 11 in the setting of AA amyloidosis and one in the setting of Waldenstrom’s macroglobulinaemia [3]. The pathogenesis is not fully understood, but appears to involve mesangial cell dysfunction due to nodular expansion and amyloid fibril-induced capillary loop rupture with fibrin entering Bowman’s space. This is supported by a spatial co-existence of amyloid deposits and crescents on light and electron microscopy and glomerular basement membrane rupture associated with amyloid fibrillary deposition.

A retrospective analysis by Nagata et al. of 44 renal biopsies and 61 autopsy specimens with a diagnosis of renal amyloidosis revealed that 14/105 specimens demonstrated between 5% and 77% crescents. Of the specimens demonstrating crescents, eight were autopsy specimens, and six were antemortem renal biopsies. In 12/14 cases, there was AA amyloid deposition, the majority of which was secondary to rheumatoid arthritis. Of interest, in 2/14 of these cases, crescents were observed in association with AL amyloidosis. The clinical features of these particular cases were not described in any detail.

In conclusion, this patient developed rapidly progressive glomerulonephritis in the setting of longstanding primary amyloidosis and recently diagnosed IgGκ multiple myeloma. Crescentic glomerulonephritis superimposed on renal amyloidosis was confirmed on a renal biopsy. This is a rare renal manifestation of systemic amyloidosis. We believe this is the first full clinical case report of crescentic glomerulonephritis complicating primary renal amyloidosis and multiple myeloma.

Conflict of interest statement. The results presented in this paper have not been published previously in whole or part, except in abstract format.

References


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