Case Report

Renal disease in Waldenström’s macroglobulinaemia

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Introduction

In Waldenström’s macroglobulinaemia (WM) renal disease is less common than in multiple myeloma [1–3]. It is usually caused by IgM deposits along the glomerular basement membrane, infiltration of the interstitium with lymphoid cells or amyloidosis. Monoclonal (type I) cryoglobulinemia may develop. Cast formation is rare in WM [1,3–6]. Little is known about the prognosis of renal disease in WM and about the influence of chemotherapy for WM on renal disease. Only two cases have been reported in which WM was associated with a nephrotic syndrome. Renal disease was caused by IgM deposits in the glomerular basement membrane in one case and intramembranous deposits of IgM and IgG of monoclonal origin and C3 in the second case. In both cases the nephrotic syndrome disappeared during treatment with chlorambucil and prednisone [7,8].

We describe a patient with renal failure in WM with the histopathological findings and the course of renal disease during treatment with chemotherapy. Also, a review of the literature is given.

Case report

In a 53-year-old male blood donor anaemia was found in 1994. He did not have signs or symptoms. No abnormalities were found on physical examination, in particular no hypertension, hepatosplenomegaly or lymphadenopathy.

Laboratory studies yielded the following values: erythrocyte sedimentation rate (ESR) 94 mm/1st hour; haemoglobin 10.2 g/dl; haematocrit 0.30; MCV 91 fl; white blood cell count 6,500/mm³ with 1% myelocytes, 1% eosinophils, 1% basophils, 56% polymorphonuclear leukocytes, 29% lymphocytes with normal morphology, 12% monocytes, platelet count 109,000/mm³; urea 8.9 mmol/l; creatinine 138 µmol/l; creatinine clearance 78 ml/min; calcium 2.21 mmol/l; uric acid 0.47 mmol/l; LDH 148 U/l; total protein 75 g/l with albumin 39 g/l; alpha-1-globulin 2 g/l; alpha-2-globulin 7 g/l; beta-globulin 7 g/l and gamma-globulin 20 g/l. Electrophoresis revealed a monoclonal (M) component in the gamma region, which was classified as an IgM M component bearing kappa light chains by immunoelectrophoresis of 17 g/l (IgM normal 0.6–2.5 g/l). IgG was 5.9 g/l (normal 8.0–18.0 g/l) and IgA was 1.1 g/l (normal 0.9–4.5 g/l). Cryoglobulins were absent. Serum viscosity (ratio serum water) was normal with 2.0 at 22°C. Urine sediments contained many erythrocytes, sporadic erythrocyte casts, and sporadic granular casts. Proteinuria was 0.63–0.83 g/24 h. Urine immunoelectrophoresis revealed kappa light chains 0.2 g/l. Bone-marrow histology showed an immunocytoma according to the REAL classification [9]. A chest X-ray and computer tomography of the abdomen did not show lymphadenopathy or hepatosplenomegaly.

Light-microscopic examination of the renal biopsy revealed lobular changes of the glomeruli with expansion of mesangial matrix and diffuse proliferation of mesangial cells with extensions along capillary loops (Figure 1). In glomerular capillary loops some influx of inflammatory cells was seen, which consisted mainly of lymphocytes. In some glomeruli visceral and parietal epithelial cells were slightly swollen, but crescents were absent. Some glomeruli were sclerotic. Focal tubular atrophy was observed with some interstitial infiltrate consisting of scattered lymphocytes, histiocytes and some plasma cells without signs of atypia. Focally there was some fibrosis. Branches of interstitial vessels showed an asymmetric broadening of the walls with splitting of the elastica fibrosa. Congo-red staining was negative. By immunofluorescence local granular deposition of IgM in glomerular capillaries was shown, at some places extending in the mesangial matrix. Light chains, predominantly kappa type, were found along capillaries. Stains for IgG, IgA, lambda C3, and C1q were virtually negative. Electron-microscopy did not reveal clear electron-dense deposits in the glomerular basement membrane.

Because active glomerular disease existed treatment
was started with cyclophosphamide 300 mg/m$^2$ p.o. for 5 days, vincristine 2 mg i.v. and prednisone 40 mg/m$^2$ p.o. for 5 days. This regimen was repeated every 4 weeks. After nine courses of chemotherapy the interval between the courses was increased to 6 weeks and after 11 courses to 8 weeks. Figure 2 shows the levels of serum creatinine, gamma-globulin and the IgM component during treatment with chemotherapy. After 16 courses of chemotherapy the following laboratory data were obtained: ESR 36 mm/1st hour, haemoglobin 14.1 g/dl and platelet count 253 000/mm$^3$. The IgM component decreased to 8 g/l. Serum creatinine is stable with 105 $\mu$mol/l and the creatinine clearance is 110 ml/min, but the sediment still contains several erythrocytes and sporadic erythrocyte casts. An urological cause for haematuria was excluded. Proteinuria is below 0.1 g/24 h. Urine immunoelectrophoresis does not reveal kappa light chains anymore. Chemotherapy was well tolerated and until now no complications have occurred.

Discussion

Monoclonal macroglobulinaemia can be found (1) as part of WM, (2) in association with malignant forms of lymphoma and, rarely, associated with infectious and inflammatory conditions, and (3) as a relatively stable abnormality in the absence of other identifiable disease ('benign monoclonal gammopathy' or 'monoclonal gammopathy of unknown significance'). In our patient monoclonal macroglobulinaemia was caused by WM. WM is an uncommon disorder occurring less frequently than multiple myeloma. The incidence of renal failure is infrequent in WM compared to multiple myeloma. Debré et al. have shown renal failure in two of 27 patients with WM [2]. Morel-Maroger et al. have found chronic renal failure in five of sixteen patients with WM selected on the basis of renal manifestations [3].

In our patient renal disease presented as renal failure with microscopic haematuria of glomerular origin and a slight proteinuria with kappa light chains on immuno-electrophoresis. Renal involvement in WM presents as a usually mild non-selective proteinuria and microscopic haematuria. Massive proteinuria and a nephrotic syndrome may develop and is in most cases caused by amyloidosis. Bence Jones proteinuria is present in 80–90% of the patients, but the quantity is much smaller than in multiple myeloma. Cryoglobulinaemia may be present [1,3,4,10,11]. Acute renal failure is rare in WM. Berkel et al. have described a case of acute renal failure as the first manifestation of a diffuse plasmacytic disorder with many of the features of macroglobulinaemia [12]. Acute renal failure after administration of contrast medium has been described in only one case [13]. In most cases renal failure is chronic, but follow-up data are rare and
therefore little is known about the course of renal failure in WM. Only Bradley et al. have described a case of end-stage renal failure caused by WM developing in the transplanted kidney within months after transplantation. This patient had unsuspected WM with an initial deterioration of renal function gradual over a period of 6 years before transplantation [14].

Histopathological findings in our patient consisted of IgM deposits in the glomerular capillaries with mesangiocapillary glomerulonephritis without immunofluorescence and electron-microscopic findings compatible with mesangiocapillary glomerulonephritis type I or II. The characteristic lesions of WM are amorphous deposits in the glomerular capillaries. These deposits begin as PAS-positive subendothelial deposits and may occlude the capillary lumen. Staining for amyloid and fibrin are negative. On immunofluorescence, the deposits stain with antisera against IgM heavy chains and the light chain type found in the circulating M component [1,3,4]. By electron-microscopy the subendothelial deposits consists of nonamyloid fibrillar material [6]. Glomerular proliferations are absent. Other glomerular lesions causing renal insufficiency in WM are rare. Most have been published in case reports [1,3,4,8,11,14–19]. Mesangiocapillary glomerulonephritis type I lesions have been described in some case reports. Immunofluorescence studies in these cases revealed that glomeruli were positive for IgM as was the case in our patient. Electron-microscopic findings in these patients showed scattered electron-dense deposits. This was not seen in our patient, probably because lesions in our patient were discovered at an earlier stage since renal failure was more severe in other case reports [14,16,17]. In older literature, cases have been described with nodular glomerular sclerosis. Mesangial nodules were PAS positive and had a close resemblance to those in diabetic glomerulosclerosis [11,15]. Retrospectively, these cases were probably examples of systemic light-chain deposition as is often seen in multiple myeloma. Martelo et al. have described a case of intramembranous deposits of IgM, IgG and C3 without proliferation, resembling membranous nephropathy. In this case IgG and IgM were of monoclonal origin [8]. Hory et al. have described a case of nephrotic syndrome caused by minimal-change disease [19]. Renal amyloidosis associated with WM is relatively rare and was not present in our patient [3].

Infiltration of the interstitium with lymphoid cells was not obvious in our patient. In contrast to multiple myeloma this is quite common in other reports of WM [1,3,4]. In the series of Morel-Maroger et al. infiltration of the interstitium with malignant cells was present in 10 of the 16 patients [3]. Occasionally, infiltration is massive causing enlarged kidneys [20].

Although the serum viscosity was normal in our patient, hyperviscosity caused by the higher molecular weight of IgM proteins comparing to IgG- and IgA proteins has been proposed as the most likely mechanism of the development of intraglomerular deposits. Glomerular capillaries appear to be a particularly vulnerable site for deposition of IgM since ultrafiltration increases the protein concentration further. Although viscosity was not measured in the series of Morel-Maroger et al., the mean concentration of IgM in patients without cryoglobulinaemia who had intraglomerular deposits of IgM was higher [3]. The quantity of Bence Jones proteinuria, if present, is usually much smaller in WM than in multiple myeloma and may explain why tubular casts and so-called ‘myeloma kidney’ are rare in WM.

Treatment with chemotherapy in our patient resulted in an improvement to a normal renal function and disappearance of proteinuria. The IgM M component was still present after 21 months of chemotherapy, but at a lower concentration. Haematuria persisted, suggesting that glomerular damage did not completely disappear. Information about the influence of chemotherapy for WM on renal disease is virtually absent.

In conclusion, we described a patient with WM and renal failure caused by IgM deposits along the glomerular basement membrane and mesangiocapillary glomerulonephritis. Although renal function recovered, ongoing haematuria suggests persistence of glomerular disease. This can be expected, because chemotherapy could thus far not completely suppress the production of the IgM M component.

References


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