Case Report

Acute tubular necrosis in a patient with Waldenström’s macroglobulinaemia and hyperviscosity syndrome

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Keywords: acute tubular necrosis; hyperviscosity syndrome; ischaemia; plasma exchange; vacuolar nephropathy; Waldenström’s macroglobulinaemia

Introduction

Waldenström’s macroglobulinaemia is a rare disease characterized by a monoclonal increase in serum IgM associated with lymphoid proliferation. While it could potentially involve various organs with hyperviscosity syndrome as the predominant presentation, its effect on the kidney has not been clearly delineated. On the other hand, ischaemic acute tubular necrosis (ATN), being a severe manifestation of ischaemic insult to the kidney, is rarely encountered in patients with macroglobulinaemia. We report a case of Waldenström’s macroglobulinaemia complicated by acute renal failure (ARF) due to ATN. The hyperviscosity syndrome was likely to be the major contributing factor.

Case

A 59-year-old man presented with a 1-month history of dizziness, blurring of vision, headache, weight loss, tiredness, anorexia, progressive generalized weakness, and numbness over his extremities. There was no musculoskeletal pain, Raynaud’s phenomenon, or skin rash. Physical examination revealed that he was afibrile and his blood pressure was 160/80 mmHg. Multiple inguinal lymph nodes were palpable. Neurological examination showed that he had weakness of all four limbs with power of grade 4/5. There was also generalized areflexia and sensory loss of glove and stocking distribution. Cranial nerves examination was normal but fundoscopy showed haemorrhages and tortuous engorged retinal veins. Examination of cardiorespiratory systems and abdomen was unremarkable.

Investigations revealed that the patient had a normochromic normocytic anaemia with Hb 7.8 g/dl. White cell count was 6800/mm³ and platelet count was 188 000/mm³, erythrocyte sedimentation rate was 67. Peripheral blood smear showed rouleaux formation. Serum globulin was grossly elevated to 117 g/l. Measurement for plasma viscosity was not available. Serum albumin was 28 g/l, while the liver function test was normal and serum urate was 0.59 mmol/l. Serum immunoglobulins were IgA 0.27 g/l, IgG 2.98 g/l, IgM 92.4 g/l. Serum immunoelectrophoresis and immunofixation confirmed the presence of monoclonal IgM with lambda light-chain restriction. Bone marrow examination was unremarkable with only 3% plasma cells and 5% lymphocytes. Biopsy of the groin lymph node demonstrated lymphoplasmacytoid immunocytoma. Chest X-ray and skeletal survey were unremarkable. Computerized axial tomography (CAT) of the abdomen revealed hepatosplenomegaly, and ultrasonography of the kidneys was normal. Nerve conduction study and sural nerve biopsy confirmed the presence of a mixed axonal and demyelinating neuropathy with no inflammatory cell infiltrate and absence of IgM staining. Antinuclear factor and antineutrophil cytoplasmic antibodies were negative, and complement level was within normal limit. The patient was HbsAg(−), HbsAb(+), and anti-HCV(−), and no cryoglobulinaemia could be detected. The renal function test on admission was unremarkable with serum urea 7.7 mmol/l, creatinine 114 μmol/l. Urine microscopy revealed albumin (2+), leukocytes 10–50/μl, granular casts 1–4/μl. Urine culture was negative. Twenty-four-hour protein excretion was 4.4 g. Urine immunoelctrophoresis and Bence Jones protein were negative.

One week after admission, the patient’s renal function started to deteriorate with a rising serum creatinine. The daily urine output was about 1 litre initially and it subsequently decreased to 400 ml per day. There was no history of recent exposure to nephrotoxic agents and the haemodynamic status was stable during hospitalization. Urine culture remained negative. In view of the clinical diagnosis of macroglobulinaemia-associated hyperviscosity syndrome with increasing
mental dullness, the patient was started on intensive plasma exchange therapy. Succinylated gelatine (Gelofusine®, B Braun, Switzerland) was used as the colloid plasma expander in plasma exchange. His mental state improved promptly thereafter.

A percutaneous renal biopsy was performed after two sessions of plasma exchange in view of the deteriorating renal function. The biopsy specimen contained 12 glomeruli: all glomeruli showed mild to moderate increase in mesangial matrix but no increase in cellularity. The capillary basement membrane was unremarkable apart from focal wrinkling in some glomeruli. Many proximal tubules showed marked cytoplasmic vacuolation of the lining epithelial cells. Some of the tubules were dilated and occasional mitoses were noticed in tubules, suggestive of regenerative activity (Figure 1). There were some wavy hyaline oesinophilic cast-like materials in the tubular lumina but there was no evidence of cast nephropathy. There were one large and several small foci of atypical lymphoplasmacytoid infiltration in the interstitium. Immunohistochemistry confirmed that those atypical lymphoid cells were of B cell origin and exhibited lambda light-chain restriction. Immunofluorescence examination revealed grade 1 granular deposition of IgM and C3 on the capillary basement membrane and in the mesangium. Electron microscopy showed only mild increased mesangial matrix substance with focal effacement of podocytic foot. The histological diagnosis was ATN with atypical lymphoplasmacytoid infiltration, vacuolar nephropathy, and minor glomerular abnormalities.

The urine output did not improve immediately after the plasma exchange and it remained 400–600 ml/day. However, it started to increase to above 1 litre per day after 6 days and four sessions of plasma exchange. The serum creatinine also fell. The patient’s serum creatinine decreased from a peak of 308 μmol/l to 78 μmol/l over a period of 3 weeks except for a transient increase in serum creatinine probably secondary to the contrast toxicity from the CAT abdomen scan on day 20 (Figure 2). A total of 10 sessions of plasma exchange were instituted over that period, and the clinical improvement in the patient’s mental state was prompt. The serum globulin levels were kept at 30–60 g/l by regular maintenance plasma exchange of one or two sessions per week. In addition, the patient was started on a daily dose of oral chlorambucil with allopurinol cover. Twenty-four hours protein excretion repeated at 3 weeks showed a mild reduction in protein excretion to 2.4 g/24 h, and repeated urine microscopy was otherwise unremarkable.

Discussion

Waldenström’s macroglobulinaemia is a rare disease first described by J. Waldenström in 1944. It was a clinical entity characterized by monoclonal IgM paraproteinaemia, hyperviscosity, and haemorrhagic
tendency. Concerning its renal manifestations, proteinuria is common but usually mild and may be associated with Bence Jones proteinuria. Haematuria may be present. Severe renal problems such as ARF and nephrotic syndrome are rare. The most common renal involvement in Waldenström’s macroglobulinaemia is direct infiltration of the kidney by atypical lymphoid cells, which may occur in 50–60% of the patients. Other renal manifestations include urate nephropathy, cast nephropathy, light-chain deposit disease, renal amyloidosis, type I cryoglobulinaemia, and intraglomerular occlusive thrombi deposition with IgM protein [1]. In addition, there are anecdotal reports of associated membranous nephropathy, minimal-change disease, and crescentic glomerulonephritis. The association with ATN, however, has never been described in the literature.

Our patient presented with ARF complicating Waldenström’s macroglobulinaemia and clinical manifestations of hyperviscosity syndrome. Renal biopsy revealed features suggestive of ischaemic ATN with minor glomerular lesion and unremarkable immunofluorescence study. In general, ATN usually occurs as a result of ischaemic or nephrotoxic renal injuries although it might also complicate primary renal disease such as glomerulonephritis. Our patient did not have any hypotensive episode throughout his clinical course of illness and there was no significant drug history. The atypical cellular infiltration in the renal biopsy also seemed to be not severe enough to account for the ATN. Interestingly, the patient’s renal failure appeared to emerge with the progression of the hyperviscosity syndrome and the renal function improved with a delay of 6 days after plasma exchanges.

Although hyperviscosity syndrome has been put forward as one of the important factors contributing to the renal complication in multiple myeloma [2,3], the degree of renal dysfunction attributed to the hyperviscosity syndrome per se remains unclear. There are usually multiple contributing factors such as hypercalcaemia, uric acid nephropathy, dehydration, cast nephropathy, and urinary tract infection, which render segregating individual effects difficult or impossible. Our patient, however, presented with classical symptoms and signs of hyperviscosity syndrome without those complicating factors. Although we have not been able to document the effect of the hyperviscosity on the renal blood flow, the close temporal relationship and intriguing benefit conferred to the renal function by plasma exchange seem to argue for the existence of a causal relationship between the ARF and hyperviscosity. We postulate that the renal perfusion was compromised, resulting in ischaemic injury and ATN. In the literature there is a case report describing an analogous situation in which a patient with Waldenström’s macroglobulinaemia and hyperviscosity syndrome presented with central retinal artery occlusion. The retinal blood flow was restored after plasma exchange, as documented by Doppler ultrasound of the retina [4].

Details of the effect of hyperviscosity on the kidney are scarce. An animal study performed by McDonald [5] showed that hyperviscosity induced by isoncotic dextran could lead to a global decrease in renal blood flow. No comparable study has been done in the human. Nevertheless, based on clinical and experimental observations, Anderson et al. [6] has suggested that hyperviscosity due to hypercholesterolaemia might cause progressive glomerular injury by increasing the renal vascular resistance. The associated glomerular capillary hypertension might then result in glomerulosclerosis. Moreover, another study showed that elevated plasma viscosity might be associated with more rapid progression of renal failure in diabetic nephropathy [7]. It seems that plasma viscosity is emerging as an important factor affecting not only the renal haemodynamic status but also the clinical outcome.

In addition to ATN, our renal biopsy demonstrated minor glomerular abnormalities that might have contributed to the albuminuria, and prominent vascular changes at the proximal tubular cells suggestive of vascular nephropathy or osmotic nephrosis. The renal biopsy was performed before the CAT abdomen scan but after the onset of renal deterioration. The occurrence of vascular nephropathy was therefore probably a result of the usage of succinylated gelatine in plasma exchanges and, in fact, vacuolar nephropathy has been reported to be associated with the use of osmotic diuretic, plasma expander such as dextran, mannitol, and gelatine, or hypertonic radiocontrast material. It appears to be more common if there is underlying renal ischaemia or insufficient [8–10]. In our patient, the underlying renal ischaemia due to hyperviscosity might have rendered the tubules more susceptible to vacuolar nephropathy. Nevertheless, the pathogenic mechanism is not entirely clear and the overall impact on the renal function appears to be variable. Reversible ARF has been reported [10]. Our patient, however, developed ARF well before the institution of plasma
Hyperviscosity-associated ATN did not appear to have significant long-lasting detrimental effect on the renal function. With the alleviation of hyperviscosity, his renal function improved after a short delay and it was consistent with a recovery from ATN.

References


Received for publication: 6.1.00
Accepted in revised form: 10.5.00