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Case report

Fibrillary Nephropathy and Amyloidosis – Two Morphological Faces of the Myeloma Kidney

Vesna Ristovska[1] and Gordana Petrusevska[2]

[1]University Clinic for Nephrology, [2]Institute of Pathology, Faculty of Medicine, University "Ss. Cyril and Methodius", Skopje, Republic of North Macedonia

Abstract

Myeloma-induced renal failure is associated with significant morbidity and mortality. Rapid intervention is critical to reverse kidney damage and improve renal function. We report two cases, one with fibrillary nephropathy and other one with kidney amyloidosis due to multiple myeloma, diagnosed by renal biopsy and treated in our department. Both patients had no other signs of multiple myeloma present, apart from acute renal failure and histological findings on renal biopsy. The renal biopsy was performed because of acute renal failure to exclude rapidly progressive glomerulonephritis. The histological analysis showed fibrillary glomerulopathy in one patient and kidney amyloidosis in the other, changes consistent with the diagnosis of multiple myeloma with kidney involvement. Further clinical investigation confirmed multiple myeloma and the patients treated accordingly.

Keywords: multiple myeloma, biopsy, chronic renal failure

Introduction

Multiple myeloma (MM), also known as plasma cell myeloma and simple myeloma, is a malignant disease of plasma cells, which are white blood cell that normally produce antibodies. Frequently, no symptoms are noticed initially [1]. However, bone pain, bleeding, infections, and anemia may occur during the clinical course of the disease. The cause of multiple myeloma is not known. Various complications of the disease can occur, and amyloidosis represents one of them [2]. In this study we report two cases of multiple myeloma and kidney involvement diagnosed by renal biopsy. One patient had fibrillary glomerulopathy and the other one renal amyloidosis. Both patients were treated at the Department of Nephrology, University Clinic of Nephrology, in Skopje.

Case 1

A 70-year-old woman was admitted to our department with a history of hypertension, actual presence of fatigue, inappetence, nausea, vomiting and weakness over a period of several weeks along with oedema in her legs. At the time of admission, she had impaired renal function (serum creatinine: 273μmol/l) and proteinuria (urinary protein: 2.14 g/24h). During her hospitalization, the renal function showed deterioration (serum createnine increased to 862 μmol/l) and the patient needed hemodialysis. The routine laboratory tests at admission and during hospitalization were as follows - Hb levels: 107 and 88 g/l; RBC: 3.74 and 3.11x10^9/l; Ht: 33% and 28%; WBC: 6.3, 3.8 and 6.3x10^3/l; total protein: 65 and 57g/l; albumin: 45 and 37 g/l; BUN: 16.5, 20.3 and 12.3 mmol/l; creatinine 408, 719 and 768 μmol/l; serum sodium: 143 and 136 mmol/l; serum potassium: 4.6 and 4.5 mmol/l; serum calcium: 2.13 mmol/l; uric acid: 389 and 285 μmol/l. Lipid levels were within normal range. Immunoglobulin IgA levels were 0.3 g/l; IgM: 0.2 g/l; IgG: 5.3 g/l and CRP levels 4.3 mg/L and 28.2 mg/L, respectively. Proteinuria increased to 3.8 g/24 hours. The ultrasound scan of the kidneys showed two normal kidneys with parenchyma of 20-22mm. A renal biopsy was performed to identify the cause of renal failure.

Renal biopsy findings: The histological examination showed enlarged glomeruli due to increased cellularity in the mesangial area and increased mesangial matrix deposition (Figure 1). There was also ischemic folding of the basement membrane. In tubulointerstitial area acute tubular lesions with dense eosinophilic protein casts, as well as focal lymphocytic infiltrates were identified. The immune-fluorescent analysis showed positive staining for IgG in deposits as well as in the intra-tubular protein casts. Ultrastructural analysis showed ischemic collapse of the glomerular basement membrane partially thickened with amorphic basal membrane deposits as well as irregularly thickened tubular membrane. On higher magnification fibrillary structures were recognized in the glomerular and tubular basement mem-

Correspondence to: Vesna Ristovska, University Clinic for Nephrology, 1000 Skopje, R. N. Macedonia; E-mail: v.ristovska@yahoo.com

brane, in subepithelial and subendothelial area (Figure 2). These fibrils were larger than amyloid fibrils, (from 12 to 24 nm) without any branching between them. These findings were compatible with fibrillary glomerulopathy, an entity usually associated with plasmocytic dyscrasias.

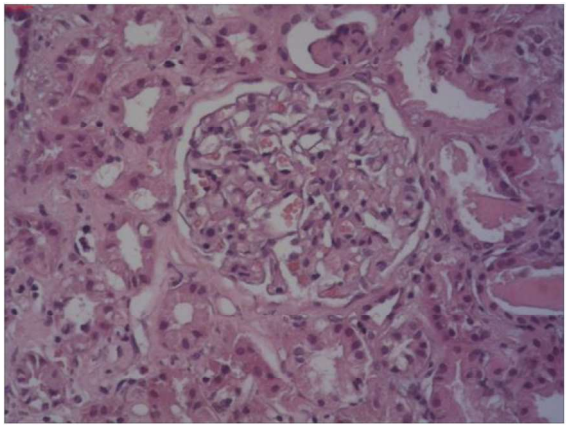

Fig. 1. Fibrillary glomerulonephritis HBE x400, Nikon Eclipse 80; Increased mesangial matrix deposition and slightly increased mesangial cellularity

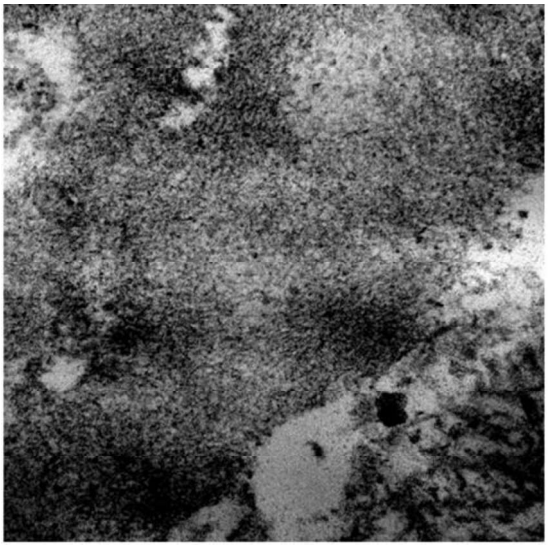

Fig. 2. Ultrastructural presentation of fibrillary glomerular deposits

A consultation from hematologists was requested and after the confirmation of neoplastic plasmocytic proliferation, chemotherapy using CTD protocol was applied to the patient who was also managed with intermittent hemodialysis. After 12 months of treatment the patient is in a good condition with a regular follow up from hematologist and nephrologist.

Case 2

A 57-year-old woman with fatigue, inappetence, nausea and vomiting was admitted in our Department as acute renal failure after dehydration. According to her history she has arterial hypertension properly regulated with antihypertensive drugs. She reported back pain but no treatment with medication known to be associated with renal dysfunction. The cardiac and pulmonary examination was normal.

Routine laboratory tests at admission and during the hospitalization were as follows: Hb: 99 and 86g/l; RBC: 3.54 and $3.0x10^9$/l; WBC: 8.6, 7.7 and $9.5x10^3$/l; Ht: 29%, 22% and 24%; serum protein: 77 and 76 g/l; albumin: 47 and 48 g/l; BUN: 22.1, 13.6 and 22.4mmol/l; serum creatinine: 886, 773 and 889μmol/l; uric acid: 607 and 324 μmol/l; serum sodium: 141 and 138 mmol/l; serum potassium: 6.7 and 4.4 mmol/l; serum calcium: 2.5 and 2.7mmol/l. Complement component C3: 0.73 g/l and C4: 1.2 g/l. Serum immunoglobulin levels were within the normal range. Proteinuria was progressively increased from 1.78 to 4.0 g/24hr but oedema was not present. The patient became anuric and treatment with hemodialysis was started.

The renal ultrasound scan showed enlarged kidneys with parenchyma 23mm, increased echogenicity and no evidence of obstruction.

A renal biopsy was performed to identify the cause of acute renal failure.

Renal biopsy findings: The histological examination showed slightly thickened glomerular basement membrane and amyloid resembling deposition in the paramesangial area (Figure 3). In the tubulointerstitial area the classical changes of myeloma kidney with dilated tubules and dense protein casts, giant cells and huge focal lymphoplasmacytic infiltration were recognized. Nodular hyaline thickening was also found in the blood vessels. The immune-fluorescent analysis was inconclusive due to non-specific staining. The ultrastructural analysis showed fine fibrillary branched and tangled fibrils

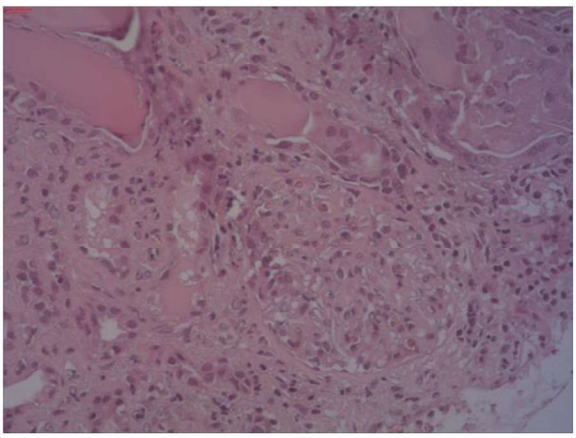

Fig. 3. Amyloid deposits in glomerular mesangium confirmed on TEM analysis

(7 to 13 nm-s), compatible with amyloid which widened the subendothelial spaces (Figure 4). A bone marrow biopsy was performed that revealed presence of neoplastic plasmocytic infiltrates. Although no radiological le-

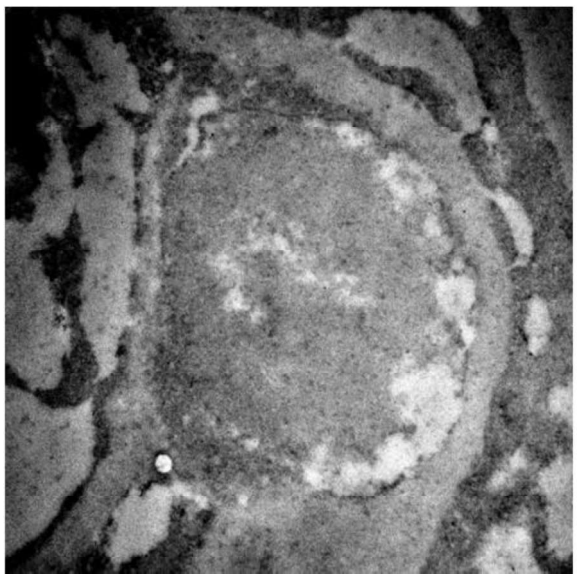

Fig. 4. Ultrastructural confirmation of the presence of amyloid deposits. There are dense protein casts in the tubule with giant cell

sions were found in the scull, the diagnosis of plasmacytoma-multiple myeloma was made.
A consultation from hematologists was requested and the patient was treated with chemotherapy, according to the proper protocol. The patient is in a good condition, but she remains in chronic intermittent hemodialysis.

Discussion

In this study we present the importance of meticulous exploration of the underlying cause of renal impairment in patients with acute kidney failure. In the first case the possible diagnosis of rapidly progressive glomerulonephritis had to be excluded whereas in the second case multiple myeloma was presented with acute renal failure.
The patients with multiple myeloma usually have lytic lesions, back pain or hypercalcemia. The lack of such typical clinical manifestations that occurs not very frequently makes the diagnosis of the disease difficult [3-5]. In patients with acute renal failure and anemia of unknown origin the possibility of an underlying multiple myeloma should always be investigated. In such cases three entities should be considered: fibrillary glomerulopathy (fibrillary glomerulonephritis, FGN), immunotactoid glomerulopathy (immune-tactoid glomerulonephritis, ITGN) and amyloidosis [4,6-8]. Fibrillary GN has been defined as an immune complex-mediated GN with amyloid-like but larger to amyloid fibrils which are IgG positive and usually Congo red negative. The specificity of the morphologic criteria is important for establishment of the diagnosis of fibrillary GN [6,7]. The fibrils are usually found in subepithelial, subendothelial and mesangial areas. Fibrillary glomerulonephritis is a rare idiopathic condition linked to malignancy, autoimmune disorders, monoclonal gammopathies and hepatitis C virus infection. No standardized treatment for the disease exists and the prognosis is usually poor resulting to end-stage renal disease within a few years [9-11]. The diagnosis of FGN can only be established by renal biopsy. FGN is defined by the ultrastructural finding of organized, randomly oriented, nonbranching fibrils with a mean diameter of 20 nm (range 12-24 nm). The incidence of FGN in native renal biopsies is less than 1% [2-5]. The deposition of fibrils that characterize FGN are predominantly restricted to the glomeruli and stained intensely in IF for IgG, C3, κ, and λ chains. These findings strongly suggest that the fibrils are composed of a complex of antibodies and antigens. Amyloid in renal amyloidosis is characteristically stained positive with Congo Red stain and has typical ultrastructural morphology with branching fibrils measuring from 7 to 12 nm-s. The differentiation between the two entities needs ultrastructural analysis. The diagnosis of FGN and its differentiation from amyloidosis and from immunnotactoid glomerulonephritis that is not described in this study, is not possible in the absence of electron microscopy.

Conclusion

Performance of renal biopsy is very crucial for the diagnosis in patients with renal failure of unknown origin. The examination of the kidney tissue with electronic microscopy sometimes is necessary for discrimination among various causes. FGN is a rare form of glomerular disease characterized by distinctive randomly oriented, nonbranching fibrils with a mean diameter of 20 nm (range 12-24 nm). The prognosis of FGN as well as of renal amyloidosis is poor, therapeutic options are limited, and optimal therapy remains to be defined. Although sometimes the typical clinical signs of multiple myeloma are absent, the early diagnosis is important for diagnosis of the disease.

Conflict of interest statement. None declared.

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