

Waldenström's macroglobulinaemia presenting with nephrotic syndrome

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INTRODUCTION

Minimal change nephropathy (MCN) is a major cause of nephrotic syndrome in both children and adults. It is characterised by normal appearing glomeruli by light microscopy and the absence of immunoglobulin deposits by immunofluorescence microscopy. On electron microscopy there is diffuse fusion of the epithelial foot processes. MCN is suggested to be caused by a T-cell or B-cell dysfunction and/or a yet undefined circulating glomerular permeability factor. Most cases of MCN are idiopathic, but sometimes MCN seems to be associated with an underlying cause such as drugs, neoplasms, atopy, other glomerular diseases or infection.

Here we describe a case of a 55-year-old male who was diagnosed with a nephrotic syndrome caused by MCN, which seems to be associated with Waldenström's macroglobulinaemia. Treatment not only resulted in complete remission of the Waldenström's macroglobulinaemia but also in complete remission of the nephrotic syndrome.

CASE

A previously healthy 55-year-old male was referred to the cardiology outpatient clinic because of oedema of both legs as well as an irregular pulse. He was diagnosed with mitral valve insufficiency grade 4/4, caused by mitral valve

What was known about this topic?

Nephrotic syndrome in the presence of lymphoplasmacytic lymphoma with IgM monoclonal gammopathy (Waldenström's macroglobulinaemia) can have several causes of which amyloidosis is probably the most thought of. The occurrence of nephrotic syndrome caused by minimal change nephropathy occurring as a paraneoplastic manifestation of Waldenström's macroglobulinaemia is a rare phenomenon, with only two cases previously reported in the literature.

What does this add?

With this case we hope to raise awareness that minimal change nephropathy should be considered as a rare but possible cause of nephrotic syndrome in Waldenström's macroglobulinaemia. Curing Waldenström's macroglobulinaemia can result in complete remission of the minimal change nephropathy.

prolapse (Barlow's syndrome) as well as atrial fibrillation for which cardioversion was performed. He showed signs of (mostly right-sided) cardiac failure. At the same time, a normocytic anaemia and hypoalbuminaemia were found for which the patient was referred to the department of internal medicine. Physical examination revealed a systolic murmur II/VI on the apex of the heart and pitting oedema of both legs up to the inguinal area. Further physical examination was unremarkable.

Laboratory testing showed an erythrocyte sedimentation rate of 132 mm/hour, haemoglobin (Hb) 7.5 mmol/l,

MCV 92 fl, reticulocytes $27 \times 10^9/l$, thrombocytes $175 \times 10^9/l$, leucocytes $5.6 \times 10^9/l$ with normal differentiation, creatinine 55 $\mu\text{mol/l}$, urea 4.9 mmol/l, normal liver function tests, normal electrolytes, albumin 16.1 g/l, total serum protein 57.0 g/l, monoclonal protein (M-protein) IgM kappa 10 g/l, IgG 7.0 g/l, IgA 1.54 g/l, IgM 9.8 g/l, and β_2 -microglobulin 3.7 mg/l. Immunophenotyping showed monoclonal B-cells IgM (IgD) type kappa: $0.03 \times 10^9/l$ in the peripheral blood and 7% in bone marrow aspirate (probably underestimated because of blood admixture). Bone marrow biopsy showed a large part of the bone marrow cavities infiltrated by lymphoplasmacytoid cells. Serology testing for autoimmune diseases showed absence of antinuclear factor and antineutrophilic cytoplasmic antibodies, antiglomerular basement membrane antibodies of 0.6 kU/l, and normal C3 and C4 complement. Urine analysis revealed proteinuria of 5.6 g/24 hours and Bence Jones protein type kappa (<0.1 g/l) as well as M protein IgM type kappa (<0.1 g/l).

Renal biopsy was performed which showed nine normal glomeruli on light microscopy. Immunofluorescence showed only minor granular deposits of kappa light chains in the mesangium and electron microscopy showed diffuse flattening of the podocytes as well as an intact but thin glomerular basement membrane and no signs of amyloid deposition or lymphoma localisation.

A computed tomography scan of the chest and abdomen revealed no abnormalities, especially no pathologically enlarged lymph nodes or spleen.

The patient was therefore diagnosed with a nephrotic syndrome caused by MCN, as well as an indolent non-Hodgkin's lymphoma: lymphoplasmacytic lymphoma with bone marrow involvement and IgM monoclonal gammopathy, also known as Waldenström's macroglobulinaemia.

Treatment was instituted with prednisone 60 mg daily but the nephrotic syndrome showed only a partial response: the oedema diminished but did not disappear, the proteinuria dropped to 1.9 g/24 h, while the serum albumin stabilised at 20 g/l in six weeks time. During prednisone therapy, the patient developed a sensorimotor polyneuropathy and his anaemia worsened (Hb 6.5 mmol/l), while the M protein rose to 25 g/l.

Because the response of the nephrotic syndrome was only partial and other Waldenström's macroglobulinaemia-associated symptoms developed at the same time (polyneuropathy, worsening anaemia and rising M protein), the treatment with prednisone was discontinued and a combination of rituximab ($375 \text{ mg/m}^2 = 750 \text{ mg iv}$) and chlorambucil ($6 \text{ mg/m}^2 = 12 \text{ mg orally on day 1-14}$) every four weeks was started. He received a total of six courses after which his blood count and albumin normalised and the M protein was absent. Both the proteinuria and the polyneuropathy had fully resolved.

Bone marrow examination showed complete remission of the lymphoplasmacytic lymphoma.

At the present time, almost five years after completion of therapy, the patient is still in complete remission of both Waldenström's macroglobulinaemia and nephrotic syndrome. He has undergone successful mitral valve surgery and is now functioning normally.

DISCUSSION

Waldenström's macroglobulinaemia is defined as lymphoplasmacytic lymphoma with bone marrow involvement and an IgM monoclonal gammopathy of any concentration.¹ The overall incidence is 3.8 per million persons per year, with the incidence increasing with age. The need for treatment is determined by symptoms caused by the tumour mass or M protein.²

With renal disease in the presence of Waldenström's macroglobulinaemia, amyloidosis might be the first thing that comes to mind. In this case, however, we have a patient who presented with MCN as well as Waldenström's macroglobulinaemia. Kidney needle biopsy showed the characteristic signs of MCN with the absence of immune-complex deposits or localisation of the lymphoplasmacytic lymphoma itself.

In the Netherlands, primary MCN is the cause of nephrotic syndrome in adults in about 21% of cases.³ Initial treatment consists of prednisone, with which only 45-60% of patients reach complete remission at six weeks, to 75-90% reaching complete remission at 16 weeks.⁴ In patients refractory to prednisone therapy or with frequent relapses of MCN, other immunosuppressive agents such as cyclophosphamide, chlorambucil, cyclosporine A and rituximab are also used.^{4,5}

In our patient, the time relationship between the occurrence of MCN and Waldenström's macroglobulinaemia is suggestive of MCN occurring as a paraneoplastic manifestation of Waldenström's macroglobulinaemia. Several glomerulopathies are known to occur as paraneoplastic manifestations of malignant disease.⁶ For instance, the occurrence of MCN as a paraneoplastic manifestation of classical Hodgkin's lymphoma is well established.⁷

Glomerulopathies are also described as a paraneoplastic manifestation in non-Hodgkin's lymphoma with MCN occurring most frequently.⁸⁻¹⁰ MCN associated with Waldenström's macroglobulinaemia, however, seems to be a rarely mentioned phenomenon with only two cases reported previously in literature.^{11,12}

Little is known about steroid responsiveness of MCN occurring as a paraneoplastic phenomenon. In MCN

occurring prior to classical Hodgkin's lymphoma, remission is accomplished in about 62.5% of patients treated with steroids alone; the prognosis of MCN seems to be directly related to the prognosis of the classical Hodgkin's lymphoma, irrespective of the therapy regimen used to treat the Hodgkin's lymphoma and whether or not this regimen contained steroids.⁷

In our patient a partial response of the nephrotic syndrome was achieved in six weeks of prednisone treatment after which it was discontinued because the Waldenström's macroglobulinaemia required treatment. In our patient as well as in the two previously reported cases of MCN and Waldenström's macroglobulinaemia occurring simultaneously, treatment of Waldenström's macroglobulinaemia resulted in the disappearance of MCN. However, it must be noted that in all three cases the medication used to treat the Waldenström's macroglobulinaemia could also be effective in the treatment of (primary) MCN.^{4,5}

Although the time relationship between Waldenström's macroglobulinaemia and MCN is suggestive of causality between these two conditions, definite proof will be furnished by reappearance of the nephritic syndrome at the relapse of the Waldenström's macroglobulinaemia. The pathogenesis of MCN as a paraneoplastic manifestation in haematological malignancies is largely unknown. In classical Hodgkin's lymphoma, there seems to be a molecular link between the two entities with induction of c-mip in both Hodgkin-Reed Sternberg cells and podocytes.¹³

We conclude that in case of nephrotic syndrome occurring in the setting of Waldenström's macroglobulinaemia, not only amyloidosis, but also MCN should be considered as a cause. Treating Waldenström's macroglobulinaemia can also cure nephrotic syndrome.

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