

*Case reports and literature review***A Modest Experience in the Treatment of Membranous Nephropathy with Classical and Alternative Medications**

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Abstract

Introduction. Membranous nephropathy (MN) is the most common morphological finding found in cases of nephrotic syndrome in adults. Etiologically it is divided into primary (PMN) and secondary (SMN). Treatment of patients with MN is carried out with corticosteroids, immunosuppressants, monoclonal antibodies and others, depending on the determined degree of risk in the respective patients.

Case reports. We describe two cases from clinical practice with biopsy established MN, as PMN, in which we carried out treatment with intermittent "pulses" of glucocorticoids and/or cyclophosphamide with simultaneous administration of medications with nephroprotective and/or anti-inflammatory effects-SGLT2 inhibitors and finerenone.

Results. The patients were followed up for six months. During this period, remission of the main manifestations of the disease was achieved in all patients without any deterioration of the renal function. Subsequent observation and non-pathogenetic treatment in the next six months also showed no disease activity.

Conclusion. The excellent results we have reported in these patients, in our opinion, are an evidence that the individual approach to treatment does not contradict the accepted rules of Good Clinical Practice, but often complements them well under the appropriate conditions.

Keywords: membranous nephropathy, nephrotic syndrome, corticosteroids, immunosuppressants, alternative medications, SGLT2 inhibitors, Finerenone

Introduction

Membranous nephropathy (MN), also known as membranous glomerulonephritis, is one of the most frequently detected morphologically chronic glomerulonephritis, clinically manifested by nephrotic syndrome-massive proteinuria (>3.5 g/day), hypo- and dysproteinemia, and edema of nephrotic-type. The etiology can be primary (75-80%) and secondary (20-25%), but remains unknown [1]. The role of viral and bacterial infections, environmental pollution, and genetic predisposition is discussed. It is believed that people of European and East Asian descent are genetically predisposed to the development of this nephropathy due to defects in two non-HLA loci that are transcriptional regulators of inflammation [2-6]. The diagnosis, as in all cases of unknown nephropathies, is proven only by renal biopsy. Differentiating the primary from the secondary form requires numerous additional studies and even then, it may not be proven definitively.

Case 1.

A 61-year-old Caucasian male with a history of long-term arterial hypertension presented with a constellation of nephrotic syndrome: pronounced edema of the lower extremities of the nephrotic type with proteinuria of 11.4 g/l, reduced total protein levels of 35.2 g/l, and albumin of 17.8 g/l, with e-GFR of 81 ml/min/1.73 m². Serological markers for hepatitis B and C were negative, as well as the immunological markers for systemic lupus in two consecutive measurements.

Kidney biopsy was consistent of Membranous nephropathy of GN, class II, with abundant deposits of IgA, IgG, IgM, C3, C1q.

After biopsy clarification, the following treatment was started (Table 1):

Table 1. The medications used for treatment were cyclophosphamide (CYC); glucocorticoids (GC); Sodium-glucose transport inhibitors 2 (SGLT2)

	1 st month	2 nd month	3 rd month	4 th month	5 th month	6 th month
CYC	+	+	+	+	+	+
GC	+	+			+	
SGLT2	+	+	+	+	+	+

The main treatment included: Cyclophosphamide from 1st to 6th monthly pulse doses of 500 mg i.v., Methylprednisolone at 1st and 2nd month with pulse doses of 500 mg/3 days in row i.v., and SGLT-2 inhibitor x 10mg/daily.

Symptomatic treatment also included olmesartan/amlodipine, diuretics, and supplementation for protein loss. After the 6-th month, the following changes were found: lack of edema in the lower extremities, reduction of body weight by 32%, decrease in proteinuria to 0.9 g/L, increase in total protein to 59.2 g/L, and albumin to 35.4 g/L, and increase of e-GFR to 100 ml/min/1.73 m².

Case 2.

A 41-year-old man, Caucasian race, arterial hypertension with a 5-year history, was admitted with a constellation of nephrotic syndrome with mild edema in the lower extremities of nephrotic type, proteinuria of 4.91 g/L, total protein of 54.6 g/l, albumin was 29.4 g/l, and e-GFR - 112 ml/min/1.73 m².

In addition, there were negative serological markers for hepatitis B and C, and negative immunological markers for systemic lupus, determined twice.

Kidney biopsy showed membranous nephropathy, class II, with abundant deposits of IgA, IgG, IgM, C3, C4, C1q. We conducted the following treatment on this patient (Table 2):

Table 2. Main medications used for treatment by month (CYC - cyclophosphamide; GC - glucocorticoids)

	1 st month	2 nd month	3 rd month	4 th month	5 th month	6 th month
CYC	+	+	+	+	+	+
GC	+	+				
Finerenone	+	+	+	+	+	+

The main treatment included: Cyclophosphamide from 1st to 6th monthly pulse doses of 500 mg i.v., Methylprednisolone at 1st and 2nd month with pulse doses of 500 mg/3 days in row i.v., and Finerenone x 10mg/daily. Symptomatic treatment also included olmesartan/amlodipine, diuretics, and protein loss supplementation. The follow up after 6 months revealed an absence of edema in the lower extremities, the proteinuria was reduced to 0.64 g/l, and total protein increased to 71.5 g/l, and albumins to 41.1 g/l, while e-GFR increased to 94 ml/min/1.73 m².

Discussion

Membranous nephropathy is a heterogeneous disease, occurring either in the absence of an established cause (80% of cases), or in association with clinical conditions, such as infections (hepatitis B), lupus erythematosus, neoplasm or any drug intoxication, thus defining the so-called primary and secondary membranous nephropathy, respectively.

The search for markers for identification of MN is associated with the discovery of the neutral endopeptidase (NEP) antigen and the phospholipase-A2 receptor antigen (PLA2R). After 2019, the following biomarkers are used to differentiate the underlying cause: exostosins 1/2 (EXT1/2)-a marker for lupus nephropathy class V; neural epidermal growth factor-like 1 protein (NELL-1)-a major biomarker in "primary" and neoplastic MN; semaphorin 3B (Sema3B)-the most common biomarker in childhood; neural cell adhesion molecule 1 (NCAM1)-a marker for lupus nephropathy class V [7].

Despite the extensive morphological findings in our patients, we did not find any positive signs of para-

neoplastic nephropathy, and triple standard immunological studies for systemic lupus remained negative. We lack laboratory facilities for testing new and specific markers - PLA2R, NELL-1, NCAM1, which limits the objectivity of diagnosis in these cases.

Currently, the approach to treating patients with MN is highly individualized, with experts recommending a conservative regimen tailored to the specific complaints of each patient, clinical manifestations and level of proteinuria.

Of the non-pharmacological factors, the following ones are important: Increased physical activity; Limited salt intake - up to 2.0 g/day; Limited protein intake - 0.8-1 g/kg/day [8].

The first choice in the presence of hypertension is the use of angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs), relying on their protective effect on the kidney, associated with the reduction of hyperfiltration, stabilization of the basement membrane and their influence on the transport of molecules across the renal mesangium.

Protein supplementation is also used in the presence of hypoalbuminemia, usually combined with diuretic therapy. Hyperlipidemia in nephrotic syndrome is a secondary phenomenon, the result of a defective compensatory mechanism and its presence indicates that it is a prolonged nephrotic syndrome. Once it occurs, however, hyperlipidemia adversely affects renal function and the performance of all major systems in the body, for which it is indicated for treatment with statins.

Increased thrombotic risk correlates with the degree of hypoproteinemia and requires the use of at least aspirin, and in more severe cases-low molecular weight heparins and indirect anticoagulants for a prolonged period [9-11].

The Kidney Disease: Improving Global Outcomes (KDIGO) guidelines from 2021 define four risk categories for classifying MN: low, intermediate, high and very high risk.

The most commonly used treatment regimens are: C. Ponticelli regimen-alternating GC and Cyclophosphamide; Calcineurin inhibitors; Rituximab-CD20-antibody therapy.

In patients with intermediate risk-rituximab or calcineurin inhibitor with or without glucocorticoids. For those with high risk-rituximab or cyclophosphamide, alternating with glucocorticoids, or calcineurin inhibitor with rituximab. For very high-risk patients, the recommended treatment includes the use of cyclophosphamide and glucocorticoids [12].

In the cases described by us, the first meets the criteria for a high-risk patient, and the second-for a moderate-high risk. Our patients were not able to purchase either calcineurin inhibitor or Rituximab at their own expense, and the use of these drugs in MN is Off-label. For this reason, we started treatment with CYC and GC-only "pulse", once a month, without the use of conventional medication, as in the classic scheme of C. Ponticelli.

The patients have been followed for 12 months after the described specific therapy, and after the 6th month, we have not used either CYC or GC in both patients, but only SGLT2 inhibitor and antihypertensive therapy with ARB. During the follow-up period, there was no significant change in proteinuria values and renal function, expressed by e-GFR.

SGLT2 inhibitors were initially indicated to improve glycemic control in type 2 diabetes. It has been established that SGLT2 inhibitors exert nephroprotective effects beyond glucose regulation and reduction of intraglomerular pressure through tubuloglomerular feedback. Inhibition of SGLT2 leads to an initial decrease in eGFR in patients without diabetes, which stabilizes over time. Studies of the effect of SGLT2 inhibitors (DAPA-CKD, EMPA-KIDNEY) have reduced proteinuria by 32% in patients with MN [13,14].

The mineralocorticoid receptor (MR) is a transcription factor that is expressed in various tissues: kidneys, heart, blood vessels, etc. The role of MR is well expressed in the distal nephron on aldosterone-sensitive renal epithelial cells expressing 11 β -hydroxysteroid dehydrogenase type 2. In these cells, MR activation is primarily associated with the regulation of blood pressure and sodium retention, but the MR receptor is also expressed in non-epithelial renal cells, in several other tissues, including adipocytes, vascular smooth muscle cells (VSMCs), immune cells, cardiomyocytes, where it may participate in the regulation of their growth. MR can promote fibrosis and inflammation, leading to progression of renal and cardiovascular disease.

MR antagonists are a relatively new class of drugs currently being tested in patients with type 2 diabetes. Phase II and III clinical trials (ARTS, ARTS-DN, ARTS-HF, FIDELIO-DKD, FIGARO-DKD, FIDELITY) have shown dose-dependent reductions in albuminuria with Finerenone and adverse events profile similar to placebo [15,16].

In addition, studies investigating the effects of the combination of Finerenone and sodium-glucose cotransporter 2 (SGLT2) inhibitors (empagliflozin) in chronic kidney disease (CKD) and T2DM (CONFIDENCE) and the selective MR modulator AZD9977 with another SGLT2 inhibitor (dapagliflozin) in HF and T2DM (MIRACLE) aim to expand treatment options. Although SGLT-2 inhibitors have been shown to reduce the risk of hyperkalemia in FIDELIO-DKD and potentially reduce the incidence of new-onset HF in FIGARO-DKD, further studies are needed. To date, the evidence for the beneficial effects of Finerenone across the spectrum of cardiorenal disease is based only to the results of studies conducted in patients with type 2 diabetes, while clinical trials of Finerenone in patients with nondiabetic kidney disease are ongoing. Finally, nonsteroidal MRAs have significant potential as key therapeutic targets across the spectrum of cardiorenal disease [17,18].

The prognosis of MN is: 1/3 of patients reach spontaneous remission, 1/3 achieve partial remission with the development of stable CKD and 1/3 are therapeutically resistant and reach relatively quickly terminal renal failure and the need for renal replacement therapy [19]. Despite the great successes in unraveling the idiopathic forms of the disease and the use of various new molecules with activity against CD19/CD20 rituximab, obinutuzumab, ocrelizumab and ofatumumab, calcineurin inhibitors and others, there is still a lack of convincing data on a serious reduction in resistant cases [20-23].

Conclusion

The reported cases are only proof that, based on established therapeutic models, we can seek individual solutions for our patients with the help of medications that are not yet approved for the treatment of one or another nephropathy, but have a positive effect on the progression of CKD through different mechanisms.

Conflict of interest statement. None declared.

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