НИРКИ KIDNEYS

UDC 616.62-07 DOI: https://doi.org/10.22141/2307-1257.12.2.2023.406

O.N. Sharapov[1, 2], Sh.S. Abdullaev[1, 2]
[1]Republican Specialized Scientific Practical Medical Center of Nephrology and Kidney Transplantation, Tashkent, Uzbekistan
[2]Tashkent Pediatric Medical Institute, Tashkent, Uzbekistan

Membranous nephropathy: the current state of the problem

For citation: Počki. 2023;12(2):111-118. doi: 10.22141/2307-1257.12.2.2023.406

Abstract. *Membranous nephropathy (MN) is an autoimmune disease of the kidney glomeruli and one of the leading causes of nephrotic syndrome. The disease exhibits heterogenous outcomes with approximately 30 % of cases progressing to end-stage renal disease. The study of MN pathogenesis has steadily advanced owing to the identification of autoantibodies to the phospholipase A2 receptor (PLA2R) in 2009 and thrombospondin domain-containing 7A (THSD7A) on the podocyte surface in 2014. Approximately 50–80 and 3–5 % of primary MN cases are associated with either anti-PLA2R or anti-THSD7A antibodies, respectively. The presence of these autoantibodies is used for MN diagnosis; antibody levels correlate with disease severity and possess significant biomarker values in monitoring disease progression and treatment response.*

Keywords: *membranous nephropathy; nephrotic syndrome; basement membrane of the glomerulus; proteinuria; antibodies; PLA2R; THSD7A; review*

Membranous nephropathy (MN) is a heterogeneous group of diseases characterized by a common histopathological picture in the form of diffuse thickening and changes in the structure of the glomerular basement membrane (GBM) as a result of subepithelial and intramembranous deposition of immune complexes and deposition of matrix material produced by affected podocytes. Podocyte injury resulting from the immune deposits increases glomerular permeability to plasma proteins, which results in proteinuria and potentially in nephrotic syndrome (NS). In the kidneys, *in situ*, immune complexes are formed, consisting of their own podocyte or exogenous antigens and autoantibodies produced for them, belonging to the immunoglobulin (Ig) G class. This leads to complement activation along the classical pathway with the formation of a membrane attack complex in the subepithelial space [1, 2].

J. Feehally, in his famous book "Comprehensive Clinical Nephrology" (2016), notes that the term membranous refers to thickening of the glomerular capillary wall on light microscopy of a kidney biopsy, but the condition now called membranous nephropathy is determined using immunofluorescence and electron microscopy. These methods reveal diffuse fine-grained immune deposits on immunofluorescence and electron-dense deposits in the subepithelial space, which are currently considered pathognomonic for MN (Fig. 1). Therefore, MN is a pathological diagnosis that is made in proteinuric patients whose glomeruli show these immune deposits without concomitant hypercellularity or inflammatory changes [3].

Although terms such as membranous glomerulonephritis or epimembranous glomerulonephritis were used to name the disease in the past, the term membranous nephropathy is often preferred today, especially because of its noninflammatory character [4].

MN is one of the most common causes of NS in adults (20–40 % of cases); in children with NS, it is observed in less than 1 % of cases [5, 6]. It is the most common cause of primary nephrotic syndrome in older (> 60 years) white adults, but the age range is wide and patients may first present during adolescence [7]. The incidence of MN is approximately 1 case per 100,000 population per year [8]. In the structure of morphological variants of chronic glomerulonephritis in adults, MN accounts for up to 10–23 % of cases [9–11].

In his excellent review article, W.G. Couser [12] notes that about 70–80 % of MN patients are classified as primary MN (PMN), while 20–30 % are classified as secondary MN. Primary membranous nephropathy is a kidney-

For correspondence: Sharapov O.N., Tashkent Pediatric Medical Institute, Bagishamal st., 223, Tashkent, 100140, Republic of Uzbekistan; e-mail: redact@i.ua
Full list of authors information is available at the end of the article.

specific, autoimmune glomerular disease that presents with increased protein in the urine associated with a pathognomonic pattern of injury in glomeruli. PMN is the most common cause of idiopathic nephrotic syndrome in nondiabetic adults worldwide, representing between 20 and 37 % in most series and rising to as high as 40 % in adults over 60. MN is rare in children (1–7 % of biopsies).

About 20 % of all cases of membranous nephropathy are associated with other diseases or exposures (secondary MN). The most common underlying causes of secondary MN are infections, drugs, malignancies, and autoimmune diseases (Table 1). The frequency of secondary MN is higher in patients diagnosed with MN in childhood or advanced ages, and detailed research should be done on the underlying causes [12].

The first evidence for MN as a kidney-limited autoimmune disease was derived via the immunization of rats with kidney extracts (Heymann nephritis rats) in 1959 [13]; this animal model was instrumental in the subsequent identification of GP330 or megalin expressed on the podocyte surface as the antigen for membranous glomerulonephritis developed in Heymann nephritis rats [14].

The first confirmation that PMN in man involved an analogous mechanism came from Debiec et al. in Paris in 2002, who showed that alloimmune MN in babies of neutral endoproteinase (NEP)-deficient mothers was mediated by maternal anti-NEP antibody that formed immune complexes *in situ* with NEP on the podocyte membranes of the infant [34].

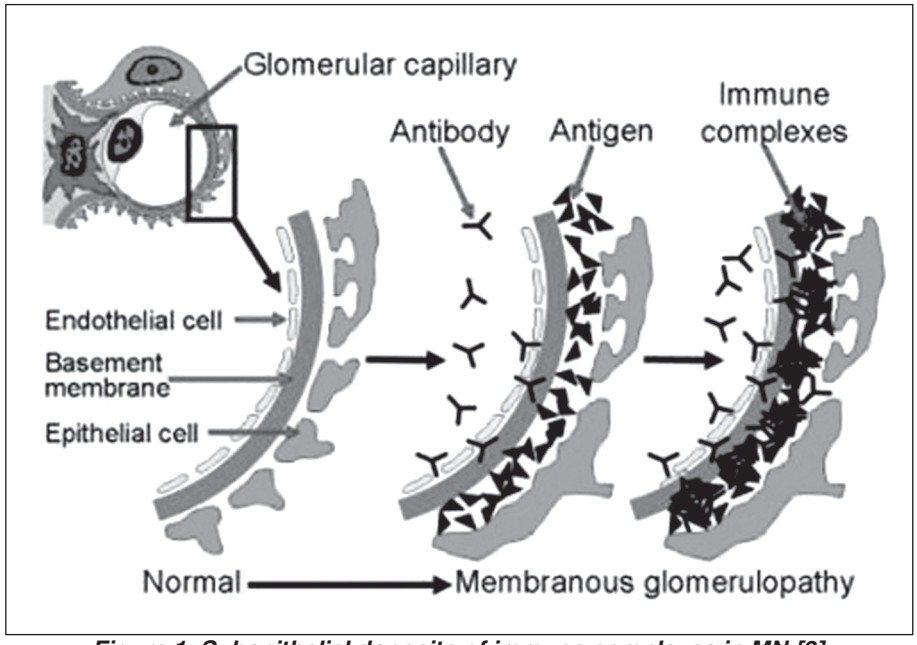

Figure 1. Subepithelial deposits of immune complexes in MN [3]

The discovery of MN-associated podocyte surface antigens in humans was greatly influenced by research by Boston University School of Medicine scientists published in the New England Journal of Medicine in 2009 and 2014. Thus, in 2009, Beck L.H. et al. reported the discovery of the M-type phospholipase A2 receptor (PLA2R) [15], and Tomas N.M. et al. reported the discovery of the thrombospondin 7A domain (THSD7A) in 2014 [16]. Both discoveries paved the way for further discoveries of other surface antigens of the glomerular basement membrane and helped

Table 1. Recognized causes of anti-PLA2R/THSD7A-negative secondary membranous nephropathy (Couser W.G. et al., 2017) [12]

Cause	Examples
Infections	HBV, HCV, HIV, parasites (filariasis, schistosomiasis, malaria), leprosy, syphilis, hydatid disease, sarcoid
Malignancy	Solid tumors (lung 26 %, prostate 15 %, hematologic (plasma cell dyscrasias, non-Hodgkin lymphoma, CLL) 14 %, colon 11 %), mesothelioma, melanoma, pheochromocytoma; some benign tumors
Autoimmune diseases	SLE (class V), thyroiditis, diabetes, rheumatoid arthritis, Sjogren syndrome, dermatomyositis, mixed connective tissue disease, ankylosing spondylitis, retroperitoneal fibrosis, renal allografts
	Anti-GBM disease, IgAN, ANCA-associated vasculitis
	IgG4 disease
	Membranous-like glomerulopathy with masked IgG κ deposits
Alloimmune diseases	Graft versus host disease, autologous stem cell transplants, *de novo* MN in transplants/ transplant glomerulopathy
Drugs/toxins	NSAIDs and cyclooxygenase-2 inhibitors, gold, d-penicillamine, bucillamine, captopril, probenecid, sulindac, anti-TNF-α, thiola, trimetadione, tiopronin
	Mercury, lithium, hydrocarbons, formaldehyde, environmental air pollution (China)
	Cationic BSA (infants)

to significantly improve the diagnosis and treatment of this disease. PLA2R, and to a lesser extend THSD7A, are the two major MN antigens expressed on the podocyte surface. Based on studies involving different cohorts, accumulative evidence reveals the presence of anti-PLA2R antibodies and anti-THSD7A antibodies in 50–80 and 3–5 % of PMN cases, respectively [17–21].

In adults, primary MN associated with the formation of antibodies to podocyte auto-antigens (primarily PLA2R) develops more frequently (70 % of cases) than secondary MN [12]. The peak incidence of MN occurs at the age of 40–60 years (the average age of patients with primary MN is ≈ 50 years); with secondary MN, the age distribution is wider [22]. Among patients with PLA2R-associated primary MN, men predominate (the ratio of men to women is 2 : 1); with other variants of MN, the predominance of males is less pronounced [23].

About 10 % of patients with typical PMN are negative for both antibodies, making it probable that more autoantibodies to podocyte antigens will be found. Dual expression of antibodies to both PLA2R and THSD7A has been reported but is rare.

In primary and secondary MN, the following antigens and antibodies have been identified (Fig. 2):

— In 80 % of patients with primary MN, autoantibodies to the PLA2R are found in the systemic circulation and/or in the kidney tissue [24].

— In 1–5 % of patients with PLA2R-negative MN, autoantibodies (mainly of the IgG4 subclass) are detected to the THSD7A in the blood and/or the THSD7A protein in the kidney tissue [16]. Since THSD7A is also expressed in a number of malignant neoplasms, the body's antitumor humoral response can also be directed to THSD7A localized in the renal glomeruli, leading to the development of MR [25]. Approximately 20 % of patients with THSD7A-positive MN are diagnosed with a malignant tumor within 3 months after the detection of kidney damage.

— In some cases of PLA2R-negative MN, neural epidermal growth factor-like 1 protein (NELL-1) is found in the glomeruli of the kidneys, it is a protein expressed by various cells, including podocytes [26]. Among all forms of MN, NELL-1-associated MN accounts for approximately 2.5 % of cases. In NELL-1-associated MN, autoantibodies of the IgG1 subclass predominate.

— In some patients with PLA2R-negative MN (mainly in children under 2 years of age, less often in adults), the transmembrane protein semaphorin 3B is found in podocytes, and autoantibodies to semaphorin 3B are found in the circulation, mainly IgG1 or IgG3 subclasses [27, 28].

— In secondary MN associated with systemic autoimmune diseases (mainly class V lupus nephritis), the immune deposits may contain exostosin 1 and exostosin 2 proteins expressed by podocytes [27, 28].

— Approximately 6 % of patients with class V lupus nephritis and 2.0 % of patients with primary MN express neural cell adhesion molecules 1 (NCAM1) in the kidney tissue, and antibodies to NCAM1 are detected in the blood serum [29].

The diagnosis should include an antigen pathogenically associated with the development of MN (for example, PLA2R-positive), since in some cases, in the absence of signs of a secondary disease, the distinction between primary and secondary MN can be blurred. Thus, in some

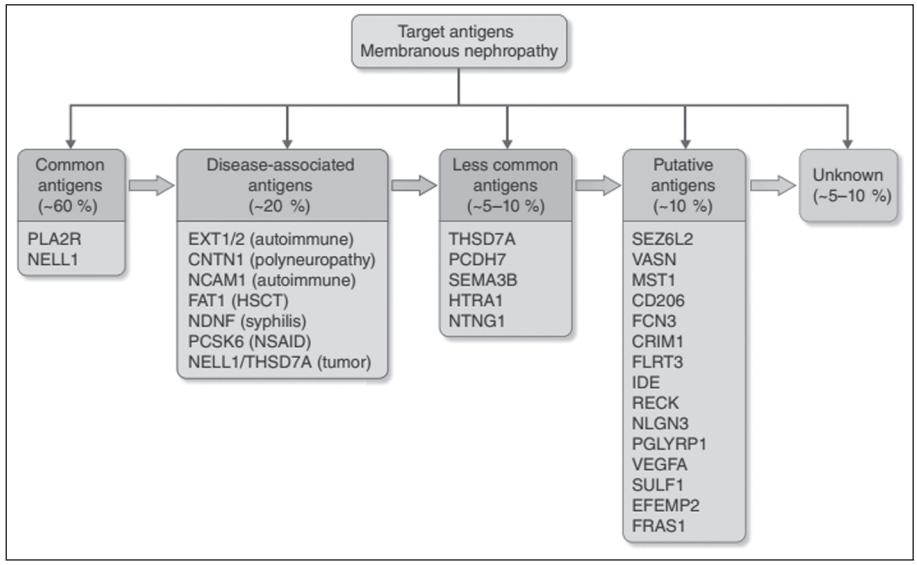

Figure 2. Practical approach and classification of MN antigens [48]

Table 2. Interpretation of serum anti-podocyte antibody and glomerular antigen staining in primary membranous nephropathy [12]

Serum antibody (±)	Glomerular antigen (±)	Biopsied patients, %	Diagnosis
Anti-PLA2R (+)	PLA2R (+)	70	PLA2R-mediated PMN (active)
Anti-PLA2R (–)	PLA2R (+)	15	PLA2R-mediated PMN (inactive)
Anti-THSD7A (+)	THSD7A (+)	3–5	THSD7A-mediated PMN (active)
Anti-THSD7A (–)	THSD7A (+)	Unknown	THSD7A-mediated PMN (inactive)
Anti-PLA2R/THSD7A (–)	PLA2R/THSD7A (–)	10	Non-PLA2R/THSD7A-mediated (pathogenesis unknown)

patients, PLA2R-positive MN is combined with diseases that can lead to the development of secondary MN (such as infections caused by hepatitis B and C viruses, sarcoidosis, malignant neoplasms, etc.) [30–33].

MN is a chronic disease, with spontaneous remission and relapses clearly documented. The clinical course is characterized by great variability in the rate of disease progression, and the natural course is difficult to assess in part because of the selection criteria, geographic variability, and genetic characteristics of the subjects presented in different studies. Although in most patients the disease progresses relatively slowly, approximately 40 % eventually develop end-stage renal disease (ESRD) after focal segmental glomerulosclerosis and lupus nephritis.

At presentation, 60 to 70 % of patients have nephrotic syndrome, with the remaining 30 to 40 % presenting with proteinuria 3.5 g/day in an otherwise asymptomatic patient. Although, more than 90 % of patients have no evidence of impaired kidney function at the time of presentation, hypertension at onset is found in 10 to 20 % of cases. The presence of microscopic hematuria is common (30 to 40 %), but macroscopic hematuria and red blood cell casts are rare and these findings should suggest an alternative diagnosis. Findings of physical examination may vary from mild peripheral edema to full-blown nephrotic syndrome, including ascites and pericardial and pleural effusions.

Spontaneous remissions occur in about 32 % of cases in an average of 14 months and up to 62 % by 5 years, and occur more commonly in patients with low anti-PLA2R/THSD7A levels [35–37]. Anti-PLA2R/THSD7A levels generally correlate with proteinuria, clinical course, and outcomes [38]. The clinical consequences of PMN can be considered as both short and long term. In the short term, they include complications of nephrotic syndrome such as development of thrombotic and thromboembolic events that are proportional to the degree of hypoalbuminemia and increase significantly below albumin levels of about 2.8 g/L [39–41]. There is also an increased risk of infection, due primarily to urinary loss of immunpglobulins, and of cardiovascular disease. An association with malignancies is well documented [42]. Cancer may be seen within 3 years in up to 20 % of patients over 60 and may be more common in the anti-THSD7A group where up to 20 % have had a malignancy detected within 3 months [42–45].

The most feared long-term consequence of MN is progressive loss of renal function as occurs in 60 % of untreated patients, with about 35 % eventually developing ESRD within 10 years [46]. Patients who never become nephrotic virtually never progress [47].

The KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases, in contrast to the KDIGO 2012 guidelines, no longer consider a kidney bi-

Table 3. Histopathological features of primary and secondary MN [3]

Primary MN	Secondary MN
Immunofluorescence microscopy	
IgG4 > IgG1, IgG3 IgA, IgM absent Mesangial Ig staining absent C1q negative or weak PLA2R-positive and co-localizes with IgG	IgG1, IgG3 > IgG4 IgA, IgM may be present Mesangial Ig staining may be present C1q-positive PLA2R-negative
Electron microscopy	
Subepithelial deposits only ± mesangial deposits rarely	Subepithelial deposits ± mesangial and subendothelial deposits

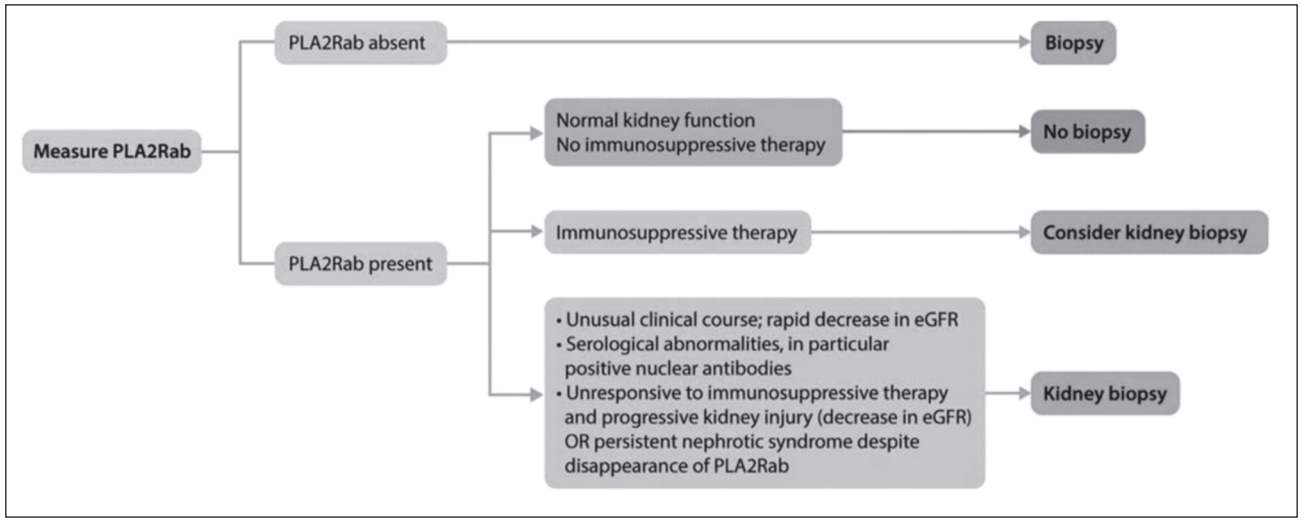

Figure 3. When to consider a kidney biopsy in anti-PLA2R antibody-positive patients [48]

opsy to be absolutely necessary to confirm a diagnosis of MN in patients with NS and a positive test for antibodies to PLA2R [48]. However, even in these circumstances, a kidney biopsy can provide important additional information.

Confirming the diagnosis of MN in patients with a compatible clinical presentation is pivotal in guiding management and treatment decisions. A kidney biopsy usually is considered the gold standard for the diagnosis of glomerular disease; however, for MN, antibodies against PLA2R is a biomarker that can establish the diagnosis of MN with high accuracy and without the associated risks of a biopsy, including insufficient tissue for a conclusive diagnosis, pain, and bleeding. Thus, a kidney biopsy should be done for purposes other than detecting MN in patients who are anti-PLA2R antibody-positive. There are currently insufficient data to support the use of anti-THSD7A antibody as a diagnostic biomarker for MN in lieu of a biopsy [48].

In patients who are anti-PLA2R antibody-negative, a kidney biopsy should be performed with staining for the PLA2R antigen, and this may disclose anti-PLA2R antibody-associated MN (Fig. 3). This can occur in patients for whom the serum enzyme-linked immunosorbent assay and immunofluorescence test are falsely negative, for example, because of low titers. Moreover, it has been suggested that antibodies may be absent in the early phase of MN, being captured in the kidney, and becoming detectable after prolonged follow-up.

On morphological examination of the biopsy specimen, the earliest pathological sign of MN is the formation of subepithelial immune complexes of IgG and comple-

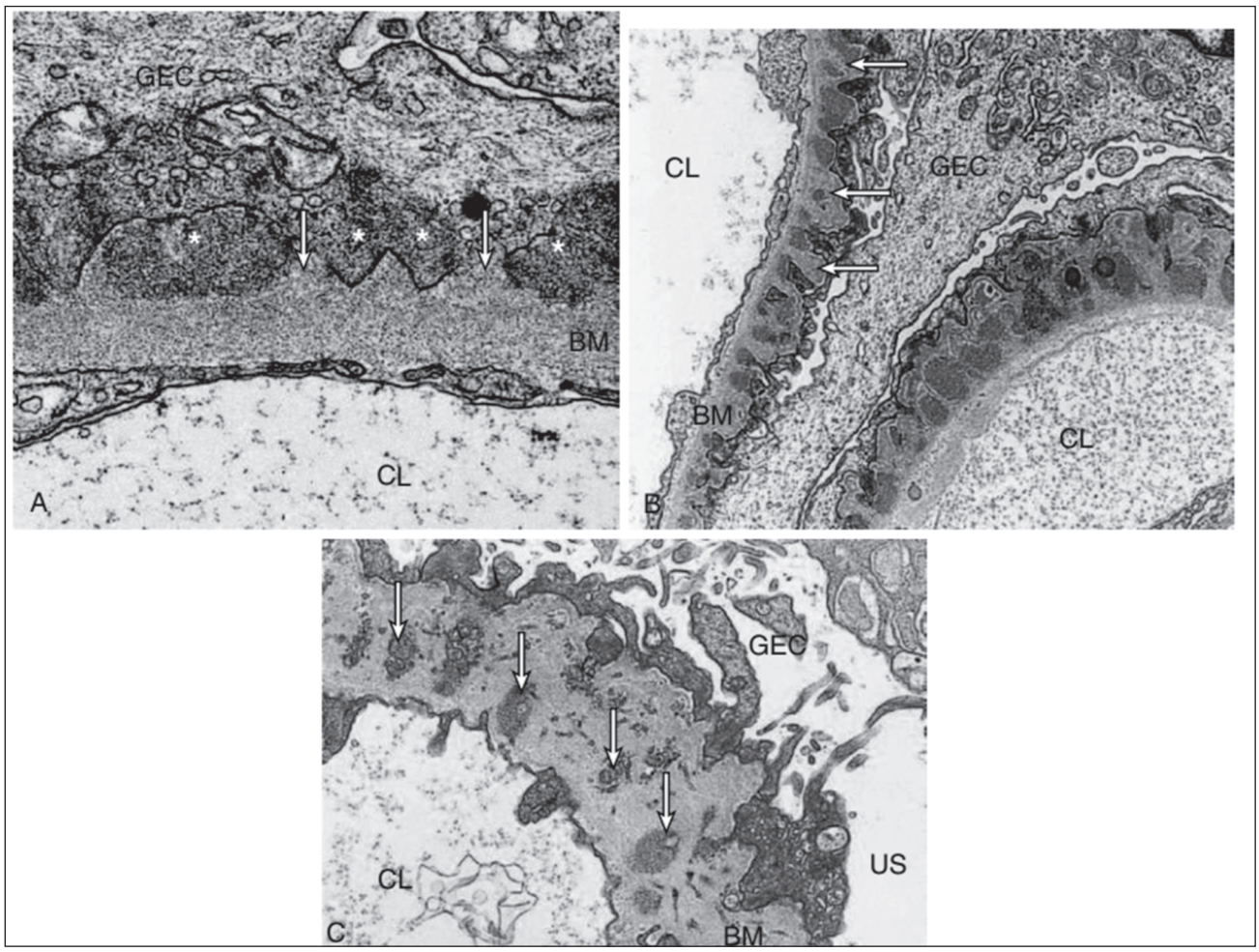

Figure 4. Electron microscopy in membranous nephropathy [3]. A. Early (stage II) MN. Glomerular capillary wall with discrete, electron-dense deposits on the subepithelial surface of the BM corresponding to granular deposits of IgG detected by immunofluorescence microscopy (corresponding to light micrograph in B). There are diffuse, granular immune complex deposits (white asterisks) along outer surface of the capillary wall, with effacement of overlying podocyte foot processes. Small extensions of the BM between deposits (arrows) are also evident and represent the projections that are seen as spikes by light microscopy with silver methenamine staining. B. More advanced (stage III) MN. Two glomerular capillary loops show involvement of the BM by the immune complex deposition (arrows). There is prominent membrane synthesis surrounding and incorporating these deposits into the BM (corresponding to spikes seen on silver-stained histologic preparations). Overlying cells continue to demonstrate widespread effacement of foot processes. C. Morphologically advanced (stage IV) MN. Capillary BM is diffusely thickened; scattered electron-dense immune deposits (arrows) are present throughout its thickness, in addition to scattered subepithelial deposits. Overlying glomerular epithelial cells continue to demonstrate effacement of foot processes (adapted from C.E. Alpers, 1998)

ment along the outer surface of the capillary wall, in which the glomeruli appear histologically normal and, therefore, can be mistaken for a disease with minimal changes if only light microscopy is performed. MN begins with the formation of immune complexes at the podocyte-GBM interface with subsequent changes in the podocyte, deposition of new extracellular matrix material between and around immune deposits, thickening of the GBM (membranous change) and, in some cases, focal glomerulosclerosis, tubular atrophy, and interstitial fibrosis. In the earliest stages of MN, the glomeruli and interstitial tissue appear normal on light microscopy, and the diagnosis is made by immunohistological examination and electron microscopy (Fig. 3).

Although most patients with MN do reasonably well long term, MN is still the second or third leading cause of ESRD in patients with primary glomerulonephritis [3]. The factor still missing from most MN survival data is the much higher-than-expected mortality from cardiovascular disease or thromboembolic events seen in patients who remain nephrotic. When another renal condition is superimposed on MN, there is often an associated acceleration in the rate of renal function loss. The most common conditions to consider in this setting are drug-induced interstitial nephritis, superimposed crescentic glomerulonephritis, including anti-GBM disease, and renal vein thrombosis.

Patients with primary MN who develop ESRD are generally suitable candidates for kidney transplantation, although the disease may recur in up to 50 %. Recurrence may be asymptomatic and found only on protocol biopsy, but those with recurrence of nephrotic syndrome have a high rate of graft loss. A high titer positive serologic test for anti-PLA2R at transplantation may predict early recurrence [49–51].

Because spontaneous remission is relatively common in MN and because immunosuppressive treatment has adverse effects, it is important to assess the risk of progressive loss of kidney function prior to deciding about whether and when to implement immunosuppressive treatment. Table 4 shows clinical criteria that may be used to divide patients into categories of low, moderate, high, and very high risk of progressive loss of kidney function.

There are caveats to the evaluation of risk in MN. In most patients, it is reasonable to wait 6 months for spontaneous remission while using maximal antiproteinuria therapy. High levels of proteinuria, anti-PLA2R antibodies, or low-molecular weight proteinuria should lead to re-evaluation earlier than 6 months. Patients with deteriorating kidney function or severe unresponsive NS may be considered for immediate immunosuppressive therapy, as the likelihood of progression is 84 % in those with a documented 20% decrease in estimated glomerular filtration rate within any time period of fewer than 24 months [52]. According to the KDIGO 2021 recommendations [48], there is currently no model that combines all of these clinical considerations, but they suggest that in clinical practice it is useful to think about risk as a combination of factors (e.g., high proteinuria in patients with low antibody titers may be judged differently than high proteinuria in the presence of high antibody titers).

Relapse from a complete remission occurs in approximately 25 to 40 % of MN cases, but the timing is unpredictable. Relapses have been reported up to 20 years after the primary remission. However, most patients will relapse only with subnephrotic-range proteinuria and will maintain stable long-term kidney function with conservative management alone [53]. In contrast, the relapse rate is as high as 50 % in those achieving only a partial remission. Achievement of either a complete or a partial remission, however, significantly slows progression and increases renal survival. Review of 348 nephrotic patients with MN documented a 10-year renal survival in those with a complete remission of 100 %; with partial remission, 90 %; and with no remission, only 45 % [54]. A recent update suggested durability of remission, whether complete or partial, drug-induced or spontaneous, is closely related to the long-term outcome [53]. This offers hope that complete and partial remission may become acceptable end-points for clinical trials rather than reduction in glomerular filtration rate, which commonly takes years to evolve in MN [55].

Thus, the discovery in 2009 and 2014 of surface antigens of the glomerular basement membrane spurred scientists to

Table 4. Clinical criteria for assessing risk of progressive loss of kidney function (KDIGO, 2021) [48]

Low risk	Moderate risk	High risk	Very high risk
Normal eGFR, proteinuria < 3.5 g/d and serum albumin > 30 g/l OR Normal eGFR, proteinuria < 3.5 g/d or a decrease > 50 % after 6 months of conservative therapy with ACEi/ARB	Normal eGFR, proteinuria > 3.5 g/d and no decrease > 50 % after 6 months of conservative therapy with ACEi/ARB AND Not fulfilling high-risk criteria	eGFR < 60 ml/min/1.73 m^2 and/or proteinuria > 8 g/d for > 6 months OR Normal eGFR, proteinuria > 3.5 g/d and no decrease > 50 % after 6 months of conservative therapy with ACEi/ARB AND at least one of the following: — serum albumin < 25 g/l; — PLA2R antibodies > 50 RU/ml; — urinary α_1-microglobulin > 40 μg/min; — urinary IgG > 1 μg/min; — urinary β_2-microglobulin > 250 mg/d; — selectivity index > 0.20	Life-threatening nephrotic syndrome OR Rapid deterioration of kidney function not otherwise explained

further identify other possible antigens that play a role in the pathogenesis of membranous nephropathy. Today is an exciting time for the study of MN, as all the research and discovery of new antigens and biomarkers contributes to the further improvement of methods for diagnosing and managing patients with membranous nephropathy.

References

1. Ronco P, Debiec H. Molecular Pathogenesis of Membranous Nephropathy. Annu Rev Pathol. 2020 Jan 24;15:287-313. doi:10.1146/annurev-pathol-020117-043811.
2. Alsharhan L, Beck LH Jr. Membranous Nephropathy: Core Curriculum 2021. Am J Kidney Dis. 2021 Mar;77(3):440-453. doi:10.1053/j.ajkd.2020.10.009.
3. Johnson RJ, Feehally J, Floege J, Tonelli M, editors. Comprehensive Clinical Nephrology. 6th ed. Edinburgh: Elsevier; 2019. 1360 p.
4. Özer H, Baloğlu I, Fervenza FC, Türkmen K. Membranous nephropathy: current understanding in the light of new advances. Turk J Nephrol. 2023;32(2):103-111. doi:10.5152/turkjnephrol.2023.22123421.
5. Ozturk S, Sumnu A, Seyahi N, et al. Demographic and clinical characteristics of primary glomerular diseases in Turkey. Int Urol Nephrol. 2014 Dec;46(12):2347-2355. doi:10.1007/s11255-014-0838-3.
6. United States Renal Data System (USRDS). 2018 USRDS Annual Data Report: Epidemiology of kidney disease in the United States. Bethesda, MD: NIDDKD; 2018. Available from: https://www.niddk.nih.gov/about-niddk/strategic-plans-reports/usrds/prior-data-reports/2018.
7. Ayalon R, Beck LH Jr. Membranous nephropathy: not just a disease for adults. Pediatr Nephrol. 2015 Jan;30(1):31-39. doi:10.1007/s00467-013-2717-z.
8. Hofstra JM, Wetzels JF. Introduction of a cyclophosphamide-based treatment strategy and the risk of ESRD in patients with idiopathic membranous nephropathy: a nationwide survey in the Netherlands. Nephrol Dial Transplant. 2008 Nov;23(11):3534-3538. doi:10.1093/ndt/gfn350.
9. Li LS, Liu ZH. Epidemiologic data of renal diseases from a single unit in China: analysis based on 13,519 renal biopsies. Kidney Int. 2004 Sep;66(3):920-923. doi:10.1111/j.1523-1755.2004.00837.x.
10. Dobronravov VA, Mayer DA, Berezhnaya OV, et al. Membranous nephropathy in a Russian population. Ter Arkh. 2017;89(6):21-29. doi:10.17116/terarkh201789621-29. (in Russian).
11. Hu R, Quan S, Wang Y, et al. Spectrum of biopsy proven renal diseases in Central China: a 10-year retrospective study based on 34,630 cases. Sci Rep. 2020 Jul 3;10(1):10994. doi:10.1038/s41598-020-67910-w.
12. Couser WG. Primary Membranous Nephropathy. Clin J Am Soc Nephrol. 2017 Jun 7;12(6):983-997. doi:10.2215/CJN.11761116.
13. Heymann W, Hackel DB, Harwood S, Wilson SG, Hunter JL. Production of nephrotic syndrome in rats by Freund's adjuvants and rat kidney suspensions. Proc Soc Exp Biol Med. 1959 Apr;100(4):660-664. doi:10.3181/00379727-100-24736.
14. Kerjaschki D, Farquhar MG. The pathogenic antigen of Heymann nephritis is a membrane glycoprotein of the renal proximal tubule brush border. Proc Natl Acad Sci USA. 1982 Sep;79(18):5557-5561. doi:10.1073/pnas.79.18.5557.
15. Beck LH Jr, Bonegio RG, Lambeau G, et al. M-type phospholipase A2 receptor as target antigen in idiopathic membranous nephropathy. N Engl J Med. 2009 Jul 2;361(1):11-21. doi:10.1056/NEJMoa0810457.
16. Tomas NM, Beck LH Jr, Meyer-Schwesinger C, et al. Thrombospondin type-1 domain-containing 7A in idiopathic membranous nephropathy. N Engl J Med. 2014 Dec 11;371(24):2277-2287. doi:10.1056/NEJMoa1409354.
17. Du Y, Li J, He F, et al. The diagnosis accuracy of PLA2R-AB in the diagnosis of idiopathic membranous nephropathy: a meta-analysis. PLoS One. 2014 Aug 19;9(8):e104936. doi:10.1371/journal.pone.0104936.
18. Akiyama S, Akiyama M, Imai E, Ozaki T, Matsuo S, Maruyama S. Prevalence of anti-phospholipase A2 receptor antibodies in Japanese patients with membranous nephropathy. Clin Exp Nephrol. 2015 Aug;19(4):653-660. doi:10.1007/s10157-014-1054-2.
19. Hofstra JM, Wetzels JF. Anti-PLA_2R antibodies in membranous nephropathy: ready for routine clinical practice? Neth J Med. 2012 Apr;70(3):109-113.
20. Iwakura T, Ohashi N, Kato A, Baba S, Yasuda H. Prevalence of Enhanced Granular Expression of Thrombospondin Type-1 Domain-Containing 7A in the Glomeruli of Japanese Patients with Idiopathic Membranous Nephropathy. PLoS One. 2015 Sep 22;10(9):e0138841. doi:10.1371/journal.pone.0138841.
21. Akiyama S, Imai E, Maruyama S. Immunology of membranous nephropathy. F1000Res. 2019 May 24;8:F1000 Faculty Rev-734. doi:10.12688/f1000research.17589.1.
22. Yamaguchi M, Ando M, Yamamoto R, et al. Patient age and the prognosis of idiopathic membranous nephropathy. PLoS One. 2014 Oct 20;9(10):e110376. doi:10.1371/journal.pone.0110376.
23. Wang Y, Wang GP, Li BM, Chen QK. Clinicopathological analysis of idiopathic membranous nephropathy in young adults. Genet Mol Res. 2015 May 4;14(2):4541-4548. doi:10.4238/2015.May.4.12.
24. Xu Z, Chen L, Xiang H, Zhang C, Xiong J. Advances in Pathogenesis of Idiopathic Membranous Nephropathy. Kidney Dis (Basel). 2020 Sep;6(5):330-345. doi:10.1159/000507704.
25. Xian L, Dong D, Luo J, et al. Expression of THSD7A in neoplasm tissues and its relationship with proteinuria. BMC Nephrol. 2019 Aug 23;20(1):332. doi:10.1186/s12882-019-1489-5.
26. Sethi S, Debiec H, Madden B, et al. Neural epidermal growth factor-like 1 protein (NELL-1) associated membranous nephropathy. Kidney Int. 2020 Jan;97(1):163-174. doi:10.1016/j.kint.2019.09.014.
27. Sethi S, Debiec H, Madden B, et al. Semaphorin 3B-associated membranous nephropathy is a distinct type of disease predominantly present in pediatric patients. Kidney Int. 2020 Nov;98(5):1253-1264. doi:10.1016/j.kint.2020.05.030.
28. Hayashi N, Beck LH Jr. Moore's law for membranous nephropathy. Kidney Int. 2020 Nov;98(5):1081-1084. doi:10.1016/j.kint.2020.06.020.
29. Caza TN, Hassen SI, Kuperman M, et al. Neural cell adhesion molecule 1 is a novel autoantigen in membranous lupus nephritis. Kidney Int. 2021 Jul;100(1):171-181. doi:10.1016/j.kint.2020.09.016.
30. Ahmad SB, Appel GB. Antigens, antibodies, and membranous nephropathy: a decade of progress. Kidney Int. 2020 Jan;97(1):29-31. doi:10.1016/j.kint.2019.10.009.
31. Stehlé T, Audard V, Ronco P, Debiec H. Phospholipase A2 receptor and sarcoidosis-associated membranous nephropathy. Nephrol Dial Transplant. 2015 Jun;30(6):1047-1050. doi:10.1093/ndt/gfv080.
32. Xie Q, Li Y, Xue J, et al. Renal phospholipase A2 receptor in hepatitis B virus-associated membranous nephropathy. Am J Nephrol. 2015;41(4-5):345-353. doi:10.1159/000431331.
33. Larsen CP, Messias NC, Silva FG, Messias E, Walker PD. Determination of primary versus secondary membranous glomerulopathy utilizing phospholipase A2 receptor staining in renal biopsies. Mod Pathol. 2013 May;26(5):709-715. doi:10.1038/modpathol.2012.207.
34. Debiec H, Guigonis V, Mougenot B, et al. Antenatal membranous glomerulonephritis due to anti-neutral endopeptidase antibodies. N Engl J Med. 2002 Jun 27;346(26):2053-2060. doi:10.1056/NEJMoa012895.

35. Polanco N, Gutiérrez E, Covarsí A, et al. Spontaneous remission of nephrotic syndrome in idiopathic membranous nephropathy. J Am Soc Nephrol. 2010 Apr;21(4):697-704. doi:10.1681/ASN.2009080861.

36. Hofstra JM, Beck LH Jr, Beck DM, Wetzels JF, Salant DJ. Anti-phospholipase A_2 receptor antibodies correlate with clinical status in idiopathic membranous nephropathy. Clin J Am Soc Nephrol. 2011 Jun;6(6):1286-1291. doi:10.2215/CJN.07210810.

37. Hoxha E, Harendza S, Pinnschmidt H, Panzer U, Stahl RA. PLA2R antibody levels and clinical outcome in patients with membranous nephropathy and non-nephrotic range proteinuria under treatment with inhibitors of the renin-angiotensin system. PLoS One. 2014 Oct 14;9(10):e110681. doi:10.1371/journal.pone.0110681.

38. Beck LH Jr, Salant DJ. Membranous nephropathy: recent travels and new roads ahead. Kidney Int. 2010 May;77(9):765-770. doi:10.1038/ki.2010.34.

39. Li SJ, Guo JZ, Zuo K, et al. Thromboembolic complications in membranous nephropathy patients with nephrotic syndrome-a prospective study. Thromb Res. 2012 Sep;130(3):501-505. doi:10.1016/j.thromres.2012.04.015.

40. Rankin AJ, McQuarrie EP, Fox JG, Geddes CC, MacKinnon B; Scottish Renal Biopsy Registry. Venous thromboembolism in primary nephrotic syndrome - is the risk high enough to justify prophylactic anticoagulation? Nephron. 2017;135(1):39-45. doi:10.1159/000448628.

41. Lee T, Biddle AK, Lionaki S, et al. Personalized prophylactic anticoagulation decision analysis in patients with membranous nephropathy. Kidney Int. 2014 Jun;85(6):1412-1420. doi:10.1038/ki.2013.476.

42. Leeaphorn N, Kue-A-Pai P, Thamcharoen N, Ungprasert P, Stokes MB, Knight EL. Prevalence of cancer in membranous nephropathy: a systematic review and meta-analysis of observational studies. Am J Nephrol. 2014;40(1):29-35. doi:10.1159/000364782.

43. Hoxha E, Wiech T, Stahl PR, et al. A Mechanism for Cancer-Associated Membranous Nephropathy. N Engl J Med. 2016 May 19;374(20):1995-1996. doi:10.1056/NEJMc1511702.

44. Timmermans SA, Ayalon R, van Paassen P, et al. Anti-phospholipase A2 receptor antibodies and malignancy in membranous nephropathy. Am J Kidney Dis. 2013 Dec;62(6):1223-1225. doi:10.1053/j.ajkd.2013.07.019.

45. Stahl PR, Hoxha E, Wiech T, Schr der C, Simon R, Stahl RA. THSD7A expression in human cancer. Genes Chromosomes Cancer. 2017 Apr;56(4):314-327. doi:10.1002/gcc.22440.

46. Cattran DC, Brenchley PE. Membranous nephropathy: integrating basic science into improved clinical management. Kidney Int. 2017 Mar;91(3):566-574. doi:10.1016/j.kint.2016.09.048.

47. Salant DJ, Cattran DC. Membranous nephropathy. In: Floege J, Johnson RJ, Feehally J, editors. Comprehensive Clinical Nephrology. 5th ed. Philadelphia, PA: Elsevier/Saunders; 2015. 239-251 pp.

48. Rovin BH, Adler SG, Barratt J, et al. Executive summary of the KDIGO 2021 Guideline for the Management of Glomerular Diseases. Kidney Int. 2021 Oct;100(4):753-779. doi:10.1016/j.kint.2021.05.015.

49. Seitz-Polski B, Payré C, Ambrosetti D, et al. Prediction of membranous nephropathy recurrence after transplantation by monitoring of anti-PLA2R1 (M-type phospholipase A2 receptor) autoantibodies: a case series of 15 patients. Nephrol Dial Transplant. 2014 Dec;29(12):2334-2342. doi:10.1093/ndt/gfu252.

50. Kattah A, Ayalon R, Beck LH Jr, et al. Anti-phospholipase A receptor antibodies in recurrent membranous nephropathy. Am J Transplant. 2015 May;15(5):1349-1359. doi:10.1111/ajt.13133.

51. Quintana LF, Blasco M, Seras M, et al. Antiphospholipase A2 Receptor Antibody Levels Predict the Risk of Posttransplantation Recurrence of Membranous Nephropathy. Transplantation. 2015 Aug;99(8):1709-1714. doi:10.1097/TP.0000000000000630.

52. Howman A, Chapman TL, Langdon MM, et al. Immunosuppression for progressive membranous nephropathy: a UK randomised controlled trial. Lancet. 2013 Mar 2;381(9868):744-751. doi:10.1016/S0140-6736(12)61566-9.

53. Cattran DC, Kim ED, Reich H, Hladunewich M, Kim SJ; Toronto Glomerulonephritis Registry group. Membranous Nephropathy: Quantifying Remission Duration on Outcome. J Am Soc Nephrol. 2017 Mar;28(3):995-1003. doi:10.1681/ASN.2015111262.

54. Troyanov S, Wall CA, Miller JA, Scholey JW, Cattran DC; Toronto Glomerulonephritis Registry Group. Idiopathic membranous nephropathy: definition and relevance of a partial remission. Kidney Int. 2004 Sep;66(3):1199-1205. doi:10.1111/j.1523-1755.2004.00873.x.

55. Thompson A, Cattran DC, Blank M, Nachman PH. Complete and partial remission as surrogate end points in membranous nephropathy. J Am Soc Nephrol. 2015 Dec;26(12):2930-2937. doi:10.1681/ASN.2015010091.

Received 26.03.2023
Revised 12.04.2023
Accepted 19.04.2023

Information about authors
Sharapov O.N., Republican Specialized Scientific Practical Medical Center of Nephrology and Kidney Transplantation, Tashkent Pediatric Medical Institute, Tashkent, Uzbekistan
Abdullaev Sh.S., Republican Specialized Scientific Practical Medical Center of Nephrology and Kidney Transplantation, Tashkent Pediatric Medical Institute, Tashkent, Uzbekistan

Conflicts of interests. Authors declare the absence of any conflicts of interests and own financial interest that might be construed to influence the results or interpretation of the manuscript.

Шарапов О.Н.[1,2], Абдуллаєв Ш.С.[1,2]
[1]Республіканський спеціалізований науково-практичний медичний центр нефрології та трансплантації нирки, м. Ташкент, Узбекистан
[2]Ташкентський педіатричний медичний інститут, м. Ташкент, Узбекистан

Мембранозна нефропатія: поточний стан проблеми

Резюме. Мембранозна нефропатія (МН) — автоімунне захворювання ниркових клубочків, одна з провідних причин нефротичного синдрому. Захворювання характеризується гетерогенними наслідками, приблизно в 30 % випадків прогресує до термінальної стадії ниркової недостатності. Вивчення механізму розвитку МН неухильно вдосконалюється завдяки ідентифікації автоантитіл до рецептора фосфоліпази А2 (PLA2R) у 2009 р. та тромбоспондинового домена 7А (THSD7A) на поверхні подоцитів у 2014 р. Приблизно 50–80 і 3–5 % первинних випадків МН пов'язані з антитілами або PLA2R, або THSD7A відповідно. Наявність цих автоантитіл використовується для діагностики МН. Рівні антитіл корелюють із тяжкістю захворювання і мають значення як біомаркери при моніторингу прогресування захворювання та відповіді на лікування.

Ключові слова: мембранозна нефропатія; нефротичний синдром; базальна мембрана клубочка; протеїнурія; антитіла; PLA2R; THSD7A