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Clinicopathological Features of Glomerulopathies and Their Prognostic Significance in Cancers of Different Sites

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ABSTRACT

This review analyzes international studies from the past five years that focus on glomerulopathies associated with malignant neoplasms of different sites. This study aimed to conduct a comparative analysis of histological and immunohistochemical features of morphological characteristics in glomerulopathies in cancer of different localizations, as well as identification of the specificity of the revealed features. Relevant publications were identified through *Scopus*, *PubMed*, and the *Cochrane Library*, with a search limited to studies published from 2019 to 2024. The review provides a detailed analysis of histological and immunohistochemical alterations in the glomerular apparatus in glomerulopathies associated with carcinomas of different sites. The identified morphological changes were assessed for their specificity. Particular attention is given to pathogenetic mechanisms that may underlie the development of glomerulopathies associated with carcinomas of different sites. A detailed analysis of the available literature demonstrates that understanding the histological and immunohistochemical features of glomerulopathies associated with malignant tumors contributes to improving diagnostic approaches for these conditions. Research in this area is of considerable importance, as it may offer new insights for the development of innovative strategies aimed at advancing prognosis and quality of life in patients with malignancies. Malignant cells are capable of expressing various substances, including proteins, that may contribute to the pathogenesis of glomerulopathies. Morphological evaluation of the glomerular apparatus enables the identification or exclusion of a pathogenetic association between the tumor and glomerulopathy, thereby allowing adjustment of the patient's treatment plan. The review also discusses potential pathophysiological mechanisms of tumor-associated glomerulopathies, contributing to more accurate interpretation of glomerular changes and enabling differentiation between specific and paraspecific morphological features. In summary, this review presents an analysis of the histological and immunohistochemical features of glomerulopathies associated with malignant tumors of different sites, highlighting the importance of an interdisciplinary approach to diagnosing this condition as one of the clinical manifestations of malignancy.

Keywords: glomerulopathies; malignant neoplasms; membranous nephropathy; review.

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Клинико-морфологические особенности гломерулопатий и их прогностическое значение при злокачественных опухолях различной локализации

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АННОТАЦИЯ

В обзоре литературы проанализированы результаты зарубежных исследований, которые посвящены гломерулопатиям при злокачественных новообразованиях различной локализации, полученных за последние 5 лет. Целью обзора является проведение сравнительного анализа гистологических и иммуногистохимических особенностей морфологических характеристик гломерулопатий при злокачественных новообразованиях различной локализации, а также определение специфичности выявленных особенностей. Данные исследования найдены с использованием баз данных Scopus, PubMed, Cochrane Library и ограничены датой публикации с 2019 по 2024 г. В работе выполнен детальный анализ гистологических и иммуногистохимических изменений гломерулярного аппарата при гломерулопатиях, ассоциированных с карциномами различной локализации. Выявленные изменения оценены для определения специфичности приведённых морфологических особенностей. Особое внимание уделено патогенетическим механизмам, предположительно объясняющим развитие гломерулопатий при карциномах различной локализации. Подробный анализ данных литературы по приведённой теме доказывает, что понимание гистологических и иммуногистохимических особенностей морфологических характеристик гломерулопатий при злокачественных новообразованиях способствует совершенствованию методов диагностики подобных состояний. Важность исследований в этой области невозможно переоценить, т. к. они могут предоставить новые данные для создания инновационных подходов, направленных на улучшение прогноза и качества жизни пациентов, страдающих онкологическими заболеваниями. Клетки злокачественной опухоли способны экспрессировать различные вещества, в том числе белки, которые могут приводить к развитию гломерулопатии. Анализ морфологических изменений гломерулярного аппарата позволяет выявить наличие или отсутствие патогенетической связи опухоли с гломерулопатией и скорректировать курс лечения больного. Кроме того, часть обзора посвящена разбору возможных патофизиологических механизмов развития гломерулопатий при злокачественных новообразованиях, что способствует более точной диагностике морфологических изменений клубочков, позволяет разграничить между собой специфические и параспецифические морфологические характеристики. Таким образом, обзор литературы представляет собой анализ гистологических и иммуногистохимических особенностей морфологических характеристик гломерулопатий при злокачественных новообразованиях различной локализации, с учётом значимости междисциплинарного подхода в диагностике данного состояния, как одного из клинических проявлений злокачественных опухолей.

Ключевые слова: гломерулопатии; злокачественные новообразования; мембранозная нефропатия; обзор.

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Onconephrology is the study of complex relationships between renal pathological conditions and cancer [1]. Significant progress has been made in understanding the mechanisms contributing to renal disease in patients with malignant neoplasms [2]. However, studies on this issue are few.

A clinical manifestation of malignancy is *glomerulopathy* (GP). A number of criteria indicate a link between GP and malignancy. First, GP and malignancy should occur simultaneously [2]. Second, clinical and histological remission of GP should be observed after malignancy remission. Third, recurrence of GP may occur after malignancy recurrence. Fourth, there should be an identified pathophysiological link between GP and malignancy, such as the same antigen expressed by tumor cells and glomerular structures. Several studies refer to GPs with the abovementioned characteristics as *paraneoplastic glomerulopathies* [3]. This term was first used by Galloway in 1922 [4]. However, such conditions are better classified as malignancy-associated GPs considering the insufficient study of the pathophysiological relationship between GP and paraneoplastic syndrome. Nevertheless, paraneoplastic syndrome may cause secondary GP in patients with malignancies.

GPs may be categorized based on localization of morphological changes in the glomeruli: intracapillary and extracapillary forms of GP [5, 6]. Intracapillary forms are characterized by localization of the inflammatory process in the *endothelium* and subendothelial layer of the basement membrane of the capillaries and mesangium and manifest clinically in the form of nephritic syndrome [7]. Conversely, malignancy-associated GPs are most commonly extracapillary forms, wherein inflammation involves the visceral and parietal sheets of the Bowman's capsule with clinical picture consistent with nephrotic syndrome [8]. Massive proteinuria, hypoproteinemia, hypoalbuminemia, hyperlipidemia, edema, etc., may be observed in patients with this syndrome [9, 10].

The most common malignancy-associated GP is *membranous nephropathy* (MN), which is the most common cause of nephrotic syndrome in adults [11–13]. Previous studies have reported a 7.9% overall incidence of malignancy in patients diagnosed with MN [12, 13]. The study of other malignancy-associated forms of GP remains equally crucial [14].

This study aimed to identify the histological and immunohistochemical features of the morphological characteristics of GP in malignancies of different sites and determine the specificity of these features through comparative analysis comprising the results of studies over the last five years.

Relevant research data were primarily analyzed using *Scopus*, *PubMed*, and *Cochrane Library*, with a search limited to studies published in 2019–2024. The search keywords were *malignancy-associated glomerulopathy*, *nephrotic syndrome*, *paraneoplastic syndrome*, *MN*, *PLA2R*, *THSD7A*, *NELL-1*, and *membranoproliferative glomerulonephritis*.

Variability in morphological changes in the renal glomerular apparatus in malignancy-associated GP emphasizes the difficulty in identifying a single mechanism underlying the development of such conditions [15]. The pathogenetic mechanisms of GP in malignancy are unclear; however, the association between GP and malignant neoplasms is known [15]. In a study by Liu et al. [9] involving 128 patients with malignant neoplasms, 90 patients suffered from nephrotic syndrome after tumor diagnosis. This indicates that the association between GP and malignancy is due to a complex interaction between carcinogenesis and renal pathology. The development of GP in patients with malignancy may be attributed to *tumor lysis syndrome* (TLS), which is a group of metabolic disorders caused by massive tumor cell lysis. TLS may result from a large tumor or anticancer therapy. The entry of tumor cell decay products into the bloodstream results in their deposition in the renal glomeruli and the development of GP [16].

Among the described malignancy-associated GPs, the most common are MN-associated with solid tumors and *minimal change disease* associated with Hodgkin's lymphoma. Additionally, cases of membranoproliferative glomerulonephritis, focal segmental glomerulosclerosis, and IgA nephropathy have been reported [15]. In the adult population, MN is the most common pathological form of nephrotic syndrome, which occurs in middle-aged and elderly people [17, 18]. It is characterized by deposition of electron-dense deposits containing Ig along the epithelial side of the *glomerular basement membrane* (GBM) [19]. Approximately 30% of MN cases are associated with secondary factors [20], of which autoimmune diseases are the most common, with most cases related to *systemic lupus erythematosus*. The second most common secondary etiology is malignancy (5%–20%) [17, 20]. The solid tumors commonly linked to MN are lung and gastric cancers [19]. Other MN-associated malignancies include renal cell carcinoma; prostate cancer; thymoma; and colorectal, pancreatic, esophageal, and hepatocellular carcinoma [21]. MN clinically manifests as nephrotic syndrome, which is a severe complication of the underlying disease in patients with malignancy [21]. Moreover, diagnosing the morphological variant of malignancy-associated MN is challenging because of the nonspecificity of morphological changes in the glomeruli and contraindications to nephrobiopsy because of the severe condition of patients [21].

Accurate diagnosis of the MN form is critical owing to different treatment approaches. Hormone therapy used to treat idiopathic MN (IMN) can prompt growth of various solid tumors, which are a common cause of MN [19]. Treatment of malignancy-associated MN focuses on surgical or chemotherapeutic eradication of the malignancy.

The main role in the pathogenesis of MN is attributed to the body's immune response against its own antigenic complexes located on the surface of podocytes [17]. In 80% of cases, the target antigens are phospholipase A2 receptor (*PLA2R*), thrombospondin type-1 domain-containing 7A (*THSD7A*), and neuroepidermal growth factor-like protein 1 (*NELL-1*) [22], whereas in the remaining cases, the target antigen remains unknown. Recent studies have identified new antigens that may be targeted by the body's immune response

in MN: semaphorin *3B* (*SEMA3B*) [22], exostosin 1/2 (*EXT1/EXT2*) [23], protocadherin-7/*FAT1* (*PCDH7/FAT1*) [24–26], and neural intercellular adhesion molecule 1 (*NCAM1*) [27]. The long-established theory of MN indicates that circulating antibodies against podocyte antigenic complexes enter the glomerular capillaries from the bloodstream and are deposited to the GBM [28–30]. Synthesis of new GBM components leads to antibody immersion in the GBM, followed by their appearance on the subepithelial side of the GBM, where the antibodies attach to antigenic complexes on podocytes. Some studies noted that in IMN cases, antibodies belong to the IgG4 subclass, and in secondary forms, IgG1, IgG2, and IgG3 exceed IgG4. The appearance of such circulating antibodies is due to various undertakings; thus, several secondary forms of MN are distinguished [28]. However, the direct cause of autoreactive antibody synthesis is immune response dysfunction, resulting in the body attacking its own antigens [29, 30]. Tumor cells in malignancy-associated MN have the ability to synthesize proteins similar to podocyte antigens. The body responds to tumor proteins with immune aggression, leading to cross-immune reaction with circulating antibodies, which are initially synthesized against foreign tumor proteins, attaching to the body's own antigenic complexes on the podocyte surface. *T-helper cells* play a crucial role in this process [17]. Formed immune complexes bind to GBM components and are immersed in it, because of active synthesis and GBM component accumulation between immune deposits. The antigen–antibody complex causes activation of the membrane attack complex of the complement system, which induces proteases and reactive oxygen species that partially dissolve immune complexes [29, 30].

The abovementioned concept of circulating antibodies that attach to podocyte antigens is confirmed by the discovery of phospholipase A2 receptor (*anti-PLA2R*) antibodies. Further studies [31–34] reported that the positive *anti-PLA2R* antibody rate in IMN patients from different countries was 57.1%–77.7%. Based on these data, it can be deduced that the detection of *anti-PLA2R* in the serum of patients may be considered a reliable diagnostic criterion for IMN [35]. However, several studies [36–38] reported cases of malignancy-associated MN wherein *anti-PLA2Rs* were also detected in the serum. IgG subtypes to *PLA2R* in the serum from patients with *PLA2R-positive* malignancy-associated MN were found to be similar to those in the serum from patients with IMN. This indicates that the pathogeneses of *PLA2R-positive* malignancy-associated MN and *PLA2R-positive* primary MN have common pathways [38]. Additionally, *PLA2R* is expressed by cells of various tumors, and its role in carcinogenesis is unclear [17]. Thus, the presence of *anti-PLA2R* in the serum of cancer patients does not rule out tumor-associated MN. The relationship between *anti-PLA2R* and malignancy-associated MN requires further investigation.

Antibodies to thrombospondin type-1 domain-containing 7A (*anti-THSD7A*) are circulating antibodies that can be found in the serum of patients with malignancy-associated MN. *THSD7A-positive* MN accounts for 1%–3% of all MN cases [39, 41]. In various studies of patients with malignancy-associated MN, the frequency of *anti-THSD7A* in serum ranged from 6% to 25% [39–41]. In recent years, studies on the expression of *THSD7A* by tumor cells have been conducted. *THSD7A* was relatively frequently observed in patients with colorectal, kidney, breast, and prostate cancers, and the transcription and protein levels of *THSD7A* were significantly upregulated in gastric cancer [42]. As previously mentioned, T-helper cells play a major role in the pathogenesis of malignancy-associated MN, triggering an immune response to tumor antigens. *THSD7A* may play a role in the pathogenesis of malignancy-associated MN involving T-helper cells [17]. However, studies confirming a link between *THSD7A-MN* and malignancy are lacking, and this issue remains to be explored.

Sethi et al. [43] detected *NELL-1* protein using laser microdissection and mass spectrometric analysis of renal biopsy specimens from *PLA2R-negative* patients with MN, which accounts for approximately 10% of all MN cases. However, in the same cohort, 11.7% of patients positive for *NELL-1* were found to have malignancy-associated MN. In another study, Caza et al. [44] reported that in 30% of patients with *NELL-1-positive* MN, the disease was associated with malignancy. However, in a study by Wang et al. [45], malignant tumors were not detected in any of the 15 patients with *NELL-1-positive* MN at the time of diagnosis. Such differences may be due to the different ethnicities of the patients [17]. Interestingly, in the studies by Caza [44] and Wang [45], serum antibodies were less frequently detected than positive immunohistochemical staining for *NELL-1*. In the first study, antibodies were found in 20 of 28 (71.4%) *NELL-1-positive* patients, whereas in the second study, only 2 of 15 patients with positive *NELL-1* staining were serum-positive for antibodies against *NELL-1*. Wang et al. indicated that the sensitivity of *NELL-1* immunohistochemical staining is considerably higher than that of serum antibody detection. Notably, *NELL-1* is expressed by various tumor cells, such as prostate and lung cancers [46]. Thus, the involvement of *NELL-1* in the pathogenesis of MN may have a similar mechanism to that of *THSD7A*, which is also expressed by cells from different tumors. However, the detailed pathophysiological mechanism of *NELL-1* involvement in the development of malignancy-associated MN remains controversial. Further studies on this issue are warranted.

Considering the previously described pathogenetic mechanisms, a literature review was performed, and studies that performed immunohistochemical staining of renal tissues to identify specific antigens presumably involved in the development of malignancy-associated MN were selected. In their study, Zhang et al. [38] conducted immunohistochemical staining of renal glomeruli and tumor tissue to detect *THSD7A* and immunofluorescence analysis to detect glomerular *PLA2R*, and the IgG subclass in the glomeruli was determined according to the method described by Zhang [47]. In addition to glomerular staining, serum antibodies to *PLA2R*

and *THSD7A* were identified using immunofluorescence techniques. The results of a study including 36 patients with malignancy-associated MN revealed that both *PLA2R-antigen* in the renal glomeruli and serum *anti-PLA2R* antibodies were detected in 12 (22%) patients. Additionally, two patients were positive for only one of the two criteria. In the other 22 (61%) patients, *PLA2R* in the glomeruli and *anti-PLA2R* in the serum were not detected. Among the 20 *PLA2R-negative* patients in whom the IgG subclass of the immune deposits in the glomeruli could be detected, IgG1 was found in 10 (50%) patients, IgG4 in 3 (15%), and both subclasses in 7 (35%). In the 13 *PLA2R-positive* patients in whom the IgG subclass of the immune deposits in the glomeruli could be determined, the IgG4 subclass was predominant. Furthermore, the pathomorphological features of glomerular alterations in the *PLA2R-positive* and *PLA2R-negative* groups were evaluated. In the *PLA2R-positive* patients, IgA, IgM, and C1q in the glomerular deposits were more frequently detected. No significant differences were observed regarding glomerulosclerosis and IgG and C3 staining intensity. Among the 14 *PLA2R-positive* patients, *THSD7A* in the renal glomeruli was detected in 1 patient (7.1%). In the *PLA2R-negative* group, *THSD7A* was observed in 2 of 22 (9.1%) patients. Tumor tissue was available for examination in 9 of 36 patients, and in 5 of the 9 patients, tumor cells were positive for *THSD7A*. In one patient with a *THSD7A-positive* tumor, *THSD7A* deposits were found in the glomeruli. *THSD7A* in the glomeruli was not detected in any of the patients with *THSD7A-negative* tumors [38].

In another study, Wang et al. identified the presence of *PLA2R*, *THSD7A*, and *NELL-1* antigens in the renal glomerular tissue by immunohistochemical staining using rabbit antibodies [46]. Moreover, serum antibody levels of *anti-PLA2R* by indirect immunofluorescence assay and *anti-THSD7A* and *anti-NELL-1* by indirect immunofluorescence were evaluated. Wang et al. presented the results of their study together with the other studies [48–50], as no significant differences were found between the baseline characteristics among all patients. Thus, the results from the studies in 40 patients with malignancy-associated MN were compared with those from the studies in 101 patients with IMN. The frequency of *PLA2R* detection in the kidney tubules of patients with IMN was significantly higher than that of those with MN-associated with malignant tumors (92.1% vs. 40.0%). However, the frequency of *THSD7A* detection in the kidney tubules of patients with MN with associated tumor (42.5%) was significantly higher than that in the tubules of those with IMN (2.0%). IgG subclass staining of renal tissue showed that the frequency of IgG4 positivity was significantly lower in patients with malignancy-associated MN than in those with IMN (59.3% vs. 90.1%), and the frequency of IgG2 positivity in these patients was significantly higher (36.0% vs. 16.5%). Positive staining for *NELL-1* in the glomeruli was observed in 4 (10%) patients with malignancy-associated MN. Specific staining of malignant neoplasm tissues for the detection of antigens involved in the development of MN was performed in 26 patients with available tumor samples. In 11 (42.3%) patients with *THSD7A-positive* tumors, the same antigen was detected in the renal glomeruli. Three (14.3%) patients had *NELL-1* expression in the renal and tumor tissues, one (4.8%) patient had *PLA2R* expression in the renal and tumor tissues, and one (4.8%) patient had *PLA2R* and *THSD7A* expressions in the renal tissue and only *THSD7A* expression in the tumor tissue.

The expression level of *PLA2R* in the renal glomeruli of patients with malignancy-associated MN was considerably lower than that of patients with IMN. However, in both mentioned studies, *PLA2R* was detected in the glomeruli of patients with malignancy-associated MN. This result indicates that *PLA2R* as a single indicator is not an appropriate criterion for the diagnosis of IMN. Further investigation of other target antigens in malignancy-associated MN is warranted. Combined detection of such antigens in conjunction with *PLA2R* may be key to the differential diagnosis of idiopathic and malignancy-associated MN.

The frequency of detection of *THSD7A* in the renal glomeruli of patients with malignancy-associated MN was significantly higher than that of patients with IMN. This finding supports the theory that *THSD7A*, as a tumor cell product, plays a role in the pathogenesis of MN involving T-helper cells [17].

In all the mentioned studies, the immune deposits found in the glomeruli of patients with malignancy-associated MN predominantly contained IgG1 and IgG2 subclasses. Moreover, in patients with IMN, IgG4 is the predominant subclass found in the glomerular immune deposits. The difference in IgG subclasses detected in IMN and malignancy-associated MN may be due to the different T-helper cells involved in the pathogenesis of these forms of MN. IgG1 and IgG2 are associated with Th1 and IgG4 with Th2 [51]. Primarily, Th1 cells are involved in the development of an immune response against tumor antigens, which explains the predominance of IgG1 and IgG2 subclasses in the glomerular immune deposits in this form of MN. However, in this pathogenetic mechanism, why the detection rate of antibodies against the abovementioned target podocyte antigens in serum is usually lower than the detection rate of the antigens in the glomeruli is unclear [44, 45]. This may be because of differences in the sensitivity of the antigen and antibody detection tests. Nevertheless, the fact that the actual pathogenetic mechanisms are more complex than is assumed should be considered; thus, a more thorough study is required.

Membranoproliferative glomerulonephritis (MPGN) is a group of diseases characterized by GBM thickening and mesangial cell proliferation. The modern classification of MPGN is based on ultrastructural, immunohistochemical, and pathogenetic features, and three types of MPGN are distinguished: type I, with subendothelial deposits; type II, with dense deposits inside the GBM (*dense deposit disease*); and type III, with subendothelial and subepithelial deposits. Data on the association between MPGN and malignancies are limited. Five articles [52–56] that reported cases of malignancy-associated

MPGN were selected and analyzed. The malignant tumors included MALT lymphoma [52], papillary thyroid carcinoma [53], gastric adenocarcinoma [54], colorectal carcinoma [55], and ductal carcinoma of the breast [56].

The following morphological changes were observed in the glomeruli of patients with malignancy-associated MPGN: light microscopy in all cases showed proliferation of mesangial cells and an increase in the mesangial matrix, with the glomeruli having a lobular appearance [52–56]. Methenamine silver staining revealed contouring of the glomerular capillary wall [54]. In various studies, electron microscopy revealed diffuse thickening of the GBM, with different localization of immune deposits [52–56]. In a study by Taira [56], immune deposits had predominantly subendothelial location. In studies by Sugihara and Pattanashetti [52, 53], immune complexes were found in both the subendothelial layer and mesangium. Moreover, in a study by Severova [55], immune deposits were noted in the subendothelial and subepithelial layers.

Thus, the identified morphological changes were not specific for malignancy-associated MPGN. Furthermore, the pathogenetic mechanisms of the association between MPGN and malignancy remain unclear. Immune complexes resulting from the body's immune response to tumor-secreted proteins may be involved in the development of malignancy-associated MPGN. The features of malignancy-associated MPGN are yet to be explored.

Focal segmental glomerulosclerosis (FSGS) is a form of GP characterized by sclerosis of separate glomeruli, involving a portion of the capillary loops in the affected glomerulus. FSGS is rarely associated with malignancies, among which renal cell carcinoma and thymoma are the most common, and cases of association of FSGS with lung, breast, and esophageal cancers have been described less frequently [57, 58]. According to research data, glomerular apparatus changes in malignancy-associated FSGS are nonspecific [57]. No studies have confirmed any pathophysiological link between FSGS and malignancy. However, the pathogenesis of the idiopathic form of FSGS is notably considered as one of the stages of *minimal change disease* (lipoid nephrosis), and lipoid nephrosis may be related to damage of the visceral sheet of the Bowman's capsule by cytokine-like circulating substances [59]. Thus, the production of cytokine-like substances by the tumor may lead to the development of FSGS. Further studies on this issue are warranted.

Minimal change disease is more commonly associated with Hodgkin's lymphoma. In addition, it has been reported to be associated with solid tumors such as lung cancer, colorectal cancer, renal cell carcinoma, and thymoma and rarely with pancreatic, prostate, bladder, breast, and ovarian cancers [60–62].

IgA nephropathy may be linked to renal cell carcinoma, thyroid cancer, and solid tumors of the respiratory tract, oral mucosa, and nasopharynx [63].

Thus, one of the main tasks of onconeuphrology is to study the relationship between GP and malignancy. The development of GP often complicates the course of the underlying malignancy and, in some cases, can be fatal. The timely diagnosis of GP in patients with primary cancer is challenging for several reasons. First, the severe condition of most patients with cancer makes it difficult to perform the required tests (e.g., renal biopsy) to identify the exact nature of the GP. Second, in patients with malignancy, most alterations detectable in the renal glomeruli are nonspecific. Hence, it is difficult to understand whether the patient's GP is a clinical manifestation of a tumor or the two are unrelated diseases, which largely determines further treatment.

Current research data on malignancy-associated GP are contradictory. The issues of morphological alterations in the glomeruli and pathogenetic mechanisms of the development of GP in cancers of different sites require further studies.

ADDITIONAL INFORMATION

Authors' contribution. D.L.V. — conceptualization, methodology, investigation, writing — review & editing, visualization; D.V.B. — conceptualization, validation, investigation, data curation, supervision, project administration; P.V.L. — software, formal analysis; A.R.M. — validation, investigation, visualization; Y.S.P. — formal analysis, resources. Thereby, all authors made a substantial contribution to the conception of the work, acquisition, analysis, interpretation of data for the work, drafting and revising the work, final approval of the version to be published and agree to be accountable for all aspects of the work.
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ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

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Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с проведенным исследованием и публикацией настоящей статьи.

СПИСОК ЛИТЕРАТУРЫ / REFERENCES

1. Bonilla M, Gudsoorkar P, Wanchoo R, et al. Onconephrology 2022: An Update. *Kidney360*. 2023;4(2):258–271. doi: 10.34067/KID.0001582022

2. Thet Z, Lam AK, Ranganathan D, et al. Critical evaluation of cancer risks in glomerular disease. *Transl Oncol*. 2022;19:101376. doi: 10.1016/j.tranon.2022.101376

3. Zhang X, Khurana A, Hirani S, et al. Paraneoplastic Glomerulonephropathy Associated With Renal Cell Carcinoma: A Descriptive Analysis of Published Reports. *Cureus*. 2023;15(3):e36928. doi: 10.7759/cureus.36928

4. Galloway J. Remarks ON HODGKIN'S DISEASE. *Br Med J*. 1922;2(3234):1201–1208.2. doi: 10.1136/bmj.2.3234.1201

5. Romagnani P, Kitching AR, Leung N, Anders HJ. The five types of glomerulonephritis classified by pathogenesis, activity and chronicity (GN-AC). *Nephrol Dial Transplant*. 2023;38(Supplement_2):ii3–ii10. doi: 10.1093/ndt/gfad067

6. Yang CK, Lee CY, Wang HS, et al. Glomerular disease classification and lesion identification by machine learning. *Biomed J*. 2022;45(4):675–685. doi: 10.1016/j.bj.2021.08.011

7. Lamba P, Nam KH, Contractor J, Kim A. Nephritic Syndrome. *Prim Care*. 2020;47(4):615–629. doi: 10.1016/j.pop.2020.08.003

8. Bharati J, Chander PN, Singhal PC. Parietal Epithelial Cell Behavior and Its Modulation by microRNA-193a. *Biomolecules*. 2023;13(2):266. doi: 10.3390/biom13020266

9. Liu S, Wan Y, Hu Z, et al. Nephrotic syndrome associated with solid malignancies: a systematic review. *BMC Nephrol*. 2024;25(1):215. doi: 10.1186/s12882-024-03632-9

10. Mizdrak M, Smajic B, Mizdrak I, et al. Endocrine Disorders in Nephrotic Syndrome-A Comprehensive Review. *Biomedicines*. 2024;12(8):1860. doi: 10.3390/biomedicines12081860

11. Yu X, Fan Z, Chen W, Wang Z. Lung cancer with nephrotic syndrome as a paraneoplastic syndrome: A case report. *Mol Clin Oncol*. 2020;13(6):86. doi: 10.3892/mco.2020.2156

12. Kaira K, Amano H, Imai H, et al. Membranous Nephropathy as a Paraneoplastic Syndrome in Cancer of Unknown Primary. *In Vivo*. 2024;38(3):1503–1508. doi: 10.21873/invivo.13598

13. Wang L, Wang J, Xu A, et al. Future embracing: exosomes driving a revolutionary approach to the diagnosis and treatment of idiopathic membranous nephropathy. *J Nanobiotechnology*. 2024;22(1):472. doi: 10.1186/s12951-024-02633-y

14. Garkusha TA, Stolyarevich ES, Khorzhevsky VA, Ivliev SV. Glomerulopathy in kidney neoplasms: frequency of occurrence, structure of morbidity. *Russian Journal of Archive of Pathology*. 2023;85(2):21–26. doi: 10.17116/patol20238502121

15. Rosner MH, Jhaveri KD, McMahon BA, Perazella MA. Onconephrology: The intersections between the kidney and cancer. *CA Cancer J Clin*. 2021;71(1):47–77. doi: 10.3322/caac.21636

16. Arnaud M, Loiselle M, Vaganay C, et al. Tumor Lysis Syndrome and AKI: Beyond Crystal Mechanisms. *J Am Soc Nephrol*. 2022;33(6):1154–1171. doi: 10.1681/ASN.2021070997

17. Hu X, Wang G, Cheng H. Specific antigens in malignancy-associated membranous nephropathy. *Front Med*. 2024;11:1368457. doi: 10.3389/fmed.2024.1368457

18. Baker LW, Jimenez-Lopez J, Geiger XJ, Aslam N. Malignancy-Associated Membranous Nephropathy with Positive Anti-PLA2R Autoantibodies: Coincidence or Connection. *Case Rep Nephrol Dial*. 2021;11(3):334–339. doi: 10.1159/000520399

19. Hoxha E, Reinhard L, Stahl RAK. Membranous nephropathy: new pathogenic mechanisms and their clinical implications. *Nat Rev Nephrol*. 2022;18(7):466–478. doi: 10.1038/s41581-022-00564-1

20. Xu Q, Li J, Yang Y, et al. Prevalence and prognosis of malignancy in THSD7A-associated membranous nephropathy: a systematic literature review and clinical case study. *Ren Fail*. 2024;46(1):2355353. doi: 10.1080/0886022X.2024.2355353

21. Plaisier E, Ronco P. Screening for Cancer in Patients with Glomerular Diseases. *Clin J Am Soc Nephrol*. 2020;15(6):886–888. doi: 10.2215/CJN.09000819

22. 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;98(5):1253–1264. doi: 10.1016/j.kint.2020.05.030

23. Efe O, So PNH, Anandh U, et al. An Updated Review of Membranous Nephropathy. *Indian J Nephrol*. 2024;34(2):105–118. doi: 10.25259/ijn_317_23

24. Fu N, Yuan S, Yang G, et al. Concurrent glomerular PCDH7 deposits in PLA2R-associated membranous nephropathy. *CEN Case Rep*. 2024;13(4):297–301. doi: 10.1007/s13730-023-00842-2

25. Sethi S, Madden B, Debiec H, et al. Protocadherin 7-Associated Membranous Nephropathy. *J Am Soc Nephrol*. 2021;32(5):1249–1261. doi: 10.1681/ASN.2020081165

26. Sethi S, Madden B, Casal Moura M, et al. Hematopoietic Stem Cell Transplant-Membranous Nephropathy Is Associated with Protocadherin FAT1. *J Am Soc Nephrol*. 2022;33(5):1033–1044. doi: 10.1681/ASN.2021111488

27. Caza TN, Hassen SI, Kuperman M, et al. Neural cell adhesion molecule 1 is a novel autoantigen in membranous lupus nephritis. *Kidney Int*. 2021;100(1):171–181. doi: 10.1016/j.kint.2020.09.016

28. Moroni G, Ponticelli C. Secondary Membranous Nephropathy. A Narrative Review. *Front Med*. 2020;7:611317. doi: 10.3389/fmed.2020.611317

29. Dantas M, Silva LBB, Pontes BTM, et al. Membranous nephropathy. *J Bras Nefrol*. 2023;45(2):229–243. doi: 10.1590/2175-8239-JBN-2023-0046en

30. Ronco P, Debiec H. Molecular Pathogenesis of Membranous Nephropathy. *Annu Rev Pathol*. 2020;15:287–313. doi: 10.1146/annurev-pathol-020117-043811

31. Gu Y, Xu H, Tang D. Mechanisms of Primary Membranous Nephropathy. *Biomolecules*. 2021;11(4):513. doi: 10.3390/biom11040513

32. McDonnell T, Wu HHL, Sinha S, Chinnadurai R. The Role of PLA2R in Primary Membranous Nephropathy: Do We Still Need a Kidney Biopsy? *Genes*. 2023;14(7):1343. doi: 10.3390/genes14071343

33. Ragy O, Rautemaa V, Smith A, et al. Can use of the serum anti-PLA2R antibody negate the need for a renal biopsy in primary membranous nephropathy? *PLoS One*. 2023;18(2):e0281726. doi: 10.1371/journal.pone.0281726

34. Kaya B, Paydas S, Balal M, et al. Renal expression of PLA2R, THSD7A, and IgG4 in patients with membranous nephropathy and correlation with clinical findings. *Int J Clin Pract*. 2021;75(4):e13855. doi: 10.1111/ijcp.13855

35. Kukuy OL, Cohen R, Gilburd B, et al. The Prognostic Value of Anti-PLA2R Antibodies Levels in Primary Membranous Nephropathy. *Int J Mol Sci*. 2023;24(10):9051. doi: 10.3390/ijms24109051

36. Mathew D, Gupta S, Ashman N. A case report of breast cancer and membranous nephropathy with positive anti phospholipase

A2 receptor antibodies. *BMC Nephrol*. 2021;22(1):324. doi: 10.1186/s12882-021-02511-x

37. Bobart SA, Han H, Tehranian S, et al. Noninvasive Diagnosis of PLA2R-Associated Membranous Nephropathy: A Validation Study. *Clin J Am Soc Nephrol*. 2021;16(12):1833–1839. doi: 10.2215/CJN.05480421

38. Zhang C, Zhang M, Chen D, et al. Features of phospholipase A2 receptor and thrombospondin type-1 domain-containing 7A in malignancy-associated membranous nephropathy. *J Clin Pathol*. 2019;72(10):705–711. doi: 10.1136/jclinpath-2019-205852

39. Juarez A, Galindo L, Ragunathan A, Gondal M. Thrombospondin Type 1 Domain-Containing 7A (THSD7A)-Associated Membranous Nephropathy Leading to Metastatic Neuroendocrine Carcinoma. *Cureus*. 2023;15(2):e35277. doi: 10.7759/cureus.35277

40. Tesar V, Hruskova Z. Autoantibodies in the Diagnosis, Monitoring, and Treatment of Membranous Nephropathy. *Front Immunol*. 2021;12:593288. doi: 10.3389/fimmu.2021.593288

41. Ren S, Wu C, Zhang Y, et al. An update on clinical significance of use of THSD7A in diagnosing idiopathic membranous nephropathy: a systematic review and meta-analysis of THSD7A in IMN. *Ren Fail*. 2018;40(1):306–313. doi: 10.1080/0886022X.2018.1456457

42. Shen K, Chen B, Yang L, Gao W. Integrated analysis of single-cell and bulk RNA-sequencing data reveals the prognostic value and molecular function of THSD7A in gastric cancer. *Aging*. 2023;15(21):11940–11969. doi: 10.18632/aging.205158

43. Sethi S, Debiec H, Madden B, et al. Neural epidermal growth factor-like 1 protein (NELL-1) associated membranous nephropathy. *Kidney Int*. 2020;97(1):163–174. doi: 10.1016/j.kint.2019.09.014

44. Caza TN, Hassen SI, Dvanajscak Z, et al. NELL1 is a target antigen in malignancy-associated membranous nephropathy. *Kidney Int*. 2021;99(4):967–976. doi: 10.1016/j.kint.2020.07.039

45. Wang G, Sun L, Dong H, et al. Neural Epidermal Growth Factor-Like 1 Protein-Positive Membranous Nephropathy in Chinese Patients. *Clin J Am Soc Nephrol*. 2021;16(5):727–735. doi: 10.2215/CJN.11860720

46. Wang G, Hu X, Ye N, et al. Analysis of Clinicopathological Characteristics of Malignancy Patients with Membranous Nephropathy and Literature Review. *Cancer Manag Res*. 2024;16:677–689. doi: 10.2147/CMAR.S465211

47. Qin HZ, Zhang MC, Le WB, et al. Combined Assessment of Phospholipase A2 Receptor Autoantibodies and Glomerular Deposits in Membranous Nephropathy. *J Am Soc Nephrol*. 2016;27(10):3195–3203. doi: 10.1681/ASN.2015080953

48. Yasuda I, Tokuyama H, Hashiguchi A, et al. Malignancy-associated membranous nephropathy with PLA2R double-positive for glomeruli and carcinoma. *CEN Case Rep*. 2021;10(2):281–286. doi: 10.1007/s13730-020-00556-9

49. Matsumoto A, Matsui I, Mano K, et al. Recurrent membranous nephropathy with a possible alteration in the etiology: a case report. *BMC Nephrol*. 2021;22(1):253. doi: 10.1186/s12882-021-02457-0

50. Chen M, Zhang L, Zhong W, et al. Case Report: THSD7A-Positive Membranous Nephropathy Caused by Tislelizumab in a Lung Cancer Patient. *Front Immunol*. 2021;12:619147. doi: 10.3389/fimmu.2021.619147

51. Ohtani H, Wakui H, Komatsuda A, et al. Distribution of glomerular IgG subclass deposits in malignancy-associated membranous nephropathy. *Nephrol Dial Transplant*. 2004;19(3):574–9. doi: 10.1093/ndt/gfg616

52. Sugihara A, Ureshino H, Yamasaki M, et al. Type II Cryoglobulinemic Membranoproliferative Glomerulonephritis Caused by Mucosa-associated Lymphoid Tissue Lymphoma. *Intern Med*. 2023;62(13):1983–1988. doi: 10.2169/internalmedicine.0756-22

53. Pattanashetti N, Kapatia G, Nada R, et al. Association of Membranoproliferative Glomerulonephritis with Papillary Carcinoma Thyroid. *Indian J Nephrol*. 2019;29(5):368–369. doi: 10.4103/ijn.IJN_215_18

54. Kakeshita K, Yamazaki H, Imamura T, et al. Cryofibrinogen-associated glomerulonephritis accompanied by advanced gastric cancer. *CEN Case Rep*. 2021;10(4):527–536. doi: 10.1007/s13730-021-00602-0

55. Severova G, Karanfilovski V, Naunovska L, et al. Association Between Membranoproliferative Glomerulonephritis and Colorectal Cancer – A Case Report. *Pril (Makedon Akad Nauk Umet Odd Med Nauki)*. 2024;45(2):31–36. doi: 10.2478/prilozi-2024-0013

56. Taira S, Kawagoe M, Anzai H, et al. Immunoglobulin A-dominant membranoproliferative glomerulonephritis-like pattern of injury as a possible paraneoplastic nephropathy in a breast cancer patient. *CEN Case Rep*. 2024. doi: 10.1007/s13730-024-00936-5

57. Dabrowski D, Ozluk E, Barbeito S, Wei EX. Focal Segmental Glomerulosclerosis Preceding Type 2 Papillary Renal Cell Carcinoma. *Case Rep Pathol*. 2020;2020:8811905. doi: 10.1155/2020/8811905

58. Zhou J, Yang Z, Yang CS, Lin H. Paraneoplastic focal segmental glomerulosclerosis associated with gastrointestinal stromal tumor with cutaneous metastasis: A case report. *World J Clin Cases*. 2021;9(27):8120–8126. doi: 10.12998/wjcc.v9.i27.8120

59. Gupta P, Gupta RK. *Pathology of Glomerular Diseases. Atlas of Clinical Case Studies*. Springer; 2022. doi: 10.1007/978-981-19-1430-0

60. Masuda S, Koizumi K, Moriya H, et al. Secondary Minimal Change Disease Due to Pancreatic Cancer Improved by Chemotherapy. *Intern Med*. 2021;60(2):251–257. doi: 10.2169/internalmedicine.5499-20

61. Cai X, Wu Y, Wan Q, Zhang X. Minimal change disease associated with thyroid cancer: a case report. *Front Med*. 2023;10:1132259. doi: 10.3389/fmed.2023.1132259

62. Nakano Y, Yoshida M, Muraki N, et al. Prostate Cancer Associated with Minimal Change Disease: A Case Report. *Glomerular Dis*. 2022;2(3):145–150. doi: 10.1159/000525040

63. Mei Z, Li F, Chen R, et al. Causal associations between thyroid cancer and IgA nephropathy: a Mendelian randomization study. *BMC Genomics*. 2023;24(1):525. doi: 10.1186/s12864-023-09633-6

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