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Н.В. Фомина[1, 2], Е.В. Уткина*[2]

[1] — ГАУЗ Кемеровская областная клиническая больница им. С.В. Беляева, Кемерово, Россия
[2] — Кемеровский государственный медицинский университет Минздрава России, Кемерово, Россия

МОНОКЛОНАЛЬНАЯ ГАММАПАТИЯ РЕНАЛЬНОГО ЗНАЧЕНИЯ: МОРФОЛОГИЧЕСКИЕ ВАРИАНТЫ ПОРАЖЕНИЯ

N.V. Fomina[1,2], E.V. Utkina*[2]

[1] — Kemerovo Regional Clinical Hospital named after S.V. Belyaev, Kemerovo, Russia
[2] — Kemerovo State Medical University of the Ministry of Health of Russia, Kemerovo, Russia

Monoclonal Gammapathy of Renal Significance: Morphological Variants of Lesion

Резюме

В статье рассматривается понятие моноклональная гаммапатия ренального значения, которое объединяет различные почечные заболевания, вызванные отложением моноклонального иммуноглобулина и/или их компонентов в клубочках и тубулоинтерстиции. Данная нозологическая группа была выделена из группы моноклональная гаммапатия неопределенного значения (в 2012 году). Представлены данные по изучению морфологического поражения почек, ассоциированного с моноклональной гаммапатией ренального значения. Спектр почечных заболеваний при моноклональной гаммапатии ренального значения разнообразен, и его классификация основана на локализации почечных поражений в клубочках, канальцах, интерстиции сосудов и стромы, а также особенностью отложения иммуноглобулинов (организованные и неорганизованные). Биопсия почки показана в большинстве случаев для определения локализации поражения, оценки его тяжести и прогноза выживаемости для пациента. Диагностика требует интеграции морфологических изменений с помощью световой микроскопии, иммунофлуоресценции, электронной микроскопии, а в некоторых случаях применяют окрашивание моноклонального белка на изотипы Ig (окраска гематоксилином/эозином, реакция Шиффа (PAS-реакция), серебрение по Джонсу, окраска по конго-рот, трихромальная окраска по Массону). Ранняя диагностика и своевременное назначение гематологом и/или гематоонкологом клон-ориентированной терапии позволяет остановить прогрессирование злокачественного процесса и снижения функции почек. В свою очередь, нефролог, взаимодействуя с гематологом и/или гематоонкологом, ведет наблюдение за пациентом.

Ключевые слова: *моноклональная гаммапатия неопределенного значения, моноклональная гаммапатия ренального значения, моноклональный белок, нефробиопсия*

Конфликт интересов

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Abstract

The article discusses the concept of monoclonal renal gammopathy, which combines various renal diseases caused by the deposition of monoclonal immunoglobulin and / or their components in the glomeruli and tubulointerstitium. This nosological group was identified within the group

*Контакты: Екатерина Владимировна Уткина, e-mail: goll1997.2011@mail.ru
*Contacts: Ekaterina V. Utkina, e-mail: goll1997.2011@mail.ru
ORCID ID: https://orcid.org/0000-0002-2000-3562

of monoclonal gammopathies of undetermined significance (in 2012). The data on the study of morphological kidney damage associated with monoclonal renal gammopathy are presented. The spectrum of renal diseases in monoclonal renal gammopathy is diverse, and its classification is based on the localization of renal lesions in the glomeruli, tubules, vascular interstitium and stroma, as well as the peculiarity of the deposition of immunoglobulins (organized and unorganized). Kidney biopsy is required in most cases to locate the lesion, assess its severity, and predict patient survival. Diagnostics requires the integration of morphological changes using light microscopy, immunofluorescence, electron microscopy, and in some cases, staining of monoclonal protein for Ig isotypes is used (staining with hematoxylin / eosin, Schiff stain (PAS reaction), Jones stain, Congo Red stain, Masson's trichromal stain). Early diagnosis and timely prescription of clone-oriented therapy by a hematologist and / or a hemato-oncologist can stop the progression of the malignant process and kidney malfunction. A nephrologist should monitor the patient, interacting with the hematologist.

Key words: *gammopathies of undetermined significance, monoclonal gammopathy of renal significance, monoclonal protein, nephrobiopsy, light microscopy, immunofluorescence microscopy, electron microscopy*

Conflict of interests

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AH — heavy chains, AHL — light and heavy chains, AL — light chains, C3GP — C3-glomerulopathy associated with monoclonal gammopathy, CKD — chronic kidney disease, CSH — crystal storing histiocytosis, GBM — glomerular basement membrane, HCDD — heavy chain deposition on disease, Ig — immunoglobulin, LCDD — light chain deposition on disease, LCPT — light-chain proximal tubulopathy, LHCDD — light and heavy chain deposition on disease, MGRS — monoclonal gammopathy of renal significance, MGUS — monoclonal gammopathy of undetermined significance, MIDD — monoclonal immunoglobulin deposition disease, MM — multiple myeloma, RRT — renal replacement therapy, TMA — thrombotic microangiopathy associated with monoclonal gammopathy, PGNMID — proliferative glomerulonephritis with monoclonal immunoglobulin deposits, TBM — tubular basement membrane

Introduction

Monoclonal gammopathy of undetermined significance (MGUS) includes a number of diseases resulting from the malfunction of B-lymphocytes, leading to persistent pathological secretions of one clone of immunoglobulins or their constituent chains [1–7]. The term "monoclonal gammopathy of undetermined significance" (MGUS) was first used by R. Kyle et al. in 1978. MGUS is an asymptomatic pre-malignant clonal plasma cell proliferative disease. In some patients, this disorder remains benign for a long time; it is a precursor to multiple myeloma (MM) and other B-lymphocytic tumors. In 40% of patients with MGUS, the disease is benign for a long time; 50% of patients at different times have malignant progression; and 10% of patients develop diseases of a non-tumor nature due to the tissue and toxic effect of M-protein. Therefore, upon detection of paraproteinemia, it is hard to say whether or not it will transform into hemoblastosis over time [1–8]. Among other terms previously used to describe MGUS in practical medicine were idiopathic, non-myelomatous, discrete, cryptogenic and rudimentary monoclonal gammopathy, disimmunoglobulinemia, idiopathic paraproteinemia and asymptomatic paraimmunoglobulinemia [6, 7]. Until 2012, the term MGUS was widely used in the medical literature. N. Leung et al. found that some patients with MGUS may have clinical and morphological damage to the renal parenchyma with M-component. Following this discovery, the International Kidney and Monoclonal Gammopathy Research Group (IKMG) proposed a new nosological group in modern nephrology and hematology: monoclonal gammopathy of renal significance (MGRS). The introduction of this term made it possible to differentiate the concept of MGUS and bring a number of clinical cases out of the "undetermined" group [1–8].

MGRS suggests a pathological condition with the characteristic features of the proliferation of a clone of B-cells or plasma cells producing nephrotoxic monoclonal immunoglobulin or its fragments (only a light chain and/or only a heavy chain) [9]. According to the diagnostic parameters, this group of patients cannot be classified as patients with multiple myeloma since this group is characterized by average plasma cells of the bone marrow (BM) — 2.2%, and M-protein level — 1.1 g/l [2–5]. A clone is a population of cells that arose from a single progenitor cell. It inherits all properties, including the ability to actively produce a monoclonal paraprotein (M-protein, monoclonal protein) or its part (only a light chain or only a heavy chain). The result of the effect of monoclonal protein on renal parenchyma is the steady progression of renal dysfunction up to the loss of organ function and a deterioration in the patient's life prognosis [1-9]. Kidney diseases associated with MGRS vary, and their number continues to rise. Therefore, the problem of MGRS remains extremely relevant for physicians of any specialty and is partly due to the lack of knowledge among professionals. A multidisciplinary approach is required to solve this

problem since this problem is most often between two specialties — hematology and nephrology [1–5].

Epidemiology

It has been proven that MGUS is detected in 4.2% in a group of people aged over 50; 5.3% — over 70, and up to 8% in men over 80. MGUS prevalence in African Americans is two to three times higher than in white people from the same population [7, 10]. The incidence of chronic kidney disease (CKD) also increases after the age of 60 [7, 11, 12]. Due to the rising age of the population, CKD development is based on progressive chronic diseases with the formation of nephrosclerosis (diabetes mellitus, arterial hypertension, and others). MGUS gradually results in CKD. Consequently, the same patient may have both manifestations of MGUS and CKD that are not associated pathogenetically [7].

Renal damage due to monoclonal paraprotein is a rare abnormality in the structure of kidney diseases. The prevalence of kidney pathology associated with any variant of monoclonal gammopathy is 7.5% among all patients who underwent diagnostic nephrobiopsy. MGRS was found in only 4% [2–5, 7]. Considering that this disease can only be confirmed via morphological verification of the diagnosis, MGRS is an orphan disease (10.2 cases per 100 thousand adults per year) [7].

Mechanisms and Structure of Kidney Damage in Monoclonal Renal Gammopathy

Pathogenetic mechanisms of the effect of paraprotein on the renal parenchyma vary and have not yet been fully studied. The pathogenesis of this process is due to the structural features and changes in the physicochemical properties of the paraprotein molecule itself and the action of abnormal monoclonal immunoglobulins or its fragments (only the light chain and/or only the heavy chain) (Fig. 1) [1, 4–5, 7].

The range of kidney damage associated with monoclonal gammopathy of renal significance is wide enough to include damage to different nephron sites: glomerulus, tubules; interstitium and vessels. Therefore, there is a variety of clinical manifestations of MGRS in the form of isolated syndrome or combination (arterial hypertension, nephrotic, etc.) [1–7]. Without additional examination methods, clinical and morphological damage in MGRS is difficult to distinguish from other renal pathologies not associated with monoclonal gammopathy. The type of kidney damage is determined by the innate structural characteristics and physicochemical properties of monoclonal immunoglobulin and not by the characteristics of the clone that produces it [1–7].

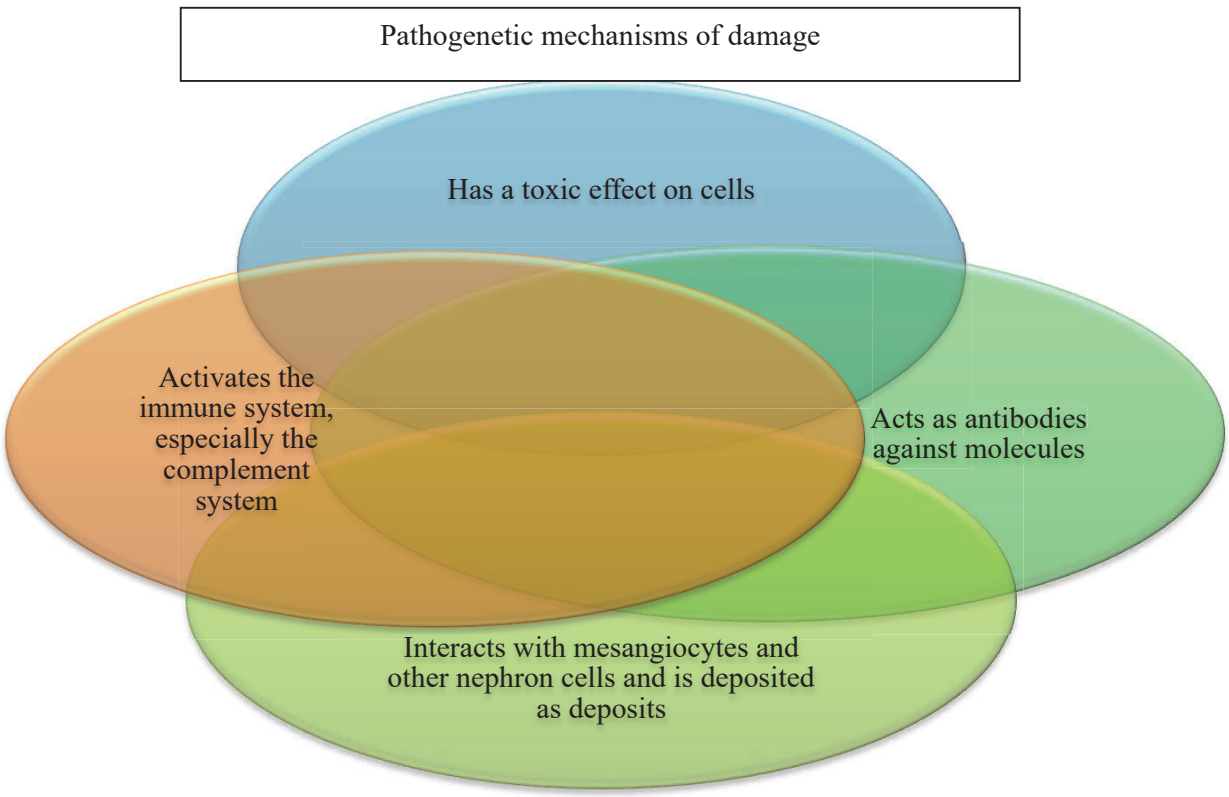

Figure 1. *Pathogenetic mechanisms of damage to the renal parenchyma by paraprotein*

Diagnosis of Monoclonal Gammopathy of Renal Significance (MGRS)

The establishment of the diagnosis of MGRS requires determining the specificity of kidney damage arising from the action of the monoclonal protein produced by the clone. Considering the significant variety of possible kidney damage, the morphological examination of renal tissue remains the main diagnostic method for MGRS (tab. 1) [1, 4, 6, 7].

The morphological analysis result emphasizes the specific features of the MGRS lesion in each case, and also provides information regarding the renal prognosis [1, 4, 6, 7].

In 2017, the International Kidney and Monoclonal Gammopathy Research Group (IKMG) introduced a new classification for MGRS-associated kidney damage based on morphological results of studies (light microscopy, immunofluorescence studies with a full set of antibodies and electron microscopy). Kidney deposits were

Table 1. *Morphological diagnosis of monoclonal gammopathy of renal significance (MGRS)*

Light-optical research
Application of the following stains: · Hematoxylin/eosin · Schiff (PAS reaction) · Jones stain · Congo Red · Masson's trichrome stain
Immunofluorescence study
· Detection of deposits in the kidney parenchyma monoclonal immunoglobulin molecules (panel of antibodies to IgA, IgM, IgG (typing IgG), IgD, λ и κ chains, C3, C1q). · For the purpose of differential diagnosis of fibrillary glomerulonephritis which deposits may be congophilic, a DNAJB9 study is used. DNAJB9 is a protein of the chaperone family specific for this type.
Microscopic examination (ultrastructural)
Allows to assess the degree of damage and the nature of the deposits formed by the monoclonal protein (organized / non-organized).

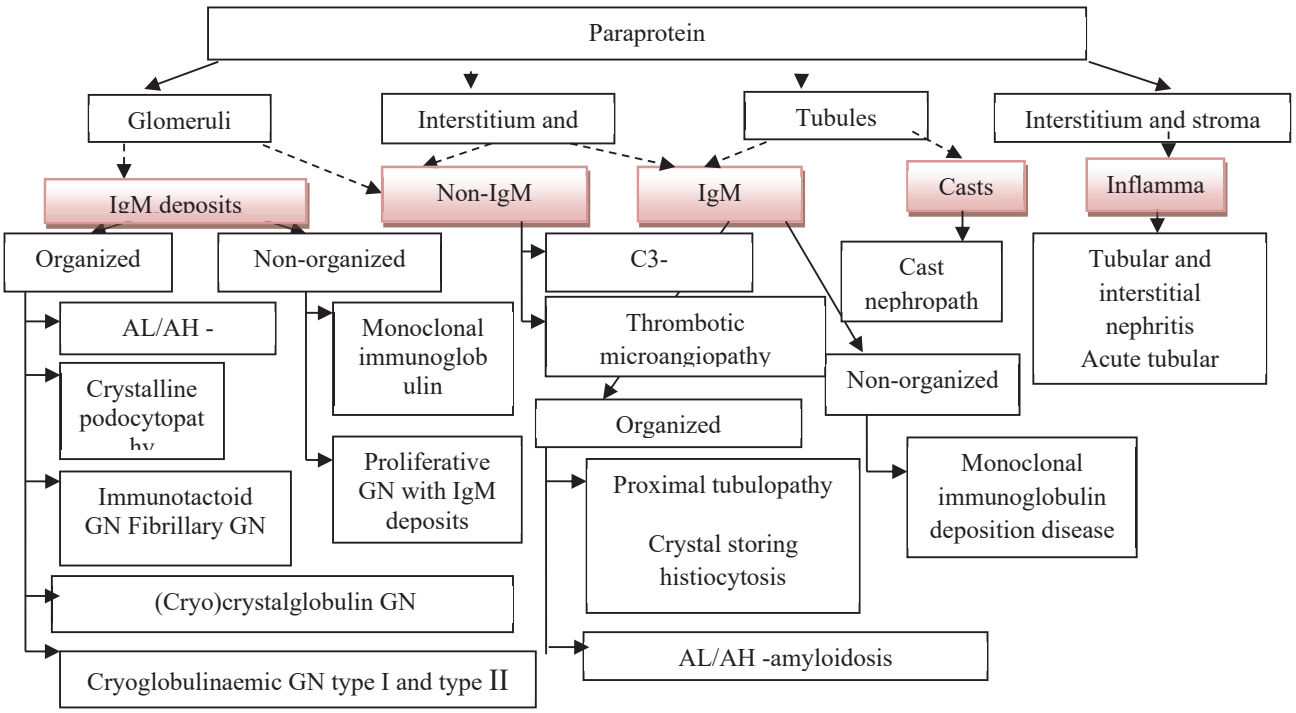

Figure 2. *Pathological variants of renal damage due to paraprotein (adapted from Smirnov A.V., Afanasyev B.V., Poddubnaya I.V. et al., 2020)*

originally classified into the following categories: organized, unorganized and non-immunoglobulin gammopathies [4, 6, 7, 13, 14]. Two additional subcategories were added to the 2017 classification [13]. The subcategory of thrombotic microangiopathy (TMA) and the subcategory of pathological deposits that are ultrastructurally similar to monoclonal gammopathies, but are not always them, have been added to the category of non-immunoglobulin gammopathies (Fig. 2) [7, 14].

Damage with Organized IgM Deposits

Organized deposits of monoclonal immunoglobulins are divided into fibrillar (in amyloidosis), microtubular (in cryoglobulinemic and immunotactoid nephritis), crystalline and/or inclusive forms in proximal light chain tubulopathy, with or without Fanconi syndrome, and with CHS [4, 6, 7]. This pathology is detected via nephrobiopsy. The leading diagnostic method is light, immunofluorescence, and electron microscopy. The primary method for verifying the structure and type of organized deposition is staining monoclonal immunoglobulin and/or its fragments in different ways: hematoxylin/eosin, Schiff reaction (PAS reaction), Jones stain, Congo-red stain, Masson's trichrome stain [4, 6, 7].

Fibrillar Forms of Monoclonal Immunoglobulin Deposition

Fibrillar forms include amyloidosis, which includes subtypes with the deposition of light chain (AL), heavy chain (AH), and heavy and light chains (AHL). For a long time, this condition remained the only one in the group of fibrillar deposits. However, monoclonal fibrillary glomerulonephritis was recently discovered [7, 15–19].

Amyloid fibrils are more likely to affect glomeruli and blood vessels as well as the interstitium (in 60% of patients). Intratubular cytoplasmic amyloidosis is rare [20]. In most cases, M-protein-associated amyloidosis develops from fragments of monoclonal light chains (AL) that are more often of the λ isotype than the κ isotype, and in rare cases — from fragments of intact immunoglobulin (Ig) or only heavy chains (AH) [6, 7, 20]. During light microscopy, amyloid fibrils look like continuous unbranched and randomly arranged deposits with a diameter of 7–12 nm. Staining with hematoxylin/eosin reveals pale eosinophilic inclusions; staining with Schiff's reagent (PAS-reaction) gives a negative or weakly positive reaction; interaction with trichrome (Masson's stain) gives a blue or silver color (negative). Congo red stain (with distinctive bright green refraction in polarized light) remains the indispensable gold standard for amyloid detection for more than 50 years. Immunofluorescence microscopy demonstrates monotypic staining of amyloid deposits. Electron microscopy shows amyloid deposits in the kidneys that look like unbranched fibrils, which are randomly arranged and visible in the mesangium, glomeruli or tubules, interstitium and vessels [6, 7].

Amyloidosis is a systemic disease, and in most patients, not only renal tissue but also other organs are involved in the pathological process (subcutaneous fat, gastrointestinal tract, bone marrow) [6, 7, 20]. A small group of patients (7–17%) with fibrillary glomerulonephritis (monoclonal fibrillary glomerulonephritis) clinically meets the criteria for monoclonal gammopathy. The formation of "fibrillar" deposits (IgG deposits limited by light chain) is found in 3–15% of this group of patients [6, 7, 15, 16, 18, 21, 22].

In fibrillary glomerulonephritis, fibrils are arranged randomly and are on average twice thicker (10–30 nm) than those observed in amyloidosis and usually do not stain with Congo red. Light microscopy can help confirm fibrillary glomerulonephritis by staining the glomeruli for a homologue DnaJ Heat Shock Protein Family (Hsp40) Member B9, which is a reliable marker of the disease. Immunofluorescence assay is not specific (IgG staining: mostly IgG4, less often IgG1 and C3 complement components) [6, 7, 18, 21].

These differences can be used to distinguish monoclonal glomerulonephritis from the subtypes of heavy chain (AH) or heavy and light chain (AHL) deposition [6, 7, 23, 24].

Microtubular Forms of Monoclonal Immunoglobulin Deposition

Immunotactoid glomerulonephritis and cryoglobulinaemic glomerulonephritis are two diseases characterized by immunoglobulin deposits in the form of microtubules. Microtubules can be distinguished from fibrils by their hollow center and large diameter (17–90 nm) [6, 7, 21, 22]. There are three types of cryoglobulinemia. Type I (simple cryoglobulins) includes monoclonal immunoglobulins of the same class (A, G or M), less often — monoclonal light chains of immunoglobulins. Type II (mixed cryoglobulins) includes one monoclonal immunoglobulin in the role of an antibody (usually IgM, less often IgA or G) combined with polyclonal IgG. Type III (mixed cryoglobulins) includes several classes of polyclonal immunoglobulins and sometimes non-immunoglobulin molecules (fibronectin, lipoproteins, C3-component of complement) [1, 4, 6, 7, 21, 25].

Therefore, monoclonal renal gammopathies (MGRS) include type I and type II cryoglobulinemia since type III cryoglobulinemia is associated exclusively with polyclonal immunoglobulins [1, 4, 7, 21].

Type I cryoglobulinemia is characterized by loss of M-protein at temperatures below 37 °C and dissolution when serum is heated. This can cause glomerulonephritis associated with cryoglobulinemia (20–30%), and systemic manifestations (vasculitic eruptions, peripheral neuropathy — Raynaud's syndrome and arthralgia). The most common cause of type II cryoglobulinemia is hepatitis C infection. Only about 10–30% of cases are associated with B-cell lymphoproliferation [1, 4, 7, 21]. A typical sign of cryoglobulinemia during light microscopy is membranoproliferative glomerulonephritis with endocapillary proliferation. Moreover, numerous WBC with intracapillary infiltration are found, and Schiff's reagent (PAS reaction) reveals huge PAS-positive intraluminal immune deposits (protein hyaline thrombi). Immunofluorescence microscopy shows intraluminal Ig and deposits of C3, C4, C1q complement components. Electron microscopy reveals the substructures of microtubules, fibrils and deposits in the form of "fingerprints" [1, 4, 6, 7, 21]. Immunotactoid glomerulonephritis is often monoclonal, in contrast to fibrillar glomerulonephritis. More often it is a renal-limited disease and, unlike cryoglobulinemia, it does not show typical signs of cryoglobulinemic glomerulonephritis (formation of glomerular protein thrombi, vasculitis of arteries and/or arterioles) [1, 6, 7, 21].

Glomerular deposits in immunotactoid glomerulonephritis are uniformly composed of microtubules (with limited λ or κ isotypes) and are more often arranged in parallel rows with predominantly subepithelial and subendothelial localization [6, 7, 21, 26, 25, 27]. Congo red stain gives a negative result (no dichroism detected: reddish and green-yellow glow).

Immunofluorescence microscopy shows distinct hollow centers and staining of C3 complement component. During electron microscopy, focal parallel arrays 30–90 nm in diameter are determined [6, 7, 21].

Crystalline and/or Inclusive Forms of Deposition of Monoclonal Immunoglobulins

Light-chain proximal tubulopathy (LCPT), crystal storing histiocytosis (CSH), and (cryo) crystalglobulin glomerulonephritis are diseases characterized by immunoglobulin deposits in the form of crystals and/or inclusions. Proximal tubulopathy has crystalline and non-crystalline variants. In the crystalline version of LCPT, numerous crystals of light chains of various shapes are found inside the cells of proximal tubules, inside lysosomes, or are freely located in the cytoplasm. This version is primarily associated with the deposition of the κ-light chain and is clinically manifested by complete or partial Fanconi syndrome that develops in young patients [6, 7, 28–32]. During light microscopy, *κ* light chains have a rod or rhomboid shape. They are hypereosinophilic and do not stain when exposed to Schiff reagent (PAS reaction). Pronase (a biochemical mixture of proteinases isolated from the extracellular fluid of Streptomyces griseus) is used to render a crystalline inclusion during immunofluorescence microscopy of proximal tubule cells. Electron-dense intracytoplasmic inclusions are rendered during electron microscopy [6, 7, 28–30].

In cases of the non-crystalline version of LCPT, cells of proximal tubules are stretched and damaged due to the accumulation of numerous non-crystalline inclusions of light chains in lysosomes. This type is usually associated with the deposition of λ light chains. Fanconi syndrome is rarely manifested. The type is favorable compared to the crystalline variant of kidney damage. The non-crystalline variant of LCPT can sometimes look like acute tubular necrosis or acute interstitial nephritis [6, 7, 28, 30, 33].

In patients with CSH, light chain crystals, predominantly of *κ* chains, are often found in renal histiocytes and cells of proximal tubules; they can have a wide extrarenal distribution, including the bone marrow, lymph nodes, lungs, thyroid gland, parotid gland, cornea, synovium, skin, subcutaneous fat, stomach, liver and brain [6, 7, 34–37].

Infiltration by histiocytes and deposition of light chain crystals (more often *κ*) lead to interstitial fibrosis and tubular atrophy. Diagnosis of crystal storing histiocytosis (CSH) can be challenging since crystalline inclusions cannot always be identified by immunofluorescence microscopy. Therefore, the use of the pronase or immunoperoxidase method may be required [6, 7]. Crystal storing histiocytosis (CSH) can develop concurrently with proximal light chain tubulopathy. In this case, organized cytoplasmic inclusions — needle- or oval-shaped crystals in proximal tubular cells — are visible with the help of electron microscopy [6, 7, 34, 35]. (Cryo) crystalglobulin glomerulonephritis is a rare monoclonal gammopathy characterized by immunoglobulin thrombi in the arterioles and capillaries of glomeruli [6, 7, 39].

These thrombi have a crystalline structure; in some patients, the crystallization process is accelerated by exposure to cold — this is cryocrystalline globulinemia [6, 7, 32, 39, 40].

Renal biopsy specimens from patients with cryocrystalline globulinemia show large extracellular crystals in the capillaries and arterioles of glomeruli that are

often associated with fibrin thrombi and inflammation. Mesangial and endocapillary hypercellularity is often absent during microscopic investigation. As with cryoglobulinemia, intravascular deposition of crystals leads to the occlusion of small vessels, thrombosis and/or inflammatory vasculitis [6, 7].

Damage with Unorganized IgM Deposits

Unorganized deposits of monoclonal immunoglobulins are observed in patients with monoclonal immunoglobulin deposition disease (MIDD) and in patients with proliferative glomerulonephritis with monoclonal immunoglobulin deposits — PGNMID) [4, 6, 7].

Monoclonal immunoglobulin deposition disease (MIDD) includes three subtypes that are characterized by light chain deposition on disease or both light and heavy chain deposition on disease [6, 7, 21, 22]. Light chain deposition disease (LCDD) is the most common subtype (isotype κ). Kidneys are almost always affected; extrarenal lesions are common in the heart, liver, and lungs. During light microscopy, nodular glomerulosclerosis and nodular mesangial enlargement are visible along with the thickening of the glomerular and tubular basement membranes (GBM and TBM). Non-specific manifestations are as follows: varying degrees of tubular atrophy, interstitial fibrosis and inflammation. Immunofluorescence microscopy demonstrates monotypic, linear and amorphous light chains that are deposited in the mesangium and along the glomerular and tubular basement membranes (GBM and TBM) [6, 7, 21, 22]. With light and heavy chain deposition disease (LHCDD) and heavy chain deposition disease (HCDD), light microscopy shows linear deposits. Monotypic γ, α, or μ light chains are visible along the glomerular and tubular basement membranes (GBM and TBM). During electron microscopy, granular deposits look non-fibrillar, electron-dense, and are located in glomeruli subendothelially, in the mesangium, and on the outer side of the tubular basement membrane [6, 7, 21, 22].

On the contrary, in cases of proliferative glomerulonephritis with monoclonal immunoglobulins deposition (PGNMID), deposits of intact monoclonal IgG, rarely IgA or IgM, occur in glomeruli [6, 7, 22, 41]. Light microscopy shows predominantly endocapillary proliferation and/or membranoproliferative glomerulonephritis (MPGN) or without morphological changes. According to immunofluorescence microscopy, IgG deposits are limited to glomeruli and include one isotype of a light chain and one isotype of a heavy chain, most often IgG3κ [6, 7, 22, 41, 42]. Positive staining for C3 and C1q indicates the activation of the complement system. During electron microscopy, granular and disorganized deposits are limited to glomeruli, where they are located in the mesangium and subendothelial space, less often — in the subepithelial space [6, 7].

Non-Immunoglobulin Gammopathies

Not all kidney damage associated with monoclonal gammopathy of renal significance (MGRS) includes deposits of monoclonal immunoglobulins. A common form of MGRS-related disorder with no such deposits is C3-glomerulopathy associated with monoclonal gammopathy, C3GP, which is detected in about 30% of patients [6, 7, 43]. C3-glomerulopathy associated with monoclonal gammopathy leads to kidney dysfunction via an indirect mechanism. This mechanism is a process when M-protein acts as an autoantibody to C3-convertase, or as an autoantibody to other regulating proteins for complement; this leads to the dysregulation of the alternative complement pathway [6, 7, 43–45]. Light microscopy shows mesangial proliferative, membranoproliferative, or endocapillary proliferative glomerulonephritis. It looks like large subepithelial deposits — in the form of a "hump". C3GP is characterized by the deposition of a fragment of the C3 component of the complement system in the glomeruli, at least twice as intense as any combination of IgG, IgM, IgA and C1q [6, 7, 31, 44, 46]. Immunofluorescence microscopy in 5–10% of patients reveals membranoproliferative glomerulonephritis with masked monoclonal deposits. These patients require additional immunofluorescence tests: use of proteases to identify monoclonal immunoglobulin in deposits [6, 7, 31, 46]. Electron microscopy reveals electron-dense mesangial, subepithelial and subendothelial deposits [6, 7]. The group of non-immunoglobulin gammopathies also includes thrombotic microangiopathy associated with monoclonal gammopathy (TMA), which is characterized in some patients by microangiopathic hemolytic anemia. TMA can occur simultaneously in patients with monoclonal gammopathies, including MM and Waldenstrom macroglobulinemia (WM) [6, 7, 47]. This disease is relatively rare and new, with a few cases described in the literature. Ravindarn et al. established a connection between gammopathy, TMA and a high level of monoclonal immunoglobulins in 21% of patients aged 50 and over [6, 7, 48]. The pathophysiology of these disorders is not always well understood, but it may be associated with monoclonal immunoglobulin that acts as an autoantibody against the regulatory complement of protein.

Kidney damage due to TMA is characterized by the formation of blood clots in the capillaries of glomeruli, swelling of the endothelium, mesangiolysis with microaneurysms and the formation of a double contour

of the walls of the capillaries of the glomeruli. Therefore, the process is based on acute tubular damage with varying degrees of tubulointerstitial scarring [6, 7, 49, 50].

New Approaches in the Diagnosis and Administration of Monoclonal Gammapathies of Renal Significance

Until now, monoclonal gammopathies were diagnosed through the quantitative determination of circulating abnormal protein: serum protein electrophoresis with the determination of the M-gradient level, immunofixation of proteins with the determination of their type, electrophoresis and immunofixation of proteins in daily urine. A new method for determining free light chains in blood serum — Freelite — emerged in the early 2000s; it is based on the interaction of type λ and κ light chains with highly specific antisera. The proliferation marker is impaired κ/ λ ratio (normal range 0.26–1.65).

The attention of a hematologist and/or hematooncologist should be focused on the identification of the clone, since any detected variant of damage in MGRS requires the timely initiation of clone-oriented therapy, which allows preserving kidney function and preventing uncontrolled progression of the malignant process by reducing the accelerated secretion of abnormal immunoglobulin and/or its chains. In the diagnosis and treatment of this disease, a nephrologist plays an important role; he/she works with a hematologist and/or hematooncologist. First of all, the nephrologist should correct the prescribed clone-oriented therapy considering the nephrotoxicity of chemotherapeutic agents and assess the renal response to the hematological treatment taking into account the glomerular filtration rate. With the progression of the pathological process and deterioration of renal function, the nephrologist decides on the prescription of renal replacement therapy (RRT) methods since these methods allow the removal of abnormal immunoglobulins and/or its chains from the body, thus reducing their toxic effect on kidney parenchyma. With the development of terminal stage chronic kidney disease (CKD S5) and when constant RRT is required, the nephrologist puts the patient on the waiting list and prepares the patient for kidney allotransplantation [1–8].

Conclusion

MGRS is a new group of diseases based on the hyperproduction of nephrotoxic monoclonal immunoglobulin (M-protein, paraprotein) and/or their MGRS-constituent chains. The discovery of the pathogenetic mechanisms of renal tissue damage (pathological activation of the complement system, toxic effect of a cell clone, interaction of antibodies with glomerular antigens of nephron cells). It was this discovery that made it possible to classify MGRS as a separate nosological unit. Renal tissue damage associated with MGRS has a specific morphological pattern associated with the deposition of monoclonal immunoglobulins. Monoclonal immunoglobulin detected in serum and/or urine should be identical to that detected in nephrobiopsy.

Timely initiation of clone-oriented therapy allows preserving kidney function and preventing uncontrolled progression of the malignant process by reducing the secretion of abnormal immunoglobulin and/or its chains.

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Фомина Н.В.: концепция исследования, сбор, анализ и интерпретация данных, подготовка черновика рукописи

Уткина Е.В.: сбор, анализ и интерпретация данных, подготовка черновика рукописи

Author Contribution:

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Utkina E.V.: data mining, analysis and interpretation, preparation of a draft of the manuscript

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