



MORPHOLOGICAL CHANGES IN THE ADRENAL GLANDS IN RHEUMATOID ARTHRITIS

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Annotation: Relevance. Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease of connective tissue with joint damage of the type of symmetrical erosive-destructive polyarthritis and a variety of extra articular manifestations. Renal pathology is found in RA with a high frequency - about 60%, according to various authors. Patients with RA may have various renal diseases: secondary renal amyloidosis, glomerulonephritis, interstitial nephritis, renal vascular vasculitis, nephrosclerosis, and in some cases, combinations thereof. Etiologically, kidney damage in patients with RA can be divided into 2 groups: firstly, nephropathy as one of the acute manifestations or complications of RA itself, for example, renal vascular vasculitis, chronic glomerulonephritis, secondary amyloidosis, and secondly, as a complication of drug therapy of RA: analgesic nephropathy (AN), medicinal glomerulonephritis. The pathogenesis of such different kidney diseases cannot be the same. Renal vascular vasculitis and glomerulonephritis have an immune nature, mainly immunocomplex; in severe cases, signs of an autoimmune process are recorded. The toxic effects of long-term NSAID intake on the enzyme systems of renal tubule epithelial cells and interstitium underlie the development of AN.

According to Bely M. et al., during autopsy of patients with RA, systemic vasculitis involving internal organs occurred in 36 out of 142 cases, which is 22.4%, while kidney damage was noted in half of the patients, that is, in 17 out of 34. In one of them, the cause of death was vasculitis, complicated by thrombosis of one of the renal arteries, renal infarction and acute renal failure. The fact that vasculitis of internal organs, including renal vessels, is rarely diagnosed in vivo - in 0.1 - 0.2% of patients, apparently due to the presence in most cases of poor clinical symptoms and nonspecific symptoms. In patients with rheumatoid vasculitis of the renal vessels, a slight transient decrease in renal function is more often detected along with transient hematuria, indicating local inflammation, and severe renal insufficiency is rarely observed. The examination of a renal biopsy is crucial for diagnosis. but a kidney biopsy, due to the high cost and the possibility of severe complications, is not indicated with minimal urinary syndrome.

M. Boers reports a heterogeneous, focal vascular lesion in RA, which can lead to the capture of an intact section of renal tissue during a kidney biopsy, therefore, the frequency of renal vascular vasculitis in RA, detected during autopsy, is much higher than that diagnosed in vivo according to kidney biopsy data. Vessels of any caliber can be affected in RA, but inflammation of medium and small arteries of the type of panarteritis is most often found. Deposits of Ig G, Ig M and C are found in the walls of blood vessels in rheumatoid vasculitis, which indicates the immunocomplex nature of vasculitis. This is also indicated by a decrease in the level of C, C4 and activation of C in the blood serum, high levels of RF, circulating immune complexes (CIC) and cryoglobulins in the blood.

In the presence of systemic manifestations, the level of CIC is significantly higher than in the articular form, regardless of the activity of the articular process. It is believed that immune complexes cause a number of chain reactions that induce and support inflammation in RA, which causes the progressive course of the disease with the addition of damage to internal organs, including kidneys. With kidney damage in RA patients, an increase in the level of Ig M and Ig A is often detected. B-cell activation in RA leads to hyperproduction of various autoantibodies, including antibodies to native and denatured DNA. In patients with RA, in the presence of antibodies to DNA, systemic vasculitis with heart, kidney, and liver damage was significantly more often diagnosed.

Rheumatoid vasculitis is associated with antibodies to neutrophil cytoplasm (ANCA), antiendothelial antibodies and an increase in the level of von Willebrandt factor in blood serum. The association between high levels of At-2 and von Willebrandt factor in RA patients with different forms of vasculitis has also been studied. Boers M. in 1990 reported on the activation of the renin-angiotensin system in the form of increased activity of renin and prorenin in blood plasma in patients with severe RA, referring this to indirect evidence of renal vascular vasculitis.

All these data may indicate a higher incidence of renal vascular vasculitis in RA than is traditionally considered. In the presence of urinary syndrome - proteinuria and/or hematuria - glomerulonephritis is often present in RA patients: according to kidney biopsies - up to 67% of the total number of nephropathies. The pathogenesis of glomerulonephritis in RA is immune and almost always immunocomplex. Currently, the mechanism of immunocomplex kidney damage is well understood. The CEC entering the kidneys with a plasma current under physiological conditions is either removed with urine, or it enters the mesangium, where it is phagocytized by mesangial macrophages, and also dissolved due to local complement activation.

3 groups of factors contribute to the excessive deposition of CEC in the mesangium: the properties of the CEC themselves - their large size and poor solubility, depending on the activation of the complement system (CEC containing Ig M are poorly removed due to their large size, and Ig A due to weak complement activation); increased formation of CEC due to for example, chronic inflammation; and increased intracapsular pressure. When the pressure in the glomerular capillaries increases, the flow of CEC into the mesangium increases. If too much CEC is received, mesangial phagocytes do not have time to remove them, and they persist in the mesangium for a long time, forming aggregates of large insoluble immunocomplex deposits. If immune inflammation continues, new antibodies (e.g. RF) are included in the immune complexes, creating conditions for fixation and subsequent activation of complement and causing the development of immunocomplex glomerulonephritis. Activation of the complement system plays an important role in the development of inflammation and immune response, phagocyte activation and cytokine synthesis. Proinflammatory cytokines primarily include interleukin-1 (IL-1) and tumor necrosis factor alpha (TNF-α). It was noted that in RA, an increase in the level of the soluble forms of TNF-α and IL-6 receptors correlates with the inflammatory activity of the disease: its laboratory parameters (the value of ESR and the concentration of C-reactive protein) and clinical parameters of joint inflammation (severity of pain, duration of morning stiffness).

Platelet growth factor (tc-FR) and transforming growth factor (TFR) have a sclerosing effect. The fibrogenic properties of TFR have been demonstrated in experiments when repeated injections of cytokine sham caused severe renal and hepatic fibrosis [20]. It was also found that At-2 induces the expression of tc-FR and TFR in smooth muscle and mesangial cells, and this effect is significantly suppressed by the administration of i-ACE. mesangioproliferative (34%) and membranous (31%) glomerulonephritis are most often found in RA, glomerulonephritis with minimal changes (11%) and membranoproliferative (7%) are much less common. Light microscopy of mesangioproliferative glomerulonephritis correlates with hypercellularity of the mesangium, immunofluorescence in the mesangium reveals granules of deposits containing Ig G, A and M and complement C. Clinically, mesangioproliferative glomerulonephritis is usually associated with high RA activity, increased blood levels of Ig M and IgA, which can be part of immune deposits. Urinary syndrome can be transient or persistent for several years, depending on the severity of the disease. With the progression of glomerulonephritis, A G is attached. The outcome of the disease is nephrosclerosis with the development of CRF. When analyzing the relationship of renal pathology with RA treatment, it was found that glomerulonephritis with minimal changes is usually a complication of therapy with nonsteroidal anti-inflammatory drugs (NSAIDs), appearing more often 2 to 6 weeks after the start of treatment. Electron microscopy reveals the fusion of short processes of podocytes with each other. In some cases, there is mononuclear infiltration and significant interstitial edema. dystrophy of the epithelial cells of the renal tubules, which suggests a combination of glomerulonephritis with minimal changes with acute interstitial nephritis. Clinically, isolated proteinuria is observed - moderate or massive with the development of nephrotic syndrome, sometimes requiring the use of glucocorticosteroids (GCS). Membranous glomerulonephritis in 2/3 of cases is also clearly associated with treatment with gold preparations or D-penicillamine. or less often with NSAIDs. In 1/3 of cases, membranous nephropathy is not related to therapy, since changes in urine tests appeared before any treatment was prescribed. In this case, it can be considered as a manifestation of the rheumatoid process. Morphological changes in membranous nephropathy include immune deposits, the pages of a young scientist 73 placed subepithelially and thickening of the basement membrane, detected in the late stage. Clinically, the appearance of isolated protenuria or in combination with hematuria is observed, nephrotic syndrome is usually observed with the drug etiology of membranous glomerulonephritis.

Glomerulonephritis with a rapidly progressive course is extremely rare in RA. Harper L. co-authors (1995) reported 10 RA patients with focal segmental necrotizing glomerulonephritis. Half of them showed signs of extrarenal vasculitis and showed ANCA; 9 developed terminal CHIN in a short time, despite aggressive therapy using GCS and cytostatics (CS). However, even in these cases, antibodies to the glomerular basement membrane were not detected in the blood serum, which allows us to conclude about the immunocomplex nature of these severe nephritis variants. Medicinal nephropathy often occurs when treating RA with gold salts or D-penicillamine. "Golden nephropathy" develops not only in parenteral, but also in oral treatment with gold preparations in 2-10% of patients, manifested by proteinuria. 1-2% develop severe nephrotic syndrome.

Histological changes include various morphological variants of glomerulonephritis. Most often, membranous, less often glomerulonephritis with minor changes and membrane-proliferative is detected. "Golden jade" is characterized by a pleasant natural course with complete normalization of urine tests on average 11 months after discontinuation of the drug. Gold salt therapy is less likely to cause other types of kidney damage: tubular dysfunction, acute interstitial nephritis with acute renal vascular vasculitis. In the treatment of D-penicillamine, proteinuria is found in 9% of RA patients, usually 6 months after the start of therapy, when the concentration of the drug in the blood becomes maximal. 10% of them develop nephrotic syndrome.

Morphologically, classical immunocomplex membranous glomerulonephritis is revealed. The mechanism of kidney damage is presumably associated with the accumulation of the drug in the proximal and distal tubules, damage to the epithelium and the release of the autoantigen of the brush border. This triggers the formation of immune complexes that fix themselves on the basement membrane subepithelially and leads to the development of membranous glomerulonephritis. This hypothesis has been experimentally confirmed in rats. A relationship has been established between seropositivity, increased levels of Ig M and Ig A and the severity of renal pathology in RA. It is believed that the frequent presence of immune deposits in the kidneys, which is generally found in RA, greatly contributes to the development of drug lesions, including during therapy with D-penicillamine. This explains the fact that nephropathy develops much more frequently during treatment with D-penicillamine in RA patients, than in patients with Wilson-Konovalov disease, although the latter receive this therapy on a vital basis.

Secondary renal amyloidosis is a formidable complication of RA and one of the main causes of renal failure and death in RA patients. In patients with juvenile RA, secondary renal amyloidosis is the cause of death in 30% of cases, and is detected on autopsy in 40%. In adult patients with RA, renal amyloidosis is diagnosed in 2-3% of cases. Posthumously, amyloidosis is found in 10-25% of patients with RA. In many countries, RA is in the first place among the causes of secondary amyloidosis, since up to 56% of patients with amyloidosis suffer from RA. Numerous authors have noted that the most important factor in the development of amyloidosis is the constant activity of RA. With inflammation, the synthesis of alpha globulin SAA by cells of different types (hepatocytes, neutrophils, fibroblasts) increases sharply, an acute-phase protein similar in functional properties to C-reactive protein. Cytokines produced by activated monocytes-macrophages cause the expression of the acute-phase protein SAA, as well as the expression of proteolytic enzymes that normally cleave this protein. It is believed that the formation of soluble AA protein is carried out as a result of incomplete cleavage of SAA by proteases associated with the membrane of monocytes-macrophages. Polymerization of soluble AA-protein into amyloid fibrils also occurs on the surface of macrophages by the mechanism of cross-linking of polypeptides with the participation of membrane enzymes. It is possible that there is a genetic predisposition to the formation of amyloid fibrils, since in recent years evidence has been obtained for the existence of several molecular forms of SAA in humans. Fragments of only five of them were found in the composition of amyloid fibrils, which, apparently, explains the development of amyloidosis in only a part of RA patients. The process of precipitation of amyloid proteins in tissues is facilitated by local factors: pH, electric charge, hydration voltage of cell membranes. The nature of amyloid deposition in the kidneys can be glomerular and vascular - with predominant deposition of amyloid in the glomeruli or in the walls of large vessels, the stroma of the pyramids and the capsule according to the check. In the glomeruli, amyloid is deposited first in the mesangium, then along the basement membrane. At the same time, the degree of proteinuria does not depend on the massiveness of amyloid deposition in the glomeruli, but on the degree of destruction of the legs and the podocyte cell bodies themselves.

Pages of the young scientist 73 Proteinuria is detected in 100% of cases of amyloidosis in RA, and in 70% - massive proteinuria (more than 3.5 g / day) with the subsequent development of nephrotic syndrome. Hyaline and waxy cylinders are also detected; sometimes tubular dysfunctions occur due to massive deposition of amyloid masses in the interstitium. Hematuria is uncharacteristic. Hypertension is observed in 11-20% of cases at the onset of the disease, in the absence of damage to the adrenal glands, and does not correlate with the massiveness of amyloid deposition in the vessels. Secondary amyloidosis always has a systemic character, affecting, along with the kidneys, the gastrointestinal tract, liver, spleen, heart, adrenal glands, and pancreas. The prognosis for secondary amyloidosis is extremely unfavorable, the average life expectancy of patients is 1-3 years. The causes of death are not only terminal CRF, but also complications of nephrotic syndrome (hypovolemia, severe infections), as

well as cardiac insufficiency and damage to other organs and systems. The diagnosis of amyloidosis is based on a histological examination of biopsies of the submucosal layer of the rectum or stomach (the accuracy of the study is 70-85%), or a kidney biopsy (95-100% confidence).

The biopsy material is examined by various methods. The main methods in the clinic are okra juicy methods with congo red, hyacinth-vio-let, iodine gruen. In recent years, it has been proposed to use monoclonal antibodies to amyloid fibrillar protein. To diagnose and control the dynamics of amyloid tissue deposits during treatment abroad, the method of c cintigraphy with a labeled Jm serum P component is currently used, which reversibly binds to amyloid deposits in the body and can be quantified on a series of c cintigrams. Currently, the significance of an active treatment of RA aimed at reducing the level of serum amyloid precursors is being investigated. It was found that during the treatment of cancer with cytostatics (cyclophosphane, chlorambucil and possibly metagrexate), amyloidosis occurs much less frequently, and with already developed amyloidosis, there is a decrease in its clinical manifestations and a significant prolongation of patients' lives. When using NSAIDs, patients with RA can develop a variety of types of renal pathology: acute tubular necrosis with acute renal failure, acute interstitial nephritis, chronic interstitial nephritis with papillary necrosis (analgesic nephropathy), and medicinal glomerulonephritis. Acute renal lesions that occur when taking NSAIDs are associated with their effect on renal hemodynamics.

Conclusions: Kidney function largely depends on the production of local renal proglanidins (PG), which are synthesized from arachidonic acid using two cyclooxygenase isoenzymes - COX-1 and COX-2. COX-1 is responsible for the production of PG, which regulates the physiological activity of cells. COX-2 participates in the synthesis of proinflammatory PG. Most NSAIDs suppress activity and COX-1, which is associated with their potential nephrotoxicity. In an experiment by Elisevsky Yu.M. in 1995, it was shown that with prolonged administration of indomeacin to rabbits, an inflammatory reaction of the interstitium and dystrophic changes in the tubules, morphologically proven, develop. Other authors report a deterioration in filtration function in RA patients against the background of NG1VP ema in the form of a decrease in GFR and a decrease in sodium reabsorption.

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