ORIGINAL ARTICLE

PATHOMORPHOLOGICAL CHARACTERISTICS OF IMMUNOCOMPLEX RENAL DISEASE IN PATIENTS WITH IMMUNODEFICIENCY VIRUS AND HEPATITIS C VIRUS, RECEIVING ANTIRETROVIRAL THERAPY

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ABSTRACT
The aim is to verify and describe the morphological substrate of renal impairment in HIV/HCV co-infection among patients receiving ART to assess and predict the morphogenesis of immunocomplex lesions.

Materials and methods: To assess and predict the morphogenesis of immunocomplex renal disease, we examined retrospectively the kidney tissue samples of 15 patients, who died with HIV/HCV co-infection and received ART. Histological, histochemical and immunohistochemical research methods were used.

Results: Segmental and diffuse mesangial proliferation with extracellular matrix expansion with glomerular damage ≥50% in 9 (60%) cases, and involving <50% of glomeruli in 5 (33%), with CD68 expression as single cells were detected. In 12 (80%) cases, there was uneven swelling and focal proliferation of endothelial cells with the involvement of 20-50% of the glomeruli, as well as the presence of cellular infiltrates in the lumen of capillary loops in 3 (20%) cases with monomorphic intensity in "+". Sclerotic changes were present in various degrees of severity – from cases of complete glomerulosclerosis with obliteration of the Bowman's lumen to focal and microfocal depressions 8 (55%), sclerosis 10 (66%), hyalinosis 1 (6%), uneven thickening, focal cleft 8 (55%) and perihilar focal sclerosis. These areas were positive for IgG and C1q complement fractions within the "+", "++" intensity. Among the study group, no case of HIV-associated nephropathy was found that coincided with the predicted spectrum of kidney damage for patients in this sample. The described morphological changes were mainly verified as immuno-mediated by HCV.

Conclusions: A comprehensive morphological study revealed the morphological substrate of kidney damage and its morphogenesis in patients with HIV/HCV co-infection, receiving ART.

KEY WORDS: immunodeficiency virus, viral hepatitis C, kidney, morphology, morphogenesis

INTRODUCTION

There are more than 30 million people living with the human HIV worldwide. With effective ART, progression to acquired immunodeficiency syndrome (AIDS) is less common, while morbidity and mortality is associated with complications not related to the development of AIDS, including various forms of kidney disease [1]. HIV and HCV are involved in the pathogenesis of specific glomerular diseases. HIV/HCV co-infection has been shown to be associated with a significantly increased risk of kidney disease, but the morphological substrate and stages of morphogenesis contain many unresolved issues [2, 3]. Both viruses are associated with immune dysregulation, which can contribute to the development of comorbid kidney disease. In addition, complex antiviral treatment regimens for HIV and HCV often include drugs with nephrotoxic potential [1, 2].

The two most common forms of HIV-related kidney damage are collapsing glomerulopathy and circulating immunoglobulins related glomerulonephrites, collectively known as HIV-immunocomplex kidney diseases (HIV-ICKD). HIV-associated nephropathy (HIV-AN) was the first kidney disease to be described in HIV-infected people, but is rare among cohort of patients receiving ART. HIV-AN is classically associated with rapid progression to end-stage renal disease, occurs in the late stages of HIV infection, predominantly in the African population, accounting for up to 90% of HIV-related cases of chronic kidney disease (CKD) [4]. HIV-AN is mostly found in people primary diagnosed with the end-stage HIV and may have the first manifestation as acute renal failure or progressive CKD. In addition to HIV-AN, the spectrum of kidney diseases among HIV-infected patients includes immunocomplex kidney disease and, less commonly, thrombotic microangiopathy. HIV-AN has a known morphological substrate – a collaptoid form of focal-segmental glomerulosclerosis in combination with cystic dilatation of the tubules. According to theories of pathogenesis, the

development of HIV-AN manifests by local epithelial cells contamination of tubules and glomeruli by HIV, where systemic persistence of the virus and systemic immune dysfunction is a part. A strong racial relationship between HIV-AN and end-stage CKD is associated with polymorphism of the APOL1 genes, which encode apolipoprotein-1, and chromosome 22, which is also associated with a predisposition to trypanosomiasis [4-7].

Two forms of kidney disease among HIV-infected people have a common pathological finding – glomerular hyperplasia of different genesis. According to some data the main role in the pathogenesis of this pathology is assigned to the damage of podocytes (podocytopathy), however, the predictor of the proliferation of glomerular epithelial cells is not known. There are hypotheses that this lesion is directly related to epithelial cell infection, particularly for HIV-1, but the mechanism of the virus entry into non-lymphoid compartment is unclear. Viral proteins, responsible for the induction of renal failure, have been identified in models of transgenic rodents, but all aspects of the immune activation process could not be successfully restored [7, 8].

Electron microscopy of kidney biopsies from HCV patients, irrespective of type of glomerulonephritis and presence of cryoglobulinemia, detects virus-like particles in paramesangium in 50% of studies [9]. In addition to glomerular damage in HCV, tubulo-interstitial changes play an important role, which is also a significant predictor of renal dysfunction. The persistence of the virus in tissues is facilitated by inhibitions of infected cells apoptosis and increasing fibrosis, in particular in the mesangial cells of the kidneys. These processes are realized due to the activation of the immune system, increasing pro-inflammatory activity, and proliferation of macrophages, which causes the expression of viral proteins by cells. The direct cytopathic effect of HCV in the mechanism of development of renal damage is evidenced by the presence of certain viral proteins and viral RNA in various renal structures among patients with HCV and the presence of signs of kidney damage [9, 10]. Such mechanisms can be immune-mediated or direct, which indicates the etiological and pathogenetic role of HCV in the development of renal pathology.

The pathogenesis of any viral infection consists of several steps – entry of the virus into the tissue, adhesion on the cell surface, penetration into the cell, replication and collection of viral particles, exit from the cell, often with its subsequent lyses. HCV can penetrate into the kidney structures as a part of immune and lipoprotein complexes, as the form of free viral particles [11, 12]. In the cryoglobulinemic form of HCV-associated glomerulonephritis, the histological substrate is determined by the formation of circulating immune complexes with their sedimentation within the microcirculatory system and the subsequent formation of deposits with damage to the walls of blood vessels. Under light microscopy, renal deposits are visualized in the form of homogeneous linear inclusions along the capillary loops of the renal glomeruli and vascular walls of the tubule-interstitial component. In mesangial cells, they can be found in the form of granular cytoplasmic

inclusions and in paramesangial space. The composition of the deposits reveals structured and unstructured HCV proteins, immunoglobulins with a predominance of IgM and C3 fraction of complement by immunohistochemical staining [12, 13]. Glomerular deposition of immune complexes is associated with a partial affinity of IgM rheumatoid factor to the glomerular matrix. In the future, this leads to the launch of the cascade of complement activation and blood coagulation factors, which in the case of pathological induction of reactions leads to the development of partial thrombosis and reactive thickening of the basement membrane [12]. Accumulation of deposits also stimulates the proliferative activity of mesangial cells and their fibroblastic transformation with increasing production of the mesangial matrix and migration of immune cells with the subsequent fibrosis development. Widespread mesangial proliferation and expansion of the mesangial matrix with fields of centrilobular sclerosis are considered as unfavorable prognostic factors of kidney disease [14, 15].

Pathomorphological research of kidney diseases among patients with HIV/HCV co-infection mainly include cases with clinical manifestations of renal failure. However, in a retrospective analysis of a cohort of co-infected patients without clinical signs of glomerular disease, cases of membranoproliferative and mesangioproliferative glomerulonephrites, focal glomerulosclerosis, and nonspecific glomerular disease were diagnosed [16].

THE AIM
The aim is to verify and describe the morphological substrate of renal impairment in HIV/HCV co-infection among patients receiving ART to assess and predict the morphogenesis of immunocomplex lesions.

MATERIALS AND METHODS
We conducted a retrospective analysis of 278 deaths during 2014-2020 among HIV patients who received ART and selected 15 cases according to the research design. We used for the following inclusion criteria for the outlined group: diagnosis of HIV and HCV, receiving ART for at least 0.5 years; and following noninclusion criteria: established clinical or pathological diagnosis of somatic disease with kidney damage (diabetes, hypertension, atherosclerosis with renal arteries damage); generalized infection with kidney damage (opportunistic, viral, and bacterial infections laboratory confirmed); registered data on systemic injecting drug use; registered side effects in the form of renal disorders (including acute renal failure) due to ART. In the course of the research, additional criteria of non-inclusion according to morphological indicators of acute necrotic nephrosis (toxic, ischemic action) were established. Clinical trials, laboratory and instrumental tests were performed in accredited institutions and laboratories. The immunological examination was performed as part of screening for CD 4 and viral load in the blood.

The kidney tissue samples were placed in a neutral buffered solution of formaldehyde (pH 7.4) and fixed for 24-48 hours,
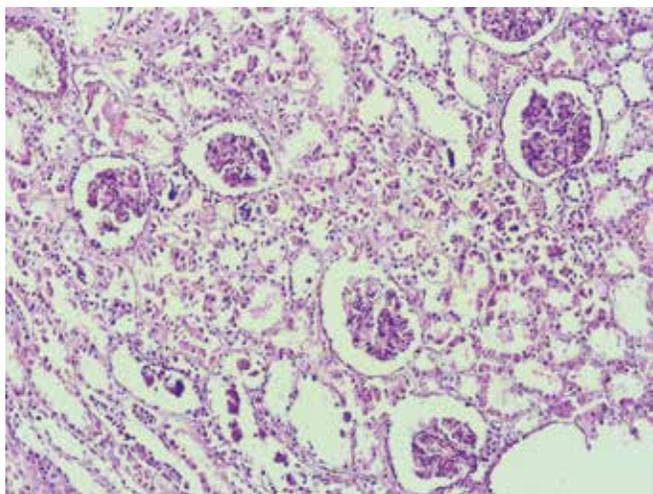
Fig. 1. Mesangial hypercellularity, degenerative changes in the epithelium of the tubules, focal-segmental glomerulosclerosis. Hematoxylin and eosin staining, × 50.
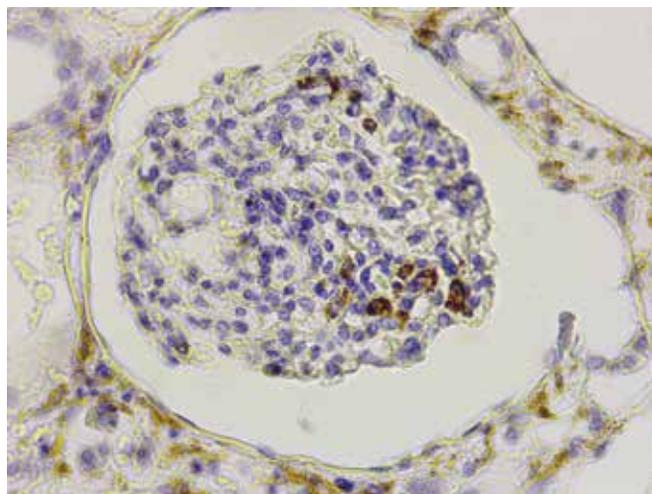

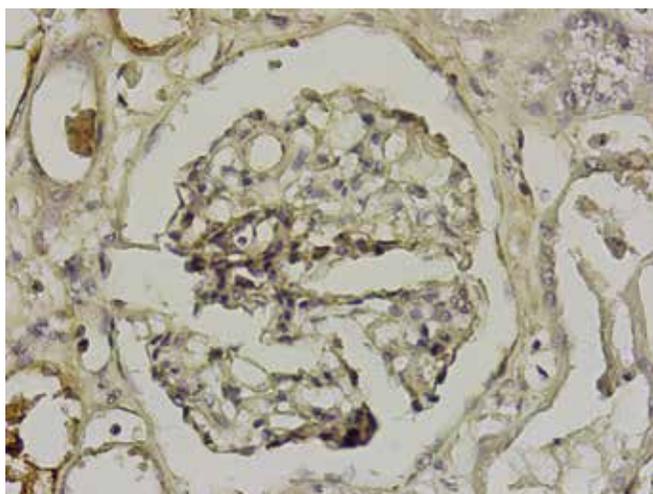**Fig. 2.** Positive expression of macrophages in the mesangial zone. IHCA with CD 68, × 400.

Fig. 3. Granular IgA deposits in the areas of peripheral capillary loops and the basement membrane of the tubules. IHCA with IgA, × 400.
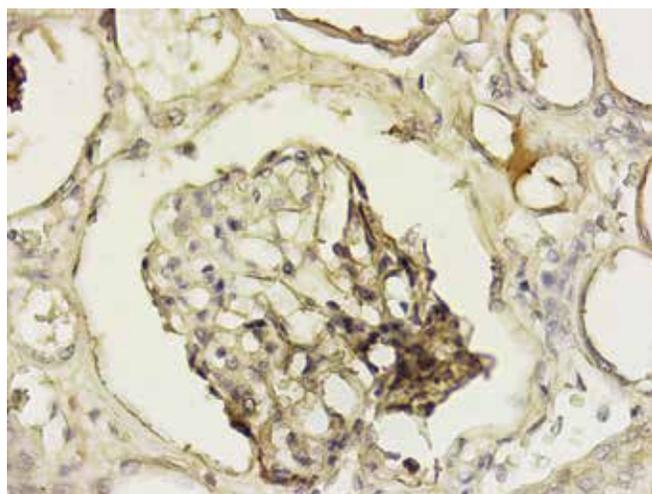

Fig. 4. Granular IgG deposits in the area of collapsed peripheral capillary loops. IHCA with IgG, × 400.

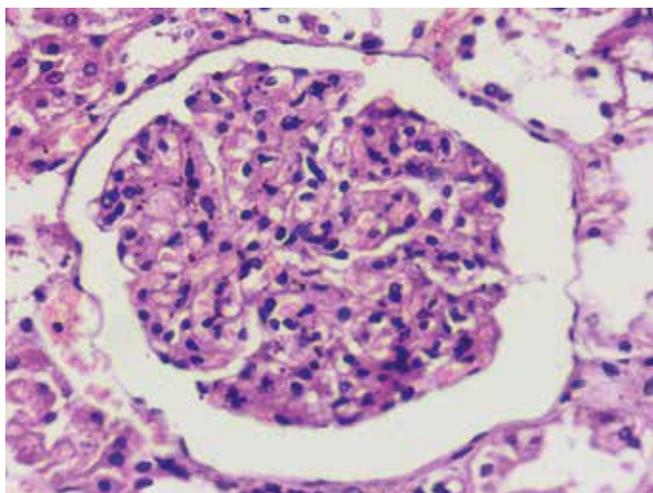**Fig. 5.** Infiltration of glomerular capillary loops by monocytes and neutrophils, moderate cell proliferation. Hematoxylin and eosin staining, × 400.
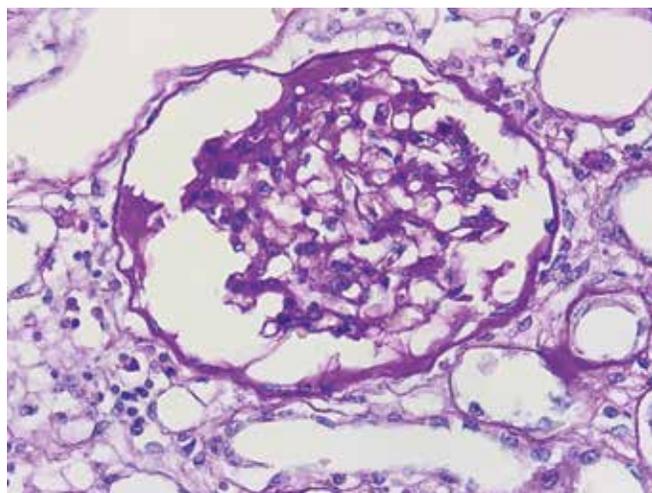

Fig. 6. Perichilar sclerosis, sclerosis of the peripheral capillary loops and thickening of the basement membrane of the Bowman's capsule. PAS reaction, × 400.
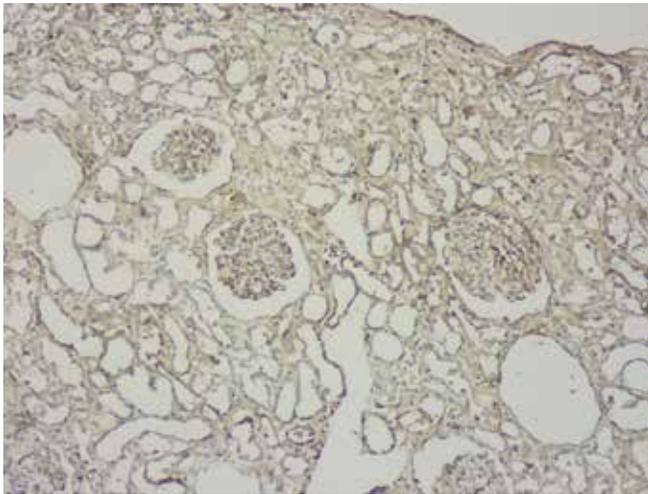
Fig. 7. Linear, segmental granular IgM deposition along the capillary endothelium, in areas of sclerosis, focally in the basement membrane of the Bowman's capsule. IHCA with IgM, × 50.
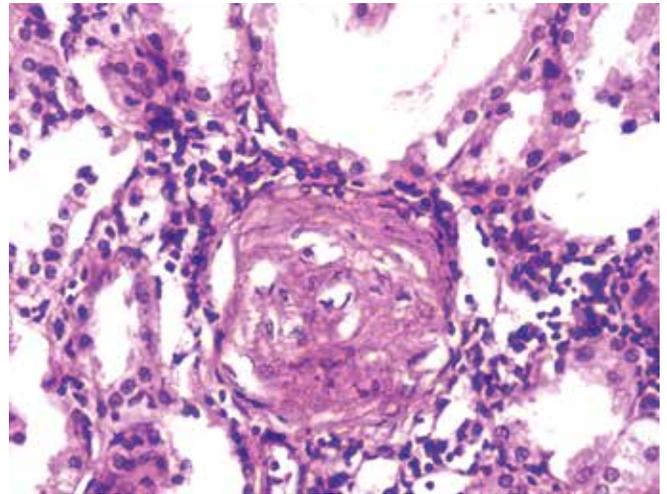

Fig. 8. Total glomerulosclerosis, periglomerular lymphohistiocytic cell infiltration, degenerative changes of tubular epithelium. Hematoxylin and eosin, × 400.
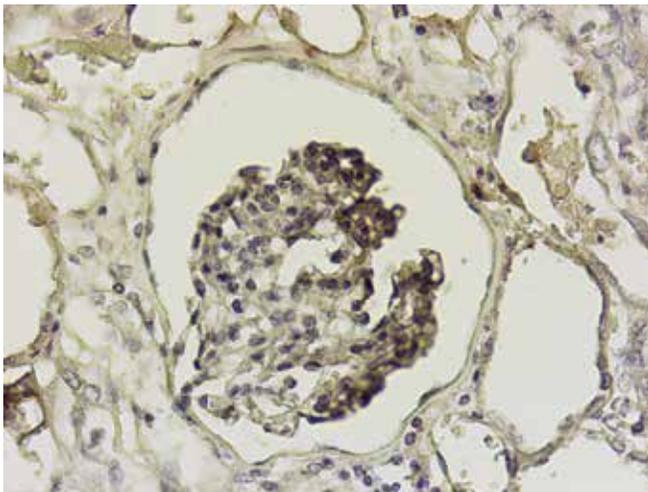
Fig. 9. Granular IgG deposits in the periferic areas of capillary loops with collaptoid and sclerotic changes. IHCA with IgG, × 400.

Fig. 10. Initial interstitial fibrosis in the area of cellular infiltration, focal thickening of the tubular basement membrane of the stroma. Van Gieson staining, × 400.

Fig. 11. Accumulation of B-lymphocytes in the cellular infiltrate between the tubules in the stroma. IHCA with CD 20, × 400.

Fig. 12. Positive expression of macrophages in the interstitial cellular infiltrate. IHCA with CD 68, ×400.

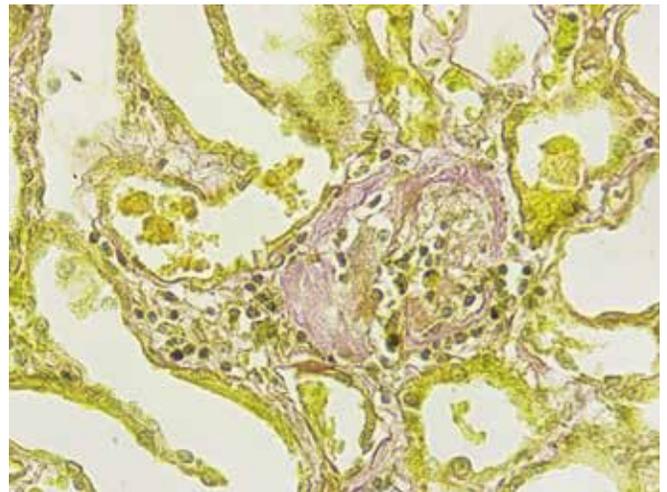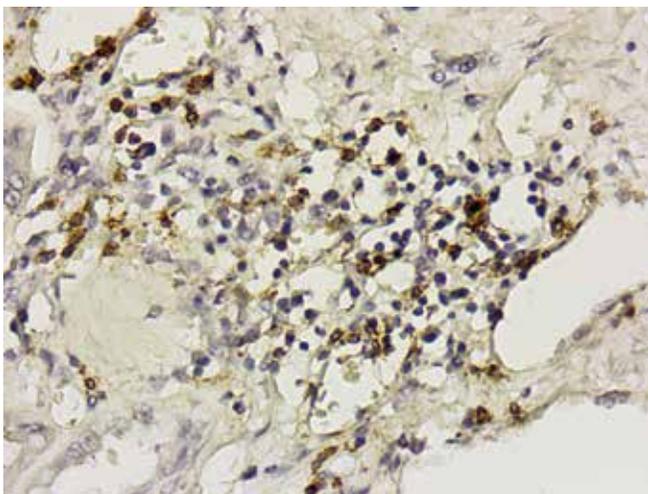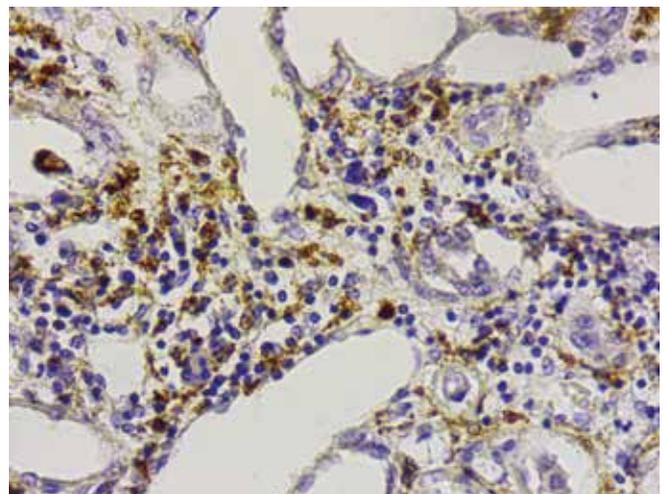the processed material was poured into paraffin according to standard methods. On a rotary microtome Microm HM325 (Carl Zeiss, Germany) serial histological sections 2-3 microns thick were made and stained with hematoxylin and eosin, van Gieson, Congo, Masson, and PAS [17, 18]. For immunohistochemical assay (IHCA), sections were placed on adhesive-coated Super Frost Plus slides (Menzel, Germany). Citrate buffer with pH6, EDTA buffer, pH8 was used for the high-temperature processing of antigen. Detection system UltraVision Quanto HRP, chromogen DAB Quanto manufactured by Thermo Fisher Scientific (USA) were used. The following IHCA stains were used: monoclonal murine antibodies to B-cells CD 20 (clone L26, Thermo Fisher Scientific, USA), monoclonal mouse antibodies to macrophages CD 68 (clone KP1, Thermo Fisher Scientific, USA), monoclonal murine antibodies to T-helpers CD 4 (clone 4B12, Thermo Fisher Scientific, USA), rabbit monoclonal antibody to T-suppressors CD 8 (clone SP16, Thermo Fisher Scientific, USA), rabbit polyclonal antibodies to IgA, IgG, IgM (DAKO, Denmark). The samples were stained with Mayer's hematoxylin. Subsequently, the stained sections were enclosed in a semi-synthetic medium Eukit (Kaltek, Italy).

Methods of morphological diagnosis of kidney damage in HIV and HCV are common: light microscopy for routine staining with hematoxylin and eosin, histochemical staining – Masson's trichrome, PAS reaction, Congo red, complete immunohistochemical (immunofluorescent) immunoglobulin spectrum, and fractions of the complement system C3, C1q (so-called "full house") [19].

When assessing the morphological profile, we performed a description without verification of nosological forms with the predominant use of the criteria of morphological assessment from the Oxford classification (OC) [20-23].

Mesangial hypercellularity (M) is determined by the presence of more than 4 mesangial cells in any mesangial region of the glomerulus and is estimated as "M0" in the presence of <50% of glomeruli, or "M1" at ≥50% [17, 22, 24]. Endocapillary proliferation (E) is defined as hypercellularity due to an increase in the number of cells in the lumen of the glomerular capillaries and is assessed as "E0" – the absence of such, or "E1" – in the presence of at least one. One of the important components of the morphological substrate of nephropathy is segmental glomerulosclerosis (S), which is defined as the presence of adhesions and sclerosis (obliteration of the capillary lumen by the matrix), partially but not the entire glomerular tuft. This indicator is evaluated as "S0" in the absence and "S1" in the presence of segmental glomerulosclerosis, respectively [17, 23, 24]. Regarding the tubular component, the OC "T" criterion was also used – tubular atrophy/interstitial fibrosis, which were defined as the calculated percentage of the biopsy area with atrophy (if any) of tubules and interstitial fibrosis. Depending on the area of the event, it is distributed as follows: "T0" – <25%, "T1" – is 25-50% and "T2" is > 50% [17, 23, 24].

The intensity of staining of immunoglobulin deposits was indicated as absent, weak, moderate and pronounced (from 0 to "+++", respectively). When analyzing the presence of CD 20 positive B-lymphocytes – 10 fields of view were studied at ×200 magnification. To calculate the average number of positive cells determined the area of each field of view, we performed a quantitative count of positively stained cells (brown staining), then calculated the average number of cells per unit area (per 1 mm^2). Microscopic examination and photoarchiving of samples were performed using light optical microscopes "Carl Zeiss" Primo Star with Axiocam105 color camera, "Carl Zeiss" AX10 (Germany), "Nikon eclipse 100" with Delta optical PRO 5 MP camera and data processing system "Axiovision" at magnification of the lens 10, 20, 40, binocular nozzle 1.5 and 10 ocular.

Statistical processing of the results was performed on a personal computer in the program "STATISTICA 10 for Windows", (Copyright® StatSoftInc., USA, license № STA999K347156-W).

RESULTS AND DISCUSSION

HIV and/or HCV-associated kidney disease has never been reported in inpatient and outpatient clinical records neither clinically, nor pathologically. In 12 patients a disorder of renal function was documented, without the etiological factor verification. The mean age of patients was 34.6±11.8 years. Gender distribution: women – 6 (40%) and men – 9 (60%) cases, respectively. All studied cases were Caucasian.

In the assessment of M, we observed segmental and diffuse mesangial proliferation with extracellular matrix expansion with glomerular damage ≥50% in 9 (60%) cases, and involving <50% of glomeruli in 5 (33%) cases. However, taking into account that 8 glomeruli are sufficient to evaluate the data by OC, and the average number of glomeruli in the studied kidney tissues was 50, we interpreted the detected changes as "-" – in the presence of less than 5% of glomeruli, "+ -" – for presence in 5-20% of glomeruli, and "+" or "++" in the detection of M in 20-50% and ≥50% of glomeruli, respectively (fig. 1). IHCA demonstrated CD 68 expression in M zones (fig. 2). The presence of this macrophage component allows us to assess the identified changes as an activated pathological process, rather than changes in residual effects that developed before the ART administration and HIV suppression.

Study of immunoglobulin deposition revealed expression of IgA at the level of "+" – as granular deposits (fig. 3) and IgG with expression up to "+++" (fig. 4).

To describe the "E" component, we evaluated glomerular infiltration by monocytes, the presence of neutrophils and macrophages (exudative component of the inflammatory reaction), which was detected in 1 (6%) case with lesions of up to 20% of the glomeruli. There were also uneven swelling and focal proliferation of endothelial cells in 12 (80%) cases involving 20-50% of the glomeruli. Cellular infiltration in the lumen of capillary loops (monocytes, polymorphonuclear leukocytes, focal karyorexis, fibrinoid necrosis areas) was verified in 3 (20%) cases with monomorphous intensity of "+" (fig. 5). Positive expression of CD 68 macrophages was also obtained, along with negative expression of CD 20 B lymphocytes.

We had sclerotic changes detected in our study group, such as focal tip adhesions of peripheral capillary loops with the epithelium of the Bowman's capsule in 2 (13%) cases, and only in 1 case (6.6%) the lesion was observed in 20% of the glomeruli. Sclerosis of glomerular parietal capillary loops (fig. 6) was detected in 8 (53%) cases, in these areas the expression of IgA, IgG, IgM and C1q in symmetrical areas from "+" to "++" was present (fig. 7).

Total sclerosis of glomeruli was observed in 3 (20%) cases (fig. 8), which was accompanied by a marked periglomerlular infiltrate, indicating the involvement of interstitium in the pathological process with activation of cellular infiltration as in areas with preserved structural elements, and around glomerulosclerosis. In IHCA expression of CD 4 and CD 8 was negative, moderate expression of CD 68 macrophages was observed.

We found changes that were regarded as predictors of sclerosis – focal and microfocal collapse of capillary loops in 8 patients (55%), sclerosis in 10 patients (66%), hyalinosis in 1 patient (6%), focal splitting of capillary loops in 8 patients (53%), Bowman's capsule sclerosis in 5 patients (33%) and thickening of the capillary loops' walls (basement membranes, which are often subjected to pseudo-splitting with the formation of double-contour basement membranes – the phenomenon of "tram tracks"), prechillar focal sclerosis in multiple cases. In these areas, the expression of IgG and C1q was observed within the "+" and "++" intensity, respectively (fig. 9).

Initial interstitial stroma fibrosis was detected in 8 (53%) cases when stained according to Van Gieson (fig. 10), mainly within the "T0" – "T1" range. Degenerative changes in the form of different types of dystrophy with foci of subatrophy and atrophy of the epithelium with thickening and splitting of the tubular basement membrane were present in 3 (20%) cases with a degree of "T0" – "T1". In 7 (46.6%) cases interstitial focal lympho-histiocytic infiltrates were detected, and in 1 case (6.6%) cystic dilatation of the tubules was present. The composition of cellular infiltrates was predominantly monomorphic, represented mainly by CD 20 B-lymphocytes (fig. 11) and CD 68 macrophages (fig. 12). CD 4 expression was observed as single cells outside the infiltrate.

Updated OC includes the presence of crescents – "C", but in our research group, they were not detected. Among the study group, no case of HIV-AN was found to coincide with the predicted spectrum of kidney damage for patients in this cohort, because the lack of HIV replication due to ART eliminates the direct cytopathic effect on the kidneys, and the type of nephropathy itself is not the most common of Caucasian race [18, 25]. For patients with co-infection, one could expect immunocomplex-associated nephropathy of mixed genesis – HIVICK and HCV nephropathy, given the characteristic hyperglobulinemia in HIV, the hyperproduction of which is mainly targeted to viral proteins gp120 and gp41, and immunocomplex kidney damage in HCV [25-27]. However, with ART and a positive immune and virological response (lack of virus replication, increased CD 4/CD 8 levels in the blood), the HIV-ICK component should be absent or minimal, and the detected morphological substrate of immunocomplex renal disease can be regarded as HCV conditioned. Among the study group, the morphological picture was polymorphic, with a predominance of proliferative processes, and moderate changes in the basement membranes of the glomerular capillary loops, often without the development of sclerosis and hyalinosis. Immunocomplex deposits were detected in the glomeruli in areas with corresponding changes (predictors of sclerosis, sclerotic changes of the focal segmental glomerulosclerosis type). At the same time, a discordant response to ART should be considered – no viral replication (minimal viral load in the serum) and low, or

minimal increase in CD 4/CD 8 in the blood, which is regarded as immunosuppression due to hyperactivation of the immune system. The low serological level of T-lymphocytes is mainly due to their inefficient restoring, high susceptibility to apoptosis, asymmetric division, etc. One of the consequences of such disorders is the appearance of "defective forms" of lymphocytes, which lose the ability to competent antigen presentation, which in turn leads to a disorder of the humoral immune system – a cascade of dysfunction of B-lymphocytes. In this case, we can expect the absence of morphological substrate of HIV-AN and HIVICK (no target for the production of antibodies and the launch of complement); at the same time, HCV-associated immunocomplex lesion will also be mildly expressed – due to refractory immunosuppression [18, 27, 28].

CONCLUSIONS

1. No case of HIV-AN corresponding to the literature data and the predicted spectrum of kidney damage for this group of patients was detected.
2. Existing morphological changes can be verified as immune-mediated changes (immunocomplex lesions) of the kidneys by HCV.
3. The study group shows pathological polymorphism with a predominance of proliferative processes and moderate changes in the basement membranes of the glomerular capillaries, often without the development of sclerosis and hyalinosis of capillary loops.
4. Patients with HIV infection belong to the group of high risk of kidney damage, which necessitates the increase of renal damage markers monitoring and renal biopsy performance.
5. CD 68 expression in areas of mesangial hypercellularity and in interstitial infiltrates, as a predictor of interstitial fibrosis and tubular damage, is in favor of prolonged active tissue responses rather than residual changes that developed prior to ART and HIV suppression.

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