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Clinical and Morphological Characteristics of Kidney Damage Caused by Covid 19

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Annotation: SARS-CoV-2 is a betacoronavirus (b-CoV) first described in patients with pneumonia symptoms in Wuhan, China in December 2019 [2]. The emergence of a novel zoonotic betacoronavirus has been hypothesized to cause a pandemic. Based on studies of SARS-CoV and MERS-CoV, in 2015, circulating b-CoVs in bats were shown to have the potential to infect humans by using human angiotensin-converting enzyme 2 (ACE2) as a transfer protein and then binding the resulting complex to the ACE2 receptor on the host cell membrane. A similar mechanism was demonstrated by the 2002 SARS-CoV strain, and the affinity for ACE2 was enhanced in the 2003 SARS-CoV strain [13].

INTRODUCTION. Phylogenetic analysis of SARS-CoV-2 shows that this b-CoV has a highly similar receptor-binding domain (spike glycoprotein) to that of SARS-CoV [6]. The common ancestor of SARS-CoV-2 and SARS-CoV is similar to bat b-CoV HKU9-1 [4]. Recently published genetic sequence results of SARS-CoV-2 show 80% similarity to SARS-CoV and 50% similarity to MERS-CoV, making SARS-CoV-2 the seventh representative of the b-CoV family with an anthropozoonotic mechanism of infection and the third b-CoV with proven bat origin [9]. The first step of SARS-CoV-2 infection is binding to the host cell receptor and penetrating the target cell. B-CoVs have a three-dimensional structure of the spike protein, through which they bind to ACE2. Cells expressing ACE2 may be susceptible to COVID-19 infection. Moreover, this applies not only to type II alveolar cells, but also to epithelial cells of the intestine, stomach, proximal renal tubules, testes and ovaries, tongue and oral mucosa, heart and blood vessels, as well as arterial smooth muscle cells [9, 10].

Thus, the assumption that SARS-CoV-2 can penetrate not only the lungs, but also the upper respiratory tract, intestines, heart and kidneys, especially in the case of viremia, is based on knowledge of the mechanisms of infection and persistence of the virus in the human body, as well as data from cytogenetic morphological comparison of related b-CoVs.

Clinical presentation and extrapulmonary manifestations of COVID-19

Classic lung injury associated with SARS-CoV-2 occurs as pneumonia. Complications of COVID-19 include acute respiratory distress syndrome (ARDS), arrhythmia, shock [11], acute kidney injury (AKI), acute heart failure (AHF), liver dysfunction, secondary infection, sepsis [3, 14]. SARS-CoV-2 has a cytopathic effect and causes direct diffuse damage to type II alveolar cells [13]. Data from numerous studies show that SARS-CoV-2 infection increases markers of the systemic inflammatory response (SIR), such as C-reactive protein (CRP), interleukin-6 (IL-6), interferon-γ (INF-γ), tumor necrosis factor-α (TNF-α), which leads to the development of a cytokine storm, which significantly worsens the treatment prospects and prognosis for the life of a patient with COVID-19 [12, 18]. The complexity of the course of pneumonia in COVID-19 is due not only to the direct cytopathic effect of SARS-CoV-2, but also to severe lymphopenia and hypoxia, which leads to the progression of lung dysfunction and the involvement of other organs and systems in the pathological process. It is assumed that SARS-CoV-2 is able to penetrate lymphocytes and initiate apoptosis processes in them [19]. A number of studies have shown that b-CoV causes direct myocardial damage such as myocarditis [16, 17]. In addition, in patients with chronic heart disease, b-CoV significantly worsens the prognosis [19–21]. In a comparative cytogenetic and morphological analysis between SARS-CoV and SARS-CoV-2 and based on the clinical, pathological and laboratory features of SARS-CoV infection in patients with SARS in 2003, AKI was found to be rare but characterized by extremely high mortality (33 out of 36 cases, i.e. 91.7%). Due to the high homology of SARS-CoV-2 and SARS-CoV, the results of this study were associated with the idea of direct renal injury by SARS-CoV-2 [22]. Studies in small cohorts of COVID-19 patients have shown that proteinuria and hematuria are common findings, detected in almost 40% of patients on hospital admission. In addition, AKI is more common in patients infected with SARS-CoV-2 when infected with SARS-CoV [23].

Thus, SARS-CoV-2 causes:

- direct damage to type II alveocytes, which often leads to the development of viral pneumonia and ARDS;
- SIRS and has a lymphopenic effect, which can lead to damage to other organs and systems, the development of multiple organ failure and disseminated intravascular coagulation (DIC syndrome) in patients with COVID-19 [24].

Kidney involvement in the pathological process in COVID-19.

The main manifestation of kidney damage in COVID-19 is considered to be AKI [25–27]. High expression of ACE2 in the kidneys is observed in the proximal tubules and, to a lesser extent, in podocytes. At the same time, ACE2 expression in the glomerular endothelium and mesangium is minimal. This explains the predominant damage to the renal tubular apparatus and the development of AKI as acute tubular necrosis [34].

In early studies, Chinese scientists observed 138 patients with COVID-19 and found that their azotemia levels were within the reference range of normal values [29]. When analyzing the medical records of 1099 patients with COVID-19, serum creatinine levels above 133 μmol/L were observed in only 1.6% of patients. Based on the data from the first two studies, it was concluded that AKI is rare in COVID-19, and SARS-CoV-2 infection is not associated with hyperazotemia [24].

The first study was conducted between January 6 and February 21, 2020, and included 193 patients with COVID-19, including 128 patients with mild to moderate COVID-19 and 65 patients with severe disease, including 32 deaths; and 28 patients with non-SARS-CoV-2 associated pneumonia, including 15 non-SARS b-CoV pneumonia and 13 patients with mycoplasma pneumonia. At admission, 59% of patients had proteinuria, 44% had hematuria, 14% had elevated plasma urea, and 10% had hypercreatininemia. It is important to note that all kidney damage indicators were more pronounced in the group of patients with COVID-19 compared to patients with non-SASR-

associated pneumonia. There was no reason to characterize the changes detected upon admission as AKI, however, as lung damage progressed and the duration of hospitalization increased, these indicators tended to worsen and in some cases could and were interpreted as AKI. In a univariate Cox regression analysis, the researchers found that proteinuria, hematuria, hyperazotemia, hyperuricemia, and an increase in D-dimer levels were significantly associated with mortality in patients with COVID-19. In addition, the risk of death in patients with COVID-19 who developed AKI was 5.3 times higher than in patients without AKI [20].

Another study included 355 patients with confirmed COVID-19, 56 patients (15.8%) had signs of AKI at the time of hospitalization. It was found that the oxygen saturation level and excretory renal function (ERF) in patients infected with SARS-CoV-2 did not significantly correlate with each other. When conducting a multivariate logistic regression analysis, it was found that the three main risk factors (RF) determining the development and progression of AKI in patients with COVID-19 were age over 75 years, diabetes mellitus, and male gender. It is important to note that the mortality rate among 56 patients with AKI and COVID-19 on the 11th day of the disease reached 33.9%, which is significantly higher than the average risk of death compared to the group of patients with COVID-19, but without AKI. The presence of AKI in the group of patients with COVID-19 is an independent, prognostically unfavorable risk factor that determines the mortality of patients with COVID-19 [21]. Another study analyzed data from 116 patients with COVID-19, of which 59 people (50.8%) were diagnosed with mild pneumonia, and 46 people (39.7%) with severe pneumonia; 11 people (9.5%) were initially diagnosed with ARDS, which required treatment in the intensive care unit. Comorbidity with other somatic pathologies was observed in 51 patients (43.9%). In this case, arterial hypertension accounted for 37.1%, diabetes mellitus - 15.5%, oncological pathology - 10.3%, acute cerebrovascular accident - 6.0% and chronic kidney disease (CKD) stage 5, requiring hardware methods of replacing lost organ functions by hemodialysis (HD) and its modifications - 4.3%. This study found that patients with COVID-19 without CKD did not have a decrease in EFP either after SARS-CoV-2 infection or during treatment for pneumonia. In 12 patients (10.8%) without CKD, a slight increase in plasma urea and / or creatinine was detected after SARS-CoV-2 infection, which tended to increase during treatment for pneumonia. It is important to note that all patients with COVID-19 showed signs of increasing azotemia within 48 hours of hospitalization. Proteinuria was also a common diagnostic finding [22].

From January 14, 2020, to February 17, 2020, 37 cases of COVID-19 were reported among 230 hemodialysis patients and 4 cases among staff [23]. Most patients had mild symptoms of COVID-19, while others were admitted to the intensive care units. During the epidemic, 7 hemodialysis patients died, including 6 with COVID-19 and 1 without COVID-19. The causes of death were apparently not related to pneumonia. Analysis of peripheral blood samples from SARS-CoV-2-infected HD patients showed a marked decrease in the numbers of T cells, T helpers, killer T cells, and NK cells in peripheral blood mononuclear cells (PBMCs), as well as lower serum levels of inflammatory cytokines compared with non-HD patients with COVID-19. Collectively, this study reported that HD patients with COVID-19 experience mild disease that does not progress to full-blown pneumonia, likely due to decreased immune function and reduced effects of “cytokine storms” [23, 24]. Thus, the evolution of knowledge about renal involvement in the pathological process of COVID-19 has undergone significant changes in a short period of time. Understanding the mechanisms of interaction of the SARS-CoV-2 virus with target cells, the role of ACE2 in increasing infection, the expression of ACE2 on the membranes of alveocytes, intestinal epithelium, renal tubules and much more allows us to assume the widespread involvement of organs and systems in the pathological process with the development of both secondary complications associated with the persistence of the virus, activation of the immune system, hypoxia, and ongoing therapeutic measures, drug load, primary damage to these cells by SARS-CoV-2.

Pathological picture of the kidneys in COVID-19

Light microscopy revealed benign hypertensive nephrosclerosis and autolysis in most cases. However, no specific glomerular pathology was observed in the kidneys. Varying degrees of acute tubular necrosis were detected in all seven samples examined. Case 3, a patient with concomitant myelodysplastic syndrome, showed paraprotein deposition in the kidneys. No interstitial infiltrate or interstitial nephritis was detected in all other cases. Careful ultrastructural examination of glomerular and tubular epithelial cells did not reveal the virus or virus-like particles. Immunofluorescence studies on frozen sections were not performed due to the high virulence of the samples. In situ hybridization did not detect SARS-CoV-2 in any of the samples. Diffuse alveolar damage was detected in the lungs in all seven cases. In kidney fragments from four patients with developed renal dysfunction, moderate or severe acute tubular necrosis, as well as autolysis, were observed, and the degree of necrosis and the frequency of autolysis correlated with the level of serum creatinine and the rate of its increase during the development of AKI [20]. According to the results of our own observations during an autopsy of a 67-year-old patient who died from pneumonia caused by SARS-CoV-2, thrombus formation and loss of fibrin threads were detected in the renal glomeruli (Fig. 5, A–G). Earlier studies during the 2003 SARS outbreak found that only 6% of patients infected with SARS-CoV suffered from AKI. Although it was a relatively uncommon feature of the disease, AKI was identified as a fatal complication of ARI, given that nearly 92% of ARI patients with AKI died. To assess whether AKI was caused by active SARS-CoV replication in tubular cells that express high levels of ACE2, Lai and colleagues examined the presence of SARS-CoV viral particles by transmission electron microscopy in kidney specimens from deceased ARI patients with AKI. SARS-CoV was not detected in any of the patients analyzed, suggesting that renal failure was likely due to multiple organ failure [16].

They also suggested that AKI in patients with SARS may be the result of specific pathogenic conditions, including cytokine release syndrome [12], rather than active viral replication in the kidneys. Indeed, the growth of viral infection in alveolar cells leads to massive recruitment of immune cells that produce large amounts of cytokines, causing multiple organ failure. That this may be the case for SARS-CoV infection was revealed in a subsequent study, which showed that an interferon-gamma-induced “cytokine storm” was induced by SARS-CoV, leading to severe organ damage in patients [23]. This process is not new to nephrologists, as cytokine-mediated inflammatory AKI has been reported in a number of clinical settings, such as treatment with immune checkpoint inhibitors and chimeric antigen receptor (CAR) T cells in cancer patients [24], as well as in thymoglobulin treatment in kidney transplant patients [15].

Regarding the novel coronavirus, a recent study has shown that the human kidney is a specific target for SARS-CoV-2 infection [26]. In situ viral nucleocapsid protein assay in postmortem kidney revealed that SARS-CoV-2 antigens accumulated in the renal tubules [27-32]. This suggests that SARS-CoV-2 directly infects the human kidney, causing AKI, which facilitates the dissemination of the virus in the body. The difference between the higher renal tropism of SARS-CoV-2 and SARS-CoV may be explained by the increased affinity of SARS-CoV-2 for ACE2, which allows it to enhance kidney injury and act as a viral reservoir. Immunohistochemical analysis showed that SARS-CoV-2 NP antigen accumulates in the renal tubules. Viral infection not only causes activation of CD68+ macrophages with their infiltration into the tubulointerstitium, but also enhances the deposition of complement C5b-9 in the tubules [19].

CONCLUSION. Kidney damage in COVID-19 is an integral part of the pathological process, and the severity of lung damage determines the involvement of the kidneys. Clinical and morphological associations between pathomorphological changes in the lungs and kidneys revealed common patterns of damage to the vascular bed with increased thrombus formation and fibrinolysis, which may be associated not only with systemic manifestations of DIC syndrome, but also be an independent kidney injury in COVID-19. Acute kidney injury is associated with the severity of lung damage, and its occurrence should be considered in the context of multiple organ failure. A separate mechanism of kidney tissue damage in COVID-19 is the "cytokine storm",

which is associated, in turn, with the viral load. SARS-CoV-2 accumulation in renal tubules may serve as a viral reservoir, and activation of CD68+ macrophages leads to their infiltration into the tubulointerstitium and enhances C5b-9 deposition in the tubules.

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