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Review Article

Renal involvement in COVID-19: a review report

Pinki Pandey[1], Megha Palli[2]*, Anshul Sawhney[3], Alok Dixit[4]

[1]Department of Pathology, UPUMS, Saifai, Uttar Pradesh, India
[2]Department of Pathology, [3]Department of Dentistry, MSD ASMC, Bahraich, Uttar Pradesh, India
[4]Department of Clinical Pharmacology, UPUMS, Saifai, Uttar Pradesh, India

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***Correspondence:**
Dr. Megha Palli,
E-mail: drmegharalli@gmail.com

ABSTRACT

COVID-19 is recent emerging pandemic caused by SARS-CoV-2 (severe acute respiratory syndrome- Coronavirus). It is seen mainly affecting lungs, but many recent studies have shown involvement of hematological, kidney, gastrointestinal and other systems. In kidneys it mainly affects the tubules and interstitial areas. The main pathology behind involvement of renal system in COVID-19 is due to presence of ACE 2 receptors in proximal tubules. These receptors are same like that found in lungs and they form binding sites for coronavirus and hence causing the disease. Therefore, patients presenting with raised serum urea and creatinine should be checked for potential renal damage caused by virus and their urine samples should also be tested for presence of coronavirus. Effective testing and prompt management will prevent this virus from being transmitted in community.

Keywords: COVID-19, Renal, ACE 2, Acute tubule injury

INTRODUCTION

Novel Coronavirus disease (COVID-19) is a caused by SARS-CoV-2 and is contagious disease. This disease is primarily manifesting as an acute respiratory illness with interstitial and alveolar pneumonia, but it can affect multiple organs such as the kidney, heart, digestive tract, blood, and nervous system. Following rapid spread in China in December 2019, it was declared a global pandemic by world health organization (WHO) in February 2020.[1] The virus is seen to enter the blood, accumulate in kidney, and cause damage to renal cells. In 15% cases, COVID-19 RNA was found in the plasma of by real-time polymerase chain reaction.[2] Around 6.7% patients with SARS developed acute kidney injury (AKI), and the mortality of those with AKI was 91.7%.[3] However, it has been observed that kidney injury has appeared relatively less with COVID-19 than with Middle East respiratory syndrome or hantavirus infections, this may be due to the different pathological mechanisms. Clinically, the incidence of AKI in COVID-19 varied from 0.9% to 29% in different centers.[4] Thus, understanding how the kidney is affected by SARS-CoV-2 is urgently warranted.

SARS-CoV-2 belongs to the Betacoronavirus Genus and its genome sequence has shown close relationship with bat SARS-like coronavirus strain BatCov RaTG13.[5] COVID-19 is more contagious than SARS and MERS (Midddle East Respiratory syndrome) and it spreads by human-to-human transmission via droplets, fecal, or direct contact, and has an incubation period estimated at 1 to 14 days (usually 3 to 7 days). Infection has been reported in all ages, including children. The majority of infections are mild, presenting with a flu-like illness.

This review will help in understanding kidney lesions in COVID-19 cases and hence help in early diagnosis and prevention of complicated cases.

PATHOGENESIS

Many theories have been put up to understand involvement of kidneys in COVID-19. Few studies

believe that there is direct cytopathic effect of novel coronavirus on the kidneys. This is supported by detection of virus fragments by polymerase chain reaction (PCR) in blood and urine in patients with SARS and COVID-19.[2,6] Similar to SARSCoV, it has been shown that novel coronavirus uses angiotensin converting enzyme 2 (ACE2) as a cell entry receptor. These receptors are seen in kidney and lungs, so an ACE 2-dependent pathway has been postulated for mechanism of kidney disease in COVID-19 cases.[7,8] Binding sites for SARS-CoV and MERS-CoV identified as angiotensin converting enzyme and dipeptidyl peptidase-4, were expressed on renal tubular cells. Both these viruses affected kidney and viral RNA was found in urine of these patients.[6]

Another study suggests that there is deposition of immune complexes of viral antigen or virus-induced specific immunological effector mechanisms (specific T-cell lymphocyte or antibody) causing damage the kidney as supported by case of immune-mediated glomerulonephritis. However, no electron dense deposits were seen in kidney specimens of SARS patients.[3]

Another study suggests there is indirect effect on renal tissue, such as hypoxia, shock etc due to release of virus induced cytokines.[9] This theory was supported by Cheng et al who observed increased creatine kinase levels in 138 patients with COVID-19 and kidney involvement.[10]

Recently, SARS-CoV-2 was shown to also invade target cells by CD147, a transmembrane glycoprotein along with interaction with cyclophilins, caveolin-1, integrins etc. CD147 is highly expressed on the cell surface of proximal tubular epithelium and infiltrating inflammatory cells. Cyclophilins play an important role in replication of coronavirus. And interrupting CD147-cyclophilins axis may be a promising strategy to treat COVID-19.[11,12]

Few studies consider that there is state of dehydration leading to pre-renal failure with acute tubular necrosis or kidney involvement may be a part of drug toxicity.[13]

PATHOLOGICAL FEATURES

Su et al studied histopathological changes in 26 postmortem kidney specimens of COVID-19 cases. They observed vacuolar degeneration, dilatation of the tubular lumen with cellular debris and loss of brush border indicating proximal acute tubule injury (ATI) along with areas of frank necrosis. Four cases showed detachment of epithelium with bare tubular basement membrane. In 2 patients, they observed acute pyelonephritis along with multiple foci of bacteria and diffuse polymorphonuclear casts in the lumen of tubules. There were cases with diffuse RBC aggregates and obstruction present in peritubular and glomerular capillary loops. There was no fragmentation of erythrocytes or platelets or fibrin thrombi. Occasional cellular swelling and edematous expansion of the interstitial space was seen in distal tubules and collecting ducts without significant inflammation. Lymphocytic infiltrates were present in areas of nonspecific fibrosis including subcapsular areas. Nodular mesangial expanding and hyalinosis of arterioles was seen in glomeruli along with evidence of diabetic nephropathy in 2 of the patients with diabetes, and arteriosclerosis of medium-size arteries with ischemic glomeruli in 11 of the patients with hypertension.[12]

Li et al studied 193 COVID-19 cases in whom 59% presented with proteinuria and 44% with hematuria, Blood urea nitrogen raised in 14% cases and serum creatinine was raised in 10% cases. They defined patients with AKI according to kidney disease: Improving global outcomes (KDIGO) criteria, which states AKI as any of following (not graded): (1) increase in serum creatinine (SCr) by=0.3 mg/dl (=26.5 µmol/l) within 48 hours; or (2) increase in SCr to=1.5 times of baseline, which is known or presumed to have occurred within the prior 7 days; or (3) urine volume <0.5 ml/kg/hour for 6 hours.

They observed through a univariate Cox regression analysis that proteinuria, hematuria (blood in urine), along with elevated levels of blood urea nitrogen, serum creatinine, uric acid as well as D-dimer were significantly associated with the death of COVID-19 patients. They also noticed that COVID-19 patients that developed AKI had approximately five times higher mortality risk of those without AKI. They concluded that to prevent fatality in such cases, caution in monitoring the kidney functions of severe COVID-19 patients is essential.[8]

Mou et al did a large meta-analysis in 5448 COVID-19 cases in China and statistically analyzed the incidence of AKI, the mortality rate with AKI and the risk of death with AKI during a COVID-19 infection. They observed that though the incidence of AKI in COVID-19 cases is about 3.8%, but the in-hospital mortality rate with AKI was up to 86.8% and the odds of death with AKI in COVID-19 infected patients was about 24.2 times higher than those without AKI.[14]

Volbeda et al did study on histopathological findings of diagnostic and postmortem kidney biopsies from patients with COVID-19 in 2021. They studied 89 diagnostic and 194 postmortem renal biopsies and observed that most common lesion was in glomerulus (74%). according to their study, most common glomerular lesions were collapsing focal segmental glomerulosclerosis (c-FSGS) in 54% and thrombotic microangiopathy (TMA) in 9% of patients. In post mortem group also, TMA was reported in 10% cases. Most common tubular lesion was acute tubular necrosis (ATN) in both groups.[15]

Gambella et al did retrospective study on 9 cases of COVVID-19 with symptoms of nephritic syndrome and AKI. They observed minimal change disease (four cases), acute tubular necrosis (two cases), collapsing glomerulopathy (two cases), and C3 glomerulopathy (one

case). None of the cases showed viral or viral-like particles on ultrastructural analysis.[16]

May et al showed that majority of cases showed Collapsing glomerulopathy which is now known as COVID-19 associated nephropathy (COVAN). Kidney biopsy showed COVAN harbored 2 risk alleles APOL1 variant amongst 91.7% of African American or Hispanic descents. On the other hand, only 35.6% of patients with non-COVAN possessed 2 risk alleles of the APOL1 variant. Association of high-risk APOL1 genotype and kidney disease have also been reported to be associated with infections like cytomegalovirus, parvovirus B19, Epstein-Barr virus and particularly HIV. [17]

HIV associated nephropathy (HIVAN) was reported by Velez et al and showed diffuse CG, tubular injury and distended tubules containing proteinaceous cast forming "tubular microcysts". Electron microscopy shows collapsed capillaries with wrinkled glomerular basement membrane and diffuse foot process effacement. Tubulo-reticular inclusions, known as "interferon footprint", are often observed in glomerular endothelium.[18]

Apart from clinical correlation between COVID-19 and kidney, transmission microscopy also helped in establishing viral particles in kidney and lung biopsies.[19]The recent detection of the viral RNA in urine samples strongly supports the evidence of viral tropism in renal tissue. The ultrastructural studies have been done in other organs like CNS. Also, electron microscopy serves an important tool in fast identification of viral RNA, its location; cellular or subcellular. In study by Su et al they observed spherical virus particles in the cytoplasm of renal proximal tubular epithelium as well as in the podocytes and less so in distal tubules. In diabetic cases, they observed features related to diabetic nephropathy without any other deposits. They observed virus particles in podocytes, along with foot process effacement and vacuolation. They observed changes in capillary loops in form of obstruction due to erythrocytes aggregation and areas of endothelial injury.[12]

Immunohistochemical staining have also been used to study histological changes in COVID-19 cases. Su et al observed CD235a positivity in areas of microvascular obstruction and confirmed that obstruction was majorly due to erythrocytes. They also observed minimal staining with CD 61 owing to platelet aggregation. They also studied ACE 2 staining in 5 patients and expression was seen in proximal tubular cells and areas of AKI.[12]

CLINICAL FEATURES

Incubation period for COVID-19 is of 1-14 days. The most common symptoms are fever, fatigue, and dry cough, headache, nasal congestion, sore throat, myalgia, or arthralgia.[20] Few patients, especially children, had nausea, vomiting and diarrhea. Around second week, patients may progress to shortness of breath and hypoxemia.[1,2]As disease progresses, complications like shock, sepsis, acute cardiac injury, AKI and even multi-organ dysfunction may occur.[21,22] Coagulopathy and thrombocytopenia are also common complications for COVID-19 infection, which increase the risk of hemorrhage and thrombosis.[23] Laboratory data of COVID-19 cases reveal lymphocytopenia, and few severe cases showing increased D-Dimer, prolonged prothrombin time.[1,2,21] Few patients presented with damage to liver and heart and showed raised levels of aminotransferase, creatine kinase, and myoglobin.[2,22] patients with renal dysfunction presented with increased serum creatinine or blood urea nitrogen.[24] Few cases showed raised infection related biomarkers like C-reactive protein (CRP), interleukin-6 (IL-6) and erythrocyte sedimentation rate (ESR).[24] The summary of observations is given in Table 1.

Table 1: Summary of involvement of kidney in COVID-19 cases.

Variables	Glomeruli	Tubules and interstitium
Light microscopy	Segmental fibrin thrombi Focal segmental glomerosclerosis (FSGS) Collapsing glomerulopathy	Acute tubular injury Bacterial foci Pigmented casts Arteriosclerosis
Electron microscopy	Dense deposits	Virus particles in podocytes Subendothelial lucent expansion
Immuno-histochemical		CD 235, CD 61, CD 31 in peritubular capillaries ACE 2 in proximal tubules

DIAGNOSTIC TESTING

Real time RT-PCR of nasal and pharyngeal swab, sputum, blood, faeces and urine specimens is done to confirm coronavirus cases. RNA is extracted from these samples and RT-PCR detection with appropriate probes and primers is done. Value of cycle threshold (Ct)<37 is considered negative and >40 is considered positive.[1,20]

Detection of IgM and IgG antibodies can also be used for diagnosis but due to high false negative results, it is not being used widely.[20]

CONCLUSION

COVID-19 is mainly seen affecting lungs, but presence of kidney abnormality in form of AKI is also been

observed in elderly patients. Kidney function tests and biopsy tests are recommended in cases with raised serum creatinine and urea. Early detection of kidney involvement may save patients from landing in severe conditions leading to dialysis as only option. Early and prompt intervention may reduce overall death rate among infected patients.

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