SARS-CoV-2 infection of kidney tissues in some severe and fatal cases of COVID-19

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Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection can lead to diverse clinical manifestations and pathologies that involve multiple organs. Even though the disease severity is manifested mainly in the respiratory tract, which is the primary target of SARS-CoV-2 infection, acute kidney injury in the form of acute tubular necrosis has also been noted in some COVID-19 cases. It is not entirely clear whether renal cells can be infected by the virus that might be involved in acute kidney disorder. In a recent publication by Radovic and colleagues (1) that has been selected as the editor's choice paper published in the Journal of Medical Virology, the authors provided strong histopathological and immunofluorescence evidence of SARS-CoV-2 infection and tissue injury of renal parenchymal and tubular epithelial cells, which strongly suggest an active viral replication in the kidney of some severe and fatal COVID-19 cases, and to a lesser extent, a potential role for innate immune cells in viral infection and renal disease pathogenesis.

Commentary

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Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection can lead to diverse clinical manifestations and pathologies that involve multiple organs. Even though the disease severity is manifested mainly in the respiratory tract, which is the primary target of SARS-CoV-2 infection, acute kidney injury in the form of acute tubular necrosis has also been noted in some COVID-19 cases. It is not entirely clear whether renal cells can be infected by the virus that might be involved in acute kidney disorder. In a recent

publication by Radovic and colleagues (1) that has been selected as the editor's choice paper published in the Journal of Medical Virology, the authors provided strong histopathological and immunofluorescence evidence of SARS-CoV-2 infection and tissue injury of renal parenchymal and tubular epithelial cells, which strongly suggest an active viral replication in the kidney of some severe and fatal COVID-19 cases, and to a lesser extent, a potential role for innate immune cells in viral infection and renal disease pathogenesis.

Main Texts

SARS-CoV-2 infection can lead to diverse clinical pathologies that involve multiple organ systems (2). The virus mainly targets pneumocytes and endothelial cells in the respiratory tract that can lead to pulmonary tissue damage and acute respiratory syndrome. In some severe cases, acute kidney injury has also been associated with an unfavorable prognosis for the patients (3). Previous studies have established that human kidney cells express cellular factors, e.g., the angiotensin-converting enzyme II (ACE2) that serves as the main receptor of SARS-CoV-2 and the transmembrane protease serine 2 (TMPRSS2) that cleaves the viral spike protein into the S1 and S2 subunits to form the virion envelope structure, which are needed to mediate virus entry into cells (4,5).

The authors of the current study (1) used histopathological and immunofluorescence methods to provide evidence of direct viral infection and tissue damage of renal parenchymal and tubular epithelial cells in anonymized postmortem kidney specimens of four adult COVID-19 cases that were overseen by the autopsy service at the Icahn School of Medicine at Mount Sinai, New York, USA. Additional details of these fatal COVID-19 cases have been published elsewhere (6). Using the conventional hematoxylin-eosin (H&E) staining and indirect immunofluorescence (IF) assay, the authors showed various degrees of acute tubular necrosis, segmental glomerulosclerosis, and autolysis of the renal tubular cells in 3 of the 4 cases. These findings are consistent with a previous report (7), which also showed evidence of kidney injury in some fatal COVID-19 cases. On the contrary, none of these histopathological findings were noted in renal tissues of healthy individuals in the current study.

Since there were clear evidence of kidney tissue damage in some of the COVID-19 cases under examination, it was important to know whether this was due to a direct virus infection of the kidney and which cell types were involved. Toward this end, the authors used IF assay with antibody that was known to react to the viral S1 protein to show S1 presence in groups of cells in the renal parenchyma in all four fatal COVID-19 cases but not in healthy controls. To determine which renal cell types were infected by the virus, the authors performed dual-IF staining for the viral S1 protein along with other known markers of some of the major kidney cell types, such as tubular epithelial cells, vascular endothelial cells, and mesangial cells, and found viral S1-positive staining only in the tubular epithelial cells in COVID-19 cases but not in healthy controls. These findings are consistent with previous reports of SARS-CoV-2's distinct tropism for this cell type in the kidney (8,9). To ensure that the detection of the S1 viral protein in kidney cells was due to authentic viral infection, the authors cleverly stained kidney tissues with a different antibody that is known to react to the viral nonstructural protein 8 (NSP8) that is only expressed following viral genome replication and protein translation and processing. Accordingly, the authors observed NSP8 staining in similar groups of cells in the renal parenchyma in all four fatal COVID-19 cases but not in healthy controls, confirming active SARS-CoV-2 replication in renal cells.

As a previous report (6) has provided evidence of infiltration and infection of various immune cells in the lung tissue of severe COVID-19 cases, the authors decided to perform dual-IF staining of the viral S1 protein and some known markers of innate immune cells (i.e., monocytes, macrophages, and natural killer cells) and of adaptive immune cells (i.e., B cells, CD8 T cells) as well as of the T-cell activation marker in COVID-19 kidney tissues. They found a limited number of immune cell infiltrates in 3 of 4 cases and more immune cells in the kidney tissues of a patient who was known to suffer from chronic kidney disease. Among the immune cell types examined, the authors clearly observed S1-positive staining only in a very small number of monocytes, macrophages, and NK cells, but not in any of the lymphocytes (B and T cells) examined. In a couple of the cases, the authors only observed infiltration of monocytes and macrophages, but failed to detect any S1 positivity. Similarly, only a few NK cells in the kidney tissues stained positive for the S1

protein. This aspect of the study requires some careful interpretations. Whereas the authors attributed the relatively low levels of S1 staining for limited virus-replication capacity in these immune cells, it might be important to correlate it with the level of NSP8 staining, which was not performed. It might also be possible that some of these rare and seldomly infected innate immune cells in the kidney represented bystander cells that got infected as they infiltrated the kidney in response to kidney injury.

In summary, the authors of the current study (1) provided strong evidence of SARS-CoV-2 infection of renal tubular cells that might explain the potential role of those cells in COVID-19-associated renal disease pathology. The biological and physiological significance of these findings lie in the fact that renal tubular cells are known to be involved in the renin-angiotensin-aldosterone-system (RAAS), which plays an important role in blood pressure regulation as well as in maintaining the body's water-salt balance (10). This RAAS system is regulated by angiotensin II (Ang II), which acts on both the type 1 and type 2 angiotensin receptors (AT1R and AT2R) to regulate blood pressure and renal sodium and water resorption by stimulating vasoconstriction. The ACE2 protein acts as a counteractive regulator to RAAS activation to lower blood pressure and to promote vasodilation of blood vessels and preventing tissue-associated oxidative stress and inflammation. Thus, it is possible that binding of the ACE2 receptor to the viral spike protein during SARS-CoV-2 infection process could lead to dysregulated RAAS pathway and might result in hypertension and renal failure (10). However, it remains to be determined whether ACE2 serves as the predominant cellular receptor for SARS-CoV-2 in the kidney and whether viral infection of the renal tubular cells can directly or indirectly contribute to RAAS system dysregulation and/or cardio-renal dysfunctions in severe and fatal COVID-19.

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