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Review Article

The pathophysiology and pathology of SARS-CoV-2 infection

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ABSTRACT

SARS-CoV-2 infection is a major pandemic that has involved all continents in the world. It has caused almost seven million deaths since its onset. SARS-CoV-2 commonly enters cells by binding to angiotensin-converting enzyme 2 (ACE2) molecules on the surface of cells in the human body. SARS-CoV-2 infection, although mild in many patients, has the potential to cause dysfunction of many organ systems in the body. The body response to the internalisation of the virus in the epithelial cells of the lungs can lead to alveolar epithelial inflammation, commonly referred to as the exudative phase of acute respiratory distress syndrome (ARDS). Cardiac symptoms shown by patients infected with SARS-CoV-2 include chest tightness/pain and palpitations. These features can be because of newly developed or worsening ischaemic heart disease and arrythmias, respectively. SARS-CoV-2 infection is known to cause a clinical condition known as COVID-19-associated nephropathy (COVAN), a disease quite similar to HIV-associated nephropathy (HIVAN). Like HIVAN, COVAN is relatively more common in people of African descent and is associated with the APOL1 variant gene. Researchers have not identified unique morphological changes that could be used to identify the infection in tissues. Hence, the use of RT-PCR for diagnosis is still very important.

Keywords: SARS-CoV-2, Angiotensin II, ACE2, AIDS-associated nephropathy, Inflammation

INTRODUCTION

SARS-CoV-2 infection is a major pandemic that has involved all continents in the world. It has caused almost 7 million deaths since its onset.[1] The viral particle is known to infect the epithelial cells of the respiratory system, where it can have devastating consequences that can eventually lead to the death of patients.

The virus is known to usually spread through airborne aerosols. It has a high propensity to spread from one individual to another. Despite all the natural protective mechanisms that could curb its spread, the virus is able to bypass many protective measures.

SARS-CoV-2 commonly enters cells by binding to ACE2 molecules on the surface of cells in the human body. ACE 2 is an enzyme that is responsible for converting angiotensin II to other molecules. This serves as a negative regulatory mechanism that helps to reduce the concentration of angiotensin II in the body. When SARS-CoV-2 binds to ACE2 and the molecule is internalised, there is a reduction in the concentration of ACE2 on the surface of the cells. This will lead to an increased concentration of angiotensin II, which can cause various effects on the heart and the blood vessels of the human body.

RESPIRATORY SYSTEM

Symptoms and signs of dysfunction of the tissues of the respiratory system are major features of SARS-CoV-2 infection and are very useful in the clinical identification of cases. These clinical features include cough, dyspnea, and cyanosis. Affected patients are also known to be highly susceptible to the development of respiratory failure.

The epithelial cells lining the respiratory tract express ACE2, through which the virus is internalised. This is a

very common event in SARS-CoV-2 infection, and it accounts for the high incidence of pulmonary symptoms in patients that are affected.[2-4] ACE2 is most strongly expressed in alveolar type II epithelial cells.[5]

Dry cough is a well-known symptom of SARS-CoV-2 infection. Like other infections of the upper and lower respiratory tracts, it is likely due to the activation of the vagal reflex secondary to the irritation of the airways. The presence of exudates during the illness also contributes to the development of coughs.

The body response to the internalisation of the virus in the epithelial cells of the lungs can lead to alveolar epithelial inflammation, commonly referred to as the exudative phase of ARDS. ARDS is due to non-specific cell mediated immune damage of the viral infected epithelial cells and the accompanying inflammatory response. A massive release of proinflammatory cytokines is believed to increase the risk of developing ARDS.[6] It is associated with fluid accumulation in the alveoli and interstitial spaces of the lungs. The fluid collection in the alveoli increases the surface tension of the alveoli because it decreases the concentration of surfactant in the alveoli. This leads to the collapse of the alveoli and impaired gas exchange in the lungs, which is a primary reason for the reduced oxygenation of the blood in affected patients. This worsens the dyspnea and/or cyanosis that the patients might have had from the onset of the illness.

The exudative phase is followed by the proliferative phase, during which a repair process occurs, like in inflammation. This phase is associated with the proliferation of fibroblasts and alveolar type II cells due to the release of cytokines. The alveolar type II cells differentiate to the type I cells, which cover a major proportion of the surface area of the alveoli. Many patients who recover from SARS-CoV-2 infection end at this phase.

The last phase, the fibrotic phase, is mainly found in patients who have had a very severe infection. The fibrotic phase, an extensive proliferation of fibroblasts with collagen deposition, is found in patients who have had widespread destruction of the epithelial lining of the alveoli with disruption of the architectural framework. Lung fibrosis is particularly prominent when epithelial regeneration is suppressed. In this case, there is no complete resolution of the lung tissue but a loss of function because of fibrous tissue deposition. The fibrosis involves the intra-alveolar and interstitial spaces.

The presence of extensive fibrosis contributes to impaired pulmonary function in patients who have recovered from the acute phase of the illness.[7,8] After the acute phase of the SAR-CoV-2 infection, many patients can have respiratory dysfunction for many months thereafter. These mainly present with cough and dyspnea. The pulmonary fibrosis significantly contributes to diminished diffusion capacity, which often necessitates further oxygen supplementation or even mechanical ventilation.[9-11] Contributory pathologies include consolidation of the lungs and obstructive and restrictive lung disease. Patients with pre-existing obstructive and restrictive lung disease can develop worsening symptoms after recovering from the acute phase of the SARS-CoV-2 infection.

Many of the patients with severe SARS-CoV-2 infection have underlying illnesses like hypertension, cardiac disease, and diabetes mellitus.[12-15] Some of these background illnesses are associated with imbalances in the renin-angiotensin-aldosterone-system (RAAS). These imbalances may lead to overexpression of ACE2 in the epithelial cells covering the airways, which will make the patients more susceptible to the infection.

CARDIOVASCULAR SYSTEM

Cardiac symptoms shown by patients infected with SARS-CoV-2 include chest tightness/pain and palpitations. These features can be because of newly developed or worsening ischaemic heart disease and arrythmias, respectively.

ACE2 is expressed on cardiac myocytes and vascular endothelial cells. It is the medium by which the virus enters the cell. As ACE2 is responsible for the conversion of angiotensin II to angiotensin I which has more vasodilatory end effects on blood vessels, the internalisation of ACE2 because of the SARS-CoV-2 infection will reduce the production of the vasodilatory molecules.[1-7] This will, in effect, lead to vasoconstriction and increase the risk of endothelial injury. Hence, SARS-CoV-2 infection causes vascular symptoms.

SARS-CoV-2 is known to cause acute myocarditis either due to the cell-mediated immune destruction of cardiac myocytes with a secondary inflammatory response or due to myocardial cell death from coronary ischaemia. This should necessitate the monitoring of troponin levels in patients, especially if they develop severe symptoms or arrythmias.

Coronary artery disease has been seen in a number of SARS-CoV-2 patients.[16,17] These patients have a high risk of progressive artherosclerotic lesions during an acute phase of SARS-CoV-2 infection. This is most probably due to the inflammatory reaction of the vessels as a result of infection of endothelial cells, coupled with the increased coagulability of the blood in these patients.[18]

The effects of SARS-CoV-2 infection of the lungs can eventually lead to right heart failure. The inflammation that occurs due to the activity of the virus in the lungs is believed to reduce the oxygenation of the blood. The ventilation-perfusion mismatch that results from this will likely cause hypoxic vasoconstriction in many areas that are poorly ventilated. This is an adaptative mechanism to

help divert blood flow from poorly ventilated alveoli to areas with adequate ventilation. However, widespread vasoconstriction will increase pulmonary pressure. The resultant pulmonary hypertension can potentially lead to right heart failure.

Arrythmias has been observed in patients with SARS-CoV-2 infection. This can be seen as a palpitation.[19] This symptom can easily be masked by the dyspnea that many patients have. Researchers have associated the presence of arrythmias with severe forms of SARS-CoV-2 infection, especially in cases requiring intensive care unit admissions.[20] It is possible that these arrythmias are due to the effect of the virus acting directly on the cells of the conduction systems of the heart. It could also be due to myocarditis or a manifestation of worsening ischaemic heart disease. A specific study on the ECG changes in SARS-CoV-2 infections with associated factors is required to know the nature and causes of the arrythmias.

The infection is more severe in patients with underlying heart conditions like hypertensive heart disease and coronary heart disease. Patients have been reported to develop cardiac disease after SARS-CoV-2 infection. SARS-CoV-2 infection is known to initiate the development of cardiac failure or worsen pre-existing chronic cardiac failure.[21,22] These has been seen in cases of the recent SARS-CoV-2 pandemic.[23,24] This could be due to the destruction of cardiac myocytes by the virus or to the effect of worsening coronary artery stenosis. The reduced vasodilatory effect of the infection probably contributes to this.

Patients with severe SARS-CoV-2 infection can be bedridden for long periods of time, especially when they are unconscious. The prolonged immobility will increase the risk of thrombotic events, especially in the deep veins of the legs. A major vascular lesion suspected to be due to the effect of SARS-CoV-2 on blood vessels is a clinical condition called COVID toes. COVID toes present as painful red or purple lesions on the toes, believed to be due to vascular injury from SARS-CoV-2 infection.

SARS-CoV-2 infection can sometimes be very stressful, leading to stress-related organ dysfunction. This has been found to contribute to the worsening of heart conditions. The Takotsubo cardiomyopathy, the stress-induced transient left ventricular systolic dysfunction, has been found to be associated with some SARS-CoV-2 infection cases.[25]

Some cardiac dysfunction observed during SARS-CoV-2 infection may not be a direct effect of the virus or a sequela of the immune response of the host. Many drugs used in treating patients are known to have side effects involving the heart. Statins used to treat hyperlipidemia are a well-known cause of rhabdomyolysis, which can worsen pre-existing heart disease. Chloroquine, which was used for treating SARS-CoV-2 infections in some areas, has well-known cardiotoxic effects.

GASTROINTESTINAL SYSTEM

ACE2 is expressed on the squamous epithelial cells lining the oral cavity. SARS-CoV-2 can easily infect cells of the oral mucosa using surface ACE2. This is believed to be contributing to the loss of taste felt by patients in the initial stages of the infection. ACE2 is highly expressed in the minor salivary glands, and virus particles are commonly present in the saliva of symptomatic patients. It is important to note that this feature makes it easy to diagnose SARS-CoV-2 infection by taking a swab of the oral mucosa. Research has shown that children have very low expression of ACE2 in the epithelial cells of their oral mucosa. This may be partly contributory to the low rates of infection in children or the relatively reduced severity of symptoms in the very young.

ACE2 is seen in epithelial cells of the brush border of the intestines. It is believed that the involvement of these cells and their destruction contributes to the diarrhoea and gastrointestinal disturbances associated with SARS-CoV-2 infection.

There have been reports suggesting strong evidence of the destruction of hepatocytes in SARS-CoV-2 infections.[26-29] It has been suggested that this may be an effect of the direct cytopathic activities of the virus or a sequela of the general manifestation of the infection. Some authors have also identified the presence of cholangiocellular damage in some of the affected patients.[29,30] This was identified through the elevation of serum alkaline phosphatase and γ-glutamyl transferase during the illness. Although the liver pathology in SARS-CoV-2 infection remains to be fully elucidated, findings suggest severe liver dysfunction is associated with the presence of pre-existing liver disease. Patients with relatively normal liver prior to the infection do not seem to have serious liver abnormalities.

RENAL SYSTEM

ACE2 is highly expressed in proximal tubule epithelial cells and some cells in the glomerulus of the kidney. Viral inclusions have been found in the glomeruli of the patients. It is believed that the presence of the virus drives the inflammatory response in the glomeruli. SARS-CoV-2 has been found in some cells of the renal tissues using various laboratory techniques. These include the use of reverse-transcriptase polymerase chain reaction (RT-PCR), immunofluorescence, immunohistochemistry, *in situ* hybridization, and electron microscopy. RT-PCR has been found to be the most preferred technique, as it is more sensitive and specific compared to other techniques. RNA-based detection was also found to be very useful in formalin-fixed and paraffin-embedded sections.[31]

It is believed that the surge in pro-inflammatory cytokines leads to infiltration of the capillaries of the kidneys by lymphocytes and macrophages. This is known as glomerulitis and peritubular capillaritis. This

contributes to intersitial nephritis and the acute kidney injury that is found in many cases of SARS-CoV-2 infection.

Glomerulosclerosis, hyaline arteriolosclerosis, basement membrane thickening, and other lesions seen in SARS-CoV-2 infection patients are believed to be age-related. These lesions may also be due to pre-existing subclinical conditions in the patients.

The glomerular lesion most commonly found in SARS-CoV-2 patients that is believed to be strongly related to the viral infection is collapsing-focal segmental glomerulosclerosis (c-FSGS). This lesion is more common in patients of African descent. C-FSGS is associated with the presence of apolipoprotein L1 (APOL1) genotype.[32,33]

Thrombotic microangioathy is another glomerular lesion commonly seen in SARS-CoV-2 patients.[18,34] This may be related to an endothelial injury caused by the virus or the pro-coagulative state caused by the infection.

Acute tubular necrosis is the most common tubular lesion seen in patients. It has been suggested that reduced blood supply to the peritubular capillaries because of thrombotic narrowing of upstream vessels may contribute to the death of the tubular epithelial cells.

SARS-CoV-2 infection with the resultant decrease in ACE2 present on the surface of the cells will lead to a relative upregulation of the concentration of Angiotensin II. This will lead to increased blood pressure and an increase in sodium and water retention. This can worsen any pre-existing high blood pressure or renal disease. It is believed that this contributes significantly to the relatively higher morbidity and mortality seen in SARS-CoV-2 infections in patients with hypertension and/or renal disease. SARS-CoV-2 infection has been associated with tubular and glomerular impairment.[35]

SARS-CoV-2 infection is strongly associated with acute kidney injury. Acute kidney injuries found in many admitted patients range from moderate to severe, with quite a significant number of patients requiring renal replacement therapy.

Many patients with severe SARS-CoV-2 infection have been seen to have membrane thickening, an increased mesangial matrix, and nodular glomerulosclerosis. These lesions are non-specific and have been found in diabetic nephropathy. They are not likely due to the SARS-CoV-2 infection.[36]

Some patients with SARS-CoV-2 infection develop sepsis and disseminated intravascular coagulopathy (DIC). In this condition, there is the presence of microthrombi in the blood which get deposited in many capillaries in the body. Platelet-fibrin thrombi are deposited in the glomerulus of the kidneys of such patients.[37]

Vascular congestion may be seen in the kidneys of some patients. Vascular congestion likely results from stasis-induced vasoconstriction or inflammation. The presence of right ventricular failure can also contribute to vascular congestion.[38]

Oxalate crystals have been seen in the kidneys of some patients. However, it is believed that this might be due to the high consumption of vitamin C tablets by patients rather than a direct effect of the virus.[39]

SARS-CoV-2 infection is known to cause a clinical condition known as COVID-19-associated nephropathy (COVAN), a disease quite similar to HIVAN. Like HIVAN, COVAN is relatively more common in people of African descent and is associated with the APOL1 variant gene.

It is necessary to note that many patients with acute kidney injury, especially during a severe SARS-CoV-2 infection, do not fully recover their renal function. It is essential that these patients are followed up to see the long-term sequelae of the disease and to explain the pathogenetic mechanism of any condition that may arise.[40]

ENDOCRINE SYSTEM

ACE2 is believed to be more expressed in the islet cells of the pancreas than in the exocrine cells. Therefore, it is possible that SARS-CoV-2 destroys these cells in higher proportions, leading to a reduction in insulin production and a worsening of glucose homeostasis. This could be responsible for the increased morbidity and mortality in the SARS-CoV-2 infection.[41,42] This could also worsen the condition of patients with borderline or absolute pre-existing dysfunction in glucose homeostatic mechanisms.

Moreso, Furin, a protease known to increase viral infection of cells, is upregulated in patients with diabetes mellitus. This may contribute to the increase in morbidity in diabetic patients, as the virus is more likely to invade cells of other organs of the body.

CENTRAL NERVOUS AND PERIPHERAL NERVOUS SYSTEM

There have been varying reports on the effect of the SARS-CoV-2 infection on brain tissue. Some researchers have demonstrated its presence in brain tissue. There is no certainty about the route of entry of the virus into the tissues of the central nervous system. It has been postulated that the virus can enter through the olfactory route. Some authors have postulated disruption of the blood-brain barrier by perivascular inflammation and micro-thrombosis as contributory mechanisms to the entry of the virus into the central nervous system.[43-47] The

white blood cells are believed to be agents that can carry the virus to the brain in favourable situations.[48]

ACE2 is expressed on neurons and glial cells. It is involved in baroreflex regulation. Hence, it is possible that SARS-CoV-2 infection can contribute by this means to blood pressure dysregulation, sometimes seen in patients with severe cases.[49] Distortion in ACE2 concentration on the surface of neural cells in SARS-CoV-2 infection is believed to be responsible for the neurogenic hypertension found in some of the patients.[50,51]

Some authors have directly demonstrated the presence of the virus in cells of the brain stem and cranial nerves arising from them. It is possible that SARS-CoV-2 can spread to the CNS via infection of the olfactory bulb. Marked astrogliosis and microgliosis have been found in the olfactory bulb. It has been postulated that this may be responsible for the anosmia experienced by the patients.[52] The invasion of neurons in the brainstem, which contains the vital centre that controls respiration, could be responsible for the rapid deterioration in respiratory effort seen in some patients with severe COVID.[53] COVID-19 virus is also believed to cause viral encephalitis.[54]

No specific changes have been identified to be pathognomonic of the SARS-CoV-2 infection of the brain. Many of the lesions seen in the brain sample obtained at the autopsy of the fatal cases are known to be seen in many co-morbid conditions like diabetes mellitus and systemic hypertension. These changes include arteriosclerosis and haemorrhages.

Some changes seen in the brain of SARS-CoV-2 infection patients are not believed to be due to a direct cytopathic effect of the virus but linked to the patient's pre-existing medical condition or treatment offered during the illness. Extracorporeal membrane oxygenation and mechanical ventilation used to treat severe cases of SARS-CoV-2 infection are known to be occasionally complicated by intracerebral haemorrhage and ischaemic stroke.[55] Hence, some haemorrhagic lesions seen in the patients may be a result of the treatment procedures. Since many of the patients are known to have background hypertension, these brain changes could be complications of the hypertension or other co-morbidities rather than a direct cytopathic effect of the virus or immunological sequelae of the infection.

Some patients are treated with anticoagulants. This is particularly necessary for obese patients who are bedridden. It is possible that the use of anticoagulants may play a role in the pathogenesis of the micro-haemorrhages that are seen in many of the patients.

Similar to what is seen in many other organs, thrombi or microthrombi is seen in the brain tissue of the patients.[47] Some researchers believe that these thrombi may be responsible for the neurological symptoms seen in the patients.

Many lesions in the brain tissues show vasculitis.[56] This is not unexpected, as vasculitis is seen in many other organs of the body. The endothelial cells are usually the site of attack by the viruses.

Other features noticed in SARS-CoV-2 patients without concrete evidence of a direct link to the virus include demyelination and the presence of microglial nodules.[57] Demyelination is found in degenerative diseases like multiple sclerosis. Its presence is not specific and cannot be suggestive of SARS-CoV-2 infection. Microglial nodules, which are quite similar to fibrous lesions in other organs, are also found in many other conditions.

Some patients have nuchal rigidity. Histology of the meninges has shown infiltration of the meninges by cytotoxic T lymphocytes. This is likely a reactive feature rather than a direct effect of the virus.[52]

CONCLUSION

SARS-CoV-2 infection, although mild in many patients, has the potential to cause dysfunction of many organ systems in the body. This is due to the virus's ability to infect cells through ACE2 found on the surface of many cells in the body. The virus can cause catastrophic ARDS that is potentially lethal or disrupts the renin-angiotensin-aldosterone-system, which can worsen pre-existing heart and renal disease. Researchers have not identified unique morphological changes that could be used to identify the infection in tissues. Hence, the use of RT-PCR for diagnosis is still very important.

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