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Review Article

A critical review of autopsy findings in deaths due to COVID-19

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ABSTRACT

Not much is known about the pathological post-mortem findings of people dying of the novel coronavirus disease. There is a great need of such information for better clinical management of COVID-19 cases. A detailed literature search was conducted followed by its critical review. The search was made in databases like Pub Med, Scopus and EMBASE. The histopathological alterations were found to be mainly confined to the lungs. This included diffuse alveolar damage with formation of hyaline membrane and pulmonary microvascular thrombosis. There was a high incidence of deep venous thrombosis and pulmonary embolism in COVID-19 patients which hints towards possible endothelial involvement. The findings of the review have been derived from very few and restricted studies. These claims need to be substantiated by doing further studies.

Keywords: COVID-19, Autopsy findings, Lungs

INTRODUCTION

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection was declared a pandemic by the World Health Organization on 11 March 2020.[1] COVID-19 had posed many challenges for the health care system worldwide.

COVID-19 infection releases a significant amount of pro-inflammatory cytokines which aggravate interstitial pneumonia and acute respiratory distress syndrome (ARDS). This results in viral sepsis with hypercoagulability and multiorgan dysfunction.[1]

Post-mortem findings are essential for better understanding of pathophysiology of SARS-CoV-2.[2-4] Histopathological evidence of damage of airway surface epithelial cells and massive pulmonary involvement with diffuse alveolar damage (DAD) and microvascular thrombi have been reported.[5,6]

The aim of the present review is to gather the current pathological data on COVID-19 infection making a distinction between minimally invasive autopsy and complete autopsy.

METHODS

A systematic literature search was made on the autopsy findings of COVID-19 infected patients. It was followed by a critical review of the collected studies. A thorough and complete electronic search of Pub Med, Scopus and EMBASE databases was conducted. The key words for the said electronic search were- "SARS-CoV-2", "COVID-19", "post-mortem", "autopsy", "histology", "biopsy" and "pathophysiology".

The references of the scientific papers were examined and cross-referenced to further identify relevant content. A meticulous appraisal of each study was conducted to exclude any bias. The data collection process included study selection and data extraction. Independent examination and analysis of the scientific papers were performed by the authors. Data extraction and verification were performed by separate authors.

RESULTS

Minimally invasive autopsies

Xu et al performed core biopsies of a patient dying from cardiac arrest after two weeks of progressive respiratory insufficiency.[5] The lungs showed diffuse alveolar damage with oedema and hyaline membrane formation apart from lymphocytic infiltration of the interstitium. The pneumocytes exhibited multinucleated syncytium. Myocardium was found to have interstitial mononuclear infiltrate. Liver showed microvascular steatosis. A possible role of over-reactive T cells was implicated as a basis for the immune mediated damage to lungs, heart and brain.

Zhang et al performed transthoracic pulmonary needle biopsies in a 72 years old patient who succumbed to respiratory insufficiency from COVID-19.[6] Lungs showed diffuse alveolar damage and alveolar fibrous exudate with interstitial chronic inflammatory infiltrate along with pulmonary fibrosis.

Dolhnikoff et al performed minimally invasive autopsies and took biopsy of lungs, heart, liver, kidney, spleen, brain, skin and skeletal muscle.[7] They observed diffuse exudative and proliferative alveolar damage alongside focal alveolar haemorrhage. They also observed lymphocytic infiltration along with arteriolar fibrin microthrombi in lungs, kidney and skin.

Yao et al performed minimally invasive autopsies of three cases of death due to COVID-19.[8] They observed hyaline membrane formation into the alveoli with serous and fibrinous exudate. The inflammatory infiltrate contained macrophages and lymphocytes. The lymphocytes were mainly helper T cells. Multinucleated giant cells were also observed. Pulmonary capillaries were found to be oedematous and congested with luminal hyaline thrombus formation infiltrated with monocytes and lymphocytes. Polymerase chain reaction and immunohistochemistry substantiated the presence of COVID-19 in alveoli and macrophages infiltrating them.

Tian et al performed core biopsies of four patients dying from COVID-19 infection.[9] The lung tissue showed diffuse alveolar damage with hyaline membrane formation and type II pneumocyte activation. Fibroblast proliferation and fibrin cluster formation were also observed. There was pulmonary vascular congestion and some alveoli lacked blood cells.

Magro et al have established septal capillary injury with significant capillary fibrin deposition and polymorphonuclear infiltrate in lungs of patients dying from COVID-19 infection.[10] Relevant indications of systemic complement cascade activation were evident in pulmonary and cutaneous biopsies. SARS-CoV-2 spike glycoproteins and C4d and C5b-9 could be detected in alveolar septa.

Complete autopsies

Su et al mainly concentraed on renal biopsies.[11] The cardinal renal histological features were acute tubular injury, pyelonephritis, arcuate artery inflammatory infiltrate and red blood cell aggregation in peritubular and glomerular capillaries. Viral particles could be observed in podocytes of Bowman's capsule.

Barton et al performed complete autopsies of two subjects dead from COVID-19 infection.[12] Swabs from nasopharynx and lungs parenchyma of the dead subjects tested positive for SARS-CoV-2. Post-mortem radiography exhibited bilateral opacification of lungs. Histopathology of lung tissue revealed acute diffuse alveolar damage with pulmonary microvascular hyaline membrane and thrombi formation. Immunohistochemistry demonstrated CD3, CD4 and CD8 positive T cells and focally consolidated macrophages in pulmonary tissue.

Varga et al reported signs of diffuse alveolar damage and ARDS in the lungs of two patients who died from COVID-19 infection.[13] Lymphocytic endothelitis was observed in lungs, heart, liver and kidney. Endothelitis was also observed in pulmonary, cardiac and small intestinal vessels. Ischaemic necrosis was observed in mucosa of small intestine.

Pulmonary thromboembolism with occlusion of one or both pulmonary arteries was observed in autopsy of two patients by Grimes et al.[14] These findings were confirmed by histological examination. Associated deep venous thrombosis was reported in the two cases as well. Viral inclusion was established in the pneumocytes by electron microscopy.

Bradley et al reported heavy oedematous lungs with intrapulmonary haemorrhage and pulmonary emboli.[15] Diffuse alveolar damage in acute and organizing stage was observed by them with reactive type II pneumocytes. Acute bronchiolitis and bronchopneumonia were also observed. Electron microscopy depicted viral inclusions in trachea, lungs, kidney and large intestine. Acute tubular necrosis was seen in kidney and liver showed periportal lymphocytic infiltration.

Lacy et al demonstrated heavy, firm, oedematous lungs with thick bronchial tree mucosa and mediastinal lymphadenopathy in case of a 58 years old lady dying due to COVID-19 infection.[16] Pulmonary septa also displayed mononuclear infiltrate with pulmonary parenchyma showing oedema and hyaline membrane formation. Desquamated, hyperplastic pneumocytes were observed with multinucleate cells and foamy macrophages. Focal alveolar haemorrhages were marked in the lungs as well. Liver was congested. Kidney showed global glomerular and mesangial sclerosis.

Prilutsky et al reported acute exudative diffuse alveolar damage in the lungs in the autopsy conducted on four

patients dying due to COVID-19 infection.[17] Lymph nodes were enlarged and showed hemophagocytic histiocytes. One case showed splenomegaly with haemorrhagic red pulp and hemophagocytic histiocytes. The bone marrow was found to have myeloid hyperplasia.

Yan et al have reported autopsy of a 44 years old Hispanic woman dying from COVID-19 infection related multiorgan dysfunction.[18] Autopsy revealed oedema, infarction and cytopathic damage to pneumocytes in the lungs of the deceased. Right atrium was streaked and right ventricle was dilated. There was myxoid oedema, myocardial hypertrophy and focal pyknotic necrosis in the heart. Left ventricular papillary muscles showed CD45-positive lymphocytes. There was peritubular congestion and focal tubular damage in the kidneys.

Edler et al reported autopsy of 80 people suffering from COVID-19.[19] Lungs were heavy with a mosaic like pattern on the exterior in the patients. Lungs of the autopsied bodies were solidified as well. Deep vein thrombosis was discovered along with pulmonary artery embolism in these cases. In addition, advanced fibrosis and squamous metaplasia were observed in the affected lungs. Small pulmonary arteries showed lymphocytic and plasma cell infiltration. Granulocyte focal confluent broncho-pneumonia could be observed in some cases.

Witchman et al have reported pleurisy; heavy, firm, congested lungs and evidence of shock in various organs in subjects dying from COVID-19 infection.[20]

Carsana et al have observed diffuse alveolar damage with focal interstitial pneumonia or acute fibrotic organizing pneumonia.[21] The type 1 and type 2 pneumocytes showed the presence of assumed virions on electron microscopy of the affected lung tissue.

DISCUSSION

Autopsy information of patients of patients dying from COVID-19 helps a lot in understanding the pathophysiology of the infection as well as planning of the therapy and patient care. Autopsies were avoided in some countries in early phase of the pandemic.[1] The first histopathological changes of COVID-19 in human body were obtained from the biopsies of various organs from live patients as well as post-mortem biopsies. It was soon established that safe autopsies could be performed in dead COVID-19 patients with proper precautionary measures.[22] Thereafter autopsies were conducted on patients dying of COVID-19 infection.

The autopsies revealed grossly congested and oedematous lungs. On histopathological examinations, lungs were found to have both exudative and proliferative diffuse alveolar damage. The affected lungs also had hyaline membrane formed in the alveoli. The alveoli showed microvascular congestion and inflammatory infiltrate could be noted as discussed earlier. These features resemble the lung damage in patients of severe acute respiratory syndrome (SARS) and Middle Eastern respiratory syndrome (MERS).[23,24]

The SARS-COV-2 causes endothelial dysfunction leading to multiorgan dysfunction and shock.[25-27] A possible explanation of the endothelial dysfunction is expression of the receptor binding domain on the SARS-CoV-2 surface that binds to angiotensin converting enzyme 2 (ACE 2). These ACE 2 receptors are found in many human tissues as well as endothelium of the blood vessels.[28]

A probable role of complement system activation has been proposed in the pathophysiology of COVID-19 infection by Magro et al.[10]

Another pathognomonic feature of COVID-19 infection is microvascular thromobosis of the affected lungs. There is ample evidence of thromboembolic episodes involving lungs as stated by various scientific papers included in the current review.[18,19]

Renal and cardiovascular systems are found to be adversely affected in COVID-19 patients indicating a possible role of multisystemic involvement in the pathogenesis of this dreaded infection.[13]

There seems to be insufficient evidence to define the pathophysiology of morbidity and mortality in patients affected by COVID-19 infection. As evident in our review, most of the authors have focussed only on alveolar and pulmonary microvascular alterations in their autopsy studies. And these studies have reported minimal multisystemic involvement in patients dying of COVID-19 infection.

CONCLUSION

The pulmonary and extra-pulmonary histopathological alterations described in our review should aid in formulating a probable pathophysiological basis of the morbidity and mortality in patients affected by COVID-19 infection. A possible cause of multiorgan dysfunction in the form of endothelitis and involvement of ACE 2 receptor binding domains can be postulated from the data gathered by various studies included in our review. However advanced and cohesive studies need to be conducted in future involving all the organ systems to help prevent and manage COVID-19 infection better.

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