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A Review

Histopathological basis of COVID-19: A short review

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Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the cause of the global pandemic in 2020 resulting a massive morbidity & mortality. The lung is the predominant organ involved in symptomatic patients with Coronavirus disease-2019 (COVID-19) along with involvement of other organs. Understanding the histopathological changes of lung and other organs in COVID-19 become essential for not only formulating future management protocols but also for determing prognosis. The collection of potentially contaminated tissues during the autopsy and further processing of them in histopathology laboratory with proper maintenance of safety protocol is of immense importance. A review of the available scientific articles shows the diffuse alveolar damage and microvascular thrombi are common observation found in lung tissue in patients who died due to COVID-19.

Keywords: Autopsy, Diffuse alveolar damage, Glomerulosclerosis, Microvascular thrombi

Introduction

In the late December 2019, a few cases of pneumonia were reported which was later linked to Huanan Seafood Market of Wuhan, China; subsequently, those are confirmed by Chinese health authorities that the cause of pneumonia was due to a novel coronavirus, later termed as Severe Acute Respiratory Syndrome Corona Virus 2 (SARS-CoV-2)[1]. Italy was the first European country to document a huge number of cases. Now, this SARS-CoV-2 pandemic has spread to almost globally affecting millions of people.

The pathogenesis of SARS-CoV-2 commences with virus-host cell interaction by binding of spike envelope protein to angiotensin-converting enzyme2 (ACE2) receptor, richly expressed on the epithelial cell surface of lung and intestine, making them vulnerable to virus[2]. This is followed by an exaggerated inflammatory response due to liberation of profuse quantity of pro-inflammatory cytokines by activated cytotoxic T-cells ultimately causing interstitial inflammation, exudates and severe pneumonitis in lung and also endothelial damage, hypercoagulation & disseminated intravascular coagulation[3]. The Lung is the predominantly involved organ, and the common manifestation is acute respiratory distress syndrome. With the progression of the pandemic, the involvement of other organs has been demonstrated. In this review, the understanding the pathological changes in lung and other organs from the various studies reported in the literature was discussed.

Review of Literature

The most common reported histopathological findings in the lung of patients infected with SARS-CoV-2 are as follows[4,5]. interstitial inflammation, necrotizing bronchitis or bronchiolitis; early diffuse alveolar damage characterized by intra alveolar edema and fibrin deposition with hyaline membrane formation; interstitial pneumonia manifested by leucocyte infiltration in alveolar septa; cytolysis and presence of a moderate number of multinucleated giant cells with the absence of any inclusion bodies[4.5]. These findings were not very much dissimilar from lung pathology in case of other viral infection[6]. A similar feature has been observed in a case report[7].

A Chinese study of the limited post-mortem examination found desquamation of type II alveolar lining cells and hyaline thrombi in small vessels [5] in addition to common observations by others[4,7]. In an advanced case, the presence of fibrinoid necrosis of small vessels of lungs along with the hyperplasia of type II pneumocytes, and all components of diffuse alveolar damage were observed[8]. In the liver,

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small lymphocyte infiltration in hepatic lobules and centrilobular sinusoidal dilation along with the patchy necrosis were found[8]. Mild myocardial hypertrophy with focal fibrosis was also observed; those changes are most likely associated with the underlying co-morbid conditions[8].

A study at Oklahoma, USA observed patchy hyaline membranes and thrombi in a few small branches of pulmonary arteries[9]. Histological examination of kidneys showed fibrin thrombi which is consistent with disseminated intravascular coagulation (DIC) [10]. In a study in Basel, superimposed bronchopneumonia, pulmonary emboli, and evidence of vasculitis were found in addition to other common findings[11]. One histopathological examination of the heart after autopsy from COVID-19 infected patients showed scattered individual myocyte necrosis without significant lymphocyte infiltration which is typical of viral myocarditis[11]. In that study, it was also observed pulmonary megakaryocytes, with nuclear hyperchromasia and atypia within alveolar capillaries apart from the common finding of diffuse alveolar damage and thrombi in microvasculature[11].

The complement-mediated thrombotic microangiopathy in both the lung tissues (haemorrhagic pneumonitis with fibrin deposits in capillaries and endothelial cell necrosis) and in skin samples were reported[12]. Other studies reported diffuse alveolar damage with perivascular T-cell infiltration along with the severe endothelial injury and alveolar-capillary microthrombi formation along with evidence of angiogenesis in alveolar microcirculation[13,14].

Endothelitis and accumulation of inflammatory cells in several organs such as lung, heart, kidney, liver, and small intestine were observed[15]. Autopsy of COVID-19 patients who suffered from acute kidney injury showed stagnation of red cells in glomerular and peritubular capillary lumen along with endothelitis and fibrin thrombi[16]. In a study from Italy, noticeable derangement of intra-hepatic vasculature is found, characterised by an increase in a number of branches in the portal vein along with the lumen dilatation, and/or thrombosis of the portal and sinusoidal vasculature, and portal tract fibrosis[17]. Other studies found acute tubular necrosis as the most common observation in kidneys; other varieties of observations were myoglobin casts, thrombotic microangiopathy, crescentic glomerulonprhites, glomerulosclerosis, collapsing glomerulopathy, membranous glomerulopathy[18,19]. The presence of hemosiderin in tubules or pigmented casts in kidneys was also reported[20]

The presence of diffuse alveolar damage was documented in most of the cases, but endothelitis was found in very few cases[21]. As in previously mentioned[4,5,8], thickened alveolar septa with inflammatory infiltrate (mostly lymphocytes and macrophages), fibroblasts, and type II hyperplastic pneumocytes were also observed in a case report[22]. Another study from Italy found features of the exudative and proliferative phases of diffuse alveolar damage, which included capillary congestion, necrosis of pneumocytes, type 2 pneumocyte hyperplasia in all subjects; hyaline membranes, interstitial and intra-alveolar edema, squamous metaplasia with atypia, and platelet-fibrin thrombi in most of the subjects[23].

One extensive study had shown not only common and similar pulmonary findings (Diffuse alveolar damage-hyaline membranes, edema, pneumocyte hyperplasia; lymphocytic infiltrate, multinucleated giant cells and enlarged, atypical pneumocytes), but also relevant observation in different organs such as lymphocytic myocarditis, hepatic shock necrosis, steatosis, and acute tubular necrosis in kidney[24].

One systematic review observed that the histopathological pattern of COVID-19 related pneumonitis appears to include epithelial, vascular, and

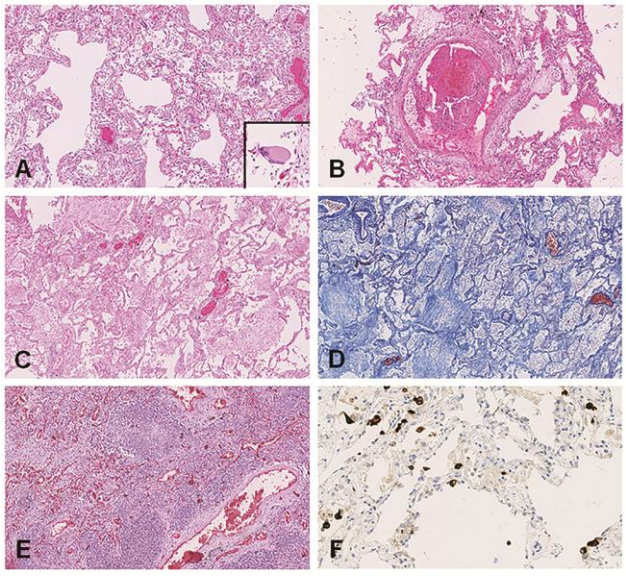

Fig. 1 — Pulmonary histological findings (A) Early-stage diffuse alveolar damage (DAD): hyaline membrane (H & E, × 50 magnification) with a zoom on a giant cell (× 100 magnification); (B) Fibrin thrombi in a pulmonary artery (H & E, × 50 magnification); (C) Late-stage DAD: fibroblastic proliferation (H & E, × 50 magnification); (D) Late-stage DAD: fibroblastic proliferation (Trichrome staining, × 50 magnification); (E) Acute pneumonia (H & E, × 50 magnification); and (F) Anti-SARS-CoV immunohistochemistry (IHC)-positive cells (× 200 magnification)

fibrotic patterns of lung injury[25]. A clear timeline was also identified to some extent, such as epithelial changes in all phases, vascular changes in the early phase, and fibrotic changes usually about three weeks after the onset of initial symptoms. The non- specific epithelial damage and inflammatory infiltrate along with evidence of microvascular damage in the heart, liver, kidneys, gastrointestinal tract and skin were also observed[25].

Pulmonary histopathology with evidence of diffuse alveolar damage, organizing pneumonia, acute fibrinous and organizing pneumonia; fibrotic non-specific interstitial pneumonia, acute interstitial pneumonia along with micro thrombotic event has been substantiated by thorough searching of few more literatures[26-31] across the globe.

Evidence has been gathered that COVID-19 infection can be linked with extensive vascular endothelial damage in lung and other organs. Viral presence in the endothelium leads to an inflammatory response and microthrombi are the outcome. Alveolar capillary angiogenesis is evidenced in the lung, but its role is not yet known. Increased evidence of thrombosis in intravenous cannulae, extracorporeal circuits for dialysis ,or membrane oxygenation indicates the effects of COVID-19 on the coagulation system of the body[32].

It is evident from a review of available literature across the globe that the predominant prototype of lung pathology in COVID-19 patients is diffuse the alveolar damage which can be described in three phases, namely the exudative phase (*e.g.* pneumocytes desquamation, hyaline membrane formation, exudates protein- rich or cellular, fibrinoid necrosis of microvasculature, alveolar hemorrhage); Organizing phase (*e.g.* interstitial and intra alveolar fibroblasts proliferation, type II pneumocyte hyperplasia, lymphocytic infiltration, fibrin deposition); Fibrotic phase (*e.g.* dense collagenous fibrosis, architectural remodeling), these third phase findings are not commonly reported so far[33].

As found in one study, the pattern of lung damage in severe SARS-CoV-2 infection is not diffuse alveolar damage which was the most predominant observations of almost all other researchers. As per their finding histologic pattern was an acute fibrinous and organizing pneumonia (AFOP) evidenced by intra-alveolar fibrin deposition known as fibrin balls, in place of hyaline membrane formation[34].

Besides diffuse alveolar damage, another major common observation from the histopathological study was diffuse thrombotic vascular involvement in multiple organs including the lungs. This finding is linked with high levels of D-dimers in the blood and could be pertinent in targeted management of SARS-CoV-2 patients, with a good potential to modify the prognosis.

Conclusion

Though the histopathology is not a part of a routine investigation in the case of COVID-19, pathologists may find suspected cases at autopsy, or in biopsy samples. In COVID-19 victims, predominant histopathological observations are diffuse alveolar damage in lung and multiorgan microvascular thrombi. Hence finding a link between the signs and symptoms and pathological (both macroscopic and microscopic) evidence are not only significant for autopsy pathologist, but also for identifying the better therapeutic approaches to reduce the morbidity and mortality due to COVID-19.

Acknowledgement

Fig. 1: Remmelink M, De Mendonça R, D'Haene N, De Clercq S, Verocq C, Lebrun L et al. Unspecific post-mortem findings despite multiorgan viral spread in COVID-19 patients. Critical Care (2020) 24:495. https://doi.org/10.1186/s13054-020-03218-5.

Conflict of interest

All authors declare no conflict of interest.

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