Abstract: Background: The rapid spread of the COVID-19 has posed complex challenges to the global public health and it was declared as a public health emergency of international concern. Understanding the histopathology of COVID-19 will be crucial to propose effective therapies. However, studies on the pathological diagnosis of COVID-19 have been relatively deficient, scattered with a few summarized evidence. Objective: The objective of this review article was to have current state of knowledge about the histopathological changes detected in major organs due to COVID-19 disease, in order to enable the current understanding of it. Methods: The literature search for this document was carried out comprehensively by accessing PubMed, Google scholar, Web-of-Science and other data bases. In addition helpful documents were added. Result and conclusion: The most histopathological findings were in the pulmonary system. The primary pathology was diffuse alveolar damage with virus located in the pneumocytes. However, other major organs including the heart, liver and kidneys may be susceptible to viral replication and impairment leading to increased mortality in those with disseminated disease. The main histopathological findings in kidney were varying degrees of acute tubular necrosis, luminal brush border sloughing and dilated capillary vessels in the glomeruli. Liver injury is more common in severe cases of COVID-19.

Keywords: COVID-19, Histopathology, Review

1. Introduction

The 2019 novel coronavirus pneumonia was officially named by the World Health Organization (WHO) as Coronavirus Disease 2019 (COVID-19) on 11th February 2020. It is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) which was first emerged in December 2019 in Wuhan city, China. It was declared as a public health emergency of International concern on 30th January 2020 by WHO and as a global pandemic by WHO on 11th March. SARS-CoV-2 mainly invades alveolar epithelial cells and thought to infect host cells through ACE2 [1].

It is transmitted from person to person when a case coughs or exhales producing droplets that reach the nose, mouth or eyes of other person [2]. The virus was also detected in stool, gastrointestinal tract, saliva, urine, tears and conjunctival samples [3, 4]. The most common population effected was adult males in age group of 45-55 years [2].

Most common symptoms were fever, dry cough, muscle pain, and dyspnea. Less common symptoms were headache, diarrhea, vomiting, hemoptysis and sputum production [5-7].

The reported mortality in different countries varies ranging from 0.3% to 10%. The respiratory, coagulation and immune systems are the major targets of this disease. The incidence of acute kidney injury in COVID-19 varied from 0.9% to 29% in different centers. Furthermore, in some aggravated cases, infection has led to severe acute respiratory syndrome, renal failure, and even death [8].

Following the spread of the new coronavirus and its impacts on human health, the research community has responded rapidly.

The pathological diagnosis of COVID-19 has been relatively deficient, scattered with no summarized evidence. Accurate documentation of its histopathology may have implications on patient management and for development of antiviral treatment. Furthermore, understanding the pathology of COVID-19 will be crucial to design effective therapies.
2. Histopathologic Changes in the Lung of COVID-19 Cases

The major pathological findings in the COVID-19 cases involve the pulmonary system.

2.1. Changes in the Early Phase of the Disease

According to Tian S et al. the histopathological changes obtained from resected lung specimens of two pre-symptomatic COVID-19 cases were edema, proteinaceous exudate, multinucleated giant cells, focal hyperplasia of pneumocytes and the absence of hyaline membranes (Figure 1) [9].

Likewise, the main histopathologic features of early lung involvement by COVID-19 in a surgical sample resected for carcinoma were pneumocyte damage, alveolar hemorrhage, clustering of macrophages, and interstitial inflammatory infiltrates, with prominent and diffuse neutrophilic margination within the septal vessels (Figure 2) [11].

2.2. Changes in the Postmortem of the Disease

The main findings in the lungs of the four patients died with COVID-19 were fibrin exudates, epithelial damage, diffuse type II pneumocyte hyperplasia, injury to the alveolar epithelial cells and mild thickening of alveolar walls was seen in some cases (figure 3) [12].

According to Luo W et al. the pathological findings of critical patient died with COVID-19 showed the whole lungs displayed diffuse congestive appearance and partly haemorrhagic necrosis on gross examination. The cut surfaces of the lung displayed severe congestive and haemorrhagic changes (Figure 4). The main histopathological findings of pulmonary system were bronchiolitis and alveolitis with proliferation, atrophy, desquamation and squamous metaplasia of epithelial cells, pulmonary interstitial fibrosis, partly hyaline degeneration and variable degrees of hemorrhagic pulmonary infarction. In addition small vessels hyperplasia, lumen stenosis, occlusion and microthrombosis formation, multinucleate giant cells and intracytoplasmic viral inclusion bodies were found (Figures 5, 6) [13].
Figure 5. Pulmonary alveoli changes; (A) Necrotizing bronchiolitis, necrotic bronchial epithelial cells are present in the lumen (B) Atrophy of alveolar epithelial cells and diffuse alveolar hemorrhage (C) Squamous metaplasia of bronchiole epithelial cells (D) Squamous metaplasia of alveolar cells (E) Widened alveolar septum (F) Necrosis and desquamation of alveolar epithelial cells. (G) Inflammatory cells and massive fibrinous exudate in the lumen. (H) Multinucleate giant cell. (I) Intracytoplasmic viral inclusion body in alveolar epithelial cell (square frame indicates) [13].

Figure 6. Pulmonary changes by special stain. (A) The whole slide imaging by Masson staining. (B) Interstitial fibrosis by Masson stain. (C) The thickening of the vessel wall by Masson staining. (D) Fibrotic walls of dilated bronchioles by Masson staining. Desquamation of epithelial cells and inflammatory cells including macrophages in the lumen. (E) Massive fibrinous exudate in the bronchiole lumen. (F) Enlarged alveolar septum, and partly ruptured septum. (G) Interstitial fibrosis by sirius red staining. (H) Interstitial fibrosis by reticular fibers staining. (I) Fibrinous transudation by PAS staining [13].

Similarly, according to Bradley BT et al. post-mortem examinations performed on 12 COVID-19 cases in Washington the major pulmonary findings were diffuse alveolar damage (DAD) in the acute and/or organizing phases, enlarged and reactive type II pneumocytes with nucleomegaly. In addition, half of the cases showed focal areas of acute bronchiolitis with an additional two cases showing bronchopneumonia (Figure 7) [14].

On the other hand, as Zhang H et al. histopathologic changes seen on postmortem biopsies from a patient died with COVID-19 were DAD (Figure 8, A arrow 1 with reactive type II pneumocyte hyperplasia (Figure 8, A arrow 2); Intra-alveolar fibrinous exudates (Figure 8, B, arrow 3), along with loose interstitial fibrosis and chronic inflammatory infiltrates (Figure 8, B, arrow 4) and intra-alveolar loose fibrous plugs of organizing pneumonia (Figure 8, C, arrow 5) with presence of intra-alveolar organizing fibrin (Figure 8, D, arrow 6).

Figure 7. Histopathology of COVID-19 infections (A) Hyaline membranes. H and E; x100. (B) Diffuse alveolar damage, organizing phase. H and E; x100. (C) Multinucleated giant cells and pleomorphic, reactive pneumocytes. H and E; x400. (D) Multinucleated giant cells. H and E; x400 [14].

Figure 8. Histopathologic changes of lung tissues from a case COVID-19 (×100 magnification) [10].

3. Renal Histopathological Postmortem Findings with COVID-19

SARS-CoV-2 virus can directly infect human renal tubules and consequently lead to acute renal tubular injury and lymphocyte infiltration. Acute kidney injury has been reported in 5-15% of patients and higher at 15-39% for critically ill patients. The kidney demonstrated viral particles in the tubular epithelium, endothelium, and podocytes without significant inflammation [14]. Emerging data suggest that the kidney may be an important target organ for COVID-19 (22). Recent human tissue RNA-sequencing data demonstrated that ACE2 expression in urinary organs (kidney) was nearly 100-fold higher than in respiratory organs (lungs) [15].
By light microscopy findings from autopsies of 26 patients who died from COVID-19 were diffuse proximal tubule injury with the loss of brush border, non-isometric vacuolar degeneration, dilatation of the tubular lumen with cellular debris, and occasional frank necrosis was observed. Furthermore, occasional hemosiderin granules, erythrocyte stagnation in the lumen of glomerular and peritubular capillaries, pigmented casts and detachment of epithelium with bare tubular basement membrane were identified. However, there was no interstitial hemorrhage and diagnostic vasculitis [16, 17] (Figure 9).

Electron microscopic examination showed clusters of coronavirus particles with distinctive spikes in the tubular epithelium and podocytes (Figure 10). In severe lethal infection direct parenchymal infection of tubular epithelial cells and podocytes with marked acute tubular injury and erythrocyte aggregation occurs.

The other study conducted by Diao B et al. on the histopathological examination of kidney specimens from autopsy of six COVID-19 subjects showed varying degrees of acute tubular necrosis, luminal brush border sloughing, dilated capillary vessels in the glomeruli and vacuole degeneration. Severe infiltration of lymphocytes in the tubule interstitium was observed in two patients, and moderate infiltration was seen in three cases, and the remaining one case manifested absence of lymphocyte infiltration. Moreover, viral infection associated-syncytia were observed in three cases (Figure 11) [18].

However, according Bradley BT et al no specific viral cytopathic changes occur, but by electron microscopy, abundant viral particles were seen in proximal tubules of kidney [14]. The etiology of kidney disease involvement in patients with COVID-19 is likely to be multifactorial. First, the novel coronavirus may exert direct cytopathic effects on kidney tissue. This is supported by the detection of polymerase chain reaction fragments of coronavirus in blood and urine in the patients with COVID-19 [19]. Another is through deposition of immune complexes of viral antigen and virus-induced cytokines or mediators might exert indirect effects on renal tissue, such as hypoxia, shock and rhabdomyolysis [20].

4. Histopathological Changes of the Liver

Changes in the liver is limited or related to the underlying diseases and may not have serious clinical consequences. Although abnormalities of liver function indexes are common
in COVID-19 patients, it is still not clear whether this is due to
direct viral infection or secondary to other causes [21, 22].
According to Tian S et al, the liver biopsy specimens of the 4
patient with COVID-19 exhibits mild lobular infiltration by
small lymphocytes, centrilobular sinusoidal dilation and
patchy necrosis (Figure 12). In addition, as Xu Z et al study the
liver biopsy specimens of the patient with COVID-19 showed
moderate microvascular steatosis and mild lobular and portal
activity [21].
Liver injury is more prevalent in severe cases than in mild
cases of COVID-19 [23]. In a large cohort including 1099
patients from 552 hospitals in 31 provinces or provincial
municipalities, more severe patients with disease had
abnormal liver aminotransferase levels than did non-severe
patients with disease [24].

5. Histopathological Changes of the Heart
The heart shows only focal mild fibrosis and mild
myocardial hypertrophy, which is likely related to the
underlying conditions [12]. There were no obvious
histological alterations in heart tissue suggesting that the
detected clinical cardiac dysfunction reported in one study
with COVID-19 may not be related to direct SARS-CoV-2
infection [15, 25]. Furthermore, histological examination of
50-year-old man who died with Covid-19 in China showed a
few interstitial mononuclear inflammatory infiltrates, but no
other substantial injury (figure 14) [21].
Understanding of the cardiac effects of SARS-CoV-2
infection is evolving. In a study documenting the clinical
course of intensive care unit (ICU) patients in Kirkland,
Washington, it was found that 33% of patients experienced
cardiomyopathy of unclear etiology [26]. In addition,
myocardial injury with elevated troponins was identified in
22% of ICU patients [15].

Figure 12. Histopathological changes in the liver with COVID-19 A) Dense
portal infiltration by atypical small lymphocytes and focal glycogenated
nuclei in hepatocyte in Case 1. B) Corrhotic nodules with thick fibrosis in Case
2. C) Mild sinusoidal dilatation with increased lymphocytic infiltration. D)
Higher power view showing sinusoidal lymphocytes. E) Focal hepatic
necrosis in periportal zone. F) Focal centrilobular hepatic necrosis in case 4
[9].

Likewise, histopathologic examination of the needle biopsy
specimen performed in the patient who died of COVID-19
revealed mild sinusoidal dilatation and minimal lymphocytic
infiltration (Figure 13) [23].

Figure 13. Histopathologic changes in the liver [23].

6. Conclusion
SARS-CoV-2 infection has emerged as major global health
threats since December, 2019. The WHO has declared it a
Public Health Emergency of International Concern. The
complete clinical manifestation is not clear yet, as the reported
symptoms range from mild to severe, with some cases result in
death.
The most pathological findings involved the pulmonary
system. The main pathological lung changes were injury to the
alveolar epithelial cells, hyaline membrane formation,
alveolar cavity congestion and type II pneumocyte
hyperplasia. The main histopathological findings in kidney
specimens from autopsy COVID-19 subjects were varying
degrees of acute tubular necrosis, luminal brush border
sloughing and dilated capillary vessels in the glomeruli and
vacuole degeneration. Liver injury is more common in severe
cases of COVID-19 and exhibits mild lobular infiltration by
small lymphocytes, and centrilobular sinusoidal dilation,
whereas the heart shows only focal mild fibrosis and mild
myocardial hypertrophy.

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Ethical Consideration

Ethical clearance was not required for this manuscript according to our institution.

Conflict of Interest

The author declares that has no competing interests.

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References


