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Review Article

Pathology Section

Pathology of COVID-19: A Review of Emerging Evidences from Autopsy Studies

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ABSTRACT

Coronavirus Disease 2019 (COVID-19) is caused by novel Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2). The disease was first reported from Wuhan, China, in December 2019 and since then it continues to spread worldwide. Although, there are rapidly increasing number of studies on epidemiologic characteristics and clinical aspects of COVID-19, its pathology still remains a largely unexplored territory, mainly due to limited autopsy studies. Autopsy studies are essential to demonstrate the spectrum of COVID-19-associated organ changes. This article reviews and highlights the important histopathological findings observed in different organ systems as evident from various published and anecdotal reports from across the world. Major histopathological findings in the lungs include different stages of Diffuse Alveolar Damage (DAD) and microthrombi along with variable degree of inflammation. Microscopic analysis of renal parenchyma may show acute tubular injury and fibrin thrombi in the glomerular capillaries. Heart, liver and brain show no significant inflammatory changes.

Keywords: Acute tubular injury, Coronavirus disease 2019, Diffuse alveolar damage, Microthrombi, Severe acute respiratory syndrome coronavirus-2

INTRODUCTION

The outbreak of COVID-19 pandemic, caused by novel SARS-CoV-2, began in Wuhan, the capital city of Hubei province of China, in December 2019 [1]. In the Indian subcontinent, the first case of COVID-19 was reported on 30 January 2020 in the state of Kerala [2] and the total number of affected people has now crossed forty lacs as on 6th September 2020 [3]. The clinical spectrum of COVID-19 ranges from asymptomatic cases to severe respiratory distress requiring mechanical ventilatory support to critical illness manifesting as respiratory failure, septic shock, and/or multiple organ dysfunction [4]. Fatalities are more likely to occur in elderly patients and patients with pre-existing co-morbidities such as diabetes, cardiovascular diseases, chronic respiratory diseases and malignancies [4].

Although respiratory system is the disease conduit and primary site of affection of SARS-CoV-2, varying degrees of pathological changes are evident in other organs too. As compared to studies focusing on clinical and epidemiological aspects of COVID-19, there is relative paucity of autopsy studies mainly because "if a death is believed to be due to confirmed COVID-19 infection, there is unlikely to be any need for a post-mortem examination" [5]. This is an attempt for minimising the exposure risk of the health care personnel, especially in the absence of mandatory pre-autopsy testing for SARS-CoV-2. Other constraining factors include lack of desired mortuary facilities, trained staff in mortuary and availability of personal protective kit, especially in resource poor countries. However, if such an autopsy is performed, Centers for Disease Control and Prevention (CDC) recommends tissue sampling of the respiratory system in addition to postmortem nasopharyngeal and lung swabs [6]. A minimum of 2 sections of the large airway (trachea and/or bronchi) and a minimum of 3 different representative sections of lung parenchyma should be ideally sampled [6].

PATHOLOGICAL ABNORMALITIES IN VARIOUS ORGANS

In this article, the authors have reviewed and analysed the available literature on COVID-19 autopsies and have comprehensively summarised the range of pathological abnormalities noted in various organs.

Lungs

For obvious reasons, lung remains the most studied organ. Gross examination of the lungs reveals diffuse pulmonary congestion and oedema leading to increased lung weight [7-13]. Few investigators found the combined weight of bilateral lungs to be almost double than the normal reference range [12,14-16]. Focal haemorrhagic changes [14,15,16] and macroscopic pulmonary emboli/thrombi [7,11-14] can also be noted. Other gross findings of the respiratory tract may include mucoid secretions within trachea and bronchi, mucosal oedema and congestion of tracheobronchial tree, pleuritis and pleural effusion [9,15,16-18].

Tian S et al., were one of the earlier researchers to report SARS-CoV-2 related lung changes [19]. They noted oedema, proteinaceous exudate, patchy chronic inflammatory infiltrates, hyperplasia of pneumocytes and multinucleated giant cells in the lung parenchyma of two COVID-19 patients who underwent lobectomies for lung adenocarcinoma and had no pneumonia-like symptoms at the time of surgery. Hyaline membranes were not seen because the histopathological examination was conducted during the early phase of the disease in these patients.

Subsequent studies showed Diffuse Alveolar Damage (DAD) at various stages as the major microscopic feature [8,9,11-13,17,18,20-23]. Mild to moderate lymphoplasmacytic interstitial inflammatory infiltrate is a usual accompanying finding [9,11,24-28]. Polak SB et al., carried out a systematic meta-analysis of published histopathological findings in lungs of COVID-19 patients and established that three histological patterns of lung injury can be present at different times during disease progression or simultaneously [29]. The three histological patterns are: 1) epithelial pattern, characterised by DAD, varying degrees of organisation, pneumocytes hyperplasia and denudation, squamous metaplasia of alveolar epithelium, presence of multinucleated giant cells; 2) vascular pattern, characterised by capillary congestion, diffuse intra-alveolar fibrin, presence of microvascular fibrin thrombi, endothelial injury; and 3) fibrotic pattern, characterised by fibrotic DAD and/or interstitial fibrosis [29]. A subset of patients may show super-imposed bronchopneumonia and bacterial abscess [8,11,13]. In a report from Switzerland, all the 21 cases examined exhibited pulmonary congestion and DAD and 10 out of 21 had diffuse or focal bronchopneumonia [11]. Carsana L et al., noted four cases of bacterial

and one case of fungal abscesses in their cohort of 38 Italian patients [8]. Grosse C et al., found pulmonary infarcts in 2 out of 14 deceased patients with one of them showing superadded infection of the infarcted parenchyma [15]. The key microscopic findings in lungs are mentioned in [Table/Fig-1]. Such histopathological alterations are comparable to those encountered in Haemagglutinin Type 1 and Neuraminidase Type 1 (H1N1) influenza virus, SARS and Middle East Respiratory Syndrome (MERS)-coronavirus infections [30]. Apart from epithelial and vascular changes, viral inclusions of SARS-CoV-2 can be seen upon light microscopy [9,19,26,28]. The presence of SARS-CoV-2 in the lungs tissue has been confirmed by several researchers using either immunohistochemistry or Reverse Transcription Polymerase Chain Reaction (RT-PCR) [7,11,12,21,27,28,31,32].

Organs	Histopathological findings
Lungs	• Diffuse alveolar damage at varying stages • Microthrombi in the pulmonary vasculature • Bronchopneumonia and/or bacterial abscess may be present
Heart	• Mild lymphocytic infiltrate in the interstitium • No significant myocarditis • No significant myocyte necrosis
Liver	• Mild lobular and portal inflammation • Mild to moderate steatosis may be seen • No significant hepatitis
Kidneys	• Acute tubular injury • Glomerular congestion • Fibrin thrombi within the glomerular capillaries • No glomerulonephritis
Brain	• Signs of hypoxic injury • No significant inflammatory infiltrates

[Table/Fig-1]: Main histopathological findings in different organs in COVID-19.

Vasculopathy, in the form of microthrombi in the pulmonary vasculature, has emerged as an important pathophysiological event in COVID-19 [8,9,11,13,15,17]. Thromboembolic complications have been documented across many COVID-19 autopsy studies [9,11,12,17,33,34]. However, the presence of microthrombi in the pulmonary vasculature are not specific to SARS-CoV2 infection and have been earlier documented in H1N1 influenza virus infection [30]. Ackermann M et al., who comparatively analysed 7 lungs obtained from COVID-19 deceased patients with 7 lungs obtained from patients who died from Acute Respiratory Distress Syndrome (ARDS) secondary to influenza A (H1N1), concluded that alveolar capillary microthrombi and degree of neo-angiogenesis was more prevalent in COVID-19 patients as opposed to patients with influenza [23].

Heart

The cardiovascular complications of COVID-19 can manifest as heart failure, acute cardiac injury (including Myocardial Infarction (MI) and myocarditis), arrhythmias and cardiac arrest [35-40]. Roca E et al., described Takotsubo syndrome as a rare cardiac complication of COVID-19 [41]. High-sensitivity cardiac troponin I (hs-cTnI) has emerged as a potential indicator of acute cardiac injury and predictor of in-hospital death [42,43]. Analysis of cardiac biomarkers in COVID-19 patients showed that the values of cTnI were significantly higher in patients with severe disease than those with milder symptoms [4,44,45]. However, Deng Q et al., and Ammirati E and Wang DW concluded that the increase in troponin levels in COVID-19 is non-specific and is attributed to systemic damage rather than being a specific biomarker of myocarditis [45,46]. Tavazzi G et al., was first to demonstrate coronavirus particles in the interstitial macrophages present within the endomyocardial biopsy of a 69-year-old COVID-19 patient with respiratory distress, hypotension, and cardiogenic shock [42]. The morphologic alterations noted were mild interstitial and endocardial inflammation and mild interstitial fibrosis without any evidence of myocyte necrosis [Table/Fig-1].

In another case series, two patients' postmortem cardiac biopsies showed only changes related to patients' underlying condition (mild focal interstitial fibrosis and myocardial hypertrophy) without any inflammation [32]. Similarly, Barton LM et al., and Xu Z et al., found no histomorphologic evidence of myocarditis in three COVID-19 cases, who died due to cardiac arrest [13,20]. Fox SE et al., examined the heart of three COVID-19 decedents from New Orleans and found right ventricular dilatation with mild to moderate serosanguinous pericardial effusion, macroscopically [9]. Microscopy showed scattered individual myocyte necrosis without significant inflammation. In yet another report from Houston, USA, the cardiac changes noted were epicardial lymphocytic infiltrates (CD4/CD8 ratio of 2:1) and scattered myocyte damage with hyperchromatic nuclei [17]. Notably, many investigators have observed mild cardiomegaly on autopsy [7,11,12] which is plausibly attributed to the pre-existing cardiovascular pathology, rather than COVID-19. Elsoukkary SS et al., reported mild cardiomegaly in 28 patients in an autopsy study of 32 deceased, amongst whom 23 were hypertensive, 10 had coronary heart disease and 6 had chronic heart failure [14].

Liver and Gastrointestinal Tract

Although patients may present with varying degrees of derangement in serum levels of alanine aminotransferase, aspartate aminotransferase, total bilirubin, alkaline phosphatase and albumin (14.8%-78.0%), no independent correlations have found between these parameters and disease severity [47,48]. Histopathologically, liver parenchyma does not show significant inflammation [Table/Fig-1]. In a small autopsy series of four patients, the investigators found liver to exhibit mild lobular lymphocytic infiltration and centrilobular sinusoidal dilation in all cases, focal macrovesicular steatosis in one case and patchy necrosis in one case [32]. Three autopsies performed at Huston revealed similar findings of moderate macrovesicular steatosis without evidence of hepatitis [17]. Another autopsy report showed moderate micro-vesicular steatosis, and mild lobular and portal inflammation in liver [20]. These findings are common in critically ill patients and cannot be definitively attributed to SARS-CoV-2 per se.

Several hospital-based studies across China described gastrointestinal symptoms in 2-73% cases and also highlighted that digestive symptoms can be the only presenting complaint with no respiratory symptoms [49-52]. Microscopically, the gastrointestinal tract may show epithelial damage, endothelitis and ischaemic enterocolitis [12,53].

Kidneys

Acute tubular injury has emerged as a consistent histopathological finding in postmortem renal biopsies of COVID-19 patients [11,18]. Evidence of endothelial damage and fibrin thrombi in glomerular capillaries has also been noted [11,53,54]. Glomerulonephritis due to SARS-CoV-2 infection has not been documented till date, suggesting that renal damage in COVID-19 is not related to inflammatory process, but secondary to other complex mechanisms.

Su H et al., detailed out the light microscopic and ultrastructural changes in kidney biopsies obtained from autopsies of 26 COVID-19 patients (19 males and 7 females, average age was 69 years, age range=39-87 years) who died from respiratory failure [54]. Nine showed biochemical signs of kidney injury in the form of increased serum creatinine and/or proteinuria. The most frequent histopathological feature noted was acute tubular injury along with diffuse erythrocyte stagnation in the peritubular and glomerular capillary loops [Table/Fig-1]. None of the cases showed interstitial haemorrhage which is deemed as a characteristic feature of acute kidney injury induced by hantavirus [54,55]. Other morphologic findings noted were glomerular fibrin thrombi with ischaemic collapse, endothelial damage, haemosiderin deposition, pigment casts related to rhabdomyolysis and bacterial colonies with white blood cell casts secondary to lung pathology. Transmission Electron Microscopy (TEM) revealed spherical virus particles (size: 65 nm to 136 nm) with 20 to 25 nm spikes arranged in "corona" fashion, in the cytoplasm of renal proximal tubular epithelial cells and podocytes of seven out of the nine cases analysed. Two of

these seven cases also had concurrent expression of SARS-CoV nucleoprotein on indirect Immunofluorescence (IF) technique with anti-SARS-CoV nucleoprotein antibody. Interestingly, their study cohort had one case each which was positive on TEM and negative on IF and vice-versa, there by pointing towards complementary role of TEM and IF in detecting the virus in renal biopsies. Also, electron microscopy findings should be cautiously interpreted as certain cellular structures such as cross-sections of the rough endoplasmic reticulum, clathrin-coated vesicles and multivesicular bodies may be mistaken as viral particles [56-58].

Brain

In a study of 214 COVID-19 cases in Wuhan, China, incidence of neurologic complications, which included acute cerebrovascular diseases, impaired consciousness and skeletal muscle injury, were significantly higher in severe cases as compared to non-severe cases {40 (45.5%) vs. 38 (30.2%), p<0.05} [59]. Also from Wuhan, Li Y et al*.,* reported 5% (n=11/221) cases with ischaemic strokes secondary to large-vessel occlusion [60]. Jin H et al*.,* suggested both ischaemic and haemorrhagic strokes as potential complications of COVID-19 [61]. Chen T et al., documented hypoxic encephalopathy in 20 out of 113 COVID-19 patients [62].

COVID-19 patients can also present with signs and symptoms of meningitis and/or encephalitis. Moriguchi T et al*.,* reported the case of a 24-year-Japanese admitted with headache, fever, fatigue, seizures and neck rigidity [63]. Cerebrospinal Fluid (CSF) analysis revealed 10 mononuclear and 2 polymorphonuclear cells per µ/L and CSF RT-PCR was positive for SARS-CoV-2 [63]. But, other investigators have failed to demonstrate SARS-CoV-2 by CSF RT-PCR in COVID-19 despite concurrent neurological manifestations [64-67]. Hitherto, reports addressing detailed post-mortem evaluation of brain are limited. In autopsies conducted on 18 patients (median age: 62 years; M:F=7:2; neurologic symptoms were present in 6) at Boston, macroscopic inspection of brain showed no evidence of acute stroke, increased intracranial tension or olfactory bulb damage [68]. On microscopy, there were signs of acute hypoxic injury in the cerebrum and cerebellum in all cases. There was no evidence of encephalitis/thrombi/vasculitis/abnormalities in the olfactory bulbs and tracts. Low viral load was detected in the brain tissue of 5 patients by quantitative RT-PCR for the SARS-CoV-2 nucleocapsid protein. Similar microscopic features were noted in the study from Switzerland, wherein three out of four brains examined showed mild hypoxic injury and none of them showed inflammatory infiltrates or neuronal necrosis [11]. More studies pertaining to detailed histopathological analysis of affected brains, superior techniques for isolation of SARS-CoV-2 from CSF or brain tissue, prognostic implication of SARS-CoV-2 positivity in CSF and identifying a biomarker in CSF/serum to predict neurological disease severity should encouraged to be undertaken in future.

Other Organs

Common findings in the spleen include attenuation of white pulp, red pulp expansion, congestion and haemorrhage [11,12,17,69]. Postmortem bone marrow examination in four cases showed reactive left-shifted myelopoiesis in three cases and prominent hyperplasia of cytotoxic CD8-positive T-cells in one case [11]. Hosier H et al*.,* histologically examined the placenta of a 35-year-old gravida which revealed diffuse intervillous fibrin and a dense infiltrate of T lymphocytes and macrophages with no evidence of vasculopathy [70]. In the same case, SARS-CoV-2 was shown to be localised to syncytiotrophoblast cells at the feto-maternal interface of the placenta.

In a study cohort of 88 Italian COVID-19 patients, approximately 20% showed cutaneous involvement consisting of erythematous rash, wide-spread urticaria and vesicular lesions resembling varicella-zoster [71]. The knowledge of biopsy findings of such lesions remains sparse, limited to few case reports and case series. The histopathological findings include dermal oedema, vacuolar degeneration of the basal layer of the epidermis with occasional scattered apoptotic keratinocytes and superficial and deep perivascular and peri-eccrine lymphocytic infiltrate [72-74]. Most of the cutaneous manifestations noted in association with COVID-19 are non-specific, clinically as well as histopathologically, and bear no prognostic significance [71,73].

BRIEF PATHOGENESIS

The transmembrane protein, Angiotensin-Converting Enzyme 2 (ACE2) serves as the gate for viral entry [32,54,75]. The binding of the spike S1 glycoprotein of SARS-CoV-2 to the enzymatic domain of ACE2 on the target cell surface results in the internalisation and subsequent replication of the virion [32,54,75]. ACE2 is present in various human tissues including type II pneumocytes of lungs, enterocytes of the small intestine, bile duct epithelium, endothelial cells of both arterial and venous system, cerebral cortex, striatum, hypothalamus, brainstem and hence, the multiorgan affection [32,75]. CD147 is postulated as another possible cell receptor for viral entry [76]. The disease pathogenesis is complex and remains poorly understood. It involves direct virulence and cytopathic effects, host humoral and cellular immune responses, pulmonary and peripheral endothelial injury, deranged coagulation machinery, cytokine storm and complement activation culminating in multiorgan inflammation and microangiopathy [23,31,53,54,77-79]. Macrophages hyperactivation and haemophagocytosis has also been observed in some cases [7,80,81]. Secondary insults like hypoxia, superadded infections and thromboembolic state contributes to disease progression and worsening.

CONCLUSION(S)

This article sums up the current knowledge of COVID-19 related histopathological changes. This would serve as a comprehensive guidance for clinicopathological correlation and might provide new insights into the pathophysiology of SARS-CoV-2, which, inturn may aid in formulating better management strategies. Also, detailed molecular research on fresh or formalin-fixed tissues obtained from various organs during autopsy is needed to ascertain the molecular basis and pattern of SARS-CoV-2 tropism and the extent of its effects on different organs.

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