Review Article

Lung Pathology in COVID-19: A Systematic Review

Abstract

Sparse literature is available regarding autopsy findings of coronavirus disease 2019 (COVID-19) despite high mortality due to its highly contagious nature and lack of robust infrastructure for appropriate handling of the infected cases. Based on clinical findings and various diagnostic tests, it is evident that it holds the potential to affect multiple organ systems of the body preferably lungs and immune and coagulation systems. Cytokine storm-induced thrombotic complication such as disseminated intravascular coagulation is a significant feature in severe cases of COVID-19. This review captures the current information on lung histopathology in COVID-19 infection and severe respiratory failure. In COVID-19, lungs are affected bilaterally, become edematous and red/tan mottled to maroon in color with firm consistency. Distinct parenchymal changes, firm thrombi in the peripheral pulmonary vessels along with diffuse alveolar damage, have been the most consistent feature of COVID-19-related lung pathology. Electron microscopy has also been used to demonstrate viral particles.

Keywords: *Acute respiratory distress syndrome, alveolar damage, COVID-19, lung pathology, pneumonia*

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Introduction

It was at the end of 2019 when a new pandemic caused by a novel coronavirus-severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) subsequently hit the world after originating from Wuhan, Hubei province, in China, and the disease thus caused in human was named coronavirus disease 2019 (COVID-19) by the World Health Organization (WHO) and on January 30, 2020, it was declared as a global health emergency.[1] The 21st century, since its beginning, has witnessed three coronavirus pandemics so far namely SARS-CoV which also had originated in China in 2002 and led to 8098 cases with 774 deaths worldwide, followed by Middle East respiratory syndrome-coronavirus (MERS-CoV) in 2012 that began in Saudi Arabia and resulted in 2458 cases with 848 deaths[2,3] and latest in the row is the most pathogenic and widely spread COVID-19 pandemic, of which 4,993,470 cases have already occurred worldwide with 327,738 deaths as on May 22, 2020, as declared by the WHO.[4] Compared to SARS-CoV and MERS-CoV, SARS-CoV-2 is far more infective and transmissible but with lower mortality rate[5] which is 2%–3% in hospitalized patients.[6] The reported case fatality rate for SARS is 9.6%[7] and that for MERS is 34%.[8] Coronaviruses are known to cause diseases in both humans and animals, affecting pulmonary, intestinal, hepatic, renal, and neurologic systems.[9] SARS-CoV-2 is the seventh member of the family of coronaviruses that infects humans. Zoonotic coronaviruses after crossing the species barrier resulted in these pandemics associated with severe morbidity and mortality in humans.

Study design

For the present review, a systematic literature search was undertaken over online databases such as PubMed, MEDLINE, medRxiv, bioRxiv, ChemRxiv, Google Scholar, and CNKI using relevant keywords: "SARS-CoV-2," "2019-nCoV epidemiology," "COVID-19 lung pathology," "coronavirus," "COVID-19 autopsy findings," SARS, and MERS. Articles written in English or Chinese language and those that were accepted, in preprint stage, in press, and published between August 2016 and May 5, 2020, were included. Only publications covering lung pathology in COVID-19 were chosen. This review is entirely based on the

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Etiopathogenesis

Coronaviruses are enveloped, positive-sense, single-stranded, RNA viruses which are genotypically and serologically divided into four genera, namely, α, β, γ, and δ infecting mammals and birds.[2,10] SARS-CoV-2 is β-CoV just like SARS-CoV and MERS-CoV, which are known to cause deadly respiratory tract infection in humans.[11] Structurally, SARS-CoV-2 genome is of size 29.9 kb.[12] Infection with SARS-CoV-2 is acquired through respiratory droplets, by contact through mucosal surfaces and potentially by feco–oral route (though it is yet to be studied).[7,13] SARS-CoV-2, just like SARS-CoV, utilizes host angiotensin-converting enzyme 2 (ACE2) as a receptor for its binding.[14,15] ACE2 is expressed in many tissues including alveolar cells, bronchial cells, and vascular endothelium in the lung and is involved in the pathogenesis of acute lung injury and pulmonary edema.[16-18] Viral interaction with its receptor causes proteolytic cleavage involving the viral spike protein, leading to membrane fusion and infection,[19] releasing the viral RNA genome into the cytoplasm to be translated into structural and polyproteins, resulting in viral replication within endoplasmic reticulum and Golgi apparatus followed by fusion of virus-containing vesicles with plasma membrane and release of virus.[20,21] Rapid viral replication may lead to epithelial and endothelial cell damage, causing vascular leakage, and virus-mediated ACE2 downregulation and shedding and antibody-dependent enhancement (ADE) altogether cause prominent systemic inflammatory response where various immunological cells including CD4 T cells and CD8 T cells produce and regulate the release of different pro-inflammatory cytokines and chemokines that include interleukin (IL)-8, IL-18, IL-1, tumor necrosis factor-α, IL-6, and IL-10.[22-24] ADE, observed in many viral infections, further enhances the infection of target cells by assisting in cellular uptake of infectious virus–antibody complexes.[25]

Two interrelated and mutually reinforcing phenomena, that is, thrombosis and inflammation, are together believed to result in disseminated intravascular coagulation (DIC) and consumption coagulopathy as a terminal event in COVID-19,[26,27] which is far more likely in nonsurvivors (71.4%) compared to survivors (0.6%).[28] In a recent report from Italy, hospitalized COVID-19 patients had arterial and venous thromboembolic complications, occurring at a cumulative rate of 21%, and DIC as a secondary outcome was present in 2.2% cases with associated elevated D-dimer levels indicating inflammatory and procoagulant state in these patients, particularly in those patients who succumbed to their illness.[29] Latest literature showed that COVID-19 acute respiratory distress syndrome (ARDS) patients experienced much higher (11.7%) rate of thromboembolic complications compared to non-COVID-19 ARDS patients.[30] A recent series on 12 COVID-19 autopsy cases reported deep-vein thrombosis in seven cases, in which venous thromboembolism was not suspected antemortem.[31] Apart from hemostatic functions, both coagulation factors and platelets also act as an immunomodulator through their pro-inflammatory properties.[32]

Clinical Features

The mean incubation period is 5.2 days (95% confidence interval, 4.1–7.0).[33] The most frequent clinical manifestations in COVID-19-infected patients include fever (83%–98%), dry cough (76%–82%), fatigue, and dyspnea. Patients also present with symptoms pertaining to multiple systems such as headache, confusion, hemoptysis, sputum production, rhinorrhea, sore throat, dyspnea, diarrhea, chest pain, nausea, vomiting, myalgia, and conjunctival injection.[13,34] Poor prognosis and higher mortality were observed in elderly patients and those with underlying cardiovascular disease, chronic respiratory disease, diabetes, cancer, and hypertension where the reported case fatality rate was 10.5%, 6.3%, 7.3%, 5.6%, and 6.0%, respectively.[5,35,36] Published reports have documented that in severe cases, patients also develop acute kidney injury, arrhythmia due to cardiac dysfunction, shock, hepatic dysfunction, and hematological abnormalities such as lymphocytopenia.[37,38]

Diagnostics

Real-time-polymerase chain reaction for detection of SARS-CoV-2 done on nasopharyngeal swab, tracheal aspirate, or bronchoalveolar lavage carries very high specificity. SARS-CoV-2 RNA has also been detected in blood and stool samples. Frequently found hematological abnormalities are leukopenia; leukocytosis; lymphopenia; thrombocytopenia; and elevated levels of alanine aminotransferase, aspartate aminotransferase, and lactate dehydrogenase.[6,39] There is elevation in D-dimer, ferritin, and C-reactive protein levels, whereas fall in procalcitonin levels has been reported. Radiological findings such as ground-glass opacity, consolidations, and the crazy-paving pattern are frequently observed mainly in the peripheral portions of lower lobes of lung on computed tomography. These are nonspecific signs and are probably due to alveolar septal edema and interstitial hyperplasia.[40,41]

Pathology

Sparse literature is available regarding autopsy findings of this novel virus despite the high mortality probably because of its highly contagious nature and limited information on its prevention and lack of robust infrastructure for appropriate handling of infected cases at several centers across the globe. However, autopsy remains the gold standard for ascertaining the exact cause (s) of death

and provides necessary information for optimizing clinical management as it permits adequate sampling and study of multiple organs for diagnostic and research purposes.[42] Significance of autopsies is further emphasized by the finding that in up to 30% cases, antemortem diagnostic errors or unrecognized diagnoses were disclosed on autopsies.[43,44] The Royal College of Pathologists has presented latest guidelines for pathologists and mortuary technicians on autopsies in confirmed or suspected cases of COVID-19.[45,46] Pathology-related information obtained through autopsies is essential for understanding its pathogenesis and critical morphological findings. Moreover, postmortem tissue sampling will also be needed for enhanced understanding of current novel virus through *in situ* and molecular studies.[47]

There is marked resemblance in the histopathological findings of SARS-CoV, MERS-CoV, and SARS-CoV-2. The focus of the current review is to capture the currently available information on lung histopathology in COVID-19 infection and severe respiratory failure. Details of published literature discussing pulmonary involvement from pathologists' perspective are tabulated in Table 1.

Lungs

For pathological study of lung, tissue from patients who succumbed after acquiring SARS-CoV-2 infection at various centers across the globe, was obtained after complete postmortem examinations in seven studies,[31,42,48-52] whole-lung biopsy in one study,[18] postmortem autopsy lung tissues in one study,[53] and thoracoscopic resection of lung lobe in one study performed for two cases of carcinoma lung;[54] in other five studies, postmortem needle core biopsies, ultrasound-based minimally invasive autopsies, and minimally invasive autopsies were performed.[26,55-58] Of all these studies, the largest series was based on 38 cases[53] from Northern Italy.

A gross description of COVID-19-related lung pathology was available in 9[18,31,42,48-53] out of 15 studies included in the present review. In a study by Tian *et al*.,[54] two patients underwent thoracoscopic resection of lung lobe for carcinoma lung, however on gross description, only tumor-related findings were described and lung changes due to COVID-19 were not mentioned probably because lobectomy was done very early during the disease course, much before the gross changes could have become apparent.

Gross Features

In COVID-19, lungs being the primary organ to be affected are bilaterally involved and are heavy ranging on the left side – 680–1269 g and on the right side – 800–1183 g.[31,42,48-50] There is diffuse or spotty involvement of lung parenchyma which is edematous and red/tan mottled to maroon in color with firm consistency similar to ARDS. Distinct parenchymal changes also include congestion, punctuate hemorrhages, and hemorrhagic necrosis, particularly at the peripheral edges of the pulmonary lobe, especially right lower lobes. Further, Luo *et al*.[18] mentioned the presence of hemorrhagic necrosis preferentially in the outer edge of the lower lobe of the right lung, suggesting it as one of the initial sites of origin of main lesions in COVID-19 and could be the result of CD4 and CD8 T cell-induced cytokine storm, which further progresses to severe and at time fatal respiratory dysfunction in critical patients. Buja *et al*.[50] also described empyema and atelectasis in one of the cases in their study.

Cut surfaces after fixation have shown alternating consolidated tan-gray area and patchy hemorrhagic areas. Notable gross examination finding as reported by several authors[31,48-52] is the presence of small or large, firm pulmonary thrombo-emboli in the peripheral or central parenchyma and segmental or sub-segmental regions. The upper and lower airways may remain patent with glistening white mucosa, or the bronchi may show mucinous and hemorrhagic exudation or pink froth in the airways.[18,42,48,53] Menter *et al*.[51] also observed severe mucous tracheitis/tracheobronchitis in one-third of the patients and in addition to consolidation also described extensive suppurative bronchopneumonic infiltrates. Pericardial and pleural effusions with mild-to-moderate serosanguinous fluid has also been reported.[48,49] In autopsy cases of SARS-CoV infection, the gross features are described as firm, edematous, heavy lungs with congestion and hemorrhages along with hilar and abdominal lymphadenopathy with small spleen size.[59,60]

Microscopic Features

Studies have found remarkable similarities in the microscopic features of lung lesions in all the three coronavirus pandemic cases of the 21st century. Diffuse alveolar damage (DAD) has been the consistent feature of COVID-19-related lung pathology. In the largest autopsy series comprising 38 cases,[55] lung histopathological features relating to cellular and interstitial damage were extensively studied and semi-quantitatively graded. Histopathological features conforming to exudative, proliferative, and fibrotic phases with other associated findings such as alveolar multinucleated giant cells and interstitial and alveolar inflammation were assessed. Bilateral DAD in the exudative and proliferative phases is the most consistent finding.[31,48-51,53,56]

Features of exudative phase included capillary congestion, pneumocyte injury with sloughing and scattered syncytial giant cell formation, dilated alveolar ducts, interstitial edema, and thickening of alveolar capillaries along with intra-alveolar hyaline membranes which are composed of serum proteins and condensed or organized fibrin; there may be massive fibrinous exudate with intense mononuclear inflammatory cells and multinucleated giant

Table 1: Salient features of the papers and patient characteristics as mentioned in the studies

Study	Type of study, method of sampling, and number of cases	Age range in years, gender	Duration of illness and clinical presentation	Risk factors	Cause of death	DAD on lung pathology
Fox *et al.*[48]	Series of autopsies, 4 cases	44-76, male and female	Three days of mild cough and fever Acute respiratory distress syndrome	Obesity, hypertension, insulin-dependent Type 2 diabetes, chronic kidney disease	Thrombotic microangiopathy	Present
Barton *et al.*[42]	Original article, complete postmortem examinations, 2 cases	Case (1) 77-year-old male Case (2) 42-year-old male	Case (1) six days of fever and chills Case (2) abdominal pain followed by fever, shortness of breath, and cough	Case (1) obesity, hypertension Case (2) obesity, myotonic muscular dystrophy	Case (1) COVID-19, with coronary artery disease Case (2) Complications of hepatic cirrhosis, with muscular dystrophy, aspiration pneumonia	Case (1) present Case (2) acute Broncho-pneumonia
Luo *et al.*[18]	Case report Whole-lung biopsy	60-year-old male	High fever and cough	Hypertension	Respiratory failure	Interstitial fibrosis, and hyaline degeneration
Zhang *et al.*[55]	Brief research report postmortem Transthoracic needle biopsy	72-year-old male	Fever and cough	Diabetes and hypertension	Respiratory failure	Present
Tian *et al.*[56]	Article Postmortem needle-core biopsies, 4 cases	59-81 years, three males and one female	Fever	Chronic lymphocytic leukemia, renal transplantation, cirrhosis, hypertension, and diabetes	Not mentioned	Present
Xu *et al.*[57]	Case report Postmortem needle-core biopsy	50-year-old male	Fever, chills, cough, fatigue, and shortness of breath.	Travel history to Wuhan	Coronavirus pneumonia	Present
Tian *et al.*[54]	Case report Thoracoscopic lung resection Case (1) right middle lobe Case (2) right lower lobe	Case (1) 84-year-old female Case (2) 73-year-old male	Case (1) difficulty in breathing, chest tightness, wheezing, and dry cough Case (2) fever on postoperative day 9 with dry cough, chest tightness, and muscle pain	Case (1) lung adenocarcinoma, hypertension for 30 years, Type 2 diabetes Case (2) lung adenocarcinoma, hypertension	Case (1) Coma Case (2) Recovered alive	Case (1) adenocarcinoma, with alveolar damage Case (2) adenocarcinoma with DAD
Dolhnikoff *et al.*[26]	Letter to editor, ultrasound-based minimally invasive autopsies for COVID-19, ten cases	33-83 years, five males and five females	Not mentioned	Hypertension, diabetes mellitus, ischemic heart disease, and chronic obstructive pulmonary disorders	Not mentioned	Present
Carsana *et al.*[53]	Original article, Postmortem autopsy lung tissues 38 cases	32-86 years, 33 males and 5 females	Not mentioned	Diabetes, hypertension, cardiovascular disorders, chronic obstructive pulmonary disorders	Not mentioned	Present

Contd...

Table 1: Contd...

Study	Type of study, method of sampling, and number of cases	Age range in years, gender	Duration of illness and clinical presentation	Risk factors	Cause of death	DAD on lung pathology
Yao *et al*.[58]	Minimally invasive autopsies from multiple organs	Three cases	Not mentioned	Not mentioned	Coronavirus pneumonia	Not mentioned
Bradley *et al*.[49]	Original article, Autopsy 12 cases	42-84 years, five males and seven females	Respiratory distress (83.3%), fever (58.3%), cough (50%), altered mental status, and gastrointestinal distress	Hypertension, chronic kidney disease, diabetes, and obesity	Coronavirus pneumonia	Present
Buja *et al*.[50]	Original article, Autopsy, three cases	Case (1) 62-year-old male Case (2) 34-year-old male Case (3) 48-male	Case (1) found dead in his car with few-day history of respiratory illness Case (2) headache, shortness of breath, hemoptysis for 4 days, and fever for 1 day Case (3) found dead at his residence	Case (1) obesity Case (2) hypertension, heart failure, Type 2 diabetes mellitus, and microcytic anemia Case (3) obesity	Case (2) respiratory failure	Case (1) present Case (2) acute thromboemboli with pulmonary hemorrhage and infarction Case (3) present
Wichmann *et al*.[31]	Original article, Autopsy, 12 cases	52-87 years, nine males and three females	Not mentioned	Obesity, coronary heart disease, asthma or chronic obstructive pulmonary disease, and diabetes mellitus type 2	Pulmonary embolism in four cases, sudden cardiac death, respiratory failure	Present
Menter *et al*.[51]	Original article, Autopsy, 21 cases	53-96 years, 17 males and 4 females	Dry cough and fever, dyspnea	Hypertension, obesity, cardiovascular diseases, diabetes mellitus, 65% had blood group A	Respiratory failure	Present
Grimes *et al*.[52]	Case report, Autopsy, two cases	Case (1, 2) both middle-aged males	Case (1) fever, chills, myalgia, dry cough, and dyspnea Case (2) fever, chills, productive cough, and dyspnea	Case (1) hypertension Case (2) asthma, hypertension and HIV	Case (1, 2) pulmonary thromboembolism	Pulmonary thromboembolism

DAD: Diffuse alveolar damage

cells in air spaces.[18,26,42,48-51,53-58] Many inspissated spherical secretions or globules are also described.[54]

Findings conforming to proliferative phase of DAD include Type-2 pneumocyte hyperplasia of varying degrees with or without reactive atypia, and interstitial myofibroblastic proliferation together causing thickening of alveolar walls, alveolar granulation tissue, obliterating fibrosis, alveolar macrophages, interstitial thickening, and plugs of proliferating fibroblasts or "fibroblast balls" in the interstitium. Mild-to-moderate lymphocytic infiltrate with foci of hemorrhages can also be seen.[26,48-51,54,56,58]

Bronchi and bronchioles may show chronic inflammation with marked thickening of bronchial mucosa due to edema.[18,42,49] Other features such as necrotizing bronchiolitis and alveolitis with atrophy, proliferation, and squamous metaplasia in alveolar epithelium have also been reported in SARS-CoV-2.[31,50,59,60]

In another case reported by Barton *et al*., the patient had features of acute bronchopneumonia with rare aspirated foreign material of vegetable matter seen within the airways with infiltration of peribronchiolar airspaces by neutrophils and histiocytes and DAD was not present, hence the cause of death in this case was aspiration pneumonia and not COVID-19 although he tested positive for it.[42]

Features corresponding to fibrotic phase such as pleural involvement, mural fibrosis, scars, microcystic honeycombing, and arterial hypermuscularization were uncommon probably due to the short duration of disease which ranged from 5 to 31 days between the onset of symptoms and death in the largest series of the present review.[53]

The most remarkable and clinically important finding mentioned in most of the reports is diffusely or focally present platelet-fibrin thrombi involving the peripheral or central pulmonary arterial vessels and capillaries in affected and preserved lung parenchyma and entrapped in these thrombi, many inflammatory cells including neutrophils can be seen.[18,26,31,42,48,50-53]

Few studies also mentioned about the presence of endothelial tumefaction and platelet-producing pulmonary megakaryocytes displaying nuclear hyperchromasia and atypia within the alveolar capillaries as an indicator of coagulopathy.[26,48,50]

Patients developing severe disease frequently show deranged coagulation profile with elevated levels of D-dimer in blood, for which targeted therapy in the form of anticoagulants has to be instituted. This hypercoagulative status is further supported by the frequent presence of pulmonary microthrombosis, which leads to hypoxemia and respiratory failure in these cases.[18,26]

Another finding in favor of viral etiology is the presence of definite or suspected viral cytopathic effects in pneumocytes characterized by cytomegaly, nuclear enlargement, prominent eosinophilic nucleoli, and eccentrically placed intracytoplasmic inclusions in the intra-alveolar spaces.[18,26,48,49,54,57]

Blood vessels may show fibrinoid necrosis, wall thickening, luminal stenosis, or occlusion, leading to the development of pulmonary hypertension in later stages in some critical patients.[18,56] Secondary infection is uncommon and may occur in immunocompromised patients manifesting as superimposed bacterial bronchopneumonia, as described in literature.[26,48,49,51,56]

Neutrophil extracellular traps showing partially degenerated neutrophils entrapped in fibers lying in close association with CD4+ mononuclear cells aggregates are mentioned in a report by Fox *et al*.[48] Rarely, interstitial fibrosis, usually of mild-to-moderate degree, and inflammation, mainly of lymphocytic, may be identified.[18,26,42,48,50,51,54-58]

Ancillary Testing

Few studies have used special stains to highlight the findings seen on hematoxylin and eosin stain or immunohistochemistry (IHC) for typing and distribution of lymphocytic infiltrate and electron microscopy for virus particles. Masson trichrome stains are used for the demonstration of fibrin deposition, pulmonary interstitial fibrosis, and thickening of the vessel wall.[18,48] IHC markers employed in different studies were CD3, CD4, CD8, CD20, CD79a, CD5, CD38, CD68, CD61, CD45, CD68, CD61, TTF1, p40, Ki67, SARS-CoV-2 antigen, and Rp3 NP protein of SARS-CoV-2. Results of IHC showed the presence of both T and B cells with a mixture of CD4+ and CD8+ lymphocytes in the peribronchiolar region and interstitium, whereas the perivascular area mainly had CD4+ lymphocytes.[18,48] CD68 and CD61 positivity was seen in macrophages and megakaryocytes, respectively.[42,48,50] SARS-CoV-2 antigen can be identified in alveolar epithelial cells and macrophages.[55,58] Electron microscopy has demonstrated viral particles ranging between 60 and 120 nm with viral projections of about 13 nm in length which were localized along the plasmalemmal membranes, in the cytoplasmic vacuoles of pneumocytes, and bronchial mucosal cells.[49,52,53,58]

Conclusion

Various clinical, biochemical, and radiological parameters suggest multiorgan pathology in COVID-19. Lungs being the primary site for COVID-19 pathology are currently under extensive study, and recent literature have shown DAD as the most consistent finding along with platelet fibrin thrombo-emboli in pulmonary vessels. Increased D-dimer levels indicate the ongoing inflammatory and hypercoagulable state in these patients and represent poor prognostic factor associated with high mortality rate. Being a novel virus, not much is known about its pathogenesis,

treatment, and prevention, hence fast-paced research activities are warranted for optimal management of these cases.

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Conflicts of interest

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