

Histopathologic Findings of Coronavirus in Lung: A Mini-Review

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Clinical Pathology
Volume 13: 1–4
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DOI: 10.1177/2632010X20951823



ABSTRACT: Coronaviruses (CoVs) are important human and animal pathogens. There have been several outbreaks of lung involvement by this category of viruses in the world, ie, severe acute respiratory syndrome (SARS-CoV-1) in 2002 and 2003, the Middle East respiratory syndrome (MERS-CoV) in 2012, and the new coronavirus (2019-nCoV) outbreak of pneumonia from Wuhan, China, since December 2019. There have been several studies about the clinical features and imaging features, but very few reports have been published about pathologic findings in lung tissue, which was partly because of the lack of tissue diagnosis secondary to suddenness of the outbreak. Overall, less than 30 reports have been published in the literature about histologic findings of lung in these viruses, so far. In this report, we will review the published reports about the histopathologic findings of lung tissue in the patients infected with SARS-CoV-2 in comparison with 2 other coronaviruses that have caused outbreaks, ie, SARS-CoV-1 and MERS-CoV.

KEYWORDS: Coronaviruses, Lung, Pathology

RECEIVED: July 22, 2020. **ACCEPTED:** July 30, 2020.

TYPE: Review

FUNDING: The author(s) received no financial support for the research, authorship, and/or publication of this article.

DECLARATION OF CONFLICTING INTERESTS: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Introduction

Coronaviruses (CoVs) are important human and animal pathogens. These are the largest group of viruses in the *Nidovirales* order, including *Coronaviridae*, *Arteriviridae*, and *Roniviridae* families. Electron microscopy of *Coronaviridae* is spherical or oval shape under the microscope, with regularly arranged cystic collagen fibers, which looks like a crown, so it has been named as coronavirus (virus with crown). According to phylogenetic clustering, the *Coronavirinae* are subdivided into 4 groups: the alpha, beta, gamma, and delta CoVs.¹

These are enveloped, nonsegmented positive-sense RNA viruses, containing very large genomes (30 kilobases). *Coronaviridae* can infect respiratory and gastrointestinal (GI) tract, as well as liver and central nervous system (CNS), in the human being and other animals such as bat and mouse.²

There have been several outbreaks of lung involvement by this category of viruses in the world, ie, severe acute respiratory syndrome (SARS-CoV-1) which happened in the years of 2002 and 2003, the Middle East respiratory syndrome (MERS-CoV) occurred in 2012, and the new coronavirus (2019-nCoV) pandemic of respiratory tract infection from the province of Wuhan, China, since December 2019.²

The later virus was renamed as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the pandemic has been called as coronavirus disease (COVID-19), which declared by World Health Organization (WHO) as “a global health emergency” on January 30, 2020.³

Patients with SARS-CoV-2 present with fever, which can be accompanied by respiratory tract signs or symptoms with different degrees of severity. This can be seen on imaging modalities, especially on chest computed tomography (CT) imaging. Most of the involved patients show mild pulmonary

illness, but less than 20% eventually fall in the severe group, needing assisted ventilation. This group of patients has a high mortality rate, mostly in older age, and patients with underlying diseases such as diabetes or on treatment with immunosuppressive like transplant patients. There have been several studies about the clinical features and imaging features, but very few reports have been published about pathologic findings in lung tissue. This has been due to the outbreak that did not let the researchers to perform enough numbers of autopsies.⁴

In this report, we will review the published reports about the histopathologic findings of lung tissue in the patients infected with SARS-CoV-2 in comparison with 2 other CoVs that have caused outbreaks, ie, SARS-CoV-1 and MERS-CoV.

Methods

Case reports and case series that have been published in the medical literature have been gathered by searching in PubMed and Google Scholar.

The keywords for searching were “lung,” “pulmonary,” and CoVs, ie, “severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2],” “coronavirus disease (COVID-19),” “pathology,” “biopsy,” “autopsy,” “histopathology,” “severe acute respiratory syndrome (SARS),” and “Middle East Respiratory syndrome (MERS).”

Each keyword was used alone and together with other key words to find the most relevant papers regarding the histopathologic findings to be selected and included in this review.

Results

During the last years since 2002, from the beginning of SARS-CoV-1 epidemics, then MERS-CoV and now for SARS-CoV-2, less than 20 papers in English have been published



Table 1. Characteristic pathologic findings in 3 coronaviruses associated with epidemics and pandemics.^{1,21}

HISTOPATHOLOGIC FINDINGS	SARS-COV-1	MERS-COV	SARS-COV-2
Edema	+	+	+
Consolidation (pneumonia and bronchopneumonia)	++	++	+
Alveolar hemorrhage	+	+	++
Diffuse exudative alveolar injury	+	+	++
Alveolar hyaline membrane	++	++	+
Inflammation	+	+	+/-
Necrosis and septal destruction	+	++	+
Pneumocyte shedding	+	+	+
Eosinophilic inclusion in pneumocytes	+	+	+
Pneumocyte transformation to multinucleated giant cells	+	+	++
Alveolar epithelial hyperplasia	+	+	++
Alveolar wall thickening and extracellular matrix deposition	-	-	+/-
Neutrophilic capillaritis	-	-	+/-
Pulmonary fibrosis	-	-	+/-

with specific consideration of the histopathologic findings of lung tissue in human, most of which have been autopsy findings after the patients' death; therefore, most of the findings demonstrate the fatal forms of the diseases. Table 1 shows the characteristic findings of 3 CoVs in the lung.

Histopathologic findings of SARS-CoV-1

The macroscopic picture of the lung shows edema with congestion. Cut sections of the lung show irregular and patchy areas of consolidation (pneumonia). Frequent bronchopneumonia has also been reported. Mucopurulent material was seen in the upper respiratory tract. Lung histomorphology of early phase of the disease (<10 days) mostly shows acute diffuse alveolar damage. Later phase of the disease also shows "diffuse alveolar damage" with "acute fibrinous and organizing pneumonia." Other findings were "pulmonary infarction, squamous metaplasia, giant cell transformation, and microthrombi. Intracytoplasmic viral inclusions have also been reported in alveolar epithelial cells."^{5,6}

In other studies, "desquamative alveolitis and bronchitis, with proliferation of alveolar epithelial cells, exudation of mononuclear cells, lymphocytes and plasma cells" were reported. The epithelial cells are enlarged and fuse to create syncytia.⁷

There is also a case report about the histologic findings of a lung biopsy taken during surgery approximately a week after the beginning of symptoms in a patient finally diagnosed as SARS-CoV-1. Histopathologic findings of this biopsy revealed

nonspecific change such as mild increase in interstitial lymphocytes with moderate increase of intra-alveolar macrophages as well as formation of "hyaline membrane." Pneumocytes have been reported to show cytomegaly and karyomegaly with prominent nucleoli.⁸

Large syncytial cells with multiple nuclei were also reported. Small vessel vasculitis was also seen.⁹ Another finding in lung tissue has been severe neutrophilic capillaritis and small vessel injury that has been described to be correlated with the severity of lung injury.¹⁰ In addition to lung, systemic organ involvement has been reported, as "degeneration and necrosis" of the hepatocytes, parenchymal cells of kidney and adrenal as well as heart myocardial cells.⁷

In the reported cases of SARS, patients' outcome has not been directly correlated with the pathology of injury of the lung and other organs.^{7,11-14} None of the histopathologic findings were specific and characteristic for the diagnosis of SARS disease.^{14,15}

Histopathologic findings of MERS-CoV

There has been only a single autopsy case reported by Ng et al on a patient who died after infection with this MERS-CoV. Histopathologic features include diffuse alveolar damage, pulmonary consolidation, edema, and exudative pneumonia.

Hyaline membrane has also been reported. Pneumocytes, multinucleated epithelial cells, and submucosal glands of bronchi were the main infected cells.¹⁶

Another reported patient was a known case of lymphoma on chemotherapy who has been infected by MERS, also showed diffuse alveolar damage with necrotizing pneumonia as well as congestion. Ultrastructural studies showed viral inclusions in the respiratory epithelium. There is also the possibility of necrosis to be secondary to prior chemotherapy. This case was reported based on the findings on a needle biopsy.^{16,17}

The histopathologic changes in this patient showed heterogeneous severity. Alveolar spaces and interstitium showed fibrin deposits as well as pigmented pulmonary macrophages and lymphocytes. In the mostly injured parts of the lung, the alveolar spaces showed a lot of blood and fibrin, mixed inflammatory cell infiltrate, and cellular debris. Pneumocyte hyperplasia and reactive changes, denudation and sloughing of alveolar cells, rare multinucleated syncytial cells, congestion of the alveolar walls, and hyaline membrane formation were also reported. Peribronchiolar spaces showed focal infiltration of polymorphonuclear (PMN) leukocytes and lymphocytes. The infiltration of CD4-positive T-helper lymphocytes in the wall of arteries (“intimal arteritis”) is consistent with an active immune response to the lung injury secondary to viral infection.¹⁷

It is worthy to note that there have been very few autopsy cases of MERS, but pulmonary pathology reported from animal studies was compatible with human cases.¹⁸

In MERS cases, similar histopathologic changes such as multinucleated cells and viral inclusion have been reported in many other organs such as brain, kidney, and liver.¹⁸

Histopathologic findings of SARS-CoV-2

Histological examination of lung in rare cases reported from SARS-CoV-2 showed “edema, bilateral diffuse alveolar damage with cellular fibromyxoid exudates, desquamation of pneumocytes and hyaline membrane formation,” indicating acute respiratory distress syndrome. Interstitial lymphocytic infiltrates were also reported. “Syncytial cells with multiple nuclei and large and atypical pneumocytes have been reported with large nuclei, amphophilic granular cytoplasm, and prominent nucleoli in the intra-alveolar spaces, showing viral cytopathic-like changes.”¹⁹

Two other cases have reported resected lung tissue for adenocarcinoma, which turned out to be infected with SARS-CoV-2 at the time of surgery. Sections away from the tumor showed diffuse alveolar damage, with edema and proteinaceous exudates. Prominent inspissated globules of secretions were also noticed. Vascular congestion and mild inflammatory infiltration were also present. Multinucleated giant cells were reported within the alveolar spaces. There were also histopathologic findings of ongoing “reparative process,” such as marked and patchy hyperplasia of pneumocytes and abundant alveolar macrophages as well as interstitial thickening, proliferation of fibroblasts, and fibroblast plugs. Histopathologic findings of viral cytopathy such as inclusions were also noted in some of the pneumocytes.⁴

In another study, the blood vessels of alveolar septum showed congestion, edema, and moderate infiltration of monocytes and lymphocytes as well as exfoliation of bronchial epithelial cells. Hyaline thrombi were seen in a few of small vessels. Focal hemorrhage in lung tissue, organization of exudates in alveolar spaces, and pulmonary interstitial fibrosis were also noted.²⁰

Another finding that has just reported is the consolidation created by fibroblastic proliferation with extracellular matrix and fibrin forming clusters in airspaces.²¹

Discussion

The pathological features of SARS-CoV-2 are very similar to those seen in SARS-CoV-2 and MERS-CoV infections. There is no specific finding in these pulmonary infections.^{18,21} Even the autopsy findings of H1N1 pandemic of influenza in the lung of victims in 2009 were very similar, and small vessel thrombosis and diffuse alveolar damage have been the main features that are very similar to CoV-infected lungs.¹⁵

Table 1 summarizes the histopathologic findings of the lung in these 3 CoVs reported during their epidemics and pandemics. The most important finding in all of pulmonary involvement in all 3 of them is diffuse alveolar damage that clinically is presented as acute respiratory tract disease.^{4,15} Microvascular involvement and alveolar capillary microthrombi, as well as new vessel formation, were reported to be significantly more common in patients with COVID-19 compared with influenza.¹⁹

One histopathologic finding in the new SARS-CoV-2-infected lung disease that has not been reported in the previous epidemics of coronaviruses is the presence of pulmonary fibrosis that can be indicative of future pulmonary dysfunction if the patient recovers.^{4,20} Progressive pulmonary fibrosis and marked thickening of alveolar wall were also reported, which is the main factor leading to pulmonary dysfunction. In the early stages, there is no mature fibrosis, but survived patients for longer periods have reported to show advanced stages with extracellular matrix deposition and interstitial fibrosis.^{19,21-24}

Another important finding in the victims of these 3 viruses is the involvement of vital organs such as kidneys and livers, especially in the fatal cases.^{4,12,15,16} Ultrastructural findings in 3 viruses showed evidences of viral entry via different organs, and viral inclusions have been reported especially in the respiratory epithelium, kidney, and heart.^{16,17,25}

There are some limitations in these studies:

1. Most of these histopathologic findings have been based on autopsy findings that are related to the fatal cases. There is very limited data related to mild or moderate infections with recovery.
2. In the cases of MERS-CoV, the number of human cases is very limited and cannot be accurately distributed. For SARS-CoV-2, it is still soon to decide about the details of pulmonary histopathology, although the main findings have already been reported and analyzed.

Conclusions


The pathological features of SARS-CoV-2 are similar to those seen in SARS-CoV and MERS-CoV infections, the most important of which are diffuse alveolar damage and hyaline membrane disease. However, pulmonary vascular damage, fibrosis and alveolar wall thickening, and extracellular matrix deposition are mostly seen in SARS-CoV-2.

Author Contributions

Bitra Geramizadeh: Idea of the research, Literature search, Writing the paper.

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