



## Histological Changes in the Lung Tissue in Association with COVID-19: Review Article

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### ABSTRACT

**Background:** It has been shown that SARS-CoV-2 is a multi-systemic virus and can affect number of body systems including the respiratory tract, the gastro-intestinal tract, the liver, the kidney and the nervous system. Despite the high mortality rate, there is little literature on postmortem findings of this unique virus, perhaps due to its highly contagious nature, inadequate information on prevention, and a lack of robust infrastructure for appropriate management of infected cases at various centers throughout the world.

**Aim of the study:** The aim of the current study was to review and list the main histological changes seen in patients died because of COVID-19.

**Methods:** A systemic search was carried out including Google Scholar, PubMed, and MEDLINE and the Google search Engine in order to scan all available published articles dealing with histological changes affection the lung in patients with documented COVID-19. The following key words were used to accomplish the search mission: COVID-19, SARS-CoV-2, Lung Histology, Pulmonary Histology, Histopathology. The search was limited to articles written in English language. Any article published between the end of 2019 and the time of initiating the current work was reviewed. The information in the current review is totally based on reviewed articles that are mentioned in the section of references.

**Results:** The main sources of lung tissues were Whole lung biopsy, Postmortem study, Core needle biopsy and Ultrasound based samples from autopsy. The exudative changes include injury to pneumocytes, congestion of capillaries, giant cell formations, dilation of alveolar ducts, thickening of capillaries, edema of interstitium and formation of hyaline membrane. The proliferative changes include hyperplasia of Type-2 pneumocytes with some reactive atypia with proliferation of myofibroblastic cells leading to granulation tissue formation, thickening of alveolar wall accumulation of alveolar macrophages, interstitial thickening which harbors collections of proliferating fibroblasts together with foci of hemorrhage and lymphocytic infiltration.

**Conclusion:** The main histopathological changes in lung of patients with COVID-19 can be grouped into three main phases, exudative, proliferative and fibrotic phases in addition to changes involving vascular tissues, bronchi and bronchioles and the main changes are the diffuse alveolar damage seen in exudative and proliferative phases.

**KEYWORDS:** COVID-19, Histology, Lung.

### INTRODUCTION

The sequence of events in association with the discovery and spread of sever acute respiratory syndrome corona virus (SARS-CoV2) is dated back to the end of 2021, when a novel viral causative agent in association with vague pneumonia syndrome was isolated in Chinese patients in Hubei province, city of Wuhan (1-3). Later on the virus rapidly got spread all over the world and global pandemic was declared by the world health organization (4-6). The way of spread of the virus by direct personal contact through respiratory droplets and the relatively high mortality rate in association with this novel viral agent make the health authorities all over the world in a shock like state because of the difficulty to control such "horrible" health issue (7, 8).



Actually during the last here decades, the world witnessed the rise of three viral agents, all belonging to Corona virus family, namely SARS-CoV, MERS and lastly SARS-CoV2, all associated with high mortality rate but differ in mode of transfer and they resulted in strict health measures being adopted by the WHO to limit the overall fatality rate, nevertheless, the rapid form of spread of the later SARS-CoV2 resulted in both economic and health disasters affecting all regions of the globe (9-11). The fatality rate in association with SARS-CoV was 9.6 % (12) and that in association with MERS was 34 % (13) whereas that in association with SARS-CoV-2 was estimated to range between 2 to 3 % (14) but the high infectivity and transmission rate and the spread all over the world has made the total human fatality in association with SARS-CoV-2 far more than that associated with previous 2 versions of this family of viruses (9-11).

It has been shown that SARS-CoV-2 is a multi-systemic virus and can affect number of body systems including the respiratory tract, the gastro-intestinal tract, the liver, the kidney and the nervous system (15).

Despite the high mortality rate, there is little literature on postmortem findings of this unique virus, perhaps due to its highly contagious nature, inadequate information on prevention, and a lack of robust infrastructure for appropriate management of infected cases at various centers throughout the world. Autopsy, on the other hand, remains the gold standard for determining the exact cause(s) of death and gives vital information for optimizing clinical therapy since it allows for proper collection and investigation of many organs for diagnostic and research purposes (16). The importance of autopsies is underscored by the fact that autopsy revealed antemortem diagnostic mistakes or undiagnosed diagnoses in up to 30% of instances (17). The Royal College of Pathologists has released the most recent autopsy guidelines for pathologists and mortuary staff in verified or suspected COVID-19 instances (13).

Understanding etiology and important morphological findings need pathology-related knowledge gained through autopsy. Furthermore, postmortem tissue collection will be required for in situ and molecular studies to further our understanding of the present new virus (18). The aim of the current study was to review and list the main histological changes seen in patients died because of COVID-19.

## METHOD

A systemic search was carried out including Google Scholar, PubMed, and MEDLINE and the Google search Engine in order to scan all available published articles dealing with histological changes affection the lung in patients with documented COVID-19. The following key words were used to accomplish the search mission: COVID-19, SARS-CoV-2, Lung Histology, Pulmonary Histology, Histopathology. The search was limited to articles written in English language. Any article published between the end of 2019 and the time of initiating the current work was reviewed. The information in the current review is totally based on reviewed articles that are mentioned in the section of references.

## RESULTS AND DISCUSSION

Sources of lung tissues for purpose of identifying histological changes are shown in table 1. These sources were whole lung biopsy, postmortem study, core needle biopsy and ultrasound based samples from autopsy.

The main features seen up on microscopical examination were reviewed and we tried to summarize them in well defined categories as shown in table 2. One of the main findings that have been described in lung tissues obtained from patients with COVID-19 is the diffuse alveolar damage (13). This finding was seen in proliferative phase and exudative phase of lung damage (20, 21, 23, 27, 28, 29). Indeed, the phases of lung changes were grouped into three main phases included exudative, proliferative and fibrotic ones (13, 30). Alveolar and interstitial inflammation was the whole mark in most examined cases with abundance of multinucleated giant cells (13). The main histopathological changes are outlined in table 2.

The exudative phases was characterized by injury to pneumocytes, congestion of capillaries, giant cell formations, dilation of alveolar ducts, thickening of capillaries, edema of interstitium and formation of hyaline membrane with protein and fibrin as the main constituents. In addition, to filling of air spaces by multi-nucleated giant cells and fibrinous exudate (16, 19, 20, 21, 23, 24, 29, 30, 31, 32, 27).

In the proliferative phase the main findings were: hyperplasia of Type-2 pneumocytes with some reactive atypia with proliferation of myofibroblastic cells leading to granulation tissue formation, thickening of alveolar wall accumulation of alveolar



macrophages, interstitial thickening which harbors collections of proliferating fibroblasts together with foci of hemorrhage and lymphocytic infiltration (21, 23, 24, 25, 27, 29, 31, 32) Necrotizing alveolitis and squamous metaplasia have also been described (23, 31, 33). The phase of fibrosis was identified in a rarity of cases because of short duration of time and the features signifying fibrosis were in the form of arterial hypermuscularization, microcystic honeycombing, scars mural fibrosis and pleural involvement (20).

Changes are not limited to alveolar tissues but also can involve bronchi and bronchioles in the form of edema with marked thickening of the wall and chronic inflammatory infiltrate (19, 16, 29), in addition to necrotizing bronchiolitis (23, 28, 33).

Vascular changes have also been described and probably they are the most important findings as they may represent the real cause of death and these changes were in the form of focal or diffuse platelet-fibrin thrombi in the pulmonary arterial circulation and even in capillaries and these thrombi harbored a lot of inflammatory cells such as neutrophils (16, 19, 20, 21, 22, 23, 24, 28, 31). Blood vessels may have wall thickening, fibrinoid necrosis, occlusion or luminal stenosis (19, 27).

Viral cytopathic effects have been described in the form of eccentrically placed intracytoplasmic inclusions, prominent eosinophilic nucleoli, nuclear enlargement and cytomegaly involving pneumocytes (19, 23, 24, 26, 29, 32, 34) and these cytopathic effects are the main link between histological changes and viral etiology (13).

**Table 1:** Sources of lung tissues for purpose of identifying histological changes

Rank	Source of lung tissue	Reference
1	Whole lung biopsy	19
2	Postmortem study	20-23
3	Core needle biopsy	24
4	Ultrasound based samples from autopsy	25-27

**Table 2:** The main histopathological changes seen in the lung of patients with COVID-19

Phases or sites	Main pathological findings
Exudative phase	<ul style="list-style-type: none"> <li>● injury to pneumocytes,</li> <li>● congestion of capillaries,</li> <li>● giant cell formations,</li> <li>● dilation of alveolar ducts,</li> <li>● thickening of capillaries,</li> <li>● edema of interstitium</li> <li>● formation of hyaline membrane</li> <li>● filling of air spaces by multi-nucleated giant cells and fibrinous exudate</li> </ul>
Proliferative phase	<ul style="list-style-type: none"> <li>● hyperplasia of Type-2 pneumocytes with some reactive atypia</li> <li>● proliferation of myofibroblastic cells leading to granulation tissue formation,</li> <li>● thickening of alveolar wall</li> <li>● accumulation of alveolar macrophages,</li> <li>● interstitial thickening which harbors collections of proliferating fibroblasts together with foci of hemorrhage and lymphocytic infiltration</li> <li>● Necrotizing alveolitis</li> <li>● squamous metaplasia</li> </ul>



Fibrotic phase	<ul style="list-style-type: none"> <li>● arterial hypermuscularization,</li> <li>● microcystic honeycombing,</li> <li>● scars</li> <li>● mural fibrosis</li> <li>● pleural involvement</li> </ul>
Bronchi and bronchioles	<ul style="list-style-type: none"> <li>● edema with marked thickening of the wall</li> <li>● chronic inflammatory infiltrate</li> <li>● necrotizing bronchiolitis</li> </ul>
Vascular changes	<ul style="list-style-type: none"> <li>● focal or diffuse platelet-fibrin thrombi in the pulmonary arterial circulation and even in capillaries and these thrombi harbored a lot of inflammatory cells such as neutrophils .</li> <li>● Blood vessels may have wall thickening, fibrinoid necrosis, occlusion or luminal stenosis</li> </ul>
Cytopathic effects	<ul style="list-style-type: none"> <li>● eccentrically placed intracytoplasmic inclusions</li> <li>● prominent eosinophilic nucleoli</li> <li>● nuclear enlargement</li> <li>● cytomegaly</li> </ul>

**CONCLUSION**

The main histopathological changes in lung of patients with COVID-19 can be grouped into three main phases, exudative, proliferative and fibrotic phases in addition to changes involving vascular tissues, bronchi and bronchioles and the main changes are the diffuse alveolar damage seen in exudative and proliferative phases.

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