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A Systematic Review in:

Histopathological changes in the lungs after COVID-19 infection

Submitted to the Council of the College of Medicine, Diyala University, In Partial Fulfillment of Requirements for the Bachelor Degree in medicine and general surgery.

Submitted by

Zainab Taher Ali

Supervised by

Dr. Manar Abdalrazaq Hassan

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Abstract

Coronavirus disease 2019 (COVID-19), which is zoonotic in origin and most commonly spread through respiratory droplets or aerosol transmission, has caused a big threat to mankind. Though majority recovery from this infection, those who are elderly or with underlying comorbidities, frail or immunocompromised states face severe outcomes including Acute Respiratory Distress Syndrome (ARDS), ICU (Intensive Care Unit) admissions, use of ventilator and deaths. The appearance of a new disease generally creates emerging challenges in morphological examinations due to the lack of available data from autopsy- or biopsy-based research Since late December 2019. Thus we carried out the systematic review to identify the histopathological changes in the lung after COVID-19 infection.

Methods: we collected the data from online databases and we found 25 article but after the exclusion we reviewed only 7 articles.

Results: we found clear dominance for the pulmonary congestion, DAD, hyaline membrane infiltration, microthrombi and diffuse tissue edema in almost all the researches we reviewed.

Conclusion: DAD, tissue edema and infiltration, microthrombi were main causes of mortality and morbidity.

Keywords: ***COVID-19, histopathological changes, lung pathology.***

1. Introduction

Coronavirus disease 2019 (COVID-19), which is zoonotic in origin and most commonly spread through respiratory droplets or aerosol transmission, has caused a big threat to mankind. The disease was originated in the seafood market of Wuhan, Hubei, China, in early December 2019 with clinical presentations greatly resembling viral pneumonia. This disease has affected most of the countries in the period of 2 months itself. The outbreak of COVID-19 has been declared a pandemic by World Health Organization (WHO) and presents a great challenge for the healthcare communities across the globe (1).

Though majority recovery from this infection, those who are elderly or with underlying comorbidities, frail or immunocompromised states face severe outcomes including Acute Respiratory Distress Syndrome (ARDS), ICU (Intensive Care Unit) admissions, use of ventilator and deaths. Although the majority of patients heal by itself, it is estimated that 13.8% of infected is at risk of severe disease and up to 6.1% can be involved by a critical form of COVID-19 disease, with respiratory failure, septic shock and multiple organ dysfunction or failure (2).

Compared to SARS-CoV and MERS-CoV, SARS-CoV-2 is far more infective and transmissible but with lower mortality rate which is 2%–3% in hospitalized patients. The reported case fatality rate for SARS is 9.6% and that for MERS is 34%. Coronaviruses are known to cause diseases in both humans and animals, affecting pulmonary, intestinal, hepatic, renal, and neurologic systems. 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 (3).

Recently published studies have shown that a SARS-CoV-2 infection, like a SARS or MERS infection, can cause progressive lung damage. There is increasing evidence that microvascular damage plays a role in the progression of the disease (4).

The appearance of a new disease generally creates emerging challenges in morphological examinations due to the lack of available data from autopsy- or biopsy-based research Since late December 2019. An increased risk of death had been reported in men over the age of 60 and the case-fatality rate seemed to be elevated in patients with underlying diseases. It is assumed that severe disease progression might result in death due to proceeded pulmonary injury with massive alveolar damage and progressive failure (5).

Given the current situation of the pandemic, we carried out a systematic review of the literature describing histopathological findings from samples received at surgical pathology laboratories and from postmortem studies.

2. Methods

we searched the online scientific databases such as Google scholar, PubMed, and NCBI for specific keywords (COVID-19, lung pathology, post infection, histopathological changes). We found 25 articles about the given subject and we excluded the systemic reviews and included the scientific experimental researches only which are 7.

3. Results

Kommoss et al. (6), performed an analysis on 17 COVID-19 dead people and found that Pulmonary parenchymal consolidation was found to a variable degree in all of the patients who died. Histological examination revealed patchy

alveolar damage associated with microthrombosis of alveolar capillaries (n=7) and intra-alveolar hemorrhages (n = 9). Patients who died within the first two weeks of the onset of disease, even if they had not been invasively ventilated, displayed patchy microvascular damage with edema and the formation of alveolar hyaline membranes.

They also found that Patients who died at a later phase of the disease displayed hyperplasia and squamous epithelial metaplasia of the pneumocytes. There were also rare polynucleated cells within the alveoli, as well as more pronounced interstitial infiltration, predominantly lymphocytic (figure 1).

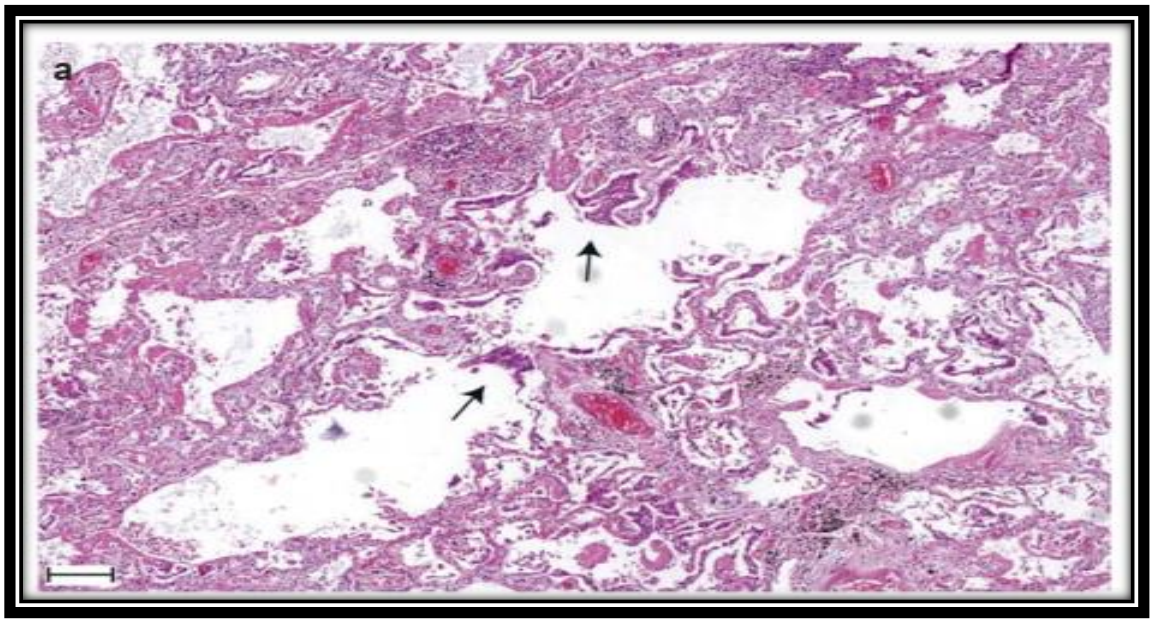

Figure 1. patchy alveolar damage with focally prominent interstitial lymphocytic infiltrates and squamous metaplasia of type II pneumocytes (arrows) (6).

Suess et al. (7), performed an autopsy on a deceased patient who died due to COVID-19 complication and found a predominance of pulmonary congestion and early stage diffuse alveolar damage with marked hyaline membrane formation, proteinaceous exudates, alveolar hemorrhage, and intra-alveolar fibrin deposition.

In addition, there was a patchy distribution of intra-alveolar foamy macrophages filling some airspace throughout all lobes, proved by immunhistochemical staining with CD68. The immunhistochemical staining with TTF1 confirmed patchy and severe type II pneumocyte hyperplasia characterized by atypically enlarged pneumocytes with large nuclei, amphophilic granular cytoplasm, and prominent nucleoli showing viral cytopathic-like changes and many mitotic figures. (figure 2).

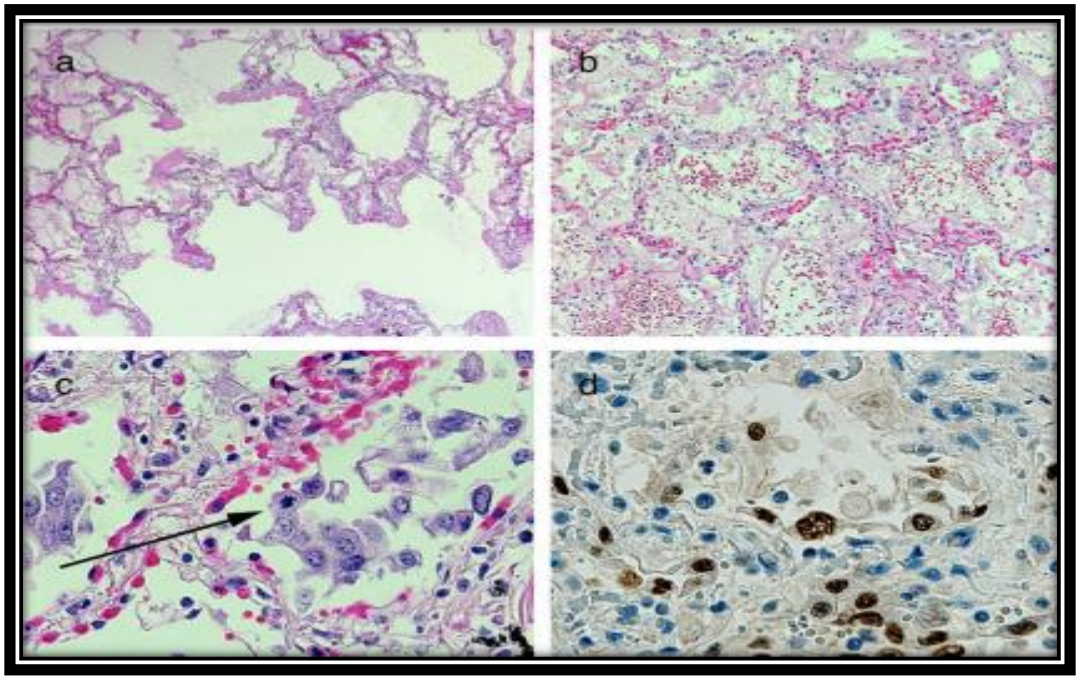

Figure 2. Histologic changes in lung parenchyma (H&E and TTF-1). A Low power demonstrating the predominance of acute diffuse alveolar damage. b Intermediate power demonstrating edema, hemorrhage, and fibrin deposition. c High power demonstrates atypical enlarged intra-alveolar cells characterized by large nuclei with increased mitotic figures (arrow). d. Immunhistochemical staining with TTF-1 confirmed the atypical enlarged cells with type II pneumocytes (7).

Dogolini et al. (8), in their 12 case study found that Vascular changes characterized by dilated and hyperplastic interstitial capillaries and venules were present in all cases, including those where AECII hyperplasia was either minimal

or absent. The venules also showed dilatation and tortuosity of the lumen and thickened, edematous walls, without overt vasculitis nor endothelialitis. Scattered microthrombi were observed in 2 cases.

A patchy lymphocyte infiltrate, more prominent around the venules, was observed in 9/12 cases, ranging from isolated to heavy nodular clusters. Interstitial plasma cells, neutrophils, and eosinophils were either absent or extremely rare. Interstitial and luminal organizing changes were absent in all cases, except a single case exhibiting focal myofibroblast accumulation. Irregular clusters of mononuclear cells were demonstrated within alveolar spaces in 9/12 cases, without evidence of intraluminal granulocytes (figure 3).

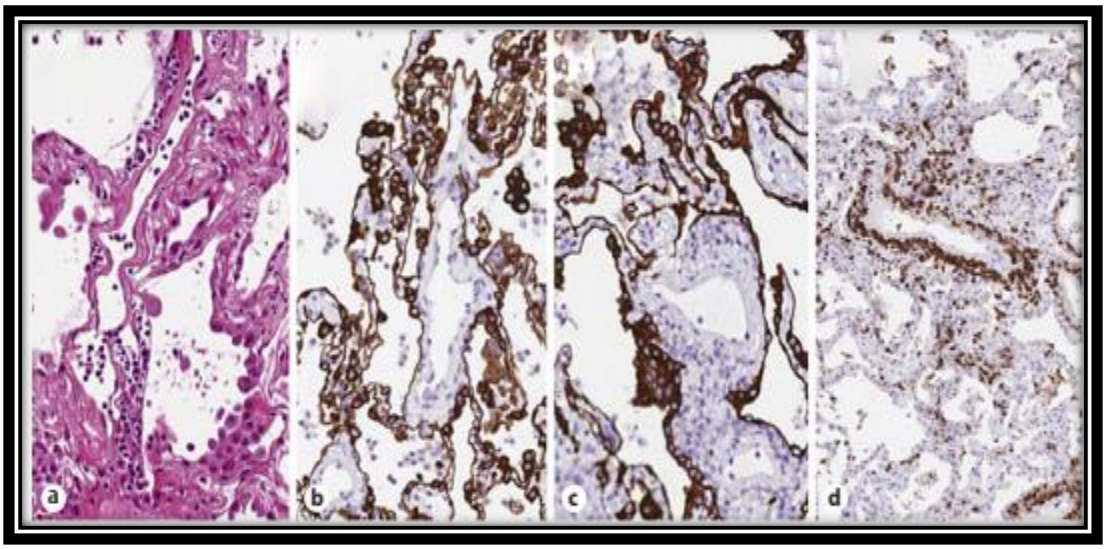

Figure 3. Abnormal morphology and phenotype in enlarged vascular endothelial cells: H&E (8).

Diaz et al. (9), conducted a cohort study on group of survivors from COVID-19 to identify the possible pathological changes and found that there was evidence of small-airway disease, including basement membrane fibrosis, which was present in 67% of COVID-19 survivors and in 60% of control patients. Airway inflammation was minimal in COVID-19 survivors and controls.

There were high rates of emphysema in COVID-19 survivors (92%) and controls (100%). Smoker's macrophages, metaplastic changes, and occasional poorly formed granulomas were seen in the alveolar spaces in a subset of both groups as well Areas of mild fibrosis were seen in COVID- 19 survivors and controls, with 50% of COVID-19 survivors having focal fibrosis and 60% of control patients having some areas of fibrosis. Histologic evidence of mild pulmonary hypertension was present in 42% of COVID-19 survivors and in 60% of controls, but the vasculature was otherwise unremarkable.There was no significant vasculitis in any of the assessed COVID-19 survivors or the end-stage patients. While scattered microthrombi and gross pulmonary emboli have been reported in the acute COVID-19 setting.

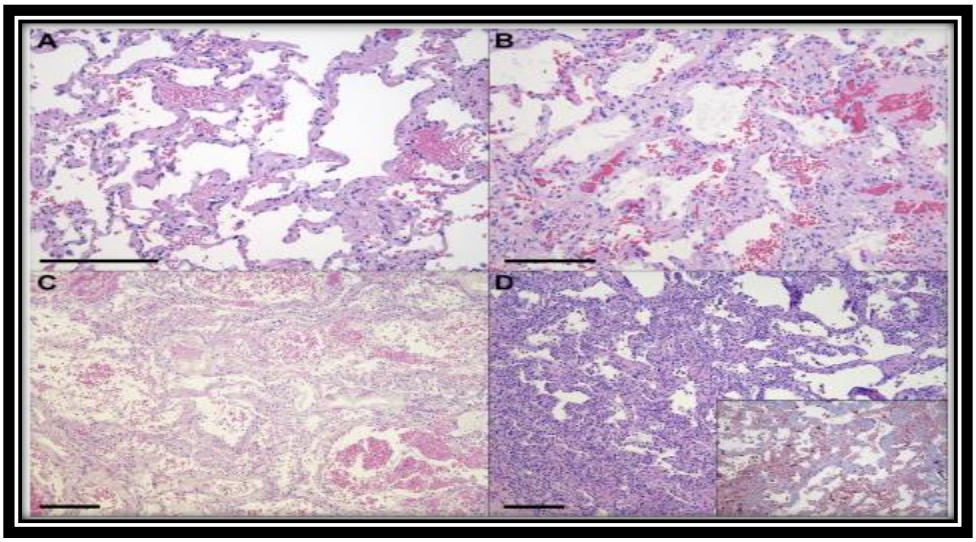

Figure 4. Representative histologic images (hematoxylin and eosin stain) of the alveoli and interstitial regions (9).

Another study conducted by *Nunes et al.* (10), revealed that The morphological changes in the lung that were 1.5 to over 10 times more common in the COVID+ than the COVID- group included: organizing pneumonia (31% vs 10%), hyaline membrane formation (64% vs 29%), overall pneumocyte

proliferation (85% vs 62%), and specifically cytomegaly (76% vs 45%), nucleomegaly (75% vs 45%), multinucleation (63% vs 38%) and syncytia formation (33% vs 2%). Stratifying the COVID+ group by HIV infection status did not reveal major differences between HIV status, with only intra-alveolar fibrin being more common in HIV-infected (60%) compared with HIV-uninfected (38%) decedents.

A study by *Merdji et al.* (11), showed that Exudative changes were present in 3of the 4 patients (75%) within the first week of ARDS related to COVID-19, 8 of the 11 patients (72%) within the second and third weeks, and none of the 7 patients with more than 3 weeks of evolution. Intra-alveolar loose fibrin exudate and hyaline membranes gradually decreased over weeks. No differences in histologic findings were observed between patients who received steroids and those who did not. Regarding patients who developed a ventilator associated pneumonia (VAP) and those who did not, there was significantly more fibrosis in the patients who developed VAP.

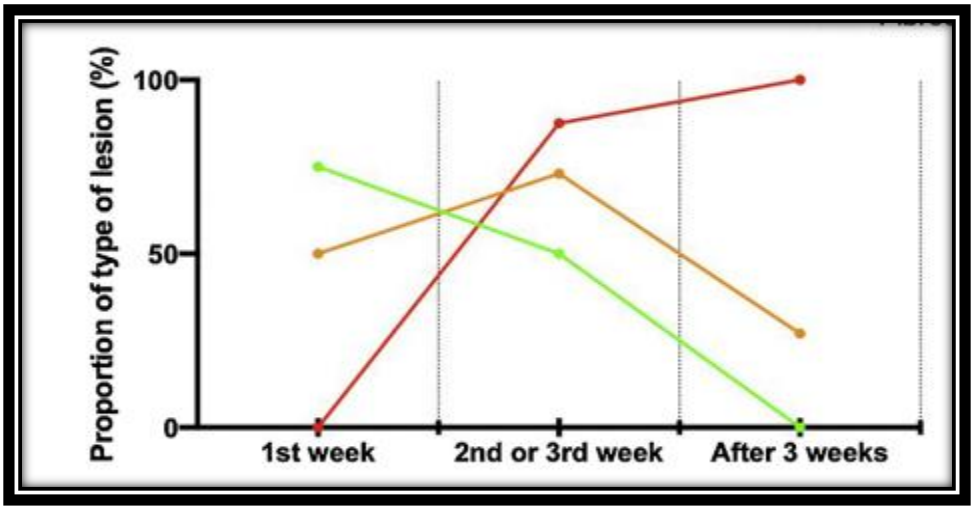

Figure 5. Time to onset and evolution of histological lesions noted over time (exudative phase, proliferative phase and end-stage fibrosis) in 22 patients with ARDS related to COVID-19 (11).

Montero et al. (12), found that DAD is the histopathological pattern seen in patients with acute lung injury or acute respiratory distress syndrome (ARDS), who will require mechanical ventilation. Clinically, these two entities were defined by the American-European Consensus Conference on ARDS. The consensus defined ARDS as the presence of acute hypoxemia with a ratio of partial pressure of arterial oxygen to the fraction of inspired oxygen (PaO2:FiO2) of 200mmHg or less, whilst acute lung injury is a less severe entity defined with the same criteria, but with a PaO2:FiO2 of 300 mg Hg . The mortality rate for ARDS is 50% to 60%, and it increases with age. On a morphological basis, most cases of clinical ALI and ARDS will have DAD.

4. Discussion

The early pathological findings identified in the COVID-19 suggested that SARS-CoV-2 can widely spread in the epithelial lining of the respiratory tract, digestive tract, distal convoluted tubules of the kidney, the sweat glands of the skin and testicular epithelium including spermatogonia and sertoli cells. Now, it has been found that, in addition to respiratory transmission, the virus might also be transmitted through faeces, urine and skin. The new findings have also necessitated new ways to prevent the transmission of disease. Many studies on epidemiology and clinical characteristics of COVID-19 have been published but data on pathological changes in different organs are still scanty (13).

Patients with affected upper respiratory tract usually present with mild to moderate symptoms but patients with lower respiratory tract infection show features of pneumonia and land up with organ failure. The severity increases with presence of comorbidities like hypertension, chronic kidney disease, obstructive sleep apnoea and metabolic diseases like diabetes and obesity, and the pathological

changes may even vary between right and left lung. Macroscopically, lungs appear congestive, with patches of haemorrhagic necrosis. Alveolitis with atrophy, vacuolar degeneration, proliferation, desquamation and squamous metaplasia of alveolar epithelial cells, with presence of exudative monocytes and macrophages are prominent features microscopically (14).

The autopsies revealed a characteristic pattern of histological changes in the lungs; the pulmonary changes were considered the cause of death, or at least the main cause of death. When alveolar capillary microthromboses were found along with evidence of right heart failure, a cardiopulmonary cause of death was postulated, i.e., the combined effect of lung damage and acute right heart failure, according to *kommoss et al*. (6).

5. Conclusion

According to the researches above, there was clear predominance to the diffuse alveolar damage, pulmonary consolidation, edema and less common microthrombi in the alveoli. Post mortem examinations revealed thrombosis, fibrosis and infiltration as main causes of death or at least associative causes.

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