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COVID-19–Related Lung Injury: A Histopathological Overview

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ABSTRACT

Objective: *To provide a comprehensive review of the key histopathological features associated with COVID-19–related lung injury and to clarify the extent of vascular and inflammatory involvement in the disease.* ***Method:*** *A literature review analyzing reported histopathological findings in COVID-19 lung specimens, comparing them with other viral infections such as H1N1 influenza, and correlating them with clinical and radiological data.* ***Results:*** *Findings consistently highlight diffuse alveolar damage (exudative and proliferative phases), type II pneumocyte hyperplasia, squamous metaplasia, intra-alveolar hemorrhage, microthrombosis, and occasional osseous metaplasia. Additional observations include inflammatory infiltrates, endothelial injury, and cytokine-related damage (e.g., IL-6 upregulation). COVID-19 shows more extensive alveolar and vascular involvement than many other viral infections, though findings vary across patients and comorbidities.* ***Novelty:*** *The review underscores that although several histopathological features overlap with other viral pneumonias, the severity of vascular injury and the complexity of the inflammatory response in COVID-19 distinguish it. It also stresses the diagnostic value of integrating histopathological, clinical, and radiological evidence to better understand disease pathogenesis.*

INTRODUCTION

A wholesale sea food market was epidemiologically Linked to several clusters of pneumonia cases of unknown origin reported by multiple healthcare facilities in Wuhan, Hubei Province, China, at the end of December 2019 [1]. In response, the Chinese Center for Disease Control and Prevention deployed a response team to collaborate with local health authorities in conducting epidemiological and etiological investigations into the emerging outbreak. They came to the conclusion that the pneumonia was caused by a virus. Due to the large number of people travelling from Wuhan to other Chinese and international cities, the virus was impossible to quarantine. The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus, a novel human pathogen with a high zoonotic capability, was discovered to be the cause of coronavirus disease 2019 (COVID-19) at this time. On March 11, 2020, the World Health Organization (WHO) classified it as a pandemic and proclaimed it an emergent public health issue of global relevance [2], [3].

In 215 countries, COVID-19 was responsible for around 617,000 deaths and 15 million confirmed infections as of July 22, 2020 [2], [4]. Over 142,000 fatalities and over 3.92 million illnesses have been confirmed in the US. Over 2.16 million COVID-19 cases have been recorded in Latin America, with Brazil reporting the second-highest number globally. COVID-19 patients had mortality rates ranging from 1% to 20% [4]. Given the

pandemic's present stage, we thoroughly reviewed the literature on histopathological findings from postmortem exams and surgical pathology specimens.

RESEARCH METHOD

COVID-19 Histopathological Characteristics

Our knowledge of SARS-CoV-2 infection and how it spreads across tissues and organs is quickly changing. Numerous studies have examined autopsy results in COVID-19-related fatalities worldwide in an effort to identify any potential patterns [5]-[9]. With an emphasis on pulmonary involvement, we will discuss the most commonly reported and, in our view, most important histological abnormalities in patients infected with SARS-CoV-2 in this chapte, see Figure 1.

Histopathology of the Lungs and Respiratory Tract

In research pertaining to COVID-19, the respiratory system is undoubtedly the primary area of focus. Autoptic tissues have yielded several histological results [10]. However, it should be noted that none of the histological characteristics mentioned are particularly specific or pathognomonic [11], and these specimens should be the subject of future gene expression profiling investigations. Diffuse alveolar damage (DAD), in both its exudative and proliferative phases—though the latter does not always manifest—is the most frequently reported morphological hallmark of COVID-19 [11]-[27]. Despite considerable variability among case series, with differing degrees of edema [12], [16], [18], [19], [20], [21] and hyaline membrane formation [13], [15]–[19], [21]–[25], the exudative phase generally persists for approximately 10 days.

Conversely, the proliferative phase is marked by the buildup of intra-alveolar fibrin, the deposition of extracellular matrix, and the proliferation of fibroblasts and myofibroblasts [26], [27]. There have been reports of cases where the primary histological characteristic of COVID-19 linked to organised pneumonia is the deposition of intra-alveolar fibrin; these cases are referred to as acute fibrinous and organizing pneumonia (AFOP) [28]. Osseous metaplasia has occasionally been noted during the proliferative phase. Furthermore, the organizing phase has been associated with the presence of Masson bodies and micro-abscesses. The two stages of DAD might occur at various times in different parts of the pulmonary parenchyma, therefore they are not synchronized processes across the lung [29]. Despite being one of COVID-19's most prevalent morphological manifestations, Diffuse alveolar damage (DAD) is a common histopathological finding in both infectious and non-infectious lung conditions and is therefore not specific to SARS-CoV-2 infection [11]. In addition, several non-specific alterations in alveolar architecture and epithelium have been observed. Among the most frequently reported changes are type II pneumocyte hyperplasia [12], [14], [17], [19], squamous metaplasia [12], [17], [22], intra-alveolar hemorrhage [13], [17], [19], and epithelial desquamation [13], [17].

The inflammatory pattern was also assessed; the majority of the immune cell population that was found was made up of mono-nucleated cells, with lymphocytes making up the largest percentage of these cells [11]-[13], [15].However, neutrophils were

detected in a significant proportion of patients, ranging from around 25% to 30% [12], [13], [16], [19], [20] to 50% [26]. Some experts attribute the neutrophilic component of the inflammatory response in COVID-19 to bacterial superinfection [12]. Supporting this hypothesis, one autopsy series reported neutrophilic inflammation exclusively in the single immunocompromised patient studied [18]. Other respiratory tract tissues including the bronchi, trachea, and throat have also been documented to experience inflammation in the form of lymphocytic infiltration. Giant multinucleated cells were commonly seen in the lung syncytium together with lymphocytic infiltration [23], [24], [28]. Instead of expressing macrophage markers like CD68, These cells have been shown to express the pulmonary differentiation marker TTF-1. Pleural fluid cytoblock preparations from COVID-19 patients have revealed aggregates of multinucleated syncytial cells and dysmorphic mesothelial cells with enlarged nuclei [15]. While this cytological feature of pleural effusion is intriguing, it remains clinically impractical for routine assessment in COVID-19 patients. Unlike some other diseases, pulmonary histology alone lacks specificity for COVID-19, as previously noted. Notably, a study demonstrated that the pulmonary histopathological features in patients who died from COVID-19 and those who died from H1N1 influenza share a common pattern characterized by diffuse alveolar damage (DAD) and inflammatory cell infiltration [14].

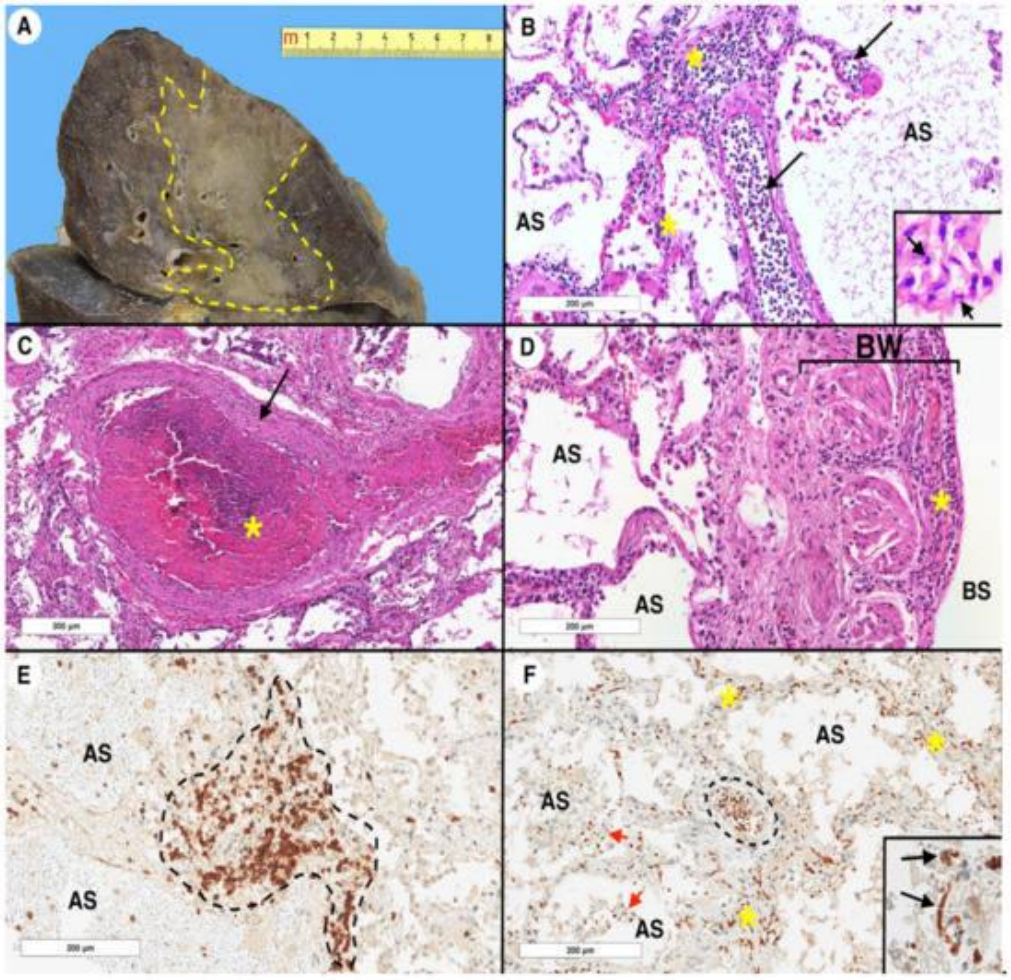

Figure 1. An Illustration of Lung Pathology in a COVID-19 Case.

The lung results of a 69-year-old lady who passed away following COVID-19 complications are depicted in this picture. The University Hospital of Padua was the site of the autopsy.

A) A yellow dotted line delineates a sizable, greyish region of consolidation in the gross anatomy of the upper right lung lobe.

B) Histological analysis reveals that the interstitial blood vessels (black arrows) are crowded with inflammatory cells (a condition called margination), which also penetrate the surrounding interstitial tissue (yellow asterisks). Eosin and haematoxylin stain; initial magnification: ×200. Polymorphonuclear leukocytes (black arrow) are easily observable at greater magnification (inset, H&E stain; original magnification ×600).

C) A fibrin thrombus (yellow asterisk) totally blocks a centrilobular arteriole (black arrow) (H&E stain; original magnification ×100).

D) A segment of the bronchial wall demonstrates severe inflammation in the submucosal layer (yellow asterisk) and total mucosal depletion (H&E stain; original magnification ×200).

E) The interstitial gap noticeably widens due to a dense lymphocytic infiltration (seen by the black dashed line). The bulk of these inflammatory cells are T lymphocytes, as confirmed by CD3 immunostaining (CD3 immunoperoxidase stain; Novocastra, clone NCL-L-CD2-565; original magnification ×200.

F) IL-6 immunohistochemistry shows that lymphocytes in the interstitial space (yellow asterisks), alveolar spaces (red arrows) and blood vessels (dashed black line) have positive staining. There are also alveolar macrophages, which may be identified by their vast, unstained cytoplasm (original magnification ×400; Abcam, clone ab9324; IL-6 immunoperoxidase stain). Certain endothelial cells (black arrows) exhibit IL-6 expression at increased magnification, particularly in response to injury. With a distinctive perinuclear enhancement, the staining pattern is cytoplasmic (inset, original magnification ×400.

Abbreviations: AS = alveolar space; BW = bronchial wall; BS = bronchial space. (Adapted from reference [51]).

RESULT AND DISCUSSION

Results

Gross Findings

According to the findings of the gross examination of the COVID-19 patients' lungs during autopsy surgical operations, their tracheae had normal calibre and were somewhat erythematous. Between 583±216g and 680-1030g, and between 663±239g and 800-1050g, the lungs get heavier. Furthermore, it has been shown that COVID-19-infected lungs typically feature lobes and fissures, but in certain fatal instances, a previous partial lobectomy on the right lung was noted [30]. Thick, white mucus in the bronchi and pink froth in the airways are typical symptoms of COVID-19 patients. Additionally, mild to moderate serosanguinous pericardial and pleural effusions have been described in them.

Additionally, each lung is stated to have hard, diffusely edematous parenchyma, a feature that is common to acute respiratory distress syndrome (ARDS). Every patient, with the exception of one who passed away, had areas of dark-coloured hemorrhage with focal demarcation across the peripheral parenchyma of their lungs, as seen in Figure 2A. The regions of cut sections that showed exterior surface hemorrhage were indicative of frank hemorrhage [31]. Due to blockage of the respiratory system, roughly half of COVID-19 patients could have heart failure. Nevertheless, inflammatory cellular infiltration is unlikely to occur in the membranes of the heart and endocardia [32]. Darkened cytoplasm and an apparent localised irregularity in the myocardium's form are present, but these alterations are insufficient to be characterized as an acute myocardial damage. The findings of the study by Sufang et al. show that focal edema, interstitial fibrosis, and myocardial hypertrophy linked to COVID-19 disease vary in severity, suggesting previous alterations in underlying conditions such as myocardial hypertrophy linked to hypertension and previous ischemic injury [33].

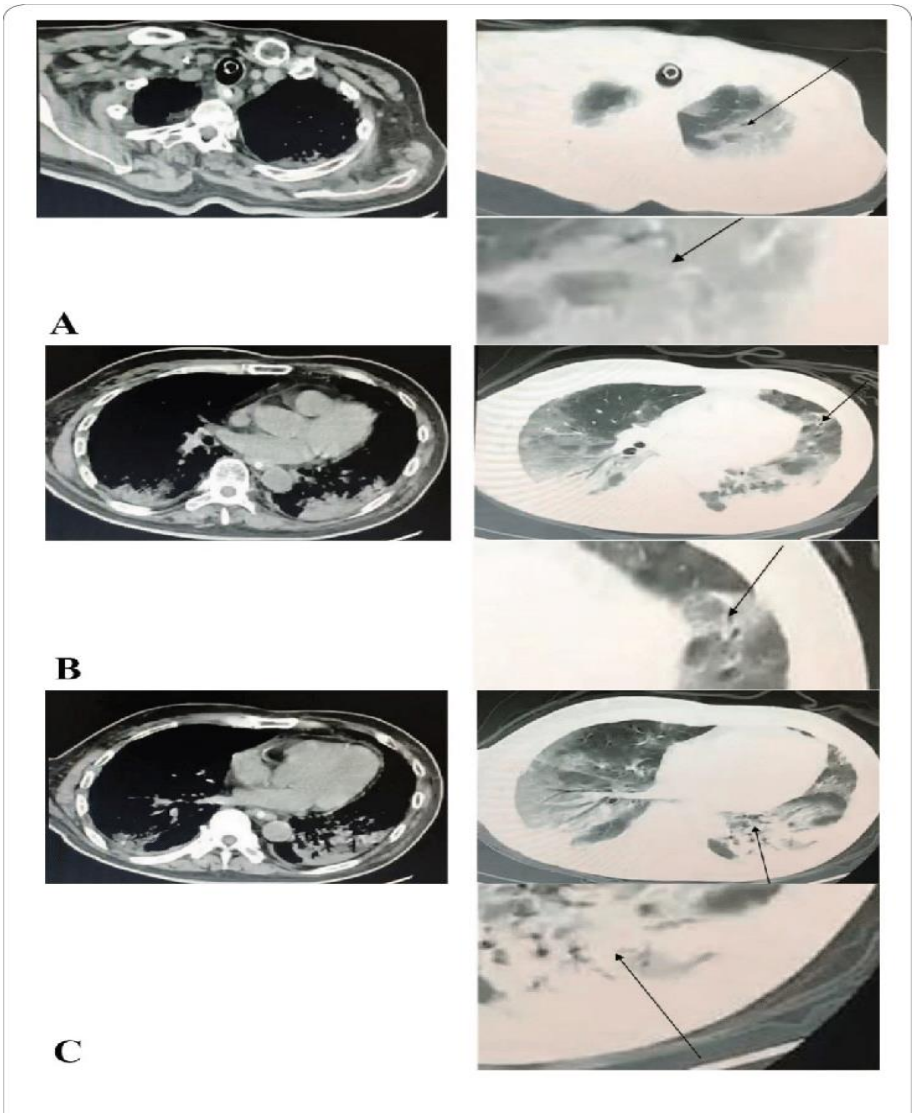

Figure 2. CT Imaging in a COVID-19.

Patient Computed tomography (CT) scans were obtained from a patient with COVID-19 three weeks after symptom onset and two weeks before undergoing a transthoracic lung biopsy.

A) Left upper lobe – anterior segment.
B) Left upper lobe – lingular segment.
C) Left lower lobe – segmental view.

(Adapted from reference [50]).

Histopathology and immunohistochemistry

Because COVID-19 shares many clinical features with other respiratory viral infections, including a cough that lasts for many days before developing into severe pneumonia, it is challenging to distinguish it clinically. Additionally, COVID-19 and other respiratory viral infections may present with little to no symptoms [34]–[36]. Severe illness has been associated with respiratory failure, chills, arthralgia or myalgia, thrombocytopenia, leukopenia, lymphocytopenia, increased inflammatory biomarkers, and hepatic and renal dye function. In these situations, only respiratory tissues exhibit histopathologic abnormalities that are directly attributable to the virus [37]–[39].

Huilan et al. conducted routine hematoxylin-eosin staining for histopathologic examination [40]. Then, using a Mach 4 Universal AP Polymer Kit with Permanent Red Chromogen and a rabbit polyclonal antibody made against the SARS-CoV nucleocapsid at 1:100 dilutions, they conducted an IHC test for COVID-19. Finally, they used heat-induced epitope retrieval and a citrate-based solution (Biocare Medical) to pretreat the slides.Additionally, they substituted normal rabbit serum for the main antibody in order to execute appropriate negative controls in parallel. They next confirmed the anti-SARS antibody's cross-reactivity with COVID-19 by evaluating controls made from COVID-19-infected Vero cells implanted with healthy human tissues [40].

This choice served as the positive control for the subsequent IHC tests. Martines et al.'s study's histopathologic results and their testing of FFPE tissues showed that mild to moderate tracheobronchitis was consistently present. It was characterised by mononuclear inflammation, sub mucosal congestion, and epithelial denudation, see Figure 4. According to their findings, the most common lung pathology was diffuse alveolar damage (DAD), and acute and organizing stages were present in 87.5% of the patients [35]. However, there hasn't been any evidence of a strong relationship between the pathologic phase of DAD and the duration of recognized symptoms. This might be because older residents of long-term care facilities (LTCF) tend to underestimate the length of their disease and fail to recognize early symptoms [40]. According to an analysis of histopathologic findings linked to underlying problems in fatal COVID-19 illness, hemo-siderin-laden macrophages, hemorrhage, mucus aspiration, emphysema, and microthrombi were seen in 50%, 50%, 37.5%, 25%, and 12.5% of cases, respectively, see Figure 3 [35]. All of the elderly patients with CO VID-19 had lung hilar lymph nodes, and the majority had anthracosis from long-term carbon buildup. Furthermore, around 75% of the patients displayed sinus histiocytosis in their lymph nodes and hemo-phagocytosis in their subcapular sinuses, as shown in Figure 3. Additionally, a

correlation between localized myocardial fibrosis, cirrhosis, hepatic steatosis, acute renal tubular injury, and chronic renal illness was found by pathologic findings of extra-pulmonary tissues, see Figure 5. Nevertheless, none of the subjects showed any notable intestinal histopathologic alterations or cardiac necrosis or myocarditis [35].

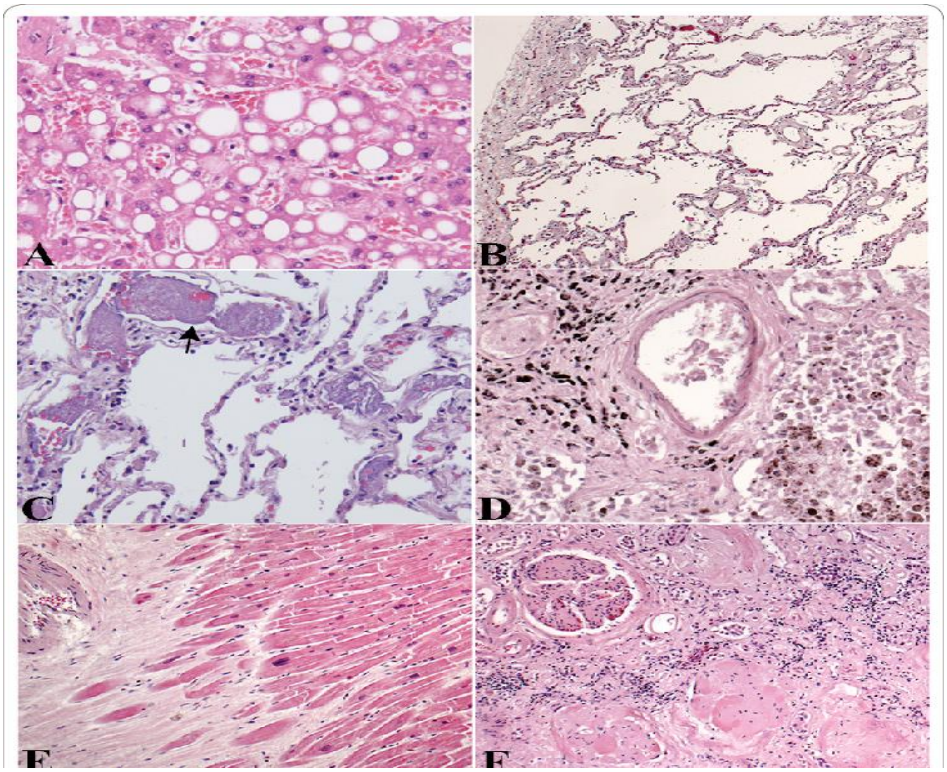

Figure 3. Histopathological Findings in Fatal COVID-19 Cases.

This figure highlights various histological abnormalities observed in patients who died from COVID-19, each with significant pre-existing comorbidities.

A) Extensive glomerulosclerosis in the kidney of a patient with underlying renal disease (original magnification ×10).
B) Emphysematous changes in the lung of a patient with chronic obstructive pulmonary disease (original magnification ×5).
C) Pulmonary microthrombosis (arrow) in lung tissue (original magnification ×20.(
D) Myocardial fibrosis with mild cardiomyocyte hypertrophy in the heart of a patient with cardiomegaly (original magnification ×5).
E) Hemosiderin-laden macrophages (brown pigment, lower left) and anthracosis (black pigment, upper right) in the lung of a patient with congestive heart failure (original magnification ×20).
F) Hepatic steatosis in the liver of a patient with morbid obesity (original magnification×20).

(Adapted from reference [50]).

Previous studies Results insight

In their investigation of 17 COVID-19 fatalities, Kommoss et al. [41] discovered that pulmonary parenchymal consolidation was present in all of the deceased patients to varying degrees. Histological analysis showed spotty 4 alveolar damage linked to intra-alveolar hemorrhages (n = 9) and microthrombosis of alveolar capillaries (n = 7). Even if they had not had invasive ventilation, patients who passed away within the first two weeks of the disease's beginning showed patchy microvascular damage, including edema and the development of alveolar hyaline membranes. Additionally, they discovered that patients who passed away later in the course of the illness had pneumocyte hyperplasia and squamous epithelial metaplasia. Rare polynucleated cells were also seen in the alveoli, and there was a more noticeable interstitial infiltration that was mostly lymphocytic, see Figure 4.

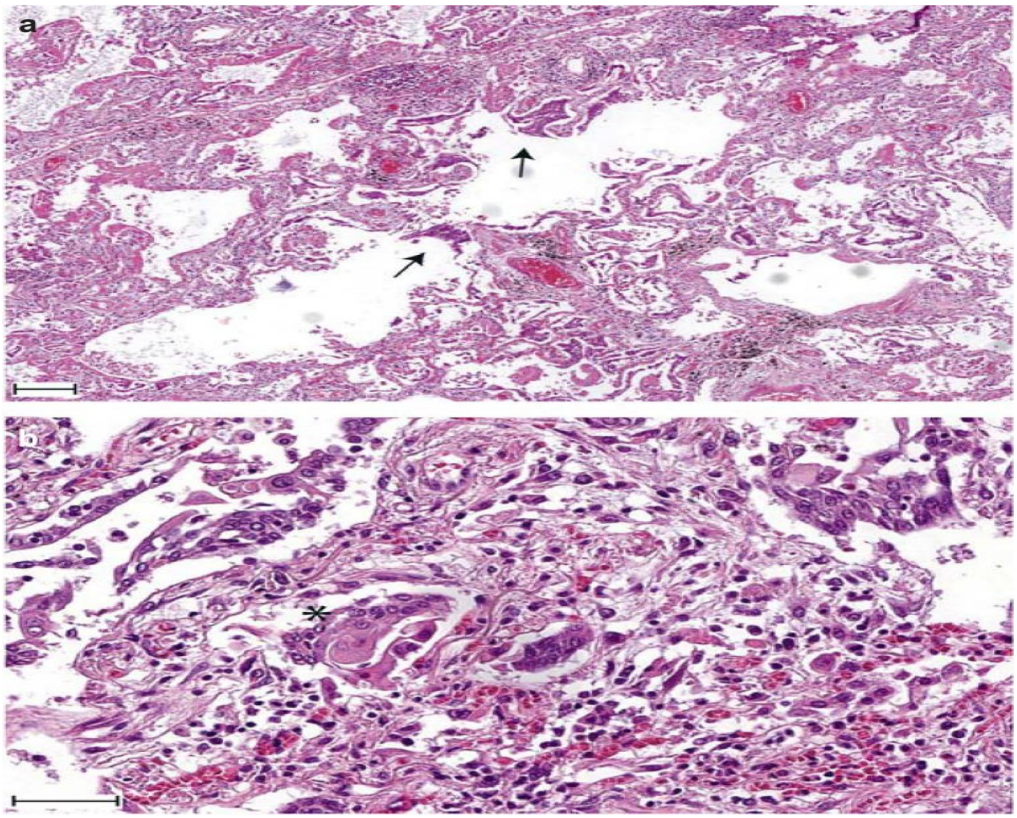

Figure 4. Squamous metaplasia of type II pneumocytes and focally significant interstitial lymphocytic infiltrates accompany patchy alveolar injury [41].

Suess et al. observed early-stage diffuse alveolar damage (DAD) during an autopsy on a patient who passed away from COVID-19-related symptoms [42]. Prominent hyaline membrane development, proteinaceous exudates, alveolar hemorrhage, intra-alveolar fibrin deposition, and pulmonary congestion were among the histological findings. All lung lobes had a patchy distribution of intra-alveolar foamy macrophages, according to CD68 immunohistochemistry. Type II pneumocyte hyperplasia, which is typified by abnormally enlarged pneumocytes with big nuclei, amphophilic granular cytoplasm,

prominent nucleoli, viral cytopathic-like alterations, and many mitotic figures, was further validated by immunohistochemistry staining for TTF1, see Figure 5.

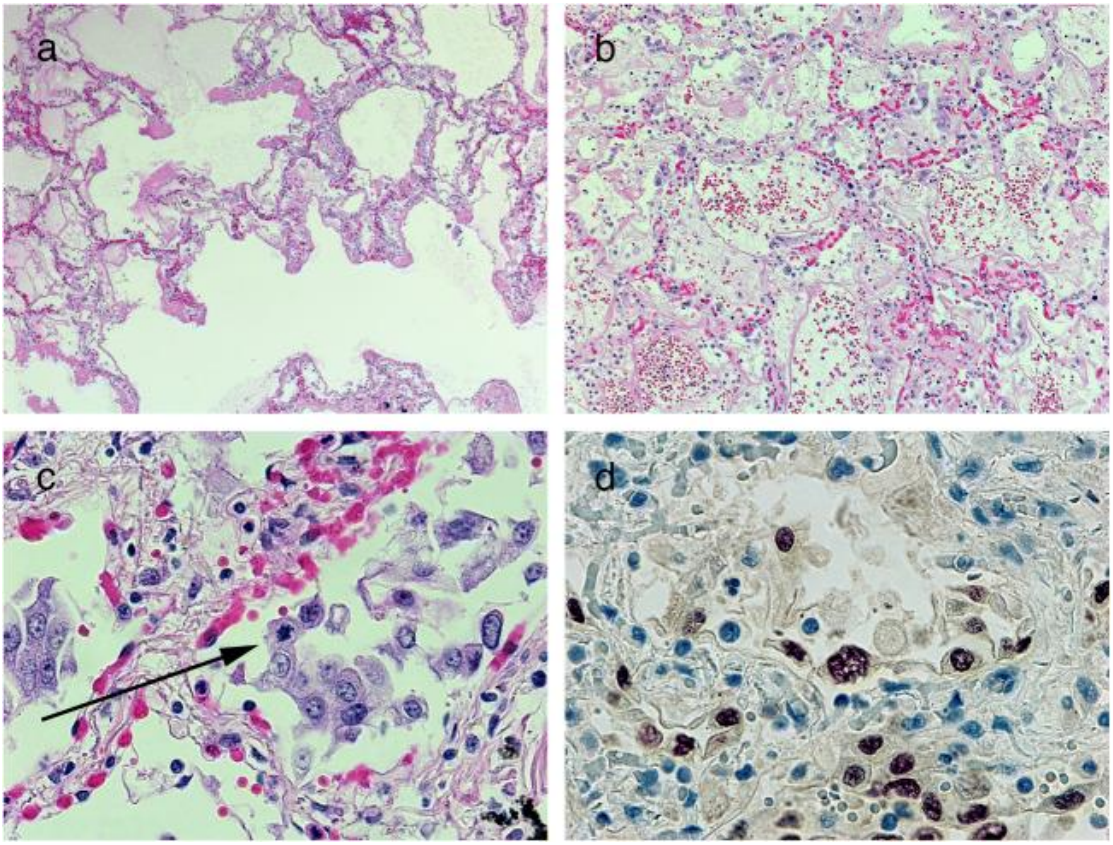

Figure 5. Lung parenchymal histologic alterations (H&E and TTF-1). A low power shows that acute diffuse alveolar injury is the most common kind. b Intermediate power showing fibrin deposition, haemorrhage, and oedema. Atypically enlarged intra-alveolar cells with big nuclei and enhanced mitotic figures are seen at high power (arrow). TTF-1 immunohistochemical staining verified the presence of type II pneumocytes in the atypically expanded cells [42].

In their 12-case investigation, Dogolini et al discovered that vascular alterations marked by dilated and hyperplastic interstitial capillaries and venules were present in every instance, including those in which AECII hyperplasia was either modest 6 or nonexistent [43]. Along with thicker, edematous walls and lumen dilatation and tortuosity, the venules lacked obvious endothelialitis or vasculitis. In two cases, scattered microthrombi were found. In 9 out of 12 patients, a patchy lymphocyte infiltration that ranged from solitary to substantial nodular clusters was seen, with the infiltrate being more noticeable surrounding the venules. Neutrophils, eosinophil's, and interstitial plasma cells were either nonexistent or very few. With the exception of one instance with localized myofibroblast buildup, all instances lacked interstitial and luminal organizing alterations. In 9 out of 12 patients, irregular clusters of mononuclear cells were seen in the alveolar gaps; intraluminal granulocytes were not seen, see Figure 6.

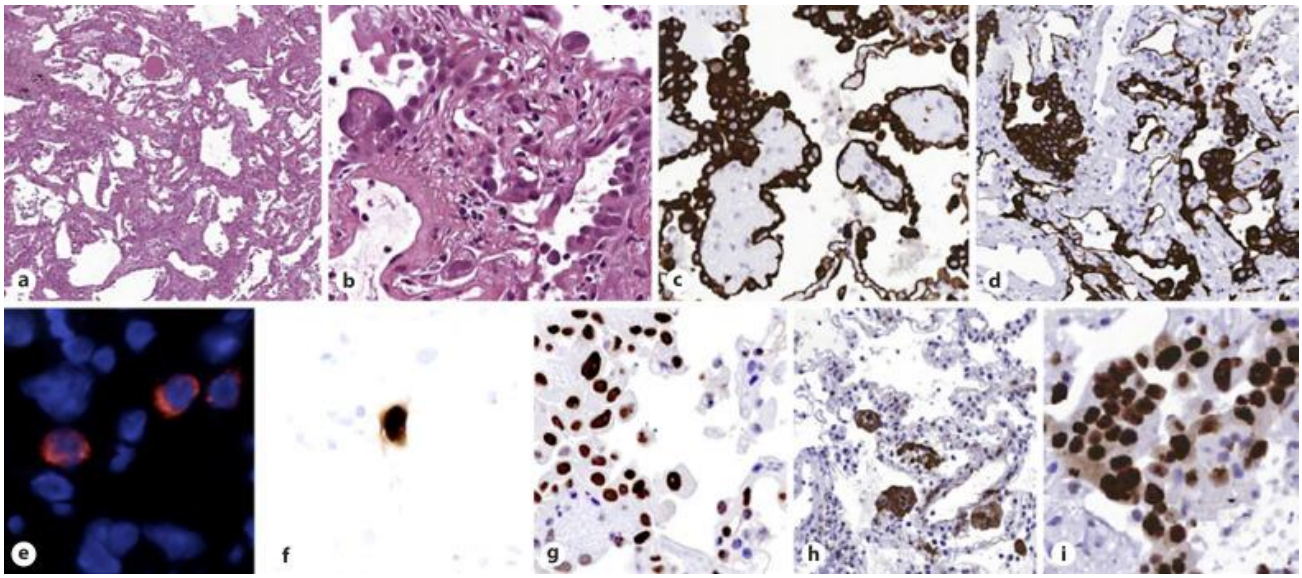

Figure 6. Histopathological and Molecular Features of Alveolar Epithelial Cell Type II (AECII) in COVID-19 Lung Tissue.

A, B) Hematoxylin and eosin (H&E) staining shows variable alterations in lung parenchyma, including AECII hyperplasia, vascular enlargement, and interstitial thickening.

C, D) Cytokeratin 7 (CK7) immune-staining reveals AECII forming small nodules, aggregates, and pseudo-papillary projections.

E) In situ hybridization for SARS-CoV-2 RNA demonstrates cytoplasmic (red) signals in scattered cells identified as AECII based on their morphology and anatomical location.

F) In situ hybridization for IL-6 mRNA shows strong signal in dispersed AECII, indicating active cytokine expression.

G) Phosphorylated STAT3 (pSTAT3) immunohistochemistry reveals strong nuclear staining in the majority of AECII, consistent with IL-6 pathway activation.

H) Tubulin beta-3 immuno-staining shows strong positivity in AECII, while the surrounding dilated interstitial spaces remain negative.

I) Ki-67 immunohistochemistry demonstrates high proliferative activity in AECII, with more than 50% of cells showing nuclear positivity. Abbreviation: CK7 = cytokeratin 7.

A high incidence of emphysema was observed in both COVID-19 survivors (92%) and control subjects (100%). Additionally, a subset of individuals in both groups exhibited smoker's macrophages, metaplastic changes, and occasional poorly formed granulomas within the alveolar spaces. Moderate fibrosis was also present in specific areas in both groups, with 60% of control patients and 50% of COVID-19 survivors showing localized fibrotic changes. Although the overall vascular architecture appeared largely normal, histological signs of moderate pulmonary hypertension were identified in 42% of COVID-19 survivors and 60% of control subjects. Notably, no significant vasculitis was observed in any of the evaluated COVID-19 survivors or end-stage

patients. However, in the context of acute COVID-19, both gross pulmonary emboli and scattered microthrombi have been reported. According to Montero et al. [44], diffuse alveolar damage (DAD) is the predominant histological pattern in patients requiring mechanical ventilation due to acute respiratory distress syndrome (ARDS) or acute lung injury. The American-European Consensus Conference on ARDS identified these two entities in a clinical context. According to the agreement, acute respiratory distress syndrome (ARDS) is defined as acute hypoxaemia with a partial pressure of arterial oxygen to fraction of inspired oxygen (PaO2:FiO2) ratio of 200 mmHg or below. Acute lung damage is a less severe condition with the same criteria, but a PaO2:FiO2 of 300 mg Hg. ARDS has a 50% to 60% fatality rate, and it rises with age. The majority of clinical ALI and ARDS patients will have DAD based on morphology.

COVID-19 controlling strategies

Individuals, labs, hospitals, and society may all respond to the COVID-19 epidemic. Restrictions on travel and big meetings, such as sporting, cultural, religious, and educational activities, are examples of measures implemented at the societal level [45]. All of the aforementioned techniques are primarily employed as a mitigation approach with the goal of halting the virus's fast spread and minimizing undue strain and expense on healthcare systems. Other precautions should be taken to keep patients safe from infection in addition to these, such as regular yearly and preventative medical appointments. Additionally, hospitals should increase their capacity so they can respond to big instances of infection [46]. Prioritizing essential healthcare interventions would reduce the number of needless outpatient visits and hospital admissions. To reduce dangerous interactions between individuals, medical Centre and laboratory personnel must work in shifts. In order to detect COVID-19 early and accurately conduct viral testing, isolation, and quarantine measures in emergency scenarios, Tan et al. advised laboratory personnel to take their temperature twice daily [47]. The main preventative measures for anyone suspected of having COVID-19 are quarantine and consultation with medical specialists. Additionally, laboratory personnel should be equipped with enough tools to handle emergency and backup plans for patients under COVID-19 quarantine [48].

Discussion

With over a million fatalities globally, COVID-19 is a serious health concern. Additionally, all non-urgent medical treatments have been delayed due of this epidemic [49]. To help doctors enhance disease therapy and prognosis, a thorough knowledge of the immunopathological processes and histopathological characteristics of COVID-19 is essential. As previously stated, The morphological features of COVID-19 remain poorly understood and often vary across different organs; however, histopathological changes are most prominently observed in the lungs and blood vessels, where they appear to have the greatest clinical significance. To determine if additional organs and tissues are impacted by COVID-19 and, perhaps, to determine the extent of their participation, more research and data on tissue samples are thus needed. Additionally, the immune-

pathological situation of COVID-19 is not well described. One theory to explain the extreme inflammatory response that is believed to be responsible for the disease's most severe symptoms is the so-called cytokine storm. Although many of the molecular processes that have been suggested are fascinating, the specific pathways that are involved in COVID-19 are still not fully understood, and it is still necessary to determine whether they are major actors or incidental events. In summary, the current understanding of COVID-19 immunopathology and histopathology is still incomplete and inadequately specific; as a result, further research is required to collect information that might help physicians better treat this illness.

CONCLUSION

Fundamental Finding : COVID-19 lung pathology is characterized by diffuse alveolar damage, vascular injury, inflammatory infiltrates, and variable epithelial alterations that overlap with other viral pneumonias yet manifest with notable combined severity. **Implication :** The interplay of extensive alveolar injury, microthrombosis, and cytokine-driven inflammation, including IL-6 involvement, underscores a complex pulmonary response that shapes clinical interpretation of disease progression. **Limitation :** These histopathologic features lack specificity for SARS-CoV-2, making isolated tissue findings insufficient for definitive diagnostic distinction. **Future Research :** Further studies should integrate histopathologic, clinical, and radiologic data to clarify disease mechanisms and refine understanding of COVID-19–related respiratory pathology.

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