

Entry

SARS-CoV-2 Associated Pulmonary Pathology

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Definition: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a novel entry in the betacoronaviridae group of coronaviruses. This is the second member of this group, and the third of the family overall to emerge in the last 20 years, which has caused significant health concerns due to the clinical severity and spread of the disease it causes—coronavirus disease identified in 2019 (COVID-19). While initially emerging as a respiratory disease, and while most cases experience symptoms predominantly from this system, SARS-CoV-2 has emerged as a multisystem pathogen. From a pathomorphological point of view, the severity of changes in the respiratory system can be summed up as diffuse alveolar damage—desquamation of the alveolar epithelium with exudative and proliferative changes—pulmonary hyaline membranes, Clara cell hyperplasia, squamous cell metaplasia, and fibrosis. The second most prominent way the disease affects the lung is through endotheliitis—damage to the endothelial cells of the pulmonary vasculature, predominantly affecting the medium and large caliber blood vessels that cause the well-established clinical phenomenon of thrombosis/thromboembolism of the pulmonary vasculature. As the spread of the disease continues with the emergence of new variants and the number of cases continues to grow, including a large percentage of recurrent cases, it is essential to remember that the viral effects are not only acute but, due to the proliferative phenomena, can produce chronic sequelae. Therefore, in the background of dwindling publication interest, it is critical to focus on the histopathological aspects of the pulmonary disease, with the goal of better understanding the effects of the virus on the organism and identifying probable future complications after infection.

Keywords: SARS-CoV-2; COVID-19; pathology; autopsy; diffuse alveolar damage; pulmonary pathology; virus-induced lung damage; long COVID



Citation: Stoyanov, G.S.; Popov, H.; Petkova, L.; Stoyanov, D.; Ivanov, M.; Tonchev, A.B. SARS-CoV-2 Associated Pulmonary Pathology. *Encyclopedia* **2022**, *2*, 1698–1709. <https://doi.org/10.3390/encyclopedia2040116>

Academic Editor: Stephen Bustin and Raffaele Barretta

Received: 30 July 2022

Accepted: 22 September 2022

Published: 30 September 2022

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1. Introduction

The novel representative of coronaviruses (SARS-CoV-2) and the clinical disease it causes (COVID-19), which emerged at the end of 2019, have led to healthcare and social consequences not seen in the last 100 years [1–6]. The rapid spread of the infection, the severe organ damage to multiple systems, and the lack of effective prevention forced the World Health Organization (WHO) to officially declare a pandemic of the disease [7–9]. Given the new nature of the infectious agent and the many unknowns surrounding it, the WHO implemented protocols developed during the most closely related infectious agents—MERS and SARS-CoV, namely, social distance, personal protective equipment, quarantine of healthy disease carriers and contacts of the sick, and strict monitoring of the epidemiological process [10–12]. The severe health challenges including the unknowns surrounding the course of the disease and the epidemiological process, the large number of healthy infection spreaders, the severe clinical course with high and sometimes sudden mortality in some patients, the lack of healthcare personnel, and effective prevention and misinformation (at the beginning of the pandemic due to lack of scientifically proven facts,

and, in the later stages, for non-medical reasons) led to the mobilization of medical science in the study of SARS-CoV-2 not only towards the origin of the virus and the study of its clinical consequences and morphology, but also to the rapid development of effective vaccine prophylaxis, largely possible based on the experience gained in the previous two severe coronavirus diseases [9,13–16].

With the abatement of the pandemic in 2022 and given the mutational variants of the disease leading to a significantly milder clinical course and a decrease in overall mortality, as well as due to the availability of widespread effective vaccine prevention, not only the public but also the publication interest in the subject has gradually subsided [17–19]. The question remains open not only about the origin of the virus and, to a large extent, the characteristics regarding organ involvement, but above all about the chronic consequences of the illness, which the medical community has yet to face [20–27].

Historically, this is not the first time that medicine has encountered a similar situation; numerous pandemics, not only of viral origin but also of bacterial origin, have led to the permanent disability of those who have suffered, and subsequently to the development of new and, at first glance, unexpected long-term consequences [28]. A relatively recent example is the HIV-AIDS infection, which, in addition to immune deficiency, has been proven to lead to many severe consequences, including neoplasia and dementia [29–32]. In the history of medicine, there are many more such examples, such as von Economo's disease (lethargic encephalitis), often confused as a consequence of the Spanish flu; although, the epidemic process began several years before it and led to postencephalitic parkinsonism [33–35].

It is for these reasons that it is necessary to retain the interest of medical science in the matter of the detailed study of the acute and chronic effects of the virus that are yet to be encountered and that can be used in combating future pandemic variants of coronavirus infections [36–39].

Autopsies of patients with COVID-19 have revealed a myriad of gross and especially histological changes in multiple internal organs, namely, the lungs, where the changes lead to the dominating clinical symptom of hypoxia, but also the liver, heart, and other organs [40–44]. It is important, however, that autopsies reveal only the most severe effects of the disease in patients who had either a severe protracted clinical course or those who expired suddenly. It is highly likely that in cases with a moderate clinical course, either a significantly less diffuse and developed set of complications is present or it did not manifest at all.

Furthermore, it is likely that in patients with mild clinical disease, a whole new spectrum of changes can be present, with all of these further developing and evolving into chronic changes in the spectrum of post-COVID syndrome. Post-COVID syndrome, or long COVID or persistent COVID, are a direct result of the persistent damage caused by the viral infection. While mainly focusing on the diverse pulmonary pathology, which leads to chronic complications, this spectrum also includes sequelae from other systems and organs, such as the kidneys, cardiovascular, gastrointestinal, and especially the central nervous system [21,45–48].

Safety Precautions during Autopsy—Determining the Hazard Group

As the causative agent of the disease has been identified by the WHO as a pandemic entity, special precautions must be taken during the autopsy of suspected, probable, and identified cases [49]. Furthermore, as a general precautionary rule in the presence of diffusely spreading infectious pandemic entities, safety precautions should be taken in all cases, even if the autopsy case is not suspected or even has been ruled out to be a carrier of the disease.

For autopsy practice, especially for infectious disease entities, cases are separated into hazard groups (HG) based on the ability of the pathogens to infect new hosts, the severity of the disease it causes, and the presence of effective prevention, treatment, or the lack thereof [50]. HG1 refers to pathogens that are unlikely to cause human disease, cause minimal illness, or there is effective prevention and treatment; HG2 refers to pathogens that

can lead to infection in the personnel but are unlikely to spread to the general population, and there is effective prevention and treatment; HG3 refers to pathogens that cause severe disease to the personnel and can spread to the community, but there is effective prevention and treatment; and HG4 refers to pathogens that cause severe diseases, can spread in the general population, and there is no effective prevention and treatment. It is essential to know that in many regions, based on their legislation, HG4 autopsies are counter-indicated, while in others, HG4 is mandated as it is viewed as a threat to national and regional security [49,51–54].

During the initial phases of the pandemic, there was a broad discussion regarding which HG COVID-19 should be placed in, with initial decisions putting it in HG4, and, hence, the number of autopsy cases was very low [49,51,55]. As data started to accumulate and there was a relatively low incidence of periautopsy infection, it was gradually moved down to HG3 and, in some areas after the introduction of vaccinations, even to HG2. Based, however, on the significant mutation frequency of the virus and the evasion of acquired immunity by the new variants, in the future, it would be sound to keep SARS-CoV-2 in HG3 to prevent the spreading of potentially deadly variants of the virus to healthcare personnel and the population in general [56].

2. Gross Findings

The respiratory system in patients who have died from COVID-19 shows a myriad of gross changes. The mucous membranes of the trachea and bronchi are moderate to severely erythematous, most prominently in the interchondral areas, and often have scattered mucosal hemorrhages and ulcerations (Figure 1) [57]. In the thoracic cavity, a large subset of patients had pleural effusions, varying from serous to hemorrhagic [41]. The characteristics of the pleural surface correspond to the presence and nature of pleural effusions, ranging from preserved pleural surfaces to edematous ones, diffusely scattered fibrin deposits, or hemorrhagic areas [58]. However, the lungs have the most striking changes to them. They are significantly enlarged, weighing more than a kilogram (i.e., more than twice their average weight), and can reach nearly two kilograms in the most severe cases. The parenchyma is firm to the touch, red-violet, and often deformed (Figure 1) [55,59–61]. On sectioning, the cut surface is diffusely consolidated, with a scant amount of mucohemorrhagic fluid flowing from it spontaneously when the parenchyma is compressed [60,61]. In cases with extremely severe parenchymal involvement, hepatization results in the bulging of the large and medium-sized blood vessels, giving the parenchyma a beef meat appearance (Figure 1). A large subset of patients also have a positive gross probe for pulmonary thromboembolism, and the vessel section reveals thrombi in smaller branches of the vessels, some in different stages of organization and/or areas of hemorrhagic infarction [44,62,63].

Normal lung		SARS-CoV-2 associated gross pulmonary changes	
Weight		Weight	
Left	Right	First 10 days	After the 10 th day
~400g	~450g	Up to more than 1kg each	~800g each
Soft, pinkish parenchyma, on section aerated		Firm and deformed, red-purple parenchyma, consolidated and airless, with beef meat appearance	Firm and deformed, violet-gray parenchyma, consolidated, few aerated zones may be noted peripherally

Figure 1. Comparison between gross features of normal lung and SARS-CoV-2 infected lung.

In patients with a more protracted clinical course (survival more than ten days from the onset of symptoms), the lungs are relatively lighter, regularly around 800–900 g, and grossly have a more grayish-red-violet color; they are firmer to palpation, deformed,

and some peripheral areas may have re-aeration resembling emphysematous deformation (Figure 1) [60]. When a secondary bacterial infection is superimposed, areas of suppuration and/or abscessation are visible in the parenchyma, and the bronchi are filled with purulent-hemorrhagic exudate [44,59,63]. In some patients, a fungal superinfection may be present, with aspergillus and mucormycosis being the most commonly isolated causative agents [64,65].

In chronically and severely ill patients and the elderly, the lungs may have significantly fewer changes, varying from focal and mild consolidation to nearly normal-looking lungs, with some cases showing only histological changes [58–60].

Histology largely depends on the innate resilience of the organism and the virulence and pathogenicity of the viral variant. In most cases, however, there are at least minimal signs of diffuse alveolar damage correlating to the clinical constellation of acute respiratory distress syndrome [44,55,59].

Practical Tips for Obtaining Respiratory System Specimens

In our practice, the authors have implemented a harvesting protocol for respiratory system specimens, intending to identify, even if minimally present, the changes induced by the virus on histology. When obtaining samples from the respiratory system, the authors open the ribcage with bone cutters, which is an important safety tip, as if opened with an electrical saw, as in some institutions, the vibrations produced can mobilize vital viral particles and spread them in the air, increasing the risk for the personnel present. Secondly, the respiratory system is sectioned only after in situ probing of the pulmonary artery for the presence of large thrombi/emboli. Once the respiratory system is eviscerated, the authors take at least three tissue specimens from every pulmonary lobe—one hilar, one central, and one peripheral, with other areas harvested as desired by the obductor. Furthermore, the authors take specimens from the trachea, bronchial bifurcation, and principal bronchi.

3. Histological Findings

The histological findings are largely non-specific, as similar changes can be observed in MERS, SARS-CoV-2, respiratory syncytial virus, pandemic variants of influenza and others, and some opportunistic viral infections to the lung and respiratory system [66–71].

3.1. Trachea and Large Bronchi

The trachea and large bronchi in patients with COVID-19 generally have histologic findings of extensive desquamation of the respiratory epithelium, basal cell hyperplasia, scant interstitial infiltration by lymphocytes, and goblet cell hyperplasia in the submucosal glands (Figure 2) [57].

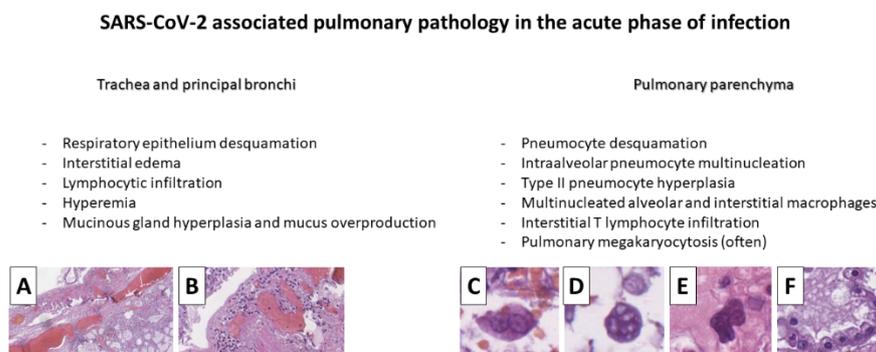


Figure 2. Histological features of SARS-CoV-2-induced damage in the trachea, principal bronchi, and the acute phase of pulmonary involvement: (A) respiratory epithelium desquamation, edema, lymphocytic infiltration, and mucinous gland hyperplasia in the trachea; (B) lymphocytic infiltrate in the tracheal submucosa around hyperemic blood vessels; (C) alveolar multinucleated cell of pneumocyte origin; (D) alveolar multinucleated cell of macrophage origin; (E) pulmonary megakaryocyte; (F) type II pneumocyte hyperplasia. Note: Histology sections adapted from ref. [60].

3.2. Pulmonary Histopathology

As already mentioned, pulmonary histopathology is non-specific and follows the pattern of diffuse alveolar damage and vascular endothelial damage—its two coexisting forms.

Diffuse alveolar damage consists of severe damage to the respiratory and alveolar epithelium, occurring in two primary forms—an exudative phase (acute), which is observed in patients who die within the first week of the onset of symptoms, and a proliferative (initial and advanced) phase, which is observed in patients with survival of more than ten days from the onset of symptoms [44,59,72]. The initial phase of proliferative diffuse alveolar damage combines the findings of the exudative and advanced proliferative phases [44,60,69].

3.2.1. Acute Phase of the Infection—Diffuse Alveolar Damage

The first histological changes observed in the exudative phase of diffuse alveolar damage (patients who died by the seventh day from the onset of symptoms) are the desquamation of the epithelium of the terminal bronchioles and alveoli, as well as the hyperplasia of type II pneumocytes, the formation of alveolar and interstitial multinucleated cells, scarce interstitial infiltration comprised by predominantly T lymphocytes, intra-alveolar and interstitial macrophage infiltration with multinucleation, and occasionally pulmonary megakaryocytes (Figure 2) [58,60,63]. The alveolar multinucleated cells originating from pneumocytes have characteristically ground glass opacity cytoplasm, peripheral inclusions, up to six nuclei (predominantly, these cells have two or three nuclei) with a central, sometimes ruby-red nucleoli, and a diameter varying between 20 and 40 μm (Figure 2) [60,61]. The second type of multinucleated cells, with macrophage origin, also presents intra-alveolarly, but the cells are mostly interstitially located, smaller (about 20 μm in diameter), primarily trinucleated, but may have up to seven nuclei, and their cytoplasm is more basophilic and positive for CD68 (Figure 2) [59–61,73].

3.2.2. Organization Phase of Diffuse Alveolar Damage

In patients with a survival of about ten days from the onset of symptoms, a transformation of changes with an initial phase of organization is observed. Alveolar macrophages decrease in number, and in the terminal and respiratory bronchioles, there is hyperplasia of Clara-type cells—non-ciliated cells of the bronchioles—with a secretory function (Figure 3) [60]. Other than their secretory function, which plays a significant role in local homeostasis regulation and stress response, these cells also play a role in tissue repair as they serve as a regenerative “reservoir” but are also susceptible to metaplastic change [74]. Fibrous changes also begin with the thickening of the alveolar walls and focal interstitial fibrosis (Figure 3) [41,44,58,63].

SARS-CoV-2 associated pulmonary pathology in the organizing phase of infection

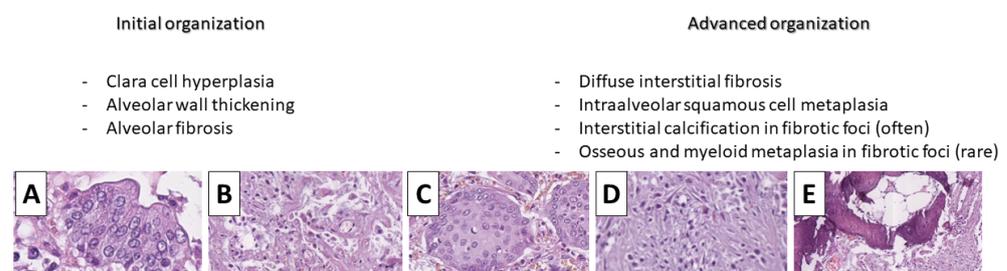


Figure 3. Organizational changes in COVID-19: (A) Clara cell hyperplasia in alveolar tracts and alveoli; (B) fibrosis with thickening of the alveolar septa; (C) intra-alveolar squamous cell metaplasia; (D) diffuse fibrosis; (E) osteoid and myeloid metaplasia in fibrotic foci. Note: Histology sections adapted from ref. [60].

In patients who died 15 days after the onset of symptoms, advanced organization of the lung parenchyma can be noted, with pronounced fibrosis—diffuse interstitial, thickening of the alveolar septa to a bronchiolitis obliterans organizing pneumonia pattern with intra-alveolar fibroblastic proliferation and alveolar obliteration [47,60,75].

In this phase, several interesting phenomena can also be observed, the most striking of which is the transformation (metaplasia) of Clara-type cells into squamous epithelium that diffusely fills the alveoli and respiratory tracts without the involvement of the larger bronchi (Figure 3) [60,63]. Secondary to fibrosis, diffuse calcium deposition can also be observed in some cases with further osteoid and myeloid metaplasia (Figure 3) [43,60].

3.3. Vascular Changes

The second most prominent group of changes—those of the pulmonary blood vessels—is more monomorphic and does not undergo such great dynamics. These changes manifest with endotheliitis (endothelialitis)—swelling, palisading, and desquamation of the endothelium of the larger vessels with focal intravascular endothelial proliferation in the regeneration phase (Figure 4) [57,60,62,76,77]. CD34-labeled vessels show extensive areas of endothelial desquamation, with sometimes interconnected endothelial cells freely “hanging” in the lumens of large vessels like a curtain (Figure 4). Interestingly smaller blood vessels, especially capillaries, do not constitute such an endothelial change [60].

SARS-CoV-2 associated pulmonary vascular pathology

- Endotheliitis with endothelial palisading and bulging
- Endothelial delamination
- Thrombosis
- Vascular wall edema and remodeling
- Fibrinoid necrosis



Figure 4. SARS-CoV-2 associated pulmonary vasculature pathology: (A) endothelial cell edema; (B) endothelial cell palisading; (C) endothelial cell desquamation in groups; (D) fibrinoid necrosis; (E) fibrin thrombus with organization partially attached to the wall of a large vessel; (F) homogenization and thickening of the vascular wall. Note: Histology sections adapted from ref. [60].

These described endothelial changes have two immediate effects—thrombosis, a well clinically manifested phenomenon, and degenerative changes in the vascular wall due to increased permeability [60,62,77,78].

Although pulmonary thrombosis is clinically comparable to thromboembolic disease, given the severe single-vessel involvement and advanced organization in some cases, it is more likely an autochthonous thrombosis of the pulmonary circulation (Figure 4) [44,62,77–79].

The changes in the vessel wall as a result of the increased permeability are represented by distortion of the cellular arrangement in the structure of the vascular wall and degeneration of the extracellular matrix—the walls of the vessels are eccentrically thickened, acellular and amorphous, akin to hyalinized, with focal fibrinoid necrosis, lymphocytic infiltrate in the vascular wall, and subintimal foamy macrophages may be observed in some cases (Figure 4) [60].

Special histochemical stains show that these changes develop due to simple extracellular matrix edema, with only focally positive proteinaceous deposits (PAS-positive), while Congo red, Phosphotungstic acid hematoxylin (PTAH) and Van Gieson stains, Mason trichrome, and Alcian blue are negative (Figure 4) [60]. Immunohistochemically, the larger vessels show a distortion of the smooth muscle cell arrangement and focal loss of fibroblasts (Figure 4). It is important to note that the changes described up to this point involve the vessels of mostly medium and small caliber, with the larger vessels having less pronounced changes, while in the microcirculation, these changes are hardly noticeable.

Precisely because of this, as already mentioned, fibrin thrombi are present in these branches in most of the cases, while thrombi in the microcirculation are present in a significantly smaller proportion of patients.

3.4. Non-Time Associated Changes

Changes observed in the lung parenchyma, which are not associated with the time since the onset of infection, are again non-specific and associated with diffuse alveolar damage (pulmonary hyaline membranes) and secondary infections [41,58,59,63,72,73,80].

3.4.1. Pulmonary Hyaline Membranes

Pulmonary hyaline membranes (alveolar fibrinous exudate) present with classic morphology; however, the intra-alveolar edema in these areas has a more vacuolated appearance due to increased albumin (Figure 5) [58,60,63]. It is important to note that hyaline membranes are only seen in half of the patients who have expired from COVID-19 [43,57,59,60,63]. These reflect the severe direct alveolar epithelium damage and the dysregulation of alveolar homeostasis. The spectrum of vascular phenomena also plays a big part in it, as the alveolar walls are comprised of capillaries. At the onset of hyaline membranes, the alveoli are no longer able to carry out their gas exchanging function. As such, the condition of these patients deteriorates rapidly with a sudden drop in peripheral oxygen saturation [81–83]. Furthermore, as already stated, these changes do not appear in a time-related manner and can be seen in the exudative, early, and late organizational phases of diffuse alveolar damage [59,60]. In patients with more prolonged survival, mainly those on invasive lung ventilation, the hyaline membranes are thick and layered, in some areas resembling intra-alveolar globules.

Non-specific SARS-CoV-2 associated pulmonary pathology

- Vacuolated intraalveolar edema
- Pulmonary hyalin membranes due to alveolar damage
- Secondary bacterial infections
- Secondary fungal infections, often aspergillosis and mucormycosis

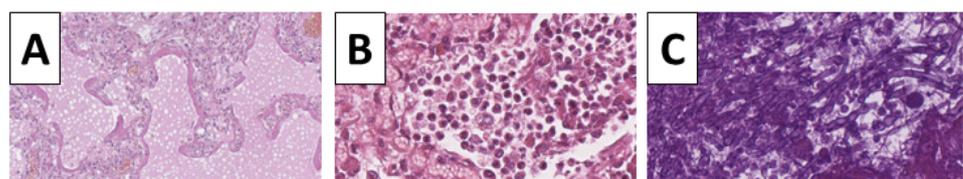


Figure 5. Non-specific pulmonary changes associated with SARS-CoV-2 infection, Hyaline membranes, and edema in COVID-19: (A) pulmonary hyaline membranes and vacuolated intra-alveolar edema; (B) secondary bacterial infection (purulent bronchopneumonia); (C) secondary fungal infection.

3.4.2. Secondary Infections

Secondary infections, in the form of suppuration and abscessation in the lung parenchyma, as a time-independent complication, can develop in around one-third of patients, regardless of antibiotic prophylaxis, and can be not only bacterial but also fungal, with aspergillus and mucormycosis being the most prevalently isolated pathogens from this group (Figure 5) [64,65].

3.5. Practical Tips for Reporting Histopathology in Autopsy Protocols

If the patient tests positive antemortem, then COVID-19, as a socially significant disease, should be noted as the main/principal disease that unlocked the mechanisms of tanatogenesis [50]. In cases where the patient has multiple severe conditions, such as malignancy, other infectious diseases (e.g., tuberculosis), or immune suppression, all of

these should be mentioned together as primary diseases, while COPD, CVDs, etc., should be specified as background diseases [50].

In cases where the patient was not tested antemortem or tested negative, but the clinical symptoms and morphology are compatible with COVID-19, then instead of COVID-19 being recognized as the primary disease, the main illness should be specified as an acute viral infection and its components listed, such as diffuse alveolar damage in organization phase with alveolar and interstitial multinucleated cells, scant lymphocytic interstitial infiltration, Clara cell hyperplasia, squamous cell metaplasia, fibrosis, and medium caliber pulmonary vessel degeneration and thrombosis. While many institutions allow for postmortem PCR tests and recognize them as valid, hence, for postmortem COVID-19 diagnosis, it is important to note that all commercially available tests have been validated for use only on the living, and none for postmortem evaluation. Immunohistochemistry on neutral formaldehyde-fixated tissue specimens, although a validated method for postmortem evaluation, should also be noted as not always being reliable depending on the antibody used, i.e., if the antibody targets a frequently mutated part of the antigenic structure of the virus, it may not detect a positive case. At the same time, cross-reactivity with other members of the coronaviridae family should not be underestimated, such as SARS-CoV, and MERS, which present with virtually identical morphology, as well as different non-pandemic variants of coronaviruses such as those causing seasonal common cold [44,51,68,73,84].

4. Conclusions

- The pulmonary pathology induced by SARS-CoV-2 follows a relatively strict pattern of evolution with:
 - Diffuse alveolar damage—desquamation of the alveolar epithelium with exudative and proliferative changes—pulmonary hyaline membranes, Clara cell hyperplasia, squamous cell metaplasia, and fibrosis;
 - Endotheliitis—endothelial cell infection, edema, bulging, desquamation, and vascular thrombosis with vascular wall remodeling;
 - Opportunity for secondary infections—bacterial and fungal.
- These changes are not pathognomonic COVID-19, as multiple other viruses, including some other coronaviruses (SARS-CoV-2 and MERS), present with similar morphology.
- The described acute changes have further implications to chronic sequelae in the respiratory and cardiovascular systems.

Author Contributions: G.S.S. and L.P. conceptualized the study; G.S.S. and H.P. performed the initial literature review; G.S.S. and D.S. performed detailed review on available data of acute effects; L.P. and M.I. performed detailed review on chronic effects; D.S., M.I. and A.B.T. reviewed the mechanisms of viral biology and functional changes; G.S.S. and H.P. wrote the initial draft; G.S.S., D.S., M.I. and H.P. devised the figures; A.B.T., M.I., H.P. and L.P. revised the initial draft critically; A.B.T. performed the final revision and approved the manuscript for submission. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

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