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Lung Pathology in Patients with Acute Respiratory Distress Syndrome Associated with the Novel SARS-Cov-2 Virus

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Abstract

Acute Respiratory Distress Syndrome (ARDS) is a well-recognized clinical problem first described in the late sixties. However, its relevance seems to have increased since the severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2) outbreak, as 14% (CI 95% 2% to 59%) of patients admitted to the hospital present with this syndrome.

Conceptually, a syndrome is a group of symptoms and signs that correspond to several diseases. Although defining disease is much harder than may appear at first glance, we can view it as the association between a syndrome and a pathology pattern. Diffuse alveolar damage (DAD) is the morphological hallmark of ARDS, although studies performed in autopsies and patients have demonstrated that it is present in only half of ARDS patients. The SARS-CoV-2 outbreak and the high incidence of ARDS associated with this infection have triggered a natural question: is the lung pathology similar in patients with ARDS associated with traditional risk factors than to SARS-CoV-2 infection?

This review aims to analyze the lung pathology results of patients infected with the novel SARS-Cov-2. As this article targets non-intensive care physicians, we will first describe the main characteristics of the novel SARS-Cov-2 and the ARDS definition, and then the lung pathology results from the UCI in this group of patients.

Keywords: coronavirus, SARS-Cov-2 infection, lung pathology, acute respiratory distress syndrome

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Acute Respiratory Distress Syndrome (ARDS) is a well-recognized clinical problem first described in the late sixties [1, 2]. However, its relevance seems to have increased since the severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2) outbreak, as 14% (CI 95% 2% to 59%) of patients admitted to the hospital present with this syndrome [3].

Conceptually, a syndrome is a group of symptoms and signs that correspond to several diseases. Although defining disease is much harder than may appear at first glance, we can view it as the association between a syndrome and a pathology pattern [4]. Diffuse alveolar damage (DAD), a term coined by Katzenstein et al. [5], refers to a type of lung injury characterized by «endothelial and alveolar lining cell injury which leads to fluid and cellular exudation and in some cases progresses to extensive interstitial fibrosis». DAD is the morphological hallmark of ARDS [6], although studies performed in autopsies and patients have demonstrated that it is present in only half of ARDS patients [7, 8]. The SARS-CoV-2 outbreak and the high incidence of ARDS associated with this infection [3] have triggered a natural question: is the lung pathology similar in patients with ARDS associated with traditional risk factors than to SARS-CoV-2 infection?

Coronavirus and SARS-CoV-2

Coronaviruses are a large and diverse group of enveloped viruses containing positive-sense single-stranded RNA as their genetic material. These viruses are responsible for various respiratory diseases (including the common cold) in humans and other mammals [9]. Coronaviruses are characterized by club-shaped protein spikes on their envelope, giving them a crown-like appearance when viewed by transmission electron microscopy (hence the term Coronavirus) [10]. Other members of the coronavirus family are the SARS-CoV (SARS-Cov-1), the causative agent of the Severe Acute Respiratory Syndrome (SARS), and the Middle East Respiratory Syndrome-Related Coronavirus (MERS-CoV), the causative agent of Middle East Respiratory Syndrome (MERS).

Phylogenetically, SARS-Cov-2 shares a remarkable (79%) identity in its nucleotide sequence with SARS-CoV, which caused a significant epidemic during the first years of this century [11]. MERS-CoV shares 50% homology with SARS-Cov-2 [11]. The principal mode of transmission is through the respiratory pathway, primarily by large droplets or aerosols. Infected surfaces and fomites have been the routes of infection in some instances. Typically, close and prolonged contact for over 15 min significantly increases the likelihood

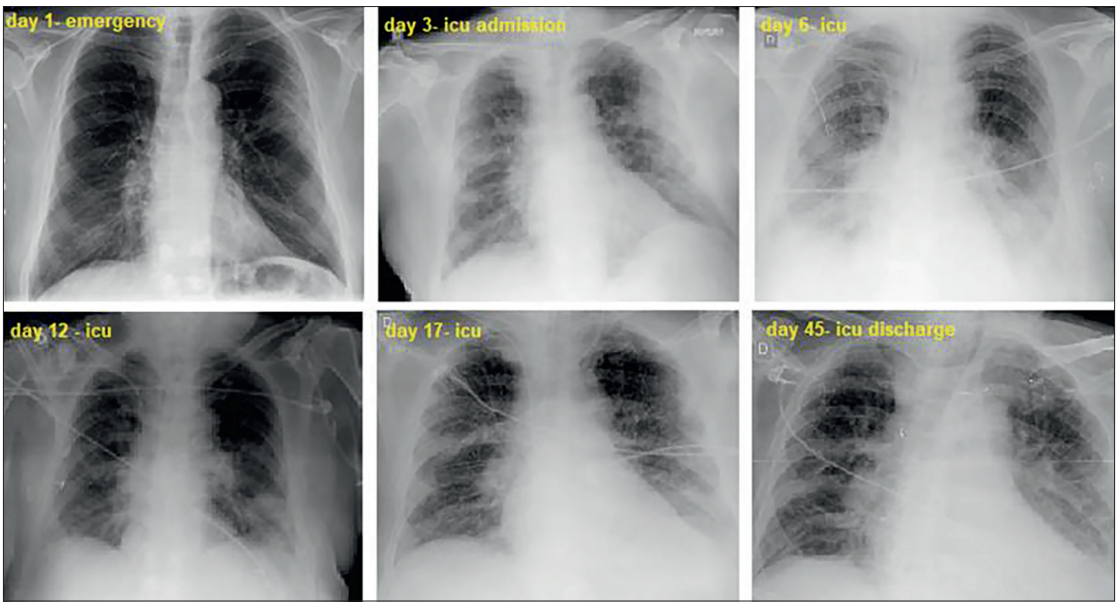

Fig. 1. *Chest x-ray evolution*

Note: *This Male of 73 years old presented to the emergency unit with respiratory insufficiency. He was transferred to the ward and received antimalarials, steroids, tocilizumab, and antibiotics. After 72 hours his respiratory status deteriorated and he had to be transferred to the intensive care unit, where he was intubated and pronated three times (every 16 hours). After 45 days in the ICU and 32 days of invasive mechanical ventilation, he was discharged to the ward.*

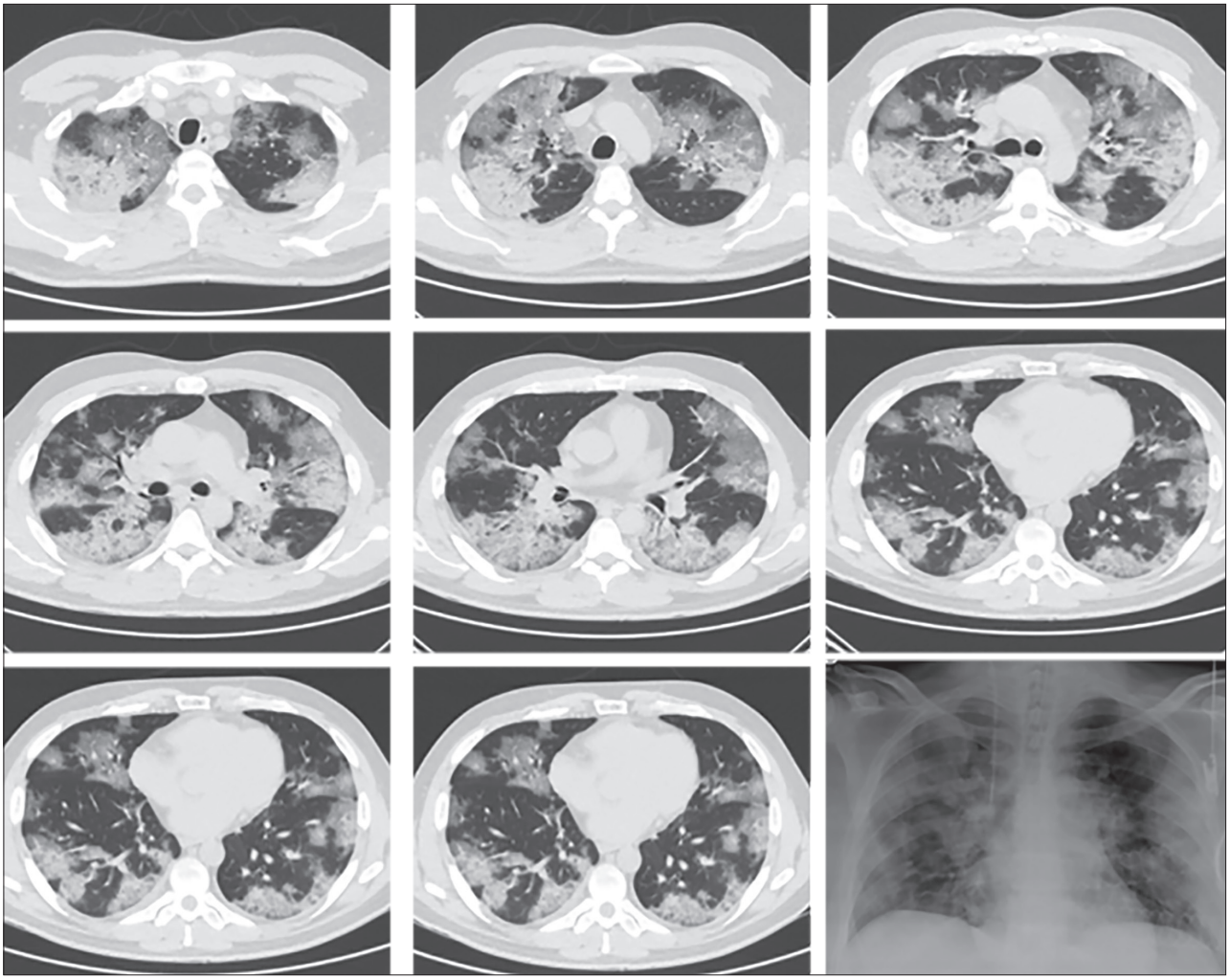

Fig. 2. *Computer tomography results at emergency unit and chest X-ray at ICU admission*

Note: *This 40 years old male, without a previous disease that was in contact with a COVID19 patient 14 days before the emergency unit (EU) consultation. At EU he was tachypneic with an oxygen saturation of 75 with supplementary oxygen. He was transferred to the intensive care unit, intubated and sedated.*

of acquiring the infection. Infectivity is much increased by repeated or prolonged exposure, making healthcare workers particularly vulnerable. The mean incubation period, so far, has been five days. However, some reported cases have shown an unusually prolonged incubation period - as high as 24 days. Viral shedding occurs during the convalescent period (ranging from 8 days to 37 days, with a median of 20 days). However, in fatal cases, it continues until death [12].

The most typical lung images of SARS-CoV-2 pneumonia include bilateral patchy ground-glass opacities, extensive bilateral interstitial airspace opacities, and consolidation with air bronchograms (Fig. 1–2). The distribution of the opacities is usually peripheral. Central distribution of infiltrates, pleural involvement with effusion, and lymphadenopathy can be present but are less frequent.

Definition of Acute Respiratory Distress Syndrome

Berlin is the name of the newest ARDS definition [6]. At the bedside, this definition considers ARDS as (a) an acute process developing within 1 week of a known clinical insult or new or worsening respiratory symptoms, (b) with a chest image that shows bilateral opacities not fully explained by effusions, lobar or lung collapse, or nodules (Fig. 1) and (c) associated to severe impairment in oxygenation as measured by a PaO2/FIO2 (oxygen partial pressure / fraction of inspired oxygen) not exceeding 300 mmHg in the presence of positive end-expiratory pressure of at least 5 cm H2O [6]. However, the Berlin definition also provides a more complex concept of ARDS that includes three complementary perspectives: (1) pathobiological, a type of acute diffuse and inflammatory lung injury leading to increased pulmonary vascular permeability, increased lung weight, and loss of aerated lung tissue; (2) clinically (vide supra); and (3) morphologically (vide supra) [13]. The two greatest barriers to operationalize the concept of ARDS are (a) the fact that knowing the ARDS pathology requires obtaining a lung sample by an invasive procedure (e.g. open lung biopsy) that could potentially deteriorate the patient's condition (currently, the only subrogate biomarker for ARDS histology is procollagen type III, but it is still not validated in a wide population [14]) and (b) the lack of a correlation between clinical and pathological findings (vide infra).

Effect of lung pathology in patients with ARDS

Before the SARS-CoV-2 era, we have demonstrated that only half of autopsies and patients with ARDS presents DAD [7, 8, 15]. Indeed, the presence of DAD determines relevant effects on ARDS outcome [7, 8, 15]; for example, we have reported in a cohort of 149 autopsied patients who had been invasively mechanically ventilated and met the criteria for ARDS within 14 days of the death that ARDS associated with DAD differed from ARDS without DAD in several variables: age, proportion of alcoholism, dynamic respiratory system compliance, PaO2/FIO2 ratio and Sequential Organ Failure Assessment (SOFA) score. Moreover, the main reason for death differed in both groups (patients with DAD were about five times as likely to die of refractory hypoxemia than patients without DAD; in contrast, patients without DAD were about twice as likely to die of a shock than patients with DAD) (15). In line with the previous report, but in patients with ARDS and open lung biopsy, a meta-analysis published by our group that included 350 participants demonstrated that mortality is almost twice as high if DAD is present (OR 1.81; 95% CI, 1.14–2.80). Indeed, an international collaborative study, also conducted by our group, that included 249 patients from France, Colombia, Taiwan, and Switzerland confirmed that DAD increases the risk of death in ARDS patients (OR 2.081; CI95% 1.053; 4.114) [8].

This clinical and pathological discrepancy leads to propose two entities, the «real» ARDS (ARDS with DAD) and the mimics (ARDS without DAD) [7, 16–18].

Lung pathologic findings in patients with ARDS associated to SARS-CoV-2 infection

As happens in patients with ARDS not caused by the SARS-CoV-2, studying the lung pathology of ARDS associated with SARS-CoV-2 infection is a real challenge due to the risk associated with the procedure for obtaining the sample. Indeed, studying post-mortem samples in this group of patients is also a challenge because of the associated biological risk. Likewise, it is hard to interpret the results because most cases are highly biased by other factors (e.g. autopsies represent the most severe spectrum of the disease, small series of cases that do not represent the universe of patients, the procedure for obtaining the sample may differ [full autopsy,

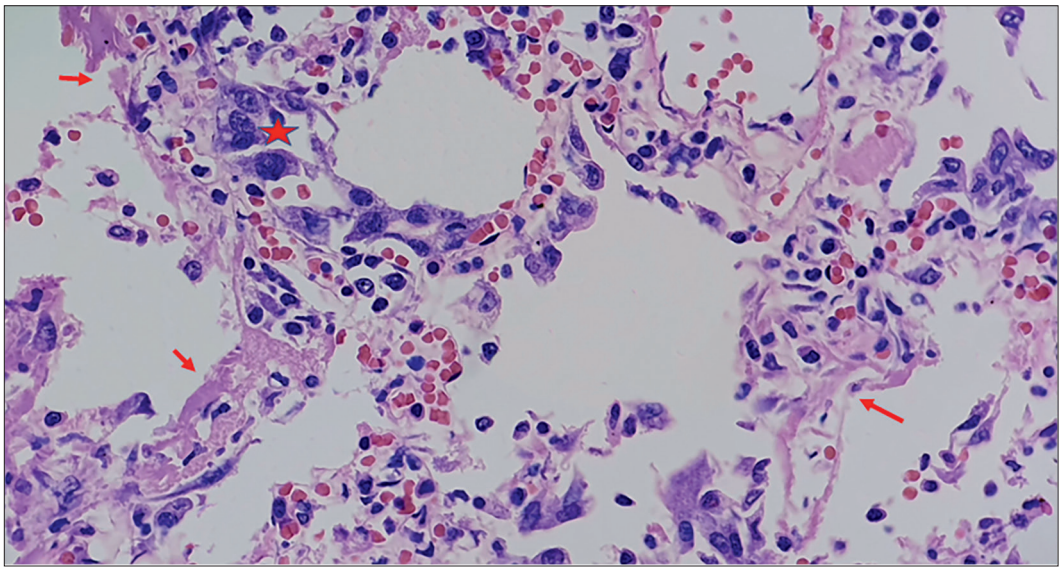

Fig. 3. *Diffuse alveolar damage associated with SARS-Cov2 infection (40x, HE - post-mortem biopsy)*

Note: *Arrow: hyaline membrane; start: pneumocytes with atypies (enlarged nucleus with hyperchromatine)*

post-mortem biopsy or post-mortem needle], etc.). Despite all these limitations, it is evident that autopsy data has provided extremely valuable information. Specifically, it revealed non-specific histopathologic findings, none of which are pathognomonic of COVID-19. A common finding in fatal cases is DAD (Fig. 3).

However, it is worth to mention that DAD could be a non-prominent finding (the proportions of DAD in patients with ARDS is unknown) and is not the unique finding (vide infra) [19]. Both features are similar to what happens in traditional ARDS (lack of correlation between clinical and pathological findings) and may have a relevant impact on the concept and definition of the ARDS.

Interstitial abnormalities have also been described (Fig. 3). The alveolar septa show patchy expansion by a mild-to-moderate inflammatory infiltrates composed primarily of lymphocytes. These cells are an admixture of CD4+ and CD8 + T-lymphocytes. However, focal collections of neutrophils have also been reported in a subset of cases. These have been variably interpreted as acute bronchopneumonia, neutrophil extracellular «traps», or, in rare instances, capillaritis [20, 21]. Since neutrophils are not typically encountered in uncomplicated viral infection and do typically occur in superimposed bacterial infection, it is unclear whether the neutrophils reported in COV-ID-19 cases are related to viral injury or reflect a superimposed bacterial infection or other unrelated processes.

One of the main findings in SARS-CoV-2 infections is the high prevalence of thrombotic and embolic events. The systematic review performed by Chen Liao et al., which included 19 studies and 1835 patients, reported a pulmonary embolism incidence of 15.3% (95%: 9.8–21.9), which is higher than in patients with seasonal and pandemic influenza (3%) [22, 23]. This observation could be explained by several factors: prolonged immobilization, aberrant and exuberant activation of inflammatory and coagulation cascades (termed «immunothrombosis»), together with elevated levels of IL-6, D-dimer, lactate dehydrogenase (LDH), and ferritin, direct vascular and endothelial injury, etc. [24]. From a pathologic point of view, lung specimens showed thrombotic microangiopathy in more than half of the cases, partially justifying the severe hypoxemia found in critical cases of COV-ID-19 with minor radiological abnormalities on imaging [25, 26].

Conclusion

In summary, DAD is considered the pathological correlate of ARDS, but not all patients with ARDS have DAD. Patients with ARDS associated with SARS-CoV-2 infection seem to present with a high proportion of DAD. However, as happens in traditional ARDS and despite the relatively scarce information available at this moment, the clinical and pathological correlation is unknown. Future studies should focus their interest on this fact.

The benefit of knowing the correlation between ARDS and DAD is that it would allow identifying a subpopulation of patients with a uniform histological diagnosis for potentially specific therapies targeting the cellular and molecular mechanisms of DAD.

The authors declare no conflicts of interest.

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