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Histopathology and genetic susceptibility in COVID-19 pneumonia

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Introduction

Due to the outbreak of the COVID-19 pandemic, the first quarter of 2020 has seen levels of burden on health care systems which have not been seen in relation to a viral infection since the influenza pandemic of 1918¹⁻³.

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While social distancing, testing and containment have undoubtedly led to a significant reduction in morbidity and loss of life, their societal impact and resulting economic upheaval are unprecedented. The extent of the measures taken across the globe vary significantly, and range from stringent testing and isolation to more lenient ‘intelligent lockdowns’, and these by-and-large reflect national and regional cultural and ethical differences in weighing the acceptability of limitation of personal freedoms against strain on the health care system and ensuing loss of life, as well as the level of preparedness to accept the consequences of a potential ‘second wave’ in case of a delay in the development of an effective vaccine. However, differences in practice are probably also related to our as yet limited understanding of the natural evolution of the disease, which varies greatly between populations, and is probably related to a host of patient-related and environmental risk factors.

The clinical features of a patient with COVID-19 range from a mild illness with slight complaints such as sore throat and headache, to patients who have to be admitted to hospital because of hypoxemia caused by pneumonia, to patients with a very severe illness who have acute hypoxic respiratory failure and need to be admitted to an Intensive Care Unit³⁻⁷. In general, mortality rates are approximately 2%, but once admitted to hospital this rate can increase to 28%^{4,6,7}. Risk factors for a fatal disease are older age, an increased D-dimer and an increased SOFA score⁴. Until now, there is no evidence-based effective treatment options for COVID-19. Therefore, hypotheses need to be generated about the underlying pathophysiological mechanisms of a mild to very severe disease, so that new treatment strategies for these different categories of patients can be developed and investigated.

Thus, while we now know that higher age and a range of comorbidities (such as respiratory disorders, cardiovascular disease, diabetes and obesity) pose significant risks for those infected with SARS-CoV-2, little is known about the mechanisms behind the infrequent idiosyncratic clinical demise in otherwise healthy young subjects (although there may be an effect of the level of exposure), and the reasons for observed differences in resolution of the disease following an otherwise comparable clinical course in patients with similar risk factor profiles. As in other diseases, the answer to some of these questions may in time be provided by genotyping as well careful clinical, serological, radiological and histopathological phenotyping, which enable mechanistic insights into the differences in pathogenesis and underlying immunological and tissue regenerative response patterns. While little is known so far regarding COVID-19 histology, we will aim to provide a brief overview of the existing evidence for such differences in host response and outcome, and

generate hypotheses for divergent patterns and avenues for future research, by highlighting similarities and differences in histopathological appearance between COVID19 and influenza as well as previous coronavirus outbreaks, and by discussing predisposition through genetics and underlying disease.

Respiratory tract histopathology in influenza

The archetypical previous pandemic leading to a massive worldwide loss of life due to pneumonia and respiratory failure is the influenza pandemic of 1918, which killed approximately 50 million people worldwide, and which was caused by an RNA virus of the family orthomyxoviridae that contains a negative-sense (as opposed to the positive strand in coronaviruses), single-stranded, segmented RNA genome. The histopathology described in cases of various influenza pandemics stems mainly from autopsy cases, and therefore leads to bias towards severe cases. Larger case series are available for the 1918 pandemic, as well as limited descriptions of later pandemics and inter-pandemic cases, and only 3 autopsy cases of the more recent H5N1 Highly Pathogenic Avian Influenza Infection⁸. Nonetheless, it has become clear that while there is a wide range of pulmonary histological response patterns to influenza infection, which varies with both clinical picture and length of the disease course before death, the range appears to be similar for most influenza subtypes. The respiratory tract histology of influenza reflects its cellular tropism, as influenza virus replicates in respiratory epithelial cells throughout the respiratory tree, with non-fatal infections predominantly involving the upper respiratory tract and trachea, but fatal cases of influenza usually result from pneumonia. Coincident or secondary bacterial pneumonias are extremely common in severe influenza and also complicate the histopathologic appearance. As these are primarily related to outcome, we will restrict our commentary to the histopathological changes observed in the lower respiratory tract. Changes in the smaller airways include necrosis and complete loss of the epithelial layer (both ciliated and goblet cells), often resulting in the formation of hyaline membranes at these sites. Neutrophilic inflammation may be present in the lumen, and extend into surrounding alveoli. In addition, a more chronic lymphoplasmahistiocytic infiltrate is often seen in influenza-infected airways. The parenchyma shows evidence of acute injury with interstitial congestion, edema, and inflammation (predominantly neutrophilic with some eosinophils), as well as desquamated alveolar epithelial cells, intra-alveolar edema, intra-alveolar hemorrhage, fibrin, hyaline membrane formation, and sometimes necrosis of the alveolar septa (necrotizing alveolitis), the latter possibly resulting from frequently observed vascular changes with capillary congestion and thrombosis. Mitotic activity and regeneration of respiratory epithelium start after approximately 5 days

and the level of regeneration is possibly related to outcome. Thus, variable mitotic activity but no evidence of true regeneration of the epithelial layer has been seen in rapidly lethal cases. If the patient survives, organizing diffuse alveolar damage, increased numbers of intra-alveolar macrophages, epithelial regeneration (incl. type II alveolar hyperplasia), squamous metaplasia, chronic interstitial inflammation and eventually interstitial fibrosis may be seen. Megakaryocytes lying within the capillary bed are also commonly seen. Coincident bacterial pneumonias frequently occur and complicate the pathologic picture by massive infiltration of neutrophils into alveolar spaces. In general, most interpandemic cases seem to be associated with fewer changes of primary influenza virus pneumonia (such as edema), and more changes attributable to secondary bacterial pneumonia.

Respiratory tract histopathology in coronavirus infection (COVID-19, SARS, MERS)

Limited data are available regarding the histopathological spectrum of COVID-19 pneumonia. Of the 41 SARS-CoV-2-infected patients admitted in the early stages of the outbreak, six died from acute respiratory distress syndrome (ARDS)², and four subsequent reports⁹⁻¹² on the histological examination of the lungs of in total seven patients with SARS-CoV-2 indeed showed signs compatible with ARDS. These included bilateral acute changes with diffuse alveolar damage (DAD) with vascular congestion, intra-alveolar edema, hemorrhage, proteinaceous exudate, macrophages, denudation and reactive hyperplasia of pneumocytes, patchy inflammatory cellular infiltration, and multinucleated giant cells, but hyaline membrane formation was not prominent. The infiltrate consisted of lymphocytes (mostly CD4-positive), eosinophils and neutrophils. Hyaline thrombi were found in microvessels. We have recently also observed similar changes in COVID-19 autopsy cases, with evidence of extensive microvascular damage and thrombotic occlusion as the foremost pattern of injury, resulting in intra-alveolar fibrinous exudates akin to acute fibrinous and organizing pneumonia (AFOP) (Fig.1). This spectrum of abnormalities is highly reminiscent of changes seen in the context of the chronic lung allograft rejection (CLAD) of the restrictive phenotype (restrictive allograft syndrome (RAS)), which we have recently described, and which is presumed to occur secondary to antibody-mediated endothelial damage and complement activation of humoral rejection episodes¹³. Such vascular changes are likely to play a central role in the pathogenesis of COVID-19, and may in part be attributable to dysregulation of the endothelial ACE2 receptor with ensuing bradykinin-dependent local lung edema¹⁴, as well as a highly pro-thrombotic state, which can manifest itself in the lung as well as in extra-pulmonary tissues¹⁵. Direct

infection of endothelial cells may play a central role in this process¹⁶. More chronic changes included intra-alveolar organization with fibroblastic proliferation and diffuse fibrotic thickening of alveolar walls, consisting of proliferating interstitial fibroblasts. In RAS, we have found this to eventually result in chronic fibrotic patterns of intra-alveolar fibroelastosis and non-specific interstitial pneumonia (NSIP)¹³. Time will tell if a similar progression to fibrosis will take place in a subset of survivors of severe COVID-19, and whether this is indeed secondary to vascular damage, primarily related to the initial epithelial infection, or a combination of these response patterns (Fig. 2). Apart from the prominent microvascular changes, the pathological features of COVID-19 thereby appear to resemble those seen in SARS and Middle Eastern respiratory syndrome (MERS) coronavirus infection¹⁷⁻¹⁹. Thus, early SARS-CoV infections were found to be typified by acute diffuse alveolar damage, and late stages by a combination of diffuse alveolar damage and acute fibrinous and organizing pneumonia. MERS-CoV infections also showed exudative diffuse alveolar damage with hyaline membranes, pulmonary edema, type II pneumocyte hyperplasia, (lymphocytic) interstitial pneumonia, and multinucleated syncytial cells.

Bedside observations and future guidance in COVID-19 : translation from histopathology

Poor oxygenation requiring ventilation and oxygen administration in influenza as well as coronavirus infection is likely to be in part directly related to decreased diffusion capacity due to parenchymal destruction as well as increased diffusion distances due to 1) intra-alveolar aggregates of edema, fibrin, hyaline membranes, cells and organization, 2) widening of alveolar septa due to edema and inflammation, 3) vascular changes with capillary congestion and thrombosis and 4) eventually, intrabronchiolar, intra-alveolar and interstitial fibrosis. While regeneration and reversal of the first 3 phenomena is theoretically possible, and as in influenza may be related to the regenerative capacity of the host, it may occur at lower rates in SARS-CoV-2 infection as compared to other viral pneumonias. Intra-alveolar and interstitial fibrosis, however, are most likely irreversible, and may have contributed to the remarkably high number of patients who cannot be weaned off ventilation in the current COVID-19 outbreak. Also, in survivors we may eventually see a significant number of cases with irreversible fibrotic lung damage and limited pulmonary function, which has previously been termed COLD ('Corona Obstructive Lung Disease'). To which extent this term truly reflects the underlying physiology remains to be seen, as the interstitial fibrotic changes which have thus far been observed are likely to also lead to a restrictive lung defect as well as permanently decreased diffusion capacity, and are thus more akin to other types of (idiopathic) interstitial lung fibrosis, such as forms of the abovementioned intra-

alveolar fibroelastosis and fibrotic NSIP, and could therefore perhaps be more accurately termed *Corona-Associated Lung Disease* ('CALD'). This will require multi-center studies which correlate histopathological findings with clinical and radiological data.

Genetics in COVID-19

A sudden demise in COVID-19 may be related to a cytokine storm, which can be an important component of ARDS, multiple organ failure and eventual death in SARS-CoV-2, SARS-CoV and MERS-CoV infections⁹, and is reflected by the release of large amounts of pro-inflammatory cytokines (incl. IFN- α , IFN- γ , IL-1 β , IL-6, IL-12, IL-18, IL-33, TNF- α , TGF β) and chemokines (incl. CCL2, CCL3, CCL5, CXCL8, CXCL9, CXCL10, etc.) by immune effector cells¹². In the case of influenza, hypercytokinemia has been found to be correlated with the occurrence of hemophagocytosis, which was observed to a varying degree in cases of influenza pneumonia. Whether a similar mechanism is at play in COVID-19 has yet to be resolved from hematological, immunological and histopathological assessment. In general, however, an overly active inflammatory response is likely to contribute to tissue damage and systemic effects in COVID-19, and this may be related to genetically determined differences in inherent individual immune response mechanisms as well as being subject to the influence of concomitant diseases. Thus, previous research shows that numerous HLA polymorphisms correlate with the susceptibility of SARS-CoV and MERS-CoV infection, and gene polymorphisms of MBL (mannose-binding lectin) associated with antigen presentation have also been linked to the risk of SARS-CoV infection²⁰. Also, the single-nucleotide polymorphism rs12252-C/C in the gene IFITM3 (which encodes interferon-induced transmembrane protein 3) has been demonstrated to be a risk factor for severe influenza, and has also been found in a patient with COVID-19²¹. Genetics may also play a role through polymorphisms of genes which encode for 1) proteins that are exploited by SARS-CoV-2, such as the highly conserved Angiotensin Converting Enzyme 2 (ACE2), which, as was also the case for SARS-CoV, it uses for docking and cellular entry in respiratory cells, or 2) proteins which provide protection against the effects of the virus (such as surfactant proteins, but also ACE2 itself)²². Genetic association studies are currently ongoing to unravel such hypotheses, and have found correlations between ACE2 variants and COVID-19 susceptibility^{23,24}. Interestingly, as an X-linked phenotype, the effectiveness of interaction-booster and interaction-inhibitor variants of ACE2 can be more definite in males than females, and could contribute towards a higher mortality rate in males, accounting for up to ~70% of death caused by SARS-CoV2, SARS-CoV or MERS-CoV²⁵, in addition to a likely higher rate of risk factors (e.g. smoking) and a possibly different

immune response in males. Other entry mechanisms may also play a role, such as transmembrane protease serine 2 (TMPRSS2), and TMPRSS2 variants and expression have indeed been linked to differences in COVID-19 severity²⁶. Susceptibility to the development of post-COVID-19 pulmonary fibrosis could also have a genetic component, as variants in numerous genes or their promoters (such as MUC5B and TERT) have been found to predispose to lung fibrosis, both in the context of idiopathic pulmonary fibrosis and in interstitial fibrosis related to hypersensitivity pneumonitis and collagen vascular disease²⁷⁻³⁰.

Underlying disease in COVID-19

ACE2 could also be pivotal in the particular susceptibility of diabetic and hypertensive patients for fulminant COVID-19. While diabetic patients are known to have impaired immune responses, diabetes (as well as hypertension) are associated with activation of the renin-angiotensin system in different tissues, and are often treated with ACE inhibitors and angiotensin receptor blockers (ARBs), which can lead to increased expression of ACE2, thereby potentially facilitating viral uptake. Similarly, in MERS, dipeptidyl peptidase 4 (DPP4) inhibition in diabetic patients could have potentiated entry of the virus MERS-CoV, which uses DPP4 as its receptor³¹. Discontinuation of ARBs would be premature at this stage, however, as ACE2 is also likely to protect against the effects of SARS-CoV-2 infection³²⁻³⁴. Obesity is a further important risk factor for mortality following COVID-19, and may be related to the fact that the majority of those with obesity also have impaired lung function and underlying diseases, such as chronic lung disease, including asthma, cardiac problems, or diabetes, which are risk factors on their own for survival following ICU admission, but also for mortality in COVID-19, in which multi-organ failure is a common occurrence and good baseline cardiorespiratory function of crucial benefit³⁵.

Conclusion

In summary, despite the relatively recent outbreak of the COVID-19 pandemic, an impressive body of preliminary evidence has already been accumulated which points to a remarkable heterogeneity of disease patterns from a clinical, radiological, and histopathological point of view. This has identified broad risk groups, but sometimes also idiosyncratic responses of individual patients in these groups are seen. These may be in part related to underlying genetic variations, which contribute to differences in outcome in the short term, but possibly also affect the extent of residual pulmonary damage following survival of the acute phase of the disease. More research is required to expand and confirm these associations, in order to enable adequate prevention, prognosis, follow-up and possibly treatment in at-risk populations.

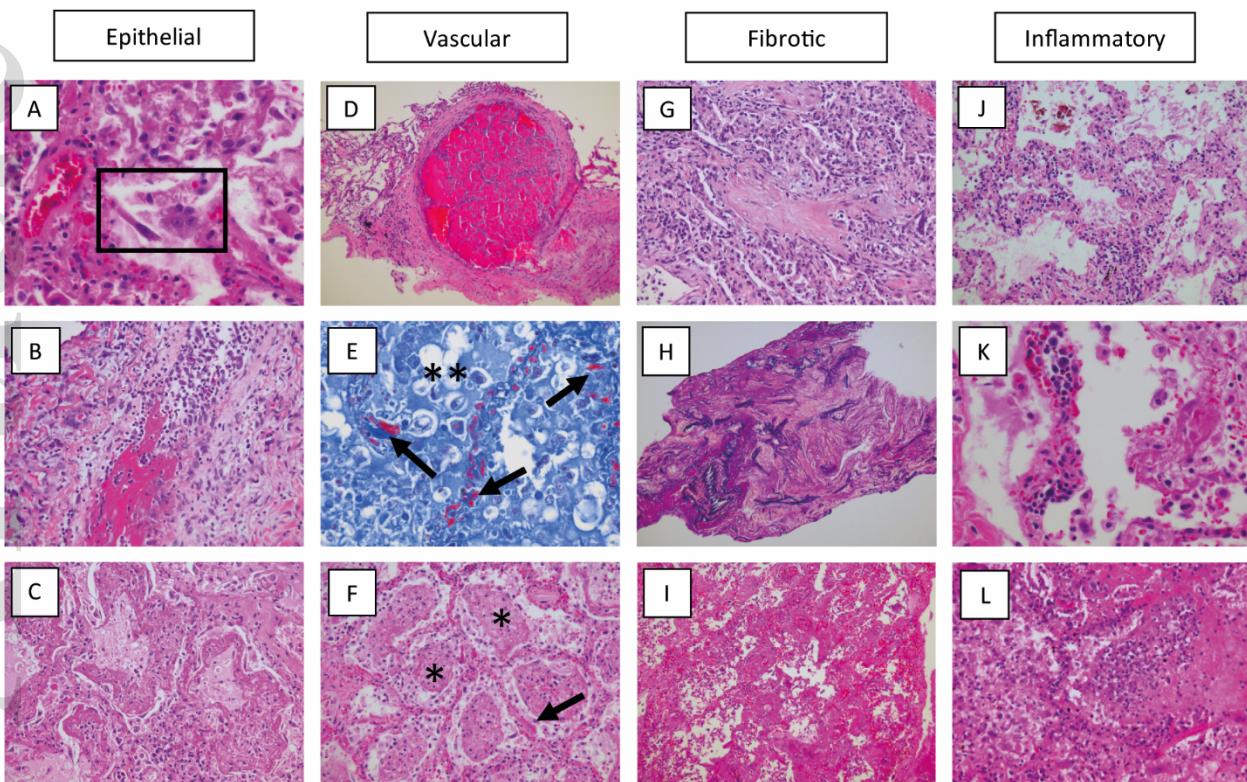


FIGURE 1: Spectrum of tissue response patterns in COVID-19 pneumonia.

In the lung tissue of patients who died of respiratory failure due to COVID19 pneumonia, there can be evidence of epithelial infection with cytopathic effects of pneumocytes (A, box); denudation of bronchiolar epithelium (B), and evidence of diffuse alveolar damage (DAD) with hyaline membrane formation with organization (C). Observed vascular changes include extensive bilateral and diffuse (micro)vascular damage and its sequelae, with arterial thrombosis with organization (D), microvascular fibrinoid change with hyaline thrombi (E, fibrin-Lendrum (MSB) stain, arrows) and edema (**), and extensive intra-alveolar fibrinous aggregates (F) with an acute fibrinous and organizing pneumonia (AFOP) pattern (F, *). Fibrotic changes vary in appearance and include organizing pneumonia with progression to fibrosis (G), intra-alveolar fibro-elastosis (Elastic-van Gieson, H) and fibrotic non-specific interstitial pneumonia (F-NSIP; I). There is often relatively sparse interstitial chronic inflammation with an acute interstitial pneumonia pattern (AIP; J), foci of lymphocytic vasculitis (K) and acute inflammation, especially in relation to areas of necrosis and possible secondary infection (L).

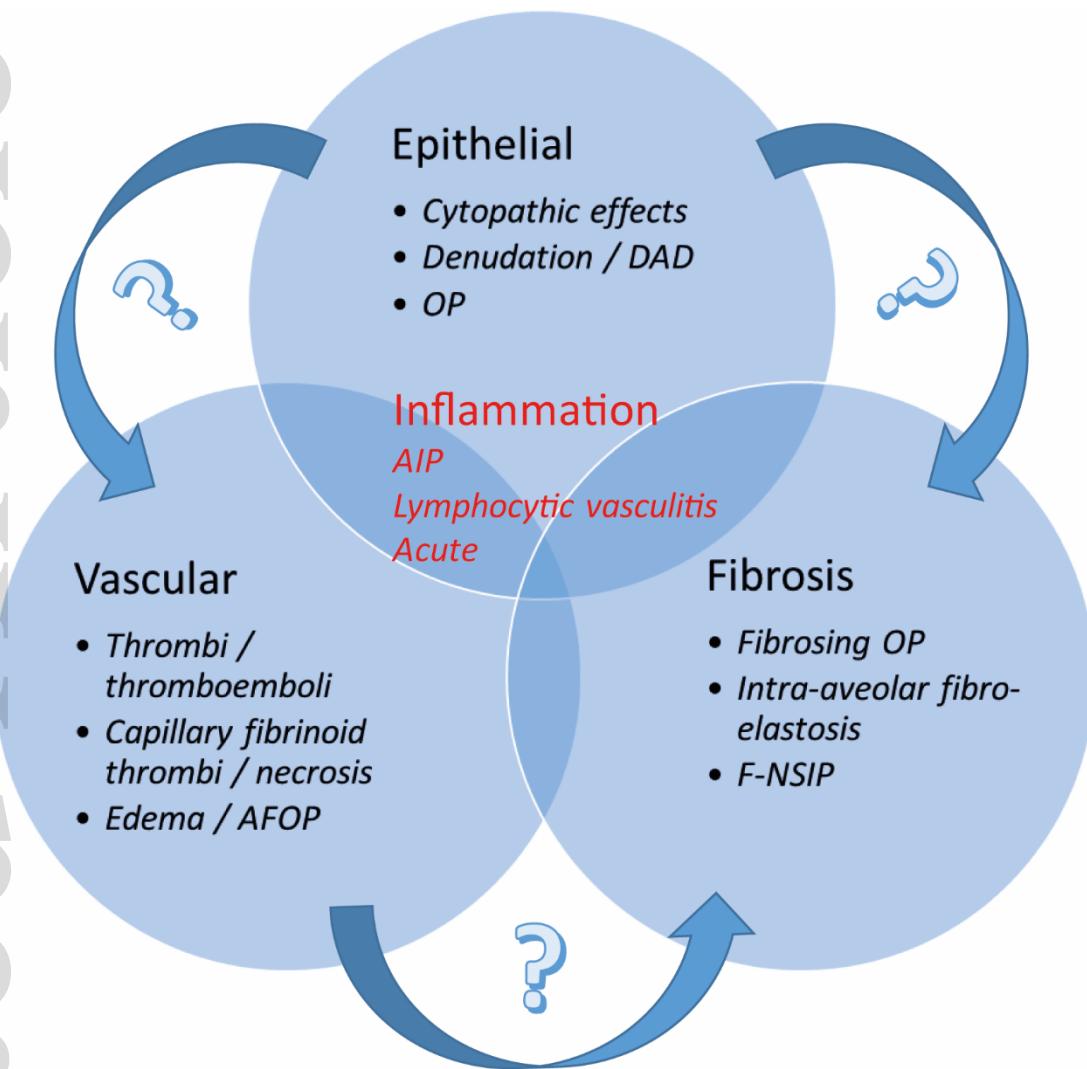


FIGURE 2: Co-occurrence and potential progression of tissue response patterns in COVID-19 pneumonia.

DAD=diffuse alveolar damage; OP=organizing pneumonia; AFOP=acute fibrinous and organizing pneumonia;
F-NSIP=fibrotic non-specific interstitial pneumonia; AIP=acute interstitial pneumonia

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