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REVIEW ARTICLE

A systematic review of pathological findings in COVID-19: a pathophysiological timeline and possible mechanisms of disease progression

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Abstract

Since the outbreak of the COVID-19 pandemic, much has been learned regarding its clinical course, prognostic inflammatory markers, disease complications, and mechanical ventilation strategy. Clinically, three stages have been identified based on viral infection, pulmonary involvement with inflammation, and fibrosis. Moreover, low and high elastance phenotypes can be distinguished in mechanically ventilated patients, based on lung mechanics, ventilation-to-perfusion ratio, and CT scans; these two phenotypes have presumed differences in their underlying pathophysiology. Although essential for therapeutic guidance, the pathophysiology of COVID-19 is poorly understood. Here, we systematically reviewed published case reports and case series in order to increase our understanding of COVID-19 pathophysiology by constructing a timeline and correlating histopathological findings with clinical stages of COVID-19. Using PRISMA-IPD guidelines, 42 articles reporting 198 individual cases were included in our analysis. In lung samples ($n = 131$ cases), we identified three main histological patterns: epithelial ($n = 110$, 85%), with reactive epithelial changes and DAD; vascular ($n = 76$, 59%) with microvascular damage, (micro)thrombi, and acute fibrinous and organizing pneumonia; and fibrotic ($n = 28$, 22%) with interstitial fibrosis. The epithelial and vascular patterns can present in all stages of symptomatic COVID-19, whereas the fibrotic pattern presents starting at ~3 weeks. Moreover, patients can present with more than one pattern, either simultaneously or consecutively. These findings are consistent with knowledge regarding clinical patterns of viral infection, development of hyperinflammation and hypercoagulability, and fibrosis. Close collaboration among medical staff is necessary in order to translate this knowledge and classification of pathophysiological mechanisms into clinical stages of disease in individual patients. Moreover, further research, including histopathological studies, is warranted in order to develop reliable, clinically relevant biomarkers by correlating these pathological findings with laboratory results and radiological findings, thus, increasing our understanding of COVID-19 and facilitating the move to precision medicine for treating patients.

Introduction

In December 2019, an outbreak of COVID-19—the disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus—occurred in Wuhan, China, rapidly leading to a global pandemic [1]. As the disease spreads, new information is emerging regarding the clinical course [2].

COVID-19 has three consecutive stages of increasing severity [3]. The early stage is characterized by infection with SARS-CoV-2. In this phase, flu-like symptoms can develop, mainly due to the viral infection itself. Subsequently, patients can develop viral pneumonia, requiring hospitalization, or even mechanical ventilation. The second stage is also characterized by pulmonary inflammation and coagulopathy, which can develop consecutively but often

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overlap. In addition, increased levels of inflammatory biomarkers such as C-reactive protein (CRP), ferritin, IL-6, IL-1, and D-dimer are associated with the development of acute respiratory distress syndrome (ARDS) and an unfavorable clinical course [3, 4]. Finally, the third stage of the disease is characterized by fibrosis. With respect to patients who require mechanical ventilation, two respiratory phenotypes—the low (L) elastance type and the high (H) elastance type—can be differentiated. In the H-type, increased pulmonary edema leads to high lung weight and decreased lung compliance (high elastance). Moreover, as gas exchange is impaired, a significant fraction of cardiac output perfuses nonaerated lung tissue, leading to high right-to-left shunting (high ventilation to perfusion, V/Q, ratio). The final characteristic of the H-type is high recruitability: the high amount of nonaerated lung tissue can be recruited for gas exchange by applying positive end-expiratory pressure. The L-type is characterized by the opposite: (nearly) normal lung weight (only ground-glass densities on CT), low elastance (highly compliant lungs with nearly normal gas volumes), low V/Q-ratio due to loss of perfusion regulation and hypoxic vasoconstriction, and low lung recruitability as the amount of nonaerated lung tissue is low [5]. The underlying pathophysiological mechanisms are believed to differ significantly between the low and high respiratory phenotypes, thus, requiring different treatments and having different outcomes.

The pathophysiological mechanisms that underlie these two respiratory phenotypes are poorly understood. Since the first guidelines for autopsy on both confirmed and suspected COVID-19–positive patients were published in February 2020 [6, 7], an increasing number of biopsies and autopsies have been performed. However, our knowledge regarding the precise nature of the immunological defense in various organ systems in response to viral infection, as well as the response patterns in specific tissues, is largely incomplete but is essential in order to initiate timely and targeted antiviral, anti-inflammatory, anticoagulative, or even antifibrotic therapy.

Here, we systematically reviewed published case reports and case series reporting pathological findings in COVID-19 patients in order to establish a timeline to correlate histopathological findings with various clinical stages of COVID-19. These results will improve our understanding of the pathophysiological pathways involved in various disease stages, thereby facilitating the application of targeted therapies.

Materials and methods

Eligibility

We conducted a systematic review of original articles in accordance with the PRISMA-IPD (Preferred Reporting Items for a Systematic Review and Meta-analysis of Individual Participant Data) guidelines [8]. We considered all papers that reported macroscopic and/or microscopic (i.e., histopathological) data in patients diagnosed either antemortem or postmortem with COVID-19. Given the limited number of publications regarding this subject, no search restrictions were applied with respect to study design, number of cases reported, patient age, therapy, or cause of death. Moreover, no language restrictions were applied; where needed, a native speaker was contacted for translating articles written in Chinese.

Search

A comprehensive, systematic search was conducted on April 22, 2020 for published articles in the following databases: PubMed, the WHO COVID-19 database, BioArxiv, MedArxiv, MEDLINE (via OVID), PubMed Central, Google Scholar, Embase, Web of Science, Cochrane, Academic Search Premier, Emcare, and ScienceDirect. The search strategies used for each database are summarized in Supplementary Table S1. In addition, we searched the references in the included studies and excluded reviews in order to identify additional primary studies. Given the rapid pace of developments in the field, we attempted to include literature published right up until the time of submission.

Article selection

Suitable articles were selected in two stages. First, the title and abstract of each article was screened independently by two authors (SBP, ICvG, and/or JvP). If there was consensus that an article was not suitable for inclusion based on the title and/or abstract, the article was excluded. Next, the full-text articles were screened independently by two authors (SBP, ICvG, and/or JvP) and included if both authors agreed; if needed, the article was discussed with a third author until consensus was reached. The authors were not blinded with respect to the article's authors or the journal in which it was published.

Quality analysis

We also performed a quality analysis of the included articles. Because only case reports and case series were published by April 22, 2020, we did not expect to include studies with conventional high levels of evidence [9]. Therefore, the following criteria were used: (i) reporting of clinical data per case, (ii) reporting of microscopic evaluation per case, and (iii) reporting of macroscopic evaluation per case. Articles that met all three criteria were considered to be high quality. Articles that lacked macroscopic data were considered to be of moderate quality, and articles that

lacked clinical data or microscopic data were considered to be low quality.

Data extraction and data items

Two authors (SBP and ICvG) extracted the following predefined clinical and demographic data for each patient: gender, age, medical history, onset of symptoms, and clinical course (including the time between the onset of symptoms and tissue collection). In addition, we extracted macroscopic and microscopic pathological data, immunohistochemistry/immunofluorescence data, and the results of any additional experiments such as RT-PCR for detecting SARS-CoV-2.

Data analysis and reporting

Data were sorted per organ system and are presented as a narrative with descriptive statistics. For the respiratory system, clinical data and microscopic findings were merged to create a timeline in order to track changes in pathological findings over time. To facilitate this process, using the histological descriptions provided in the articles each case was scored by two experienced pulmonary pathologists (authors JHvdT and DC) who were blinded with respect to the patient's clinical characteristics. The following three primary histological patterns of lung injury were determined: (1) an epithelial pattern, characterized by diffuse alveolar damage (DAD) with varying degrees of organization, denudation, and hyperplasia of pneumocytes, as well as possible (viral) cytopathic changes; (2) a vascular pattern, characterized by diffuse intra-alveolar fibrin and/or the presence of microvascular (fibrin) thrombi; and (3) a fibrotic pattern, including fibrotic DAD and/or interstitial fibrosis. These three patterns were based on previous reports [10–12]. Moreover, within the vascular pattern, acute fibrinoid organizing pneumonia was recognized by intra-alveolar fibrin and/or fibrin balls filling adjacent alveolar structures, without a peripheral predominance or hyaline membranes, and with frequently intact epithelial lining, but with evidence of microvascular damage and varying amounts of organization in line with previous literature [11]. We dissected the pathological descriptions into these patterns, rather than using DAD (acute, organizing, and fibrotic) as an umbrella term, to provide more pathophysiological insight for treating physicians. Moreover, dissecting these patterns provides the opportunity to investigate whether they occur consecutively or simultaneously. In the event that time between the onset of symptoms and tissue collection, and/or pulmonary histopathological data per case could not be extracted from the article and could not be obtained from the authors, the results are mentioned only in the narrative report and are not included in the timeline.

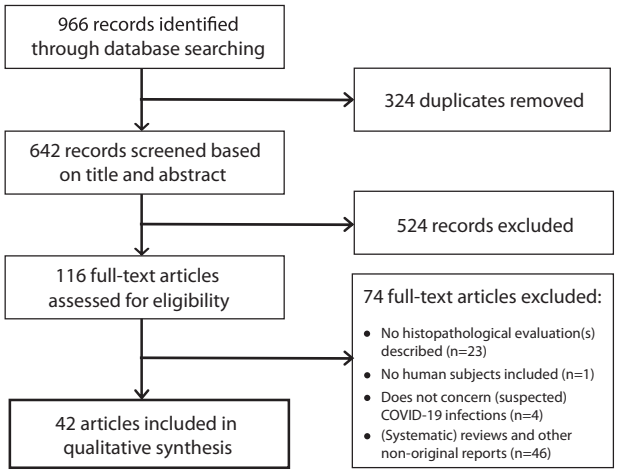

Fig. 1 Flow chart depicting the search strategy.

The study did not require approval from the local ethics committees.

Results

Literature search

The search strategy is depicted in Fig. 1. Our search of 13 scientific databases for articles published by April 22, 2020 (plus eleven additional articles published after this date, identified while writing the manuscript) yielded 642 unique records. After screening the titles and abstracts for eligibility, 116 potentially relevant full-text articles were screened, 74 of which were excluded. No additional articles were retrieved after screening the references in the included articles and excluded reviews. Thus, a total of 42 case reports and case series were included in our systematic review [11–52].

Quality analysis

The articles included in our review consisted solely of case reports and case series, ten of which (24%) were determined to be of high quality by our quality analysis (Supplementary Table S2) [12, 13, 18, 19, 29, 34, 35, 47, 49, 52]. Twenty-four articles (57%) were assessed as having moderate quality due to their lack of macroscopic evaluations per case [14, 16, 21–23, 25–28, 30–32, 36–43, 45, 46, 48, 51]. Finally, eight articles (19%) were determined to be of low quality [11, 15, 17, 20, 24, 33, 44, 50]. In 21 of the 42 articles (50%), we were able to extract time between the onset of symptoms and tissue collection and lung histopathological evaluations for individual patients; these 21 articles were therefore included in the timeline synthesis [11–13, 15, 18, 22, 26, 29, 30, 34, 35, 38–40, 42, 43, 45, 47, 48, 51, 52].

Clinical characteristics

The 42 articles described a total of 198 patients with COVID-19 ($n = 43$ full autopsy, $n = 91$ partial autopsy; $n = 4$ antemortem pneumonectomy; $n = 13$ antemortem partial lung resections; $n = 3$ placenta; $n = 1$ small intestine resection; $n = 15$ antemortem biopsy, $n = 28$ postmortem biopsy). COVID-19 was diagnosed in 183 cases (92%) by nucleic acid testing; for the other patients the diagnostic modality is not described [11, 18, 23, 29, 34, 40]. The clinical characteristics of all included patients are summarized in Supplementary Table S3. Among the 168 patients for whom gender was reported, 124 (74%) were male. Among the 120 patients for whom age was reported, the median age was 67.5 years (range: 6 months to 96 years). The most commonly reported co-morbidity was hypertension (75 out of 153 cases, 49.0%), followed by cardiovascular disease (44 out of 153 cases, 28.8%), diabetes (38 out of 153 cases, 24.8%), and past or current malignancy (31 out of 153 cases, 20.3%; 15 of these cases had lung cancer). In 43 patients tested, 8 (19%) were diagnosed with a comorbid infection with various pathogens [14, 15, 17, 37, 38]. Treatment for COVID-19 varied; 38 (19.2%) were mechanically ventilated [12, 13, 15, 16, 18, 24, 26, 29, 30, 37–41, 45, 49].

Laboratory results

The laboratory results were reported a median of 6 days after the onset of symptoms. Individual laboratory results are summarized in Supplementary Table S3 [12, 16, 18, 19, 24–27, 31–33, 36–40, 48, 49, 51, 52]. Of the 57 cases for whom lymphocyte counts were reported, 46 cases (81%) and 10 cases (18%) had lymphocytopenia and a normal lymphocyte count, respectively [16, 18, 19, 24, 26, 33, 36, 38, 39, 48, 50–52]. CRP was reported in 26 cases. The majority of these cases were measured within the first three days of illness, and CRP levels were elevated (defined as ≥10 mg/L) in all 26 cases (median: 98 mg/L); specifically, CRP levels were 10–50, 51–100, and >100 mg/L in 7, 6, and 13 cases, respectively [16, 19, 25, 26, 37, 40, 49]. Finally, D-dimer levels were elevated (>0.50 µg/mL) in 45 out of 46 cases (98%);[12, 16, 18, 24, 26, 27, 36, 40, 49, 52] in 13 of these 45 cases (29%), D-dimer levels were higher than 5.0 µg/mL, which is more than ten times the upper limit of normal [12, 16, 36, 40, 49, 52] Other relevant markers such as ferritin, IL-6, IL-1, cardiac enzymes, and coagulation tests were described in too few cases (<10 cases) to draw any meaningful conclusions.

Radiology findings

Radiological assessment (chest CT scan or chest X-ray) was reported for 87 cases, frequently revealing pulmonary ground-glass opacities ($n = 59$ cases, 68%) and pulmonary consolidations ($n = 34$ cases, 39%) [12, 13, 15, 18, 19, 22, 24, 26, 29, 31–35, 37–41, 43–49, 51, 52]. No further details were provided with respect to COVID-19 Reporting and Data System score and the percentage of affected lung tissue. No CT scans with evidence of pulmonary embolism were reported.

Pathological findings per organ system

Lung pathology

Gross examination of the lungs was described for 92 patients and is summarized in Supplementary Table S4 [12, 13, 15, 17, 18, 24, 29, 33–35, 47, 49, 52]. The main findings reported included: increased lung weight in 82 cases (88%);[13, 15, 17, 24, 29, 33, 35, 47, 49] diffusely congested and edematous parenchyma in 76 cases (83%); [12, 13, 15, 17, 18, 24, 34, 47] hemorrhagic changes in 20 cases (22%) [12, 13, 15, 18, 24, 33, 34, 44, 47–49], 3 of whom had partial hemorrhagic necrosis;[18, 34] and macroscopic pulmonary emboli in 9 cases (10%) [15, 47, 49].

Pulmonary histopathology was reported for a total of 129 cases; the main findings are summarized in Table 1, and individual patient data are presented in Supplementary Table S4 [11–13, 15–18, 22, 24, 26, 29, 30, 34, 35, 38–40, 42–45, 47–49, 51, 52]. Using the histological descriptions provided in the articles, all 129 cases were blindly scored for the presence or absence of epithelial, vascular, and/or fibrotic patterns of lung injury (Fig. 2a**;** Supplementary Figures S1–S3). A total of 110 cases (85%) had an epithelial pattern of lung injury. In cases with an interstitial inflammatory infiltrate, this infiltrate consisted predominantly of lymphocytes and/or plasma cells in 27 out of 27 cases for which the cell type was reported; [11, 13, 16, 17, 24, 30, 34, 42, 47, 48, 51, 52] in contrast, the cells identified in the intra-alveolar cavity primarily consisted of macrophages (in 32 out of 36 cases) [12, 13, 16, 17, 29, 30, 38, 39, 42, 44, 48, 51, 52]. A total of 76 out of 129 cases (59%) had a vascular pattern of lung injury, with features of vasculopathy that included microthrombi and proteinaceous and fibrinous exudates. Microthrombi were not consistently linked to intra-alveolar fibrin: in only 8 cases intra-alveolar fibrin and microthrombi co-occurred, while in 24 other cases microthrombi were present without intra-alveolar fibrin, and in 7 intra-alveolar fibrin was present in the absence of microthrombi. Finally, a total of 28 patients (22%) had a fibrotic pattern of lung injury, typified by interstitial fibrosis. Of the 78 cases for which individual patient data were available and classification was possible, 47 cases (60%) had two or more histological patterns (Fig. 2b), with the highest degree of overlap between the epithelial and vascular patterns (in 32 cases). The presence of fibrosis (occurring separately or in

Table 1 Overview of pulmonary pathology findings ($n = 129$).

Pathological characteristic	Number of cases (%)
Epithelial	110 (85%)
Diffuse alveolar damage and/or hyaline membranes	97 (75%)
Desquamation and/or reactive hyperplasia of pneumocytes	93 (72%)
Squamous metaplasia of alveolar epithelium	25 (19%)
Multinucleated giant cells	26 (20%)
Viral cytopathic changes, particles and/or inclusion bodies	26 (20%)
Intra-alveolar fibrous plugs	2 (2%)
Vascular	76 (59%)
Capillary congestion	58 (45%)
(Micro)thrombi	50 (39%)
Alveolar hemorrhage	42 (33%)
Alveolar proteinosis	31 (24%)
Intra-alveolar fibrinous exudates and/or fibrin deposition (features of acute fibrinous and organizing pneumonia)	34 (26%)
Capillary changes (i.e., proliferation or thickening, fibrin deposition, and endothelial cell detachment or - cell death)	32 (25%)
Peri- or intravascular inflammatory infiltrate	12 (9%)
Fibrotic	28 (22%)
Interstitial fibrous changes (i.e., fibroblast hyperplasia, fibrosis, septal collagen deposition)	43 (33%)
Microcystic honeycombing	9 (7%)
Other	
Interstitial and/or intra-alveolar inflammatory infiltrate	82 (64%)
Interstitial and intra-alveolar edema	59 (46%)

combination with epithelial and/or vascular injury) was not associated with mechanical ventilation: 5/23 (22%) patients who received mechanical ventilation showed fibrosis, compared with 3/15 (20%) patients who did not receive mechanical ventilation. Steroid use was too low (11 out of 69 cases) to correlate to the histological pattern of lung injury.

To investigate whether the presence of these histological patterns is characteristic of certain clinical phases of COVID-19, we examined the correlation between the clinical duration and the histological patterns. The number of days between the onset of symptoms and biopsy/autopsy was reported for 45 cases and could be approximated with reasonable accuracy for an additional 20 cases; the results of these 65 cases are presented in Fig. 3. Our analysis revealed that the epithelial pattern of lung injury occurs early, in some cases even before the onset of symptoms, and can persist throughout the clinical course, gradually declining by 28 days after the onset of symptoms. Similarly, the vascular pattern can occur early after the onset of symptoms. Finally, the fibrotic pattern of lung injury was observed primarily three weeks from the onset of symptoms. Thus, the three histological patterns can be present at different times but can also be present simultaneously. Interestingly, seven cases had a fibrotic pattern of lung injury prior to the onset of symptoms ($n = 4$ cases; 30, 38, 42, 48), or in the first two weeks of the disease course ($n =$ 3 cases, 22, 49); the pulmonary fibrosis identified in these seven cases is therefore unlikely to reflect COVID-19–associated lung disease.

The presence of SARS-CoV-2 in the lungs was confirmed in several articles using either immunohistochemistry for various spike and nucleocapsid proteins [12, 44, 45] or RT-PCR analysis [15, 30, 39, 44, 47, 49, 51, 52]. Moreover, viral inclusions were detected by light microscopy in eight cases [24, 34, 38, 48, 52], supported by other techniques, such as immunohistochemistry.

Cardiovascular pathology

Gross examination of the heart was performed in 51 cases (Supplementary Table S5) [13, 15, 24, 33, 35, 47, 49]. Aside from mild pericardial edema [33] and some serosanguinous pericardial effusion [24] reported in one case each, no notable abnormalities other than findings expected based on pre-existing conditions such as coronary heart disease ($n = 29$ cases) were found [15, 35, 47, 49]. Microscopic analyses of cardiac tissue were performed in 49 cases and revealed that aside from pre-existing pathology such as myocardial hypertrophy, atherosclerosis, and general interstitial fibrosis [13, 15, 24, 35, 37, 39, 40, 43, 44], five cases had mild myocardial edema [39, 44] and one case [39] had atypical (specifically minimal, focal, perivascular) interstitial fibrosis (Supplementary Table S5). Furthermore, a low-grade interstitial infiltration of mononuclear cells was present in nine cases [15, 24, 37, 43, 44], whereas signs of lymphocytic myocarditis were reported in two cases [15, 49]. Two cases had endotheliitis [40], but no cases of thrombosis in the cardiac vasculature were reported.

Of the 31 cases examined for the presence of SARS-CoV-2 in the heart using electron microscopy, immunohistochemistry, or RT-PCR, one heart contained viral particles in damaged interstitial cells visible by electron microscopy [37], six hearts tested positive using RT-PCR analysis [39, 49].

Hepatobiliary pathology

Gross examination of the liver was reported in 44 cases (Supplementary Table S6) [13, 15, 39, 47, 49], revealing signs of a pre-existing liver disorder in 18 cases ($n =$ 14 steatosis, and $n = 4$ cirrhosis) [13, 39, 47], and hepatic congestion in 16 cases [15, 47, 49]. Microscopic findings of

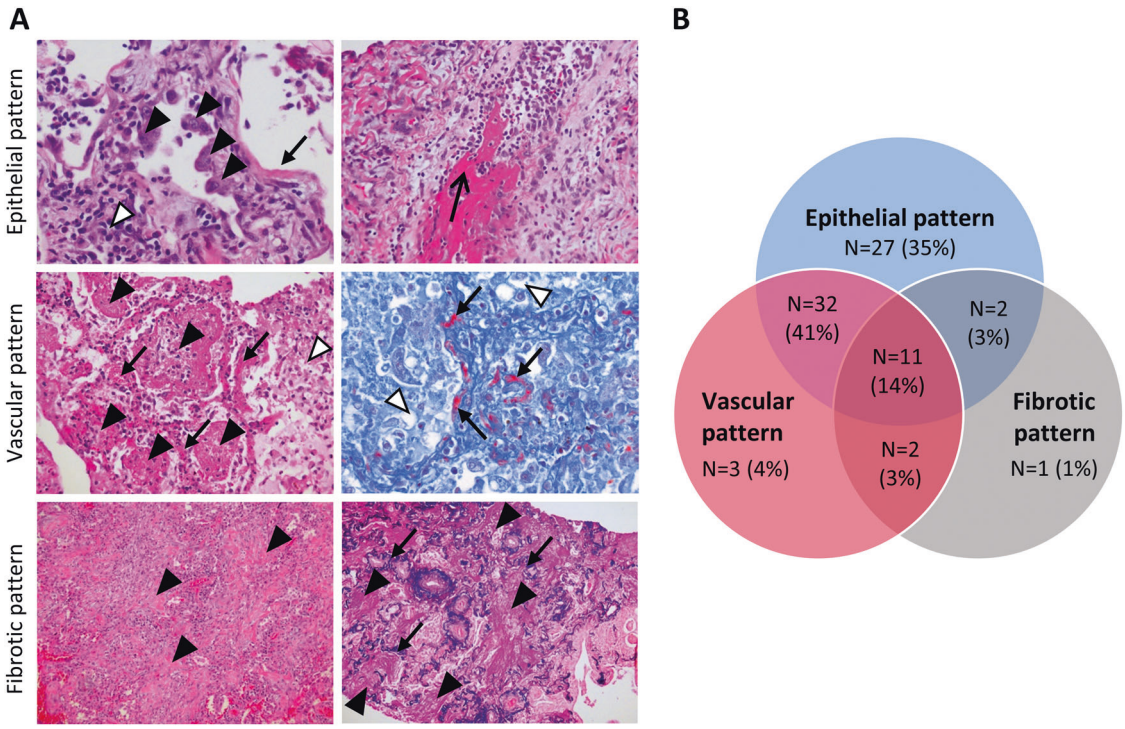

Fig. 2 Summary of cases with the epithelial, vascular, and/or fibrotic pattern of lung injury. a Example images of lung sections showing the epithelial (top; hematoxylin and eosin stains), vascular (middle; left hematoxylin and eosin stain, right fibrin-Lendrum (MSB) stain), and fibrotic (bottom; left hematoxylin and eosin stain, right Verhoeff-van Gieson stain) pattern of lung injury in COVID-19. In the top panels, atypia and detachment of type II pneumocytes (closed arrowheads), hyaline membrane formation (closed arrow), an interstitial inflammatory response (open arrowhead), and denudation of bronchiolar epithelium (open arrow) are indicated. In the middle panels, intracapillary hyaline thrombi (arrows), acute fibrinous and organizing pneumonia (closed arrowheads), and edema (open arrowhead) are indicated. In the bottom panels, notable intra-alveolar fibroelastosis (closed arrowheads) with pre-existing alveolar septal elastin (arrows) are indicated, possibly representing fibrosing organizing pneumonia. Images were obtained from autopsies of COVID-19 patients performed at the Erasmus Medical Center. For low power images, see Supplementary Figures S1–S3. **b** Venn diagram summarizing the histological patterns of lung injury in 78 COVID-19 patients.

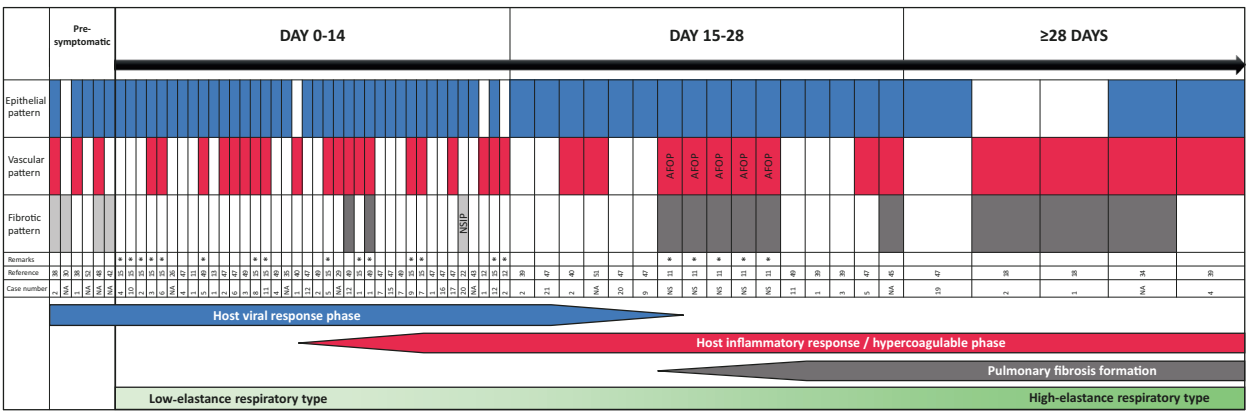

Fig. 3 Timeline correlating the epithelial, vascular, and fibrotic patterns of lung injury with the duration of COVID-19 symptoms. Shown are the identified histological pulmonary patterns (epithelial, vascular, and fibrotic) for 65 individual cases; each case is shown in a single column. Cases are organized chronologically in four time periods: the number of days since the onset of symptoms of COVID-19 symptoms is indicated. For the fibrotic pattern, cases shaded in light gray are cases in which fibrotic changes were likely pre-existing and were not associated with COVID-19, and cases shaded in dark gray indicate fibrotic changes. For cases indicated with an asterisk (*), the duration of the clinical course was estimated from a report with aggregated pathological findings. Shown below the timeline is the approximate occurrence of COVID-19 clinical phases, color-coded based on the three patterns of histological pulmonary changes, and the transition from L- to H-respiratory phenotypes [5]. In pre-symptomatic patients, tissue was obtained antemortem before the onset of COVID-19 symptoms. Other antemortem samples are: reference [18, 22] (cases 1 and 2), and 33; the other samples are obtained at autopsy. AFOP acute fibrinous and organizing pneumonia, NSIP nonspecific interstitial pneumonia, NA not applicable, NS not specified.

the hepatobiliary tract were reported in a total of 41 cases [15, 31, 35, 39, 40, 43, 44, 47, 49, 51]. In 40 cases, the main findings were mild steatosis, patchy hepatic necrosis, Kupffer cell hyperplasia, and mild zone 3 sinusoidal dilatation [15, 35, 39, 40, 43, 44]. Lagana et al. [31] reported a 6-month-old infant who tested positive for COVID-19 after undergoing a liver transplantation; liver biopsy showed a moderate, acute hepatitic pattern of injury in addition to the routine findings attributed to acute cellular rejection. In 6 of these 41 cases (15%), the number of inflammatory cells, predominantly lymphocytes, was increased in the portal tracts and/or in the sinusoids [15, 31, 39]. In addition, hepatic endotheliitis was reported in two cases [31, 40]. In contrast, no cases of thrombotic changes in the liver were reported.

Fifteen liver samples were tested for SARS-CoV-2 using RT-PCR analysis, with six samples testing positive [39, 49].

Renal pathology

Thirty-five cases were examined at the macroscopic level, showing hypertensive renal surface changes, granular and/or vascular scarring, and signs of renal shock in 5, 13, and 3 cases, respectively (Supplementary Table S7) [15, 47, 49]. In addition, a microscopic analysis of renal tissue was reported for 62 cases [15, 21, 27, 32, 35, 36, 40, 44, 47]. The most common finding was varying degrees of acute tubular injury in 42 cases (68%): this was predominantly present in the proximal tubules [15, 21, 27, 32, 35, 36, 47]. Evidence of a pre-existing condition was frequently found, including arteriosclerosis in 39 cases (72%) [15, 36, 47] and benign glomerulosclerosis in five cases (8%) [21, 47]. Focal segmental glomerulosclerosis was identified in three patients (5%) [27, 36]. Lymphocytic tubulo-interstitial infiltration was found in six patients [21, 32], but no tubulitis. Renal vascular changes included fibrin or hyaline thrombi in six cases (10%) [36, 44], glomerular capillary dilatation in six cases (10%) [21], thrombotic angiopathy in two cases (3%) [47], and lymphocytic endotheliitis in one case (2%) [40].

In 13 out of 27 cases tested, SARS-CoV-2 viral particles were identified using electron microscopy in the tubular epithelium (primarily in the proximal tubule) and/or in the podocytes and endothelial cells [15, 21, 27, 32, 36, 40, 47]. In addition, SARS-CoV-2 nucleocapsid proteins were detected in 8 out of 10 cases [21, 36] and RT-PCR analysis revealed SARS-CoV-2 in 6 out of 18 renal tissues tested [21, 27, 32, 47].

Brain pathology

Histopathological findings in the brain were available for 21 cases (Supplementary Table S8) [13, 15, 33, 47], revealing no abnormalities in 16 cases. One case had subarachnoid hemorrhages [15]. Two patients had hydrocephalus internus, with acute hypoxic ischemic encephalopathy of hippocampus in one and cerebral oedema in another [47]. Finally, in two patients findings corresponding to their medical history were found [33, 47]. Viral RNA was detected at low levels in 17 cases [47], with higher values in the olfactory bulb than in the brain stem, while no viral RNA was detected in another case [15].

Pathological findings in other organs and tissues

Pathological features possibly related to COVID-19 were also described in the gastrointestinal tract, spleen, and skin of patients (Supplementary Table S9). Specifically, epithelial damage, prominent endotheliitis, and ischemic enterocolitis was reported in the gastrointestinal tract in 4 cases [41, 44], 3 cases [40], and 3 cases [49], respectively. Common findings in the spleen included reduced numbers of lymphocytes with necrosis in 11 cases [20, 44, 50] and atrophy, congestion, hemorrhage, and infarction in nine cases [20, 49, 50]. In addition, nine patients had cutaneous manifestations, with perivascular lymphocytic or neutrophilic infiltrate in eight of these nine cases [12, 23, 25, 28, 46]. One patient had evidence of complement deposition based on immunohistochemistry [12], and three patients had thrombi [12, 25]. Thrombi were also reported in the prostate of six males [49]. Systemic angiopathy was described in one case involving the left adrenal gland, lungs, and kidneys [47]. Finally, one patient had inflammatory infiltrates in the placenta and funisitis [14], whereas three other COVID-19–positive women had no notable placental abnormalities [19]. Macroscopically, the pancreas [13, 15, 44, 47, 49], thyroid [13, 15, 44, 47], and pituitary gland [13, 15], were largely unremarkable in 14, 10, and 3 patients, respectively.

SARS-CoV-2 was detected using immunohistochemistry or RT-PCR in the entire gastrointestinal tract (but not the esophagus) in one case [41], as well as in the spleen [20, 50], hilar and subcarinal lymph nodes [15, 20], placenta [14], and skin [12] of 7, 11, 1, and 1 patients, respectively. In contrast, SARS-CoV-2 was not detected in any other organs or fetal tissues.

Discussion

Although options for treating severe cases of COVID-19 are urgently needed, such treatments are currently unavailable. Although attempting to inhibit the virus' replication may be a viable option in early stages of the disease, this approach appears to be less effective in the later stages, in which the inflammatory phenotype dominates the clinical picture

[53, 54]. Thus, decisions regarding the use and timing of either antiviral agents or anti-inflammatory drugs may lead to a difficult dilemma in the absence of detailed knowledge regarding the underlying pathophysiology. Pathologists have performed autopsies on patients in a wide range of affected countries, and many have been published either with or without peer review. Although these case reports and series provide important histopathological insights into the disease patterns and mechanisms, descriptions of individual cases are often difficult to translate into meaningful data for clinical use. Here, we systematically reviewed published case reports and case series, and summarized the histopathological findings in patients with SARS-CoV-2 infection, with the goal of providing an improved understanding of the disease pathophysiology in various stages, ultimately enabling the application of targeted therapies.

Main pulmonary pathological findings

Our analysis revealed that several histopathological findings in the lungs differ significantly between COVID-19 and the conventional ARDS and other forms of viral pneumonitis. The pulmonary changes typically found in ARDS include acute interstitial pneumonia with edema and DAD with varying degrees of organization [55]. Histopathological findings in influenza pneumonitis often include capillary and small-vessel thromboses, interstitial edema, interstitial neutrophilic and lymphoplasmahistiocytic inflammatory infiltrates, hyaline membrane formation, varying degrees of intra-alveolar edema and/or hemorrhage, and acute DAD, in addition to necrotizing bronchitis and bronchiolitis; later stages of the disease include organizing DAD, fibrosis, epithelial regeneration, and squamous metaplasia [10, 56]. In other coronavirus infections such as Middle Eastern respiratory syndrome and the previous severe acute respiratory syndrome caused by SARS-CoV, patients develop small airway occlusion by debris due to airway denudation, as well as inflammatory cell infiltrates, hemorrhage, alveolar edema, and hyaline membrane formation, clinical features typical of the exudative stage of DAD [57].

In contrast, the histopathological picture of COVID-19–related pneumonitis appears to encompass epithelial, vascular, and fibrotic patterns of lung injury. By analyzing these patterns in patients in different disease stages relative to the onset of symptoms, we identified a relatively clear timeline. Specifically, epithelial changes—including DAD, denudation, and reactive pneumocyte atypia—were present in all stages of disease; moreover, vascular changes—including microvascular damage, thrombi, intra-alveolar fibrin deposits, and other features of acute fibrinous and organizing pneumonia—also occurred during the early phases of symptomatic COVID-19 infection. This vascular pattern of COVID-19 lung injury is prominent, when compared with conventional ARDS and influenza [58], and is in line with clinical studies reporting an impressive 49% of cases with thrombotic events [59]. This is in line with the presence of the ACE2 receptor on both alveolar epithelium and capillary endothelium [40]. On the other hand, fibrotic changes—e.g., interstitial fibrous changes—generally appeared ~3 weeks after the onset of symptoms, although a few patients had fibrosis at an early stage. This finding was likely due to pre-existing lung disease and not COVID-19 infection, as these cases included four patients prior to the onset of symptoms (tissues obtained during surgery for malignancy) and one patient with nonspecific interstitial pneumonia [22, 30, 38, 42, 48].

Main pathological findings in other organs and tissues

In addition to the lungs, SARS-CoV-2 was detected in several other organs, including the heart, liver, kidneys, gastrointestinal tract, spleen, lymph nodes, skin, and placenta. However, pathological findings in these organs were generally nonspecific. Epithelial damage and notable inflammatory infiltrates—possibly related to SARS-CoV-2 infection—were found in the liver, kidneys, gastrointestinal tract, and placenta, and may occur during the later stages of COVID-19 as the disease progresses; this notion is supported by previous reports of SARS-CoV-2 in urine and feces [60]. Evidence of microvascular damage such as thrombi, endotheliitis, and complement activation was not limited to the lungs, but was also found in the heart, liver, kidneys, gastrointestinal tract, skin, adrenal gland, and prostate, possibly reflecting systemic hyperinflammation in these cases. Unfortunately, only four reports of brain pathology had been published by the time we performed our literature search, thus, precluding any meaningful conclusions, including whether the virus is—or is not—neurotropic.

COVID-19 diagnostic methods

In the included articles, PCR of SARS-CoV-2 was routinely performed on various organs of COVID-19 autopsies, yielding important information regarding distribution and viral load, which is highly useful in interpreting the histopathological findings. In addition, immunohistochemistry and immunofluorescence for SARS-CoV-2 nucleoprotein and spike protein may have a relatively low sensitivity and limited specificity, but can be useful in localizing infection, especially in cases where PCR cannot be performed when RNA quality is poor. Likewise, detection of viral particles and viral inclusions by light microscopy and electron microscopy is possible, and was used in some of the included articles and at our institution to confirm the presence of intact viral particles.

Pathogenetic hypothesis of COVID-19 pneumonia

The connection between these pathological findings and the clinical course of COVID-19 indicates the possibility that the pathogenesis follows a sequential pattern [61]. In the early phase of viral infection, respiratory epithelial cells are infected; thus, epithelial changes predominate with evidence of viral activity. Subsequent viral clearance is diminished in patients with severe disease and/or underlying risk factors. The presence of epithelial lung injury with hyperplasia and atypia of pneumocytes and multinucleation, possibly representing viral cytopathic effects, even in later stages of COVID-19, supports this finding [62]. In this early epithelial phase, if histopathological changes are mild and only a limited amount of lung tissue is affected, low-type elastance lung changes are more common. In the secondary phase of the disease, progressive pulmonary abnormalities can develop, leading to high lung elastance respiratory phenotype. This progression from low to high elastance can be attributed to multiple factors, including: self-inflicted lung injury by the patient;[5] ventilator-induced lung injury [63]; microvascular injury; hypercoagulability associated with activation of the complement pathway;[12] activation of the innate immune activation, with triggering of a proinflammatory response, including the cytokines IL-1β, IL6, and TNF-α; and an adaptive T cell–mediated immune response [64] and bradykinin-induced pulmonary angioedema [65]. Importantly, thrombotic complications often develop in this phase of the disease [66, 67]. Moreover, even in the very early stage of the disease some patients present with hyperinflammation, with secondary hemophagocytic lymphohistiocytosis characterized by hypercytokinemia [68]. This may have been the case in the patients who presented with the predominantly vascular pattern of lung injury in the early disease stages. Unfortunately, the level of D-dimer was not correlated with the presence or severity of vascular changes in this review, as information regarding D-dimer levels was available in only a minority of cases. In patients who reach the final stages of the disease, with the inflammatory response beginning to fade, fibrosis often develops [18].

Limitations

Like all systematic reviews, our review has several limitations that warrant discussion. First, COVID-19 is a relatively new disease with limited published information available. Although the number of publications regarding COVID-19 histopathology is increasing almost daily, and although we repeated our search while preparing this manuscript, we cannot rule out the possibility that we have may not have included the absolute latest publications. Second, although our analysis included 42 unique articles, some were not yet peer-reviewed, and some did not provide complete information. Although we attempted to obtain missing information from the corresponding authors, only one provided the requested data. Another limitation is that clinical information such as laboratory results, radiological findings, and treatment details were not reported consistently and were therefore not available for all cases. Of the 198 cases included in the 42 articles, whole organs were examined in 141 cases (including 134 autopsy cases), whereas the other 57 samples were based on biopsies and/or partial resections, which can be prone to sampling error. Moreover, the pathological reports were relatively heterogeneous, with differing terminologies and providing different levels of detail. Finally, we cannot exclude the possibility of publication bias, as articles reporting clear abnormalities are more likely to be submitted and/or accepted for publication.

Clinical implications and conclusions

Based on our analysis, we suggest that COVID-19 can follow three stages; moreover, it is important to note that these three stages can occur either consecutively or simultaneously. From a clinical perspective, adequate therapy should be provided based upon the underlying pathophysiological stage. When viral activity is the principal pathogenic factor, antiviral therapies will be most effective. In the vascular stage, directed anti-inflammatory, anticoagulant, and/or anticomplement agents are indicated. Finally, when fibrosis is developing biologicals and/or small-molecule antifibrotic compounds—even those in the experimental stage—should be considered. Currently, in clinical practice a patient's precise pathophysiological state cannot be determined by tissue biopsy, and clinical insight relies upon circumstantial evidence such as RT-PCR to detect viral RNA, laboratory measurements of cytokines and inflammatory markers, and radiological evaluation. Therefore, to move toward precision medicine, future research should focus on correlating this clinical information with pathological findings. This approach will require a high level of interaction between clinicians, laboratory personnel, and radiologists in order to rapidly increase and disseminate knowledge and then apply that knowledge in the clinical setting, thus increasing our understanding of COVID-19 and facilitating the transition to laboratory- and CT-guided precision medicine.

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Compliance with ethical standards

Conflict of interest All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or nonfinancial interest (such as personal or professional relationships, affiliations, knowledge, or beliefs) in the subject matter or materials discussed in this manuscript.

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