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# An overview of COVID-19 for diagnostic pathologists: clinicopathological correlation and diagnostic techniques

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## Abstract

The emergence of COVID-19 as a global pandemic has led to a rapid focus on understanding its pathobiology. The constellation of clinical, histological and laboratory findings seen in these patients is similar to other forms of viral pneumonia, but somewhat distinctive aspects exist which may raise the index of suspicion for this disease. The pathological findings are not limited to the respiratory system; cardiovascular, gastrointestinal and renal abnormalities have also been described. Establishing a link between the clinical features and macroscopic and microscopic findings is not only important for the practicing autopsy pathologist, but also for understanding of the disease as a whole. Furthermore, context-sensitive interpretation of diagnostic tests is essential. This article aims to review understanding of clinicopathological correlation in COVID-19, as well as clarifying the role of current diagnostic techniques.

**Keywords** autopsy; coronavirus; COVID-19; histopathology; pathology

## Introduction

COVID-19 is the name given to the infectious disease caused by the recently discovered severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Unknown until recently, this virus is the seventh coronavirus identified to cause disease in humans.<sup>1</sup> COVID-19 has generated a sustained global public health response due to its propensity for rapid spread and relatively high fatality rate.

The disease shares many similarities with other forms of viral pneumonia, including that caused by severe acute respiratory syndrome coronavirus (SARS-CoV), Middle East respiratory

syndrome coronavirus (MERS-CoV) and seasonal influenza. However, the characteristics of spread and exact spectrum of clinical symptoms do appear distinct. Understanding the pathophysiological characteristics is an important part of recognizing and diagnosing the disease, as well the development of future diagnostic and therapeutic strategies.

Confirmation of the diagnosis is made using molecular techniques, most commonly by identification of viral RNA through reverse transcription polymerase chain reaction (RT-PCR).<sup>2</sup> Effective large-scale molecular testing methods are therefore required to identify and monitor the disease within the population. These techniques display a range of strengths and weaknesses which should be borne in mind during interpretation.

## Pathogen

SARS-CoV-2 is a member of the coronavirus family. Coronaviruses are single-stranded, positive sense RNA viruses with a size of approximately 30 kb.<sup>3</sup> They are classified into four genera with common ancestry: *alpha*-, *beta*-, *gamma*- and *deltacoronavirus*. *Alpha*- and *betacoronavirus* are known to cause infection in mammals, whereas *gamma*- and *deltacoronavirus* mainly affect birds.<sup>4</sup> Coronaviruses are further categorized into strains based on genomic characteristics. Four strains (229 E, OC43, NL63 and HKU1) cause mild respiratory illness with symptoms of the common cold.<sup>1</sup> The strains SARS-CoV and MERS-CoV are known to have the potential for more severe respiratory disease, and were responsible for epidemics, including the SARS-CoV epidemic in China (2002–3) and the MERS-CoV epidemic in the Middle East in 2012. The recently discovered SARS-CoV-2, like SARS-CoV and MERS-CoV, is part of the *betacoronavirus* genus.

SARS-like and MERS-like viruses are frequently seen in bats. Sequencing of the SARS-CoV-2 genome reveals it to be 96% identical to a previously published bat SARS-like virus.<sup>5</sup> However, SARS-CoV and MERS-CoV are known to have passed to intermediate hosts prior to human transmission. These hosts include the civet for SARS-CoV and dromedary camels for MERS-CoV. Pangolins have been described as a putative intermediate host in the case of SARS-CoV-2.<sup>6</sup> Epidemiologically, human transmissible SARS-CoV-2 may have originated in a seafood and animal market in Wuhan, China.<sup>7</sup>

The typical cycle of RNA viral infection begins with binding of the virus to a host receptor. Coronaviruses produce a structural ‘spike’ protein which interacts with the host receptor to mediate this process. Previously, angiotensin converting enzyme 2 (ACE2) has been identified as a host receptor for SARS-CoV, whereas the dipeptidyl peptidase-4 (DPP4) receptor has been identified for MERS-CoV. Functional assessment of SARS-CoV-2 spike protein confirms that it also binds to ACE2.<sup>8</sup>

Spread of SARS-CoV-2 appears to be primarily mediated by droplet inhalation.<sup>9</sup> In the UK, the advisory committee on dangerous pathogens (ACDP) has classified COVID-19 as a HG3 pathogen on the basis of the risk of human infection and potential severity of disease. Although an autopsy is unlikely to be required if COVID-19 is considered the likely cause of death in the UK and the attending doctor feels they can issue a death certificate, appropriate autopsy protocols for reducing risk are necessary if COVID-19 is suspected. A staged approach to post

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mortem investigation may be appropriate if the possibility is clinically raised.<sup>9</sup>

### Clinical features

The clinical features of COVID-19 are heterogeneous and overlap with those of other viral respiratory tract infections. The predominant clinical presentation of patients with COVID-19 is fever and/or cough<sup>10</sup> and these are indicative symptoms in the UK for self-isolation and, where available and appropriate, viral testing. Systematic analyses show that approximately 90% of patients are observed to present with fever and approximately 60–70% with cough.<sup>10</sup> Dyspnoea and myalgia are both variably reported in approximately 30–50% of patients.<sup>10</sup> These typical symptoms are not identified in a proportion of patients, although further data from continued testing is required to explore this finding.<sup>11</sup> Other features can include diarrhoea, seen in around 6%.<sup>10</sup> Upper respiratory tract symptoms such as sneezing, sore throat and rhinorrhoea are less common.<sup>7</sup> Many of the patients with severe disease show evidence of acute respiratory distress syndrome (ARDS), although other critical manifestations include acute cardiac injury, shock and multiple organ failure. The median time between onset of symptoms and ARDS is approximately 8 days.<sup>12</sup>

Recently, a change in the sense of smell (anosmia) or taste (hypogeusia) has also been described as a potential manifestation of early COVID-19, even in the absence of other symptoms. Although its true incidence and clinical relevance are yet to be established,<sup>13</sup> these were later added to the list of symptoms as indications for COVID-19 testing and self-isolation in the UK.<sup>14</sup>

Estimating the true frequency of complications or mortality is challenging, given a bias towards testing of patients with severe or critical illness. Different countries show varying population demographics, employ a diverse range of testing strategies and use distinct case definitions. Furthermore, differences in ethnicity should also be borne in mind, with increasing concern that those from black, Asian, and minority ethnic backgrounds may be disproportionately affected.<sup>15</sup> One large study in mainland China found 14% of patients to present with severe respiratory compromise and 5% to be critically unwell with evidence of respiratory failure, septic shock or multiple organ failure.<sup>16</sup> The same study showed an overall case fatality rate of 2.3%.<sup>16</sup> Increasing age and the presence of comorbid conditions are associated with COVID-19 fatality. The case fatality rate in those aged 80 or above appears to be approximately 15%.<sup>16</sup> Comorbid conditions commonly seen include hypertension, coronary artery disease, type 2 diabetes mellitus, malignancy, asthma and COPD.<sup>12,17</sup> Obesity, autoimmune disease, cirrhosis and psychiatric disease have also been described as risk factors.<sup>11</sup> Children are susceptible to COVID-19, but only represent a small proportion of the affected population. Approximately 2% cases are seen in those aged up to 19 years old.<sup>16</sup> Additionally, children appear to exhibit less severe disease. The reason for this is unclear, but may reflect altered binding to ACE2 receptors or differences in immune function.<sup>18</sup> Nonetheless, emerging reports suggest that a hyperinflammatory systemic Kawasaki-like phenomenon is possible in young patients, albeit very rare.<sup>19</sup> As with most epidemics, it will be in retrospect in 12–18 months following the peak that a clear understanding of the true impact of the virus

will become apparent. A key indicator will be the total number of all-cause excess deaths over the period.

### Clinicopathological correlation

#### Respiratory system

The pathological features of COVID-19 during post mortem examination are heterogeneous, and centre on the thoracic cavity. Macroscopically, the lungs may be congested and heavy. Pulmonary consolidation, pleural inflammation and pericarditis have also been described.<sup>9,17</sup> Purulent material may be evident in the lungs or pleural cavity reflecting a superimposed bacterial component, as frequently seen in cases of influenza.<sup>9,17</sup>

Microscopically, the changes are mostly those of diffuse alveolar damage (DAD), and may include hyaline membrane formation, oedema and pneumocyte hyperplasia (Figures 1 and 2). Such changes are likely to be more prominent in younger patients with few comorbidities, who are likely to survive for longer before decompensation.<sup>17</sup> Lymphocytic interstitial inflammation is common, but neutrophilic infiltrates may also be seen, potentially indicating a superimposed bacterial bronchopneumonia. Multinucleated giant cells and atypical enlarged pneumocytes with prominent nucleoli have also been described, which could represent viral cytopathic effect (Figure 2).<sup>9,20</sup> The changes observed reflect the affinity of SARS-CoV-2 for the lower respiratory tract. ACE2, which represents the binding site, is highly expressed in alveolar epithelial cells. As such, direct infection of the lung parenchyma may be responsible for its respiratory effects. Additionally, large numbers of proinflammatory cytokines and chemokines are measurable in the serum, and a progressive host immune response is likely to contribute to clinical deterioration.<sup>7</sup>

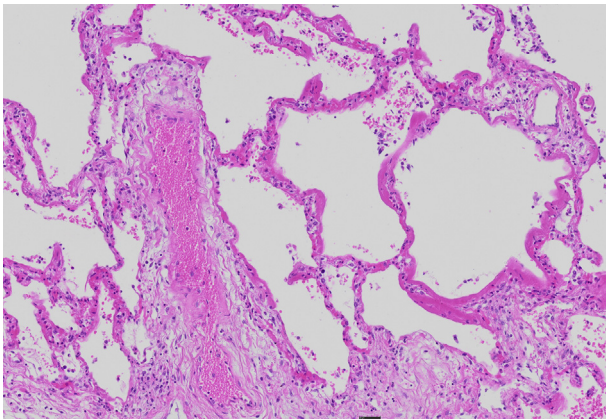
Interestingly, a high incidence of thromboembolic disease has been observed during post mortem examination. In one study, 4 out of 12 patients were found to have massive pulmonary embolism as the direct cause of death.<sup>17</sup> This may reflect a procoagulant state conferred by the systemic inflammatory response. ACE2 is also widely expressed on endothelial cells, and direct viral involvement of the vascular endothelium has been suggested as a potential trigger.<sup>21</sup>

#### Cardiovascular system

Cardiovascular comorbidities are common in patients with severe COVID-19, including hypertension and coronary artery disease.<sup>5</sup> Myocardial hypertrophy is frequently seen in COVID-19 post mortem examination, correlating with a high incidence of hypertension in fatal cases.<sup>17,22,23</sup> Histological findings generally reflect pre-existing heart disease, although a lymphocytic myocarditis has also been reported.<sup>17</sup>

The frequency of hypertension in severe and fatal cases raises the question of whether such patients may have increased susceptibility to COVID-19 infection. Antihypertensive drugs in such patients may include inhibitors of the renin–angiotensin–aldosterone axis, a key component of fluid balance regulation. It has been hypothesized that chronic administration of ACE inhibitors and angiotensin receptor blockers (ARBs) for control of blood pressure and renoprotection may lead to increased expression of ACE2 in the heart and lung. This may increase the number of available binding sites for SARS-CoV-2 leaving such





**Figure 1** Diffuse alveolar damage. A section of post mortem lung showing hyaline membranes (pink) and capillary congestion (haematoxylin and eosin). Reproduced from reference 22 under Creative Commons license.

patients more prone to infection.<sup>24,25</sup> However, evidence for acutely withdrawing ACE inhibitors and ARBs in this context remains slim.

Acute myocardial injury has also been observed, as suggested by increased levels of troponin I in a proportion of patients with COVID-19<sup>25</sup>. This may represent a systemic inflammatory response predisposing to plaque rupture and thrombosis. However, ACE2-related signaling has also been proposed to play a role, and the potentially cardiotoxic effects of antiviral agents should also be considered.<sup>25</sup>

### Gastrointestinal system

Diarrhoea was a frequent symptom in cases of SARS and MERS, occurring in 20–25% of cases.<sup>7,26</sup> Although less commonly

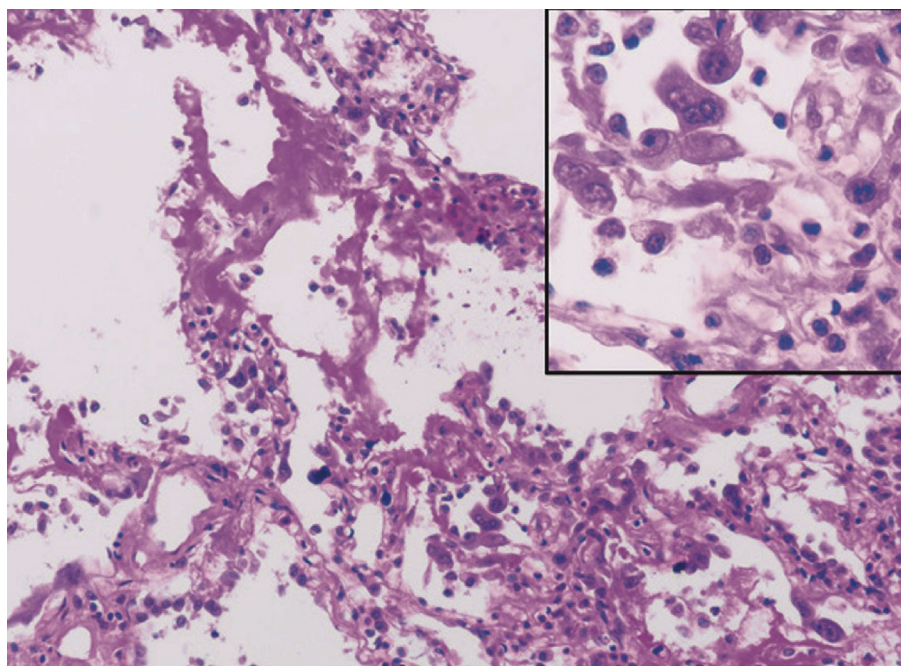
observed in COVID-19, it is still a relatively common manifestation, with reports suggesting it occurs in 2–10% of patients.

Specific macroscopic or microscopic gastrointestinal abnormalities have not been described in COVID-19 patients. However ACE2 is known to be highly expressed in gastrointestinal epithelial cells.<sup>26</sup> Indeed, viral RNA has been identified in stool specimens and anal or rectal swabs in approximately half of patients.<sup>27</sup> This finding occurred even after respiratory clearance in some patients, suggesting that this could represent an important source of viral shedding.

Biochemical markers of liver injury appear raised in a proportion of patients with COVID-19, including ALT, AST and GGT.<sup>26</sup> Histological findings in the liver appear non-specific; one report describes mild lobular and portal active inflammation on a background of moderate microvesicular steatosis<sup>20</sup> whereas others describe shock-associated necrotic change.<sup>22</sup> As well as damage related to shock, the abnormalities observed may reflect drug effects or direct viral infection of hepatocytes.

### Renal system

Development of acute kidney injury is common in COVID-19 patients and associated with poor outcome.<sup>28</sup> Histological changes include those associated with pre-existing hypertension and diabetes mellitus, such as arteriosclerosis and nodular glomerulosclerosis.<sup>22,29</sup> Changes typically related to shock are also reported, with evidence of proximal tubular dilatation, flattened epithelium and sometimes frank necrosis.<sup>22,29</sup> Electron microscopy studies demonstrate virus-like particles in podocytes, proximal tubular epithelium and endothelium (Figure 3).<sup>22,29</sup> These findings suggest that COVID-19 associated kidney disease may be multifactorial. Many of the changes would be in keeping with shock as the result of a strong systemic inflammatory response on a background of preexisting chronic renal



**Figure 2** Further example of diffuse alveolar damage. Section of post mortem lung, again showing hyaline membranes. In addition, atypical pneumocytes and multinucleated giant cells (insert) can be seen (haematoxylin and eosin). Reproduced from reference 20 with permission from Elsevier.

disease. However the presence of virus-like particles and the known high level of ACE2 expression in the kidney suggest that direct involvement of renal epithelium may play a role.<sup>28</sup>

### Diagnostic techniques

Clinical features alone cannot be used to make a definitive diagnosis of COVID-19. A range of techniques can be used to stratify risk of COVID-19 in patients and provide more conclusive evidence of infection. Radiological investigations are usually performed on inpatients. Chest X-rays may show features of pneumonia, and CT examination may show ground glass opacities, patchy consolidation or peripheral interstitial changes.<sup>30</sup> Such CT changes are seen in most patients with COVID-19 and sensitivity is reported as up to 97%.<sup>30</sup> Similar findings have also been reported in post-mortem CT investigations.<sup>17</sup> However, the features are not specific, and overlap a great deal with other viral pneumonias.

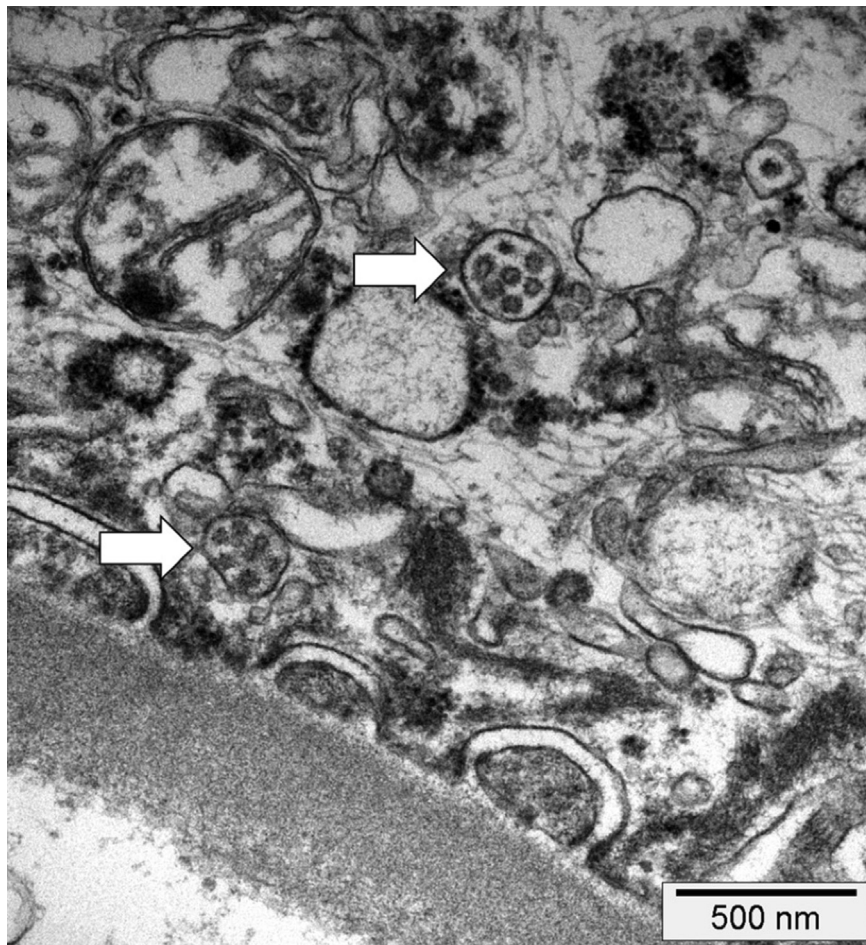
A range of biomarkers are also commonly abnormal; patients typically show lymphopenia, decreased albumin and prolonged PT, alongside raised ferritin, CRP, LDH and D-dimer.<sup>10,12,31</sup> Whilst, some of these markers can be used to help stratify risk, these features do not appear to be specific.

Molecular diagnostic techniques are required for definitive diagnosis. Different types of test are used to assess for active or previous infection, and vary in terms of sensitivity, specificity, turnaround time, throughput and cost. A successful testing strategy requires careful assessment of the strengths and weaknesses of each method. As an illustrative example, rapid antigen detection tests exist for respiratory syncytial virus (RSV) and influenza, which are low complexity, point of care investigations. However, sensitivity to rule out disease is poor. Here, we discuss the two most commonly used categories of test for COVID-19.

### Nucleic acid amplification testing

Nucleic acid amplification tests (NAATs) are currently the most widely used diagnostic test for COVID-19 and are used for screening those with suspicious symptoms as well as those currently asymptomatic. As such, the test helps inform decisions about treatment and isolation measures.

Viral RNA can be detected in a range of samples, including from the upper respiratory tract, lower respiratory tract, and faeces. Serum and urine, however, are usually negative.<sup>32</sup> Lower respiratory tract samples are the most likely to be positive in infected patients. However, collection of sputum or bronchoalveolar lavage samples is challenging, and as aerosol



**Figure 3** Transmission electron micrograph of a section of kidney showing virus-like particles within podocyte cytoplasm (arrow). Reproduced from reference 22 under Creative Commons license.



generating procedures, they are considered risky for the operator. The specimen is therefore typically obtained from the upper respiratory tract via nasopharyngeal or oropharyngeal swab. The characteristics and time course of positive results at different sites is likely to vary. For example in SARS, lower respiratory tract samples yielded high viral RNA titres three weeks after symptom onset, whereas upper respiratory tract samples declined after 10 days.<sup>33</sup> Detection is thought to be more sensitive if both upper and lower respiratory tract sampling is undertaken.<sup>33</sup>

The technique involves extraction of RNA from the sample followed by RT-PCR for amplification of a selected specific nucleic acid target. The target is specified by the probe used in the test kit and varies according to manufacturer. Such targets may include nucleocapsid gene N1 and N2, or SARS-CoV-2 specific RNA-dependent RNA polymerase (RdRP) and envelope (E) genes. The sensitivity and specificity of such tests vary according to the manufacturer, protocol and primer/probe set used.

The most important limitation of the test comes from the difficulty in correlating results with the time frame of greatest viral load. As such, it has proved difficult to rule out COVID-19 after a single negative test. Other potential reasons for a false negative result may include mismatch between the probe and viral RNA due to genetic variability, inappropriate sample collection or handling, and the presence of amplification inhibitors in the sample.<sup>34</sup> Indeed, whilst it is difficult to estimate, studies correlating radiology and sequential RT-PCR testing suggest a false negative rate of approximately 30–50%.<sup>35,36</sup> It is therefore very important that a negative RT-PCR test is not taken out of context. Furthermore, NAATs can only detect viral loads at the time of sample collection and do not provide any information on previous infection or putative immunity.

### Serology

Serological tests aim to detect antibodies to SARS-CoV-2 from clinical specimens such as blood, or potentially saliva. A detectable specific antibody response is produced in patients with COVID-19 as soon as 5 days after infection.<sup>37</sup> Although a range of techniques exist, the principle is that of introducing the clinical specimen to a protein antigen specific to the virus. If specific antibodies to the antigen exist in the clinical specimen, bound complexes form, which can subsequently be quantified. Serology can therefore be used to provide evidence of an antibody response to previous SARS-CoV-2 infection. Such testing is most valuable for surveillance and forecasting of disease. It is likely to be increasingly important for the understanding of COVID-19 epidemiology, as well as the role of antibodies in potentially providing immunity. Serological testing however, is of limited diagnostic use during acute infection when transmission risk is likely to be highest.<sup>38</sup> Additionally, specificity of the test depends on the technique and antigen used. Previous studies on SARS have confirmed a degree of cross-reactivity to other human coronaviruses,<sup>39</sup> and testing for SARS-CoV-2 is likely to face similar problems. Finally, of course, the presence of antibodies does not definitely equate to immunity and until this is better understood, the risk of false reassurance should be adequately managed. This said,

the emerging role of serological testing is likely to be adjunctive to NAATs in most cases.

### Practice implications for pathologists

For the practicing autopsy pathologist, the implications of performing invasive examinations in these high-risk cases have been covered comprehensively elsewhere, but the key message is that in addition to routine personal protective equipment (PPE) there is a need for additional respiratory protection or whole-body hazardous material suits when performing autopsies in suspected or confirmed COVID-19 deaths.<sup>9</sup> For surgical pathologists, specimens from patients with suspected or confirmed COVID-19 are possible, although elective surgery is not recommended in these patients. Routine and additional enhanced PPE are recommended depending on the circumstance. Eye protection, fluid resistance disposable gloves and surgical masks are recommended for dissection of fresh tissue. For aerosol generating procedures (e.g. lung inflation), an FFP3 mask and fluid resistant long gown are recommended, as is dissection in a fume cupboard. Increased fixation times and dissection on down-draft benches (as is recommended for all potentially infectious specimens) may be useful. Please see the excellent COVID-19 resources hub from the UK Royal College of Pathologists for more details.<sup>40</sup>

### Conclusion

Careful assessment of clinical, radiological and molecular features is required for identifying potential cases of COVID-19 and subsequently confirming the diagnosis. Although histopathology does not usually form part of the routine diagnostic process, the practicing histopathologist may encounter suspected cases at post mortem, or potentially during surgical diagnostic work. Confirmatory molecular testing can be performed during autopsy if required, and a staged approach with appropriate precautions is recommended in such cases.<sup>9</sup>

At a holistic level, an understanding of the histopathological features is important to define the multiple disease processes taking place in COVID-19 and other forms of viral pneumonia. It is clear that COVID-19, whilst primarily a respiratory illness, does affect multiple organs (summarized in Table 1). Evidence is likely to arise in due course regarding chronic effects and the involvement of further systems, including the central nervous system. The scale of the pandemic and similarity to previous MERS and SARS epidemics suggests that novel coronaviruses will continue to pose a significant public health challenge, and early recognition of similar disease at a population level is essential. Understanding and challenging the pathological processes observed will be key to the development of successful future therapeutic strategies.

### Declaration

The COVID-19 pandemic is a rapidly evolving infectious disease and the guidance changes often. The information here was correct at the time of writing (May 2020). Up-to-date guidelines should be followed when making clinical decisions. The views expressed here are those of the authors alone and do not represent those of any affiliated institution. ◆

## A summary of the clinical and pathological features of COVID-19

	Clinical, radiological and laboratory features	Macroscopic/microscopic pathology	Clinicopathological correlation
<b>Systemic</b>	<p>Fever</p> <p>Myalgia</p> <p>+/- Anosmia, hypogeusia</p> <p>Lymphopenia, decreased albumin, prolonged PT, elevated CRP, LDH, ferritin and D-dimer common.</p> <p>Comorbidities including diabetes mellitus common in inpatient cases</p> <p>Black, Asian, and ethnic minority higher risk profile</p>	—	Systemic proinflammatory cytokine and chemokine response
<b>Respiratory</b>	<p>Cough</p> <p>Dyspnoea</p> <p>COPD and asthma are common comorbidities for inpatient cases</p> <p><b>Chest X-ray:</b> May show features of pneumonia</p> <p><b>CT:</b> Ground glass opacities, patchy consolidation, interstitial changes</p>	<p><b>Macroscopic:</b> Pulmonary oedema, consolidation, pleural inflammation</p> <p>+/- purulent bronchopneumonia</p> <p>+/- pulmonary embolus</p> <p><b>Microscopic:</b> Diffuse alveolar damage (hyaline membranes, oedema, pneumocyte hyperplasia). Lymphocytic infiltrate common. Multinucleated giant cells and enlarged, atypical pneumocytes reported (representing possible viral cytopathic effect)</p> <p><b>Macroscopic:</b> Changes of preexisting cardiac disease are common, including myocardial hypertrophy (due to preexisting hypertension), coronary artery disease.</p> <p><b>Microscopic:</b> Lymphocytic myocarditis has been reported.</p>	<p>Direct viral infection of pneumocytes</p> <p>Systemic proinflammatory cytokine and chemokine response</p> <p>Relatively high incidence of thromboembolic disease</p> <p>Superimposed bronchopneumonia common</p>
<b>Cardiovascular</b>	<p>Hypertension and coronary artery disease common comorbidities for inpatient cases</p> <p>Acute cardiac injury (with elevated troponin I) common in inpatient cases</p>	<p><b>Macroscopic:</b> Changes of preexisting cardiac disease are common, including myocardial hypertrophy (due to preexisting hypertension), coronary artery disease.</p> <p><b>Microscopic:</b> Lymphocytic myocarditis has been reported.</p>	<p>Possible ACE2 upregulation increasing susceptibility</p> <p>Preexisting cardiovascular disease results in poor cardiovascular reserve</p> <p>Plaque rupture and thrombosis due to systemic inflammatory response</p> <p>Possible viral endothelial injury producing procoagulant state</p> <p>Drug cardiotoxicity</p>
<b>Gastrointestinal</b>	<p>Diarrhoea seen in minority of cases (2–10%)</p> <p>Raised ALT, AST, GGT common</p>	<p><b>Macroscopic:</b> No specific features commonly reported.</p> <p><b>Microscopic:</b> Liver may show shock necrosis. Steatosis, mild active hepatitis reported.</p>	<p>Direct viral infection of gastrointestinal epithelium</p> <p>Gastrointestinal and hepatic sequelae of systemic inflammatory response</p> <p>Drug hepatotoxicity</p>
<b>Renal</b>	<p>Acute kidney injury common and associated with poor outcome</p>	<p><b>Macroscopic:</b> Evidence of shock</p> <p><b>Microscopic:</b> Acute tubular injury (dilated proximal tubules, flattened epithelium, sometimes frank necrosis). Evidence of preexisting comorbid disease common, including hypertension/diabetes-associated changes</p>	<p>Shock secondary to systemic inflammatory response</p> <p>Direct viral infection of podocytes, tubular epithelium and endothelium</p>

Table 1

## Practice points

- COVID-19 is a heterogeneous disease with clinical and pathological features that overlap with other forms of viral pneumonia.
- Autopsy examination may reveal pulmonary oedema, consolidation, pleural inflammation and/or evidence of superimposed bacterial bronchopneumonia.
- Histology of the lungs may show evidence of diffuse alveolar damage (DAD) and atypical respiratory epithelial cells showing possible viral cytopathic effect.
- Cardiac and renal pathology are also common and may reflect preexisting chronic disease or sequelae of a systemic inflammatory response.
- A negative nucleic acid amplification test cannot reliably exclude COVID-19 if there is a high index of clinical suspicion.

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