Pathology of COVID-19 Infection

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Abstract

COVID-19 pandemic which started in 2019 in Wuhan, China, later spread to other parts of the world as a major disaster. Two years back, it was considered predominantly a pulmonary disease, however, it is now thought to be a multi-system disorder. With the emergence of new mutants, the spectrum of disease has changed and widened. The interplay of cytokines and vasculopathy with the development of vascular thrombosis is chiefly responsible for diverse manifestations. The secondary infections in many patients, during as well as in the post-COVID period have resulted in higher morbidity and morbidity. A brief description of pathology in various organs is given below.

Keywords

COVID-19 · SARS-CoV-2 · Pathology · ARDS

7.1 Introduction

COVID-19, which is caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), is now very much known to be a systemic disease. Although it can involve any system in the body, particularly with the emergence of new mutants of the virus; it is the respiratory system that is the primary organ of involvement. This is the reason why most COVID-19 patients report to the hospital with symptoms referable to upper and lower respiratory tracts. The other body organs which can be

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R. C. Sobti et al. (eds.), *Delineating Health and Health System: Mechanistic Insights into Covid 19 Complications*, https://doi.org/10.1007/978-981-16-5105-2_7

affected are the brain, heart, kidney, GIT, liver, hemopoietic, and musculoskeletal system.

7.2 The Pulmonary System

It is well known that the virus enters primarily through the respiratory route, that is, aerosols and droplets, therefore, the respiratory system bears the brunt of the disease. Lung damage is the leading cause of death in the majority of the patients afflicted with COVID-19 infection. The pulmonary pathological features of COVID-19 have been studied mainly from autopsies conducted on the COVID-dead patients. The pathological findings closely resemble to those seen in SARS and MERS (Liu et al. 2020). The affected lungs appear heavy, edematous, and diffusely congested. The pleura may show dullness, but pleural effusion is not a common feature until complicated by secondary infection. The cut surface of the lungs exhibits irregularly distributed foci of consolidation. Areas of hemorrhage or infarction with apparent thrombosis in feeder vessels may be noted (Lax et al. 2020). The infarcts are not typically wedge-shaped because these are due to thrombotic occlusion of multiple smaller vessels rather than a single large vessel. If there are superadded infections, there may be abscesses or lobar pneumonia.

Histologically, four main morphological stages of pulmonary involvement are described:

1. an early stage (day 0–1): There is edema, initial epithelial damage, and evidence of capillaritis. At this stage, the interstitial inflammation may be minimal.
2. The stage of exudative diffuse alveolar damage (DAD) (days 1–7) is characterized by fibrin-rich edematous intra-alveolar fluid, macrophage exudation, and type II pneumocyte proliferation. Occasional multinucleated syncytial giant cells, as well as enlarged pneumocytes containing large nuclei, amphophilic cytoplasm, and prominent nucleoli, are noted. These cells may show cytopathic changes but generally do not contain apparent viral inclusions. Hyaline membrane formation (Fig. 7.1) occurs during this phase (Menter et al. 2020; Polak et al. 2020; Borczuk et al. 2020). Microthrombosis may be frequently observed with associated intra-alveolar hemorrhages. Areas of dilated alveolar ducts and collapsed alveoli can occur side by side.
   The presence of occasional intravascular megakaryocytes (Valdivia-Mazeyra et al. 2021) is not an uncommon finding. It may be remembered that neither presence of intrapulmonary megakaryocytes nor microthrombi are specific for COVID-19 as it is known to occur in DAD of other causes (Valdivia-Mazeyra et al. 2021; Hariri et al. 2021). The inflammatory cells in the exudative phase consist of CD3 positive lymphocytes and rare plasma cells located in alveolar walls. In addition, the alveolar spaces are filled with macrophages which are CD68+, CD163+, and CD206+ (Pandolfi et al. 2020; Bradley et al. 2020).
3. The organizing stage (1 to several weeks): This stage is characterized by interstitial and intramural fibrosis (Fig. 7.2). The alveoli are filled with loose connective

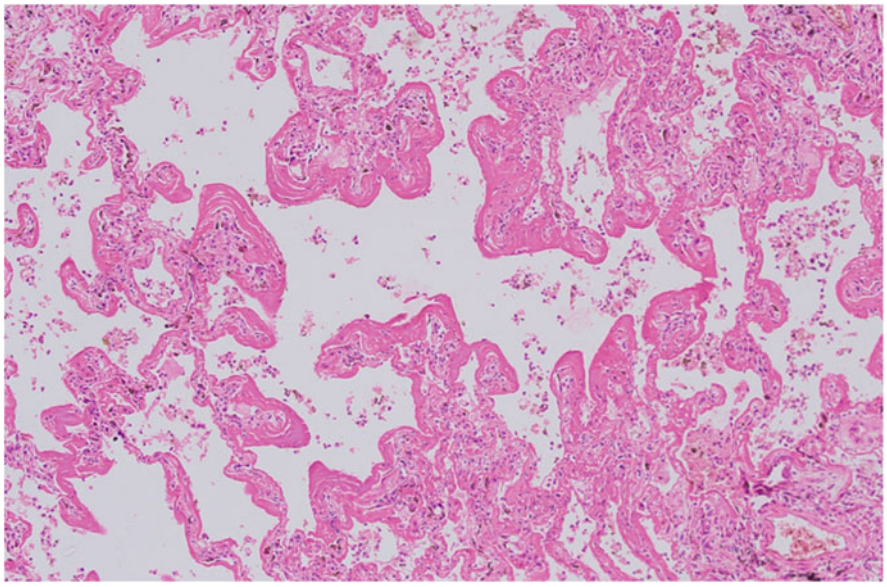

Fig. 7.1 Extensive hyaline membrane formation in lungs during the exudative phase of COVID-19 infection

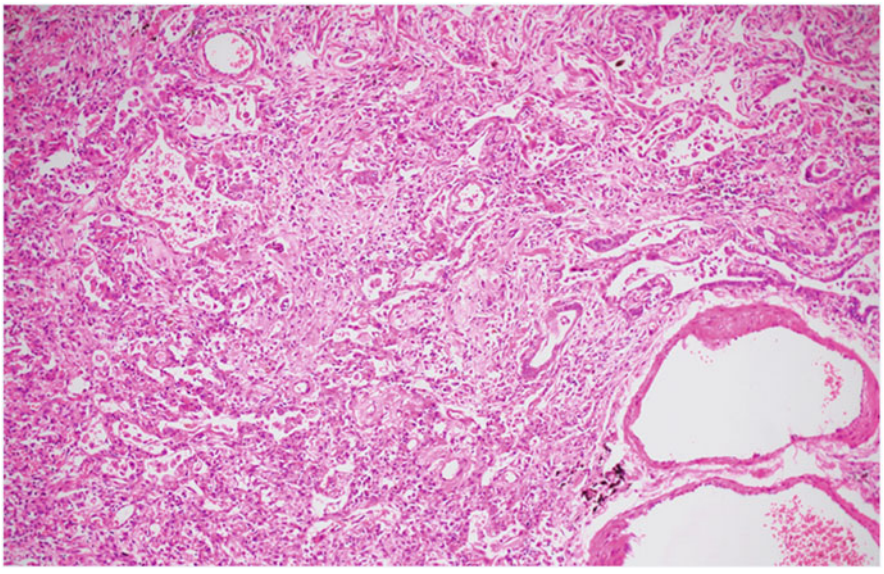

Fig. 7.2 Interstitial and intra-alveolar fibrosis of the lungs in organizing stage of alveolar damage

tissue. Interstitial myofibroblastic proliferation follows and bronchopulmonary squamous metaplasia may set in (Lax et al. 2020; Carsana et al. 2020).

4. The fibrotic stage of DAD (weeks to months): there is the deposition of septal collagen. The lungs show diffuse fibrosis and the alveolar architecture is lost. At this stage, the lungs fail to expand.

   It is pertinent to mention that different stages of COVID-19 pathology may show some overlap. Such overlap is known to happen with other diffuse interstitial lung diseases as well, at autopsy examination. Actually, the stages represent a continuum of the disease process which is very much evident from postmortem tissues. The excised antemortem biopsy samples where only limited material is examined may not show the spectrum of pathology of the entire lung, based on which staging is done. This reason explains the overlap of different stages in pulmonary findings at autopsy. Therefore, the DAD manifestations frequently coexist side by side with the organizing stage, a reflection of the temporal heterogeneity of COVID-19 (Lax et al. 2020; Calabrese et al. 2020; Ye et al. 2020).

   Fungal or bacterial superadded infections usually take over in patients in ICUs and lead to bronchopneumonia. The incidence of superadded infections in autopsy series ranges from 32 to 57% (Skok et al. 2020). The incidence of pulmonary embolism and microthrombi are evident in 20% (Hariri et al. 2021) and 57% (Edler et al. 2020) of COVID-19 patients, respectively. Pulmonary thromboembolism may be the direct cause of death in many patients.

7.3 Extra Pulmonary Involvement

7.3.1 The Cardiovascular System

It has been documented that COVID-19 contributes to cardiovascular complications, including acute myocardial injury, acute coronary syndrome, myocarditis, stress-cardiomyopathy, arrhythmias, and cardiogenic shock (Kang et al. 2020). Zou et al. (2020) published a comprehensive review and meta-analysis on the incidence, comorbidities, outcomes, and possible mechanisms of acute cardiac injury in COVID-19 patients. They concluded that the risk of cardiac injury in COVID-19 hospitalized patients is alarmingly high, particularly in old age; furthermore, that the incidence is similar in the Chinese and Western populations. Myocarditis in COVID-19 positive patients with raised troponin and ECG changes has been reported by Doyen et al. (2020). The myocarditis may be multifocal and mainly lymphocytic in nature (Fig. 7.3). Other documented histological findings in COVID-19 patients are hypertrophied cardiomyocytes along with inflammatory infiltrate, focal edema, interstitial hyperplasia, fibrosis, degeneration, fibrin thrombi, and necrosis (Fig. 7.4). The coronary artery, endocardium, and pericardium may also be affected (Yao et al. 2020a, b; Tavazzi et al. 2020).

Since the vascular endothelial cells express ACE-2 receptors, endothelial cells are an easy target for the SARS-CoV-2 virus (Hamming et al. 2004) and thus the presence of viral inclusions along with inflammatory cells and apoptotic bodies in

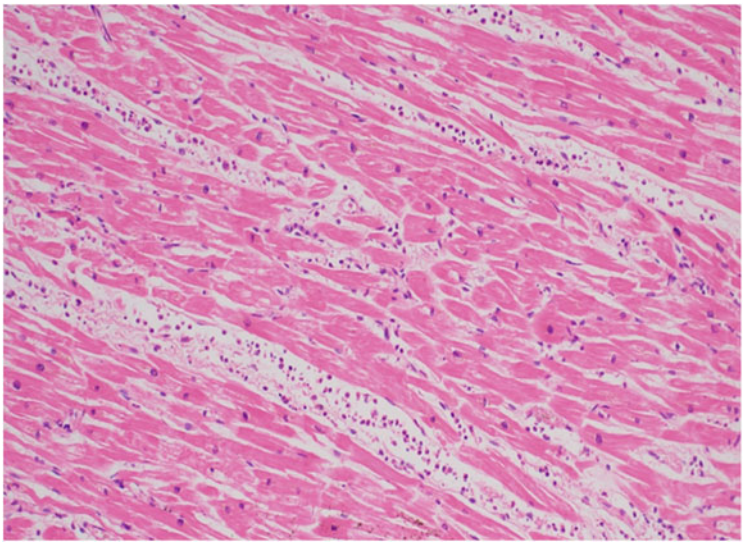

Fig. 7.3 Myocarditis showing myonecrosis, infiltration by lymphocytes and plasma cells along with interstitial edema

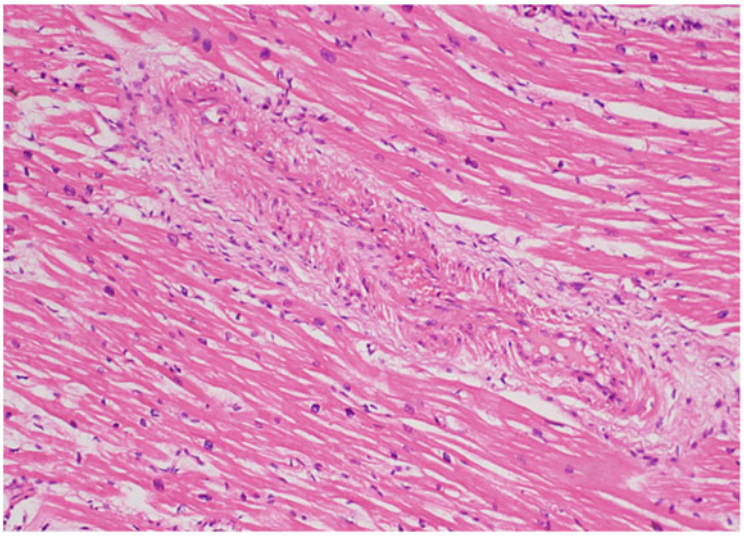

Fig. 7.4 Heart: Interstitial vessel showing organizing fibrin thrombus with luminal occlusion

these cells can be easily explained (Xiao et al. 2020). An increased risk of venous thromboembolism in COVID patients is largely due to prolonged immobilization, hypercoagulable status, active inflammation, and propensity for DIC.

7.3.2 The Nervous System

CNS involvement is being increasingly reported in COVID-19 patients and symptoms may vary from mild to severe in nature. Headache, anosmia, dizziness, dysgeusia, confusion, and impaired consciousness have all been reported in COVID-19 patients. Studies from China, France, and other European countries have reported varying percentages of neurological signs and symptoms (Mao et al. 2020; Helms et al. 2020; Paterson et al. 2020). The pathological disorders described in COVID-19 patients include stroke, Guillain-Barre syndrome (GBS), meningoencephalitis, acute hemorrhagic necrotizing encephalopathy, and cerebral venous thrombosis (Lou et al. 2021).

Meningitis and meningoencephalitis are infrequent manifestations of COVID-19 infection. Except for mild edema, the external examination of such a brain may not show any abnormality. The meningitis is usually mild and lymphocytic in nature. In meningoencephalitis cases, microglial activation, microglial proliferation with microglial nodule formation, perivascular, and parenchymal lymphocytic infiltration are noticed like any other encephalitides. In routinely stained slides of brain tissue, viral inclusions are not found, however, the SARS-CoV-2 has been detected in the brain by RT-PCR, immunohistochemistry, and electron microscopy (EM). The regions of the nervous system where the virus has been detected by these techniques include olfactory epithelium, olfactory bulbs, olfactory tubercle, frontal lobe, cerebellum, medulla, cranial nerves, and trigeminal ganglia. The virus may be present in other areas of the brain but there is no information about it due to the paucity of sampling from other areas at autopsy. The virus has also been demonstrated in cerebral endothelial cells. The combination of endotheliopathy and COVID-19 associated coagulopathy leads to thrombi formation resulting in either hemorrhage or infarcts which are more devastating and fatal manifestations of COVID-19 infection. The size of the hemorrhage may be small or large. Similarly, the size of infarcts will also vary from small to large depending upon the size of the vessel involved by coagulopathy. Pre-existing comorbidities such as hypertension, diabetes, and atherosclerosis will influence the outcome of the stroke. The brain gross and microscopic pathology will depend on the type of stroke in these patients, whether it is ischemic or hemorrhagic.

Peripheral neuropathy, demyelinating polyneuropathy, ascending paralysis, facial paresis, ophthalmoplegia have all been reported in COVID-19.

7.3.3 Musculoskeletal System

As with other viral infections, myalgia is a common manifestation of COVID-19 infection. It may be mild but at times it is very severe. Myositis, rhabdomyolysis, necrotizing autoimmune myositis, hematoma, gangrene, and COVID toes have all been described (Fig. 7.5). Elevated creatine kinase levels are noted, and acute kidney failure may ensue when rhabdomyolysis occurs. The myopathic process and myonecrosis can be diagnosed by imaging techniques (Ramani et al. 2021). The

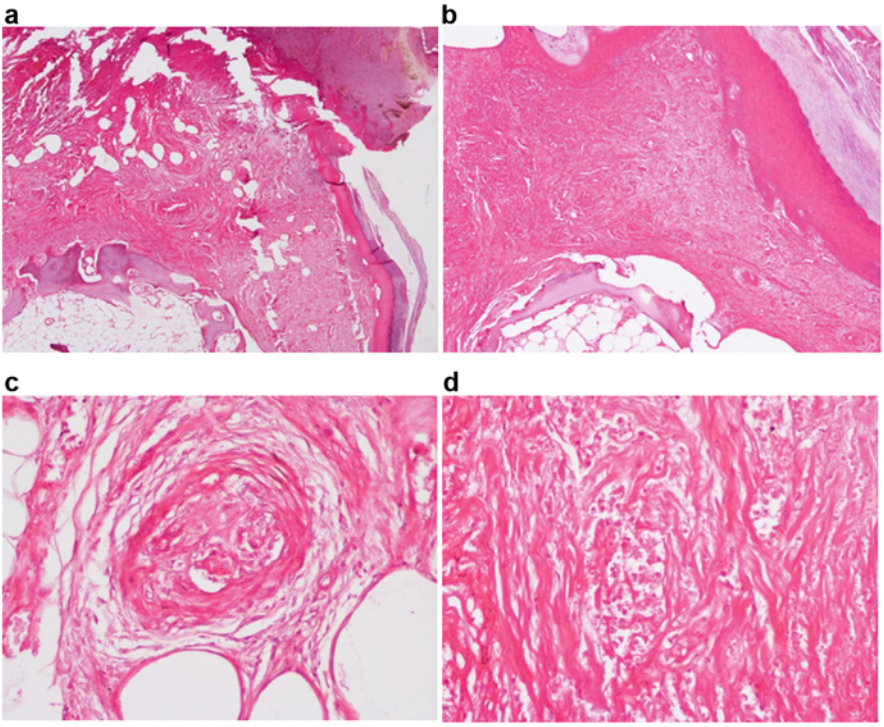

Fig. 7.5 COVID toe: (**a**) Gangrene of the toe showing necrotic skin and underlying tissue. (**b**) higher magnification of **a**. (**c**) Vascular thrombosis in underlying soft tissue. (**d**) Necrosis and neutrophilic infiltration of soft tissue

long-term survivors may demonstrate muscle loss and atrophy. Such patients may manifest with diaphragm dysfunction, respiratory inefficiency, and weaning off from ventilation may be difficult in them. The mechanism of muscle involvement may be due to the direct attachment of SARS-CoV-2 through ACE-2 receptor on a myocyte; however, an immune-mediated mechanism may be an alternate pathway. A small number of patients have shown arthralgia and arthritis as a symptom in COVID-19 infection. Serology needs to be done to exclude other causes of arthritis including other infections. The thrombotic events in COVID-19 infection and vasopressor medications given for hemodynamic support may lead to gangrene formation particularly in patients who have prior peripheral vascular disease, atherosclerosis, and diabetes.

7.3.4 The Liver

There is a dearth of literature about liver pathology and liver parenchymal changes induced or related to SARS-CoV-2. It appears that liver failure is not a main concern

and the liver is not the target of significant inflammatory damage by the virus. The pathological findings observed in liver tissue are highly suggestive of marked derangement of the intrahepatic blood vessel network, secondary to systemic changes induced by the virus (Sonzogni et al. 2020). The gross examination of the liver does not reveal any significant findings; however, it shows varying degrees of steatosis, congestion, ischemia, and fibrosis in the subset of cases. The other histological findings include lobular necro-inflammation and minimal-to-mild portal inflammation. Lobular cholestasis, sinusoidal dilatation, venous flow obstruction, newly organized thrombi, and granulomatous inflammation may be present in some cases (Lagana et al. 2020).

7.3.5 The Kidney

Acute kidney injury (AKI) is a common symptom in COVID-19 infection which occurs in 0.5–80% of patients (Sharma et al. 2021). Among kidney lesions, acute tubular injury is the most common pathology. Microscopic findings include diffuse proximal tubule injury with loss of brush border, non-isometric vacuolar degeneration to even frank necrosis (Su et al. 2020a, b). The Collapsing glomerulopathy and thrombotic microangiopathy are other notable lesions in both antemortem and postmortem tissues. The glomeruli show swollen endothelial cells with the presence of fibrin in glomerular capillaries. There is an edematous expansion of the interstitial spaces in distal collecting tubules and collecting ducts (Yao et al. 2020a, b). Non-specific fibrosis along with lymphocytic infiltrates may be found beneath the renal capsule.

Other rare findings such as anti-neutrophil cytoplasmic antibody vasculitis and anti-glomerular basement membrane disease are described. Occasional findings include segmental fibrin thrombus, podocyte vacuolation, focal segmental glomerulosclerosis, and shrinkage of capillary loops with the accumulation of plasma in Bowman's space (Yao et al. 2020a, b; Santoriello et al. 2020). Although direct viral infection of the kidney is possible and the virus has been demonstrated in some studies, it is certainly not a commonly reported finding.

7.3.6 The Gastrointestinal System

Although it is well known that most COVID-19 infected patients present with respiratory symptoms, some patients particularly those harboring new mutant strains manifest primarily with gastrointestinal (GI) symptoms like diarrhea, loss of appetite, nausea/vomiting, and abdominal pain. This is attributable to the high expression of ACE-2 receptors on GIT epithelial cells (Su et al. 2020a, b). Pathologically, the gastric mucosa shows congestion with a few bleeding points. There may be epithelial degeneration, necrosis, and shedding of the mucosa. The lamina propria and submucosa reveal infiltration by lymphocytes, monocytes, and plasma cells in the esophagus and stomach. Recently, we have seen many cases of intestinal

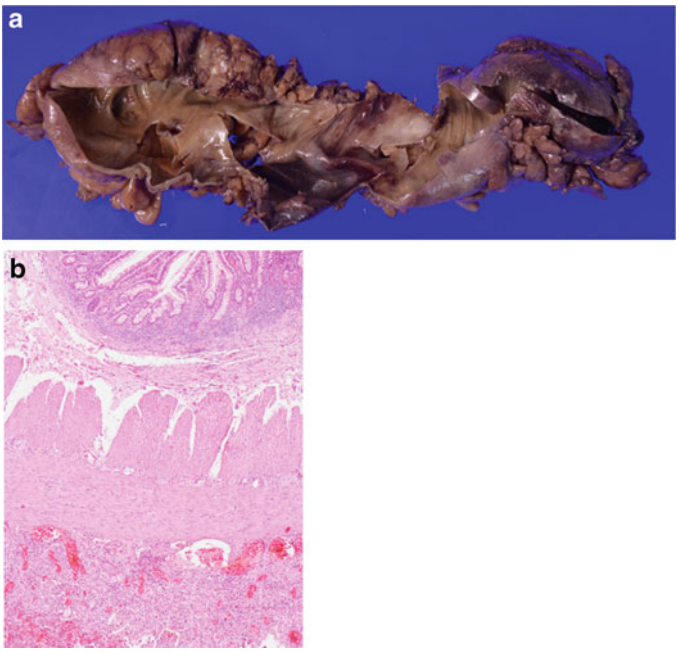

Fig. 7.6 (**a**) Resected segment of the intestine showing dull serosa. (**b**) Acute serositis of intestine due to perforation

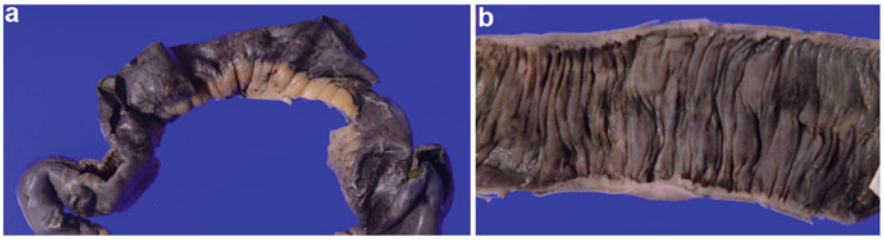

Fig. 7.7 (**a**) resected gangrenous ileum showing a blackish discoloration of the outer aspect. (**b**) On opening, there is mucosal edema and patchy ulceration

perforations presenting with acute abdomen and peritonitis (Fig. 7.6). The intestine also manifests with gangrene which develops as a result of microthrombi known to occur in this disease. (Figs. 7.7 and 7.8). It is also reported that mucosal epithelial cells of the gastrointestinal tract may be apparently normal with occasional inflammatory infiltrates (Yao et al. 2020a, b). The endocrine pancreas may show evidence of tissue degradation.

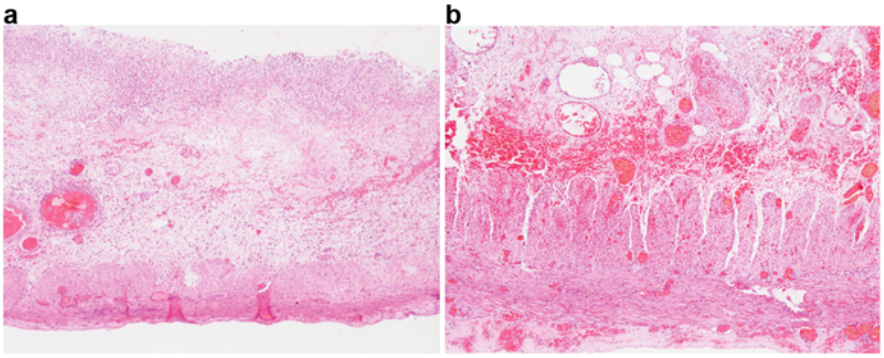

Fig. 7.8 (**a**) Section of ileum showing loss of mucosa, submucosal edema, and muscle necrosis. (**b**) Myonecrosis, submucosal hemorrhages, and vascular thrombi are seen

7.3.7 The Skin

The skin biopsies show a wide spectrum of histopathological patterns in COVID-19 infected patients. Prominent dilated blood vessels with a swollen endothelial layer and congested vessels are common findings. Perivascular infiltration by cytotoxic CD8+ lymphocytes and eosinophils is noted. In a subset of cases, diffuse coagulopathy affecting small vessels is evident. In the early phases of the disease, numerous collections of Langerhans cells in the epidermis can be seen after being activated by the virus (Gianotti et al. 2020). As a result of endothelial damage and microthrombi formation, the skin biopsies demonstrate ulceration, apoptotic keratinocytes, small vessel vasculitis, RBC extravasation, and lobular panniculitis (Fig. 7.9).

7.3.8 The Genital System (Testis)

All SARS-infected testes demonstrate histological findings with extensive germ cell destruction and decreased spermatogenesis in the seminiferous tubules. The basement membrane shows thickening and peritubular fibrosis may set in. Leucocytic infiltration and vascular congestion in the interstitial tissue are other histological findings. The Sertoli cells show swelling, vacuolation, and cytoplasmic rarefaction (Shen et al. 2020).

7.3.9 The Hematopoietic System

Recently, Elsoukkarya et al. (2021) have described pathological findings of 32 patients at autopsy from a single center. They found variable degrees of autolysis in tissue from spleen and lymph nodes. However, in preserved areas intact lymphoid follicles with centrally located germinal centers were seen. The subcapsular and

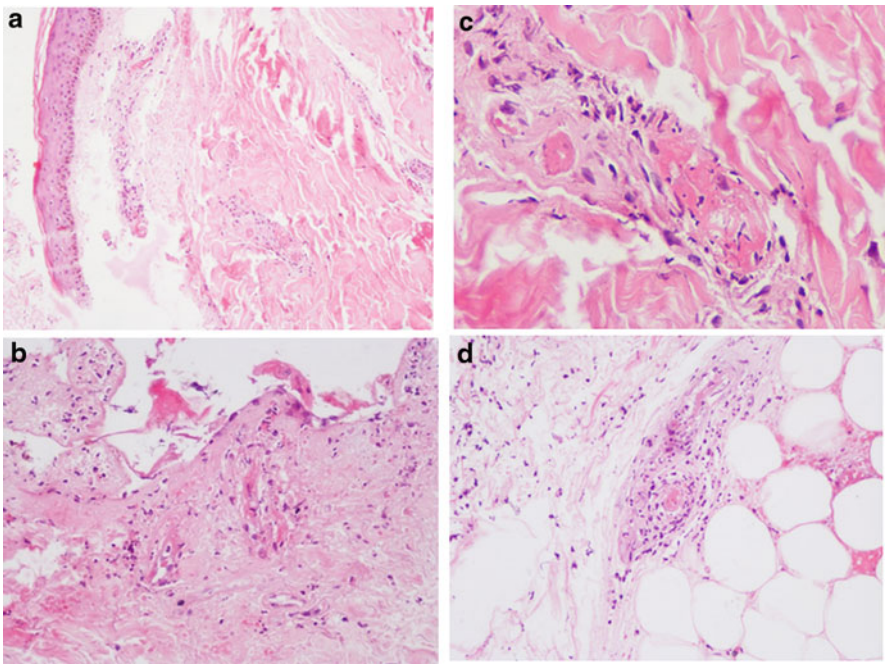

Fig. 7.9 (**a**) Skin biopsy from a COVID positive patient showing preserved epidermis and mild upper dermal infiltrate. (**b**) Complete ulcerated epidermis with only a few keratinocytes attached to basal lamina. (**c**) Small vessel vasculitis and microthrombi and (**d**) panniculitis and vascular occlusion with fibrin

intraparenchymal sinuses were frequently expanded and often contained a variable number of larger transformed cells with prominent nucleoli and amphophilic cytoplasm. The paracortical areas contained largely small lymphocytes or plasma cells. In other studies, lymphocyte depletion involving specific compartments with increased phagocytosis and sinus histiocytosis were prominent findings. Medullary areas of lymph nodes show the prominence of plasma cells and histiocytes.

Examination of the spleen has shown the reduction of cell composition, atrophy of white pulp, and infiltration by neutrophil and plasma cells. Red pulp congestion and an increase in red pulp to white pulp proportion are noted. The depletion of T and B cells occurs due to necrosis, apoptosis, and atrophy of corpuscles in the spleen of infected cases. Bone marrow samples showed reactive changes with tri-lineage hyperplasia, prominence of plasma cells, and histiocytes (Tabary et al. 2020; Hanley et al. 2020).

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