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Musculoskeletal and Emergency Imaging

Review of COVID-19, part 2: Musculoskeletal and neuroimaging manifestations including vascular involvement of the aorta and extremities

Devaraju Kanmaniraja a,*, Jenna Le a, Kevin Hsu a, Jimmy S. Lee a, Andrew Mcclelland a, Shira E. Slasky a, Jessica Kurian a, Justin Holder a, Molly Somberg Gunther a, Victoria Chernyak b, Zina J. Ricci a

a Department of Radiology, Montefiore Medical Center/Albert Einstein College of Medicine, 111 East 210th Street, Bronx, NY 10467, United States of America
b Department of Radiology, Beth Israel Deaconess Medical Center, Boston, MA, United States of America

ABSTRACT

The coronavirus disease 2019 (COVID-19) pandemic caused by the novel severe acute respiratory syndrome coronavirus (SARS-CoV-2) has affected almost every country in the world resulting in severe morbidity, mortality and economic hardship, altering the landscape of healthcare forever. Its devastating and most frequent thoracic and cardiac manifestations have been well reported since the start of the pandemic. Its extra-thoracic manifestations are myriad and understanding them is critical in diagnosis and disease management. The role of radiology is growing in the second wave and second year of the pandemic as the multiorgan manifestations of COVID-19 continue to unfold. Musculoskeletal, neurologic and vascular disease processes account for a significant number of COVID-19 complications and understanding their frequency, clinical sequelae and imaging manifestations is vital in guiding management and improving overall survival. The authors aim to provide a comprehensive overview of the pathophysiology of the virus along with a detailed and systematic imaging review of the extra-thoracic manifestation of COVID-19. In Part I, abdominal manifestations of COVID-19 in adults and multisystem inflammatory syndrome in children will be reviewed. In Part II, manifestations of COVID-19 in the musculoskeletal, central nervous and vascular systems will be reviewed.

1. Introduction

COVID-19 is primarily a respiratory infection caused by the virus SARS-CoV-2 whose roots began in November of 2019 in Wuhan, China. Pneumonia is its most common manifestation with cases complicated by acute respiratory distress syndrome (ARDS) and pulmonary embolism. Cardiac manifestations are less common but include myocardial injury, arrhythmia, arterial and venous thromboembolism, myocarditis, cardiomyopathy, cardiogenic shock and cardiac arrest. However, COVID-19 is an unpredictable infection that can take many additional paths in the human body that are extra-thoracic. The abdominal manifestations are vast including hepatobiliary, genitourinary and gastrointestinal disease. Additionally, there are numerous extra-abdominal processes that can surface in the nervous, musculoskeletal or vascular systems. This article highlights the manifestations of COVID-19 in the musculoskeletal, the central nervous system and the central and peripheral vascular systems. Prevailing theories of the pathophysiology of SARS-CoV-2, the frequency of its involvement in various organ systems, and the imaging manifestations of COVID-19 in these systems will be discussed. The information presented is based on a review of current literature on COVID-19 and the cases discussed are from our own academic medical center in a hot zone in the Bronx, New York.

2. Musculoskeletal imaging of COVID

Musculoskeletal symptoms are relatively common both at the onset and throughout the disease course of COVID-19, and include myalgia (16-19% of patients), back pain (10% of patients), arthralgia and fatigue (26-36% of patients) associated with a muscular component. 2-5 19% of patients present with myalgia as the initial symptom of COVID-19 and...
proximal muscle weakness may be a symptom of COVID-19-associated myositis.\textsuperscript{4,6} The presence of musculoskeletal symptoms is not surprising as angiotensin-converting enzyme 2 (ACE2), the major SARS-CoV-2 entry receptor has been found not only in the lung, bowel, endothelium of small vessels, and smooth muscle, but also in skeletal muscle and synovial tissue.\textsuperscript{3,5} Uncommon musculoskeletal manifestations of COVID-19 include myositis and peripheral neuropathy. In contrast, due to the frequent use of anticoagulation and prolonged hospital stays, intramuscular hematomas and ischiosacral decubiti are more commonly seen.

2.1. Myositis

Myositis, a relatively uncommon feature of COVID-19, presents with proximal muscle weakness and myalgia and may precede respiratory symptoms.\textsuperscript{7} Reflexes may be diminished on physical exam.\textsuperscript{1} Serum creatine kinase levels are elevated and antibody tests such as anti-SSA, anti-SAE 1 may also be positive.\textsuperscript{6,7} Mehan et al. reported a series of 7 cases out of 9 COVID-19 patients who underwent spine MRI for back pain, lower extremity weakness or lower extremity paresthesia and had imaging evidence of paraspinal myositis characterized by intramuscular edema and/or enhancement.\textsuperscript{8} MRI is the most sensitive imaging modality to detect myositis. In the acute setting the muscle demonstrates T2 hyperintense signal consistent with edema and diffuse hyperenhancement post contrast. In the chronic setting, muscle atrophy is characterized by decreased bulk, varying degrees of fatty infiltration, and persistent edema (Fig. 1).\textsuperscript{7} MRI is critical not only in confirming myositis.
but also in guiding potential muscle biopsy. Rhabdomyolysis has also been reported as a late complication of COVID-19, which may quickly become fatal. It is clinically suspected when some combination of myalgia, fatigue, and tea-colored urine due to myoglobinuria are present. Serum creatine kinase is markedly elevated. Potential serious complications include compartment syndrome and acute kidney injury. Aggressive intravenous hydration is vital to prevent prerenal azotemia. The involved muscle or muscle groups may be subtly enlarged on imaging. CT scan reveals heterogeneous hypoattenuation of the involved muscle that may be associated with peripheral hyperenhancement. MRI demonstrates two patterns of rhabdomyolysis. In type 1, the involved muscle has homogeneous high signal on T2-weighted images with homogeneous hyperenhancement, seen in early stages of myonecrosis before liquefaction. In type 2, the involved muscle has heterogeneous high signal on T2-weighted images with peripheral hyperenhancement, seen in more advanced cases. Advanced myonecrosis may also appear as liquefactive zones of very high signal on T2-weighted images with rim hyperenhancement or internal stippled foci of preserved enhancement along with rim hyperenhancement (the “stipple sign”).

2.2. Peripheral neuropathy

A variety of peripheral nerve abnormalities can occur with COVID-19, including postinfectious inflammatory neuropathy and traumatic neuropathy due to the use of proning management. On imaging, the affected nerve may be enlarged, with alteration of its normal fascicular architecture. On ultrasound the affected nerve will be hypoechoic and MRI demonstrates high signal on T2-weighted images. The denervated muscles demonstrate geographic or diffuse edema in the acute setting which may progress to geographic or diffuse atrophy over time (Fig. 2).

2.3. Intramuscular hematoma

Due the frequent use of anticoagulation in prevention and treatment of COVID-19 thromboembolic disease, intramuscular hematomas are common. Hematomas can present as palpable lumps, often associated with pain, ecchymosis, and induration. They sometimes cause neurologic symptoms from mass effect on adjacent neurovascular structures. On CT, acute intramuscular hematomas manifest with muscular enlargement and are hyperdense on non-contrast exam (Fig. 3). The hematocrit sign (cellular-fluid level) is common in hematomas and is considered a highly sensitive and specific sign of coagulopathic hemorrhage characterized by dependent hyperdense cellular content and nondependent hypodense fluid content. MRI signal characteristics vary based on the age of the hematoma. Over time, hematomas may develop a distinct rim on all imaging modalities and may also develop septations and calcifications.

2.4. Decubiti

Sacral and ischial decubiti are also recognized in COVID-19 patients with prolonged hospital stays (Fig. 4). Pressure ulcers are known to occur because of constant external force on dependent skin areas, typically seen in critically ill or immobile patients. COVID-19 patients who
are intubated are at higher risk as they are often difficult to turn and the risk of infectious exposure to clinical staff may reduce attempts to move the patient. Diarrhea has been considered a contributing factor to sacral decubiti in ICU patients and is a common symptom of COVID-19. Sacral “ulcers,” distinct from sacral decubiti, are also reported in COVID-19 patients and are associated with immobility, prolonged bed rest, incontinence, poor nutrition, diabetes and vascular disease. They are reported in critically ill COVID-19 patients with multi-organ disease and present clinically with a distinct cutaneous appearance including purpuric lesions, violaceous induration, livedoid plaques and black eschars. Their etiology includes a combination of systemic coagulopathy, cutaneous ischemia and pressure-induced injury. The role of wound care specialists in managing these patients becomes vital to help prevent, monitor and treat these entities, especially since these ulcers can be a portal of entry for secondary infection and sepsis. There is no literature describing any unique imaging features that distinguish sacral decubiti from sacral “ulcers” in COVID-19 patients.

3. Neuroimaging of COVID-19

Among neurological syndromes associated with SARS-CoV-2 infection, the most common are anosmia, encephalopathy and stroke. Other neurological symptoms include encephalitis, meningitis and peripheral neuropathy. While SARS-CoV-2 particle and RNA can be detected in olfactory neurons and in anatomically connected regions of the brain, the evidence to date suggests that the predominant mechanism leading to neurological disease is due to inflammatory response and prothrombotic state, rather than direct neuron infection. Studies from post-mortem series using electron microscopy indicate infection of vascular endothelial cells rather than neurons suggesting a...
The role of the endothelial bed and a hematogenous route as the most likely pathway for SARS-CoV-2 into the central nervous system. Expression of the ACE2 receptor by the vascular endothelium further supports this mechanism. Subsequent disruption of the blood brain barrier can result in the virus gaining access to the central nervous system. The relative contributions of varying pathogenic mechanisms including inflammatory response, prothrombotic state, and direct viral invasion of neurons and cerebrovascular endothelium that lead to neurologic complications still remain unclear.

The most common indication for neuroimaging in COVID-19 patients is “altered mental status” or “encephalopathy.” Most patients will have no abnormality on neuroimaging. However, among those with positive imaging findings, the most common diagnoses are infarct and hemorrhage, seen in 1.1% of hospitalized patients in one New York City study. In severely ill patients with longer hospitalization time, leukoencephalopathy and microhemorrhages can be seen. In rare cases, severe complications including large multifocal hemorrhage, cerebral edema, and anoxic brain injury can occur. Additional imaging patterns include venous thrombosis, cytotoxic lesions of the corpus callosum,
olfactory bulb involvement, Guillain Barré syndrome and cranial nerve enhancement.

Radiologists should be aware of lung findings of COVID-19 incidentally detected on CTA of the Neck or CT and MRI of the spine as these may be the first recognized manifestations of infection and should be communicated with the referring physician. A recent study has correlated the severity of lung findings on CT with the likelihood of acute neuroimaging findings. Patients with a neurological syndrome at presentation show a modest but significantly higher risk of mortality independent of overall COVID-19 disease severity.

In the following sections, neuroimaging findings of COVID-19 will be reviewed. Standard head CT and MRI brain protocols can be utilized, as they are sensitive in the detection of neurological complications of COVID-19.

3.1. Acute infarct

The overall incidence of infarct in hospitalized COVID-19 is low, reported at around 1% in large cohort studies. However, in hospitalized patients with positive neuroimaging, infarct is the most common finding and is a strong prognostic marker for morbidity and mortality. Most patients with infarction present with encephalopathy instead of focal neurological deficits. COVID-19 is a strong independent risk factor for development of stroke in hospitalized patients. Compared to patients without COVID-19, infarcts in patients with COVID-19 occurred in a younger population, with greater stroke severity, and greater morbidity and mortality. Prophylactic dose anticoagulation therapy is suggested by the American Society of Hematology in critically ill and severely ill patients with COVID-19.

The cause of infarct is likely multifactorial, related to hypercoagulability and endotheliopathy. Supporting this theory are reports of unusually large intraluminal thrombi in the carotid arteries without significant underlying plaque. Additionally, several case series have described large vessel occlusion (LVO) infarcts as the initial presenting symptom of COVID-19 infection with unexpected features including a younger than typical patient population or large clot burden with involvement of multiple vascular territories. Infarcts on CT are characterized by loss of gray-white differentiation in a vascular distribution. Large vessel occlusion can be identified on CTA or MRA as an abrupt cut-off in a proximal intracranial vessel. These findings can be confirmed on MRI with restricted diffusion on diffusion-weighted imaging (DWI).

3.2. Parenchymal hemorrhage

Hemorrhage is another possible complication in severely ill COVID-19 patients and is the second most common finding after ischemic infarct. In a reported cohort of 33 patients with hemorrhage, the majority of cases were detected during their hospital stay (median hospital day 17) with only a minority presenting at admission. The majority of cases demonstrated microhemorrhage, while five developed large hemorrhages complicated by mass effect and herniation with a mortality.
rate of 100%. In this cohort, a majority of patients were on anti-coagulation for elevated D-Dimer, which is a possible risk factor. Other possible causes include a combination of critical care therapy, extracorporeal membrane oxygenation (ECMO), and consumptive coagulopathy. Large parenchymal hematomas and multifocal hemorrhage can be seen, sometimes with rapid change (Figs. 10, 11). The rate of multifocal hemorrhage in COVID-19 patients is greater than that of the general population, reported to be 5 times the general population’s rate. Multifocal hemorrhage can be associated with more extensive parenchymal injury with complicated posterior reversible encephalopathy syndrome (PRES) and leukoencephalitis-like appearances, which will be discussed later. Microhemorrhage detectable on MRI but not on CT is more typically seen in the subacute to chronic phase of severely ill patients in combination with white matter changes and will be discussed in the next section.

Hemorrhage is detected on CT as a hyperdense collection. It can be characterized on MRI depending on the stage of blood. Susceptibility weighted imaging is sensitive for the T2 shortening effect of certain stages of blood. It can readily detect foci of microhemorrhage not seen on other sequences, and is more sensitive than gradient echo sequences in the detection of microhemorrhage.

3.3. White matter changes and hemorrhage

White matter changes with microhemorrhages are a less common imaging finding in COVID-19 patients. The incidence of these findings will vary based on image utilization and severity of cases in the hospital. In a study of 7146 COVID-19 patients, leukoencephalopathy was detected in 7 and positively correlated with clinical risks including obesity, acute renal failure, mild hypernatremia, and anemia. In a study of 7146 COVID-19 patients, leukoencephalopathy was detected in 7 and positively correlated with clinical risks including obesity, acute renal failure, mild hypernatremia, and anemia.

In most cases, leukoencephalopathy is found in patients with severe illness, long hospitalizations, and a clinical history of encephalopathy. The etiology of these findings is difficult to determine given the complex multisystem dysfunction and polypharmacy in the patients, however, vascular, demyelinating, or hypoxia related injury have been proposed. Similar findings have been reported in high-altitude cerebral edema, leading some to hypothesize that a similar pathophysiology is responsible. A more severe appearance of white matter injury with macrohemorrhages can be seen in rare cases. Similar findings have been reported with other coronavirus infections such as Middle Eastern respiratory syndrome (MERS).

On CT, the findings can be subtle with hypodensity and mild expansion in the corpus callosum (Fig. 11). On MR imaging, T2 FLAIR can show signal abnormality in the corpus callosum, periventricular white matter, and subcortical white matter and can be associated with restricted diffusion (Fig. 12). Microhemorrhages can be an associated finding in the corpus callosum or along the gray-white junction, and are much better delineated on susceptibility weighted imaging (SWI) (Fig. 13). In some instances, this can appear like PRES or acute hemorrhagic leukoencephalitis (Fig. 14).

3.4. Venous sinus thrombosis

Venous sinus thrombosis is uncommon in COVID-19 but has been reported. In a recent review of the literature, a total of 33 COVID-19 patients with cerebral venous sinus thrombosis were reported. Headache was the most common symptom seen in 48.6%, with seizure, decreased consciousness, or focal neurological deficits present in over a quarter of the patients. Contrary to cerebral venous sinus thrombosis in the general population, reported cases have had a slight male majority and an older population. Significant elevation of inflammatory markers in these patients suggests a possible systemic prothrombotic state leading to cerebral venous sinus thrombosis. Non-contrast CT of the head can show increased density and size of the dural venous sinuses or central venous sinuses and can be confirmed with CT or MRI with contrast (Fig. 15).

3.5. Anoxic injury

Anoxic brain injury can occur in severely ill COVID-19 patients although reported very infrequently (1 out of 126 patients in a descriptive literature review). Limited data is available to evaluate the cause in these patients given the few case reports, however, in severely ill patients the etiology is likely multifactorial including cardiovascular...
shock and cardiopulmonary arrest (Fig. 16). Anoxic injury is demonstrated on CT by diffuse loss of gray white differentiation progressing to cerebral edema with sulcal effacement.

3.6. Meningitis/encephalitis

Diagnosis of meningitis or encephalitis is based on a combination of clinical, laboratory (RT-PCR positive for SARS-CoV-2 in the cerebrospinal fluid), and radiological findings. Imaging findings include cortical FLAIR hyperintensities, cortical restricted diffusion, or leptomeningeal enhancement.

3.7. Cranial and spinal nerve neuropathy

Acute immune-mediated polyneuropathies such as Guillain-Barré syndrome (GBS) and its subtypes like Miller Fischer syndrome (acute onset of external ophthalmoplegia, ataxia, and areflexia) and shock and cardiopulmonary arrest (Fig. 16). Anoxic injury is demonstrated on CT by diffuse loss of gray white differentiation progressing to cerebral edema with sulcal effacement.

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polyneuritis cranialis (isolated multiple cranial neuropathy) are rare complications of COVID-19. Imaging findings include cranial nerve or cauda equina enhancement.

3.8. Olfactory bulb involvement

Anosmia and dysgeusia have been reported as common early symptoms in patients with COVID-19, occurring in greater than 80% of patients in one European series. Imaging findings are not as commonly observed, however. Increased T2 signal in the olfactory bulbs and tracts with or without contrast enhancement has been reported in only 19% of patients in one series.

Task based functional MRI in a patient with persistent olfactory and gustatory symptoms after COVID-19 infection demonstrated lack of BOLD signal in orbitofrontal cortex (secondary and tertiary olfactory and gustatory area) suggesting central olfactory pathway impairment may be involved in the underlying etiology of the persistence symptoms. However, olfactory bulb atrophy after COVID-19 induced anosmia has been described in patients with prolonged postinfectious anosmia, suggesting persistent olfactory bulb injury plays a role as well.

3.9. Optic neuritis

Orbital manifestations of COVID-19 such as optic neuritis have been reported. In a multicenter cohort of 129 patients presenting with severe COVID-19, 7% of patients had one or several FLAIR hyperintense nodules of the posterior pole of the globe. The clinical significance and etiology of these nodules are currently unknown.

3.10. Orbit

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4. Imaging of COVID-19 in the aorta and peripheral vascular system

SARS-CoV-2 can directly infect the vascular system because ACE-2 receptors are located on endothelial cells lining our vessels and organ vascular beds. Resultant endotheliitis may precipitate an immune reaction with widespread endothelial dysfunction associated with apoptosis. This leads to a complex pathway of vasoconstriction with subsequent organ ischemia, inflammation and a procoagulant state. A patient's hypoxic status and the presence of ARDS further contribute to the progression of a proinflammatory thromboembolic state. The pathogenesis of COVID-19 coagulopathy is multifactorial and not fully understood. It remains unclear whether COVID-19 follows the same path of spiraling events seen in sepsis-induced coagulopathy and thrombotic microangiopathy typical of non-COVID critically ill patients.

COVID-19 coagulopathy can manifest with varying venous or arterial thromboembolic events including deep venous thrombosis (DVT), pulmonary embolus (PE), limb ischemia, stroke and myocardial infarction. It is associated with a higher risk of death. Based on a meta-analysis of 425 studies evaluating thromboembolism (TE) in COVID-19 till June 2020, the pooled odds of mortality were 74% higher among patients who develop TE compared to those who did not. A high
It has also been suggested that TE occurs more often in COVID-19 patients than in other critically ill non-COVID patients. In a retrospective study comparing 81 COVID-19 patients to 81 non-COVID patients, 11% of COVID-19 patients had TE (5 had arterial abdominal or lower extremity TE, 4 had splenic or renal infarcts, 1 had portal vein thrombosis and one had renal vein thrombosis) and only one non-COVID patient had known portal vein thrombosis from known HCC. Finally, elevated serum markers are seen that reflect COVID-19’s unique coagulopathy. Thrombocytopenia and elevation of fibrin D-dimer and fibrinogen levels are commonly seen and are associated with poor outcomes. Additional immune-mediated inflammatory markers due to cytokine storm may also be elevated including CRP, interleukins, ESR, and ferritin.

4.1. Deep venous thrombosis (DVT)

Based on a meta-analysis of 20 studies including 1988 COVID-19 patients, the weighted mean prevalence was 31.3% for venous thromboembolism (VTE), 19.8% for DVT and 18.9% for PE. The risk of DVT is increased not just in ICU patients but also in non-ICU hospitalized patients and affects both the upper and lower extremity. Upper extremity DVT, however, is much rarer than lower extremity DVT in COVID-19 with sparse reports only of spontaneous upper extremity DVT in the literature. The risk of general VTE, including DVT, PE and
venous thrombosis of other sites, rises with prolonged hospitalization where cumulative incidence rates rose to 59% on hospitalization day 21 of ICU patients. The incidence of DVT in COVID-19 patients with PE appears lower than in non-COVID patients suggesting that an in situ thromboinflammatory insult unique to SARS-CoV-2 plays a role in triggering PE in COVID-19 patients rather than migration of peripheral venous thrombi. Based on a meta-analysis of 27 studies of patients with COVID-19, DVT was present in only 42.4% of patients with PE, lower than the usual prevalence (60%) of DVT in non-COVID patients. In a prospective study of 26 hospitalized COVID-19 patients with PE who were screened for lower extremity DVT with ultrasound, only 2 patients (7.7%) had DVT.

Venous duplex US with compression US technique remains the first-line imaging tool for diagnosis of suspected lower and upper extremity DVT and has the advantage of bedside portable performance. Thrombi typically appear as occlusive or non-occlusive echogenic venous filling defects on gray-scale images that may distend the affected vein and may arise denovo or at sites of central line placement (Fig. 17). Contrast-enhanced CT with venous timing can show a sharply defined occlusive or non-occlusive venous filling defect or an asymmetrically non-enhanced venous segment. It has the advantage of detecting IVC and intrapelvic DVT not optimally detected on lower extremity Duplex US (Fig. 18).

4.2. Aortic and peripheral arterial thromboembolism

Arterial thromboembolic events are much less common than venous thromboembolic events in COVID-19 and are potentially more deadly when their recognition is delayed. Although the true incidence of arterial thromboemboli of the aorta and extremities in COVID-19 patients is not known, there are growing reports of it in the literature. A systematic review of 27 studies reporting arterial thromboembolic events among COVID-19 patients till June 2020 included cardiac, aortic, mesenteric, central nervous system and limb ischemia and revealed a pooled incidence of arterial thromboembolic events of 4.4%. The most common site of disease was the limb arteries (39%), with the remaining distribution including cerebral arteries (24%), great vessels (aorta, common iliac, common carotid and brachiocephalic trunk, 19%), coronary arteries (9%) and superior mesenteric artery (8%). Many of the patients who suffer arterial thromboembolic events lack predisposing peripheral arterial disease and thromboprophylaxis does not always prevent arterial thromboembolic ischemia. Atrial fibrillation, although it may be concomitant in COVID-19, is not as common a predisposing condition of arterial TE in COVID-19 as it is in non-COVID patients.

Aortic involvement in COVID-19 can present as floating thrombi or segments of partial or complete occlusion. Involvement of the aorta...
tends to occur in patients with more severe infection and evidence of cytokine storm with elevated serum inflammatory markers. Both aortic floating thrombi (AFT) and abdominal aortic occlusion (AAO) are rare and life-threatening conditions in the general population. AFT are pedunculated mural thrombi that have the potential to break off causing visceral and peripheral embolism and can present silently or with chest or abdominal pain. In non-COVID patients they are associated with abnormal coagulation, abnormal aortic morphology and aortic stents. In COVID-19 patients they have been reported in the arch, descending aorta and ascending aorta in patients over 60 with elevated serum inflammatory markers. A thorough radiologic search for arterial TE is appropriate aggressive anticoagulation measures and/or endovascular therapy. Doppler Ultrasound is also valuable in monitoring of complications of COVID-19. Therefore, it is critical for radiologists to be familiar with the broad spectrum of imaging manifestations of COVID-19, and to be knowledgeable about how frequently various organ systems may be affected. Increased vigilance about the complications of COVID-19 is necessary to ensure prompt diagnosis and further aid patient management.

5. Conclusion
The SARS-CoV-2 virus is an intimidating agent because of its easy and aggressive spread all over the world and its ability to penetrate so many organ systems in the human body. There is a growing role of radiology in the second wave of the pandemic in detection and monitoring of complications of COVID-19. Therefore, it is critical for radiologists to be familiar with the broad spectrum of imaging manifestations of COVID-19, to better understand the pathophysiology of SARS-CoV-2, and to be knowledgeable about how frequently various organ systems may be affected. Increased vigilance about the complications of COVID-19 is necessary to ensure prompt diagnosis and further aid patient management.

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