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Special Review

Pathophysiology and Imaging Findings of COVID-19 Infection: An Organ-system Based Review

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Background: COVID-19 commonly presents with upper respiratory symptoms; however, studies have shown that SARS-CoV-2 infection affects multiple organ systems. Here, we review the pathophysiology and imaging characteristics of SARS-CoV-2 infection in organ systems throughout the body and explore commonalities.
Objective: Familiarity with the underlying pathophysiology and imaging characteristics is essential for the radiologist to recognize these findings in patients with COVID-19 infection. Though pulmonary findings are the most prevalent presentation, COVID-19 may have multiple manifestations and recognition of the extrapulmonary manifestations is especially important because of the potential serious and long-term effects of COVID-19 on multiple organ systems.

KEY WORDS: COVID-19, SARS-CoV-2; thrombosis; ACE2; cytokine storm; imaging; inflammation.

Abbreviations: COVID-19 Coronavirus-19, **ACE2** Angiotensin-converting enzyme 2, **IL** Interleukin, **TNF** Tumor necrosis factor, **CT** Computed tomography, **MRI** Magnetic resonance imaging, **MRA** Magnetic resonance angiography, **US** Ultrasound, **PE** Pulmonary embolism, **AKI** Acute kidney injury, **RAAS** Renin-angiotensin-aldosterone system, **MCA** Middle cerebral artery, **PCA** Posterior cerebral artery, **PICA** Posterior inferior cerebral artery, **DIC** Diffuse intravascular coagulation, **MIS-C** Multisystem inflammatory syndrome in children, **MIS-A** Multisystem inflammatory syndrome in adults, **CRP** C-reactive protein, **RT-PCR** Reverse transcriptase-polymerase chain reaction

BACKGROUND

The novel SARS-CoV-2 virus is responsible for the Coronavirus-19 (COVID-19) illness, which has affected millions worldwide and continues to spread. The virus was first identified in connection with an outbreak of pneumonia in Wuhan City, Hubei province, China in December 2019 (1,2). The most common initial presentation includes fever and dry cough, and other early symptoms include dyspnea, fever, malaise, muscle pain, loss of taste and/or smell, and myalgia (3–5,6). More severe illness includes respiratory distress, thrombosis, and multiorgan failure (7).

SARS-CoV-2 is a large, enveloped, single-stranded RNA virus which enters the body via nasal and bronchial epithelial cells and pneumocytes. A sentinel paper in Cell by Hoffman, et al. demonstrated by sequence analysis that SARS-CoV-2 uses the ACE2 receptor in a manner similar to the SARS-CoV virus. Their analysis showed conservation of the receptor binding motif which is known to make contact with the ACE2 receptor. To further support ACE2 mediated entry, they expressed ACE2 on BHK-21 cells, not otherwise susceptible to SARS-CoV-2 infection and found that this facilitated viral entry into cells (8). Viral replication results in breakdown of the epithelial-endothelial barrier, leading to an inflammatory response with resultant pulmonary damage. In severe COVID-19 infection, there is fulminant activation of the coagulation cascade. This is the proposed etiology of multiorgan dysfunction (9–11).

While the virus' effects on the pulmonary system have been extensively studied, effects on other organ systems are also being actively investigated (12) (Table 1). A unifying theme appears to be widespread increases in acute phase reactants and activation of the coagulation cascade (13,14). As severe illness and multiorgan failure portend mortality, a more comprehensive understanding of SARS-CoV-2 pathophysiology is needed. By elucidating the unifying pathophysiology, targeted therapies may be able to combat infection throughout multiple organs simultaneously.

Radiology plays a key role in evaluating the effects of COVID-19 in each organ system (Table 2). Extensive work has been done to characterize these radiographic findings. To

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TABLE 1. Overview of COVID-19 Clinical Manifestations by Organ System

Organ System	Manifestations
Cardiothoracic	Cough
	Dyspnea
	Sore throat
	Rhinorrhea
	Chest pain
Gastrointestinal	Nausea
	Vomiting
	Diarrhea
	Abdominal pain
Genitourinary	Elevated creatinine
	Proteinuria
	Hematuria
	Hyperkalemia
Neurologic/Neurovascular	Headache
	Altered mentation
	Anosmia
	Lethargy
	Stroke
	Confusion
	Hemiparesis
	Paresthesia
	Aphasia
Vascular	Edema
	Pulseleness
	Palor
	Skin change
	Necrosis

TABLE 2. Key Radiographic Findings by Organ System

Organ System	Radiographic Findings
Cardiothoracic	Lower lobe and peripheral predominant opacities
	Ground glass opacities or consolidations in advanced disease
	Septal thickening
	Air bronchograms
	Crazy paving
	Pleural effusions
	Pulmonary embolism
	Heart strain
	Myocarditis
	Acute coronary syndrome
Gastrointestinal	Bowel wall thickening
	Inflammation of adjacent mesenteric fat
	Small volume ascites
	Small bowel obstruction
	Mesenteric vessel occlusion and bowel ischemia
Genitourinary	Enlarged, echogenic kidneys
	Renal infarcts – wedge-shaped parenchymal defects
Neurologic/Neurovascular	Vasculitis pattern – punctate enhancement with extensive ischemic lesions
	Restricted diffusion throughout centrum semiovale, corpus callosum, basal ganglia, cerebellum
	Ischemic stroke
	Venous sinus thrombosis
	Hemorrhagic stroke
	PRES
	Microhemorrhages
Vascular	Venous or arterial thrombus

our knowledge, this is the first comprehensive description of multi-system radiographic findings of COVID-19. Here, we present a system-based review of the clinical presentation, underlying pathophysiology, and radiographic manifestations of COVID-19 highlighting unifying themes so as to progress our understanding of SARS-CoV-2 infection.

CARDIOTHORACIC SYSTEM

SARS-CoV-2 is primarily transmitted by respiratory droplets (8) and has a variable incubation period ranging from 0-14 days with a mean of 4-5 days. This presents the clinical challenge of many presymptomatic carriers who can spread the disease (15). COVID-19 often presents predominantly as a pneumonia (16). While the most common cardiothoracic symptoms include cough and dyspnea, less common symptoms include sore throat, rhinorrhea, and chest pain (15). Approximately 80% of patients have mild respiratory illness not requiring hospitalization, 20% require hospitalization, and 5% of these require intensive care (15). Severe pulmonary disease manifests as acute hypoxic respiratory failure (16). In addition to pulmonary parenchymal disease, pulmonary barotrauma has emerged as a frequent side effect of serious COVID-19 infection. A recent study in Radiology demonstrated a 15% rate of barotrauma in COVID-19 positive patients in invasive mechanical ventilation, compared to a 0.5% rate of barotrauma in patients without COVID-19 (17). While this study included a large cohort and provided convincing evidence of increased barotrauma in COVID-19 patients, detailed information regarding ventilator settings and comorbid conditions was not provided, leaving many unanswered questions regarding the real risk imposed by the virus itself in patients with COVID-19.

As the pandemic progresses, there is increasing recognition that the virus causes long-term damage to the lung parenchyma. An article in Lancet Respiratory Medicine reviewed early evidence suggesting fibrotic change in the lungs of patients post COVID-19 infection and suggested the use of antifibrotic medication such as pirfenidone (18). Barisione, et al. performed a study on transbronchial biopsy autopsy specimens in patients who succumbed to COVID-19. Their data demonstrated phases of alveolar damage secondary to

SARS-CoV-2, with the final phase culminating in interstitial fibroblast proliferation with sparse collagen fiber deposition (19). These data are in concert with recent radiology data demonstrating the development of pulmonary fibrosis on chest CT. Fang, et al. presented a case series of 12 patients in the recovery period of severe COVID-19 infection in which there was gradually development of increasing fibrosis (20). While a large sample size is needed to confirm these results, these data suggest serious long term pulmonary sequelae from COVID-19 infection.

Though cardiac manifestations of COVID-19 are less common than thoracic findings, they represent serious disease and require prompt recognition by clinicians and radiologists. COVID-19 myocardial injury was observed early in the study of the pandemic (4). Myocarditis has emerged as a rare, albeit serious sequalae of the disease (21,22). Acute coronary syndrome stemming from the prothrombotic state has also been reported (23). A recent case report of a COVID-19 positive patient presenting with acute myocardial infarction diagnosed on coronary angiography and cardiac MR underscored the key role that radiology plays in decision making for patients with elevated myocardial markers (24). Cardiac indices are image-based parameters that have shown predictive value for increased morbidity and mortality in a variety of conditions. A recent study by Eslami, et al. evaluated the utility of cardiac indices in patients infected with COVID-19. They found that an increased cardiothoracic ratio was associated with an increased hazard ratio of death and that extensive lung involvement was associated with an elevated cardiothoracic ratio. These data indicate that cardiothoracic indices may be a powerful predictor of mortality in patients with COVID-19 (25).

SARS-CoV-2 enters type I and II alveolar epithelial cells, bronchial epithelial cells, and vascular endothelial cells through ACE-2 receptor cell mediated endocytosis, rendering the bronchial tree an ideal entry point for infection (26). Once inside, the virus initiates a cascade of pro-inflammatory cytokines including interleukin (IL)-1B, IL-6, and tumor necrosis factor leading to cytokine storm and sepsis (16). This aggressive inflammatory response results in direct lung damage. Further, infected cells produce IL-8 which serves as a chemoattractant for cells of both the innate and adaptive immune system. This amplifies the immune response resulting in additional cellular damage (27). Ultimately, unless medical treatment can interrupt this cascade of events, the patient will go on to develop acute respiratory distress syndrome from the pulmonary edema and inflammation. Radiographically this manifests as pulmonary parenchymal opacities representing acute respiratory distress syndrome.

Chest imaging of COVID-19 has been extensively characterized and studied (28–30). Chest radiographic features include lower lobe and peripheral predominant opacities (Fig 1a) (31). Chest radiography is less sensitive than CT with a reported sensitivity of approximately 69% (32). 40-66.7% of cases with negative radiograph demonstrated abnormal findings on chest CT (33). While multiple professional societies have recommended against radiography for routine monitoring of patients with COVID-19, critically ill patients often undergo daily exams as part of their intensive care (34). Pleural effusions are relatively uncommon with one metanalysis reporting an incidence of 5.9% (35). CT demonstrates a similar distribution of ground glass opacities which may become confluent in advanced disease (Fig 1b). Less common features include septal thickening, air bronchograms, and crazy paving (28,33,36,37). Pulmonary barotrauma in the form of pneumothorax (Fig 1c) and pneumomediastinum (Fig 1d) can be seen on both chest radiography and CT. These findings are essential for the radiologist to identify because patients may require urgent intervention.

A major thrombotic complication of COVID-19 infection seen on chest CT is pulmonary embolism (38,39). In one retrospective study, 22% of patients who underwent CT angiography were diagnosed with PE (Fig 1e). Of those with PE, 55% had segmental PE, 31% had lobar PE, 13% had central PE and 5.5% had subsegmental PE. Radiographic evidence of right heart strain was seen in 11% of patients (38). In the long term, COVID-19 infection results in scarring of the pulmonary parenchyma manifesting as fibrotic change on chest CT (Fig 1f). Patients presenting with this long term sequala will likely become more prevalent as time progresses and more people recover from the acute phase of the disease (20).

Cardiac manifestations of COVID-19 are also important to identify on imaging. Cardiac MRI is the best modality for identifying the subtle findings of myocardial injury secondary to COVID-19 and its thrombotic complications. As described in Capaccione, et al., in the setting of elevated markers of myocardial injury, cardiac imaging can serve as a critical branch point for diagnosing myocarditis versus myocardial infarction. Given that treatment diverges significantly at this branch point, cardiothoracic imaging can be critical in appropriately diagnosing and treating the patient (24). Figure 2a, b demonstrates representative axial and coronal images cardiac MR images of a patient with myocarditis. Figure 2c, d are serial short axis images of a cardiac MR in a patient with acute myocardial infarction in the setting of COVID-19 infection.

Cardiothoracic imaging plays a key role in the diagnosis and management of patients with COVID-19 infection.

GASTROINTESTINAL SYSTEM

Research has shown that approximately 18% of COVID-19 patients experience gastrointestinal symptoms (40). These may be clinically evident before respiratory disease (41). Mild symptoms are nonspecific and include nausea, vomiting, diarrhea, and abdominal pain (42,43). Importantly, acute mesenteric ischemia can manifest acutely or subacutely, and can be seen in patients with or without cardiovascular risk factors or a history of arteriosclerotic disease (44). Mesenteric ischemia thought to arise from the prothrombotic state of patients with COVID-19 has been reported as a severe complication (45). Numerous studies have shown hepatic injury

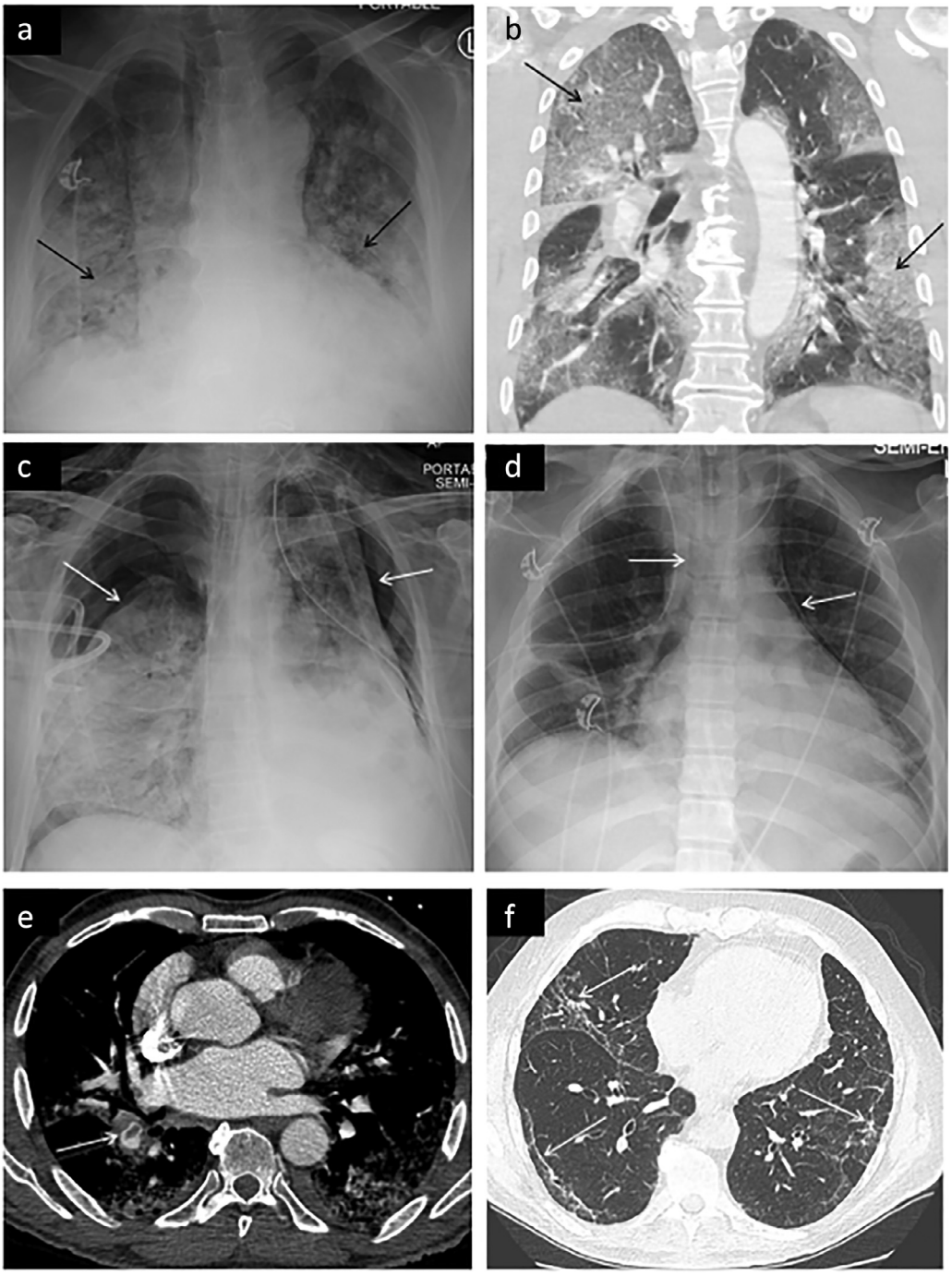

Figure 1. Demonstrates thoracic manifestations of COVID-19. (a) Characteristic chest radiograph findings of bilateral peripheral and lower lobe predominant airspace opacities (arrows) which appear as ground glass opacities or consolidation on CT (b). Pneumothorax (c) frequently occurs in critically ill COVID-19 patients, as seen in this case of bilateral pneumothoraces. (d) Pneumomediastinum is also frequently observed, as shown here. (e) Pulmonary embolism is a common vascular complication of COVID-19 infection, as shown here in the right lower lobar segmental artery of a patient infected with COVID-19. (f) Demonstrates pulmonary fibrosis, a long term sequalae of COVID-19 infection, manifesting as peripheral reticulations and traction bronchiolectasis.

manifesting as elevated liver function tests is common in SARS-CoV-2 infected patients. The mechanism of injury is currently unclear, but is hypothesized to be related to direct hepatocyte injury or indirectly via immune-related cytokine storm or hypoxia related injury (46). Multiple case reports have described pancreatitis in patients with COVID-19 (47,48). Though a causal relationship between COVID-19 and pancreatitis has not been established, the systemic inflammatory response is likely contributory.

Similar to infection of the respiratory system, SARS-CoV-2 enters enteric epithelial cells through ACE2 receptor binding (49). Diarrhea and other gastrointestinal

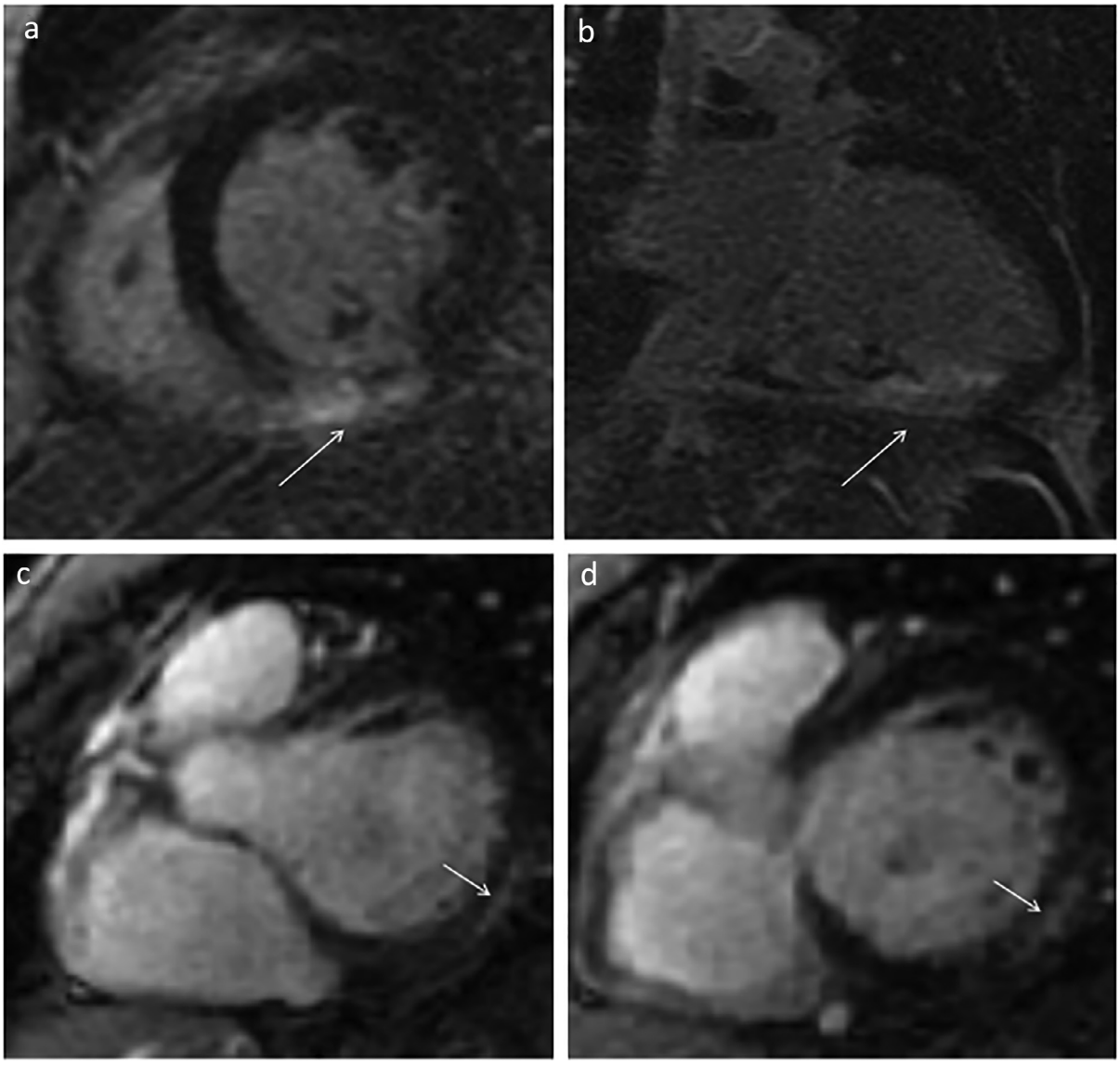

Figure 2. Demonstrates cardiac manifestations of COVID-19. (a) Short axis and (b) three chamber post-gadolinium views of a patient with RCA thrombus resulting in infarction secondary to untreated COVID-19 infection. Serial chart axis images (c, d) demonstrating delayed gadolinium enhancement of the myocardium in a patient with COVID-19 myocarditis.

symptoms observed in many COVID-19 patients are likely the clinical manifestations of cellular injury which alters intestinal cell permeability and causes enterocyte dysfunction.

The imaging features of the gastrointestinal system in COVID-19 patients are nonspecific for COVID-19 but characteristic of disease patterns such as enteritis or mesenteric ischemia. Patients with mild infectious colitis/enteritis may have bowel wall thickening, inflammation of adjacent mesenteric fat or a small amount of ascites. Some patients present with small bowel obstruction (50) (Fig 3a, b). As above, pancreatitis is increasingly being recognized in patients infected with COVID-19, and manifests as peripancreatic inflammation and edema (Fig 3c). The hypercoagulable state may lead to mesenteric vessel occlusion and bowel ischemia (Fig 3d). Studies have shown that pulmonary COVID-19 is often identified incidentally on abdominopelvic imaging for other pathology. A study by Dane, et al. identified 23 patents undergoing abdominal imaging who were incidentally noted to have pulmonary findings. The indication of the study for the majority of these cases was "abdominal pain". RT-PCR testing for SARS-CoV-2 was positive in 17 of the cases, underscoring the importance of recognizing COVID-19 even in unexpected cases and on extrathoracic imaging (51).

GENITOURINARY SYSTEM

Similar to the GI system, the renal system can be infected with COVID-19. Hirsch, et al., demonstrated that acute kidney injury (AKI) developed in 37% of hospitalized patients with COVID-19, and of these, 14% required dialysis (52). Rates of AKI were particularly high among those admitted to intensive care units, ranging from 78 to 83%, with many

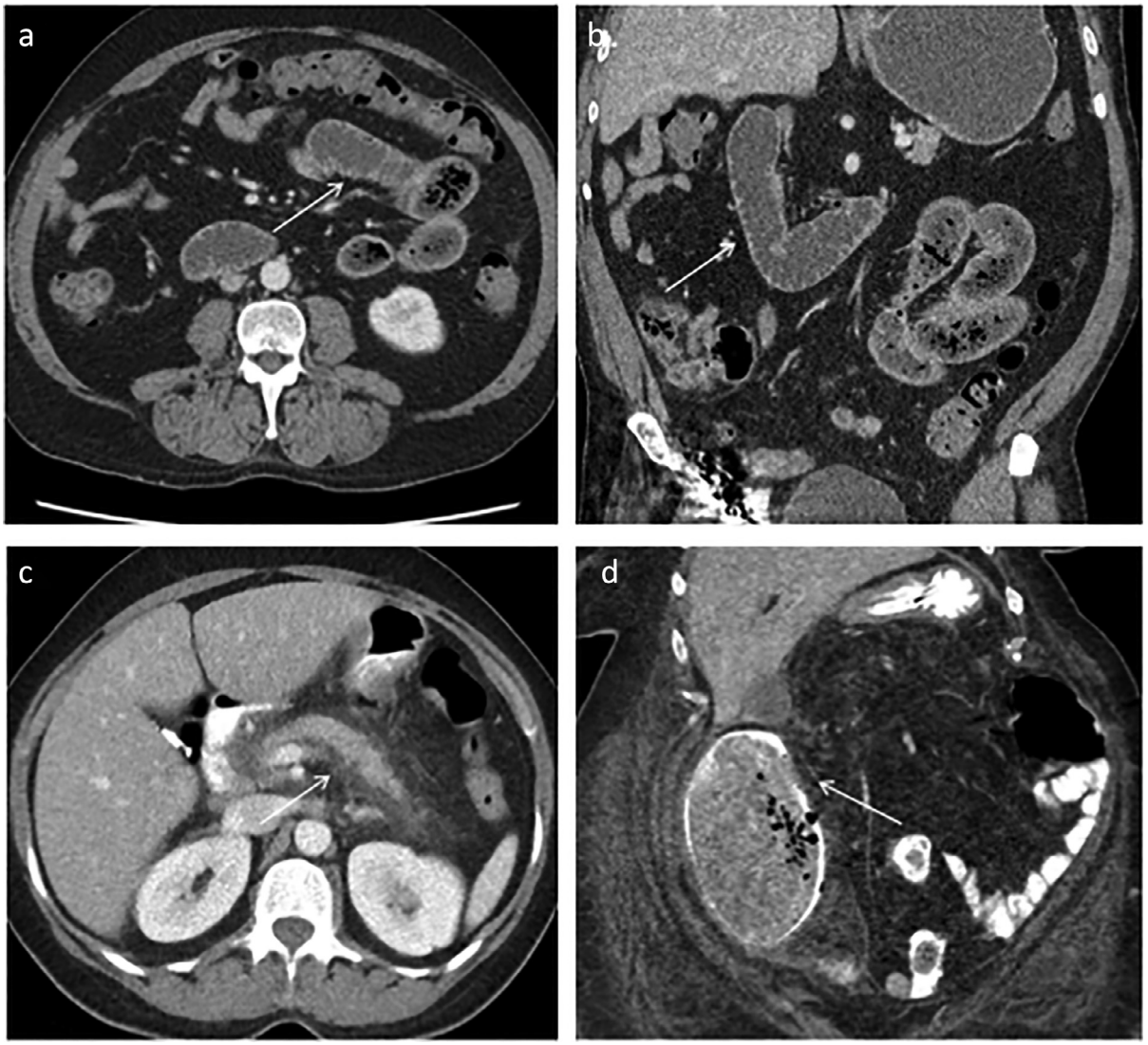

Figure 3. Demonstrates gastrointestinal manifestations of COVID-19. (a), (b) Multiple dilated, fluid filled loops of small bowel (*white arrows*) compatible with small bowel obstruction in the axial and coronal planes, respectively. (c) Edematous pancreas with extensive surrounding fat stranding and edema compatible with acute pancreatitis (*white arrows*). (d) Ascending colonic dilation and paracolonic changes with pneumatosis representing acute bowel ischemia.

patients requiring renal replacement therapy (53). Proteinuria was reported in 87% (54), hematuria in 41% (52), and hyperkalemia in 12.5% (55).

As in other organ systems, SARS-CoV-2 enters host cells via ACE2 (56). ACE2 is also a key enzyme in the renin-angiotensin-aldosterone system. ACE2 is expressed on mesangial cells, podocytes, and the brush border of the proximal tubular cells of the kidney (57). In a study of 26 autopsy specimens, Hua, et al. analyzed renal abnormalities in patients infected with COVID-19 using ultrastructural analysis and immunostaining. They identified proximal tubule injury, loss of brush border, and in some cases, necrosis. A limitation of the study was the small sample size given the challenges of performing autopsies on patients infected with SARS-CoV-2. Despite this, these findings provide valuable insight into how the virus causes clinical and radiographic findings of COVID-19 in the kidney (57). Infection of the cells described above results in acute tubular injury, erythrocyte aggregation leading to obstruction in glomerular and peritubular capillary loops, and microvascular dysfunction from endothelial cell injury (55,58,59). Acute kidney injury may also result from local disruption in renin-angiotensin-aldosterone system homeostasis. ACE2 plays a critical role in this system given that it cleaves angiotensin II into angiotensin 1-7 which in turn has vasodilatory effects (60). Finally, the cytokine storm induced by the virus with its resultant multisystem dysfunction contributes to AKI.

Renal sonography in AKI associated with COVID-19 infection may be normal or demonstrate enlarged, echogenic kidneys (Fig 4a) (61). Renal infarcts due to severe hypercoagulopathy associated with the virus (62,63) are best seen on postcontrast CT imaging as focal, wedge-shaped regions of

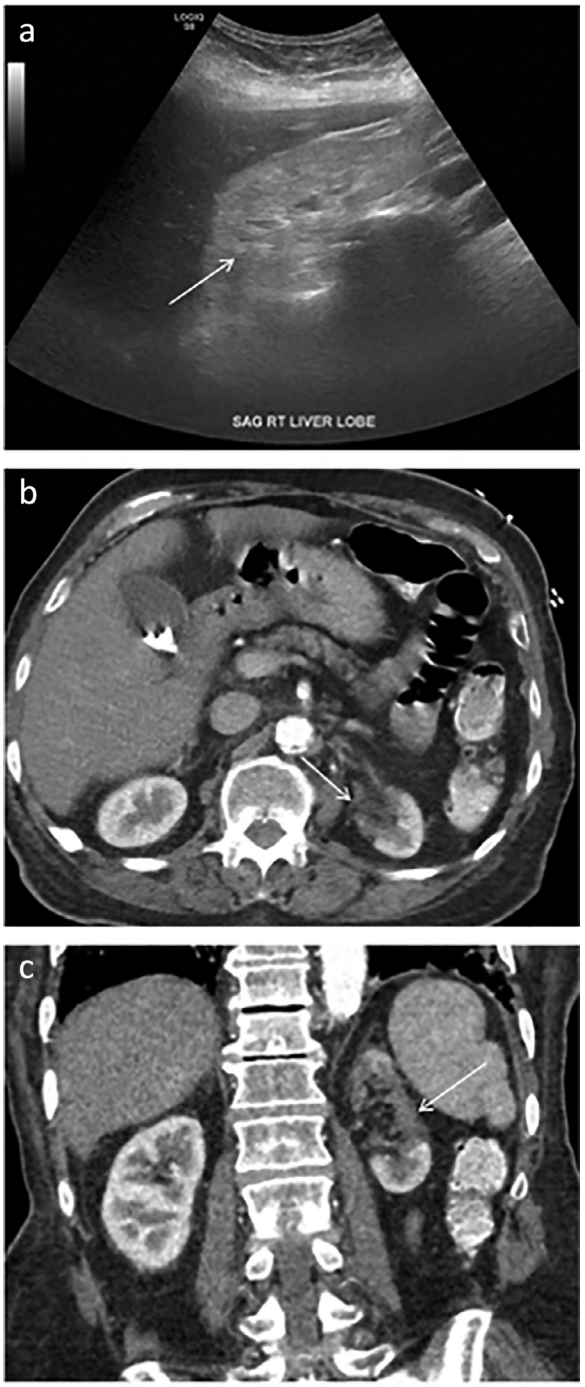

Figure 4. Demonstrates renal manifestations of COVID-19. (a) Representative ultrasound image demonstrating diffusely increased echogenicity of the right kidney (*arrow*) compared to the liver compatible with renal parenchymal disease. (b), (c) Contrast-enhanced CT images of the abdomen in the axial and coronal planes, respectively, demonstrate a large focal region of decreased enhancement involving the upper and middle left kidney (*arrow*), the result of thrombosis.

decreased enhancement involving both the cortex and medulla (Fig 4b, c). While less common than pulmonary or GI manifestations of COVID-19 infection, renal complications can be severe and have long lasting clinical sequela rendering it critical for radiologists to promptly recognize these findings in COVID-19 infected patients.

NEUROLOGIC SYSTEM

Similar to the respiratory system, neurologic manifestations of COVID-19 can be due to parenchymal disease or thrombotic complications of COVID-19. Neurologic symptoms associated with COVID-19 infection are varied and complex ranging from mild headache, anosmia, and taste impairment to stroke, meningitis, encephalitis, and seizures (64). A systematic review of the literature by Pan, et al. evaluated 61 studies with a total of 711 patients infected with COVID-19 with cross sectional imaging (CT or MRI) of the brain. The study analyzed the patients according to severity of respiratory symptoms. Predominant neurologic findings in patients with mild respiratory symptoms included cerebral infarction, cranial nerve abnormalities including olfactory bulb involvement, and white matter abnormalities. Individuals with severe respiratory disease had increased rates of cerebral infarction and white matter abnormalities, as well as hemorrhagic events. These findings suggest that neurologic sequela of COVID-19 exist on a continuum corresponding to severity of disease. In patients with severe disease there should be heightened clinical suspicion for hemorrhagic events (65).

As in other cells of the body, the SARS-CoV-2 virus enters via the ACE2 receptor, which is expressed in the neurologic system on glial cells, neurons, capillary endothelium and the olfactory bulbs (66). Neurologic clinical manifestations may be the result of intracranial viral invasion from hematogenous spread, direct extension through the olfactory bulb (67), or may be secondary to immune-mediated damage from cytokine storm (68). This massive release of cytokines can alter the blood-brain barrier leading to inflammation of the brain parenchyma. Thromboembolic events, endothelial cell and neurovascular injury via ACE2 mediated cell entry, and hemorrhage also contribute to the serious neurologic effects of COVID-19 infection (69).

Neuroimaging may be essential for diagnosis of neuropathology in patients with COVID-19. The instability of COVID-19 patients, poor renal function limiting the use of contrast agents, and contamination of the scanner and/or imaging suite present significant challenges for obtaining studies (70). Neurologic imaging manifestations are protean and may be related to direct SARS-CoV-2 CNS infection or the sequela of COVID-19 infection and associated therapy, including hypoxemic injury, cytokine release syndrome, mechanical ventilation, or extracorporeal membrane oxygenation (71,72). A common presenting clinical symptom is anosmia (73), with imaging showing increased T2/FLAIR signal of the olfactory bulb on MRI (Fig 5a, b). PRES (posterior reversible encephalopathy syndrome) with and without hemorrhage (Fig 5c,d) has also been identified as a neurologic manifestation of COVID-19 infection (74,75). COVID-19 related leukoencephalopathy (Fig 5e, f) encompasses various patterns of white matter signal abnormality (71) with some

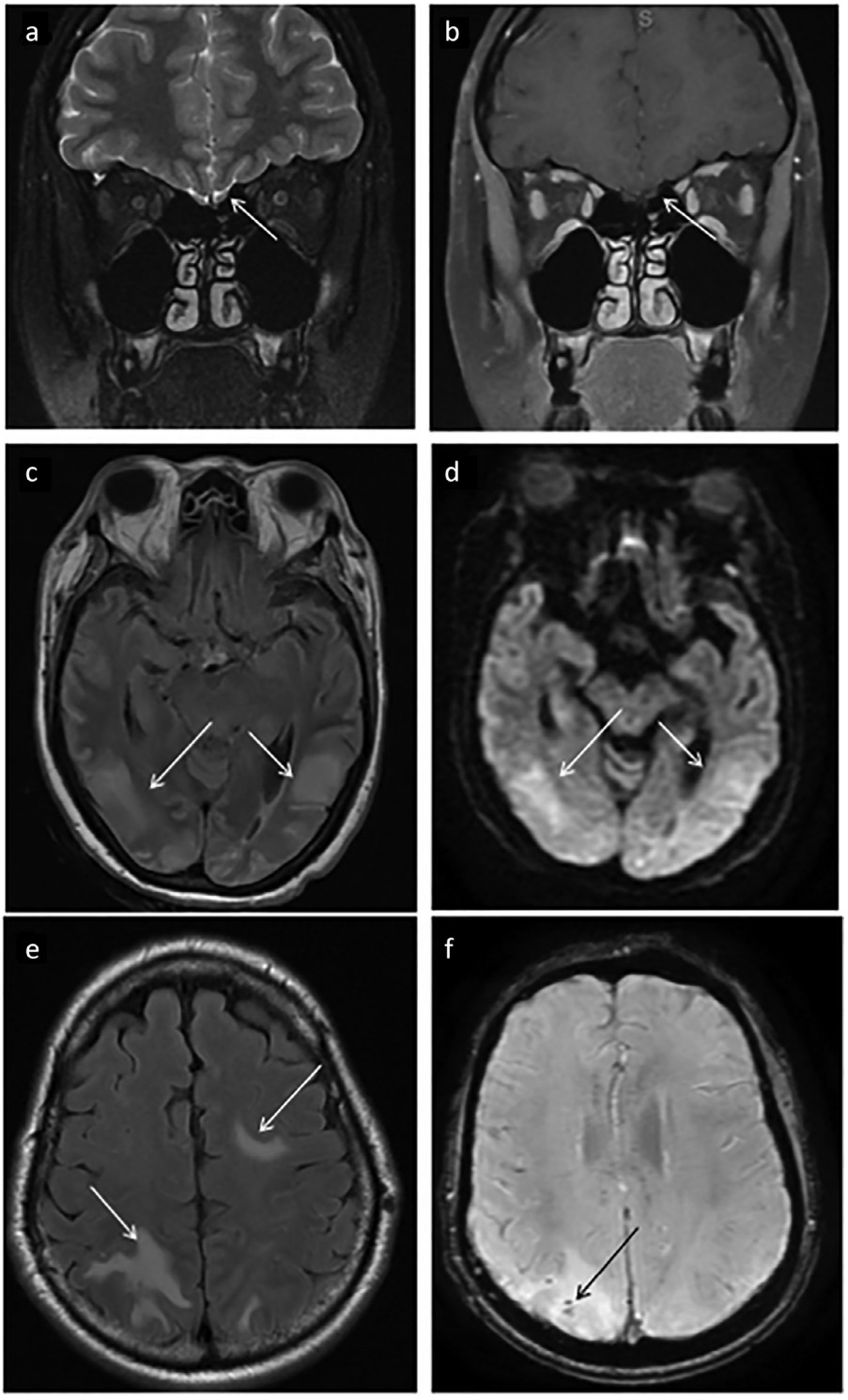

Figure 5. Demonstrates non-vascular neurologic manifestations of COVID-19. Minimal (a) T2 / (b) FLAIR hyperintensity in the left greater than right olfactory bulbs which correlated clinically with loss of smell in a COVID-19 positive patient. PRES manifesting as asymmetric T2/FLAIR hyperintensities (c) of the occipital lobes which exhibited restricted diffusion on DWI sequences (d). Leukoencephalopathy manifesting as confluent subcortical T2/FLAIR hyperintensity within the bilateral parietal, bilateral occipital, and left frontal lobes (e) is also commonly seen. In many cases as with this patient, microhemorrhages were identified on SWI sequences (f).

cases demonstrating associated parenchymal microhemorrhages (76). Additional neuropathology that has been associated with COVID-19 infection includes hypoxic encephalopathy, cranial nerve pathologies, cytotoxic lesions of the corpus callosum, demyelinating lesions, leptomeningeal enhancement, and cortical signal abnormality (71). More

studies are needed to clarify whether neurologic imaging findings are direct COVID-19 encephalopathic changes or the sequela of hypoxic/ischemic encephalopathy or post-viral demyelination.

Thromboembolic complications of COVID-19 infection are similarly an important cause of severe morbidity and mortality in COVID-19 infection (77–79). As in other organ systems, SARS-CoV-2 infection results in vascular thrombosis and endothelial inflammation. This manifests clinically as large vessel occlusions leading to ischemic stroke, venous sinus thrombosis, hemorrhagic strokes, and, less commonly, central nervous system vasculitides (78–80). Clinical presentation incudes a myriad of nonspecific neurological symptoms including headaches, altered mentation, anosmia, lethargy, and confusion. Additionally, patients may present with localizing symptoms such as hemiparesis, paraesthesias, and aphasia (81). Less commonly, non-traumatic sub-arachnoid hemorrhage and parenchymal hemorrhage has been reported (72,82). A vasculitis-like imaging pattern has also been identified, manifesting as punctate enhancement with extensive ischemic lesions with restricted diffusion throughout the centrum semiovale, corpus callosum, basal ganglia, and cerebellum. These may or may not have a detectable intra- or extracranial vessel abnormality on MRA (83).

COVID-19 thrombotic complications in the brain have similar mechanisms to thrombosis in other vessels. Slow flow of blood within microcirculation promotes viral entry into capillary endothelial cells via ACE2. Infection triggers inflammation secondary to cytokine storm damaging brain parenchyma (66,78,84). In addition to local inflammation, this cytokine storm promotes a prothrombotic state leading to vascular thromboses. Infected endothelial cells upregulate cell signaling molecules which activate thrombotic pathways and cause microangiopathy. Thrombocytopenia, elevated D-dimer, and elevated C-reactive protein (CRP) in patients with severe COVID-19 and stroke support this hypothesis. The pathophysiology behind vasculitis is proposed to be a process similar to that of varicella with viral replication in cerebral arterial walls triggering local inflammation and apoptosis (81,84).

Strokes were among the most common neurologic imaging findings across multiple studies. Yoon, et. al. demonstrated that the most frequently involved vascular territory was the middle cerebral artery (MCA) followed by posterior circulation (posterior cerebral artery (PCA)), posterior inferior cerebral artery (PICA)), multiterritorial infarcts, and watershed infarcts (85). Radiographically, stroke is often first imaged with emergent non-contrast CT which may exhibit foci of hypoattenuation (Fig 6a,b), loss of the insular ribbon

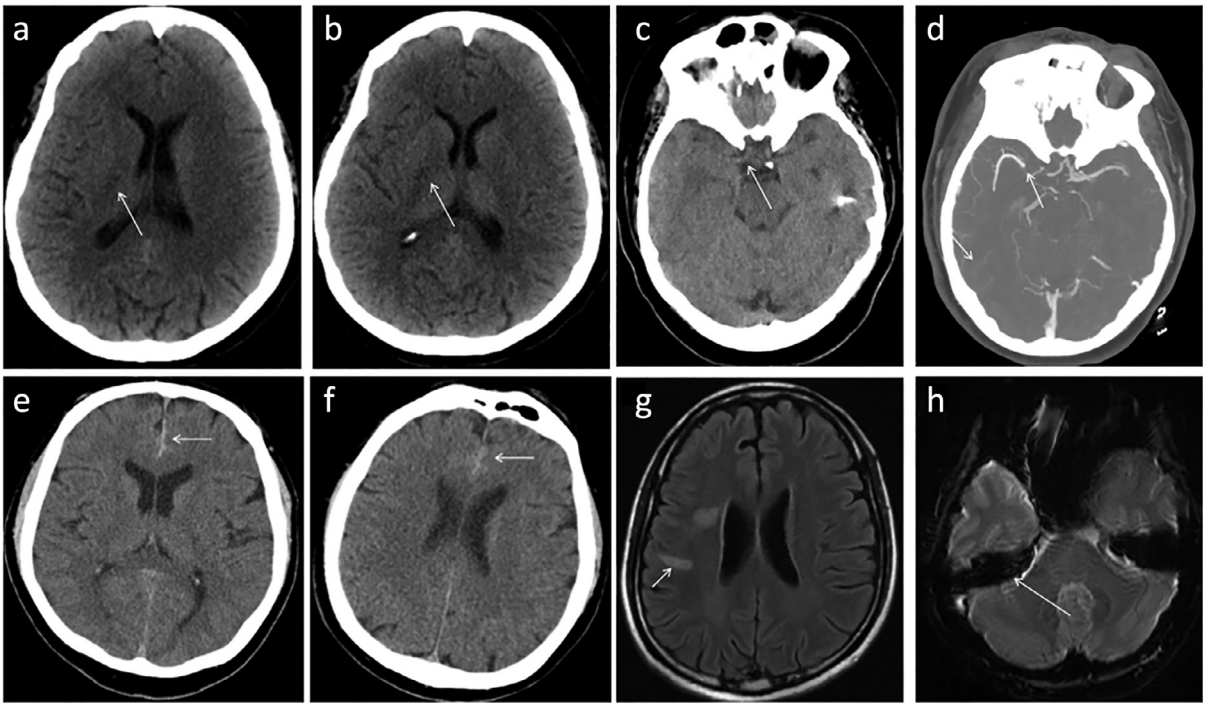

Figure 6. Demonstrates neurovascular manifestations of COVID-19. (a), (b) Serial images in an emergent non-contrast head CT demonstrating multiple foci of decreased attenuation in the right posterior limb of the internal capsule compatible with acute infarct (*arrows*). (c) Representative head CT image of a COVID-19 patient with symptoms suspicious for stroke, found to have a dense right MCA (*arrow*); subsequent CTA (d) confirmed this finding (*arrow*). (e) Represents initial head CT of a COVID-19 patient with altered mental status found to have an acute subdural hemorrhage (arrow); follow-up imaging of the same patient (f) demonstrated stability (*arrow*). (g) Venous sinus thrombosis has also been identified in patients with COVID-19 manifesting as T2/FLAIR hyperintensity secondary to vascular congestion resulting in edema; on SWI (h) blooming artifact confirms thrombus in the right sigmoid sinus in this patient, likely the sequala of hypercoagulability in the setting of COVID-19.

sign, blurred margins of the lentiform nucleus, or the dense MCA sign (Fig 6c). Acute vascular occlusion is better seen on CTA, often obtained immediately after CT suggestive of stroke (Fig 6d). On MRI, findings of acute stroke in the setting of COVID-19 infection are identical to stroke in other contexts, manifesting as regions of restricted diffusion. Other vascular neuroradiology manifestations of COVID-19 infection include subdural hematoma (Fig 6e, f) and venous sinus thrombosis (Fig 6g, h). Neuroradiology plays a key role in diagnosis of these and less common neuropathology. Radiologists should have a high index of suspicion for abnormalities when evaluating neuroimaging in patients with COVID-19.

VASCULAR SYSTEM

Given that solid organ damage secondary to thrombosis and hypoxic injury are a hallmark of COVID-19 infection, it is not surprising that numerous reports have detailed both arterial and venous thrombosis of the extremities in patients with COVID-19. A large study of 3,334 patients including 829 ICU and 2,505 non-ICU patients assessing all types of thrombosis found an overall arterial thrombosis rate of 11.1%, with systemic thromboembolism in 1.0% (86) and deep venous thrombosis in 3.9% (86). These numbers likely underestimate the true incidence of thrombosis. Surveillance imaging of COVID-19 positive patients with bilateral leg ultrasound found the rate of deep venous thrombosis as high as 65% - 69% (87,88).

The underlying pathophysiology of arterial and venous thrombosis is the same as in solid organ systems; ACE2 receptors are a key entry point for viral infection. Electron microscopy studies have demonstrated endothelial cell invasion by SARS-CoV-2 (89,90). As in solid organs systems, this results in endothelial cell injury, impaired fibrinolytic function, and release of prothrombotic von-Willebrand factor as well as proinflammatory IL-6 (91). Abnormal blood flow contributes to thrombosis via stasis which may induce further endothelial injury (92). Severe COVID-19 results in platelet dysfunction, complement activation, and cytokine storm resulting in systemic inflammation and severe illness (93–95).

Ultrasound is the imaging modality of choice for suspected venous thrombus. Positive cases demonstrate non-compressible veins with increased internal echogenicity. Color and spectral Doppler will be absent in the setting of occlusive thrombus (Fig 7a). Arterial thrombus may also be visualized sonographically with absent color and spectral Doppler flow in the occluded artery. On post contrast CT or MRI, vascular thrombus manifests as a focal contrast filling defect on CT and MRI, and can have associated vessel wall thickening or perivascular edema (Fig 7b). On noncontrast MRI, absence of the expected flow related signal void in arterial structures is suggestive of arterial thrombus.

COVID-19 IN THE PEDIATRIC POPULATION

Acute infection in pediatric patients is similar yet often more mild than adult COVID-19 symptoms. Decreased prevalence of pulmonary symptoms is hypothesized to be the result of lower ACE2 gene expression in pediatric lungs (96). However, the post infectious period is distinct. Multisystem Inflammatory Syndrome in Children (MIS-C) emerges approximately one month after acute COVID-19 infection and presents clinically as a Kawasaki-like disease causing multi-organ system damage. Cough and shortness of breath are infrequently observed in MIS-C, in contradistinction to acute COVID-19 infection. MIS-C patients most commonly present with fever, abdominal pain, diarrhea, vomiting, conjunctivitis, rash, headache and/or sore throat (97,98). Most of these patients have positive SARS-CoV-2 antibodies rather

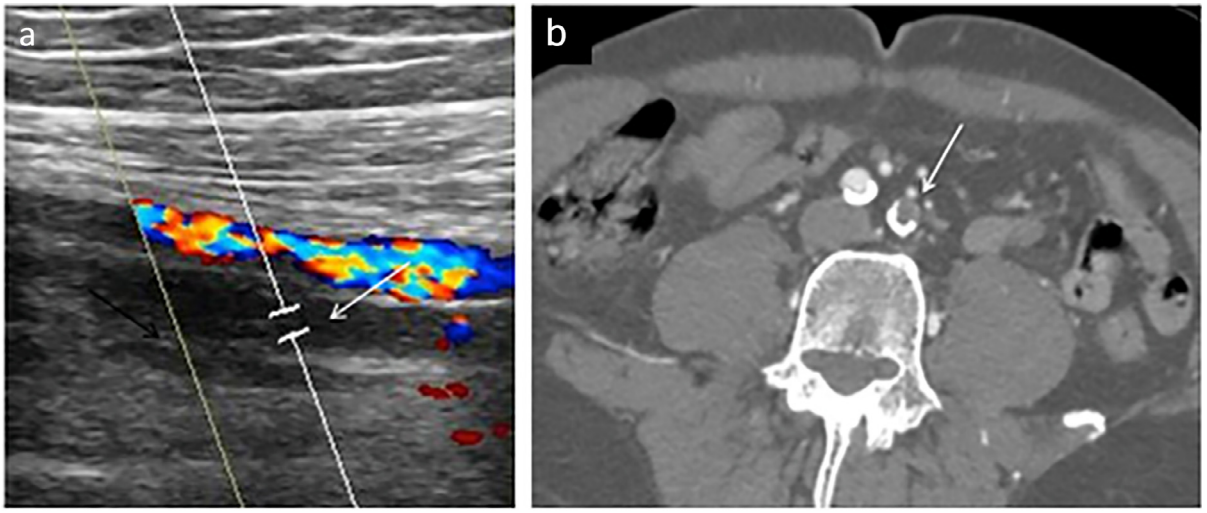

Figure 7. Demonstrates vascular manifestations of COVID-19 infection. (a) Occlusive deep vein thrombosis manifested by absent color Doppler flow in the proximal femoral vein. (b) Acute arterial thrombus, manifested by a filling defect (*arrow*) in the left common iliac artery on CT angiogram. Thrombus in this patient extended throughout the left lower extremity arterial system. (Color version of figure is available online.)

than positive RT-PCR, indicating that this syndrome occurs after acute infection (99).

The molecular pathophysiology of MIS-C is thought to be postinfectious cytokine storm (100). These patients have elevated inflammatory markers including CRP, D-dimer, procalcitonin, ferritin, and elevated erythrocyte sedimentation rate (ESR) (100). Kawasaki disease is characterized by elevated levels of tumor necrosis factor, IL-6, and IL-1β, similar to adult patients with COVID-19 (101,102). Recently there have been several case reports of a Kawasaki-like multisystem inflammatory syndrome in adults (MIS-A) (103,104). Subsequently, a comprehensive case series collected 27 adults and analyzed commonalities in order to understand the syndrome in adults better. Elevated CRP and D-dimer were characteristic laboratory findings, and a fever was to most common symptom. They concluded that although MIS-A is rare, any adult with COVID-19 is at risk for this syndrome and it should be considered clinically (105). As an increasing number of COVID-19 related multisystem inflammatory syndrome cases come to light in both adults and children, a better understanding of the molecular pathophysiology may lead to improved treatment strategies.

On imaging, acute COVID-19 infection in children is similar to that of adults, with subpleural lower lobe peripheral predominant ground glass opacities on chest imaging (106). A study by Bayramoglu, et al. demonstrated that nearly half of children with COVID-19 had ground glass opacities either with or without accompanying consolidation. Further, they identified the feeding vessel sign, halo sign, pleural thickening, interlobular interstitial thickening, and lymphadenopathy as other frequent chest imaging signs in children with COVID-19 (107). A meta-analysis evaluating imaging findings of COVID-19 in 850 children demonstrated a 61.5% rate of ground glass opacities or consolidation. They also identified additional pediatric chest imaging signs, including the halo sign, interstitial opacities, bronchial wall thickening, and crazy-paving sign (108). Although MIS-C is largely a clinical diagnosis, some characteristic imaging findings have been reported (97,98,109). Though the imaging findings are overall nonspecific, MIS-C should be considered in the differential diagnosis in a pediatric patient with prior COVID-19 exposure.

COVID-19: SINGLE PATHOPHYSIOLOGY, MULTIPLE MANIFESTATIONS

While initial reports of SARS-CoV-2 infection pointed to a highly transmissible pneumonia, extensive clinical experience and research have demonstrated that COVID-19 is a complex multisystem disorder. On a molecular level, infection via the ACE2 receptor initiates a cascade of cell signaling events resulting in generation of inflammatory cytokines, prothrombotic molecules, and acute phase reactants. These serve to both amplify the immune system's response as well as damage the surrounding tissue. Clinical and radiographic findings are the macroscopic manifestations of these microscopic findings: edema secondary to increased tissue permeability and immune cell response, micro and macrothrombi with distal ischemia, and tissue inflammation. Understanding symptoms in terms of these tissue effects can direct research into treatments aimed at addressing underlying pathophysiology, as well as inform diagnostic imaging of patients with COVID-19. Further, by pursuing therapies aimed at breaking the molecular cycle of inflammation and thrombosis, therapeutic agents can provide systemic benefit.

Though COVID-19 has proved a devastating disease extending to all corners of the globe, tremendous progress in understanding and treatment of the disease has resulted in improved clinical outcomes and decreased mortality (110). By understanding the underlying pathophysiology and imaging manifestations which extend across multiple systems of the body, we can better prepare ourselves to identify key radiographic findings and best serve our patients as we battle this pandemic together.

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