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Original Research Article

Imaging spectrum of extrapulmonary manifestations of COVID-19 infection- a multi-centre descriptive study from Southern India

Harshavardhan Mahalingam[1]*, Lokesh Murali[1], Ashwini Govisetty[2], Senthil Kumar Aiyappan[3], Karthik Krishna Ramakrishnan[2], Seena Cheppala Rajan[2], Rajeswaran Rangasami[1], Vinayagam Shanmugham[3]

[1]Department of Radiology, Sri Ramachandra Institute of Higher Education and Research, Chennai, Tamil Nadu, India
[2]Department of Radiology, Saveetha Medical College, Chennai, Tamil Nadu, India
[3]Department of Radiology, SRM Medical College and Research Centre, Chennai, Tamil Nadu, India

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***Correspondence:**
Dr. Harshavardhan Mahalingam,
E-mail harsha.mahalingam@gmail.com

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ABSTRACT

Background: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) is the causative agent for coronavirus disease 2019 (COVID-19) pandemic. While the primary organ of involvement in this disease is the lung, multiple other organ systems can be involved either due to direct viral cytopathic effects or due to thrombo-inflammation and immune system dysregulation. In this study we describe the spectrum of extrapulmonary imaging findings encountered in our patients with COVID-19.

Methods: This was a retrospective observational study conducted in three tertiary care hospitals in the city of Chennai in southern India. All cross-sectional imaging studies (other than lung imaging studies) performed in patients who had proven COVID-19 infection by RT-PCR testing during the period from April 2020 to March 2021 were included as part of the study. Extrapulmonary findings in these imaging studies were recorded and collated system-wise.

Results: A total of 96 non-lung imaging studies were performed in patients who had RT-PCR positivity for COVID-19 infection. Among these a total of 30 studies had extrapulmonary imaging findings. Vascular involvement was seen in 14 patients, central nervous system involvement in 13 patients, abdomen involvement in 2 patients, and cardiac involvement in 1 patient. Vascular manifestations included arterial and venous thrombosis. Neurological manifestations included stroke, encephalitis and demyelination. Abdominal manifestations included enteritis and acute kidney injury. Cardiac manifestation was in form of myocarditis.

Conclusions: Extrapulmonary imaging findings in COVID-19 are uncommon but not rare. Multisystem thrombotic manifestations and central nervous system involvement account for majority of extrapulmonary imaging findings in COVID-19.

Keywords: Computed tomography, COVID-19, Extrapulmonary, Magnetic resonance imaging, SARS-CoV2, Ultrasonography

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) is the causative agent for the ongoing coronavirus disease 2019 (COVID-19) pandemic. First reported in China, it has spread to every region of the world with more than 159 million confirmed cases and more than 3.3 million deaths as of twelfth of May 2021.[1] COVID-19 is primarily a disease of the respiratory system with lung pathology being the primary cause of morbidity and mortality. Features of lung involvement in COVID-19 has been widely described and are more easily recognised both on clinical examination and on imaging studies. However, extrapulmonary COVID-19 manifestations are myriad with considerable overlap of clinical features with other etiologies.

Extrapulmonary COVID-19 can occur with or without concomitant lung involvement. Mechanisms postulated for extrapulmonary involvement in COVID-19 are direct cytopathic effects of the virus, endothelial cell damage leading to thrombotic complications, dysregulation of the immune system and dysregulation of renin-angiotensin system (RAS).[2]

The resultant extrapulmonary manifestations can be broadly classified into a) vascular and hematological and b) non-vascular. Non-vascular pathologies can be further subdivided into neurological, gastrointestinal, renal, cardiac and musculoskeletal. Imaging [Ultrasonography (US), computed tomography (CT) and magnetic resonance imaging (MRI)] plays an important role in many of the clinical extrapulmonary COVID-19 syndromes by localising the site of involvement and ruling out alternate diagnoses. Knowledge of extra-pulmonary imaging manifestations of COVID-19 is evolving. Recognising the imaging spectrum of extrapulmonary COVID-19 syndromes is of paramount importance in directing appropriate patient management.

In this background, the objective of our study was to describe the spectrum of imaging manifestations of multisystem extrapulmonary involvement in COVID-19.

METHODS

This was a retrospective observational study conducted in three tertiary care hospitals (Sri Ramachandra Medical College, Saveetha Medical College and SRM Medical College and Research Centre) in the city of Chennai in southern India for a period of 12 months from the beginning of April 2020 to the beginning of May 2021. Imaging studies were retrieved from the PACS database of the institutions. The medical records were accessed from the hospital database. This study was approved by the institutional ethics committee with approval number CSP-MED/20/NOV/63/137. Inclusion and exclusion criteria for the study were as follows.

Inclusion criteria

Patients underwent cross-sectional imaging studies (excluding HRCT thorax) for extrapulmonary symptoms. Patients who were proven to have COVID-19 by RT-PCR testing on nasopharyngeal/oropharyngeal swabs either 24 hours before or after the imaging study (or) patients who had negative RT-PCR test but typical imaging features of COVID-19 on HRCT thorax (CORADS-5 in CORADS classification) done either 24 hours before or after the imaging study. Patients who had documented COVID-19 infection in recent past (<6 months prior to date of imaging study) and had a positive test for COVID-19 antibodies in serum at time of imaging study.

Exclusion criteria

>24 hours duration between the imaging study and positive RT-PCR testing. Negative RT-PCR test with CORADS-2, 3 or 4 on HRCT thorax. Negative RT-PCR test with no HRCT thorax available. Imaging studies with findings of old or chronic disease not directly attributable to COVID-19.

Due to the retrospective nature of the study and due to the relatively uncommon incidence of extrapulmonary manifestations in COVID-19 a non-probability sampling technique (convenience sampling method) was used. Minimum sample size was set as 30 extrapulmonary cross-sectional imaging studies in COVID-19 patients in order to be representative of the expected spectrum of disease. The selected imaging studies were reviewed on PACS imaging workstation and interpreted by two radiologists in consensus. The extrapulmonary imaging findings in the study patients were documented and segregated according to the system/organ involved- namely vascular/ neurological/ abdominal/ cardiac/ musculoskeletal/ others. Frequency of involvement of each system was assessed.

RESULTS

A total of 96 cross-sectional imaging studies were done in COVID-19 patients (excluding HRCT thorax) during the study period of 1 year. Among these we identified 30 imaging studies with positive imaging findings.

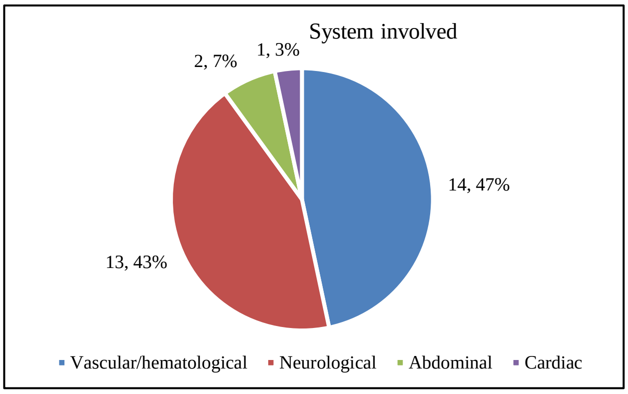

Figure 1: System-wise distribution of extrapulmonary imaging findings in COVID-19.

Absolute number of patients in each category is indicated first followed by the percentage.

Mean age of patients included in our study at time of presentation was 52.4 years (SD =16 years). Majority of the patients were male (22/30, 73.3%). Duration of symptoms at time of imaging ranged from 6 hours to 10 days with mean of 4.2 days (SD =3.5 days). 27 out of 30 patients (90%) included in our study had undergone oropharyngeal/nasopharyngeal swab RT-PCR test with all except one showing positive RT-PCR test result. The patient who had negative RT-PCR test result had undergone CT thorax which showed classical features of COVID-19 pneumonitis. RT-PCR test results were not available in 3 out of 30 patients (10%). These patients also showed classical features of COVID-19 pneumonitis on CT thorax and hence were included in the study. 26/30 patients (86.6%) underwent a CT thorax scan during the same admission. Among patients who had undergone CT thorax, 24 patients (92%) showed classical features of COVID-19 pneumonitis. System wise distribution of the extra-pulmonary imaging manifestations seen in our patients is represented in Figure 1.

Table 1: Spectrum of imaging diagnosis encountered in patients with extrapulmonary manifestations of COVID-19 in our study.

System involved	Number of patients	Diagnosis	Number of patients
Central nervous system	13	Stroke	7
		Encephalitis	2
		Demyelination	2
		Guillain Barre syndrome	1
		Spinal cord ischemia	1
Vascular/ hematological	14	Limb arterial thrombosis with ischemia	5
		Limb venous thrombosis	4
		Mesenteric ischemia	3
		Pulmonary thromboembolism	2
Abdomen	2	Acute kidney injury	1
		Small bowel enteritis	1
Cardiac	1	Myocarditis	1

The imaging diagnosis of patients included in our study is presented in Table 1.

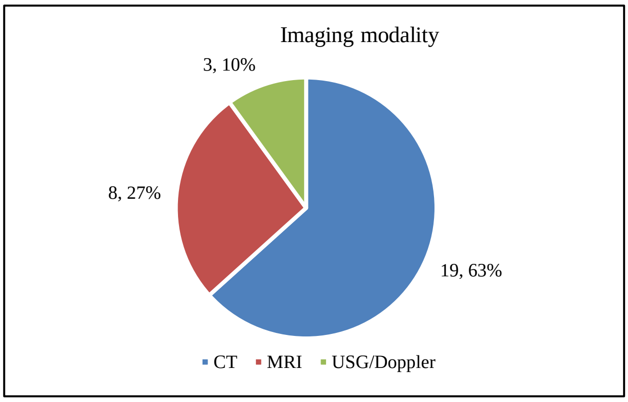

Figure 2: Distribution of imaging modality utilized for making the diagnosis.

Absolute number in each category is indicated first followed by the percentage.

CT was the most widely used modality in making the diagnosis of extrapulmonary involvement. MRI proved useful in patients with central nervous system involvement. Distribution of imaging modality utilized to make the diagnosis is represented in Figure 2.

Vascular/hematological manifestations (14/30, 46%) and central nervous system manifestations (13/30, 43.3%) accounted for majority of imaging findings encountered in our study. Among the patients with central nervous system involvement majority were strokes due to arterial thrombosis (6/13, 46.1%) (Figure 3).

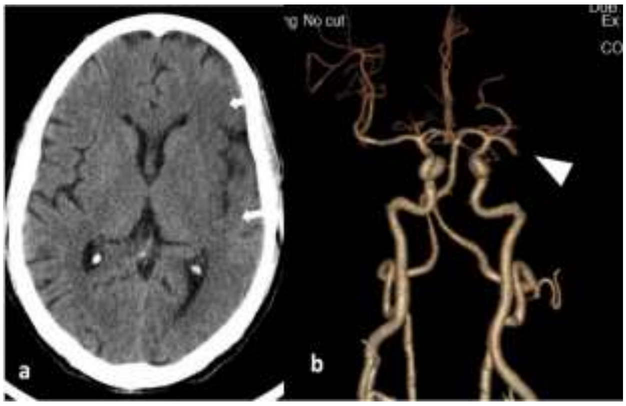

Figure 3: Acute ischemic stroke.

A 61-year-old male with sudden onset weakness of right upper and lower limb for 12 hours. Axial non-contrast CT brain (a) showing subtle hypodensity involving the left cerebral hemisphere with loss of grey-white matter differentiation (arrows) suggestive of acute infarct in left middle cerebral artery territory. Volume rendered image of CT angiogram (b) shows occlusion of the left middle cerebral artery (arrowhead).

We did not encounter any patients with venous thrombosis of the central nervous system. Two patients presented with demyelination syndromes (patient 6 and 9 in Table 1)- a 22-year-old female with T_2 hyperintense lesions in bilateral middle cerebellar peduncles and brainstem showing open-ring type of enhancement on post contrast magnetic resonance images. CSF revealed oligoclonal bands. The enhancement resolved on follow-up MRI study done after a period of 4 months (Figure 4).

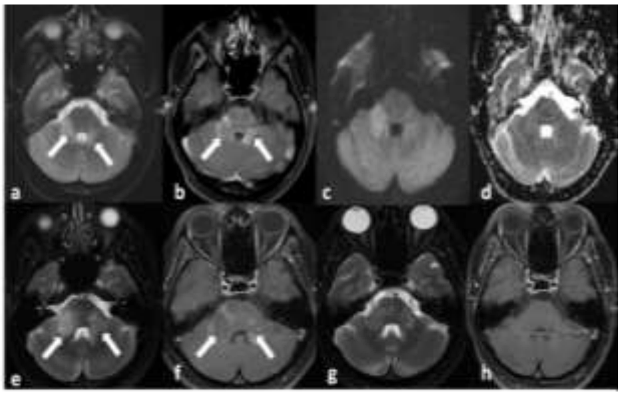

Figure 4: COVID-19 related demyelination.

A-22-year-old female with history of vertigo and difficulty in walking. MRI brain done at presentation (a-d) showed T2 hyperintense lesions (arrows) involving bilateral cerebellar peduncles (a) with peripheral rim of enhancement (b) and facilitated diffusion (c and d). MRI done after 1 month (e and f) follow-up showed increase in size of the lesions (arrows). MRI done after 3 months follow-up (g and h) showed residual gliosis in the region of the lesions with no enhancement on post gadolinium images suggesting resolution of inflammation.

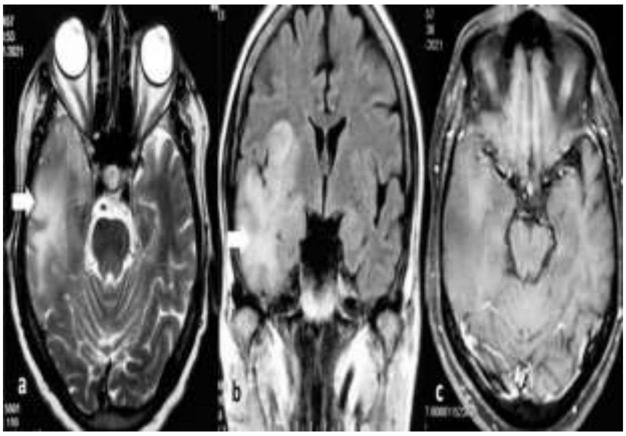

Figure 5: COVID-19 related temporal lobe encephalitis.

A-70-year old female with one episode of sensory seizure. MRI revealed T2 (a) and FLAIR (b) hyperintensity involving the right temporal lobe (arrows). Post Gadolinium T1 weighted image (c) did not reveal any abnormal enhancement. The patient was treated with course of steroids and was asymptomatic at one month follow-up.

The other was a 51-year-old male who had multiple short segment lesions in the cervicodorsal cord and at the cervicomedullary junction. CSF was cellular with elevated protein and normal glucose levels. Oligoclonal bands were negative. COVID-19 RT-PCR done at time of initial presentation was positive in both patients. Two patients presented with seizures and had temporal lobe involvement on MRI in form of T2 hyperintensity and mild swelling (patients 3 and 4) suggestive of encephalitis (Figure 5).

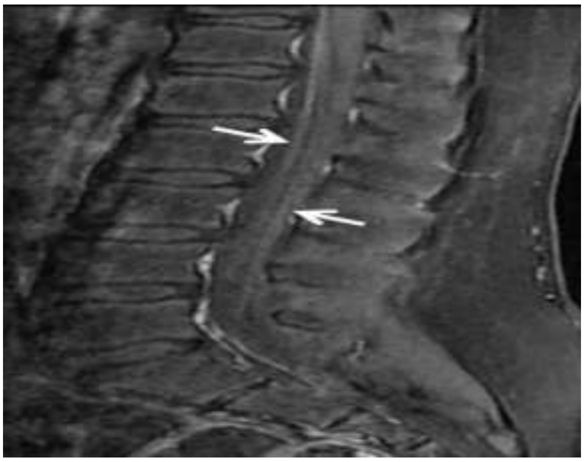

Figure 6: COVID-19 related Guillian Barre syndrome.

A 13-year-old male with difficulty in walking 15 days- Sagittal fat suppressed T1 weighted images of the lumbar spine shows leptomeningeal enhancement along the surface of the cord and enhancement of the cauda nerve roots (arrows).

Minimal to no enhancement was seen in involved region of the brain. We encountered one patient- a 13-year-old boy- with Guillian-Barre syndrome like features. Imaging revealed smooth enhancement of the cauda equina nerve roots (Figure 6).

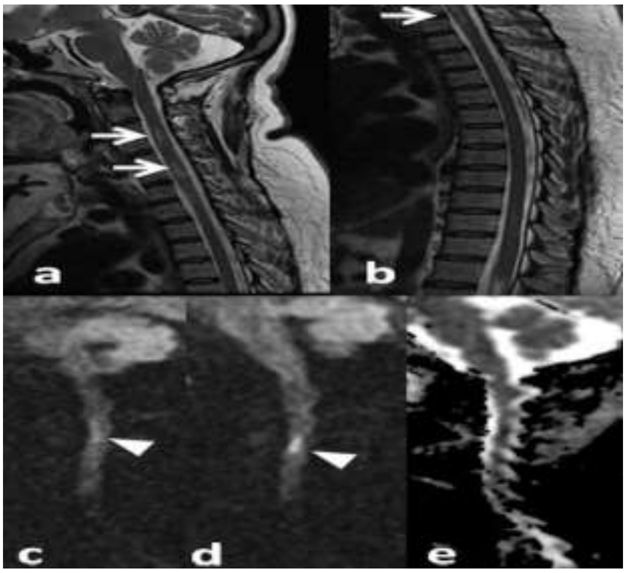

Figure 7: Spinal cord ischemia.

A-48-year old female with weakness of both lower limbs since 2 days- Sagittal T2 weighted images of the cervical and thoracic spine (a and b) show few short segment T2 hyperintense lesions in the cervical cord (arrows). These lesions showed restricted diffusion (arrowheads) on diffusion weighted imaging (c,d and e). No contrast enhancement was seen in these lesions (image not shown).

Spinal cord and brain were normal on imaging. CSF revealed high protein with albumino-cytological dissociation. Spinal cord infarcts were detected in one patient. MRI in this patient revealed multiple short segment T2 hyperintensities in the cervical cord with diffusion restriction (Figure 7). No abnormal enhancement was seen. CSF examination was within normal limits.

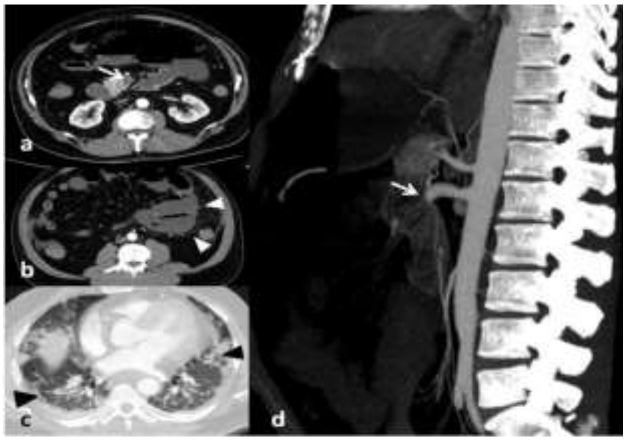

Figure 8: Mesenteric ischemia.

A 42-year-old male with diffuse abdominal pain for 6hours. Axial CT image of the abdomen (a) in arterial phase shows no opacification of the superior mesenteric artery (arrow). Axial CT image of the abdomen at lower level (b) shows fluid filled small bowel loops with lack of mucosal enhancement (arrowhead). Lung window image from same study (c) showing peripheral ground glass opacities (black arrowheads) in both lung bases consistent with COVID-19 pneumonia. Reformatted maximum intensity projection (MIP) sagittal image of the abdomen showing cut-off of the SMA (arrow).

Vascular thrombosis accounted for all cases of vascular involvement. Arterial thrombosis accounted for 50% (7/14) of cases of major vascular thrombosis outside the central nervous system. Lower limb and abdomen were the common sites of arterial thrombosis manifesting as limb or mesenteric ischemia (Figure 8) respectively.

Figure 9: Pulmonary thromboembolism.

Axial image of CT pulmonary angiogram (a and b) shows filling defects in right and left pulmonary arteries (arrows) and their branches suggestive of pulmonary embolism. Lung window image (c) from the same study show extensive ground glass opacities in both lungs consistent with COVID-19 pneumonia.

Venous thrombosis accounted for 42.8% (6/14) of vascular manifestations with majority manifesting as lower limb deep vein thrombosis. Among these patients with deep vein thrombosis two patients manifested with pulmonary thromboembolism (Figure 9) with deep vein thrombosis being later detected on imaging. Simultaneous arterial and venous thrombosis in lower limb was encountered in one patient.

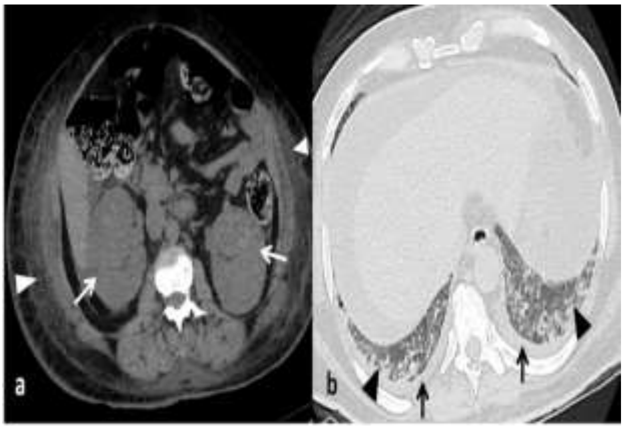

Figure 10: COVID-19 related acute kidney injury.

A 52-year-old male with abdominal pain and shortness of breath. CT abdomen axial image at level of the kidneys (a) shows bulky bilateral kidneys (arrows) with minimal perinephric stranding, free fluid and diffuse abdominal wall edema (arrowheads). Axial image lung window at level of the lung bases included in same study showing bilateral minimal pleural effusion (black arrows) and peripheral ground glass opacities (black arrowheads).

Other system manifestations were not frequently encountered in our study. We had one patient with enteritis in whom CT abdomen demonstrated showed small bowel wall thickening, one patient with acute kidney injury who had swollen kidneys on CT (Figure 10) and one patient with features of viral myocarditis.

DISCUSSION

Vascular/hematological manifestations

Microvascular and macrovascular thrombosis is now a recognised complication of COVID-19 with thromboprophylaxis now being routinely followed for patients with moderate to severe disease.[3] Exuberant inflammation along with hypoxia and direct endothelial toxicity of the virus all contribute to prothrombotic state. Both arterial and venous thrombosis affecting one or more organ systems can occur with COVID-19. Commonly reported vascular syndromes include deep vein thrombosis (DVT), pulmonary embolism (PE), stroke, cerebral venous sinus thrombosis, myocardial infarction, mesenteric ischemia and limb ischemia.[4,5] This preponderance of vascular involvement could be explained by high level of ACE-2 receptor expression in vascular endothelium. CT angiography provides comprehensive information about the vascular system and is the modality of choice for evaluation of vascular complications. Severe COVID-19 can lead to disseminated intravascular coagulation (DIC) with resultant haemorrhagic complications.

Non-vascular manifestations

Central nervous system manifestations

Mechanisms of neurological involvement in COVID-19 include direct neurotropic effects, coagulopathy and hypoxic injury secondary to severe lung involvement. Almost one-third of patients with COVID-19 referred with neurological symptoms have abnormalities on imaging.[6] Ischemic stroke, hemorrhagic stroke, encephalitis and white matter hyperintensities with or without hemorrhage have been reported in COVID-19 patients. Possible mechanisms of white matter disease in COVID-19 include encephalitis, demyelination, delayed hypoxic encephalopathy and posterior reversible encephalopathy syndrome (PRES). In addition to these, less common manifestations include acute hemorrhagic leukoencephalitis (AHLE), acute necrotising encephalopathy (ANEC) and transverse myelitis.[7]

Abdominal manifestations

It is not uncommon for patients with COVID-19 to present with abdominal symptoms. Common symptoms include diarrhoea, vomiting and abdominal pain. Angiotensin converting enzyme-2 (ACE_2) receptors are expressed abundantly in the gastrointestinal tract and biliary tract explaining the GIT tropism of this virus. Elevation of liver enzymes and bilirubin levels is also very common. Examination of basal lung sections in abdomen CT for ground glass opacities and consolidation is important so as not to miss clinically unsuspected COVID-19. Common abdominal manifestations include bowel ischemia (either due to arterial or venous thrombosis), enterocolitis, biliary stasis and acute kidney injury. Less common manifestations include solid organ infarcts and pancreatitis.[8,9]

Cardiac manifestations

Cardiac manifestations of COVID-19 include myocarditis, heart failure, arrhythmia and cardiogenic shock. Moreover, presence of pre-existing cardiac conditions marked increases risk of developing severe COVID-19, increases risk of developing cardiac complication from COVID-19 and increases overall risk of mortality.[10] MRI plays an important role in delineation of myocardial injury in suspected myocarditis- triple inversion recovery sequence of cardiac MRI is highly sensitive in detecting myocardial edema.

Musculoskeletal and peripheral nervous system manifestations

Symptoms attributable to musculoskeletal system such as myalgia and arthalgia are very common in COVID-19. Myositis, rhabdomyolysis, Guillain Barre syndrome, peripheral and cranial neuropathy have also been described.[11] Imaging can help in diagnosis by demonstration of muscle or nerve edema and enhancement.[12]

Limitations of the study include its retrospective nature and limited number of patients with cardiac, abdominal and musculoskeletal system imaging manifestations. Moreover, we did not correlate the presence or absence of extrapulmonary manifestations with severity of disease. We did not assess therapeutic considerations and prognostic indicators. A prospective study of extrapulmonary manifestations of COVID-19 with correlation of disease severity and follow-up may provide further information on this subject.

CONCLUSION

This study demonstrates the spectrum of extrapulmonary imaging manifestations in COVID-19. Vascular thrombosis and central nervous manifestations accounted for majority of extrapulmonary imaging findings in our patients with COVID-19. Awareness of extrapulmonary imaging features of COVID-19 among radiologists is essential providing timely and appropriate care to patients with atypical manifestation of COVID-19.

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