Cardiothoracic Imaging

Extrapulmonary manifestations of COVID-19: Radiologic and clinical overview

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ABSTRACT

COVID-19 is principally a respiratory illness and pulmonary manifestations constitute main presentations of the disease. According to the reported studies, SARS-CoV-2 infection is not limited to the respiratory system and other organs can be also affected. Renal dysfunction, gastrointestinal complications, liver dysfunction, cardiac manifestations, mediastinal findings, neurological abnormalities, and hematological manifestations are among the reported extrapulmonary features. Considering the broad spectrum of clinical manifestations and the increasing worldwide burden of the disease, there is an urgent need to rapidly scale up the diagnostic capacity to detect COVID-19 and its complications. This paper focuses on the most common extrapulmonary manifestations in patients with COVID-19 pneumonia. Further studies are needed to elaborate and confirm the causative relationship between SARS-CoV-2 and the reported extrapulmonary manifestations of COVID-19.

1. Introduction

On March 11, 2020, COVID-19, a viral pneumonia presented in Wuhan city of China was officially announced as the first pandemic caused by a coronavirus [1]. Chinese authorities unexpectedly reported 44 cases of etiologically unknown pneumonia over a 4-day period from December 31, 2019, to January 3, 2020. Although the disease was exclusively limited to China at first, it has spread over more than 160 countries in such a short period of time due to its highly contagious etiologic agent.

To identify the causal agent, three bronchoalveolar lavage samples were collected from a patient and underwent evaluations with real-time PCR. Studies eventually led to the isolation of SARS-CoV-2 from the patient's respiratory epithelium as the responsible agent for the disease that was subsequently named COVID-19 by WHO [2]. Researchers demonstrated that SARS-CoV-2 shares a homological sequence with SARS-CoV and MERS-CoV (of family of coronaviruses), leading to the development of similar pathogenesis and manifestations [2,3].

The mean incubation period is 5–6 days. Patients generally become symptomatic with severe pneumonia and other infectious/inflammatory signs and symptoms due to high levels of pro-inflammatory cytokines and leukocytes [2,4]. According to a WHO report on COVID-19, the disease has no specific manifestation to note and the patients'

presentation can range from completely asymptomatic to severe pneumonia and death [2]. However, some symptoms have been reported to be more common in COVID-19 patients, including fever, dry cough, fatigue, and dyspnea. Other clinical manifestations are sore throat, headache, myalgia or arthralgia, chills, nausea or vomiting, nasal congestion, diarrhea, and hemoptysis, and conjunctival congestion [2,5].

2. Extrapulmonary manifestations of coronavirus infections: lessons from SARS and MERS

Although COVID-19 is principally a respiratory illness and pulmonary manifestations are main presentations of the disease, SARS-CoV-2 infection is not limited to the respiratory system and other organs can also be affected. In fact, infections with all species of the family of Coronaviruses are known to have extrapulmonary presentations. A study on clinical manifestations of MERS by Arabi et al. found that MERS-CoV causes considerable extrapulmonary organ dysfunctions, which are associated with increased mortality. The extrapulmonary findings in their reported population were circulatory instability requiring vasopressors, hepatic dysfunction with elevated liver enzymes, acute kidney injury (AKI), gastrointestinal complications (including acute abdomen and diarrhea), and hematologic

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complications [6]. Other studies also demonstrated that gastrointestinal distress and neurological sequelae may additionally be present in MERS patients [7,8] Research on SARS pathogenesis also noted multiple organ dysfunctions with hematological, neurological, renal and gastrointestinal symptoms [9]. Comparative studies claimed that owing to the homological sequence between SARS, MERS, and COVID-19 coronaviruses, the main pathophysiology of COVID-19 can be predictable [10,11]. There are still limited evidential findings on COVID-19 pathophysiology. However, due to similarities with SARS and MERS, the possibility of nonrespiratory manifestations and complications and even isolated extrapulmonary manifestation in COVID-19 must be considered in the diagnostic and therapeutic management of the patients [12,13].

2.1. Renal dysfunction

According to a recent analysis, there is a significant co-expression of ACE2 and TMPRSSs genes in podocytes and proximal convoluted tubules which makes them a potential host for SARS-CoV-2. Studies on the pathophysiology of acute renal failure as the second incidence after respiratory syndrome and as one of the fatal complications of patients with COVID-19 showed that acute renal failure is caused by the virus-induced cytopathic effect [14]. A retrospective analysis on clinical parameters of 536 SARS patients in 2005 also concluded that acute renal failure is an uncommon but serious complication of the disease. The study noted that fatal cases had a progressive rise in plasma creatinine [15]. Another study reported three cases of SARS who developed rhabdomyolysis during the clinical course of the disease. Due to similar manifestations in SARS and COVID-19, acute renal failure, elevated plasma creatinine status and rhabdomyolysis may also be detected in SARS-CoV-2 infected pneumonia [16]. A recent study reported a COVID-19 patient with rhabdomyolysis who manifested with lower extremity pain and fatigue [17]. Although no imaging correlate of these findings has been reported in medical literature yet, ultrasound and scintigraphic features of acute renal failure (such as increased parenchymal echogenicity) can be expected in patients with SARS-CoV-2 associated renal injury. As per a recent review by Zaim S et al. on the incidence of acute kidney injury (AKI) from major published clinical cohorts, 0.5% to 19% of patients with COVID-19 may demonstrate some degrees of acute renal dysfunction. Since impaired renal function increases patients' susceptibility to contrast-induced nephropathy, it can be recommended that contrast-enhanced imaging studies (CT and MRI) should be employed with caution in COVID-19 patients. Although more studies in this area are needed, evaluations of the patient's renal function before the use of any contrast media/agents is recommended [18].

2.2. Gastrointestinal complications

The most recent reported studies on clinical manifestations of COVID-19 have demonstrated that gastrointestinal symptoms are present in a significant number of patients. A recent study has also reported a few cases of COVID-19 with gastrointestinal manifestation as the only presentation of the disease without respiratory abnormalities [19,20] (Fig. 1). In another study out of 67 COVID-19 patients with diarrhea, 13 cases had no other manifestations [21]. Although gastrointestinal symptomatology during the course of COVID-19 is not specific, they have been reported to be more common in patients with confirmed SARS-CoV-2 infection (Table 1). Despite the very low number of pieces of evidence available, Zhang et al. [22] detected the viral nucleic acid in anal swabs and fecal samples of hospitalized patients. This suggests fecal-oral transmission as an alternative route for COVID-19 spread. A report from the Chinese Society of Gastroenterology claimed that according to the homological sequence between SARS-CoV and SARS-CoV-2, there is a possibility that this recently discovered virus also uses ACE2 as the receptor for its viral antigen [23]. It is additionally noted

that because of the increased gastrointestinal wall permeability to foreign pathogens once infected by the virus, gastrointestinal symptoms, such as diarrhea, can occur due to malabsorption of infected enterocytes [24]. The radiologic manifestation of these findings can be distended fluid filled small and large bowel loops with mural post-contrast enhancement and surrounding stranding on CT and diarrhea state and ileus pattern on abdominal radiographs (Fig. 1).

2.3. Liver dysfunction

Some histopathological studies confirmed the presence of SARS-CoV-2 in the liver tissue [25]. It was formerly reported by chai et al. that there is a low frequency of ACE2 occurrence in cholangiocytes which alters them to a SARS-CoV-2 target [26]. Laboratory examinations of COVID-19 patients' blood samples also showed elevated levels of liver enzymes in many cases. Since elevated liver enzymes are not necessarily diagnostic for serious liver injury, direct tissue sampling of a COVID-19 patient was performed. Moderate microvesicular steatosis and mild lobular and portal inflammatory activity as the injury indicators were found in pathological studies and could have been caused by either drug-induced hepatic injury or SARS-CoV-2 infection [14,27]. Although no imaging correlate of these findings has been reported in medical literature, CT and ultrasound features of hepatic steatosis (such as increased parenchymal echogenicity) can be expected in patients with SARS-CoV-2 associated liver injury. These findings create new avenues for future studies regarding the pathophysiology of COVID-19.

2.4. Cardiac manifestation

ACE1 as a target receptor for SARS-CoV-2 is significantly expressed in the heart. This transmembrane aminopeptidase involved in the development of hypertension and heart function performs an extremely critical role in the cardiovascular system. Therefore, the possibility of cardiovascular injury or myocarditis should also be considered as a COVID-19 manifestation. In addition, Zheng et al. reported 5 confirmed cases of SARS-CoV-2 infection who developed myocardial injury during the course of the disease. Myocardial injury mainly manifested as an increased level of biochemical markers including cardiac troponin I (cTnI), creatine kinase (CK), α-hydroxybutyrate dehydrogenase (HBDB), and lactate dehydrogenase (LDH) [22,28]. Another study also concluded that in-hospital mortality rate and N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels are significantly higher in patients with myocardial injury (defined as 3 times increase in serum cardiac troponin levels) [29]. Multivariate logistic regression analysis on the correlation between COVID-19 severity and myocardial injury defined elevated cTnI and history of coronary heart disease as independent risk factors of critical disease status. The study also found a significant correlation between the patients' age, male gender, high NT-proBNP levels, high cTnI levels, elevated serum creatinine, underlying hypertension, and history of coronary heart disease with critical COVID-19 status [30]. Arrhythmias were also identified in some patients in another study around the cardiovascular complications of COVID-19, with patients with pre-existing coronary artery disease and heart failure at a higher risk of developing arrhythmic events. The mortality rate is associated with acute myocardial infarction, acute myocarditis, and rapid onset of heart failure [31,32]. Clear impacts of COVID-19 on acute myocardial infarction (AMI) including STEMI and NSTEMI have also been noted in recent protocols of AMI [33,34]. On imaging, the cardiac complications may manifest as cardiomegaly and pericardial effusion (Figs. 2 and 3) [35].

2.5. Mediastinal findings

Although a very uncommon finding, according to our recent systematic review, mediastinal lymphadenopathy can be seen in patients with COVID-19 [35,36]. However, a recently published article in The
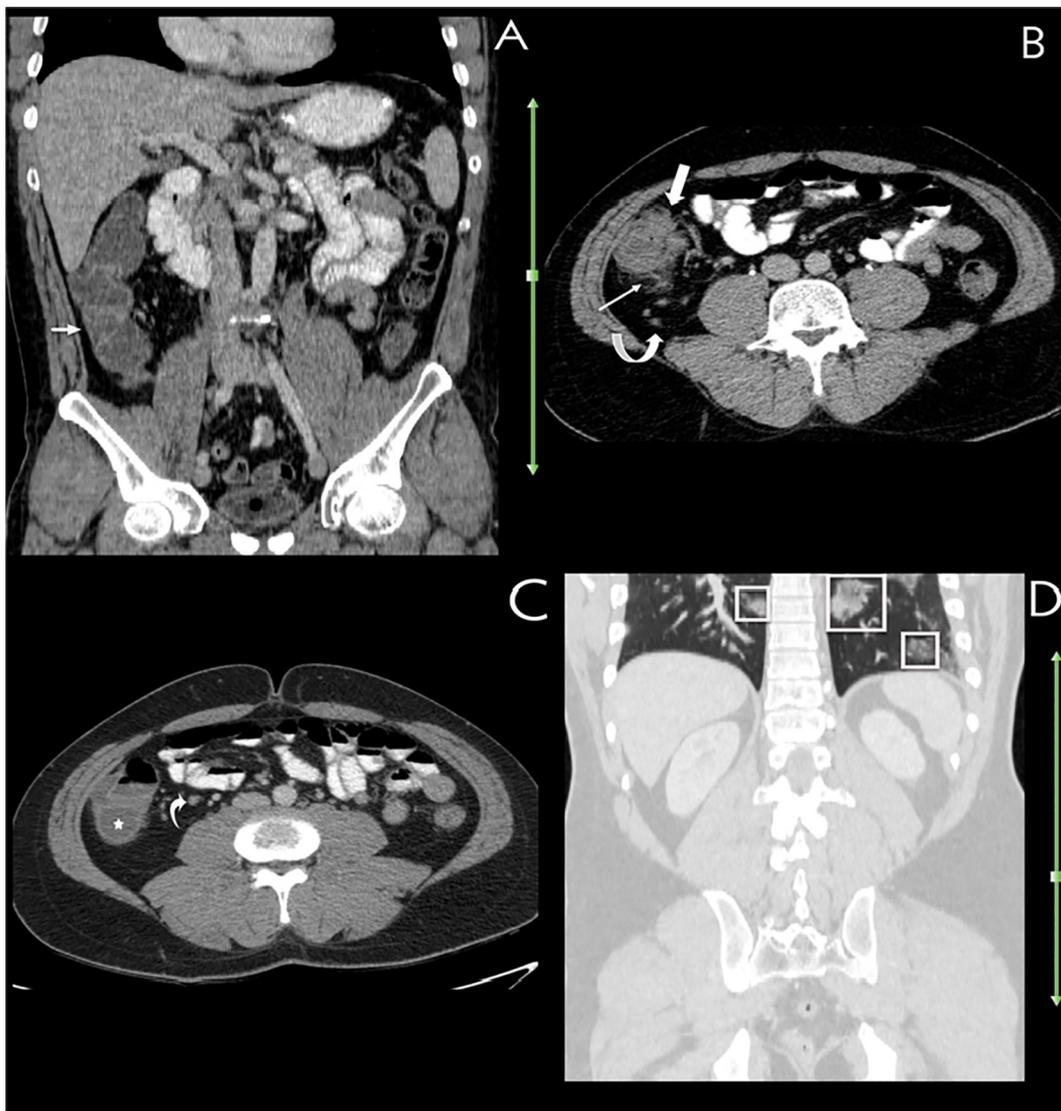
Fig. 1. A 31-year-old male was admitted for few days of abdominal discomfort and absent bowel movement. On his abdominopelvic CT, mild to moderate nonspecific stranding surrounding mildly distended fluid-filled ascending colon (A, B) without evidence of bowel obstruction was identified. Few small pericecal lymph nodes were also identified (C). Incidentally, patchy ground glass opacities with reverse halo appearance were found involving bilateral lung bases (D), concerning for COVID 19. Follow up dedicate chest CT scan and RT-PCR confirmed infection with SARS-CoV-2.

Lancet infectious disease describes mediastinal lymph nodes enlargement as a common finding in critically ill COVID-19 patients. Therefore, lymphadenopathy should not be considered as an atypical feature of COVID-19, particularly in severely ill patients [37] (Fig. 4). This is a reactive phenomenon to viral disease and inflammation.

2.6. Neurological findings

Coronaviruses may enter the CNS through the bloodstream or neuronal retrograde route. This may lead to meningitis and encephalitis with associated morbidity and risk of mortality. Although viral encephalitis may remain undiagnosed due to subtle or no symptoms, symptoms in severe viral encephalitis might present as altered mental status, altered body temperament, abnormal behavior or speech, abnormal motor movement and focal neurological abnormalities such as flaccid paralysis, paresthesia, hemiparesis, or seizures [38]. Examinations of cerebrospinal fluid in patients with SARS-CoV-2 infection had also confirmed the presence of viral RNA. Additionally, previous studies on mice have concluded that a SARS-CoV-2 infection can cause death in mice by invading the brain. Relying on remarkable similarities between

Table 1
Gastrointestinal manifestations of COVID-19.

Author	Number of patients	Gastrointestinal Manifestations
Kui Liu [10]	147	Diarrhea (13/147)
Xiaobo Yang [62]	52	Vomiting (2/52)
Jin-jin Zhang [5]	140	Nausea (24/140), diarrhea (18/140), anorexia (17/140), belching (7/140), abdominal pain (8/140), emesis (7/140)
Lei Pan [19]	204	Anorexia (83/204), diarrhea (29/204), vomiting (8/204), abdominal pain (4/204)
Ahmad Hormati [63]	Not specified	Constipation, diarrhea, nausea, vomiting, melena, epigastric pain
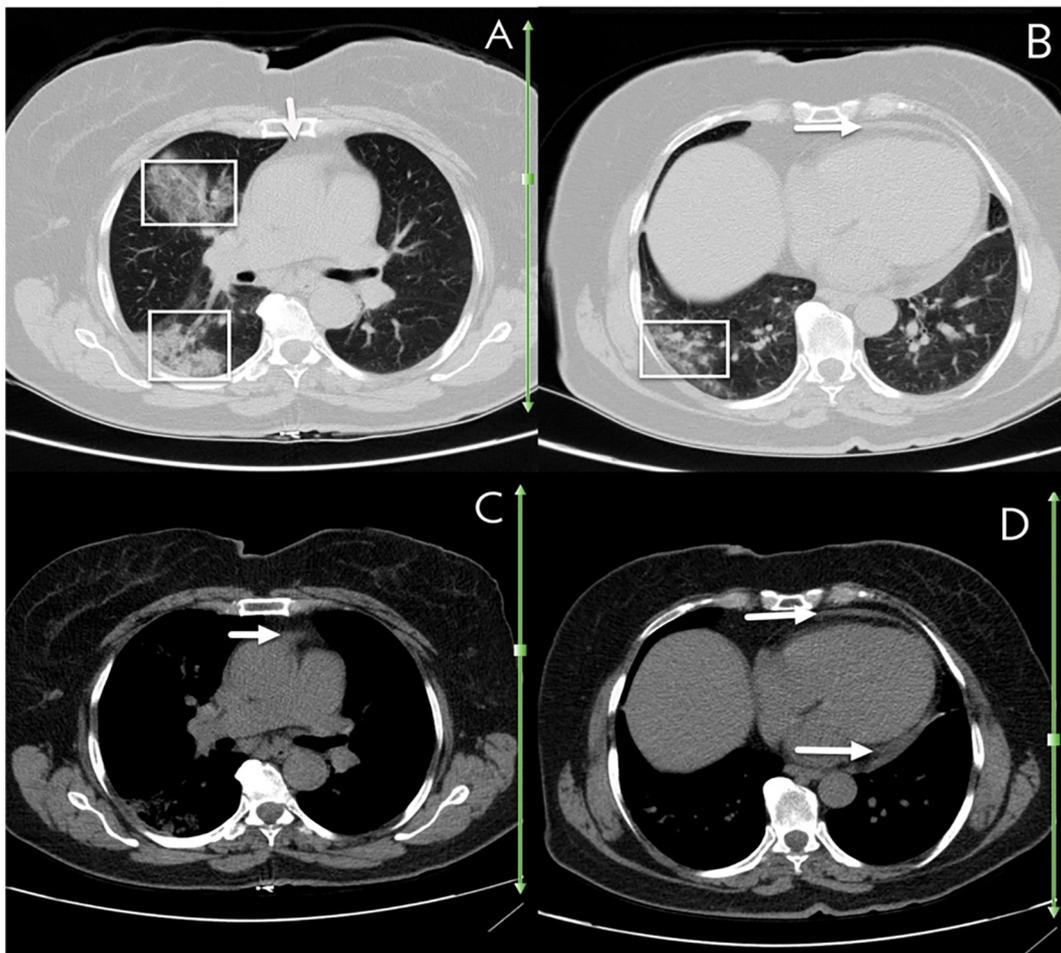
Fig. 2. A 60-year-old female presented with 4 days of dry cough without fever or dyspnea. She denied any past medical history of cardiac disease or pulmonary disease. Chest CT demonstrated multifocal peripheral patchy ground glass opacities with small superimposed consolidations (boxes, A and B). Small pericardial effusion (white arrows) was also noted. Patient RT-PCR for SARS-CoV-2 was subsequently reported as positive.

manifestations of these viral agents, a possibility for SARS-CoV-2 neuroinvasion should also be documented [11]. A recent study around the neurological invasion in COVID-19 pneumonia demonstrated that SARS-CoV-2 may invade the CNS finding its way throughout the systemic circulation or across the cribriform plate of the ethmoid bone. SARS-CoV-2 can subsequently cause damage to the neuronal tissues by interacting with ACE2 receptors. COVID-19 cerebral involvement via the cribriform plate may lead to additional complications, such as hyposmia or anosmia [39,40]. The study also mentioned a possibility of cerebrovascular endothelial rupture leading to bleeding and fatal complications [40]. Cerebrovascular accident due to intracerebral hemorrhage has been reported as a rare COVID-19 neurological sequela [41]. A recent study also reported COVID-19-associated Acute hemorrhagic necrotizing encephalopathy in a patient with altered mental status whose nasopharyngeal swab tested positive for SARS-CoV-2. Imaging findings were reported as symmetric hypoattenuation within the bilateral medial thalami on the head CT and hemorrhagic rim enhancing lesions within the bilateral thalami, medial temporal lobes, and subinsular regions in patients brain MRI [42]. However, future studies are required to evaluate causation association.

2.7. Hematological manifestations

Recent pathological investigations on SARS-CoV-2 pathogenesis concluded that the course of the disease in COVID-19 was rather a hypersensitivity pneumonitis than viral pneumonia [43]. It is believed that SARS-CoV-2 induces a hyperactive immune response, also known

as a cytokine storm, in COVID-19 patients. The storm creates systemic issues across multiple organs by spilling high levels of cytokines into the circulatory system. Multi-organ failure as one of the serious complications of SARS-CoV-2 infected pneumonia results from overproduction of pro-inflammatory cytokines combined with a diminished oxygenation capacity of the patient's blood. Septic shock, difficult-to-correct metabolic acidosis, and coagulation dysfunction are other complications seen in severe cases [4,5,10,44]. Early-onset of normal/decreased white blood cell count or decreased lymphocyte count (lymphopenia) is frequently seen in patients with COVID-19 [4,5,10,45]. Isolated (likely autoimmune) thrombocytopenia was also reported in a COVID-19 patient which led to lower-extremity purpura, epistaxis and neurological symptoms, including headache, which was attributed to subarachnoid microhemorrhage on head CT [46].

2.8. Vascular abnormalities

Recent studies around imaging findings of COVID-19 have demonstrated that vascular abnormalities can also be observed in chest CT. Vascular enlargement on patients' chest CT is the major finding referring to luminal dilation/engorgement or mural thickening of pulmonary vessels. According to another study, subsegmental vessel enlargement due to unknown causes, in which "enlargement" is defined as vessels greater than 3 mm in diameter, seems to be a common finding in patients with confirmed COVID-19. Similarly, the enlargement of intralesional vessels described by the term "microvascular dilation sign" has been reported in CT chest of patients with COVID-19. Moreover,
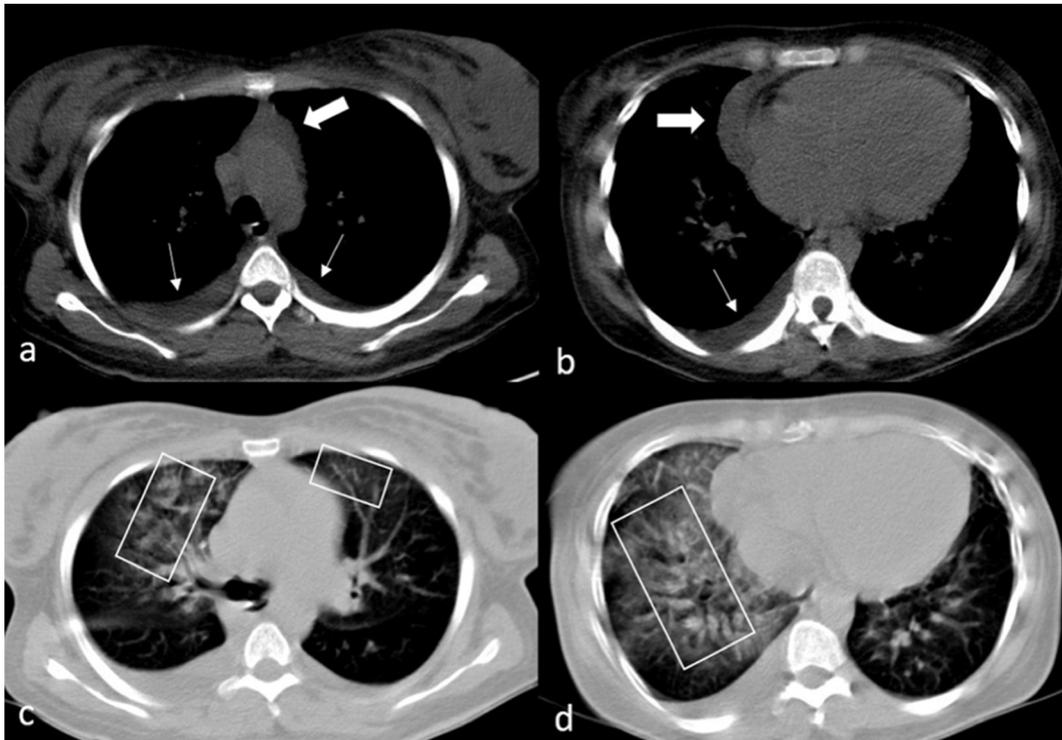
Fig. 3. Chest CT of a 20-year-old female presented with fever, dyspnea, and tachypnea for 3 days without known underlying disease or previous cardiac or respiratory condition. Small bilateral pleural effusion (right greater than left) is identified (a–d). Mild cardiomegaly/left ventriculomegaly (b) and pericardial effusion (thick arrows, a and b) are noted. Bilateral ground-glass opacities (right greater than left) with superimposed nodular consolidations (boxes) are identified. COVID-19 RT-PCR was positive for SARS-CoV-2.
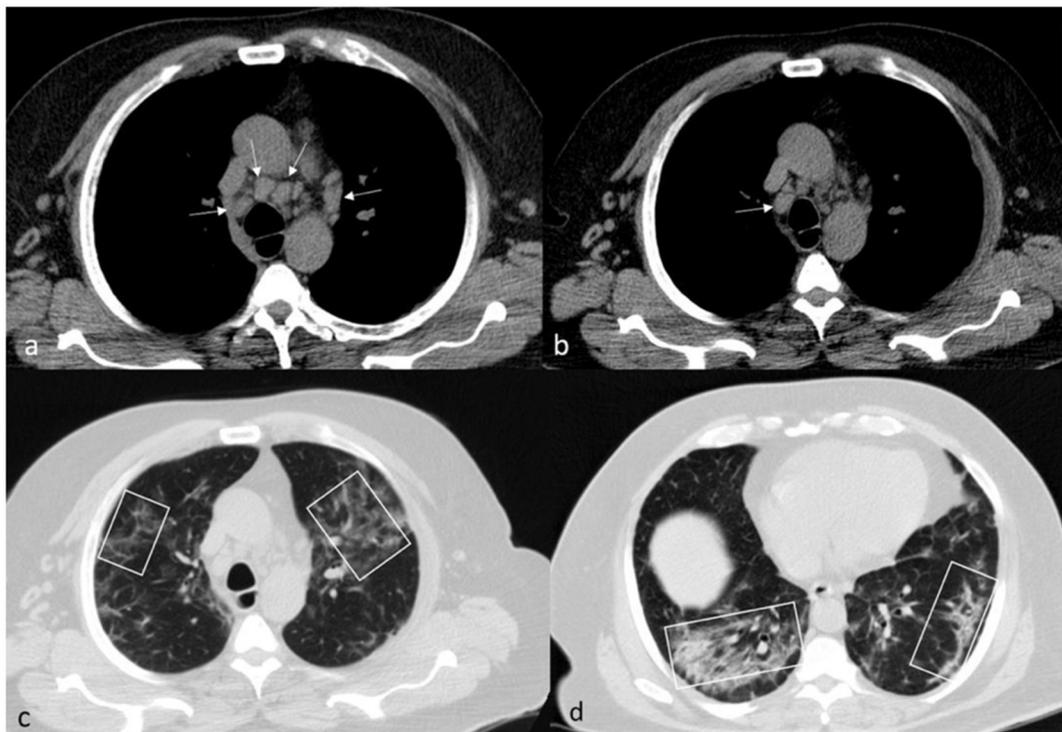
Fig. 4. Chest CT scan of a 59-year-old male with RT-PCR positive for COVID-19 who presented with dyspnea, tachypnea, myalgia and low grade fever for 5 days. Enlarged bilateral lower paratracheal and aortopulmonary window lymph nodes (white arrows, a and b) are identified. Bilateral patchy ground glass opacities and consolidations in a peripheral predominant pattern (boxes, c and d) are noted with bilateral lungs.

some authors have given diagnostic and prognostic significance to these findings [47,48].

2.9. Cutaneous manifestations

According to a recent study around skin manifestations of COVID-19, confirmed cases of SARS-CoV-2 infection may be present with cutaneous involvement. Collecting data from 88 COVID-19 patients, the study demonstrated that erythematous rash, widespread urticaria, and chickenpox-like vesicles among the skin manifestations of the disease. It was also noted that the skin lesions were not/slightly itchy and the main region involved was the trunk [49].

2.10. Reproductive system involvement

According to data available from SARS, orchitis is a rare but important complication of the disease [50]. Additionally, studies suggest that due to a high expression of ACE2 in human testes and uterus, the reproductive system may also be the target organ for SARS-CoV-2 infection [51–53]. A study has recently reported a COVID-19 patient with testicular pain which suggests that SARS-CoV-2 may invade the male reproductive system [51].

2.11. Ocular symptoms

According to the American Academy of Ophthalmology, conjunctival injection and chemosis are among extrapulmonary manifestations of SARS-CoV-2 infection [54].

3. COVID-19 and pregnancy

Recent research on the clinical characteristic of pregnant women with COVID-19 demonstrates that clinical manifestations in COVID-19 patients during the pregnancy are similar to non-pregnant adults and the main symptoms were noted to be fever and cough [55]. However, more recent studies have concluded that pregnant women are more susceptible to COVID-19 and its complications and may even progress to severe illness [56]. Although currently there is no strong evidence to confirm vertical transmission, mother to child transmission in COVID-19 or SARS infection can not be excluded [55,57–59]. Recent studies have concluded that perinatal COVID-19 may cause severe adverse effects on fetus or infants, including fetal distress, premature labor, newborn respiratory distress, thrombocytopenia associated with abnormal liver function, and even prenatal death [60]. Chen et al. reported that there were no morphological changes related to infection in three cases with COVID-19 [61].

4. Conclusion

COVID-19 is a progressive viral pneumonia with a broad spectrum of clinical manifestations. Studies on the clinical and radiological manifestations of COVID-19 show that SARS-CoV-2 infection can present with extrapulmonary features. Thus, both clinicians and radiologists need to be familiar with these extrapulmonary presentations of the disease. Further studies are needed to elaborate and confirm the causative relationship between SARS-CoV-2 infection and the reported extrapulmonary manifestations of COVID-19.

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Declaration of competing interest

None.

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