Extrapulmonary and atypical clinical presentations of COVID-19

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Abstract
The novel coronavirus (SARS-CoV2) has led to an outbreak of multiple cases of pneumonia in Wuhan city in December 2019. The disease caused by this virus was named coronavirus disease 2019 or “COVID-19”, which was declared by the World Health Organization as a global pandemic in March 2020. It typically presents with respiratory symptoms and febrile illness. However, there are few reported extrapulmonary and atypical presentations, such as hemoptysis, cardiac, neurological, gastrointestinal, ocular, and cutaneous manifestations, as well as venous and arterial thrombosis. Lack of awareness of these presentations might lead to misdiagnosis, delayed diagnosis, and isolation of suspected patients which increases the risk of transmission of infection between patients and doctors. All these issues will be discussed in this review.

KEYWORDS
atypical presentations, COVID-19, SARS-CoV-2

1 | INTRODUCTION

On the 7th January 2020, a novel coronavirus (SARS-CoV-2) was confirmed as the cause of several cases with pneumonia, which emerged at the end of 2019 in Wuhan, China.1 It rapidly spread, resulting in an epidemic throughout China, followed by an increasing number of cases in other countries throughout the world. It was declared a global pandemic by the World Health Organization on the 11 March 2020.2

The clinical features of coronavirus infection vary widely, from asymptomatic infection to severe pneumonia with respiratory failure and even death.3,4 Approximately, 80% of people infected with coronavirus develop mild to moderate disease, 13% to 14% have severe disease and about 4% to 6% develop critical disease requiring admission to intensive care unit (ICU).5 It has been noted that elderly patients with underlying conditions such as hypertension, diabetes, and cardiovascular disease are more vulnerable to severe disease and death.6

Most patients with confirmed COVID-19 present typically with fever, dry cough, sore throat, dyspnea, fatigue, and myalgia.5 Less common presentations of coronavirus infection include headache, dizziness, nausea, abdominal pain, vomiting, and diarrhea.3,4 However, it has been reported that patients with confirmed COVID-19 might present with nonspecific or atypical symptoms, which may delay testing, diagnosis and isolation.7 The exact pathophysiology behind these atypical symptoms is still poorly understood, but advanced age and increase the number of comorbidities might increase the probability of atypical presentations.8,9 Few studies proposed that cerebrovascular and neurological symptoms could be explained by hypercoagulability status in patients with COVID-19, leading thrombi formation in the vessels.10 Another explanation might be related to the fact that SARS-CoV-2 can bind angiotensin-converting enzymes 2 (ACE2) receptors, which is present in the nervous and reproductive systems.11,12

It is important that healthcare professionals are aware of the possibility of COVID-19 presenting with nonspecific symptoms.
Therefore, cases of COVID-19 with extrapulmonary and atypical presentations are not missed when they present to healthcare settings, where healthcare workers should remain vigilant, ensuring that appropriate personal protective equipment (PPE) is used. Thus, recognizing these presentations is crucial to ensure early diagnosis of these patients and reduce the risk of infection transmission. The objective of this review is to summarize the most important and interesting extrapulmonary and atypical clinical presentations of adults and pediatric patients with COVID-19 that are reported in the literature.

2 | EXTRAPULMONARY AND ATYPICAL CLINICAL FEATURES OF COVID-19

Patients with COVID-19 typically present with respiratory symptoms, such as dry cough and sore throat, associated with general constitutional symptoms, such as headache, fever, and myalgia.\(^\text{11}\) In addition, the Centers for disease control and prevention considered nausea or vomiting, diarrhea and new loss of taste and smell as recognized features of COVID-19.\(^\text{14}\) However, patients with COVID-19 might develop unusual or atypical manifestations (which means different clinical features or extrapulmonary manifestations not associated with the above typical symptoms that might not be recognized by doctors as related to COVID-19). They can occur at the onset of the disease or shortly following hospital admission. In the following sections, we will give examples of the most important and interesting extrapulmonary and atypical manifestations of COVID-19.

2.1 | Hemoptysis

Hemoptysis has been rarely reported as a clinical feature of COVID-19. A prospective analytical study of 41 patients admitted to hospital with confirmed COVID-19 by real-time polymerase chain reaction (RT-PCR) showed that only 5% of patients had hemoptysis at the onset of illness.\(^\text{17}\) In another analytical study on a larger study sample (1099 patients with confirmed COVID-19), hemoptysis was only reported in less than 1% of the patients.\(^\text{13}\) Interestingly, a case report showed that hemoptysis was the only clinical symptom during the first 10 days since the onset of the illness.\(^\text{15}\) A 57-year-old male with no travel history or history of contact with confirmed COVID-19 cases was presented to the emergency department with a 3-hour history of hemoptysis. He had no other symptoms and no previous history of respiratory diseases. The initial computed tomography (CT) scan showed localized ground-glass opacity (GGO) which further progressed to consolidation on day 8 postadmission. A presumptive diagnosis of pulmonary infection/TB was made, but the clinical condition of the patient did not improve despite treatment. On day 11 and 14 postadmission, the patient developed fever and dyspnea, respectively. A repeated CT scan on day 18 postadmission showed partial resolution of the initial findings of GGO and consolidation. However, the rest of the lung field showed diffused GGO with peripheral and subpleural distribution in addition to a crazy-paving appearance. At that time, the possibility of COVID-19 had been considered and the diagnosis was confirmed by RT-PCR.\(^\text{15}\) The main learning outcome from this case is a lack of awareness about hemoptysis as a possible clinical presentation of COVID-19 has led to initial misdiagnosis and delayed diagnosis. Therefore, COVID-19 should be considered on the differential diagnoses list when dealing with any patient presenting to the hospital with a history of hemoptysis even if the other classical clinical features of COVID-19, such as fever, dry cough, myalgia, and shortness of breath, are absent.

2.2 | Pulmonary embolism

Multiple evidence revealed that COVID-19 infection leads to a hypercoagulable state. Laboratory results for patients with confirmed COVID-19 showed an increased level of prothrombotic factors, such as fibrinogen and antiphospholipid antibodies, in addition to high D-dimer levels.\(^\text{16,17}\) The level of D-dimer was higher in severe disease compared with mild disease, which could indicate that D-dimer has a prognostic value.\(^\text{16}\) Therefore, patients with COVID-19 are at higher risk to develop venous thromboembolic (VTE) events. A 42-year-old man diagnosed with mild COVID-19 was managed effectively at home.\(^\text{18}\) However, 12 days later, he was presented to the emergency department with a history of worsening central pleuritic chest pain, dyspnea, and hemoptysis. There was no significant past medical history and no history of VTE-risk factors. On examination, he was on respiratory distress and there was mild tachypnoea with normal oxygen saturation level. The D-dimer level was markedly elevated. Chest X-ray showed infiltration in the right lower lobe, and the electrocardiogram (ECG) showed evidence of right ventricular strain. Giving the previous clinical findings, a CT pulmonary angiogram was ordered. It showed bilateral segmental pulmonary emboli (PE), right lower lobe infarction, and GGO with peripheral distribution which is classical for COVID-19 pneumonia.\(^\text{18}\) Therefore, it is important for doctors, particularly emergency medicine physicians, to appreciate the potential association between COVID-19 and increased risk of VTE events, such as PE, even in patients without previous VTE-risk factors.

2.3 | Cardiac manifestations

Inflammation of the cardiac wall leading to myocarditis, pericarditis, and pericardial effusion, are well-recognized complications of viral infections, such as influenza and parvo B19 infections.\(^\text{19}\) This raises the question of whether COVID-19 disease, considering it is a viral infection, causes similar cardiac complications. A case report described a patient who was diagnosed with acute myopericarditis secondary to COVID-19.\(^\text{20}\) The case represented a 53-year-old female with a 1-week history of flu-like illness, fever, dry cough, and fatigue before hospital admission. The patient had no history of chest
pain, dyspnea, or any other symptoms, and no significant past medical history of cardiac disease. On assessment, she was afebrile but hypotensive. The laboratory results showed a high level of troponin T and N-terminal pro-brain natriuretic peptide. Chest X-ray was normal and the ECG showed diffuse ST segments elevation. Urgent coronary angiogram did not show coronary obstruction. Echocardiogram and cardiac magnetic resonance imaging showed evidence of myocardial inflammation, pericardial effusion, and poor left ventricular function. Nasopharyngeal swab with positive RT-PCR result confirmed the diagnosis of COVID-19. This case highlights the importance of recognizing the cardiac manifestations of COVID-19 as an initial presentation to the hospital even with the absence of associated lower respiratory tract symptoms or radiological features of interstitial pneumonia.

A case series study identified 18 patients with confirmed COVID-19 presented with ST-segment elevation on ECG, in different hospitals in New York. Ten of 18 patients had ST-segment elevation during the initial presentation to the hospital, while the other 8 had ST-segment elevation on average around day 6 posthospital admission. Only 9 of 18 patients had a coronary angiogram, which showed evidence of coronary obstruction leading to myocardial infarction (MI) in 6 patients. Two more patients received a clinical diagnosis of MI based on the findings of focal ST-segment elevation with or without regional wall abnormalities on echocardiogram. Interestingly, the D-dimer level was more than two times higher in the 8 patients diagnosed with MI compared with the 10 patients who had the noncoronary myocardial injury. This further emphasizes the importance of D-dimer as prognostic value in COVID-19. Sadly, 13 out of 18 patients died in the hospital. This case series demonstrated that COVID-19 does not only cause noncoronary myocardial inflammation and injury, like other viruses but also leads to thrombotic obstructive coronary artery disease leading to MI.

### 2.4 Neurological manifestations

There are few neurological manifestations of COVID-19 reported in the literature. These are Guillain-Barre syndrome, viral encephalitis, toxic encephalopathy, acute hemorrhagic necrotizing encephalopathy, olfactory and taste disorders, stroke and nonspecific neurological symptoms, such as headache and dizziness. These clinical features might occur in isolation or in association with other classical features of COVID-19. They can be the presenting features at the time of hospital admission or occur several days postadmission. Interestingly, neurological features, on occasions, can occur early during the disease course and might precede the classical symptoms of COVID-19.

#### 2.4.1 Guillain-Barre syndrome

There are few reported cases of Guillain-Barre syndrome secondary to COVID-19. In one case series, five patients with confirmed COVID-19 developed symptoms of acute Guillain-Barre syndrome, such as lower limb weakness and paresthesia, 5 to 10 days after the onset of COVID-19 symptoms. This is similar to the interval between the onset of symptoms of other viral infections, such as the Zika virus and Cytomegalovirus, and Guillain-Barre syndrome. Interestingly, another case report, the order of symptoms was different. This case described a 61-year-old female presented to the hospital with acute lower limb weakness and fatigue. She had a recent travel history to Wuhan. Her neurological symptoms got worse over the next 3 days to involve both upper and lower limb weakness. The clinical examination, cerebrospinal fluid (CSF), and nerve conduction study findings all confirmed the diagnosis of Guillain-Barre syndrome. Laboratory results at the time of the presentation revealed lymphopenia and thrombocytopenia. Eight days after the onset of the neurological symptoms, she developed fever and dry cough. Chest CT scan showed bilateral GGO, and diagnosis of COVID-19 was confirmed by positive RT-PCR. As this is not the classical sequence of symptoms whereby the viral illness prodrome precedes the neurological symptoms, it is difficult to conclude if this was an association or coincidence. However, the presence of lymphopenia and thrombocytopenia, which are classical for COVID-19 might suggest that the patient contracted the infection during her recent stay in Wuhan and she had an initial asymptomatic phase of the disease.

#### 2.4.2 Viral encephalitis, toxic encephalopathy, and acute hemorrhagic necrotizing encephalopathy

Patients with COVID-19 may present with deterioration in conscious level and headache which occur at the time of hospital admission or during a hospital stay. This could be either due to central nervous system (CNS) infection or toxic encephalopathy. There are few reported cases of viral encephalitis secondary to COVID-19. The first case presented with a history of deterioration of conscious level and confusion 2 weeks after having classical symptoms of COVID-19. Although the CSF analysis showed evidence of CNS infection, the RT-PCR failed to detect SARS-CoV-2 genetic materials in the CSF. There was another case of COVID-19 viral encephalitis reported in Beijing Ditan Hospital in which RT-PCR analysis detected SARS-cov2 genome in the CSF. This could indicate that SARS-CoV-2 virus can cross the blood-brain barrier.

COVID-19 patients can present initially with features of altered conscious level due to toxic encephalopathy. A 74-year-old male with multiple comorbidities presented to the emergency department with a history of fever and cough followed by headache and altered mental status 24-hour later. The patient was diagnosed with encephalopathy as CSF analysis did not show evidence of CNS infection. Interestingly, a rare form of encephalopathy called acute hemorrhagic necrotizing encephalopathy has been reported. A female patient presented with a history of fever, cough, and altered mental status for 3 days. The diagnosis of COVID-19 has been confirmed by positive RT-PCR results. Brain imaging showed...
hemorrhagic lesions in bilateral medial thalami and medial temporal lobes, with no evidence of CNS infection on CSF analysis. In summary, during this pandemic, in any patient present to the emergency department with altered conscious level and/or confusion the possibility of encephalopathy or viral encephalitis secondary to SARS-CoV-2 infection should be considered.

2.4.3 | Stroke

There are multiple evidence in the literature that showed that COVID-19 disease increases the risk of both venous and arterial thrombosis. A case series study showed that three critically ill patients with confirmed COVID-19 developed multiple cerebral infarctions, confirmed by brain CT scan, 10 to 33 days after the onset of the initial symptoms of COVID-19. In another case series study, 5 of 78 patients who had confirmed COVID-19 in association with neurological symptoms had the acute cerebrovascular disease (four had an ischemic stroke and one had brain hemorrhage). The incidence of acute neurological complications, such as stroke, seems to be more common in patients having severe COVID-19 compared with patients having the mild disease. It is noticed that the incidence of arterial thrombotic events increases steadily in the first 14-day following ICU admission. This observation confirms the importance of treating all confirmed COVID-19 patients admitted to ICU with thrombo-prophylactic medications.

2.4.4 | Olfactory and taste disorders

Both olfactory and taste dysfunction have been reported as presenting symptoms of COVID-19. They might precede or occur in association with other classical symptoms of COVID-19 or occur in isolation. A survey conducted on 59 COVID-19 patients showed that almost 34% had olfactory and/or taste dysfunction. Another survey conducted on a larger sample; 417 patients with mild to moderate COVID-19, showed that more than 85% had a taste and/or smell sensation impairment. 12% had olfactory dysfunction which preceded the onset of other classical symptoms of COVID-19. A study showed that 17% of COVID-19 patients had the only anosmia as an isolated symptom. Therefore, anosmia can be used as a screening tool to identify asymptomatic carriers and test them. Self-isolation of asymptomatic carriers who tested positive for COVID-19 could massively reduce the risk of transmission of the infection. In conclusion, during this pandemic time, any patients presented with new-onset anosmia or taste dysfunction, the possibly of COVID-19 should be considered.

2.4.5 | Nonspecific neurological symptoms

There are few nonspecific neurological symptoms reported in patients with COVID-19 with varying frequency. These are dizziness (16.8%), headache (13.1%), muscle injury leading to myalgia and increased serum creatine kinase (10.7%), neuralgia (2.3%), epilepsy (0.5%), and ataxia (0.5%).

2.5 | Gastrointestinal manifestations

There are few reported gastrointestinal symptoms in patients with COVID-19. These are anorexia (83.8%), diarrhea (2% to 35.6%), nausea (1% to 10%), vomiting (1% to 6.4%), and abdominal pain (2.2% to 5.8%). On occasions, they might occur early in the disease course and precede other classical symptoms of COVID-19. A cross-sectional study showed that 48.5% of patients with confirmed COVID-19 presented to the hospital with only gastrointestinal symptoms as their presenting complaint. The same study showed that 45% of patients with confirmed COVID-19 had both gastrointestinal and respiratory symptoms, whereas 3% had only gastrointestinal symptoms. There is a case report described a patient who was presented with only fever and diarrhea without associated respiratory symptoms and then tested positive for COVID-19. Other case reports showed COVID-19 patients presented to the hospital with both gastrointestinal symptoms, such as nausea, vomiting, and diarrhea, in addition to respiratory symptoms. Patients with gastrointestinal symptoms RT-PCR detected SARS-CoV-2 virus in rectal swab and fecal sample. This might indicate the probability of fecal-oral transmission of COVID-19 infection.

An interesting case report described a 42-year-old male patient who had an 8-day history of abdominal pain, back pain, and testicular pain. On abdominal examination, there was diffuse abdominal tenderness, and the testicular exam was normal. Abdomen and pelvis CT captured the lung bases and showed basal GGO and consolidation, in addition to signs of colitis in sigmoid and distal descending colon. The patient was treated for pneumonia and colitis and discharged home with instructions to follow-up with his primary care physician. After discharge, the patient informed the primary care physician that he was tested positive for COVID-19. He was offered the test 1 day before his emergency department presentation due to a history of recent travel 2 weeks before the presentation. Therefore, it is important to recognize patients with COVID-19 presenting to the hospital with only gastrointestinal symptoms even with the absence of other symptoms. This kind of awareness improves early diagnosis and isolation of suspected patients which helps to reduce the risk of transmission from patients to patients and patients to doctors.

2.6 | Ocular manifestations

The main reported ocular manifestation in patients with COVID-19 in the literature so far was conjunctivitis. It was reported in association with other symptoms of COVID-19, and on rare occasions, excessive eye-watering (epiphora) was reported as the only initial presenting feature. A case series study showed that almost one-
third of patients with confirmed COVID-19 infection had clinical signs of conjunctivitis. It was reported in higher frequency in patients with more severe disease. About 16.7% of COVID-19 patients with clinical features of conjunctivitis had positive RT-PCR results from both pharyngeal and conjunctival swabs. In conclusion, ocular manifestations could be used as a clinical indicator of disease severity. In addition, giving the positive RT-PCR results from conjunctival swabs, transmission of COVID-19 infection by tears is a possibility to consider. This emphasizes the importance of using eye protection by healthcare professionals in the frontlines.

2.7 | Cutaneous manifestations

Skin rash has been reported in 0.2% of patients with confirmed COVID-19 infection. It can occur at the onset of the illness or during a hospital stay. The types of reported skin rash are: erythematous rash, widespread urticaria, chickenpox-like vesicles, localized pruritic lesions, and petechial skin rash. Skin rash commonly involves the trunk; however, there is a reported case of skin rash localized to heal and spare the trunk. Skin rash can be a delayed presentation in COVID-19. A case report described a patient presented with bilateral pruritic lesions in heels 13 days after the onset of typical symptoms of COVID-19. Furthermore, skin rash has been reported as the initial manifestation of the disease. In a case report, a patient presented with diffuse erythematous urticarial rash 48 hours before he developed classical symptoms and diagnosed as COVID-19. Another interesting case report described a patient who presented with petechial skin rash and thrombocytopenia. This case was initially misdiagnosed as dengue fever. The correct diagnosis of COVID-19 was eventually made when the patient developed respiratory symptoms later on in the disease course. Therefore, having knowledge regarding the cutaneous manifestations of COVID-19 is important to avoid delayed or misdiagnosis as patients can present early with skin rash even without associated fever or respiratory symptoms.

2.8 | Reproductive health issues

There is a growing concern regarding whether COVID-19 could have a negative impact on male reproductive function. It is argued that SARS-CoV-2 could cause direct testicular damage through binding with testicular ACE2 receptors, which are highly expressed in the testis. It could also damage the testis indirectly by inducing testicular inflammatory and immune response. A study conducted on 81 male patients with COVID-19 showed low testosterone level, high luteinizing hormone (LH) level, and low testosterone/LH ratio. This pattern indicates the possible viral testicular damage which subsequently affects the function of Leydig cells. In fact, it is not clear whether testicular damage induced by COVID-19 could lead to permanent fertility dysfunction. It has been reported that semen analysis following COVID-19 infection showed a low sperm concentration with low motility for up to 3 months postinfection. This might indicate that the effect of COVID-19 on male fertility might be only transient. However, as the evidence is insufficient, a long-term follow-up of recovered male patients is required to investigate the long-term impact of COVID-19 on the male reproductive function.

2.9 | Atypical presentations in children

Children with COVID-19 have been reported to present as asymptomatic or only with mild symptoms of the respiratory or gastrointestinal system. However, concerns have been raised regarding that a multisystem inflammatory syndrome similar to Kawasaki disease could be related to COVID-19 in children. Reports have described children diagnosed with Kawasaki-like illness in the setting of confirmed COVID-19 infection. A retrospective study from Italy showed a 30-fold increased incidence of Kawasaki-like disease cases in the Bergamo province following the COVID-19 epidemic, compared to the monthly incidence of the previous 5 years. Although the etiology of Kawasaki disease remains unknown, the possible association between Covid-19 and Kawasaki disease cannot be excluded. Recent studies have also shown that infants are more likely to present with atypical clinical symptoms, compared to older children. A study reported five infants diagnosed with COVID-19, who presented with isolated fever and reduced oral intake, without associated respiratory symptoms. Although four of them developed neurological symptoms at admissions such as drowsiness, hypotonia, and moaning sounds, CSF samples tested negative for SARS-CoV-2.
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How to cite this article: Abobaker A, Raba AA, Alzwi A. Extrapulmonary and atypical clinical presentations of COVID-19. J Med Virol. 2020;92:2458-2464. https://doi.org/10.1002/jmv.26157