COVID-19: Clinical Spectrum—It's Multiorgan Syndrome

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Abstract

COVID-19 outbreak caused by SARS-CoV-2 has emerged as a global challenge for the entire health care system worldwide. It has affected the developed as well as developing countries markedly. What began as pneumonia-like illness later evolved into a multiorgan disease leading to severe morbidity and even death. The clinical data and global literature explicitly suggest that in addition to respiratory symptoms, the COVID-19 patients may present with hematological, cardiovascular, renal, gastrointestinal, neurological, ocular, and skin manifestations. The underlying mechanism for multisystem involvement is the expression of angiotensin-converting enzyme 2 (ACE2) receptors at multiple extrapulmonary tissues. Injury to various organs may be attributed to cytokine storms or to disturbances of coagulation and vascular endothelium. The aim of this review is to emphasize the impact of SARS CoV-2 infection on not only the lungs but other organ systems too.

Keywords

COVID-19 · SARS-CoV-2 extrapulmonary manifestations · Multisystem disorder · Symptoms

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8.1 Introduction

The COVID-19 pandemic caused by novel Coronavirus (SARS-CoV-2) began as viral pneumonia initially reported from Wuhan city of China in December 2019. Within a period of few weeks, it engulfed the whole world and this global health crisis is still ongoing. The transmission of the virus primarily takes place through the aerosols via the respiratory route. As per the report of WHO on COVID-19, the severity of COVID-19 in patients ranges from completely asymptomatic to severe pneumonia and death (WHO report 2020). Initially, it was considered as a lung disease but later as the understanding of the disease evolved, it has been found to involve various other organs. The plausible mechanism for multisystem involvement is the expression of ACE2 at multiple extrapulmonary tissues. Apart from lung involvement, COVID-19 patients may present with hematological, cardiovascular, renal, gastrointestinal and hepatobiliary, endocrinological, neurological, ocular, and skin manifestations making it a multisystem disorder (Hoffmann et al. 2020; Guan et al. 2020).

Case definitions of COVID-19 as per the criteria defined by WHO are as follows:

1. Confirmed case: A person with positive RT PCR or SARS CoV rapid antigen test with or without clinical signs and symptoms.
2. Probable case: A person who tests inconclusive for COVID-19 virus but fits the clinical criteria and is a contact of a confirmed case.
3. Suspect case: A person who has an acute respiratory illness and has a history of contact with a confirmed or probable COVID-19 case.

8.2 Clinical Presentation

Initially, animal to human transmission was presumed to be the main mode of transmission linked to the seafood market of Wuhan. However, this could not be established in the absence of insufficient evidence and human-to-human transmission was believed to be the reason for the spread of this deadly virus. Based on the data available, the incubation period is said to vary from 3 to 7 days (median 5.1 days) and up to 2 weeks as the longest time from infection. The majority of the cases occur in about 4–5 days after getting exposed to the virus. The clinical presentation of COVID-19 patients is the variable and a large number of the cases may be asymptomatic (Midha et al. 2020). There is no clear definition of the term "asymptomatic" in regard to COVID-19 infection. Some of the patients who do not present with usual signs and symptoms of Coronavirus infection may or may not show COVID-19 changes on radiological imaging. The classic example of asymptomatic infection due to COVID-19 has been observed on the outbreak on a cruise ship. Out of the total 712 patients who tested positive for SARS CoV, 58% did not have any symptoms of COVID-19 (Batista et al. 2020). Additionally, a substantial number of all pregnant women screened at the time of delivery were found to be

asymptomatic, though confirmed positive for COVID-19 (Lopes de Sousa et al. 2020).

The clinical spectrum of symptomatic COVID-19 patients is quite variable. Most of the patients with SARS CoV infection experience mild to moderate disease without any need for admission to the hospital. The symptoms most commonly seen in these patients include fever, cough, sore throat, malaise, and so on. Other clinical findings are myalgia, headache, body ache, ageusia (loss of taste), anosmia (loss of smell), skin rash, or bluish discoloration of fingers or toes (Giacomelli et al. 2020). The severe form of the disease will include symptoms like chest pain and dyspnea and some severe cases present with atypical symptoms without fever such as loss of appetite, reduced alertness, delirium, fatigue, and so on, especially in immune-compromised and geriatric patients (García 2020). Pediatric patients are either asymptomatic or are mildly symptomatic. Based upon the clinical presentation of COVID-19, the manifestations can be divided into pulmonary and extrapulmonary. The disease presentation of COVID-19 on various organs of the human body has been illustrated in Fig. 8.1.

8.2.1 Pulmonary Manifestations

The patients infected with SARS-CoV-2 most commonly present with fever, cough, sore throat, dyspnea, and fatigue. In severe cases, the disease progresses to acute respiratory distress syndrome (ARDS) and respiratory failure. It is well known that initial manifestations of COVID-19 are similar to Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS) but the impact of COVID-19 is much more as it affects multiple organs of the body (Johnson et al. 2020). Nevertheless, a subtle indicator of COVID-19 infection is the development of dyspnea after experiencing mild flu-like symptoms. SARS CoV-2 infection leads to lung fibrosis in severely ill patients. Although fibrosis is a result of a normal repair mechanism yet the mechanism of pulmonary fibrosis in COVID-19 patients is not clearly understood. It may be the result of viral and immune-mediated mechanisms. Several other factors like advanced age, the severity of illness, smoking, and so on can predispose these patients to severe lung damage and pulmonary fibrosis in COVID-19 survivors (Ojo et al. 2020). A rare finding observed in critically ill COVID-19 patients is mediastinal lymphadenopathy. This is described as a reactive phenomenon to viral disease and inflammation (Valette et al. 2020). The clinical presentation of COVID-19 has been further classified into mild, moderate, severe, and critical illness (Acute respiratory distress syndrome, ARDS) (Guan et al. 2020; García 2020).

Mild/uncomplicated illness: This would include symptoms like mild fever, sore throat, dry cough, nasal congestion, headache, malaise, loss of taste and or smell, and gastrointestinal disturbance.

Moderate disease: Such patients usually present with respiratory symptoms like cough, dyspnea, and tachypnea.

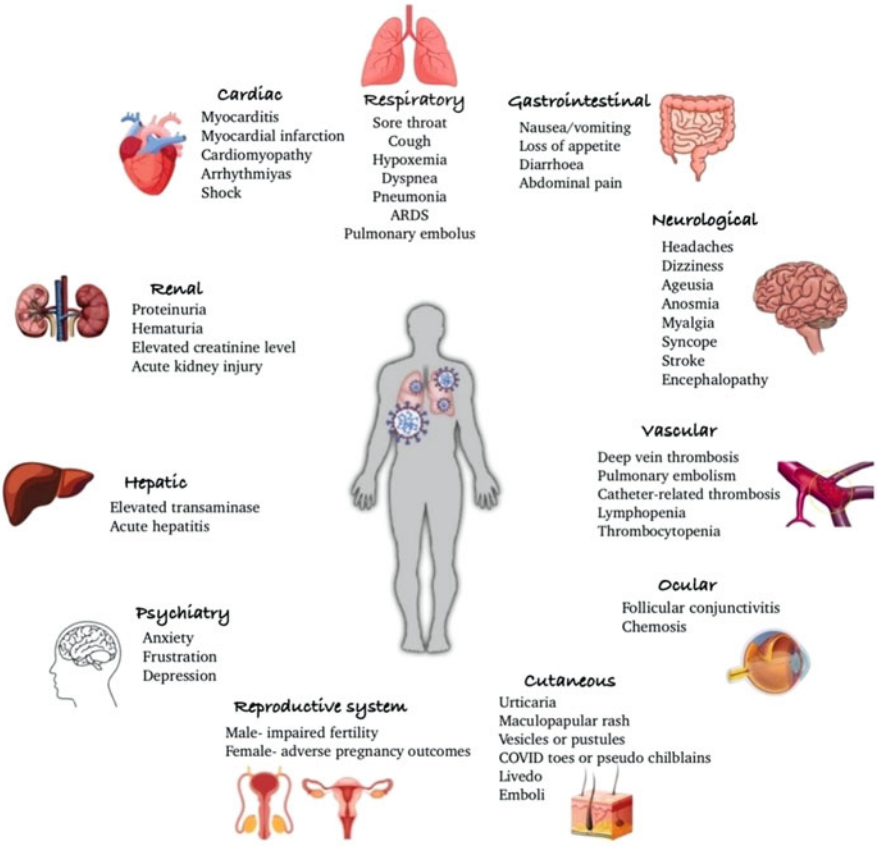

Fig. 8.1 Effect of SARS-CoV-2 infection on various organs of the human body leading to multi-organ failure in severe cases

Severe disease: These patients usually present with severe pneumonia, acute respiratory distress syndrome (ARDS), sepsis, or septic shock. Most common clinical presentations include the presence of severe dyspnea, tachypnea, respiratory distress ($SpO_2 \leq 93\%$, $PaO_2/FiO_2 < 300$), and/or more than 50% lung infiltrates within 24–48 h of onset of symptoms.

ARDS: This is a clear sign of onset or worsening of respiratory failure. According to one study, CT scan of 86% of these patients shows ground-glass opacity, 29% show consolidation and 19% have crazy paving. Bilateral involvement is seen in 76% of patients and peripheral disease distribution in 33% (Li and Ma 2020).

8.2.2 Extrapulmonary Manifestations

8.2.2.1 Gastrointestinal and Liver

The manifestation of gastrointestinal (GI) symptoms and liver involvement in COVID-19 is variable (3–70%) and is associated with the severity of the disease (Tian et al. 2020). This disease can cause acute gastritis and enteritis, leading to nausea, vomiting, diarrhea, pain abdomen, abdominal distention, and constipation. Some patients present with gastrointestinal symptoms at the onset of disease without any respiratory symptoms and some develop GI symptoms as the disease progresses (Mao et al. 2020). Mesenteric ischemia with severe hypotension has also been reported as one of the gastrointestinal manifestations of COVID-19 in patients with other comorbidities like type 2 diabetes mellitus, obesity, hypertension, and hepatic cirrhosis in the absence of any pulmonary manifestation (Norsa et al. 2020). Another rare gastrointestinal manifestation of COVID-19 is hemorrhagic colitis (lower GI bleed) reported in patients with comorbid conditions. Patients may experience flaring up of inflammatory bowel disease, that is, ulcerative colitis and Crohn's disease during COVID-19 infection (Carvalho et al. 2020; Gulen and Satar 2020). Hepatic involvement in COVID-19 has also been reported in the substantial number of patients and is presented as increased transaminase levels and acute hepatitis. One-third of critically ill COVID-19 patients suffer from hepatocellular injury and cholestatic liver dysfunction. Patients with underlying chronic diseases such as cirrhosis of the liver and autoimmune hepatitis need to be watchful of acute flare and decompensation (Fan et al. 2020).

The presence of angiotensin-converting enzyme 2 (ACE 2) receptor for viral transmembrane S-protein on the surface of certain intestinal epithelial cells in the ileum and colon is responsible for direct invasion and multiplication of the virus in the gut epithelium, leading to degeneration and necrosis of the gastrointestinal mucosa. The presence of ACE 2 receptors on oral mucosa could also explain the basic pathogenesis behind loss of taste in SARS-CoV-2 infection. Further, these receptors are also expressed on the cholangiocytes, which might indirectly dysregulate the liver function. However active multiplication of the virus has not been proven inside the hepatocytes. Cytokine storm and ischemia/ hypoxia due to respiratory complications of COVID-19 can also damage the liver. However, the possibility of liver damage due to the use of certain hepatotoxic drugs like acetaminophen, antivirals, antibiotics, steroids, and certain herbal medications during the management of COVID-19 cannot be ruled out (Chai et al. 2020; Zhao et al. 2020; Gupta and Kaushal 2021).

8.2.3 Renal Manifestations

The renal abnormalities associated with COVID-19 range from mild proteinuria, hematuria to acute renal injury (AKI). These renal manifestations can also be a marker of multi-organ dysfunction (MOD) and severe renal disease can occur often requiring renal replacement therapy (RRT). It is reported that up to 20% of ICU

patients with COVID-19 require RRT. The mortality is reported to be higher in patients of COVID-19 with acute kidney injury. According to a recent data analysis, coexpression of ACE2 and transmembrane protease serene 2 (TMPRSS) genes in renal tubular cells and kidney podocytes is necessary for the entry of SARS CoV-2 into host renal tissue.

8.2.4 Cardiac Manifestations

Cardiovascular manifestations in COVID-19 patients are more substantial than other extrapulmonary clinical manifestations. Approximately 12% of COVID-19 patients present with elevated levels of troponin T (TnT), C-reactive protein (CRP), NT-proBNP, or have myocardial infarction though they do not have any history of cardiovascular disease. The levels of these cardiac markers positively correlate with the severity of COVID-19 infection and adverse outcomes of the COVID-19 patients. Complications such as ARDS, ventricular arrhythmias, acute coagulopathy, and AKI are seen more frequently in patients with elevated TnT levels. COVID-19 may manifest itself as a cardiac event even in absence of lower respiratory tract symptoms.

Clinical manifestations like myocarditis, myocardial infarction, heart failure, shock, and increased incidence of cardiac arrhythmias are seen in COVID-19 patients. Cardiac arrhythmias sometimes go unnoticed in asymptomatic patients or maybe overshadowed by pulmonary manifestations (Gao et al. 2020; Zheng et al. 2020).

Multiple factors associated with the underlying pathophysiology of cardiovascular manifestations observed in COVID-19 patients have been reported. The presence of ACE2 receptors on cardiac myocytes, endothelial cells, smooth muscle cells, and fibroblasts explain the direct entry of virus-mediated injury in COVID-19 patients (Gallagher et al. 2008). Myocarditis in COVID-19 is presumed to be positively correlated with the viral load. Additionally, few autopsy studies have reported the isolation of the virus from the myocardial tissue thus lending credence to direct invasion and subsequent damage to cardiac tissue. Cytokine storm due to systemic inflammatory response syndrome is another presumed mechanism of myocarditis in these patients. Furthermore, higher levels of ACE2, in patients with prior cardiovascular disease may be one of the predisposing factors leading to more severe COVID-19. Moreover, ARDS, pulmonary thromboembolism, or vascular endothelial/smooth muscle tissue injury may lead to isolated right ventricular dysfunction (Gupta et al. 2020; Epelman et al. 2008; Walters et al. 2017) Disproportionately increased hypercoagulability in COVID-19 may further exaggerate the risk of myocardial infarction which otherwise also increases due to viral infections in general. In addition, many drugs used in the treatment of COVID-19 may result in prolonged ventricular repolarization and hence arrhythmias (Gupta et al. 2020; Ullah et al. 2020; Fried et al. 2020).

8.2.5 Vascular System

Elderly and immobile COVID-19 patients may frequently present with venous thromboembolism (VTE), a cardiovascular or respiratory complication due to increased coagulopathy. The occurrence of VTE was more commonly seen in lobar and segmental pulmonary arteries as compared to smaller subsegmental arteries. Some of the patients including few pediatric patients presented with Kawasaki-like disease/Kawasaki shock-like syndrome with coronary artery aneurysms. Luminal dilation/engorgement or mural thickening, subsegmental vessel enlargement microvascular dilation has been a frequent finding on the CT chest of the patients with confirmed COVID-19. The possible multifactorial mechanism responsible for vascular manifestations in COVID-19 patients includes expression of ACE 2 receptors on endothelial lining the vascular beds of different organs recruitment of immune cells to a site of viral infection, inducing apoptosis of endothelial cells, the release of cytokines and chemokines, excessive activation of the complement system leading to elevated plasma levels of lactic dehydrogenase, dimerized plasma fragment D (D-dimer), and decreased platelets (Tal et al. 2020; Porfidia and Pola 2020; Verdoni et al. 2020; Jones et al. 2020).

8.2.6 Neurologic Manifestations

Various neurological manifestations have been reported in COVID-19 patients. SARS CoV-2 can affect both the central nervous system (CNS) and peripheral nervous system (PNS). CNS related manifestations include headache, confusion, hallucinations, impaired consciousness, acute cerebrovascular disease and epileptic seizures, ataxia, acute disseminated encephalomyelitis (ADEM), and encephalopathy, whereas PNS-related manifestations are chemosensory disorders like hyposmia/anosmia, hypogeusia/ageusia, hypoplasia, neuralgia, myalgia, and Guillain-Barre syndrome (acute inflammatory demyelinating polyneuritis) (Wu et al. 2020a, b; Azhideh 2020; Sedaghat and Karimi 2020). The affinity of the virus for nervous tissue is again explained by the expression and distribution of the ACE2 receptor in neurons, astroglial cells, microglial cells, endothelial cells, and skeletal muscle tissue. According to reports, some COVID-19 patients directly present with neurologic symptoms whereas others with severe COVID-19 infection develop respiratory failure which might lead to cerebral hypoxia. Older individuals with comorbidities have a higher risk of impaired consciousness, delirium, and encephalopathy as a result of intracranial hemorrhages. COVID-19-associated epileptic seizures might be occurring due to the release of pro-inflammatory cytokines, tumor necrotizing factor α, and granulocyte colony-stimulating factors. Epilepsy/seizures may either be due to direct invasion of the virus to the brain or adverse drug reaction of antiviral drugs. Cytokine storm may also be responsible for acute necrotizing encephalopathy (ANE) observed in few patients (Sharifi-Razavi et al. 2020; Poyiadji et al. 2020; Kansagra and Gallentine 2011).

8.2.7 Hematologic Abnormalities

The hematological manifestations of COVID-19 include lymphopenia and thrombocytopenia. Lymphopenia has been found to be an important immunological marker and predictor of severe disease and mortality in critically ill COVID-19 patients (Arentz et al. 2020). Some studies revealed low counts of CD4+ T cells and CD8+ T cells in patients with severe COVID-19 (Bhatraju et al. 2020). Leukocytosis though rarely seen, is sometimes observed in older patients with underlying chronic conditions. The incidence of thrombocytopenia is variable (mild to moderate) but is often associated with poor outcomes (Terpos et al. 2020; Lippi et al. 2020; Connors and Levy 2020).

Studies have revealed that there is an increased risk of vascular thrombotic events due to COVID-19. Pathologic processes though not clearly understood, might involve either direct vascular and endothelial injury thereby producing microvascular clots or apoptosis of endothelial and mononuclear cells due to inflammation. COVID-19 induced coagulopathy leads to increased prothrombin time, low platelet counts, and elevated levels of D-dimer which has been associated with poor prognosis (Yuki et al. 2020). It has been seen that the patients with severe COVID-19 infection and multiorgan failure rarely develop overt disseminated intravascular coagulation (DIC) unlike classic DIC induced by bacterial sepsis or trauma.

8.2.8 Cutaneous Manifestations

Skin lesions in COVID-19 patients could be the result of post-viral hyperimmune activation or use of disinfectants and other drugs. Following dermatologic findings have been reported in patients with COVID-19 (Genovese et al. 2021):

- Urticarial rash with intermittent to severe itching mainly involving the trunk and limbs. Histopathological findings of the lesions include vacuolar interface dermatitis associated with superficial perivascular lymphocytic infiltrate.
- Confluent erythematous or maculopapular rash with symmetrical lesions predominantly localized on the trunk and showing centrifugal progression. Sometimes the eruptions and pruritis coexist. Superficial perivascular lymphocytic and neutrophilic infiltrates are observed on histological examination.
- Chilblain-like acral pattern mainly involving the feet or sometimes hands have become a famous COVID-19 cutaneous manifestation in otherwise asymptomatic individuals. The common symptoms seen are pain, burning sensation, and pruritus. On histology, these lesions display focal vascular necrosis.
- Papulovesicular lesions, papules, vesicles, and pustules are not very common and these involve the chest, abdominal region, and back. Histopathological examination reveals acantholysis and dyskeratosis.
- Livedo reticularis/racemosa lesions may be observed in COVID-19 patients with severe coagulopathy.

- Generalized purpuric severe vasculitic lesions evolving into hemorrhagic blisters localized in the intertriginous regions are sometimes seen Histopathological examination reveals vasculitis, cellular infiltrates, fibrin, and endothelial swelling.

8.2.9 Reproductive System Involvement

Many genitourinary complications have been reported due to COVID-19 disease progression mostly as a result of hyper coagulopathy. Decrease in total testosterone and increase in serum luteinizing hormone have been reported. In addition, an interesting case of bilateral orchitis resenting with testicular pain has been reported. COVID-19 infection impacts the male reproductive system more than the female reproductive system. The reason may be a high expression of ACE2 receptors on spermatogonia and supporting testicular cells which makes the male reproductive system a good target for SARS-CoV-2 infection (Wang and Xu 2020; Zhang et al. 2020a, b). A study has highlighted the presence of SARS CoV 2 in the semen of male patients infected with COVID-19. However, no viral RNA could be demonstrated in a biopsy taken from testes of the COVID-19 patients thereby indicating that SARS-CoV-2 does not directly infect testes or the male genital tract.

Another study supports the presence of SARS-CoV 2 in the vaginal fluid although low expression of ACE2 receptors has been demonstrated in fallopian tubes, ovaries, vagina, and endothelium. SARS CoV-2 RNA has been detected in the breast milk of infected patients (Ma et al. 2020; Song et al. 2020; Bridwell et al. 2021).

8.2.10 Ocular Manifestations

Ocular involvement in COVID-19 is uncommon with prevalence varying between 0.7 and 3%. Conjunctivitis and conjunctival congestion has been reported as one of the initial presenting symptom of COVID-19 in some studies (Zhang et al. 2020a, b; Chen et al. 2020). Additional ocular symptoms include watery eyes, ocular irritation, chemosis, folliculitis, conjunctivitis, and foreign body sensation. On examination, unilateral or bilateral eye involvement is observed. Conjunctival congestion, epiphora, and mild eyelid edema are seen. The reports of COVID-19 patients presenting with keratoconjunctivitis have also been published. The route of entry of the virus into the eyes could be from aerosols and respiratory droplets or transfer of virus from respiratory tissue to ocular tissue through the nasolacrimal system and vice versa (Wu et al. 2020a, b; Belser et al. 2013).

8.2.11 Psychiatric Manifestations

COVID-19 patients present with a wide range of psychological manifestations during the acute phase of the illness as well as following recovery from

COVID-19. Acute psychological reactions to COVID-19 infection include fear, anxiety, irritability, stress, confusion, and low mood (Sahoo et al. 2020). Psychiatric manifestations that have been noted during the illness and hospital stay are anxiety, insomnia, aggression, irritability, confusion, and varying degrees of impairment of consciousness. COVID-19 patients may also exhibit attention deficits, memory impairments and are at risk of developing post-traumatic stress disorder (Xiao et al. 2020). Negative psychological consequences such as anxiety, anger, irritability, fear, boredom, aggression, stress depression, suicidal ideation, apathy, and burnout may be noted especially during long periods of self-quarantine (Philip and Cherian 2020).

8.3 Special Considerations

8.3.1 COVID-19 and Pregnancy

Although pregnant females are more susceptible to COVID-19 infection, but the disease presentation is the same as in nonpregnant women (Wang et al. 2020; Bunyavanich et al. 2020). The changes in the maternal immune system that occur during pregnancy make pregnant females more susceptible to COVID-19 illness There is a strong concern regarding the vertical transmission of COVID-19 from mother to fetus.

Histopathological examination of placental and fetal membrane samples from a few patients with SARS-CoV-2 infection have revealed the presence of viral RNA but no virus has been demonstrated in vaginal swabs and amniotic fluid COVID-19 positive pregnant women (Akhtar et al. 2020).

8.3.2 COVID-19 and Children

Few cases of COVID-19 have been reported in children. Infected children either remain asymptomatic or experience a mild illness as compared to adults. Some children develop a serious condition called Multisystem Inflammatory Syndrome in Children (MIS-C). The most probable reason for less severe manifestations of COVID-19 in children is that ACE2 receptors are still evolving as are the T cells and associated cytokines (Williams et al. 2020). According to a review report of 72,314 COVID-19 patients from the Chinese Center for Disease Control and Prevention, less than 1% of the patients were younger than 10 years of age (Wu and McGoogan 2020).

8.4 Conclusion

COVID-19 is a disease that has put the entire world into a halt. The presentation of COVID-19 is highly variable. This article summarizes the data available on almost all pulmonary and extrapulmonary manifestations of this enigmatic multisystem viral infection that continues to evolve as the pandemic is still ongoing. Multicentre collaborative studies on this disease are further required at the national and international levels in order to improve patient care. High-quality transparent and ethical studies by researchers and clinicians will help in decreasing the morbidity and mortality associated with COVID-19 and the global community will inch closer to success against this pandemic.

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