

Extrapulmonary manifestations of SARS-CoV-2 virus infection

Manifestaciones extrapulmonares de la infección por SARS-CoV-2

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Abstract

The disease caused by a new coronavirus, which started in 2019, was named COVID-19 and declared a pandemic on March 11, 2020, by the World Health Organization. Although it is true that the first reports emphasized the respiratory manifestations of this disease as an initial clinical presentation, little by little cases with different initial manifestations began to appear, involving other systems. In cases where central nervous system involvement was identified, the most frequent findings were dizziness, headache, and alteration of alertness. Regarding the cardiovascular system, elevation of cardiac biomarkers and myocarditis are one of the most frequent findings. The main gastrointestinal symptoms described so far are: anorexia, nausea, vomiting, diarrhea, abdominal pain, and/or discomfort. Venous thromboembolism is a frequent complication and a public health problem. Skin manifestations remain a field of investigation. Maculopapular rashes, reticular livedo, acral gangrene, and among others, have been identified. Health personnel must be updated on new clinical findings and the forms of presentation of this partially known disease, which will make it possible to make more accurate and timely diagnoses, thus impacting the prognosis of these patients.

Keywords: Disseminated intravascular coagulation. Hyposmia. Myocarditis. Neurovirulence. Venous thromboembolism.

Resumen

La enfermedad causada por un nuevo coronavirus, que inició en 2019, fue denominada COVID-19 y declarada pandemia el 11 de marzo de 2020 por la Organización Mundial de la Salud. Si bien es cierto que los primeros reportes enfatizaron las manifestaciones respiratorias de esta enfermedad como presentación clínica inicial, poco a poco empezaron a aparecer casos con manifestaciones iniciales distintas, involucrando otros sistemas. En los casos en los que se identificó afectación del sistema nervioso central, los hallazgos más frecuentes fueron mareo, cefalea y alteración del estado de alerta. Respecto al sistema cardiovascular, la elevación de biomarcadores cardíacos y la miocarditis son unos de los hallazgos más frecuentes. Los principales síntomas gastrointestinales descritos hasta el momento son anorexia, náuseas, vómitos, diarrea y dolor o discomfort abdominal. La tromboembolia venosa es una complicación frecuente y un problema de salud pública. Las manifestaciones cutáneas siguen siendo un campo de investigación.

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Se han identificado exantemas maculopapulares, livedo reticular y gangrena acral, entre otros. El personal sanitario debe estar actualizado sobre los nuevos hallazgos clínicos y las formas de presentación de esta enfermedad solo parcialmente conocida, lo que permitirá hacer diagnósticos más precisos y oportunos, y así impactar en el pronóstico de estos enfermos.

Palabras clave: Coagulación intravascular diseminada. Hiposmia. Miocarditis. Neurovirulencia. Tromboembolia venosa.

Introduction

In December 2019, in the city of Wuhan, Hubei province, in China, a disease originated that stopped and captured the attention of the entire world. The disease caused by a new coronavirus, which began in 2019, was called Coronavirus Disease 2019 (COVID-19) and declared a pandemic on March 11, 2020, by the World Health Organization¹. The International Committee on Taxonomy of Viruses, as the body that authorizes and organizes the taxonomic classification of viruses, assigned the name Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) to this new virus.

This disease manifested with symptoms that were highly similar to those of severe acute respiratory syndrome (SARS), first identified in Asia in 2003; however, recent evidence has shown that SARS-CoV-2 can affect not only the respiratory system but also other organs and systems, including the central nervous system (CNS) and peripheral nervous system (PNS), as well as cardiovascular, gastrointestinal (GI), hepatic, renal, hematological, and cutaneous systems, among others.

SARS-CoV-2 has been isolated in conjunctival secretions, tears, feces, and urine, which confirms that the infection is not limited to the respiratory tract². It is a highly contagious virus, and its lethality greatly varies according to the region³.

During COVID-19 outbreak early stage, diagnosis of the disease was complicated by the diversity of symptoms and disease severity at presentation. Although the most common symptoms of COVID-19 at disease onset include fever (88%), fatigue (38%), cough (67.8%), dyspnea (18.7%), and myalgia⁴, there are other less common symptoms such as headache, abdominal pain, diarrhea, nausea, and vomiting.

This was also reported in a meta-analysis conducted by Ma et al.², in which fever (79.1%), cough (58.0%), and fatigue (29.3%) were identified as common symptoms; digestive symptoms, such as diarrhea (5.7%), nausea, or vomiting (2.0%), were relatively rare.

Most infected patients will suffer a mild form of the disease⁴ and those younger than 15 years will generally not develop severe forms and will be asymptomatic³.

The difficulty for establishing SARS-CoV-2 infection specific symptoms increases the possibility arriving at erroneous working diagnoses. This situation may be related to a higher exposure of healthy people to the virus, including health-care personnel, which makes it imperative for protective measures to be globally used in current pandemic scenario.

It has been postulated that appropriate interventions implementation and treatment establishment in a timely manner may offer a better prognosis.

The review herein presented addresses, by organs and systems, extra-pulmonary complications secondary to SARS-CoV-2 infection with the purpose to offer the reader a useful compendium for clinical practice and contribute to currently existing literature.

Neurological manifestations of SARS-CoV-2 infection

SARS-CoV-2, since its origin in the city of Wuhan, China, spread rapidly, leaving doubts about its origin, propagation form and pathophysiology, in addition to all potential clinical manifestations in humans. Cases have been occurring that fail to show the symptoms that were initially considered typical, but instead have a neurological nuance, such as headache, impaired alertness, gait disturbances or data consistent with central or peripheral focalization⁵.

Angiotensin-converting enzyme 2 (ACE2) receptor has recently been identified as the functional receptor for the acute respiratory distress syndrome secondary to SARS-CoV-2 infection. This receptor is found in numerous organs, including the nervous system (glial cells and neurons), the liver, kidneys, and muscle. Therefore, SARS-CoV-2 infection can cause neurological symptoms by direct and indirect mechanisms, similar to SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV). SARS-CoV nucleic acid has been detected in cerebrospinal fluid, and SARS-CoV-2, in brain tissue⁶.

Both viruses exhibit the S1 spike protein, which allows the virion to bind to the cell membrane by

interaction with host ACE2 receptor. SARS-CoV-2 affinity for this receptor is 10-20 times higher than that of SARS-CoV⁷. This viral surface antigen is the target of neutralizing antibodies during infection⁸.

Said receptors are also expressed in circumventricular organs and cerebrovascular endothelial cells, which play a key role in vascular autoregulation and cerebral blood flow.

Several possible routes have been described for CNS infection: spread through the olfactory bulb, from mechanoreceptors and chemoreceptors in the lung and lower respiratory tract, and by hematogenous route through brain ACE receptors⁹.

Brain angiotensin II dysfunction is likely to be involved in self-regulation disruption and blood pressure peaks that result in arterial wall rupture¹⁰.

So far, whether there is an increased risk of death attributable to ACE 2 inhibitors or angiotensin II receptor blockers chronic use has not been determined.

The main pathogenic pathways described for CNS involvement by SARS-CoV-2 are direct viral pathogenicity, brain tissue-targeted immune-mediated pathogenicity, brain blood vessels inflammatory involvement, and intravascular coagulation secondary to the systemic inflammatory response as the main cause of thrombosis, hemorrhage and stroke⁹.

SARS-CoV-2 dissemination through systemic circulation or through the ethmoid bone cribriform plate toward cerebral circulation can also lead to CNS compromise.

Due to the inflammatory response generated by viral replication in nasal mucosa nerves, one of the early findings is sense of smell alteration or hyposmia. Studies indicate that the virus is shed in large amounts from the nose in symptomatic and asymptomatic patients, in a manner more similar to influenza virus than to SARS virus³. Once inside neuronal tissues, neuronal and endothelial lining damage occurs, which causes capillary rupture and bleeding⁷.

Anosmia with dysgeusia is a common finding in viral respiratory infections, as a consequence of an inflammatory reaction of the nasal mucosa and the presence of rhinorrhea; however, recent observations in current epidemiological context turn SARS-CoV-2 into the prime suspect.

In the study by Lechien et al.¹¹, 85.6% and 88.0% of patients reported olfactory and gustatory dysfunction, respectively. Most patients (65.7%) reported sense of smell alterations after the appearance of ear, nose, and throat general symptoms; however, 11.8% of patients in this study reported that olfactory

dysfunction appeared before any other symptom, which suggests that anosmia may be important for COVID-19 early detection¹¹.

In an effort to establish the importance of these symptoms in the diagnosis and progression of the disease, the American Academy of Otolaryngology-Head and Neck Surgery has established the COVID-19 Anosmia Reporting Tool to enable physicians from all specialties around the world to assist in early detection of cases, and thereby reduce the probability for the disease to spread¹¹.

Although the effects of COVID-2019 on olfactory and gustatory perception can be transitory, the possibility for viruses and other pollutants to be the starting cause of neurodegenerative conditions such as Parkinson's disease has been suggested¹².

Viral invasion of the lung parenchyma leads to gas exchange disorders, thus causing hypoxia, promoting anaerobic metabolism and lactic acid accumulation, which can result in cerebral vessels vasodilation, cellular swelling, interstitial edema, and blood flow obstruction, with the consequent appearance of headache secondary to ischemia or congestion, which can progress to intracranial hypertension, brain dysfunction, bulbar edema, and even coma.

Researchers from Huazhong, in Wuhan, China, classified neurological findings into three classes: CNS symptoms, PNS symptoms, and musculoskeletal symptoms. Of the studied patients, 36.4% had neurological symptoms: 24.8% had CNS, 8.9% had PNS, and 10.7% had skeletal muscle manifestations. Most common findings corresponding to the CNS were dizziness (16.8%), headache (13.1%), and impaired alertness, and those secondary to PNS involvement were hypogeusia (5.6%) and hyposmia (5.1%)¹³.

More recently, other neurological phenotypes involving the CNS and PNS have emerged, characterized by anosmia, ageusia, hemorrhagic necrotizing encephalitis, and Guillain-Barré syndrome¹⁴.

Most neurological manifestations occurred early within the first 2 days in the course of the disease. The patients that were most likely to develop neurological manifestations were those with severe infection in comparison with those not severely ill (45.5% and 30.2%, respectively), in addition to those who were significantly older, with underlying comorbidities such as hypertension, diabetes, cerebrovascular and heart disease, cancer and chronic kidney disease¹³.

Another clinical presentation of neurological compromise is infectious toxic encephalopathy or acute toxic encephalopathy, which occurs as a reversible brain dysfunction syndrome, with cerebral edema. Affected individuals will experience disorientation, impaired alertness, coma, paralysis, and severe headache¹⁵. Neurotropic viral infections have been previously shown to be able to cause brain parenchymal inflammation or to elicit encephalitis and brain-targeted autoimmune responses in susceptible individuals¹⁶.

Neurotropic virus's axonal transport can transform intrinsically disordered proteins into promiscuous binders, which will have the ability to form toxic aggregates, travel along neuronal pathways, and cause cell death in brain tissue¹⁶.

Continuous care of patients who consult for neurological symptoms or signs should be ensured, mainly in the case of diseases that have high morbidity, such as cerebrovascular conditions and CNS infections.

Action protocols will be adjusted according to the suspicion or confirmation of SARS-CoV-2 infection. They should be regularly applied in patients without suspected infection, and in COVID-19 suspected or confirmed cases, preventive measures shall be stepped up, and intervention of a multidisciplinary team (internists, pulmonologists, and intensivists) that allows appropriate assessment of patient health situation and functional and vital prognosis to be obtained will be considered essential¹⁷.

SARS-CoV-2 infection cardiovascular manifestations

SARS-CoV-2 can induce new heart pathologies or exacerbate underlying cardiovascular diseases. Added to this are adverse and toxic cardiovascular effects, secondary to the use of antimalarial and antiviral drugs.

It is important mentioning that the incidence of COVID-19 in concurrence with underlying comorbidity reported in the literature is of up to 26.0%, and the majority of patients (65.3%) had cardiovascular and cerebrovascular diseases².

SARS-CoV-2 infection elicits a cytokine storm, inflammation and a state of hypercoagulation that not only cause harm to lung tissue¹⁸, but also, in severe cases, lead to multiple organ failure and death¹⁹. Development of arrhythmias, myocardial injury, vascular inflammation, acute myocardial infarction, myocarditis with systolic dysfunction, pericarditis, myopericarditis, pericardial effusion with or without cardiac tamponade,

and pulmonary thromboembolism has already been associated.

In the study conducted by Guo et al.²⁰, 27.8% of COVID-19 patients had myocardial injury, which resulted in cardiac dysfunction and arrhythmias. This study showed that myocardial injury has a significant association with COVID-19 fatal outcome, and that the prognosis of patients with underlying cardiovascular disease, but without myocardial injury, is relatively favorable²⁰; however, lethality in patients with heart disease is, so far, uncertain. In this group of studied patients, mortality was 13.33% for those with underlying cardiovascular disease and normal troponin T values, 37.50% for those without underlying cardiovascular disease and elevated troponin T values, and 69.44% for those with cardiovascular disease and elevated troponin T values²⁰.

In an observational study carried out in Wuhan, China, by Shi et al.²¹, cardiac injury was identified in 19.7% of COVID-19 patients and was an independent predictor of in-hospital mortality (51.2% vs. 4.5% in those without cardiac injury; $p < 0.001$).

Cardiac biomarker studies suggest a high prevalence of cardiac injury in hospitalized patients. Myocardial injury is likely to be associated with infection-related myocarditis or ischemia, and is an important prognostic factor²². It can cause atrial or ventricular fibrosis, thus generating a substrate for subsequent development of arrhythmias¹⁹. Hypoxemia caused by COVID-19 lung compromise can trigger atrial fibrillation, which can persist even after lung function improvement.

Renin-angiotensin-aldosterone system inhibitors abrupt withdrawal in high-risk patients, such as those with heart failure or coronary artery disease, can cause clinical instability and adverse health outcomes²³.

So far, there is no clinical or scientific evidence for treatments with ACE inhibitors or angiotensin receptor blockers to be discontinued.

SARS-CoV-2 infection GI manifestations

SARS-CoV-2 has shown tropism for the GI system, particularly for the intestine. This has been verified by detecting viral particles in patient biopsies and feces, a condition that may partially explain GI symptoms and infection potential recurrence and transmission²⁴. The main GI symptoms that have been described are anorexia, nausea, vomiting, diarrhea, and abdominal pain or discomfort²⁵.

In Hong Kong, according to Cheung et al.²⁵, out of 59 COVID-19-diagnosed patients that were studied, 25.4% had GI symptoms, and in 15.3% was viral RNA isolated in feces. Viral RNA was detected more frequently in patients with diarrhea than in those who did not experience this clinical manifestation.

In contrast to the findings published by Cheung et al.²⁵, Sultan et al.²⁶ report that GI symptoms are associated with COVID-19 in <10% of cases. This percentage was obtained by performing an analysis of the prevalence of diarrhea, nausea, vomiting, abdominal pain and liver function tests alterations through a meta-analysis of 47 studies that included 10,890 patients, based on the best clinical practice recommendations for COVID-19 consultative management.

In the study developed in Hubei, China, by Pan et al.²⁷, on COVID-19 patients clinical characteristics and digestive symptoms, patients with digestive symptoms were reported to have higher liver enzyme mean values, lower monocyte counts, and longer prothrombin time, and to require more antibiotic treatment than patients without these symptoms.

The presence of SARS-CoV-2 nucleic acids in liver tissue has confirmed direct infection. SARS-CoV-2 shares 82% similarity with SARS-CoV genome, and an incidence of liver compromise of up to 60% has been described in patients infected with the latter. In patients with severe COVID-19, a higher incidence of liver involvement has been observed²⁸.

In the study carried out by Guan et al.⁴, 18.2% of patients with non-severe disease and 39.4% of those with severe disease were observed to have aspartate aminotransferase elevation. There is a higher incidence of aspartate aminotransferase elevation in the group of patients with severe disease. Alanine aminotransferase also showed a higher incidence of increase in the group with severe disease (28.1%) in comparison with the group with non-severe disease (19.8%). Up to 60% of infected patients will have mild or moderate liver injury, characterized by transaminase elevation, hypoproteinemia, and prothrombin time (PT) prolongation²⁴.

According to the British Society of Gastroenterology²⁹, there are procedures that should continue to be performed in patients with COVID-19, such as interventions in cases of upper GI bleeding, presence of foreign bodies in the upper GI tract, lower GI tract obstructive lesions, acute biliary obstruction, and lower GI bleeding in case it cannot be resolved by interventional radiology.

The relevance of GI symptoms onset as first manifestation of the disease lies in the prolongation of the time before medical consultation and even hospital admission, as demonstrated in the study carried out by Pan et al.²⁷. Patients with GI symptoms were observed to have a significantly longer time from symptom onset to hospital admission, in comparison with those without GI symptoms (9 vs. 7.3 days). This finding may be associated with late treatment initiation and poorer clinical outcomes.

Clinical studies that include the use of standardized questionnaires aimed at evaluating GI symptoms, as well as liver function tests at hospital admission, are required to better establish their incidence and association with COVID-19²⁶.

Kidney involvement by SARS-CoV-2 infection

COVID-19 can affect multiple organs, including the kidney³⁰. In previous reports of SARS and MERS-CoV infections, acute kidney injury (AKI) did develop in 5-15% of cases and had a high mortality rate (60-90%). Early reports suggested a lower incidence (3-9%) of AKI in patients with COVID-19^{4,31,32}. The etiology of renal function compromise in COVID-19 is multifactorial.

SARS-CoV-2 can exert direct cytopathic effects on renal tissue. This is supported by the detection of coronavirus fragments in blood and urine, both in patients with the 2003 SARS virus³³ and in those with SARS-CoV-2³⁴. Kidney injury can also be caused by entry of the virus into renal cells.

Recent data on human tissue RNA sequencing demonstrated that ACE2 is expressed in the kidney almost 100 times higher than in the lung³⁵. The mechanisms of kidney involvement can be classified into three groups that are interconnected:

- Cytokine-induced damage: Cytokine release syndrome, also called “cytokine storm,” occurs in sepsis, hemophagocytic syndrome, and chimeric antigen receptor T-cell therapy³⁶. In patients with cytokine release syndrome, AKI can occur as a result of intrarenal inflammation, vascular patency increase, decreased volume, and cardiomyopathy, which can lead to type 1 cardiorenal syndrome. This syndrome includes systemic endothelial lesion, which clinically manifests as pleural effusions, edema, abdominal hypertension, fluid loss to a third space, intravascular fluid depletion, and hypotension. Pro-inflammatory interleukin 6 is considered the most important

cytokine in cytokine release syndrome. In patients with SARS-CoV-2 acute respiratory distress syndrome, interleukin 6 plasma concentration shows a significant increase³⁷. Extracorporeal therapies have also been proposed for eliminating cytokines in patients with sepsis, and might be beneficial in severely ill patients with COVID-19³⁸, by enabling the prevention of cytokine release syndrome-induced organ damage.

- Organ dysfunction: According to the study by Ronco and Reij³⁹, advanced age, disease severity, diabetes mellitus, and positive fluid balance were independently associated with the development of AKI. AKI severity was associated with advanced age, diabetes mellitus, elevated body mass index, history of heart failure, higher peak inspiratory pressure, and higher Sequential Organ Failure Assessment score.
- Systemic effects: Fluid administration can lead to a positive fluid balance in patients in state of shock, thus worsening renal vein congestion, which leads to renal compartment syndrome. Patients with severe COVID-19 develop septic shock. Sepsis-associated AKI can act synergistically with other mechanisms of kidney damage⁴.

In patients with suspected or confirmed gram-negative bacterial infections, the use of hemoperfusion with a cartridge containing polystyrene fibers with polymyxin B provides effective endotoxin adsorption⁴⁰, a strategy that is already being used in patients with SARS-CoV-2 infection.

In a study carried out in Wuhan, China, more than 40% of patients were observed to have evidence of kidney disease, with serum creatinine and blood urea nitrogen elevated values in more than 13%. The presence of kidney disease was associated with higher in-hospital mortality⁴¹.

So far, studies have shown that the prevalence of kidney disease at hospital admission and AKI development during hospitalization in COVID-19 patients is high. AKI is one of the main causes of disease severity, which contributes to multiple organ failure and death. Renal function monitoring is of great importance, as kidney failure early treatment initiation with continuous renal replacement therapy also is.

Among the baseline characteristics of patients infected with SARS-CoV-2, disease severity and mortality (20.2% and 3.1%) are highly associated with other underlying conditions, such as hypertension, diabetes, cerebrovascular diseases, chronic obstructive

pulmonary disease, and chronic kidney disease, in comparison with non-severe cases. This suggests that patients with such conditions are especially vulnerable to infection, which is why they should receive more attention and care².

Coagulation disorders caused by SARS-CoV-2 infection

There are already certain aspects to consider regarding coagulation disorders that are of great importance. Severe disease is commonly associated with coagulopathy⁴².

Coagulopathy in severe sepsis and septic shock in the clinical context of severe COVID-19 represents a relatively common complication, especially characterized by a significant elevation of D-dimer values. Fifty percent of COVID-19 patients exhibit elevated D-dimer values during disease progression, and this proportion can be as high as 100% in cases of death. D-dimer level in severely ill patients is significantly higher than in those with mild disease. Some patients suddenly deteriorate during treatment, which suggests that those with severe disease might be at higher risk of thrombosis^{4,42}.

The pathological changes described in COVID-19 patients are mainly concentrated in the lungs, where septal alveolar blood vessels are congested and edematous, and thrombi formation can be clearly observed. These fibrin thrombi are different from the white thrombi in the lungs of SARS patients⁴³.

Virus-triggered cytokine release syndrome may be related to macrophage activation syndrome or to an antiphospholipid syndrome, as part of hyperferritinemic syndromes. The presence of diffuse microvascular damage, with consequent multiple organ failure, is an important cause of death in severely ill COVID-19 patients^{31-34,42}.

In a retrospective analysis carried out by Tang et al.⁴², coagulation parameters of survivors and non-survivors were compared. Median time from admission to disseminated intravascular coagulation (DIC) identification was 4 days. At admission, non-survivors showed significantly higher levels of D-dimer and longer PT, in comparison with survivors. In the same study, the use of low molecular weight heparin was associated with a better prognosis.

Unlike the classical pattern observed in sepsis, partial activated thromboplastin time elevation is often lower than PT elevation, probably due to an increase in factor VIII levels. Thrombocytopenia is mild and no

microangiopathy is identified. The incidence of thrombocytopenia in patients with COVID-19 is variable. Some patients with severe disease have been described to have developed coagulopathy with fulminant coagulation activation and factor consumption.

Thrombotic complications and venous thromboembolism (VTE) in severe COVID-19

Activation of the coagulation cascade, both systemic and in pulmonary arterial vasculature, represents an essential physiopathogenic mechanism of the host in the presence of sepsis.

It is important to emphasize the interaction that exists between different blood cellular components, vascular endothelium and the immune system to promote the synthesis of thrombin, which in turn activates and expands said coagulation cascade. This complex phenomenon is currently known as “immunothrombosis”^{44,45}.

Tang et al.⁴² observed, in 183 patients with severe COVID-19, that the presence of severe sepsis-induced coagulopathy (SIC) and DIC, as defined by the updated criteria (and recently validated by the International Society on Thrombosis and Hemostasis) with a score > 4 points in severe COVID-19, are associated with a poorer prognosis and an increase in short-term mortality; 71.4% of deceased individuals showed evidence of having developed SIC or DIC, in comparison with 0.6% of survivors^{42,46}.

Guan et al.⁴ observed D-dimer values ≥ 500 ng/mL in 43% of non-severely ill patients in comparison with 60% of patients with severe disease.

A meta-analysis of nine studies that included 400 patients with severe COVID-19 demonstrated the association of thrombocytopenia with more severe disease, as well as an up to five-fold increase in the risk for developing more severe COVID-19 with direct admission to an intensive care unit; however, the authors conclude that thrombocytopenia was not a consistent parameter at hospital presentation that was associated with significant mortality⁴⁷.

VTE, whether deep vein thrombosis or acute pulmonary thromboembolism, is a common complication and a public health problem of great clinical relevance. Patients with severe pneumonic disease due to COVID-19 with SIC in critical condition represent a highly vulnerable subgroup, to whom vascular, systemic and pulmonary endothelium inflammation

confers a significantly elevated risk for the development of VTE.

In patients with refractory hypoxemia and significant hemodynamic deterioration, there is the need for VTE to be considered, particularly in those with risk factors such as C-reactive protein, ferritin and D-dimer elevation, prolonged PT, thrombocytopenia, high levels of fibrin degradation products, and interleukin 6 with high clinical suspicion of SIC or DIC in the context of respiratory distress syndrome¹⁹.

Cui et al.⁴⁸ have reported an incidence of VTE of 25%. These researchers found that D-dimer values > 1500 ng/mL represented a good prognostic index for high-risk VTE identification. However, it should be noted that in this study no patient did initially receive thromboprophylaxis.

Klok et al.⁴⁹ identified a total cumulative incidence of thrombotic events of 31% by analyzing patients with severe COVID-19 and pneumonia admitted to the intensive care unit. All patients received appropriate thromboprophylaxis. Acute pulmonary thromboembolism was the most common VTE complication ($n = 25$; 81%), and the most important risk factors for developing VTE were age and objective evidence of coagulopathy, characterized by a PT elevation > 3 s above controls and partial thromboplastin time alterations > 5 s above upper limit of normal.

COVID-19 skin manifestations

Cases with skin manifestations have already been documented, mainly in Italy and China. Due to the high rate of infection transmission, clinical photography is limited, and introduction of the necessary equipment for performing it is not a priority; therefore, visual material is scarce.

In Lombardy, Italy, efforts were made to document if patients hospitalized for COVID-19 had skin manifestations⁵⁰. One hundred and forty-eight patients with COVID-19 were analyzed, out of which 60 were excluded due to recent consumption of new medications, since drug intake is one of the most common causes of efflorescence and dermatosis in hospitalized patients. Skin manifestations were developed by 20.4%. The most commonly affected region was the trunk. No relationship was found between skin manifestations and disease severity⁵⁰.

There are no reports of maculopapular rashes for other coronaviruses, such as SARS-CoV and MERS-CoV⁵¹.

In Thailand, a case of a patient who presented with a petechial rash has been reported⁴⁹. Within the epidemiological context of that country, the most likely diagnosis was dengue, but the patient developed respiratory symptoms and was finally diagnosed with COVID-19.

In Spain, an 84-year-old female patient who presented with SARS-CoV-2 pneumonia was hospitalized. On admission, she received treatment with hydroxychloroquine and lopinavir/ritonavir, and 3 days later, she developed a dermatosis disseminated to flexural regions, characterized by violaceous erythematous millimetric macules with coalescence at certain points. It cannot be asserted that the cause was COVID-19, but it is highly likely, since the same drugs have been taken by thousands of patients and no skin manifestations have been reported⁵².

Non-specific viral rashes are the most common, both in children and adults. The main causes in childhood are adenovirus, parainfluenza virus, and respiratory syncytial virus⁵³; in adults, the most common cause of maculopapular rashes are medications, although many times it is impossible for a distinction between both these groups to be established only by clinical examination, since even on histopathological analysis they are very similar⁵¹. On many occasions, the cause is not found (idiopathic rashes)⁵⁴ and most resolve within 7 days⁵³. Medical history and viral tests can help distinguish other possible causes but, in the light of current situation, it is difficult for these non-crucial interventions to be carried out.

Other reports highlighted critical care patients in Wuhan, China, and informed about dusky acrocyanosis and dry gangrene⁵⁵.

Cases of pediatric and adolescent patients with ischemic acral lesions have been documented in Italy⁵⁶. These lesions are characterized for affecting the toes and sometimes the soles. They start as violaceous spots that evolve into blisters with serous content and then ulcers of necrotic borders that fortunately did resolve in all patients. The lesions are painful and have approximate duration of 2 weeks. They mainly affect children at the end of the first decade of life and adolescents.

In many cases, a confirmatory polymerase chain reaction test could not be performed given the nature of the health emergency, and neither could laboratory tests or skin biopsies. However, these reports are consistent in time with the epidemic.

Differential diagnoses include acrocyanosis due to cardiorespiratory causes, chilblain lupus and

Henoch-Schönlein-type vasculitis, but morphology is different.

DIC, S-protein deficiency, and meningococcemia should also be considered; however, these ailments are characterized by the serious condition of the patient and the lesions are much more extensive.

Another type of reported lesions that result from vascular involvement are those of transient livedo reticularis. Livedo reticularis is originated by microvascular blood flow reduction, which causes an accumulation of deoxygenated blood in the venous plexus. In the cases associated with COVID-19 reported by Manalo et al.⁵⁵, it is transient. These authors postulate that all hypercoagulability manifestations associated with SARS-CoV-2 infection are due to microthrombosis that affect different organs, including the skin. No biopsies were performed in the reported patients due to the transient nature of the phenomenon⁵⁶.

Personnel in charge of patients with this condition should be alert for skin presentations to early identify them and implement appropriate interventions.

Conclusion

The occurrence of symptoms in patients affected by this disease has not been observed to follow any type of pattern so far, and clinical manifestations comprise a wide variety of organs and systems, from asymptomatic patients, through patients with extra-pulmonary symptoms, to patients with almost exclusively respiratory symptoms.

This review offers the reader a compendium of SARS-CoV-2 infection extra-pulmonary manifestations and highlights the importance of actively seeking the presence of non-respiratory clinical symptoms and signs in patients who consult, in the scenario we are facing all over the world, with the purpose to improve the diagnostic and therapeutic approach.

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