7 Clinical Pictures of COVID-19

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Coronaviruses are very common pathogens that in most cases cause flulike symptoms. Two beta-coronavirus, severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV), can cause severe pneumonia with respiratory distress syndromes and death.

At the end of 2019, a new coronavirus, named severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), was identified for the first time in China (Wuhan). This virus spread rapidly causing a disease called COVID-19, which led to a global pandemic.

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This virus is typically transmitted through respiratory droplets and has an average incubation time of 4–5 days with a maximum of 14 days; more than 95% of patients who develop symptoms became symptomatic within 11.5 days.

Clinical spectrum is very heterogeneous, with a wide range of symptoms reported. It varies from an asymptomatic form to severe life-threatening disease [1, 2]. The respiratory tract is the principal target of SARS-CoV-2; however, many other organs and systems could be involved.

Asymptomatic infections are estimated to be about 20% of the total, reaching in some reports the 30–40%. A study performed on the passengers of the Diamond Princess (the cruise ship where a first major outbreak has been reported, becoming a model of the spread of the infection inside a close community) showed that about 19% of them were positive at the time of the screening test and 58% of them were asymptomatic at the time of diagnosis [3, 4].

COVID-19 is a pathology that mainly affects the respiratory system with variable manifestations, including in the mildest cases like dry cough (50% of patients), dyspnea (40%), and sore throat and fever (in 50% of patients and in about 90% of hospitalized patients) up to more serious cases with the appearance of a clinical picture characterized by hypoxemia, bilateral pneumonia, acute respiratory distress syndrome (ARDS), or septic shock (5% of overall patients and in 20% of the hospitalized ones). Fortunately, most infections are not serious (about 80%). Severe cases typically evolve in a two-step pattern, with a mild to moderate severity presentation in the first 8–10 days and a severe evolution thereafter [5].

COVID-19 can manifest itself with a wide clinical spectrum, and therefore it is important to identify various clinical phenotypes to optimize therapy. In a cohort of 44.500 confirmed infections, 81% was a mild form of infection, severe disease was reported in 14% of cases, critical form in 5%, and the overall case fatality rate was 2.3%. Among hospitalized patients, the proportion of critical or fatal disease is higher, with 27% of these requiring intensive care [6–8].

Some patients with an initially not serious illness can get worse, and this usually happens within a week. In a study of 138 patients hospitalized in Wuhan for COVID-19, dyspnea occurred on average 5 days after the onset of symptoms, and hospitalization occurred after an average of about 7 days [9].

The mildest and most common phenotype is characterized by fever, headache, and/or mild respiratory symptoms, such as cough (70% of patients) and sore throat, as well as asthenia; in this case, the X-ray is normal and there is no hypoxemia. The second phenotype is found in 80% of hospitalized patients, and it is characterized by the presence of hypoxemia and small opacity at chest X-ray compatible with pneumonia, the most important manifestation of this infection ($PaO_2 > 60$ mmHg with FiO_2 21%); these patients need monitoring. The third phenotype is less common (about 15–20% of hospitalized patients); the patient presents fever, marked hypoxemia with increased respiratory frequency ($PaO_2 < 60$ mmHg with FiO_2 21%), and multiple opacities at chest X-ray. This phenotype may be the evolution of the second one, or it may be the clinical manifestation of onset. Phenotypes 2 and 3 have good lung compliance and can avoid intubation. Phenotype 4 is characterized by severe hypoxemia and respiratory distress requiring intubation. At radiological evaluation, there are multiple bilateral opacities with interstitial involvement. This phenotype still has normal lung compliance. The patient generally presents a picture of "hyperinflammation," with hyperpyrexia and systemic symptoms. Phenotype 5, representing only a small percentage of cases, represents an advanced stage with overt ARDS, shock, and multi-organ dysfunction. ARDS can occur rapidly during the course of the disease (in 20% of cases within 8 days of the onset of symptoms) [10, 11].

About lung compliance, COVID-19 often shows a clinical picture of normal lung compliance associated with severe hypoxemia, a picture that is rarely found in ARDS by other causes. Gattinoni et al. postulated a different classification with two primary phenotypes, which differ on the basis of pulmonary compliance: type L, characterized by a high compliance (i.e., low elastance), with a low ventilation-perfusion ratio, and type H, characterized by a high elastance with a high right to left shunt. In

addition, in the first phenotype, lung weight and recruitability are low, while they are high in the second phenotype.

Generally, COVID-19 pneumonia has, at the beginning, the typical characteristics of the phenotype L; normal compliance indicates the presence of normal amounts of gas in the lung, so hypoxemia is due to hypoxic vasoconstriction—lung thickening is absent or present with ground-glass type, and therefore the weight of the lung is normal or slightly increased—and the non-aerated tissue is low and therefore there is only low recruitability.

This phenotype can remain unchanged, regress, or progress to the next phenotype. When pneumonia progresses or intrathoracic pressures increase (that can per se cause ventilatory stress), non-cardiogenic pulmonary edema is induced. The phenotype H is characterized by a reduced volume of gas inside the lung due to increased edema, a right to left shunt with perfusion of non-ventilated tissue, and an increase in lung weight due to the presence of lung opacity. The unventilated tissue is therefore increased, and, as in severe ARDS, there is high recruitability. The type H pattern has all criteria of severe ARDS [12].

Risk factors for the development of a serious pathology include cardiovascular comorbidity, diabetes mellitus, chronic lung diseases, malignancy (particularly hematological, lung borne, or metastatic), chronic kidney disease, obesity, and cigarette smoking; another risk factor is the male sex. Only 3% of patients have none of these risk factors. At blood testing, the following parameters are associated with a severe course: lymphopenia, thrombocytopenia, increased transaminases, LDH and inflammation indexes (e.g., PCR and ferritin), D-dimer, PT, troponin, CPK, and worsening renal function [13, 14].

Cardiovascular involvement can be a severe complication, associated with the possibility of developing arrhythmias, cardiac ischemia and shock, or thromboembolic complications, such as pulmonary embolism or cerebral ischemia [15–17].

Acute myocardial injury, defined by elevated levels of cardiac biomarkers or electrocardiogram abnormalities, is a common manifestation of COVID-19, and it's associated with an increased risk of mechanical invasive ventilation and mortality. Early data

in Chinese patients showed acute myocardial injury in 7–20% of patients with COVID-19.

Although various case reports have described myocarditis during the COVID-19 outbreak [18], few studies have included echocardiography or MRI; therefore, the real incidence of myocarditis remains unclear [19].

In a small cohort with 112 patients with COVID-19, 14 of these showed myocardial injury without the typical signs of myocarditis such segmental wall motion abnormalities of depressed left ventricular ejection fraction, suggesting a secondary genesis to the systemic condition rather than a myocardial infection [20].

Approximately 25% of patients hospitalized for COVID-19 developed heart failure [21, 22]. Heart failure with preserved ejection fraction can be triggered, especially in elderly, by fever, tachycardia, fluid overload, and impaired renal function [23]. Severe left heart failure is relatively uncommon [24].

Patients affected with COVID-19 are at an increased risk of arrhythmias due to underlying comorbidities, polypharmacy, and disease progression. Several studies have concluded that the prevalence of cardiac arrhythmias is higher in critically ill patients compared to noncritically ill patients.

Acute coronary syndrome (ACS) is a recognized complication of infectious disease. SARS-CoV-2 potentially triggers ACS through systemic inflammation that causes pro-thrombotic state or direct endothelial injury, which can result in plaque rupture, micro thrombosis, or coronary spasm. However, the exact incidence of ACS in COVID-19 patients is unknown, because during outbreaks in several countries, like Italy and the USA, the global number of hospitalization for ACS or percutaneous revascularizations is reduced [25–27], but there has been an increase in out-of-hospital cardiac arrest [28].

Venous thromboembolism is a well-known complication of COVID-19. Incidence of pulmonary embolism (PE) in hospitalized patients has been reported to be around 1.9–8.9%. Furthermore, the incidence of symptomatic venous thromboembolic events is significantly higher in ICU (27%) patients than in patients admitted in medical ward (3%) [29].

Deep vein thrombosis (DVT) is mainly localized in the distal district, with an incidence of about 12% in non-ICU patients. However, most of these events are asymptomatic and can occur despite adequate thromboprophylaxis [30].

The hypercoagulability condition that occurs in severe form of COVID-19 can manifest itself not only with major thromboembolic events but also with microvascular thrombotic angiopathy, which can worsen organ dysfunction, mainly in the lungs but also in other organs [31, 32].

Coagulopathy is frequently observed in severe COVID-19, characterized by elevations in fibrinogen and D-dimer levels, mild prolongation of PT/aPTT, and mild thrombocytopenia, which differ from the classic disseminated intravascular coagulopathy (DIC) seen in bacterial sepsis or trauma. These alterations in coagulation markers generally correlate with a parallel rise in markers of inflammation [33, 34].

Although less frequent, arterial thrombosis (AT) can also occur. In a significant systematic review, AT occurs in approximately 4% of ICU patients. Most patients were elderly male with comorbidities, and the anatomical localization included various districts with different prevalence (limb arteries 39%, cerebral arteries 24%, great vessel 19%, coronary arteries 9%, and superior mesenteric artery 8%) [35].

Stroke seems to be relatively uncommon in the setting of COVID-19 [36]. The frequency of ischemic stroke related to COVID-19 in hospitalized patients has ranged from 0.4 to 2.7%, while the incidence of intracranial haemorrhage has ranged from 0.3 to 0.9% [37] [38]. Stroke risk may differ according to the severity of COVID-19. Early case series suggest that for patients with mild illness, the risk is <1%, while for patients in intensive care, the risk may be as high as 6% [39]. Limited data suggest that ischemic stroke associated with COVID-19 occurs primarily in older patients with vascular risk factors [37].

Ischemic stroke is the most reported cerebrovascular event complicating COVID-19. The cause is often cryptogenic or attributed to large vessel thrombosis/occlusion, cardiogenic embolism, or arterial dissection [40].

Preliminary data suggest that COVID-19 is associated with a higher risk of ischemic stroke compared with influenza. In a retrospective cohort study comparing patients with emergency department visits or hospitalizations for COVID-19 (n = 1916) or influenza (n = 1486), the incidence of ischemic stroke was higher among patients with COVID-19 (1.6% versus 0.2% with influenza, adjusted odds ratio 7.6, 95% CI 2.3–25.2) [41].

While several mechanisms of stroke related to COVID-19 have been postulated, thrombophilia associated with the virus or the host immune response appears to be one important mechanism, as suggested by elevated markers of hypercoagulability and inflammation; in fact, a pro-inflammatory state may be associated with thrombophilia ("thromboinflammation"), increasing risk of stroke and other thrombotic events [42].

Cardiac dysfunction associated with SARS-CoV-2 infection may also serve as a potential embolic stroke mechanism.

Other neurologic complications—such as disorders of smell and taste, headache, dizziness, myalgia, alteration of consciousness, weakness, and seizures—are found in approximately half of hospitalized patients with COVID-19. Critically ill patients have a higher possibility of neurologic complications than patients with less acute illness [39].

By now, it is not possible to determine which of these neurologic problems are linked to COVID-19. Studies have reported that anosmia and dysgeusia (olfactory (OD) and gustatory dysfunctions (GD)) are common early symptoms in patients with COVID-19, occurring in more than 80% of patients [43]. Furthermore, they may be an initial manifestation of COVID-19 and can occur in the absence of nasal congestion, but rarely they are the only clinical manifestation of COVID-19. It has been documented that magnetic resonance imaging (MRI) signal abnormalities in one or both olfactory bulbs in patients with COVID-19 can resolve on follow-up imaging [44]. The study led by Meini et al. aims to investigate the timing of recovery from olfactory (OD) and gustatory dysfunctions (GD) in a population of 100 hospitalized patients for COVID-19 and discharged a month earlier from three Italian nonintensive care wards. Recovery from OD or GD was fast, occurring within 4 weeks in most patients.

Chemosensory dysfunctions in women were less common, but longer lasting [45]. What makes this study valuable is that it focuses on a population of hospitalized patients significantly older than those previously reported and adds data on gender differences. The damages that SARS-CoV-2 causes on taste and smell must be different from other viruses, but the pathophysiological mechanisms are largely unknown. It is reasonable to hypothesize that the OD is not related to definitive damage on neuronal cells but probably involved other cell types. In case of SARS-CoV-2-induced anosmia, magnetic resonance imaging of the olfactory bulb did not show irregular findings concerning its volume or signal intensity [46].

Encephalopathy is frequent in critically ill patients with COVID-19. In a group of 58 patients with COVID-19-related ARDS, encephalopathy was present in about two-thirds of patients [47]. It is probable that hypoxemia, especially found in patients with severe COVID-19, plays a role in many patients, like metabolic derangements due to organ failure and medication effects. The etiology is often multifactorial. A neuropathologic case series of 18 patients, who deceased for COVID-19 and who were encephalopathic before dying, has shown in all patients acute hypoxic ischemic damage and chronic neuropathology (e.g., arteriosclerosis, Alzheimer pathology) in most of them [48]. In other patients with encephalopathy, a dysregulated systemic immune response to SARS-CoV-2 may be implicated. Patients with COVID-19 may develop prominent delirium and agitation requiring sedation; others manifest encephalopathy with somnolence and a decreased level of consciousness [39].

A few cases of Guillain-Barré syndrome (GBS) have been described in patients with COVID-19. GBS is an infrequent complication of COVID-19. Among approximately 1200 patients with COVID-19 admitted over a 1-month period to 3 northern Italy hospitals, 5 cases of GBS were identified, presented with progressive, ascending limb weakness evolving over 1 to 4 days, and 3 of these required mechanical ventilation [49]. The interval between the onset of viral illness and the development of muscle weakness is 5–10 days, like that observed for other viral infections associated with GBS.

Isolated case reports have described the following syndromes in patients with COVID-19:

Meningoencephalitis—both viral and apparent autoimmune meningoencephalitis have been reported in patients with COVID-19. These complications are rare [50].

Acute disseminated encephalomyelitis (ADEM) and acute hemorrhagic necrotizing encephalopathy—a few case reports have described patients with clinical and neuroimaging findings consistent with ADEM [51]. Some patients have had myelitis with or without brain involvement [52].

Generalized myoclonus—one report has described three patients (ages 63–88 years) who have developed generalized myoclonus as an apparent postinfectious complication of COVID-19 [53].

Posterior reversible encephalopathy syndrome (PRES)—PRES has been reported in a few patients with COVID-19 [54].

Rhabdomyolysis—in Wuhan, 11% of patients were reported to have evidence of muscle injury with elevated creatine kinase (CK) (>200 U/L) and/or myalgia [39]. Myalgia was a common complaint in a series from Italy [55].

The gastrointestinal manifestations of COVID-19 are quite common but often underestimated. The first evidence of gastrointestinal involvement in patients with COVID-19 comes from a study conducted in China. It is increasingly evident that the gastrointestinal tract and the liver, where the enzyme ACE2 is expressed, are targets of SARS-CoV-2; the viral RNA was found in the stool of patients, implying a possible fecal-gold transmission, of great importance for public health.

In some studies, up to 61% of patients hospitalized with COVID-19 showed digestive symptoms, mainly anorexia (35%), diarrhea (34%), and nausea (26%). In some cases isolated gastrointestinal symptoms may precede the onset of respiratory symptoms [56, 57].

In some cases, the clinical presentation may be with asymptomatic rise of the enzymes of hepatocyte necrosis (14–58%); generally, the increase in transaminases is slight (<5 times the maximum values), with an increase in AST greater than ALT. Rarely, however, hepatitis has also been reported. Some

symptoms related to liver involvement may therefore appear, such as asthenia, abdominal pain, and anorexia, up to the typical manifestations of decompensated liver disease. In patients with known liver disease, acute worsening of liver function may occur [58, 59].

Kidney involvement is also possible during SARS-CoV-2 infection and can manifest as acute kidney injury (AKI), proteinuria, and/or hematuria [60, 61]. In a large cohort of COVID-19 hospitalized patients in New York, AKI was diagnosed in one-third of these (47% mild, 22% moderate, 31% severe), while hematuria and proteinuria were found in 46% and 42%, respectively [62].

It is still not clear if AKI is due to hemodynamic alterations, cytokines storm, or direct cytotoxicity of the virus.

COVID-19 patients have shown multiple skin manifestations, such as morbilliform rash; urticaria; pernio-like, acral lesions; livedo-like, vascular lesions; and vesicular, varicella-like eruptions. In children and adolescents with COVID-19, a severe multisystem inflammatory syndrome with mucocutaneous, systemic, laboratory, and imaging findings of atypical, severe Kawasaki-like disease has also been reported. Case series from around the world have documented a range of potential dermatologic manifestations of COVID-19 [63].

The incidence (ranging from 0.2 to 20.4% of cases) and timing of cutaneous manifestations of COVID-19 are difficult to determine [64]. Also unclear is the association of certain skin manifestations with the illness severity [65].

Moreover, it cannot be excluded that in some patients, the observed skin findings may represent cutaneous reactions to the numerous treatments used for COVID-19. Among 171 laboratory-confirmed COVID-19 patients with cutaneous manifestations from the registry, the most commonly reported were morbilliform rash (22%), pernio-like acral lesions (18%), urticaria (16%), macular erythema (13%), vesicular eruption (11%), papulosquamous eruption (9.9%), and retiform purpura (6.4%) [66].

Exanthematous (morbilliform) rash—in several case series, a morbilliform rash predominantly involving the trunk has been described as the most common cutaneous manifestation of

COVID-19 [67]. The rash has been noted either at the disease onset or, more often, after hospital discharge or recovery [64].

Pernio (chilblain)-like lesions of acral surfaces ("COVID toes") present as erythematous-violaceous or purpuric macules on the fingers, elbows, toes, and the lateral aspect of the feet, with or without accompanying edema and pruritus. They have been described across the age spectrum in patients with confirmed or suspected COVID-19, in the absence of cold exposure or underlying conditions associated with pernio [68]. Resolution may occur in 2–8 weeks. The understanding of the pathogenesis of these lesions is still under evolution, though it seems to be a primarily inflammatory process [69]. Pernio-like lesions may represent a post-viral or delayed-onset process, with 80 out of 318 cases in the American Academy of Dermatology/International League of Dermatologic Societies registry developing lesions after the onset of other COVID-19 symptoms [68]. Moreover, there are several case reports and case series of patients with pernio-like lesions testing positive for either immunoglobulin M (IgM) or immunoglobulin G (IgG) for SARS-CoV-2 infection and negative for polymerase chain reaction (PCR), possibly indicating a later stage in the disease process [70]. However, pernio-like lesions can, in some cases, appear while patients are still PCR-positive for the virus, which has potential implications for infectivity and viral spread: in fact in an Italian study that screened 22 patients presenting with pernio-like lesions, 6 (26%) were PCR positive for SARS-CoV-2 [71].

Livedo reticularis-like vascular lesions have been reported in a few patients with COVID-19 [72]. In a series of 171 laboratory-confirmed cases, these vascular lesions were noted in 5.3 and 2.3% of patients, respectively [66].

Retiform purpura and necrotic vascular lesions seem to be associated with severe COVID-19; in a series of 11 patients with retiform purpura and laboratory-confirmed COVID-19, all were hospitalized and 9 had acute respiratory distress syndrome [66].

In three patients with SARS-CoV-2 infection and severe respiratory failure who had retiform purpura or livedo racemosa, histologic and immunohistochemistry studies of skin biopsies revealed a pattern of complement-mediated microvascular injury in both

involved and normally appearing skin [31]. Acute urticaria with or without concomitant fever has been reported as a presenting sign of COVID-19 infection [73]. There are several reports describing a vesicular-pustular, varicella-like eruption associated with COVID-19 [74]. In a series of 24 patients, an eruption of small papules, vesicles, and pustules appeared 4–30 days after the onset of COVID symptoms and resolved in a median of 10 days [75]. A real-time PCR for SARS-CoV-2 from vesicle content performed in four patients yielded negative results. Seventeen of 24 patients were not taking any medications, ruling out a drug reaction. An erythematous, polymorphic rash, erythema and/or firm induration of hands and feet, oral mucositis, and conjunctivitis, along with systemic, laboratory, and imaging findings of atypical, severe Kawasaki disease, have been described in a cohort of ten Italian children during the COVID-19 pandemic [76]. Similar cases have been reported in the UK [77].

Secondary infections, particularly bacterial and fungal infections, are also possible, despite frequent prescription of empiric antimicrobial therapy in these patients [78].

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