

CLINICAL AND IMMUNE-RELATED MANIFESTATIONS IN PATIENTS WITH COVID-19

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Abstract. In late 2019 a previously unknown infection affected many people in China. The disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was identified as coronavirus disease 2019 (COVID-19). In a very short period of time, the virus spread worldwide, so on March 11, 2020, the World Health Organization (WHO) declared a pandemic. Various studies have focused on the risk factors and pathogenesis of the virus and have distinguished different phases of the disease (viremic, hyperinflammatory phase and phase of complications) characterized by a wide range of clinical manifestations. Most patients experience mild flu-like symptoms, but severe disease and even death are possible. The main clinical manifestations are of the respiratory system with lung involvement. Damage caused by COVID-19 is observed in various organs and systems (nervous, endocrine, cardiovascular, excretory system, gastrointestinal tract, liver, immune system, eyes, etc.). In some patients, some of the symptoms may persist for weeks or months after the onset of infection (so-called “long COVID”, “post-acute COVID-19” and “post-COVID syndrome (PCS)”). Antiphospholipid syndrome, systemic vasculitis, myositis, arthritis, systemic lupus, skin manifestations, hematological involvement, neurological involvement (Guillain-Barre syndrome, transverse myelitis, etc.), optic neuritis, cardiovascular involvement, acute pancreatitis, glomerulonephritis, thyroiditis, anterior uveitis, conjunctivitis, etc. stand out among them. Unfortunately, children are hit hard by COVID-19. In them, the viral load of SARS-CoV-2 is greater than in adults. More than 700 cases of a unique multisystem inflammatory syndrome in children (MIS-C) characterized by clinical and laboratory manifestations similar to Kawasaki disease and toxic shock syndrome have been described. The disease is severe - about 73% require intensive care, and the overall mortality is about 1.7%. Clinical criteria, laboratory parameters, analysis of blood oxygen saturation, imaging studies and RT-PCR (diagnostic gold standard) are used for the diagnosis of COVID-19. In patients with COVID-19, an individualized therapeutic approach is required. Since the beginning of the pandemic, affected countries have tried to flatten the epidemiological curve and avoid overloading health care systems by imposing specific hygiene measures, limiting social contact, wearing a mask, physical distance, travel restrictions, border closures, national lockdowns and mandatory quarantine for the infected and their contacts. In a short period of time, many highly effective vaccines have been developed, most with mild side effects after administration. Unfortunately, more severe reactions are possible after vaccination, but nevertheless the benefit outweighs the risk. This review aims to present the main clinical manifestations in patients with COVID-19 and the possible complications or post-covid syndromes.

Key words: COVID-19, immune-related manifestations

COVID-19

In December 2019, many people in the city of Wuhan (Hubei Province, East China) developed signs of a previously unknown infection [1, 2, 3, 4, 5]. Hospitalized individuals presented predominantly with fever, cough, and muscle pain, many showed abnormalities on chest computed tomography (CT), and 29% developed acute respiratory distress syndrome (ARDS) [1]. The disease is called coronavirus disease 2019 (COVID-19), is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and is characterized by a wide range of clinical manifestations [1, 6, 7, 8, 9, 10].

Viruses, classified as coronaviridae, are single-stranded RNA viruses, first discovered in the early 20th century. Their main animal reservoir is bats and birds. With a reduced immune response, the virus can replicate inside the host, resulting in a large number of random mutations and variants capable of infecting other species, including humans. This is also believed to be the initial spread of SARS-CoV-2 (from a snake or a bat) [1].

The index patient for COVID-19 was admitted to a Chinese hospital in early December 2019. Shortly thereafter, a cluster of 40 patients (27 of whom were at the Huanan fish market) were also hospitalized for COVID-19-related dyspnea. Confirmed

cases first appeared in Asia and the Americas. By the end of January 2020, the virus had reached Europe and Australia, and by mid-February cases had been reported in Africa [1]. As COVID-19 continues to spread around the world, the World Health Organization (WHO) declared it a pandemic on March 11, 2020 [1, 7, 11].

The number of infections decreases in the summer and increases in the cold season, but nevertheless the virus has been circulating continuously since the beginning of the pandemic. Its transmission is by air-droplet route with closer contact (< 1 m distance) and with an exposure time of several minutes [1]. The virus interacts directly with the human angiotensin-converting enzyme 2 (ACE2) receptor and with transmembrane serine protease 2, thereby causing cell damage and apoptosis and promoting clot formation [1, 5, 9, 12]. After entering the cell, the virus uses its resources for reproduction and targets multiple organs (first phase of early infection) [1]. In this viremic phase, patients have mild flu-like symptoms (fever, dry cough, upper respiratory tract involvement and arthralgias) depending on viral load, local immune response and individual ACE2 distribution [1, 8, 9, 10, 11]. Due to the hyperinflammatory response, there is production of mainly type I interferons, TNF and IL-63 [1, 2]. The secondary phase is associated with systemic inflammation, vasodilation with fluid extravasation, and the development of infiltrates leading to pneumonia. Depending on the severity of pulmonary inflammation and alveolar gas exchange disorders, hypoxia may occur. Systemic inflammation has a prothrombotic effect (it activates the coagulation cascade and expresses attachment proteins on the surface of endothelial cells, thereby forming – thrombotic clots). If after 7-10 days control of the infection is not achieved (this is determined by individual factors in the host's immune system), a „phase of hyperinflammation“ develops – activation of T-lymphocytes, production of interferon gamma, neutrophils and dysfunctional hyperactivated monocytes [1]. The generation of cytokines and radicals leads to tissue damage and organ failure (eg, acute respiratory distress syndrome, ARDS) [1, 10, 12]. ARDS is a clinical syndrome characterized by acute lung inflammation, pulmonary edema, and increased permeability. The hyperinflammatory phenotype of ARDS is characterized by increased concentrations of cytokines (‘‘cytokine storm,’’ ‘‘cytokine release syndrome’’), and is clinically manifested by fever, tachycardia, tachypnea, and hypotension [2]. The systemic phenotype of SARS-CoV-2 infection is very broad and can resemble various autoimmune and

inflammatory diseases, such as Kawasaki disease in children or hemophagocytic lymphohistocytosis (HLH), antiphospholipid syndrome (APS) or systemic vasculitis in adults [2]. Life-threatening complications are disseminated intravascular coagulation (DIC syndrome), pulmonary embolism, acute coronary syndrome, stroke [1, 10]. Extensive systemic inflammation leads to multiple organ dysfunction syndrome (MODS) or death [1, 2].

Numerous risk factors such as age, sex, concomitant diseases, genetic factors, blood type, ethnicity have been identified [1, 2]. Advanced age is associated with a higher risk of lung failure, need for mechanical ventilation, and death. A higher percentage of men experience severe or critical illness, which may be due to genetic (X-chromosome) or hormonal differences (testosterone levels), lifestyle (smoking or alcohol consumption). Comorbidities (obesity, hypertension, diabetes, respiratory diseases, cerebrovascular disease, cancer and chronic kidney disease, chronic liver diseases, immunosuppression) are important [1]. Patients over 65 with coronary artery disease, arterial hypertension and cardiac arrhythmias are at greater risk, but more worryingly, COVID-19 can cause heart damage in patients who have no history of cardiovascular problems [11]. Five genetic risk factors are associated with T-lymphocyte function and their interaction with antigen-presenting cells. Blood type A appears to increase the risk of severe infection [1].

The incubation period is on average 5-6 days (between 4 and 14 days). 95% of those infected develop symptomatic infection 10-14 days after exposure. The rate of asymptomatic infections varies widely. In symptomatic patients, the disease may be mild, severe, or critical [1]. Approximately 80-85% experience mild flu-like symptoms (fever (98%), chills, cough (76%), myalgia (18%), fatigue (18%), hyposmia, increased sputum production, sore throat, headache, nausea, vomiting, diarrhea and hemoptysis) and most of them recover within a few days or weeks [1, 7, 12]. About 15-20% suffer from more severe symptoms and/or a longer course of the disease with the development of progressive pneumonia and dyspnea or organ damage 7-10 days after the onset of symptoms and require hospitalization. Approximately 2-5% of all those infected develop a critical condition requiring admission to the intensive care unit due to prolonged hypoxia, respiratory or circulatory failure, shock, or MODS. As the pandemic spreads, it becomes clear that the clinical picture is more complex [1]. Because of the expression of angiotensin-converting enzyme 2 (ACE2) receptors

in multiple tissues, complications can occur in both mild and severe infections and multiple organs can be affected. The most common complication is progressive lung disease with a decrease in lung capacity. Patients develop hypoxia, dyspnea, bilateral pulmonary infiltrates, and respiratory failure with ARDS. Hypoxia, identified by pulse oximetry, often requires oxygen therapy, noninvasive mechanical ventilation (NIV), intubation with invasive mechanical ventilation, or extracorporeal membrane oxygenation. The risk of secondary infections is increased, with the most common being nosocomial (25%) or ventilator-associated pneumonia and bacteremia (14.9-36.3%), urinary tract infections (8.5-27.3%), and abdominal infections [1]. Another very serious complication is thrombosis, which can impede blood circulation in various organs (lungs, heart, brain and limbs) [11]. Deep vein thrombosis was recorded in 20% of patients, pulmonary embolism in 13%, stroke sinus thrombosis in 1%, myocardial infarction in 0.5%, acute limb ischemia in 0.4% [1]. Recent research, based on autopsies, has shown endotheliitis of small and medium-sized vessels (over 90% of cases), endothelial cell death and thrombotic events (30-60% depending on the organ involved) [8, 9, 12].

In some patients, levels of von Willebrand factor and p-selectin are significantly elevated (another sign of microvascular inflammation and thrombosis) [9, 12]. Neurological involvement can be divided into three categories: 1. With symptoms of central neurological disturbance (headache, dizziness, syncope, altered consciousness and ataxia); 2. Symptoms of neuro-peripheral origin (hypogeusia, hyposmia, neuralgia, peripheral neuropathy); 3. Symptoms of peripheral muscle damage, liver and kidney damage [11]. The most common manifestations are myalgias (44%), headache (37%), encephalopathy (31%), dizziness (29%), dysgeusia (15%), anosmia (11%) [7, 11]. The risk of developing encephalopathy with delirium or confusional state is high in critically ill patients and is associated with increased morbidity and mortality regardless of the severity of respiratory disease [1, 11]. Sporadic cases of Guillain-Barre syndrome have been reported in patients with ascending limb weakness, as well as inflammation of the brain, spinal cord, meninges, cranial nerves, and peripheral nerve involvement [1, 7]. Severe COVID-19 disease was associated with leukopenia in 25% and lymphopenia (high levels of ferritin, CRP, LDH, D-dimer, and IL-6) in 63% of cases [1, 12].

Table 1. Presentation of possible symptoms and organ damage caused by COVID-19 and residual symptoms after past infection [1, 2]

System/Organ [1]	Possible reason [1]	Symptom [1]	Patients with post-COVID symptoms [2]		
			In 4 weeks	In 8 weeks	In 12 weeks
Nervous system	Ischemic Stroke	Headache	14%	9%	18%
	Thrombosis of the venous sinuses	Anosmia	23%	17%	-
	Acute limb ischemia	Ageusia	24%	10%	-
	-	Anosmia and/or ageusia	28%	23%	4%
	Encephalopathy	Fatigue	35%	53%	16%
	Encephalomyelitis	Delirium	-	-	-
	Guillain-Barré syndrome	Dizziness or vertigo	-	6%	-
	-	Confusion	21%	-	-
Thyroid gland	Thyroiditis	Tachycardia, insomnia, anxiety	-	-	-
Liver	Damage related to the infection	Elevated AST, ALT and bilirubin			
	Cytokine mediated damage				
	Hypoxia damage				
	Drug-induced damage				
Gastrointestinal tract	Abdominal infection	Nausea vomiting	10%	-	-
			4%	-	-
	Disturbed gut microbiom	Diarrhea	-	3%	-
	-	Diarrhea or vomiting	17%	11%	31%
	Gastrointestinal bleeding	Loss of appetite	-	8%	-
	Ileus, mesenteric ischemia	Abdominal pain	15%	-	-
	-	Weight loss > 5%	16%	17%	-
Immune system	Hyperinflammation	Temperature	4%		-
	Sepsis	Chilblains	5%	-	-
	Increase in antibodies	Myalgia	-	6%	-
	-	Arthralgia	10-15%	16-27%	-
	-	Myalgia, headache and/or fatigue	36%	21%	-

Continuation table 1

Ocular system	Hemosis	Epiphora	-	-	-
	Conjunctivitis	Hyperemia	-	10%	-
Respiratory system	Superinfection	Rhinorrhea, sneeze, nasal congestion, rhinitis	28%	15%	-
		Sore throat	15%	7%	-
	Damage to lung tissue Fibrous scars Pulmonary edema ARDS	Shortness of breath	11-27%	8-43%	14%
		Chest pain	20%	22%	-
		Cough	43%	18%	2%
		Expectoration	-	8%	2%
		Abnormal function tests	47-54%	-	25%
Cardiovascular system	Myocarditis Myocardial infarction Arrhythmias	Chest pain and palpitations	-	-	-
		Elevated levels of troponins	-	78%	-
		Myocarditis (echocardiography)	-	60%	-
		Pericarditis (echocardiography)	-	22%	-
		Myocardial fibrosis	-	32%	-
		Thrombosis	0,5-2,5%	-	-
Renal system	Electrolyte disturbance	Proteinuria, hematuria, hyponatremia, edema	-	-	-
	Acute kidney injury (tubular necrosis, rhabdomyolysis, hypoxia, cytokines)		-	-	-
Hematological system	Hypercoagulation, thrombocytopenia	-	-	-	-
	DIC syndrome	-	-	-	-
	Venous thromboembolism	-	-	-	-
	Damage to the vascular endothelium	-	-	-	-

In February 2020, the WHO reported that the average time from symptom onset to clinical recovery is approximately 2 weeks for mild COVID-19 and 3 to 6 weeks for severe or critical COVID-19. Some of the symptoms, however, in some patients may persist for weeks or months after the onset of infection, which is described in the literature as “long COVID”, “post-acute COVID-19” and “post-COVID syndrome (PCS)”. Symptoms (fatigue, dyspnea, chest pain, cough, headache, cognitive impairment, arthralgia, myalgia, sleep disturbances, depression, anxiety) may be single or multiple, persistent or transient, or change over time and impair the quality of life [13]. The National Institute for Health and Care Excellence defines three categories: acute infection with COVID-19 (0-4 weeks), ongoing symptomatic COVID-19 (4-12), and PCS (> 12 weeks and exclusion of alternative diagnoses) [13]. It should be kept in mind that current data examining cases of persistent symptoms after COVID-19 infection are highly heterogeneous. A considerable variety of symptoms, with a variable nature, is observed among a wide range of patients. Much of the research examining the incidence of PCS has focused on the general population [13].

Immune-related manifestations are increasingly recognized conditions in patients with COVID-19,

with approximately 3,000 cases reported worldwide, involving over 70 different system and organ-specific disorders [2].

ANTIPHOSPHOLIPID SYNDROME

In critically ill patients, COVID-19 is associated with hypercoagulation and thrombosis, but SARS-CoV-2 itself does not appear to have procoagulant effects. However, 13 studies reported positive results for lupus anticoagulant (in over 90% of patients with COVID-19, admitted in Intensive Care Unit (ICU)). Much other evidence, however, does not support a central role for SARS-CoV-2 as a trigger for antiphospholipid syndrome [2].

Table 2

Antibodies	Pineton de Chambrun [44]	Harzallah et al. [45]
aPL antibodies	18 patients (72%)	-
aPL antibodies (retested after 10 – 30 days)	-	-
Multiple aPL antibodies	-	-
Lupus anticoagulant	23 patients (92%)	25 (45%)
Anticardiolipin (aCL) antibodies	13 patients (52%)	5 (10%)
Anti β 2 glycoprotein 1 antibodies	2 patients (13%)	

Systemic vasculitis

Multiple evidences support a potential link between SARS-CoV-2 and systemic vasculitis in children (as a Kawasaki disease phenotype in a significant percentage of children with MIS-C) and adults, as well as multiorgan vasculitis post mortem [2]. Of 15 adult patients with COVID-19 and vasculitis, nine had skin involvement, three had central nervous system involvement, two had pulmonary involvement, and 1 had gastrointestinal involvement, with organ-specific involvement occurring around 2 weeks after the first symptoms of infection [2]. COVID-19 is associated with various skin manifestations (morbilliform rash, urticaria, vesicular eruptions, acral lesions, petechiae, chills, livedo racemosa, and distal necrosis) that may develop before or after the onset of respiratory symptoms. A possible mechanism is lymphocytic vasculitis induced by blood immune complexes activated by cytokines [7, 12]. Cutaneous vasculitic lesions seen in children and adults represented by the acroischemic syndrome include Raynaud's phenomenon of the fingers or toes, cyanosis of the fingers, skin bullae, and dry gangrene. Dermatologic lesions are of unclear pathophysiology (although immune dysregulation, vasculitis, vascular thrombosis, and neo-angiogenesis have been suggested) and include "freezing" of the face, hands, feet, redness of the fingers, nose, ears, swelling, and temporary pain. Most of these patients are diagnosed with DIC syndrome and receive anticoagulant therapy because of the risk of high mortality [11].

Myositis

COVID-19 can cause muscle inflammation. About 24% of patients reported myalgia, with elevated creatine kinase (CK). Myalgias may remain as active, chronic symptoms in about 10-20% of patients [2].

Arthritis

About 36% of patients with COVID-19 report joint pain without evidence of inflammation on physical examination. Arthritis has been reported in isolated cases, mostly in middle-aged men, with a wide variety of joint manifestations (symmetrical polyarthritis, monoarthritis, enthesitis, psoriatic arthritis), mainly after the resolution of the COVID-19 infection [2].

Systemic autoimmune diseases

Patients with COVID-19 may have clinical manifestations typical of systemic lupus erythematosus (SLE) (cytopenia, arthralgia, serositis,

chills lesions, or aPL antibodies) [2]. Mantovani Cardoso E et al. report a case of SLE caused by SARS-CoV-2 that occurred in an 18-year-old healthy woman [14]. Parotid gland enlargement associated with Sjögren's syndrome was reported in 20 patients (mostly under 30 years of age and more often in women) [15]. According to the literature search, only one case of sarcoidosis has been reported, possibly caused by COVID-19, in a 72-year-old woman [16].

Immune-related organ-specific manifestations

In some patients, immune-related manifestations can mimic a wide range of organ-specific autoimmune diseases [2].

Skin manifestations

0.2 to 5% of patients with COVID-19 may have symptoms of skin involvement. More than 1,300 cases of chills (a rare inflammatory condition of the extremities, following exposure to cold that causes painful or itchy erythematous or violet lesions) have been reported, predominantly in children (under 18 years) and young patients (22–32 years), but only 6% of cases have confirmed COVID-19. Cases of erythema multiforme have been reported in patients with COVID-19, which in children are associated with Kawasaki disease and in adults are more likely to be drug-induced. Other skin manifestations include livid and/or acrocyanotic lesions, retiform purpura, oral ulcers, erythema nodosum, periorbital erythema, and Sweet's syndrome [2].

Hematological involvement

Lymphopenia occurs in about 50% of cases of COVID-19 and is associated with the development of ARDS, the need for intensive care, and a poor prognosis. Cytopenia is mostly asymptomatic. About 25% of patients with COVID-19 may have symptomatic thrombocytopenia: immune thrombocytopenic purpura (ITP) or thrombotic thrombocytopenic purpura. ITP mainly affects patients older than 50 years (about 75% of cases), with a platelet count below 10,000 per mm³ (in about 80%), and symptoms (purpura and mucosal bleeding) in 50% of cases appear about 2 weeks after the onset of symptoms of COVID-19. In thrombotic thrombocytopenic purpura, infection is confirmed by IgG. Hemolytic anemia was diagnosed in 59% of patients, mostly affecting over 50 years (about 70% of cases), with symptoms of asthenia and jaundice appearing in the second week of COVID-19 and hemoglobin below 8 g/l (74% of cases) [2].

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Continuation table 3

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[illegible]

[illegible]

Table 4. Biochemical/pathogenetic changes and clinical symptoms and syndromes in COVID-19 [2]

Biochemical/pathogenetic changes	Clinical symptoms and syndromes
Encephalitis	Delirium Confusion Convulsions Coma
Eye damage	Uveitis Conjunctivitis
ITP	Mucous petechiae Thrombocytopenia
Hemolytic anemia	Jaundice Severe anemia
Thyroiditis	Enlarged thyroid gland Heart palpitations
Post viral pneumonia or inflammation of the lung	Dyspnea Progression of pulmonary infiltrates frosted glass type areas
Pleural effusion	Chest pain
Acute myocarditis	Elevated troponin
Pericardial effusion	Elevated troponin Chest pain
Pancreatitis	Abdominal pain Nausea Vomiting
Adrenal infarction	An incidental X-ray finding
Glomerulonephritis	Increased creatinine Hematuria Proteinuria
GBS	Bladder dysfunction Motor weakness Flaccid weakness
Myelitis	Bladder dysfunction Motor weakness Flaccid weakness
Skin manifestations	Chilblains Erytema multiforme Livedo reticularis

Neurological involvement

Neurological involvement is related to neuro-invasion or neurotropic damage (encephalopathy, encephalitis, cerebrovascular pathology) or to neuroinflammatory damage (Guillain–Barré syndrome (GBS) or acute myelitis) and in most cases occurs about 2 weeks after the onset of COVID-19. Isolated cases of GBS associated with SARS-CoV-2 have been reported, mostly in men older than 50 years (in 90% of patients). A few cases of myelitis have been reported, again mostly in men, with two age peaks (around 30 years and around 60–70 years). Other immune-related neurological manifestations are neuropathies, optic neuritis, opticomyelitis, trans-

verse myelitis, plexopathy, or myasthenia gravis [2, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26].

Optic neuritis is an autoimmune inflammatory disease characterized by reduced vision and pain when moving the eyeball, usually affects one eye and is most often associated with multiple sclerosis (MS) or parainfectious diseases [17,18,23]. There is demyelination and swelling of optic nerve fibers due to systemic T-cell activation leading to an immunological antigen-antibody reaction [18].

Azab et al. present a case of a 32-year-old man with complaints of sudden deterioration of vision in the left eye, throbbing headache on the left, central scotoma, change in color depth, and increased intraocular pressure two weeks after a history of COVID-19 infection, having previously been hospitalized in intensive care unit for 10 days. Steroid therapy administered to the patient had a good effect. From the meta-analysis, it is clear that optic neuritis and retinal complications are more common in women who have experienced COVID-19 [18].

Sharma A et al. report a case of parainfectious optic neuritis after infection with COVID-19. They describe a healthy 22-year-old woman with a history of acute onset of blurred vision and a sensation of absolute scotoma in the lower visual field of the right eye for the past 4 days, which was not accompanied by any neurological symptoms. She reported fever, sore throat, and fatigue about 10 days ago (but was not tested for COVID-19 at onset of symptoms) and was PCR positive on ophthalmologic examination. The symptoms subsided after the treatment [19].

Josy A. et al. present three cases of patients who developed optic neuritis during the recovery period from a COVID-19 infection (mild form, without the need for hospitalization). Demyelinating lesions were identified in two of three cases, while serum antibodies against myelin oligodendrocyte glycoprotein were detected in the third patient. The first case concerns a 16-year-old girl, without comorbidities, for 3 days with a headache, a sudden sharp decrease in vision and pain in the left eye during extraocular movements. A diagnosis of retrobulbar neuritis was made. The second patient is a 35-year-old man, without comorbidities, who had COVID-19 6 months before the eye involvement. For 1 week, he experienced loss of vision in the left eye with pain during extraocular movements. The examination revealed an edematous disc with blurred edges and peripapillary edema. A diagnosis of papillitis was made. The third patient was a 38-year-old man who reported a sudden, gross decrease in vision and pain on extraocular movements in the left eye for 5 days. The

patient had similar complaints 1 month ago and was treated with intravenous methylprednisolone and oral prednisolone with good effect. He tested positive for COVID-19 a month and a half before the onset of complaints. This patient was also diagnosed with retrobulbar neuritis. All patients recovered their vision after the treatment [20].

Duran et al. report a case of a 30-year-old woman with optic neuritis after a previous COVID-19 infection. The patient, who had no previous illnesses, was admitted to hospital in July 2022 with complaints of weakness, dry throat and cough. The PCR test was positive, although the patient had been vaccinated a year ago (Pfizer-BioNTech). Home treatment was recommended, but after 4 days the patient reported a headache and decreased vision in the left eye. After the quarantine, in the ophthalmology department, they found edema of the left eye, as well as edema and leakage in the left optic nerve. Two weeks later, improvement in visual acuity and reduction in swelling was noted [17].

Roy et al. also reported cases of post-vaccination optic neuritis, with none of the patients being PCR positive for COVID-19. The first is of a 27-year-old woman, without diabetes and hypertension, who presented with sudden progressive blurring of vision in the left eye, after mild pain in the periocular area for 5 days. Examination revealed diffuse swelling of the optic nerve head, an enlarged blind spot, and flat waves on visual evoked potentials (VEP). The second case is of a 48-year-old woman who complained of a painless gradual decrease in vision in the left eye over a period of 3 days. A swollen optic disc with blurred edges, peripapillary retinal edema, an inferior arcuate visual field defect, and the VEP showed delayed latency and reduced amplitude. The third patient was a 40-year-old man complaining of sudden blurring of vision in both eyes associated with periocular pain for 7 days. Examination shows bilateral blurring, swollen edges of the optic disc, generalized reduction of visual fields in both eyes, VEP, shows bilateral flat waves. The vaccine is thought to activate the host's immune system, leading to the activation of T cells that damage the myelin sheath of the optic nerve [21].

Alvarez et al. systematized the cases of optic neuritis with three different vaccines. The average age of the patients is 45 years (between 18-75 years). In 38 of them the eye lesions were due to AstraZeneca vaccination, 13 to Pfizer – BioN Tech and 4 to Sinovac [22].

Behera et al. report a case of a 22-year-old woman with left lower motor neuron (LMN) facial palsy

and parainfectious bilateral atypical optic neuritis after COVID-19. The patient was not vaccinated. Reported sudden onset of painless bilateral vision loss (two months post-illness) and LMN facial palsy (immediately after COVID-19) treated with steroids. A year before, she suffered paralysis of the right face. Ophthalmological examination revealed color vision and contrast sensitivity disorders bilaterally, delayed pupillary light reflexes and left relative afferent pupillary defect, bilateral disc edema, increased retinal nerve fiber layer thickness on the left. The VEP showed delayed latency with subnormal amplitude bilaterally. After the treatment, the patient has fully recovered. Simultaneous involvement of multiple cranial nerves after infection with COVID-19, as well as recurrent facial palsy, are rare [23].

Transverse myelitis is a rare immune-mediated, focal disease of the spinal cord that can lead to severe neurologic complications, including autonomic, sensory, and motor deficits [24, 25, 26]. Imaging studies are necessary for the correct diagnosis of this condition, however, etiological identification can often be difficult. Mathew et al. report a case of a 56-year-old man with specific neurological symptoms without apparent cause. In December 2020, he had a COVID-19 infection and in May 2021 he received the Johnson & Johnson 2019 (COVID-19) vaccine, with the onset of neurological symptoms approximately two months later. The patient reports a past tuberculosis infection 25 years ago. Complaints are of episodic bilateral numbness of the hands, which sometimes wakes him up at night, starting at the elbow and involving the I and II fingers of both hands. Two weeks prior, the patient had an MRI showing severe swelling and enlargement from C1 to T1–2, disc protrusion causing moderate spinal stenosis at C4–5. At C5–6 and C6–7 levels, there was evidence of bilateral moderate foraminal stenosis. Corticosteroid treatment was started immediately and had a good effect. Symptoms improve gradually, with the numbness disappearing completely in about 6 weeks [24].

Naeem et al. reported 11 studies including data from 11 vaccinated patients (6 women, 5 men) with a mean age of 49.27 ± 5.47 . The clinical manifestations of most patients include pain, weakness, paresthesia, and numbness of the lower extremities. Some cases present with autonomic symptoms (urinary retention, urinary incontinence, and fecal retention) that accompany sensory and motor deficits in the limbs. In most cases, cerebrospinal fluid (CSF) analysis reveals elevated protein and white blood cells (WBC). An MRI shows acute inflammation of the spinal cord. The combination of a high abnormal

CSF protein test and acute spinal inflammation were evidences of acute transverse myelitis after administration of the SARS-CoV-2 vaccine in the cases reviewed [25].

Hirose et al. report a case of a 70-year-old man with bilateral hypoesthesia of the lower extremities and mild paraparesis that occurred 17 days before hospitalization. About a month before, the patient had been vaccinated with the first dose of the Moderna vaccine. The patient has co-morbidities (hypertension, hyperuricemia and alcoholic liver cirrhosis) and is taking medications (amlodipine, spironolactone, benzbromarone, rifaximin, lactitol, vonoprazan and ursodeoxycholic acid). Neurological examination revealed bilateral disturbances: severely impaired pinprick and vibration sensation below the level of the eighth thoracic dermatome, mild weakness and hyperreflexia of the lower extremities, and Babinski symptoms. Spinal MRI showed multiple areas of high intensity on T2-weighted image located at the Th1/2 and Th5/6 vertebral levels with weak gadolinium enhancement. CSF examination showed a normal white blood cell count, elevated total proteins (52 mg/dL), and positive oligoclonal bands. Antibodies against SARS-CoV-2 were detected in the

serum. The patient was diagnosed with acute autoimmune transverse myelitis, treated with corticosteroids, and made a full recovery [26].

Cases of transverse myelitis have also been reported following vaccination with AstraZeneca, Pfizer-BioNTech and Moderna-BioNTech. However, it is important to know that transverse myelitis is not limited to a post-vaccination complication, due to the many cases of the disease following infection with COVID-19 [24, 25, 26].

Pulmonary involvement

A significant percentage of patients had abnormal pulmonary function test (PFT) results (54%) and abnormal CT imaging (40–94%) [2]. It should be kept in mind that a normal radiographic image does not rule out an underlying disease, since the disease may occur without the development of interstitial pneumonia or because the study was performed before lung involvement. Also, the rapid dynamics in the involvement of the lungs determines a significant difference in the image in the individual phases of the disease. The imaging features of COVID-19 pneumonia and its complications detected by chest X-ray are shown in Figures 1a, 1b, 2, 3, 4 [27].

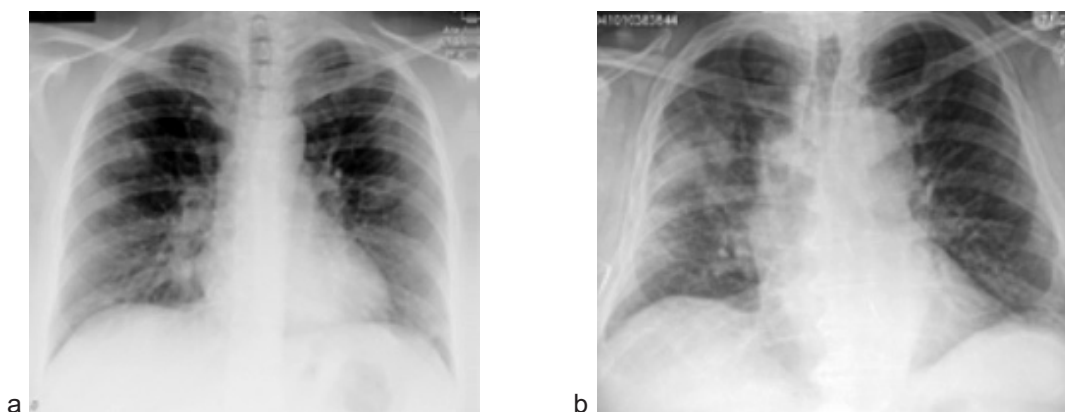


Fig. 1a and 1b. Fine, indistinctly demarcated areas of frosted glass with a peripheral arrangement [27]



Fig. 2. Indistinctly demarcated peripheral infiltrates. A zone of reverse halo (reverse halo sign) is visible in the left middle lung field, i.e. central zone of frosted glass with peripheral consolidation [27]

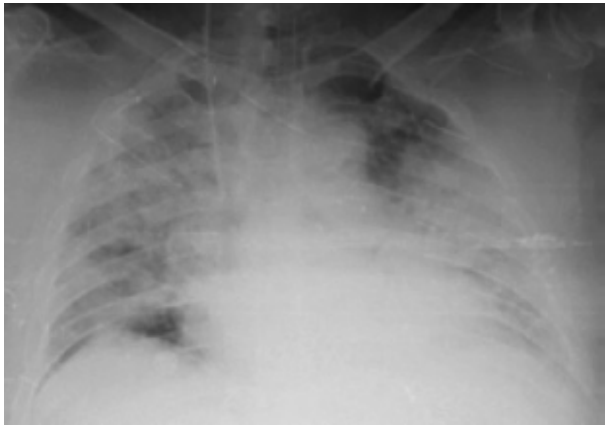


Fig. 3. Picture of respiratory distress. Presence of confluent zones of consolidation and frosted glass with mostly central location. The free lumens of the trachea and the main bronchi are traced. The position of the central venous line is marked [27]

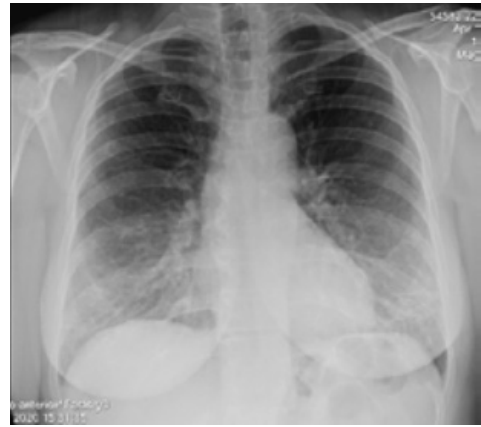


Fig. 4. Residual fibrous changes. Linear reticular changes in the bases of both lungs [27]

In the computed tomographic finding, the leading changes are focal, scattered, ground-glass-type areas with an oval or round shape with a peripheral and posterior location (Fig. 5 a and b). In some cases, the so-called reverse halo sign is observed, an image described in organizing pneumonia. Indistinctly demarcated areas of reticular changes (thickened interlobular septa) admixed with ground glass, known as the crazy paving image, are also often found. In some patients, there may be an increased transverse diameter of the pulmonary vessels, an expression of congestion, as well as the sign of air bronchography. During the course of the disease, reticular and linear areas of consolidation are seen peripherally at a distance from the pleural surface, again an image known in organizing pneumonia.

Organizing pneumonia, focal pulmonary edema, and acute alveolar injury are the most common

pathologic presentations in autopsied patients. Also, in autopsies of patients with COVID-19 and ARDS, changes corresponding to the exudative and proliferative phases of acute alveolar damage were found simultaneously – edema, interstitial lymphocytic inflammatory infiltrates, hyperplasia of type 2 pneumocytes and hyaline membranes, without the presence of squamous metaplasia.

The following imaging criteria could be used for the initial diagnosis of COVID-19 pneumonia:

1. High probability: ground-glass shadows (lower lobes, peripheral lesions, multiple, bilateral); thickened interlobular septa; crazy-paving damage model; peripheral consolidations; air bronchography; sign of organizing pneumonia (reverse halo sign); increased cross-section of vascular structures.

2. Intermediate probability: atypical disease presentation, combination of findings suggestive of

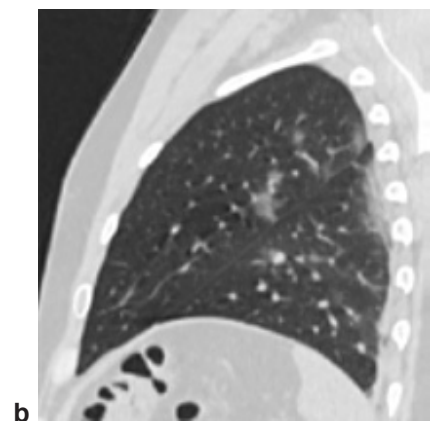
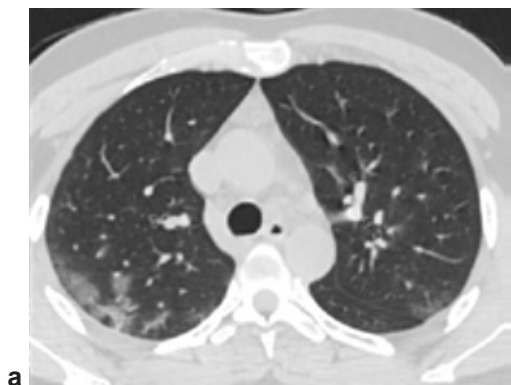


Fig. 5 a and b. Presence of focal, scattered zones of frosted glass type with oval and round shape with peripheral and rear location [27]

alternative lung disease, or superimposed COVID-19 pneumonia on underlying lung disease.

3. Low probability (normal CT image or > 70% probability of alternative diagnosis).

Imaging diagnostics during the course of the disease – typical changes in the early phase (scattered areas of ground glass bilaterally), at the height (consolidations, areas of crazy paving and reverse halo sign) and in the convalescent period (reduction of infiltrates and atelectasis, reticular and fibrous remnants changes).

One of the most serious complications of the disease is expressed in the development of acute diffuse alveolar damage, impaired permeability of the alveolar-capillary membrane with the development of pulmonary edema and loss of normally aerated lung parenchyma (a picture resembling that of respiratory distress syndrome). The natural course of the complication is in three phases - exudative, inflammatory and fibro-proliferative. Usually roentgenography show bilateral perihilar infiltrates, patchy or confluent, involving more than $\frac{3}{4}$ of the parenchyma [27].

Bacterial superinfection is a common complication (12-19%), especially in hospitalized patients. A superimposed inflammatory process should be suspected when there is a change in the X-ray picture, the appearance of cavitated lesions and pleural effusions. Less common complications include pulmonary thromboembolism, atelectasis based on retained bronchial secretions or complications of barotrauma and PEEP such as subpleural bullae, areas of hyperinflation in the upper chest, pneumomediastinum, pneumothorax, subcutaneous emphysema [27].

One study reported that 3 months after COVID-19, PFT results remained abnormal in about 25% of patients, suggesting the development of interstitial lung disease. Individual cases of patients who developed severe bilateral pulmonary fibrosis following COVID-19 have been reported. Pleural thickening is observed in about 27% of patients and pleural effusion in about 5-6% [2].

The broad differential diagnosis should be considered and imaging studies should be interpreted in the context of the overall clinical picture. Influenza pneumonia and pulmonary eosinophilia also present with diffuse ground-glass areas and peripheral consolidations. Scattered areas of ground glass and reticular changes are also encountered in patients with eosinophilic pneumonic infiltrates, in ANCA granulomatosis, as a complication of the administration of certain medications. The image of organizing pneumonia with zones of the so-called reverse hal-

lo is also well known in a number of non-infectious diseases (pulmonary embolism, pulmonary zygomycosis, etc.), which further complicates the interpretation of the X-ray finding [27, 28].

Cardiovascular involvement

A study in 100 patients with COVID-19 assessed elevated levels of troponin – I (40-80%), cardiac involvement (identified by MRI in 78% of patients) and active myocardial inflammation (myocardial interstitial infiltration by mononuclear cells and lymphocytic infiltration in about 60 %) about two months after infection. Acute myocarditis due to COVID-19 is more common in men (aged 17 to 79 years), with the main symptoms (chest pain and dyspnea) occurring within the first two weeks of infection. Patients who have recovered from COVID-19 have lower left ventricular ejection fractions and higher left ventricular volumes compared to healthy volunteers. About 5% of patients have a pericardial effusion [2].

Renal involvement

Several studies have reported patients with glomerulonephritis (biopsy-proven) and acute renal failure (in some cases accompanied by hematuria and/or nephrotic syndrome), usually 2 weeks after the onset of symptoms of COVID-19. These patients have a poor prognosis and more than half of them require dialysis [2].

Endocrine involvement

There have been reports of abnormal thyroid function potentially associated with SARS-CoV-2. Thyrotoxicosis (20%), hypothyroidism (5%), hyperthyroidism (low TSH levels (56%) and high free T4 levels), painful and enlarged thyroid gland (on physical and ultrasound examination) were observed. Patients have negative results for antithyroid antibodies. Adrenal involvement secondary to COVID-19 includes acute adrenal infarction, adrenal hemorrhage, and less commonly adrenal insufficiency [2].

Involvement of the pancreas

Acute pancreatitis (abdominal pain and elevated pancreatic enzymes), possibly related to COVID-19, is diagnosed more often in women. Direct viral damage to pancreatic cells, endothelial damage, ischemia and/or thrombotic mechanisms have been suggested [2].

Eye involvement

Some inflammatory eye diseases, such as anterior uveitis and conjunctivitis, have been diagnosed in patients with COVID-19, including children [2, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42].

Conjunctivitis is the most common ocular manifestation in patients with COVID-19. More serious vision-threatening complications are anterior, posterior uveitis, and panuveitis. Eye damage does not depend on the severity of the respiratory disease. The high doses of corticosteroids used in the treatment of COVID-19 can also worsen the eye status of patients.

A. Oscar et al. present a clinical case series in adult patients:

- anterior ischemic opticopathy (57-year-old woman, 61-year-old man with accompanying diseases (AH and DM), 77-year-old man with underlying vascular pathology);

- trunk occlusion of the vena centralis retinae (48-year-old man);

- bilateral panuveitis with granulomatous precipitates, vitritis, occlusive retinal arteritis and yellowish perivascular infiltrates (a 56-year-old woman whose CT scan revealed the typical “ground glass” type opacities with indistinct borders in both lungs);

- surgical treatment of a 46-year-old man for hemophthalmus with pars plana vitrectomy and air tamponade;

- panuveitis with peripheral retinal necrosis after having passed COVID-19 and immunization (a 50-year-old man with a history of iridocyclitis in the left eye, who underwent surgery for a partial retinal detachment);

- roth spots with complex etiology (40-year-old woman with a history of anemia due to blood loss due to myoma, as well as anoxia/hypoxia due to past COVID-19);

- vitreitis with pigmented whitish opacities and retinal ischemia (26-year-old woman with asymptomatic COVID infection after childbirth) [29].

Shantha et al. report a case of a 9-year-old boy with bilateral anterior intermediate uveitis associated with multisystem inflammatory syndrome in children (MIS-C). The child, who has COVID-19 infection needed hospitalization, has comorbidities (obesity, asthma), laboratory abnormalities (anemia, thrombocytopenia, elevated CRP), and an abnormal abdominal CT scan. He was diagnosed with MIS-C secondary to SARS-CoV-2. Despite the multidisciplinary treatment (a team of rheumatologists, hematologists, cardiologists, infectious disease specialists and nephrologists), the child's condition worsened (he developed anazarka, pulmonary edema, bilateral pleural effusion, respiratory distress, acute kidney injury and mild ectasia of 2 coronary arteries) and was hospitalized in a pediatric intensive care unit. The patient was discharged in good general condi-

tion with a recommendation for home treatment (30 mg prednisone daily and low-dose aspirin). A month later, he noticed redness of the left eye and photophobia. An ophthalmologist diagnosed unilateral nongranulomatous anterior uveitis. A few days later, the child reported photophobia in the right eye. Treatment is with prednisolone acetate 1% hourly and cyclopentolate twice daily. Three weeks later, the ophthalmological examination revealed leakage of the disc and peripheral vasculature bilaterally. The final diagnosis was bilateral nongranulomatous anterior and intermediate uveitis. The patient required prolonged treatment with corticosteroids and long-term immunosuppression, given the multiple recurrences (total of 3) of inflammation in both eyes and the development of complications (from inflammation and local treatment, including ocular hypertension and posterior subcapsular cataract) [30].

Another clinical case of bilateral uveitis as part of the multisystem inflammatory syndrome in COVID-19 was presented by Bettach E et al. Treatment with corticosteroids, vasopressors and antibiotics has had a good effect. Two weeks later, she was referred to an ophthalmology clinic for evaluation of bilateral blurred vision. Examination revealed mild conjunctival hyperemia bilaterally, central corneal edema with folds of Descemet's membrane and multiple keratic precipitates (KP) distributed in the lower half of the cornea, and a small focal intraretinal hemorrhage in the left fovea. The woman was diagnosed with bilateral acute anterior uveitis and was treated with topical dexamethasone 0.1% and cycloplegia [31].

Another team of authors (Austin Pereira et al.) presented a case of a 27-year-old male, without comorbidities, who had experienced COVID-19, unvaccinated, who complained of pain, photophobia, and redness of the left eye. He was diagnosed with acute anterior uveitis. From the tests performed, HLA-B27 was positive, with no other evidence of inflammatory joint disease. The patient underwent a one-week course of treatment with prednisolone 1% 6 times daily and atropine sulfate 1% twice daily with good effect. According to the authors, it is important to screen patients for HLA-B27 after an initial event of anterior uveitis if they have been infected with SARS-CoV-2, as they are at higher risk for ocular inflammatory dysregulation [32].

Vasileios Liolios et al. two cases of bilateral anterior uveitis after infection with COVID-19. Patients had no previous history of uveitis or other comorbidities. The first case is a 16-year-old boy with history of fever (39°C) and rash, contact (mother with

COVID-19), PCR negative. Examination revealed enlargement of the liver and spleen and mild lymphocytopenia and thrombopenia. Antibodies for Covid-19 have been detected. During his hospital stay and treatment, the rash regressed, but he developed photophobia and red eyes. The patient had increased intracranial pressure and papilloedema. Two lumbar punctures were performed, as a result of which the intracranial pressure decreased and his condition improved. The rest of the tests (neurological, for infectious diseases and autoimmune screening) were negative. The second case is a 29-year-old man who presented to the emergency department with a history of a painful red eye on the left. He was PCR positive the month before. A Mantoux test was done, which was also positive. They recovered without complications [33].

Another author group (Diana Kirakosyan et al.) recently published a series of cases (12 in number) of acute bilateral, asymmetric anterior nongranulomatous uveitis and one case of acute bilateral conjunctivitis associated with COVID-19 presenting with severe erosions of the cornea. Of the patients with anterior uveitis, 11 were female and 1 male, mean age 42 years (range 26–68 years), with a history of COVID-19 (PCR-proven severe), hospitalized for pneumonia, with no history of concomitant systemic or eye diseases. Ocular symptoms (redness, eye pain, photophobia, blurred vision, and foreign body sensation) developed a median of 39 days (range, 21–65 days) after recovery from COVID-19. Mydriasis with sectorial iris atrophy (a finding specific to ischemic vasculitis in viral uveitis) was found in two patients, and in one patient the lesions were bilateral. Drug therapy with topical corticosteroids and cycloplegic agents for all patients gave a good result with complete resolution of symptoms and signs.

Acute bilateral conjunctivitis with severe corneal erosions was reported in a 30-year-old woman. A week earlier, she developed nasal congestion, cough, and rhinorrhea and tested positive for COVID-19. Twelve days previously, she had been diagnosed with diffuse epitheliopathy, developed bilateral conjunctivitis with mucopurulent discharge, sudden onset of photophobia, eye pain, swollen eyelids, and watery discharge, symptoms for which she was referred to an ophthalmology clinic [34].

Uveitis should also be considered as a rare complication after COVID-19 vaccination. Vaccination-associated uveitis (VAU) occurred in 1526 cases, most commonly in women (68.93%) and middle-aged individuals (41–50 years: 19.71%), after the first dose (49.35%) of the vaccine, mostly in those

who received Pfizer (77.90%), followed by Moderna (15.54%) and AstraZeneca (3.01%), respectively. VAU occurs acutely (71.77%) as an inflammatory reaction (88.29%) unilaterally (77.69%), especially in the anterior part of the uvea (54.13%). Most cases were new onset (69.92%), while only a minority of patients had a history of a previous uveitis condition (30.08%) [35].

Conjunctivitis is an inflammatory or infectious condition characterized by dilation of conjunctival vessels, resulting in hyperemia and edema of the conjunctiva. Usually the secretion is of bacterial or viral etiology [36]. In patients with COVID-19, conjunctivitis may precede [37] or present with systemic disease [38], but it is also possible to be a unique find [36, 39, 41, 42], including in children. [40]. Fortunately, conjunctivitis caused by SARS-CoV-2 is self-limiting, does not lead to complications, and can improve in a few days without specific treatment [36].

Mohammad Alrawashdeh H et al. report a case of a 20-year-old male, without comorbidities, contact, asymptomatic for COVID-19, with complaints of diffuse redness of both eyes, photophobia, foreign body sensation and burning, mild swelling of the upper eyelid, itching and profuse tearing for 3 days. He was tested for COVID-19 and resulted positive. After home treatment, the patient has fully recovered [36].

Sergio Zaccaria Scalinci et al. also describe conjunctivitis as the only sign and symptom of active COVID-19. Four middle-aged men and one woman with signs and symptoms of acute conjunctivitis (conjunctival hyperemia, epiphora, discharge, and photophobia) were referred to an ophthalmology clinic. Patients were PCR positive for COVID-19, but never developed fever, malaise or respiratory symptoms. Symptomatic therapy has a good effect [42].

There appears to be a distinct pattern in the appearance of many immune-related manifestations in relation to the onset of SARS-CoV-2 infection: some features appear within the first two weeks of infection, while others appear in the post-infectious stage or in asymptomatic patients [2].

After the acute infection subsides, patients may have persistent complaints or develop post-infectious complications (the so-called “long COVID”). In 45% of cases, hyposmia / anosmia can persist for up to three months. 26% of patients may have persistent complaints due to neuropathy/myopathy. A quarter of patients reported chronic fatigue or sleep disturbances up to three months after infection [1, 2]. Psychiatric disorders (anxiety, post-traumatic stress disorder, depression or difficulty concentrating and reduced cognitive ability) may occur. Over 40% of

affected individuals were found to have dyspnea or other persistent symptoms of COVID-19 at day 100. About 63% of patients had persistent pulmonary changes detected by computed tomography [1, 27, 28, 43]. Other possible long-term symptoms are pain, chills, dysgeusia, headache, chronic fatigue syndrome, or fibromyalgia [2]. It should be noted that the frequency and duration of these symptoms are related to the severity of the initial infection [1].

Batibay and colleagues conducted a cross-sectional study (at the Department of Rheumatology of Gazi University Hospital, Turkey) among 320 patients with IRD, of whom 53 with COVID-19 infection between July 2020 and February 2021. Infection was proven by RT-PCR, clinical history and/or CT findings. Between April and July 2021, patients were further followed up for possible PCS (by telephone survey or during their routine clinic follow-up). Patient demographic characteristics (age, sex, body mass index, occupation, educational status, smoking, diagnosis, disease duration, medications and comorbidities), time of infection with COVID-19, symptoms, result of RT-PCR/antibody test/rapid antigen test, CT scan, length of hospitalization, treatment provided, complications related to COVID-19, need for oxygen/non-invasive mechanical ventilation/intensive care were recorded. Various symptoms (fatigue, weakness, arthralgia, myalgia, headache, fever, hot flashes, dyspnoea, palpitations, sore throat, runny nose, cough, diarrhea, nausea/vomiting, weight loss, loss of smell or taste, vision or hearing problems, chest pain, exercise intolerance, hair loss, rash, depression, anxiety and sleep problems) were studied over 12 weeks after the onset of COVID-19. The mean age of the patients was 48.5 ± 13.99 years, and 38 (71.7%) were women. Twenty-seven (51%) patients had at least one comorbidity. Cases of rheumatoid arthritis (in 10 patients), spondyloarthropathy (in 16), connective tissue diseases (in 10), Mediterranean fever (in 8), vasculitis (in 7), gout (in 1) and sarcoidosis (in 1). The average duration of the disease is 84 months [13].

Fourteen (26.4%) patients experienced exacerbation of rheumatological disease: rheumatoid arthritis (RA) in four, FMF attack in two, exacerbation of SpA in two, newly diagnosed interstitial lung disease in one patient with RA, exacerbation of arthritis in two patients with psoriatic arthritis and one with undifferentiated connective tissue disease, acute anterior uveitis in one patient with SpA, and exacerbation of polymyalgia rheumatica in one patient already diagnosed with giant cell arteritis. No independent risk factor for the development of PCS (such as age,

sex, duration of rheumatic disease, the presence of complications of COVID-19 or the need for oxygen) was found, except for smoking (which appeared to have a protective effect) [13].

A study conducted in Italy reported that at least one symptom (particularly fatigue or dyspnea) persisted in 87.4% of hospitalized patients at a median follow-up of 60 days from the onset of COVID-19. Another single-center study showed that patients could have persistent symptoms even 110 days after being discharged from the hospital. Older age and the presence of multiple chronic diseases have also been shown to be associated with a delayed return to normal health. In a prospective cohort study, 277 patients with mild or severe COVID-19 were evaluated approximately 2 weeks after the onset of infection, with PCS found in 50.9%. In a study including 203 patients, it was found that after three months, 5.3% of them remained positive for SARS-CoV-2 (by RT-PCR) [13].

Multisystem inflammatory response in children

There is evidence that the viral load of SARS-CoV-2 is higher in children than in adults. In April 2020, reports of children (primarily over 5 years of age) with COVID-19 with clinical and laboratory manifestations similar to Kawasaki disease and toxic shock syndrome emerged in the United Kingdom and the United States [9]. More than 700 cases of a unique multisystem inflammatory syndrome in children (MIS-C), characterized by fever, hyperinflammation of the skin and mucous membranes (74%), cardiovascular (80%), gastrointestinal (92%), neurological and respiratory symptoms (70%) have been described [2, 9]. The clinical presentation is severe – about 73% require intensive care, and the overall mortality is about 1.7% [2].

Table 5

Similarities and differences between the two diseases	Kawasaki disease	MIS-C
Age of children	< 5 years	> 5 years
Population	Asian	not Asian
Admission to intensive care unit	Higher	Higher
Mortality	Lower	Higher
Organ affected	Coronary arteries; coronary aneurysms (6-17%)	Coronary arteries; coronary aneurysms (8-23%)

In non-Asian countries with large outbreaks of SARS-CoV-2 (France, Italy, Spain, United Kingdom

and USA), most cases of MIS-C were reported at the end of the first wave of the pandemic and were diagnosed 25-45 days after the onset of infection, thus suggesting that the syndrome is due to a post-viral immune response [2].

Clinical criteria (sudden dry cough, chills, fatigue, myalgia, loss or change of taste/smell, headache, conjunctivitis, nausea, vomiting, abdominal cramps or diarrhea, dyspnea on exertion or at rest, tachypnea, crackles, tachycardia and signs of cyanosis), laboratory parameters (elevated C-reactive protein, IL-6, neopterin and a low percentage of T-helper lymphocytes are associated with a severe course of infection and a poor prognosis), blood oxygen saturation analysis (non-invasive procedures or blood gas analysis), chest CT (diagnostic gold standard), chest X-ray or ultrasound, and RT-PCR (diagnostic gold standard) are used to diagnose COVID-19. Antigen tests, which are inexpensive and easy to use, detect proteins produced by SARS-CoV-2 in body fluid samples taken from a pharyngeal or nasal swab. However, they have less sensitivity than PCR and are dependent on viral load [1].

In patients with COVID-19, an individualized therapeutic approach is required. In case of hypoxemia, supplemental oxygen is required. Antiviral drugs are useful early in the infection, while immunomodulatory therapies should be used in the later stages of the disease. Convalescent plasma therapy reduces the risk of hospital admission [1]. Anticoagulant treatment with heparin and derivatives prevents thromboembolism and endothelial lesions [10, 11].

Affected countries are trying to flatten the epidemiological curve and avoid overloading health care systems by imposing specific hygiene measures, limiting social contact, wearing a mask, physical distancing (at least 1 meter), travel restrictions, border closures, national lockdowns (closure of businesses, schools, universities, shops, restaurants, hotels and „home office“ strategies) and mandatory quarantine for the infected and their contacts [1]. Many highly effective vaccines have been developed in a short period of time. Mild side effects include pain at the injection site, gastrointestinal complaints, flu-like symptoms (fever, chills, myalgia), headache, and fatigue [1, 25, 35]. Systemic reactions are more common in young patients and after the second dose of the vaccine [1]. Unfortunately, more severe reactions are possible after the vaccine (tinnitus, thrombotic thrombocytopenia, myocarditis, uveitis, Guillain Barre syndrome, myelitis, facial nerve palsy, ischemic stroke, venous

thrombosis, etc.), but nevertheless the benefit of them outweighs the risk [1, 24, 25].

CONCLUSIONS

Although COVID-19 is a disease caused by an acute respiratory virus, its manifestations are not only seen in the respiratory system and lungs. Over time, it became clear that the disease is much more serious and dangerous, due to the multi-organ and multi-system involvement of the body, as well as the possible complications. Various clinical manifestations are observed from the side of the nervous system, endocrine system, gastro-intestinal tract, liver, immune system, eyes, cardiovascular system, excretory system, circulatory system, etc. In some patients, some of the symptoms may persist for a different period of time (the so-called “long COVID”, “post-acute COVID-19” and “post-COVID syndrome (PCS)”). Antiphospholipid syndrome, systemic vasculitis, myositis, arthritis, systemic lupus, skin manifestations, hematological involvement, neurological involvement (Guillain-Barre syndrome, transverse myelitis, etc.), optic neuritis, cardiovascular involvement, acute pancreatitis, glomerulonephritis, thyroiditis, anterior uveitis, conjunctivitis, etc. stand out among them. The viral load of SARS-CoV-2 in children is higher than in adults. About 73% of children with MIS-C require intensive care, and the overall mortality is about 1.7%. Clinical criteria, laboratory parameters, analysis of blood oxygen saturation, imaging studies and RT-PCR (diagnostic gold standard) are used for the diagnosis of COVID-19. Each patient needs an individual therapeutic approach, according to the symptoms and severity of the disease.

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