

NECROTIZING RAYNAUD'S PHENOMENON AFTER RECURRENT COVID-19 INFECTION

VI. Boyadzhieva¹, J. Doncheva-Dilova², N. Stoilov¹

¹UMHAT "Sv. Iv. Rilski", Department of Rheumatology, Medical University – Sofia

²UMHAT "Sv. Iv. Rilski", Department of Occupational Diseases, Medical University – Sofia

Abstract. Raynaud's phenomenon (RP), which can be primary or secondary, is a common vascular clinical syndrome due to abnormal arteriolar vasospasm. Its treatment is most often conservative depending on the etiology. In recent years, there have been reports of RP as a syndrome after a previous SARS-CoV-2 infection, in patients of different genders and ages. As an etiological factor for the development of vascular pathology in these cases, two main mechanisms are assumed: an autoimmune process or the thrombosis of arterial vessels, leading to tissue ischemia, and the so-called necrotizing Raynaud's phenomenon. In the pathogenesis of Raynaud's phenomenon, the influence of local, neuronal and hormonal mediators is emphasized. Some studies prove the role of estrogens, which explains the higher incidence of RP among women. At present, there is no convincing evidence for "candidate genes" to be associated with Raynaud's phenomenon, despite studies by some authors (Susol et al., 2000; Pistorius et al., 2006). Vasospasm in digital ischemia may be further complicated by COVID-19 infection. Another potential component is hypercoagulation (further complicated by the presence of antiphospholipid antibodies in certain patients) and elevated levels of D-dimer. A state of hypercoagulation is caused by the so-called cytokine storm. This inflammatory state, as a result of endovascular damage, increased platelet activity and coagulation cascade, causes the so-called phenomenon of immunothrombosis. Overactivation of the coagulation pathway during cytokine storm results from increased activity of thrombin, which has an additional role in the inflammatory process through proteinase-activated receptors (PARs). Acrocyanosis due to excessive coagulation status has been described in critically ill patients with COVID-19. In these patients, gangrene may arise from impaired blood flow and insufficient healing of digital wounds, which is associated with elevated levels of C-reactive protein (CRP). Ischemic limb lesions, usually seen in older patients with severe clinical course of the disease, represent a dangerous, although rare, complication associated with COVID-19 and are due to arterial occlusions. They are extremely difficult to treat and often lead to amputations. In patients with antiphospholipid syndrome, arterial and venous thrombi are primarily caused by the formation of neutrophil extracellular traps (NET), which in turn activate platelets, and their excessive formation can lead to local thrombosis. In addition to platelet activation, neutrophils release tissue factor, which initiates the coagulation cascade. NETs bind coagulation factor XII and activate it, and also induce an inflammatory reaction in the vessel wall. According to the available knowledge to date, the hypothesis that digital necrosis in patients with COVID-19 is primarily related to the formation of NETs has been developed. Necrotizing Raynaud's phenomenon (NRP) is a vascular clinical syndrome characterized by vasoconstriction of distal resistance vessels following low temperatures or states of anxiety and stress. The first symptom is pain, due to lack of oxygen, which leads to tissue ischemia. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) can cause endotheliopathy with microvascular and macrovascular thrombotic events. COVID-19 induces hypercoagulation, thrombosis, endothelial damage, and inflammation leading to vasculitis. The coagulopathy, inflammation, and thrombosis seen in COVID-19 are potentiated by increased activity of clotting factors, loss of protective glycocalyx function, and decreased nitric oxide levels. The effects of COVID-19 in patients with RP are still being elucidated. This review presents a series of selected clinical cases associated with Raynaud's phenomenon (necrotic, new-onset, exacerbated, or as part of another systemic connective tissue disease) secondary to past COVID-19 infection or vaccination.

Key words: Raynaud's phenomenon, necrotizing Raynaud's phenomenon, COVID-19, clinical cases

INTRODUCTION

Raynaud's phenomenon (RP) is a common vascular clinical syndrome characterized by triphasic discoloration of the fingers due to abnormal arterio-

lar vasospasm [1, 2, 3]. It can be primary or secondary [1, 3, 4]. Its treatment is mostly conservative [1]. In recent years, there have been reports of RP as a syndrome after a previous SARS-CoV-2 infection, in patients of different genders and ages, which can af-

fect both the upper and lower extremities. Two main mechanisms are indicated as an etiological factor for the development of vascular pathology: an autoimmune process or the thrombosis of arterial vessels, leading to tissue ischemia, and the so-called necrotizing Raynaud's phenomenon [2, 3, 5]. Multiple hypotheses have been proposed to explain possible mechanisms in the pathogenesis of Raynaud's phenomenon [4, 6]. Recent evidence in this field supports the multitiology of the disease, which emphasizes the impact of local, neuronal, and hormonal mediators [7, 8]. To date, no convincing evidence has been described in the literature for "candidate genes" to be associated with Raynaud's phenomenon [9]. Some literature sources indicate that possible candidate genes are the beta subunit of the muscle acetylcholine receptor and the serotonin 1B and 1E receptors [9]. However, other authors continue to suggest that there is a genetic factor contributing to the prevalence of this disease [10]. In support of this opinion is the described clinical case of a one-month-old baby diagnosed with Raynaud's phenomenon [11].

Pathogenesis of Raynaud's phenomenon and necrotizing Raynaud's phenomenon due to COVID-19

Vasoconstriction of cutaneous arterioles upon exposure to cold, which is mediated by reflex sympathetic release of norepinephrine and increased sensitization of the vasculature, is a normal physiological process [4], but when excessive leads to a pathological condition (Raynaud's phenomenon) [4, 12]. One of the main theories is that of the multi-etiology of the disease, according to which the impaired function of some of the local, neuronal or hormonal mediators leads to excessive constriction of the cutaneous arteries in response to norepinephrine [4, 13]. Norepinephrine binds to adrenergic receptors (AR), located on the surface of vascular smooth muscle cells (VSMC), which are of three types: α_1 , α_2 and β_2 . The latter are involved in vasodilation, while α_1 and α_2 -AR are responsible for vasoconstriction [4]. A decrease in temperature is sensed by mitochondria, which then release reactive oxygen species (ROS), which in turn activate the Rho/ROCK pathway. This results in the mobilization of α_2 C-AR from the endoplasmic reticulum/Golgi to the cell surface. α_2 C-AR mediates cold-induced vasoconstriction, which when exacerbated can lead to Raynaud's phenomenon (RP) [4]. Epidemiological studies and meta-anal-

yses support the potential role of sex hormones (estrogen may explain the higher incidence of RP in premenopausal women) [4, 14, 15]. Estrogen has a vasodilator effect, but on the other hand it lowers body temperature [4, 16] and increases the expression of α_2 C-AR in VSMCs [4, 17].

A possible pathogenetic mechanism in digital ischemia is vasospasm, further complicated by COVID infection. Another potential component is COVID-19-related hypercoagulation and elevated D-dimer levels in patients. The presence of antiphospholipid antibodies in certain patients further contributes to hypercoagulation (a condition seen in patients with systemic sclerosis and active SARS-CoV-2 infection) [18].

A hypercoagulable state is induced by the overproduction of major pro-inflammatory cytokines such as TNF- α , IL-6 and IL-1 β (the so-called cytokine storm). This inflammatory state, as a result of endothelial damage, increased platelet activity and coagulation cascade, causes the so-called phenomenon of immunothrombosis. Overactivation of the coagulation pathway during cytokine storm results from increased activity of thrombin, which has an additional role in the inflammatory process through proteinase-activated receptors (PARs). Additionally, acrocyanosis has been described in critically ill patients with COVID-19 due to hypercoagulable status. Physiologically, gangrene can arise from impaired blood flow and insufficient healing of digital wounds, which is associated with elevated levels of C-reactive protein (CRP) [19].

Ischemic lesions of the extremities are a dangerous, although rare, complication associated with COVID-19 and are due to arterial occlusions, usually affecting the fingers and toes. They are usually observed in patients with a severe clinical course of the disease, are difficult to treat and lead to amputations. Acute necrosis of the fingers is usually seen in older patients (mean age 66 years), more commonly in the fingers (70%) than the toes (30%). The overall mortality rate among these patients is 80%. Autoantibodies characteristic of antiphospholipid syndrome were detected in some of the patients, suggesting that arterial occlusions in patients with COVID-19 are the result of thrombotic processes triggered by an immune reaction. In patients with antiphospholipid syndrome, arterial and venous thrombi are primarily caused by the formation of NETs (net-like structures composed of DNA and proteins of nuclear and granular ori-

gin) [20]. Neutrophil extracellular traps (NETs) are an important part of the innate immune system and are released by activated neutrophils, and in turn NETs activate platelets, but their excessive formation can lead to local thrombosis. In addition to platelet activation, neutrophils release tissue factor, which initiates the coagulation cascade. NETs bind coagulation factor XII and activate it, and also induce an inflammatory reaction in the vessel wall. It is hypothesized that digital necrosis in patients with COVID-19 is primarily associated with NET formation [20].

The underlying mechanism leading to digital ischemia in RP is likely to be multifactorial. It involves a combination of endothelial hypersensitivity to circulating adrenaline and norepinephrine and reduced vasodilator innervation. RP in skin vessels involves cold-induced mitochondrial release of oxygen radicals that activate the Rho-Rho-kinase pathway. The latter in turn activates norepinephrine-sensitive digital smooth muscle vasoconstrictor adrenaline α_2C receptors [4, 21]. SARS-CoV-2 can infect endothelial cells and cause a decrease in microvascular dilator responses and increased adrenaline levels during periods of fever. All these factors worsen RP [21].

Necrotizing Raynaud's phenomenon (NRP) is a vascular clinical syndrome characterized by vasoconstriction of distal resistance vessels following low temperatures or states of anxiety and stress. The first symptom is pain, due to lack of oxygen, which leads to tissue ischemia. Treatment is conservative, but in some patients it is possible to perform neuromodulation with spinal cord stimulation (SCS) to promote ulcer healing, control pain and prevent amputation [22]. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) can cause endotheliopathy with microvascular and macrovascular thrombotic events. COVID-19 causes hypercoagulation, thrombosis, endothelial damage, and inflammation leading to vasculitis. The main pathogenetic mechanisms in the thromboinflammatory process induced by SARS-COV-2 are the direct endothelial damage and the indirect damage caused by inflammation. The coagulopathy, inflammation, and thrombosis observed in COVID-19 are potentiated by increased activity of clotting factors, loss of protective glycocalyx function, and decreased levels of nitric oxide [22]. The effects of COVID-19 in patients with RP are still being elucidated [22].

CLINICAL CASES

Mariateresa Giglio et al. report a case of severe necrotizing Raynaud's phenomenon in a 37-year-old woman involving both legs, successfully treated and controlled with spinal cord stimulation (SCS) for almost four years, which suddenly recurred during SARS-CoV infection-2 [22]. In November 2016, the patient reported severe pain, with signs of severe ischemia and necrotic ulcers on the fingers of the lower extremities and was diagnosed with necrotizing RP [22]. At low temperatures, vasospastic attacks worsen. Therapy with gabapentin, oral morphine, and intravenous iloprost was administered, but pain and necrosis worsened, so midline SCS at T9-T10 was administered [22]. The procedure has a good effect: the very next day, the pain is significantly reduced, blood circulation in the limbs improves. Medicines for the pain syndrome were stopped gradually, and the ulcers were completely healed within two months [22]. A diagnosis of "undifferentiated connective tissue disease" was made, and the patient was seen in an outpatient clinic and received a monthly vasodilator infusion [22]. In October 2020, she was readmitted with complaints of a sudden and severe increase in pain in both legs when lying down and at rest [22]. Increasing SCS amplitude did not improve. A chest radiograph showed interstitial pneumonia, after which a positive result for SARS-CoV-2 from a pharyngeal secretion was reported. The patient was admitted to the COVID-19 unit of the University Hospital of Bari (Italy) and treatment with gabapentin, oral morphine and increased SCS parameters to the maximum allowable level (5 volts) was started [22]. In the following days, the patient has fever (temperature up to 39 °C), cough and dyspnea. Therapy was continued with intravenous dexamethasone, subcutaneous low-molecular-weight heparin, aspirin, infusional iloprost, and oxygen. After 10 days, the respiratory symptoms improved, but the pain syndrome and tissue discoloration in both legs continued for the next month. Two months after the onset of symptoms, tissue perfusion improved and the pain syndrome was controlled [22].

Rachana Vanaparthi et al. report a case of a 63-year-old US resident woman with a history of comorbidities (aplastic anemia, mitral valve prolapse with regurgitation, celiac disease, and motion sickness) presenting with runny nose and dyspnea, without evidence of fever, chills, cough, or chest pain that appeared in the month of March

2020 after a visit to Europe [23]. A few days after symptomatic treatment without improvement, a PCR test for SARS-CoV-2 was performed, which turned out to be positive and confirmed the diagnosis of COVID-19. Home quarantine is recommended. About four weeks after the initial episode, the patient developed involuntary twitching of the left eye and left cheek (without pain, loss of sensation, or numbness), diarrhea, generalized weakness, palpitations, sleep disturbances, decreased appetite, skin rash, anosmia, and dysgeusia. Herpes labialis, caused by HSV-1, was diagnosed because of the typical painful red rash around the mouth [23]. The patient notices purple discoloration at the base and whitish discoloration of the fingertips with temperature changes (Raynaud's phenomenon) [23]. After four weeks of conservative treatment (profuse hydration, antipyretics, aspirin, multivitamins, and calcium supplements), clinical improvement was observed. The patient tested negative for COVID-19 on day 58, but a week later, in the middle of the night, she suddenly developed chills, vomiting, dizziness, vertigo, and an unsteady gait. The examination revealed a strong right nystagmus and a diagnosis of postviral vestibular neuritis was made [23]. On the tenth day of prednisone treatment, the patient noticed flashes and swimming in the left eye. A posterior vitreous detachment was diagnosed, which was due to increased intraocular pressure due to the use of steroids. A few weeks later, she developed a high fever (about 39 degrees, 102F), arthralgias, arthritis, and an urticarial rash on her chest and abdomen eight hours after taking 2 grams of Amoxiclav for a dental procedure. Symptoms disappear in a few days without treatment. Five months after her positive COVID-19 test, she was found to be lacking IgG [23].

Yen-Chou Chen et al. report a case of a patient hospitalized at Taipei Medical University Hospital (Taiwan) for COVID-19 who experienced acute digital ischemia and Raynaud's phenomenon associated with diffuse arterial thrombosis of the upper extremities [5]. The man is 67 years old, a smoker, with no evidence of concomitant diseases. He arrives at the emergency department with fever, tachycardia, progressive dyspnea, and oxygen desaturation. Four days before, he had been given a PCR diagnosis of COVID-19. A chest radiograph shows acute respiratory distress syndrome (ARDS). Serum tests showed elevated ferritin, fibrinogen, and D-dimer levels, while prothrombin time, partial prothrombin time, protein C,

protein S, and antithrombin III levels were normal [5]. In the intensive care unit, dexamethasone, tocilizumab, and nasal cannulation with high flow O₂ were administered. Six days after hospitalization, the distal parts of the second, third, and fourth fingers of his right hand became painful and dark with dry gangrene [5]. A cold provocation test performed on his left hand produced cyanosis and tenderness in the nail fold region, recovering after 20 min, consistent with Raynaud's phenomenon [5]. From the laboratory tests, the following indicators are found: increased serum levels of anti-Ro, anti-La, anticardiolipin immunoglobulin G, ANA, antineutrophil cytoplasmic antibodies (ANCA) and antibodies against the basement membrane. Negative were anti-double-stranded DNA (dsDNA), anti-extractable nuclear antigen (ENA), anti-Smith (Sm), anti-ribonucleoprotein (RNP), anti-cyclic citrullinated peptide (CCP), anti-mitochondrial, anti-Jo, anti-Scl-70, lupus anticoagulant, cryoglobulin and rheumatoid factor (RF) [5]. Peripheral angiography revealed diffuse thrombosis and stenosis of the right brachial and ulnar arteries and bilateral aneurysm of the iliac artery [5]. Raynaud's phenomenon was suspected as a result of the arterial thrombosis, which was treated with enoxaparin and alprostadil. Three days later, due to minimal improvement of the cyanotic and gangrenous lesions, balloon angioplasty and intra-arterial infusion of urokinase through a Fontan catheter was performed for 8 days, with gradual improvement of the gangrenous lesions and complete resolution of the intravascular thrombosis [5]. Antithrombotic therapy (rivaroxaban and clopidogrel) was administered and the patient was discharged uneventfully five days later [5].

In this case, Raynaud's phenomenon may be a consequence of in situ thrombosis of the brachial and ulnar arteries rather than an autoimmune process caused by COVID-19. However, it should be kept in mind that COVID-19 infection may increase the risk of arterial thrombosis, even in patients on anticoagulant therapy [5].

Chandra and colleagues report a case of a 48-year-old woman with SSc possibly triggered by SARS-CoV-2 infection. The patient had a medical history of anxiety and depression and was referred by the vascular medicine department to a rheumatology clinic in August 2021 for further evaluation of abnormal laboratory parameters and Raynaud's phenomenon [24]. The patient was in good health until December 2020 when she developed acute hypoxic respiratory failure secondary to COVID-19

pneumonia. After being hospitalized, the patient began to experience symptoms that included fatigue, xerostomia, dysphagia, bilateral lower extremity weakness, Raynaud's phenomenon, joint pain in both arms (decreasing with activity and worsening at rest), morning stiffness (for more than one hour), dyspnea on exertion, diarrhea, painless mouth ulcers, involuntary weight loss, and diffuse skin hyperpigmentation. Examination revealed swollen fingers, sclerodactyly, diffuse hyperpigmentation, and abnormal capillaries at the nail folds [24]. All antibodies (anti-RNA polymerase III, anti-Scl-70, anti-centromere, anti-SSA, anti-SSB, anti-Smith and anti-Smith/RNP antibodies) were negative except for ANA ($> 1:1280$) [24]. Another findings were a decreased diffusing capacity of 44% (by pulmonary function test performed in June 2021), interstitial lung disease, with findings suggestive of nonspecific interstitial pneumonia (by chest CT), a left ventricular ejection fraction of 60% and a mildly elevated right ventricular systolic pressure of 36 mmHg (by transthoracic echocardiogram), with no evidence of pulmonary hypertension (by right heart catheterization showing a mean pulmonary artery pressure of 20 mmHg with normal wedge pressure and pulmonary vascular resistance of 1, 9 wood units), sliding hiatal hernia, irregular Z-line and gastric hyperemia (by esophagogastroduodenoscopy) and Barrett's esophagus (by biopsy) [24]. The patient was diagnosed with systemic scleroderma (SSc) according to the ACR (American College of Rheumatology) and EULAR (European Alliance for Associations in Rheumatology) criteria. From August 2021 to January 2022, the patient was followed up four times at the rheumatology clinic and treated with microphenolate mofetil 2 x 1500 mg (for interstitial lung disease), amlodipine 5 mg (for Raynaud's phenomenon), methotrexate 12.5 mg once weekly and prednisone 2 x 5 mg (for inflammatory polyarthritis possibly related to SSc) [24].

Milan et al. report a case of an adolescent with acute limb ischemia secondary to COVID infection. The patient presented with a history of generalized hypo- and hyperpigmented skin lesions and a mild, nonproductive cough, intermittent arthralgia, weight loss and cyanosis of the distal fingers on exposure to low temperatures (Raynaud's phenomenon), persistent dry skin. The patient was diagnosed with juvenile scleroderma combined with COVID-19, which led to limb ischemia (both disease entities are proinflammatory and prothrombotic). Despite therapy with sildenafil 1 mg/kg

twice daily and amlodipine 0.4 mg/kg once daily, the ischemia of the distal fingers of the right hand and the cyanosis of the fingers of the left hand and both feet did not respond. Anti-phospholipid antibodies, anti-nuclear antibodies and D-dimer were found to be elevated, protein S was low, peripheral arterial disease was demonstrated on imaging studies. Control of limb ischemia was achieved after 4 months of regular infusion of cyclophosphamide, administration of peripheral vasodilators, methotrexate and anticoagulants [25].

Shih et al. also reported a case of digital necrosis in a SARS-CoV-2 positive patient with a history of systemic sclerosis. The patient is 64 years old, a former smoker, with concomitant diseases (hypertension, impaired carbohydrate tolerance, systemic sclerosis). Complaints of progressive shortness of breath and bilateral pain in the fingers date back 1 week, after which the patient was admitted with acute respiratory failure and tested positive for SARS-CoV-2. Anticoagulant treatment with low molecular weight heparin, remdesivir for 10 days, baricitinib (stopped 6 days after the start of treatment due to concerns about worsening of the patient's digital ischemia) was administered. Laboratory tests show high D-dimer ($> 20 \mu\text{g/mL}$) and the presence of antiphospholipid antibodies. The patient reported self-limiting episodes of bilateral pain and discoloration of the fingers induced by low temperature (Raynaud's phenomenon). Warming of the hands, calcium channel blockers, and phosphodiesterase inhibitors were initially used to control ischemia, but on day 9 of hospitalization, the patient worsened. The fingers of both hands were cold to the touch and markedly painful on palpation, there was dark discoloration of the distal part of the right index finger (but no signs of necrosis), the left thumb and index finger were dark and markedly swollen. Early signs of necrosis were found on the left index finger. Botulinum toxin was injected, and two days later the patient reported significant improvement in the pain in her fingers. Unfortunately, treatment did not affect the necrotic soft tissue of the proximal left index finger, so the patient was scheduled for surgical amputation [18].

Another collective of authors (Pourdowlat et al.) described two patients with COVID-19 who died with acrocyanosis and digital necrosis in the terminal stage of their disease. The first patient was a 56-year-old woman with diabetes. Complaints were of cough, headache, fever, dyspnea and hypoxemia in April 2020. Chest comput-

ed tomography (CT) showed bilateral opaque opacities. Laboratory results showed a normal complete blood count, high CRP and LDH (904 IU/L)/PT, INR and PTT were within normal limits. Treatment with oxygen, unfractionated heparin, and hydroxychloroquine was initiated. On day 5 of admission, she was intubated due to respiratory distress and sedative medications were used to control the condition. On the 6th day, ecchymosis and skin spots appeared on her extremities. Because of the possibility of bacterial superinfection, cultures of blood and tracheal secretions were obtained, and meropenem and vancomycin were added to therapy. On the 7th day, she was transferred to the COVID-19 ward. On admission she was unconscious and still intubated on mechanical ventilation. Blood pressure and heart rate were 90/65 mm Hg and 87/min, respectively, pO_2 was 61 mm Hg, and oxygen saturation was 90% with 50% FIO_2 . Meanwhile, cyanosis is observed in the fingers of the upper and lower limbs. Blood sampling showed leukocytosis (16,200 per mm^3), lymphopenia (1200 per mm^3), thrombocytopenia (91,000 per mm^3), Hb (7.8 g/L), high CRP (107 mg/L), LDH (1117 IU/L), D-dimer (7780 $\mu g/mL$), ferritin (1650 ng/mL), and IL-6 (359 pg/mL). Additional laboratory results showed negative pANCA, cANCA, anticardiolipin, lupus anticoagulant, and $\beta 2$ -microglobulin. Echocardiography is normal, while electrocardiogram shows an inverted T in V1 to V5. Atorvastatin and aspirin were added to the treatment regimen, and the dose of heparin was increased. To improve blood supply to the limbs, nitroglycerin ointment is also applied. Despite multiple treatment methods, her clinical condition worsened and the patient died [19].

The second patient is a 67-year-old woman with a history of type II diabetes mellitus and systemic hypertension, who developed respiratory distress syndrome after COVID-19. Respiratory rate was 36/min, temperature 37.5°C, and oxygen saturation 65%. Physical examination reveals coarse end-inspiratory crackles in both lung bases. A chest radiograph showed bilateral lung opacities, and a CT scan revealed diffuse ground-glass opacities. Laboratory results showed leukopenia (4200 per mm^3), lymphopenia (800 per mm^3), normal platelets (160,000 per mm^3) and hemoglobin level (13.7 g/dL), high CRP (70 mg/L), LDH (840 IU/L) and D-dimer (976 $\mu g/mL$). PT, INR, and PTT are within normal limits. Endotracheal intubation was performed due

to lack of response to oxygen therapy, sedatives, and neuromuscular blockade. Treatment was started with chloroquine 300 mg twice daily on the first day, followed by lopinavir/ritonavir 400/100 mg twice daily. Other prescribed medications include methylprednisolone, unfractionated heparin, and antibiotics. On day 9 of mechanical ventilation, despite improvement in oxygenation and reduction in positive end-expiratory pressure (PEEP), the patient developed terminal cyanosis in all of her fingers and pulselessness in both radial arteries. Blood pressure is low. Despite the administration of heparin and fluid therapy, the acrocyanosis and pulse of the radial artery of the left arm were without any improvement. A day later, the patient died [19].

Several authors have reported new-onset Raynaud's phenomenon after vaccination, but there was no evidence of necrotizing Raynaud's in any of the reported patients [21, 26, 27]. The first case involved a 28-year-old Japanese woman diagnosed with systemic lupus erythematosus and antiphospholipid syndrome. She was admitted for chest pain and Raynaud's phenomenon after a second dose of the COVID-19 mRNA vaccine BNT162b2 a month earlier. The patient's condition improved after administration of azathioprine (50 mg/day) and amlodipine (5 mg/day) and increasing doses of prednisolone (10 mg/day) and aspirin. According to the authors, it is possible that Raynaud's phenomenon is related to the vaccination against COVID-19 [26]. The second patient is a 63-year-old non-smoker diagnosed with primary Raynaud's phenomenon (RP) that worsened after two vaccinations with the Pfizer vaccine and then a booster dose. The patient has no evidence of systemic connective tissue disease [21]. The third patient is a 33-year-old man with type 1 DM on insulin therapy with good glycemic control. Three days after the second dose of Pfizer-BioNTech's COVID-19 vaccine, he developed significant glucose variation, new-onset Raynaud's phenomenon (white-pale cold hands), weight gain, fatigue, abdominal bloating, constipation, and liver dysfunction. His blood sugar profile returned to baseline 6 weeks after treatment, but his Raynaud's phenomenon persisted as clinical complaints 5 months after vaccination. The authors attribute the increase in insulin resistance, liver dysfunction, and new-onset Raynaud's phenomenon to the vaccine-induced immune response [27].

Table 1. Clinical cases of patients with necrotizing Raynaud's phenomenon after COVID-19

Author	Patient	Raynaud's phenomenon	Concomitant diseases	Connective tissue disease	Positive laboratory/immunological tests	Clinical symptoms	Treatment	Outcome
Mariateresa Giglio et al [22].	A 37-year-old woman	Necrotic Raynaud's phenomenon after COVID-19	-	undifferentiated connective tissue disease		severe pain, with signs of severe ischemia and necrotic ulcers of the fingers of the lower extremities, interstitial pneumonia, fever (39 °C), cough and dyspnea	gabapentin, oral morphine and intravenous iloprost, SCS, intravenous dexamethasone, subcutaneous low molecular weight heparin, aspirin, oxygen	Two months after the onset of symptoms, tissue perfusion improved and the pain syndrome was under control
Rachana Vanaparthi et al [23].	A 63-year-old woman	Raynaud's phenomenon after COVID-19	aplastic anemia, mitral valve prolapse with regurgitation, celiac disease and motion sickness	-	-	runny nose and shortness of breath, no evidence of fever, chills, cough or chest pain. Involuntary twitching of the left eye and left cheek (without pain, loss of sensation, or numbness), diarrhea, generalized weakness, palpitations, sleep disturbances, decreased appetite, skin rash, herpes labialis, anosmia, and dysgeusia. (month after COVID-19) Purple discoloration at the base and whitish discoloration of the fingertips with temperature changes (Raynaud's phenomenon). Chills, vomiting, dizziness, vertigo and unsteady gait, right nystagmus (postviral vestibular neuritis) – after 3 months. Flashing and swimming in the left eye (increased intraocular pressure and posterior vitreous detachment due to steroid use). High fever (102 F), arthralgias, arthritis, and urticarial rash on chest and abdomen (8 hours after taking 2 g of Amoxiclav for dental procedure).	copious hydration, antipyretics, aspirin, multivitamins and calcium supplements, meclizine, antiemetics and vestibular rehabilitation exercises, prednisone	Slow clinical improvement
Yen-Chou Chen et al. [5].	A 67-year-old man	Acute digital ischemia with dry gangrene (of the II, III and IV fingers of the right hand) and Raynaud's phenomenon associated with diffuse arterial thrombosis of the upper extremities after COVID-19	Smoker, no comorbidities	-	ferritin, fibrinogen and D-dimer: anti-Ro, anti-La, anticardiolipin immunoglobulin G, antinuclear antibodies (ANA), antineutrophil cytoplasmic antibodies (ANCA), and anti-basement membrane antibodies	fever, tachycardia, progressive dyspnea and oxygen desaturation. Acute respiratory distress syndrome (ARDS). The distal parts of the second, third, and fourth fingers of the right hand are painful and dark with dry gangrene (6 days after admission to the intensive care unit). cyanosis and pain in the area of the nail folds (Raynaud's phenomenon) on the left hand after a cold provocation test. Diffuse thrombosis and stenosis of right brachial and ulnar artery and bilateral aneurysm of iliac artery (detected by imaging studies).	dexamethasone, tocilizumab, and a high-flow O ₂ nasal cannula. Enoxaparin and alprostadil, balloon angioplasty and intra-arterial infusion of urokinase through a Fontan catheter for 8 days. Antithrombotic therapy (rivaroxaban and clopidogrel).	The gangrenous lesions gradually improved and the intravascular thrombosis resolved completely.

Continuation 1

Author	Patient	Raynaud's phenomenon	Concomitant diseases	Connective tissue disease	Positive laboratory/immunological tests	Clinical symptoms	Treatment	Outcome
Chandra et al [24].	A 48-year-old woman	systemic scleroderma (SSc) and Raynaud's phenomenon due to COVID-19	anxiety and depression, sliding hiatal hernia, irregular Z-line and gastric hyperemia, Barrett's esophagus.	SSc, possibly secondary to SARS-CoV-2 infection	ANA	acute hypoxic respiratory failure (due to COVID-19 pneumonia). Fatigue, xerostomia, dysphagia, bilateral lower extremity weakness, Raynaud's phenomenon, joint pain in both hands, morning stiffness, dyspnea on exertion, diarrhea, painless mouth ulcers, involuntary weight loss, and diffuse skin hyperpigmentation. Swollen fingers, sclerodactyly, diffuse hyperpigmentation and abnormal capillaries of the nail folds (found on examination).	microphenolate mofetil, amlodipine 5 mg, methotrexate 12.5 mg, prednisone 2 x 5 mg	improvement in joint pain and improvement in Raynaud's phenomenon
Milan MJDC et al [25].	Female (Adolescent)	acute limb ischemia due to COVID-19 infection	none	juvenile scleroderma	anti-phospholipid antibodies, antinuclear antibodies and D-dimer	generalized hypo- and hyperpigmented skin lesions and mild, nonproductive cough, intermittent arthralgia, weight loss, ischemia of the fingers of the right hand and cyanosis of the fingers of the left hand and both feet on exposure to cold temperatures and sensory deficits (Raynaud's phenomenon), constant dryness of the skin.	Enoxaparin 0.5 mg/kg subcutaneously every 12 hours, nifedipine 0.4 mg/kg/dose every 6 hours, sildenafil 2 mg/kg/dose three times a day and nitroglycerin patch on the affected fingers. Prednisone and naproxen sodium sildenafil were started but discontinued. Amlodipine 0.4 mg/kg once daily. Infusion of cyclophosphamide, administration of peripheral vasodilators, methotrexate and anticoagulants.	Control of limb ischemia was achieved after 4 months.
Shih L et al. [18].	A 64-year-old woman	digital necrosis in a SARS-CoV-2 positive patient with a history of systemic sclerosis.	former smoker, hypertension, prediabetes	systemic sclerosis	D-dimer, antiphospholipid antibodies	progressive shortness of breath and bilateral finger pain of 1 week duration. Acute respiratory failure. Self-limiting episodes of bilateral pain and discoloration of fingers induced by low temperature (Raynaud's phenomenon). Cold and painful fingers on both hands, with dark discoloration of the distal part of the right index finger (but no signs of necrosis), dark discoloration and swelling of the left thumb and index finger. The left index finger shows early signs of necrosis.	hand warming, calcium channel blockers and phosphodiesterase inhibitors, low molecular weight heparin, remdesivir for 10 days, baricitinib (stopped 6 days after starting treatment due to concerns about worsening digital ischemia). Injectable botulinum toxin.	treatment was not enough for the necrotic soft tissue of the proximal left index finger, so the patient was scheduled for surgical amputation.

Continuation 1

Author	Patient	Raynaud's phenomenon	Concomitant diseases	Connective tissue disease	Positive laboratory/immunological tests	Clinical symptoms	Treatment	Outcome
Pourdowlat et al [19].	A 56-year-old woman	acrocyanosis and digital necrosis after COVID-19	diabetes mellitus type II	-	CRP and LDH (on admission), leukocytosis (16,200 per mm ³), lymphopenia (1200 per mm ³), thrombocytopenia (91,000 per mm ³), Hb (7.8 g/L), high CRP (107 mg/L), LDH (1117 IU/L), D-dimer (7780 µg/mL), ferritin (1650 ng/mL), and IL-6 (359 pg/mL).	cough, headache, fever, dyspnea and hypoxemia. Ecthymosis and spots on the skin of the extremities (6 days after intake), cyanosis in the fingers of the upper and lower extremities (on the 7th day)	oxygen, unfractionated heparin and hydroxychloroquine. Intubated and sedated (on the 5th day of admission) due to respiratory distress. Meropenem and vancomycin. Moved to intensive care unit on mechanical ventilation and unconscious (on day 7). Atorvastatin, aspirin, and nitroglycerin ointment.	Her clinical condition is deteriorating. The patient died with acrocyanosis and digital necrosis in the terminal stage of her disease.
Pourdowlat et al [19].	A 67-year-old woman	acrocyanosis and digital necrosis after COVID-19	type II diabetes and systemic hypertension	-	leukopenia (4200 per mm ³), lymphopenia (800 per mm ³), normal platelets (160,000 per mm ³) and hemoglobin level (13.7 g/dL), high CRP (70 mg/L), LDH (840 IU/L) and D-dimer (976 µg/mL).	respiratory distress syndrome. Fever (37.5°C). Terminal cyanosis in all fingers and pulselessness in both radial arteries on day 9 of mechanical ventilation.	endotracheal intubation and mechanical ventilation due to lack of response to oxygen therapy, sedatives, and neuromuscular blockade. Treatment with chloroquine 300 mg twice daily, lopinavir/ritonavir 400/100 mg twice daily, methylprednisolone, unfractionated heparin and antibiotics.	died of acrocyanosis and digital necrosis in the terminal stage of her disease.
Kawano H et al [26].	A 28-year-old Japanese woman	new-onset Raynaud's phenomenon after vaccination	-	systemic lupus erythematosus and antiphospholipid syndrome	serum high-sensitivity troponin T, 0.027 ng/mL (< 0.014 ng/mL) and IgG 2266 mg/dL (861-1747) for SLE	chest pain and Raynaud's phenomenon obtained one month after the second dose of the COVID-19 BNT162b2 mRNA vaccine.	azathioprine (50 mg/day), amlodipine (5 mg/day), prednisolone (10 mg/day), and aspirin.	Improved clinical condition after 3 months
Bansal CJ et al [21].	A 63-year-old man	Worsened Raynaud's phenomenon after vaccination	primary Raynaud phenomenon (RP). Bioprosthetic aortic valve replacement for idiopathic severe stenosis and coronary artery bypass grafting.	None	-	several episodes of Raynaud's phenomenon every day for four days, chills and fever (≥ 38.9°C), headache, sore throat, mild cough and myalgia	aspirin 75 mg, bisoprolol 2.5 mg, rosuvastatin 20 mg and ramipril 2.5 mg daily.	Improved clinical condition after 9 days

Continuation 1

Author	Patient	Raynaud's phenomenon	Concomitant diseases	Connective tissue disease	Positive laboratory/immunological tests	Clinical symptoms	Treatment	Outcome
Zavgorodneva Z et al [27].	A 33-year-old man	new-onset Raynaud's phenomenon after vaccination	type 1 diabetes since age 5, on insulin therapy	-	glucose level ranging from 46 to 378 mg/dL with a 3.5 times higher total daily insulin requirement. Elevated levels of aspartate aminotransferase and alanine aminotransferase. elevated immunoglobulin A (384 ng/dL) and C-reactive protein (1.4 mg/L).	significant glucose variation, new-onset Raynaud's phenomenon (white-pale cold hands), weight gain, fatigue, abdominal distension, constipation, and liver dysfunction.	-	His glucose profile returned to baseline 6 weeks after treatment, but his Raynaud's phenomenon persisted 5 months after vaccination.

CONCLUSION

Raynaud’s phenomenon (RP) turns out to be one of the frequent manifestations of past SARS-CoV-2 infection, in patients of different genders and ages. The etiopathogenesis is complex, and two main mechanisms are assumed: an autoimmune process or the thrombosis of arterial vessels, leading to ischemia of the tissues, and the so-called necrotizing Raynaud's phenomenon. Vasospasm in digital ischemia may be further complicated by Covid infection. Hypercoagulation (as a result of the cytokine storm), especially in patients with antiphospholipid antibodies and elevated D-dimer levels, leads to endovascular damage, increased platelet activity and the coagulation cascade and the phenomenon of immunothrombosis. Acrocyanosis due to excessive coagulation status has been described in critically ill patients with COVID-19. Gangrene can occur from impaired blood flow and insufficient healing of digital wounds, which is associated with elevated CRP levels. Ischemic limb lesions, usually seen in older patients with severe clinical course of the disease, represent a dangerous, although rare, complication associated with COVID-19 and are due to arterial occlusions. They are extremely difficult to treat and often lead to amputations. The underlying hypothesis is that digital necrosis in patients with COVID-19 is primarily associated with NET formation.

Necrotizing Raynaud’s phenomenon (NRP) is a vascular clinical syndrome characterized by vasoconstriction of distal resistance vessels following low temperatures or states of anxiety and stress. Lack of oxygen leads to tissue ischemia and causes pain. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) can cause endotheliopathy with microvascular and macrovascular thrombotic events. COVID-19 induces hypercoagulation, thrombosis, endothelial damage, and inflammation leading to vasculitis. The coagulopathy, inflammation, and thrombosis seen in COVID-19 are potentiated by increased activity of clotting factors, loss of protective glycocalyx function, and decreased nitric oxide levels.

At present, there is considerable evidence of Raynaud’s phenomenon (necrotic, new-onset, exacerbated, or as part of another systemic connective tissue disease) as a result of past COVID-19 infection or vaccination, but the hypotheses created are still subject to further studies.

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✉ Адрес за кореспонденция:

Д-р Владимир Бояджиева, дм
e-mail: vladimira.boyadzhieva@gmail.com

✉ Correspondence address:

Vladimira Boyadzhieva, MD
e-mail: vladimira.boyadzhieva@gmail.com