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Autoimmune connective tissue diseases in the COVID-19 pandemic

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Abstract Autoimmune connective tissue diseases are a heterogeneous group of clinical entities sharing a common feature-an impairment of structural components like collagen and elastin, arising by autoimmune mechanisms. Because most patients are on a long-term immunosuppressive therapy, which renders them vulnerable to infections, a new challenge appears in front of physicians in the coronavirus disease 2019 (COVID-19) era. Immune mechanisms are substantial for the control and ceasing of viral infections, and their impairment may cause serious complications; however, data from immunosuppressed transplant patients do not reveal a higher frequency or diseases' severity in those infected by COVID-19. Several immunotherapies used to treat autoimmune connective tissue diseases favorably modulate the immune response of severe acute respiratory syndrome coronavirus (SARS-CoV-2)–infected patients. The present review highlights the problems of susceptibility, severity, and therapeutic options in patients with autoimmune connective tissue diseases during the COVID-19 pandemic. The relationship between autoimmune connective tissue diseases and COVID-19 infection is explained with antiviral protection genes expression, hypercytokinemia, and lymphohistiocytosis/macrophage activation mechanisms. Recommendations concerning therapy for prevention during the pandemic period or in case of concomitant COVID-19 infection are also presented. Clinical trials are ongoing regarding COVID-19 therapy blocking the cytokine response.

Introduction

Autoimmune connective tissue disorders (ACTDs) are a heterogeneous group of diseases and syndromes characterized by a single feature—an impairment of structures like collagen and elastin, arising by autoimmune mechanisms. This damage determines an involvement of both skin and internal organs.[1] Due to their specific clinical characteristics, the potential biomarkers of the diseases's severity and progression are various autoantibodies and other soluble mediators. [2] Because most patients with ACTDs are on long-term immunosuppressive therapy, which renders them vulnerable to infections, a new challenge confronts dermatologists treating them at the time of the COVID-19 pandemic.

SARS-CoV-2 virus, the agent of COVID-19 infection, belongs to Coronaviridae, a family of single-stranded RNA viruses affecting many animals; however, six other coronaviruses are also known to infect humans.[3] More than 17 million COVID-19 cases were reported worldwide by the World Health Organization (WHO) by the end of July 2020, subsequently causing more than 660,000 deaths.[4] The infection has been proclaimed a pandemic only for a comparatively few months.

COVID-19 infection has an incubation period of 2 to 14 days and begins with fever, fatigue, and upper and lower respiratory tract signs and symptoms, mimicking those in acute lupus erythematosus (LE).[5] Some individuals might be asymptomatic, but they are contagious and can transmit the

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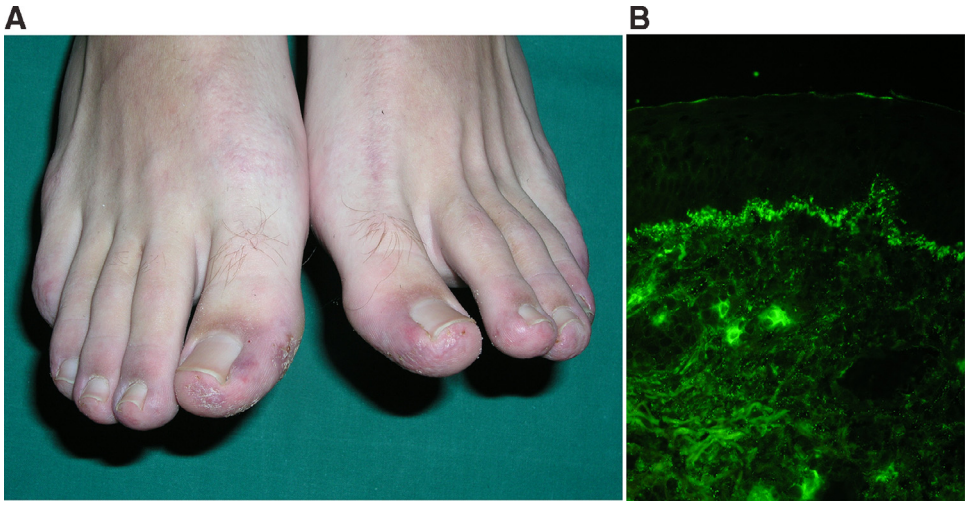

Fig. 1 Generalized acute cutaneous lupus erythematosus. (A) Diffuse and patchy periungual erythema, maculopapules and punctiform vasculitic scars on the tips of the toes in a patient with systemic lupus erythematosus (SLE); these may closely resemble the pseudo-chilblain lesions associated with COVID-19. (B) A positive lupus band test, performed by direct immunofluorescence on nonlesional unexposed skin, is highly diagnostic of SLE.

infection. The immune mechanisms are substantial for the control of viral infections, and their impairment may cause serious complications. Several immunotherapies may modulate the immune response of SARS-CoV-2–infected patients. Efforts should also be directed toward a more precise titration of immunosuppressive drugs to avoid relapses and at the same time prevent a possible COVID-19 infection.

Lupus erythematosus

The pathophysiology of LE is related to defects in the DNA methylation of various cells, especially in T cells, and overexpression of defective methylated genes such as *ACE2* (angiotensin-converting enzyme 2).[6] This makes patients sensitive to oxidative stress and relapses caused by some environmental factors. Epigenetic dysregulation of *ACE2* and interferon-regulated genes has been suggested to aggravate SARS-CoV-2 sensitivity in patients with lupus and to lead to new flares.[7] The relationship between these two diseases is explained by the pathogenesis of COVID-19, which is based on the expression of interferon genes responsible for the antiviral protection. The activation of these genes may lead to hypercytokinemia, also known as a "cytokine storm."[8] Some authors suggest that COVID-19 induces muted responses without interferon induction and results in a fulminant reaction to infections.[9] The cytokine storm leads to secondary hemophagocytic lymphohistiocytosis (HLH)/macrophage activation syndrome (MAS), which often can be triggered by infections. LE may be associated with an increased risk of HLH/MAS.[10-12] Some have speculated that patients with lupus might be at an increased risk of a cytokine storm during SARS-CoV-2 infection, whereas others have suggested that the genetically determined endogenous elevations of interferon-α could have protective and therapeutic roles.[13]

As an autoimmune disease with immune dysregulation, skin and/or internal organ damage, and potential comorbidities, LE places the patient at risk.[14,15] In these unpredictable times with a pandemic of a novel virus, many questions arise about patients at risk, especially the elderly and those with comorbidities (diabetes, cardiovascular, pulmonary, or oncologic diseases) and concomitant medications. Not enough information about the association of autoimmune disorders and COVID-19 is available in the literature; however, a recent study suggests a relatively low rate in patients with systemic LE (SLE), proposing as a possible explanation the common use of antimalarials.[16] Some signs and symptoms of the COVID-19 infection may mimic those of SLE. For instance, fatigue is a common symptom of both COVID-19 and lupus, as well as some skin manifestations. Also, in patients with SLE who suffer from fatigue, a SARS-CoV-2 infection could aggravate these complaints. A recent report of an autopsy presents the main features of COVID-19 infections: diffuse alveolar damage, interstitial mononuclear/lymphocytic infiltrates, and hyaline membrane formation.[17] In SLE, lymphopenia is a common disease activity criterion and is also associated with increased disease severity and mortality.[18]

The skin manifestations of COVID-19 are rare but are also included in the list of findings. LE presents with a wide range of lesions that indicate disease activity or disease control (Figure 1). On this basis, skin lesions could be easily confused.

An association of COVID-19 and high levels of lupus anticoagulant has been reported in 31 out of 35 patients with prolonged activated partial thromboplastin time.[19] Lupus anticoagulant is known to increase the risk of thrombosis in SLE or

Table 1 Therapeutic recommendations for ACTD management during COVID-19 pandemic.

Autoimmune connective tissue disease	Preventive measures during the pandemic period	If positive for COVID-19
Lupus erythematosus	Reduce the dose of the CS. Discontinue MTX or reduce the dose to <10 mg/week if possible. If the patient takes HCQ >200 mg/day, reduce it to 200 mg/day. If the patient takes 200 mg/day, reduce it to 200 mg every other day. Do not modify the dose in case of pregnancy and difficult-to-control LE.[68]	In newly diagnosed LE, start with HCQ. In severe cases, discontinue or reduce the dose of the CS or biologics. Alternatively, switch to HCQ.[68]
Dermatomyositis	Low doses of CS or azathioprine, MTX, IVIG, mycophenolate mofetil, cyclosporine, and cyclophosphamide can be used in patients who are unresponsive to CS.[69]	Use the lowest possible dose of CS and a second agent to be included, excluding MTX. If not responsive to CS, switch to IVIG, anakinra, cyclosporine, or adalimumab.[70]
Scleroderma	Avoid systemic CS, MTX. In severe cases of pansclerotic morphea, MTX or CSs should be reduced to the lowest effective dose.	Discontinue biologics if possible.
Vasculitis	Nonsteroidal antiinflammatory drugs, dapsone, colchicine, and low-dose systemic CS can be tried in mild cases during the pandemic period. In severe or resistant cases, low doses of MTX, IVIG, and tocilizumab can be used.[71,72]	

ACTD, autoimmune connective tissue disorders; CS, corticosteroid; HCQ, hydroxychloroquine; LE, lupus erythematosus; IVIG, intravenous immunoglobulin; MTX, methotrexate.

antiphospholipid syndrome; it could be a marker representing the risk of thrombosis in patients with COVID-19, and anticoagulant administration is recommended.[20] The levels of ferritin and C-reactive protein may be used as early detectors for a developing cytokine storm in the course of COVID-19 infection.[21]

A patient with SLE was admitted to the emergency unit due to exertional dyspnea, thoracic pain, and cough. A false-positive SARS-CoV-2 serologic test was reported.[22] The authors suggested that in patients with SLE the serologic tests have to be evaluated with caution due to possible nonspecific cross-reaction to various autoantibodies, as was reported for human cytomegalovirus.[21]

An Italian working group reported on their experience with patients with SLE and cutaneous LE. Cutaneous lesions have been stable in all patients. Most of them have been treated with hydroxychloroquine (HCQ) in combination with corticosteroids (CSs), azathioprine, thalidomide, or methotrexate (MTX). Those receiving systemic CS therapy have received the prednisone equivalent of less than 20 mg/daily. Some of the patients experienced mild to moderate COVID-19 findings. None of the patients has shown a relapse of the underlying disease.[23] Contrary to the Italian group, independent reports from Michigan and France described patients with SLE who tested positive for COVID-19 infection, all of them in a clinical remission of the underlying disease and under long-term HCQ exposure. Most of them required intensive care with ventilation, and a few patients died. SLE patients may develop more severe complications from the new virus than patients without autoimmune disease.[24,25]

Many LE patients are treated with immunosuppressive agents to control relapses and to prevent complications. The exact role of the virus in the pathogenesis of lupus and the aggravation of the signs and symptoms caused by the infection is unclear.[26]

Medications, especially CSs and biologics, can increase the risk of infections. Recommendations for therapy are shown in Table 1. Many trials are ongoing regarding COVID-19 therapy to block the cytokine response with anakinra and tocilizumab (a ClinicalTrials.gov search on January 4, 2021 showed 14 and 39 active or completed trials, respectively).

CSs have antiinflammatory and immunomodulatory effects, but their use to suppress the cytokine storm is not recommended[10]; however, they can reduce the hyperinflammation due to sepsis and decrease the mortality rate.[27] If patients should not discontinue their steroid medication, then the daily dose should be reduced to 10 mg/day or less prednisone equivalent.[15] Opinions concerning MTX are contradictory, but some authors propose its discontinuation.[28,29] Cyclophosphamide is a cytotoxic and immunosuppressive drug, which makes it inappropriate to start or to continue the

therapy during the pandemic. Immunomodulators such as intravenous immunoglobulins (IVIGs) are currently used more often as an alternative in autoimmune diseases therapy, particularly for resistant cases.[30] No data are available on the interaction between COVID-19 infection and IVIG therapy. Regarding the mode of action and the administration of the drug, it is not contraindicated nor is there a need for it to be discontinued.

Antimalarial drugs are among the most commonly used therapies in cutaneous LE. They are probably the most suitable medication during the pandemic due to their protective antiviral and antiinflammatory effect. They may reduce lipid levels, as well as the risk of thrombosis, and may control the blood sugar in lupus patients.[31-34] Chinese authors have established that these drugs relieve respiratory findings and improve the radiologic presentations, as well as the duration of the disease.[35,36] Some independent clinical studies, *in vivo* or *in vitro*, have been performed concerning the positive effect of antimalarial drugs in COVID-19 infection.[37-39] The US Food and Drug Administration has approved the drug for off-label use in some cases of COVID-19.[40] Concerning the prophylaxis of the medical professionals working with COVID-19, patient recommendations are in dispute. For example, the Indian Council of Medical Research has recommended it, whereas physicians at Johns Hopkins University Hospital in Baltimore, Maryland do not advise it.[41,42]

Dermatomyositis

Dermatomyositis (DM) is a rare ACTD belonging to the group of idiopathic inflammatory myopathies. DM affects the skin and skeletal muscles, presenting with a typical cutaneous eruption (e.g., heliotrope erythema, Gottron papules) and proximal muscle weakness. A variety of other organs and systems may be involved, such as the lungs, joints, gastrointestinal tract, and heart.

Although a few publications have suggested that patients with autoimmune disorders and immunosuppression do not appear to be more severely infected by COVID-19, data are limited. There are no large reports about the frequency of infection or the risk of severe COVID-19 in patients with ACTD involving the skin, namely LE, DM, and systemic sclerosis. Although there are a few case series available for patients with SLE and COVID-19 infection, there are none for DM, possibly due to the low incidence of the disease.[25]

Three immunogenic linear epitopes with high sequence identity to SARS-CoV-2 proteins have been reported in patients with DM, suggesting that latent exposure to the Coronaviridae family might contribute to musculoskeletal autoimmune disease development.[43] Myositis has been described in a patient with COVID-19. Although an autoimmune myositis was suspected, there was a lack of autoantibodies to confirm the diagnosis.[44]

In our opinion, in the context of the current COVID-19 pandemic, DM patients should be considered at greater risk for severe complicated SARS-CoV-2 infection.[45] The latter is not merely related to their immunocompromised state.

SARS-CoV-2 virus causes an influenza-like pulmonary illness, transmissible mainly through respiratory route. Patients suffering from an underlying lung disease, and especially those on chronic immunosuppression, are at higher risk of infection with SARS-CoV-2. This is the case for DM patients with interstitial lung disease (ILD). ILD is a common clinical feature in ACTD. Most patients with ILD, in the context of ACTD, experience a chronic benign course and have a relatively favorable prognosis; however, patients with DM or polymyositis tend to have more acute progression of ILD.[46]

Another factor, with a potentially fatal impact on DM patients, is the extent of muscle involvement. In severe DM cases, weakness of intercostal muscles may lead to breathing impairment and acute respiratory distress syndrome.[47] The risk is even greater if a viral infection occurs and exacerbates the disease course.

DM is considered a paraneoplastic phenomenon because in 24% of adult cases an underlying malignancy is present.[48] Considering that cancer patients are more at risk for infection than healthy individuals, the possibility of cancer-associated myositis should be actively excluded in every adult patient with DM, especially during the current COVID-19 epidemic. A recent cross-sectional study from China, encompassing a total of 1524 patients with cancer, suggested that cancer patients have a twofold increased risk of COVID-19 infection compared with the general population and are more likely to have higher morbidity and mortality.[49] According to another study, cancer patients infected with COVID-19 are at 3.5 times higher risk of requiring mechanical ventilation compared with the general population.[50]

Emerging data show that venous thromboembolism (VTE) occurs in approximately 20% of patients infected with COVID-19. This complication was reported predominantly in severely ill patients and was related to poor outcome. The risk of VTE remained high despite the use of guideline-recommended thromboprophylaxis.[51] Epidemiologic studies have revealed an elevated risk of VTE, including pulmonary embolism and deep venous thrombosis, in adults with idiopathic inflammatory myopathies.[52] In additions, recent data emphasized the different frequency of VTE in DM and polymyositis, respectively.[53,54] DM patients show an eight times higher risk of VTE compared with the general population, and in polymyositis the risk is six times higher.[54] Increased VTE risk may also exist in clinically amyopathic DM.[55]

Along with the gradually increasing understanding of COVID-19 pathophysiology, several drugs commonly used in rheumatology to treat autoimmune diseases have emerged as potential COVID-19 medications. In patients with DM, HCQ is routinely prescribed by dermatologists due to its beneficial effect on the skin lesions.[56]

Studies from China indicate that immunomodulatory therapies like tocilizumab and baricitinib might possess the

potential to attenuate the cytokine storm that causes terminal organ damage, multiorgan failure, and fatal outcomes in patients with severe COVID-19 pneumonia.[57]

Tocilizumab, a humanized monoclonal antibody against the IL-6 receptor, is among the four biologic therapies to consider for refractory juvenile DM treatment when indicated.[58] The presumed effect of tocilizumab in patients with severe COVID-19 is explained by the central role of IL-6 in the pathogenesis of cytokine release syndrome. A retrospective study with 21 patients severely affected by COVID-19 revealed that tocilizumab treatment improved the clinical manifestations in the majority of cases.[59]

Janus kinase inhibitor baricitinib might reduce the ability of the SARS-CoV-2 virus to infect the lung cells by inhibiting the regulator of endocytosis AP2-associated protein kinase 1 and is worth being trialed.[60] A patient with juvenile DM, refractory to wide array of antiinflammatory therapies, was described as having as having a good response to baricitinib.[61] Similar cases with improvement in adult DM patients have been reported after therapy with another Janus kinase inhibitor, ruxolitinib.

Systemic sclerosis

Systemic sclerosis (SSc) (scleroderma) is a chronic autoimmune connective tissue disease with distinctive pathognomonic features, comprising vascular derangement, immune system activation, tissue fibrosis, and a heterogeneous clinical profile. SSc is clinically characterized by Raynaud phenomenon, sclerodactyly, fibrosis, and dystrophic skin lesions associated with internal organ involvement. Localized scleroderma is limited to the skin and underlying tissues.[62] As with other ACTD, it is expected that patients with SSc may have a higher infection risk for COVID-19 than the general population due to the autoimmune dysregulation and chronic immunosuppressant therapies.[63] It is still unclear to what extent SSc patients are susceptible to SARS-CoV-2 or how severe the association of these diseases may be, as revealed in the available single case reports or small series. A SSc patient who developed very mild COVID-19 disease was successfully treated with intravenous tocilizumab.[64] Disease in three patients with severe bilateral interstitial pneumonia and sudden respiratory failure was controlled with rituximab and in one case tocilizumab.[65]

ILD is found in up to 80% of SSc patients and is one of the most severe complications.[66] Such patients are much more at risk to develop a severe COVID-19 lung infection.[67] In addition, COVID-19 may overlap with and even aggravate ILD in SSc, making the early phase of infection indistinguishable from ILD disease progression.

Systemic steroids and MTX are preferred therapeutic options. HCQ is seldom used in SSc; however, its antiviral properties have produced promising results.[73] Tocilizumab intravenously led to clinical and radiologic improvement for patients with ILD who were SARS-CoV-2 positive.[64]

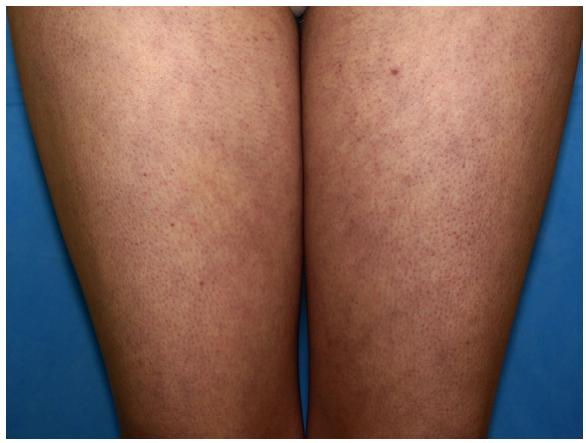

Fig. 2 Livedo reticularis–like eruption is commonly seen in systemic lupus erythematosus, but it is a cutaneous manifestation of COVID-19 as well.

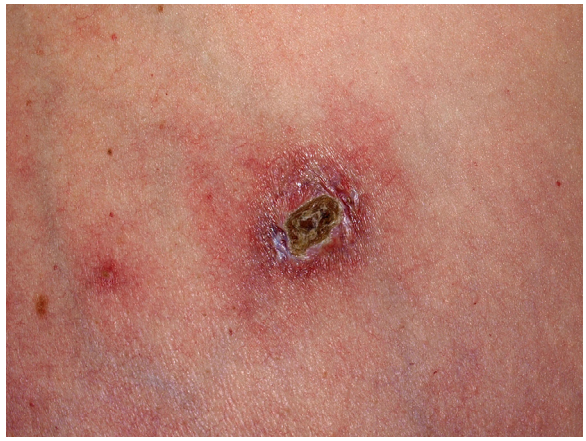

Fig. 3 Cutaneous necrosis is noted in severe systemic lupus erythematosus, dermatomyositis, and vasculitis, as well as in vasculopathies and COVID-19 infection.

Vasculitis

Cutaneous vasculitis is a large group of disorders that may progress to organ involvement.[74] Therapy depends on the diameter of the affected vessels, the density of the lesions, and the presence of organ damage. In addition, cytotoxic treatment of vasculitis usually raises the risk of infections. The diagnostic problem is that COVID-19 patients may also have cutaneous eruptions resembling vasculitis or vasculopathy.[75,76] Petechial and transient livedo reticularis–like (Figure 2) eruptions have been described.[77] A report from Wuhan, China revealed that patients with COVID-19 pneumonia developed cyanosis of their fingers, bullae, and cutaneous necrosis (Figure 3).[78] One patient developed Schamberg's purpura.[79] A patient with proteinase 3-antineutrophil cytoplasmic antibody granulomatosis with polyangiitis on CS and rituximab who developed severe COVID-19 pneumonia was successfully treated with antivirals and HCQ.[80]

Antineutrophil cytoplasmic antibody–positive polyangiitis treated with rituximab suggests that B-cell depletory therapy may not be a risk factor for severe forms and may even favor a milder course of COVID-19 disease.[81]

No data about precautions are currently available concerning therapy and prevention of new flares of ACTD. The Italian Society of Dermatologists recommends the following for patients:[82]

- Maintain social distancing, avoiding public transportation, public spaces; if necessary, stay at least 2 meters (6 feet) away from other people.
- Use face coverings.
- Observe some hygiene rules—washing the hands regularly with soap and warm water and using an alcohol-based hand sanitizer with at least 60% alcohol.
- Conduct regular follow-up visits by phone.
- Do not interrupt ongoing therapy.
- Inform your physician r in case of COVID-19 symptoms or new flares.

If signs and symptoms of COVID-19 infection occur, a period of self-isolation at home can help to reduce the transmission. If shortness of breath occurs, patients should contact their physicians.

Conclusions

Physicians should encourage ACTD patients to continue their maintenance therapies. In turn, ACTD patients may prevent infection by avoiding social contacts. In case of infections, we recommend discontinuation of immunosuppression. Larger observational studies are needed to establish the risk in patients with autoimmune diseases and to provide appropriate therapeutic guidelines.

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