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Review

Management of Patients with Connective Tissue Disease-associated Interstitial Lung Diseases During the COVID-19 Pandemic

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Abstract

The novel coronavirus disease (COVID-19) is similar to connective tissue disease-associated interstitial lung diseases (CTD-ILD) in many aspects. However, patients with CTD-ILD have required particular attention during the pandemic since they are at high risk due to immunosuppressive treatments. Thus, prompt decisions for diagnosis and treatment initiation have become more important than earlier for these patients during the pandemic. Radiological perspectives have become inevitable for the differential diagnosis of this group during the pandemic, particularly to obtain rapid and accurate results that allow the physicians to start treatment immediately. However, in addition to radiological images, a definitive diagnosis also requires access to extensive information regarding patient history, including characteristics of comorbidities, and clinical and serological findings. Consequently, the differential diagnosis of COVID-19 and CTD-ILD can yield accurate treatment regimens that differ greatly between the 2 diseases, and also prevent the spread of the outbreak with COVID-19 patients treated under isolation.

KEYWORDS: SARS-CoV-2, rheumatic diseases, radiology, lung imaging, management
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'All cases are unique and very similar to others'

—T.S. Eliot

INTRODUCTION

The novel coronavirus disease (COVID-19) has been a significant cause of morbidity and mortality since December 2019, and has spread rapidly from China to over 200 countries around the world. The novelty of the disease has also been challenging for the physicians confronting it since the first outbreak, with limited knowledge regarding its diagnosis and treatment. Distinguishing COVID-19 pneumonia from other similar pulmonary diseases or determining the real factor causing the present acute symptoms in case of comorbid pulmonary diseases have been important issues as well. Furthermore, it is also possible that the pressure on the physicians regarding the overlook of COVID-19 during this pandemic, could have led to misdiagnosis of other accompanying pulmonary diseases.

Interstitial lung disease (ILD) shares similarities with COVID-19, since both diseases may affect the lung at interstitial and alveolar levels. Connective tissue disease-related ILDs (CTD-ILD) represent a large and important subgroup of ILDs that are characterized by immune-mediated tissue injury that also affects lungs.[1] Despite a shared autoimmune nature, CTD-ILDs also present a heterogeneous group of diseases, exhibiting manifestations comparable with COVID-19 in certain aspects.[2] Thus, distinguishing between the 2 diseases based on their similar onset and progression as well as the common radiological findings may be difficult. A study from China evaluated 21 COVID-19 patients who also had rheumatogical disorders, and compared the findings with those of patients infected with COVID-19 but without rheumatological diseases. They revealed that rheumatic patients had a higher risk of respiratory failure. Moreover, patients with pre-existing CTD-ILD showed massive fibrous stripes and crazy-paving patterns at an early stage that continued to appear in the control Computed tomography (CT) scan at 36th day after first diagnosis.[3] Additionally, it was also pointed out that common medications used in both diseases, such as the interleukin-6 receptor (IL-6R) antagonist tocilizumab, may also veil the underlying disease and may cause misdiagnosis.[3]

It is also possible that acute exacerbations of ILD could have occurred during the pandemic due to the setbacks in the follow-up of chronic diseases. Physicians have to examine the clinical, laboratory, and radiological features of the diseases very carefully for accurate diagnosis and treatment, to obtain favorable clinical outcomes.

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The present review evaluating the characteristics of COVID-19 and CTD-ILD from the viewpoint of major similarities and differences aims to guide the clinicians from different disciplines confronting both diseases, both in the differential diagnosis and in their management.

CLINICAL FINDINGS

The identification of the key clinical characteristics of patients with COVID-19 has been crucial for early diagnosis and treatment initiation, and consequently has been preventing the spread of the disease. COVID-19 has a very wide spectrum of clinical manifestations, ranging from no symptoms or very mild symptoms to severe respiratory failures leading to death. In a meta-analysis evaluating 38 studies involving a total of 3062 predominantly male (56.9%) COVID-19 patients, fever (80.4%), fatigue (46%), cough (63.1%), and expectoration (41.8%) were the most common clinical findings, followed by anorexia (38.8%), chest tightness (35.7%), shortness of breath (35%), dyspnea (33.9%), and muscle soreness (33%).[4] On the contrary, in the study by Guan et al. on 1099 laboratory-confirmed COVID-19 patients, fever has not been defined as the most remarkable finding in the onset of COVID-19, since it was only present in 43.8% of the patients during admission.[5] The prevalence of COVID-19 has been reported high in older male patients with pre-existing hypertension and/or diabetes.[5,6] Smoking has also been defined as an important factor associated with disease severity.[7]

CTD-ILDs present significant differences in the clinical manifestations and management of each disease.[2] Although ILD is frequently diagnosed in patients already having CTD, it is also possible for some patients to be diagnosed with ILD prior to CTD diagnosis.[2] Dyspnea and cough are the most frequent pulmonary symptoms reported in CTD-ILD. However, neither these symptoms nor pulmonary examination findings are characteristic for CTD-ILD.[1] Pleuritic chest pain can be indicative of pleural effusion. Hence, in order to avoid overlooking the possibility of CTD-ILD, further examinations with high-resolution chest tomography (HRCT) and pulmonary function tests (PFTs) are recommended in patients with suspected CTD and having complaints of dyspnea, cough, and rales on chest exam lasting more than a month.[8] The chronic onset of pulmonary symptoms may be valuable in the differentiation from COVID-19, especially in patients with comorbidities or smoking habits who may not be aware of the duration of their symptoms. Questioning the family history of the patient with regard to ILD or CTD can support the diagnosis. Extrapulmonary manifestations due to CTD can facilitate the diagnosis of CTD-ILD. Patients frequently report findings such as rashes, Raynaud's phenomenon, constitutional symptoms, arthralgia, Sicca symptoms, dysphagia, and proximal muscle weakness. Physical examination findings including mechanic's hands, Gottron papules, sclerodactyly, digital ulcers, synovitis, oral ulcers, and proximal muscle weakness are also important extrapulmonary manifestations of CTD that physicians should consider in diagnosis.[2] Male gender and smoking have been defined as risk factors in ILDs related to rheumatoid arthritis and Sjögren's Syndrome.[1,8] Although it is unknown whether COVID-19 patients with ILD have different or more severe manifestations, patients with risk factors should particularly have a lower threshold for a more comprehensive assessment of COVID-19 and for other causes of respiratory worsening.[9] It is also crucial to notice the increased risk of coagulopathy and thrombosis in COVID-19 patients with ILD.[10]

Consequently, the nonspecific clinical presentations mostly neither guide the clinicians in ruling out the diseases included in the differential diagnosis, nor can lead to the diagnosis of COVID-19 or CTD-ILD without further diagnostic tools. It is also important to emphasize that the existence of one disease does not rule out the other. Thus, establishing a definitive diagnosis for both diseases is essential.

MAIN POINTS

- Distinguishing lung imaging findings of COVID-19 from CTD-ILD is a major concern.
- It is also very difficult to distinguish acute exacerbations of previously known CTD-ILDs triggered by COVID-19.
- Detailed clinical history, physical examination findings, as well as laboratory data are important for evaluation.
- Some key radiological imaging findings can be helpful for distinction between the 2 disorders, such as pleural effusion, widened pulmonary vessel sign, tree-in-bud appearance, and honeycomb cysts.

LABORATORY FINDINGS AND DIAGNOSTIC TOOLS

In their meta-analysis involving COVID-19 patients, Zhu et al.[4] have reported normal leukocyte counts (69.7%), lymphopenia (56.5%), elevated C-reactive protein levels (73.6%), elevated erythrocyte sedimentation rate (65.6%), and decreased oxygenation saturation (63.6%) as the most frequent laboratory findings, followed by elevated D-dimer levels (37.2%), abnormal liver function (29%) and abnormal renal function (25.5%). Real-time polymerase chain reaction (RT-PCR) test performed in nasal or oropharyngeal swabs is considered as the "gold standard" for the detection of SARS-CoV-2 virus, defined as the etiological agent of COVID-19.[11] Increased cytokine levels such as tumor necrosis factor (TNF)-α, interleukin IL-1 and IL-6 have also been reported in patients with COVID-19, and has been particularly associated with severe cases. Severe cases have also been associated with decreased CD4+ and CD8+ T cell counts.[12]

Despite the lack of characteristic routine laboratory tests used in the diagnosis of CTD-ILD, they are frequently used in the exclusion or detection in the potential context of systemic disease. On the other hand, in patients with suspected CTD and interstitial pneumonia, rheumatoid factor, antinuclear antibodies, and extractable nuclear antigen antibodies can be useful.[13] Pulmonary function test (PFT), body plethysmography, and diffusion lung capacity for carbon monoxide are important tools demonstrating the restrictive physiology and diffusion impairment, and are used in the diagnosis and follow-up of ILD patients.[8] However, PFTs during the pandemic have been discouraged as they could increase the risk of transmission, and postponement of the procedure has been recommended.[14] The benefit of bronchoalveolar lavage cytology in the diagnosis of CTD-ILD has been reported as limited, but is an important tool used for excluding alternative diagnoses.[13] Although lung biopsy is the gold standard

for diagnosing ILDs, in most suspected CTD-ILD patients, it is only required in case of atypical features on clinical or radiological presentation.[1] Considering the challenges in the diagnosis and management of CTD-ILDs, a multidisciplinary discussion approach, involving specialists from different disciplines, mainly pulmonology, rheumatology, radiology, and pathology, is recommended.

During the pandemic, rapid decisions on the diagnosis and treatment initiation became more important than before. Due to the limitations of the tests used for definitive diagnosis of COVID-19 or CTD-ILD within a short time, radiological findings have been frequently used by physicians in emergency room or outpatient clinic settings to determine a possible diagnosis and start treatment in highly suspicious cases.

RADIOLOGICAL FINDINGS

CT of chest plays an essential role in the diagsnosis of COVID-19 pneumonia since it is has the advantages of both high senstitivity and rapid results, compared to RT-PCR.[15] Although most of the imaging findings of COVID-19 pneumonia are not characteristic, considerable imaging features for the diagnosis among patients, such as peripheral or peribronchovascular ground-glass opacities (GGO) (86.1%), mixed GGO and consolidation areas (64.4%), vascular enlargement (71.3%), and traction bronchiectasis (52.5%) have been frequently reported.[16] Bilateral involvement of the lung with multifocal lesions, lower lung predominance, and peripheral-peribronchovascular distribution of the lesions have been described as typical imaging features in COVID-19 pneumonia.[15-17] Similar imaging findings are also frequently detected in the pneumonia of autoimmune and auto-inflammatory diseases as well as in some forms of CTD-ILD.[18] A recent study examining 1014 patients who underwent chest CT with the suspicion of COVID-19 showed that most of the patients had ILD features.[19] Besides, chest CT demonstrated multifocal GGO with a reticular pattern (crazy-paving pattern), consolidation, air bubble sign, pulmonary vascular enlargement inside the opacity, focal pleural thickening, and pleural retraction, which have been detected in 88% of COVID-19 patients.[18,19] It has been reported that the ILD features of COVID-19 pneumonia are usually seen in the late phase of the disease, and the incidence of ILD increases with aging.[16,18,19] Though less sensitive than chest CT, chest radiography (CXR) is ususally the first-line imaging tool in patients suspected of having COVID-19.[20] Its ease of decontamination is an important advantage over CT. The most common CXR features are bilateral and peripheral focal lung opacities with lower zone predominance[21] (Figure 1). The preferred method for evaluating the presence of complications and investigating the severity of pneumonia in children and pregnant COVID-19 patients is CXR.[20,21] However, CXR has a low sensitivity in the early phase of the disease and in mild disease[19] (Figure 2). The current recommendations of professional radiological associations are that imaging methods, especially CT, should not be used as a screening or diagnostic tool for COVID-19, but reserved for the assessment of disease severity and complications.[9,20]

On the other hand, abnormal CXR findings such as basilar, peripheral reticular, or reticulonodular opacities can be suggestive of ILD. Besides, normal CXR is also very common in the early stage of the disease.[22] Since high-resolution CT (HRCT) has a higher sensitivity and specificity compared to CXR, it is recommended in cases with suspected CTD-ILD.[22,23] Thus, both the features of the disease, as well as the extent of the CTD and ILD severity, can be assessed with HRCT.[23] GGO, subpleural reticulation, traction bronchiectasis-bronchioloectasis, and centrilobular nodules are the most common HRCT findings in CTD-ILD.[24-26] In chronic fibrotic CTD-ILD, traction bronchiectasis-bronchioloectasis and honeycombing with peripheral and lower lobe predominance can be seen. Usual interstitial pneumonia, nonspecific interstitial pneumonia, desquamative interstitial pneumonia, and organizing pneumonia are the most common patterns seen in CTD-ILDs.[13,23,27] Moreover, especially patients with granulomatosis with polyangiitis (formerly known as

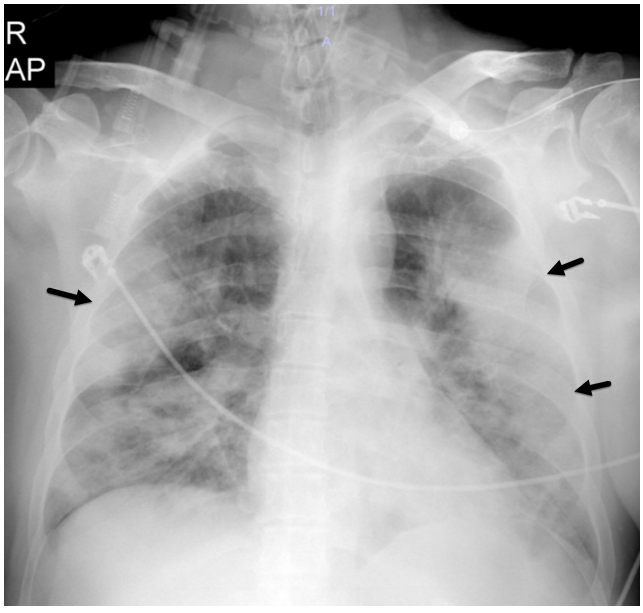

Figure 1. A 48-year-old male patient with a diagnosis of COVID-19 pneumonia. CXR shows bilateral peripheral lung opacities (arrows).

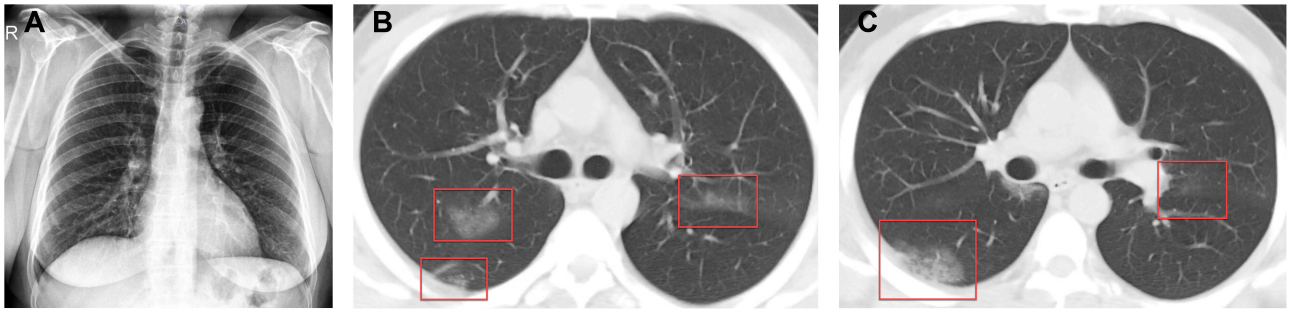

Figure 2. A 45-year-old female patient with a diagnosis of COVID-19 pneumonia. (A) CXR shows no abnormalities. (B and C) Chest CT images show bilateral peripheral ground-glass opacities (red rectangles).

Wegener's Granulomatosis) or rheumatoid arthritis can present with cavitated lung nodules, and patients with systemic lupus erythematosus can present with diffuse or focal alveolar hemorrhage.[13,22]

The common radiological manifestations in both COVID-19 and CTD-ILD can pose a challenge for physicians in the differential diagnosis. Furthermore, it is also very difficult to distinguish acute exacerbations of previously known CTD-ILDs triggered by COVID-19. It is necessary to pay attention to some imaging findings that may be useful for distinction between the 2 disorders. First, pleural effusion may be noticed in CTD-ILDs with pleura involvement, which is not expected in COVID-19 unless there are coexisting morbidities such as congestive heart failure.[16,19] Second, pulmonary vascular enlargement (widened pulmonary vessel sign) is frequently reported in patients with COVID-19 pneumonia and defined as the dilatation of the pulmonary vessels around and/or inside the lung opacity[15,16] (Figure 3). However, this sign has not yet been identified in patients with CTD-ILD. Third, ILD areas usually show continuity in patients with CTD-ILD, and healthy lung areas protected between ILD areas are not expected. However, multifocal (patchy) lung opacities and healthy lung areas between opacities are frequently detected on CT in patients with COVID-19 pneumonia.[16,19] (Figure 4). Fourth, centrilobular nodules and tree-in-bud appearance lung nodules can often be seen in patients with CTD-ILD, but are not expected in COVID-19 patients without superimposed bacterial infection[15,16] (Figure 5). Fifth, while honeycomb cysts, pleural surface irregularities, and irregular interlobular septal thickening are frequently detected in patients with CTD-ILD in the chronic phase, these findings

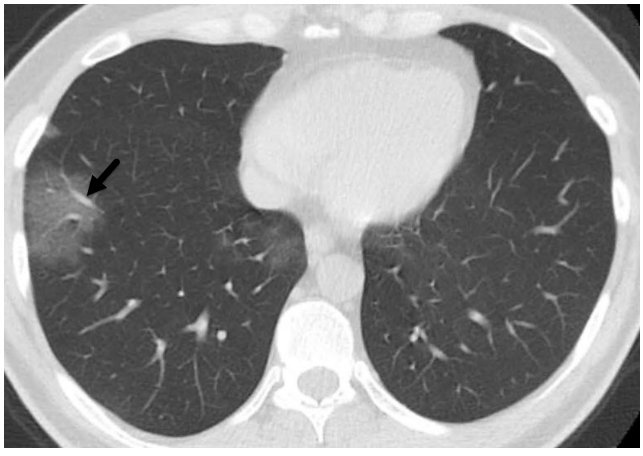

Figure 3. A 38-year-old female patient with a diagnosis of COVID-19 pneumonia. Chest CT image shows focal ground-glass opacities in the right lung and pulmonary vascular enlargement (also known as widened pulmonary vessel sign, arrow).

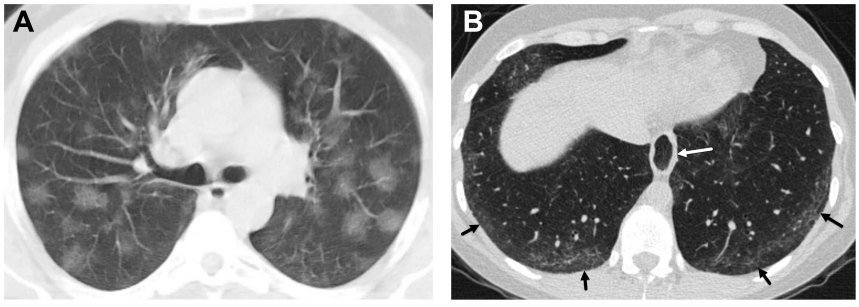

Figure 4. (A) A 55-year-old female patient with a diagnosis of COVID-19 pneumonia, axial chest CT image shows multifocal ground-glass opacities in both lungs and focal healthy lung areas between opacities. (B) A 38-year-old female patient with a diagnosis of systemic sclerosis, axial chest CT image shows ground-glass opacities (black arrows) with continuity in both lung lower lobes, compatible with nonspecific interstitial pneumonia. Note the dilatation of the distal esophagus.

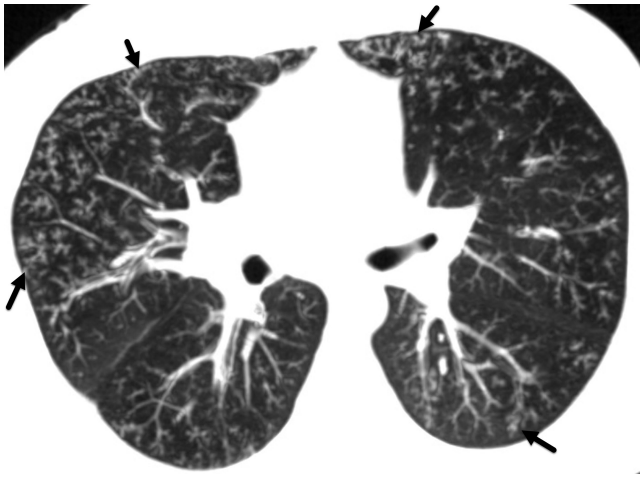

Figure 5. A 32-year-old female patient with a diagnosis of systemic lupus erythematosus. Chest CT image shows severe centrilobular lung nodules with tree-in-bud appearance in both lungs, compatible with bronchiolitis (arrows).

have not yet been detected in COVID-19 pneumonia.[13,22] (Figure 6). Sixth, the air bubble sign, also known as cystic air space changes, defined as a small air-containing space that may be a pathological enlargement of a physiological area in the alveolar sacs or bronchioles, in patients with COVID-19 pneumonia.[15,19] (Figure 7). Unlike the cavitary lesions of the lung, the air bubble does not have walls, and the "air bubble sign" has not been identified in CTD-ILD patients yet. Although all of these findings are not specific, we think they will be useful for discrimination of CTD-ILD and COVID-19 pneumonia. Moreover, since radiological findings have important roles both in the diagnosis of the 2 diseases and in facilitating treatment initiation, it is crucial to interpret the CT findings accurately in order to avoid misdiagnoses, false treatments, and mortalities.

TREATMENT

Despite the lack of a specific treatment as well as randomized controlled trials in COVID-19, favorable treatment outcomes have been obtained. For patients admitted with COVID-19, treatment regimens involving hydroxychloroquine/chloroquine, azithromycin, lopinavir/ritonavir, tocilizumab, and convalescent plasma have been suggested in the context of clinical trials.[24-26] A recent study evaluating the use of immune therapy on COVID-19, reports that convalescent plasma containing a high amount of virus-neutralizing antibodies is an effective therapeutic option for emergent use before virus-related multiple organ effects become evident.[28] Intravenous immunoglobulin (IVIG) is also among possible useful treatment alternatives as it contains antibodies that cross-react against SARS-CoV-2 and other virus antigens in vitro. Although several attempts are being made for the use of IVIG and monoclonal antibodies in COVID-19, high costs of both approaches may be a limitation. Additionally, SARS-CoV-2 is capable of mutating, further challenging the use of specific antibody therapies.[29] The routine use of corticosteroids have not been recommended in COVID-19 pneumonia except for the patients admitted with ARDS due to COVID-19.[30] On the other hand, immunomodulatory medications including prednisone, mycophenolatemofetil, azathioprine, cyclophosphamide, and rituximab are frequently used in CTD-ILDs. Presently, various anti-rheumatic agents

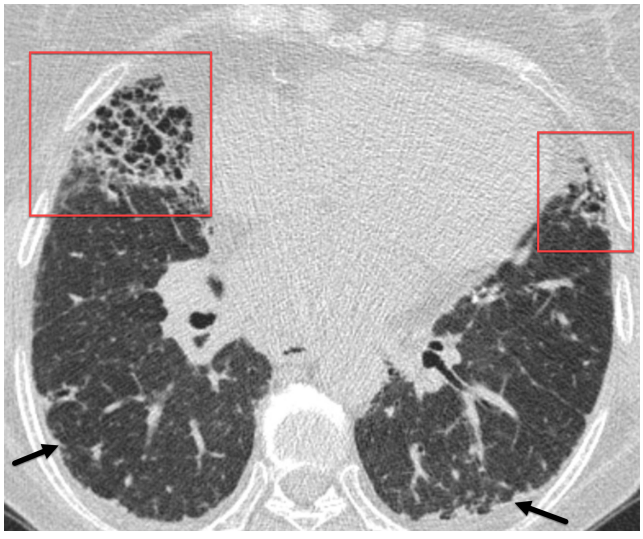

Figure 6. A 53-year-old female patient with a diagnosis of rheumatoid arthritis. Chest CT image shows interlobular septal thickening and honeycomb cyst in both peripheral lung areas (red rectangles). Also, bilateral subpleural reticulations are seen in both posterior-basal segments (arrows).

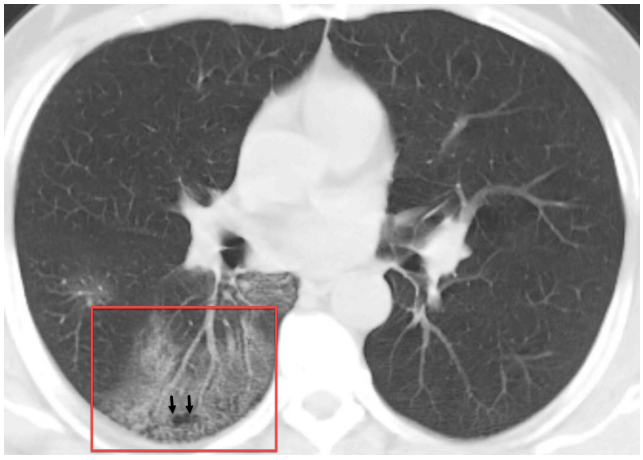

Figure 7. A 47-year-old male patient with a diagnosis of COVID-19 pneumonia. Chest CT image shows focal ground-glass opacities in the right lower lobe (red rectangle) and air bubbles in the ground-glass opacity (arrows).

including the IL-6 humanized monoclonal antibody, tocilizumab, have also been included in the treatment regimen of COVID-19 patients with severe or progressive pneumonia and are effective in the management of a massive cytokine storm.[18] Data from phase 3 randomized controlled trials of IL-1 blockade (anakinra) in sepsis demonstrated substantial benefit in the survival of patients with increased inflammation.[31] On the contrary, although tocilizumab is an effective treatment used in several CTD-ILDs, a possible association with acute exacerbation of rheumatod arthritis-ILD has also been suggested.[32]

Since there are no available data to guide the dosing of immunosuppressive therapies in the context of the COVID-19 pandemic, a moderate approach such as limiting the use of corticosteroids is currently recommended.[9] Current international society recommendations suggest that patients with rheumatic diseases on immunosuppressive therapy should not stop glucocorticoids during COVID-19 infection; however, minimum possible doses are preferred. Disease-modifying drugs should be continued; cessation may be considered during infection episodes as per standard practices.[33]

CONCLUSION

The management of novel coronavirus disease has been a major challenge for physicians due to limited information regarding the pathogenesis and effective specific treatments in COVID-19.[29] Although initiation of empirical treatment ahead of the results of diagnostic tests has been an option for many patients admitting in hospitals, this has not been a valid option, both for cases with COVID-19 and for those with CTD-ILDs. Despite common clinical, laboratory, and radiological features of both diseases, treatment regimens differ greatly. Although corticosteroids may be the mainstay of treatment in some forms of CTD-ILD, the use of low-dose corticosteroids in COVID-19 is only recommended for critically ill patients with refractory ARDS, sepsis, or septic shock.[34] Thus, diagnostic methods used in distinguishing these diseases have great importance. Furthermore, more severe symptoms and high respiratory failure rates in rheumatic patients with COVID-19 are also indicative of worse prognosis in CTD-ILD patients with COVID-19 due to immunosuppressant treatments. Possible negative effects of both diseases on each other through pathological mechanisms are also suggested.[3] In conclusion, extensive diagnostic workup and personalized approach for treatment of these patients with common features are vital, particularly during the pandemic, for the best outcomes.

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