Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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What can we learn from rapidly progressive interstitial lung disease related to anti-MDA5 dermatomyositis in the management of COVID-19?

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Dear Editor,

Coronavirus disease 2019 (COVID-19) is a newly recognized systemic condition due to the SARS-CoV-2 infection. As rheumatologists, we often found analogies between vascular inflammation, endothelial dysfunction and lung manifestations of COVID-19 and inflammatory autoimmune diseases. In the management of COVID-19 infection seems sensible to distinguish viral and host inflammatory phase since about one patient in twenty develops an uncontrolled inflammatory response with multiple organ failure. Fever, cough, dyspnoea, fatigue and myalgia are the most common symptoms and high creatine-phosphokinase, and inflammatory markers (ferritin, C-reactive protein, D-dimers, interleukin-6) are associated with a poor prognosis [1]. In this regard, several pieces of evidence point toward a central role of massive and dysfunctional endothelial activation, leading to diffuse thrombotic disease, both as a specific effect of SARS-CoV-2 and as a consequence of systemic inflammation. The so-called “cytokine storm” is the production of large amounts of mediators of inflammation that can be triggered by SARS-CoV-2 infection [2] but is also described in autoimmune and autoinflammatory diseases. Vasculopathy and thrombotic manifestations seem to characterize the more aggressive cases of COVID-19 infection [3], especially in the lungs and skin [4]. In many autoimmune diseases vascular abnormalities are associated with systemic inflammation, lung disease [5] and heart damage [6], but the clinical course is often chronic. Intriguingly, in terms of clinical picture, some epidemiologic aspects, biomarkers and pathological aspects of tissue damage, COVID-19 shows many similarities with the subset of dermatomyositis associated with anti-melanoma differentiation-associated gene 5 (MDA5) (Table 1). Anti-MDA5 dermatomyositis is a serologically-defined subtype of dermatomyositis that is characterized by a high risk of rapidly progressive interstitial lung disease, little evidence of clinical muscle inflammation, typical rashes and high prevalence of systemic symptoms. Viral infections have been considered as a possible trigger to the uncontrolled innate and adaptive immune response of anti-MDA5 dermatomyositis. Anti-MDA5 dermatomyositis has a poor prognosis but low recurrence rate in survivors and, while it is a very rare condition globally, it is reported much more frequently in East Asia, suggesting a genetic or environmental modulation of the onset of the disease. Even if direct evidence of a specific viral pathogen is lacking, this hypothesis is supported by the recognition of IFN induced with helicase C domain protein 1 (IFIH1) gene as a target of anti-MDA5 antibodies [7]. IFIH1 is indeed required for the normal immune response against some classes of viruses, including coronavirus, promoting the production of cytokines such as IFNγ, TNF-α, IL-1β, IL-6 and IL-18 and stimulation of T_H1 cells and macrophages. In case of a defective anti-inflammatory counterbalance, the result is the development of a cytokine storm with the overexpression of pro-inflammatory mediators, sustaining rapidly progressive forms of interstitial lung disease [8]. Not surprisingly, systemic symptoms like fever are particularly frequent in these patients compared to the ones with other connective tissue diseases, and hyperferritinemia is an almost invariable finding with very high levels associated with a more severe disease course and a poor prognosis [9]. Manifestations of hypercoagulability with various degrees of thromboembolism, are also a recognized risk in inflammatory myopathies and thrombotic alterations of small and medium-sized arteries represent a histopathological hallmark in skin biopsies [10]. Radiologic appearance on chest CT of anti-MDA5 disease is very close to the one of COVID-19 (Fig. 1), with a bilateral distribution of ground-glass opacities with or without consolidation in posterior and peripheral lungs and - in a substantially different way from other myositis related interstitial lung disease - with prevalent peribronchovascular consolidations [11,12]. Spontaneous pneumomediastinum is not a rare finding in both severe COVID-19 and anti-MDA5 positive dermatomyositis related interstitial lung disease while is less common in anti-MDA5 negative myositis. In the above depicted context, anti-MDA5 antibodies formation may be a simple epiphenomenon due to antigen release from infected or damaged cells or may have a pathogenetic role, directly promoting tissue damage. Consistently with this last speculation, anti-MDA5 titre correlates with disease activity, prognosis and therapeutic response[13], and B-cells depletion treatment has shown to be useful in refractory cases. The significant role of humoral immunity in anti-MDA5 myositis could appear distinctive from COVID-19. To date, a pathogenetic effect of antibodies targeted against SARS-CoV-2 cannot be excluded since their neutralizing effect is still debated and the anti-IgG response has been associated with disease severity and higher proinflammatory cytokines level[14]. The

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Table 1
Comparison between COVID-19, anti-MDA5 dermatomyositis and classic dermatomyositis.

		COVID-19	Anti-MDA5 dermatomyositis with ILD	Classic dermatomyositis with ILD
Epidemiology	Prevalence	More than two million cases globally	Rare	Rare
	Geographic clusters	First reports in China, (now in all continents)	Mainly reported in east Asia	None
	Sex predominance	None	None	Female predominance
	Natural history	Severe and rapidly progressive disease in about 20% of cases	Rapidly progressive	Slowly progressive
	Recurrence	Unknown	Rare	Relapsing-remitting
	Mortality rate	High	Very high	High
Pathogenesis	Association with viral infection	Proven association with SARS-CoV-2 infection	Possible trigger of picoRNA- or other viruses	Debated triggering role of viruses
	Inflammatory state	High grade systemic inflammation	High grade systemic inflammation	Low-moderate grade systemic inflammation
	Prothrombotic state and endothelial dysfunction	Hallmark of the disease	Hallmark of the disease	Hallmark of the disease
	Autoantibody mediated injury	Possible cross-reactivity of induced antibodies	Postulated direct role of anti-MDA5	Debated direct pathogenetic role
	Lung histopathology	DAD and microangiopathy	DAD and microangiopathy	NSIP and OP
Clinical manifestations	Lung disease	Almost always present	Almost always present	Common
	Myositis	Mild-absent	Mild-absent	Almost always present
	Skin and peripheral vascular involvement	Common	Almost always present	Almost always present
	Fever	Almost always present	Very common	Uncommon
	Association with cancer	Absent	Rare	Possible
Diagnosis and monitoring	CK	Mild-moderate high	Mild-moderate high	Very high
	Ferritin	High	High	Normal or slightly increased
	Lymphocytes	Commonly low	Occasionally low	Occasionally low
	CRP	Very high	Very high	Usually normal
	ESR	High	High	High
	Antinuclear Antibodies	Unknown	Negative	Usually positive
	Antiphospholipid antibodies	Possibly positive	Possibly positive	Possibly positive
	CT scan of the chest	Bilateral GGO or consolidation in posterior and peripheral lungs	Bilateral GGO or consolidation in posterior and peripheral lungs	Bilateral peribronchovascular GGO or consolidation
	Nailfold capillaroscopy	Unknown	Enlarged capillaries, hemorragias, neovascularization	Enlarged capillaries, hemorragias, neovascularization
Treatment	Corticosteroids	Under investigation	Commonly used	Commonly used
	Anti-IL6	Under investigation	Unknown efficacy	Unknown efficacy
	Anti-IL1	Under investigation	Unknown efficacy	Unknown efficacy
	JAK-inhibitors	Under investigation	Under investigation	Under investigation
	Anti-CD20	Not suitable	Rescue therapy	Rescue therapy

ILD interstitial lung disease, DAD diffuse alveolar damage, NSIP nonspecific interstitial pneumonia, OP organizing pneumonia, CK creatine kinase, CRP C reactive protein, ESR erythrocyte sedimentation rate, CT computed tomography, GGO ground glass opacities, IL interleukin, JAK Janus kinase.

possibility of secondary antibody-mediated organ damage would represent another common point between COVID-19 and anti-MDA5 dermatomyositis, at least in the subgroup of patients who develop an uncontrolled immunoinflammatory response after SARS-CoV-2 infection. Notably, a cross-reactivity between anti-SARS-CoV-1 (a form of coronavirus close to the one responsible of COVID-19) antibodies and lung epithelial cells has been described[15]. The analogies between these two conditions allow speculations about the rationale of targeted therapies with promising results in anti-MDA5 positive interstitial lung disease in COVID-19. High dose corticosteroids, intravenous human immunoglobulin, JAK-inhibitors and T-cell modulating drugs reported efficacy in small case series and are currently under investigation in clinical trials for the treatment of COVID-19. A therapeutic role of direct B cells depletion seems unlikely in COVID-19 due to their crucial protective role against viral infections, unless a direct pathogenic effect of SARS-CoV-2 induced antibodies in severe COVID-19 systemic disease is proven. Other pharmacological strategies, including inhibition of IL-6 (tocilizumab, sarilumab, siltuximab and clazakizumab), IL-1 (anakinra and canakinumab), anti-GM-CSF (gimsilumab) or IFNγ (emapalumab) - rarely or neither used in the treatment of anti-MDA5 interstitial lung disease - are currently being tested for COVID-19 treatment, given the crucial role of these cytokines in the disease, but with understandable concerns on the possible interference with the host response to the virus. In COVID-19, appears crucial that a structured approach to clinical phenotyping is undertaken, in order to distinguish the phase where the viral pathogenicity is dominant by the phase in which host inflammatory response prevails.

In conclusion - in early phases of COVID-19 - the eradication of SARS-CoV-2 should be the goal to prevent the subsequent inflammatory storm while in the established phases of the inflammatory response the aim should be to extinguish effectively the inflammatory-immune response. In a context where the key therapeutic targets have to be fully understood, we believe that looking at the experience with autoimmune diseases of rheumatological interest, such as anti-MDA5 related lung disease could guide and stimulate the development of useful therapeutic strategies. Moreover, even if the long-term impact of COVID-19 is not yet established, as rheumatologist we deeply expect that the medical efforts to extinguish the burden of inflammation in severe COVID-19 as soon as this occurs, may help to contain the number of patients that will develop chronic damage and functional impairment, especially in the respiratory compartment.

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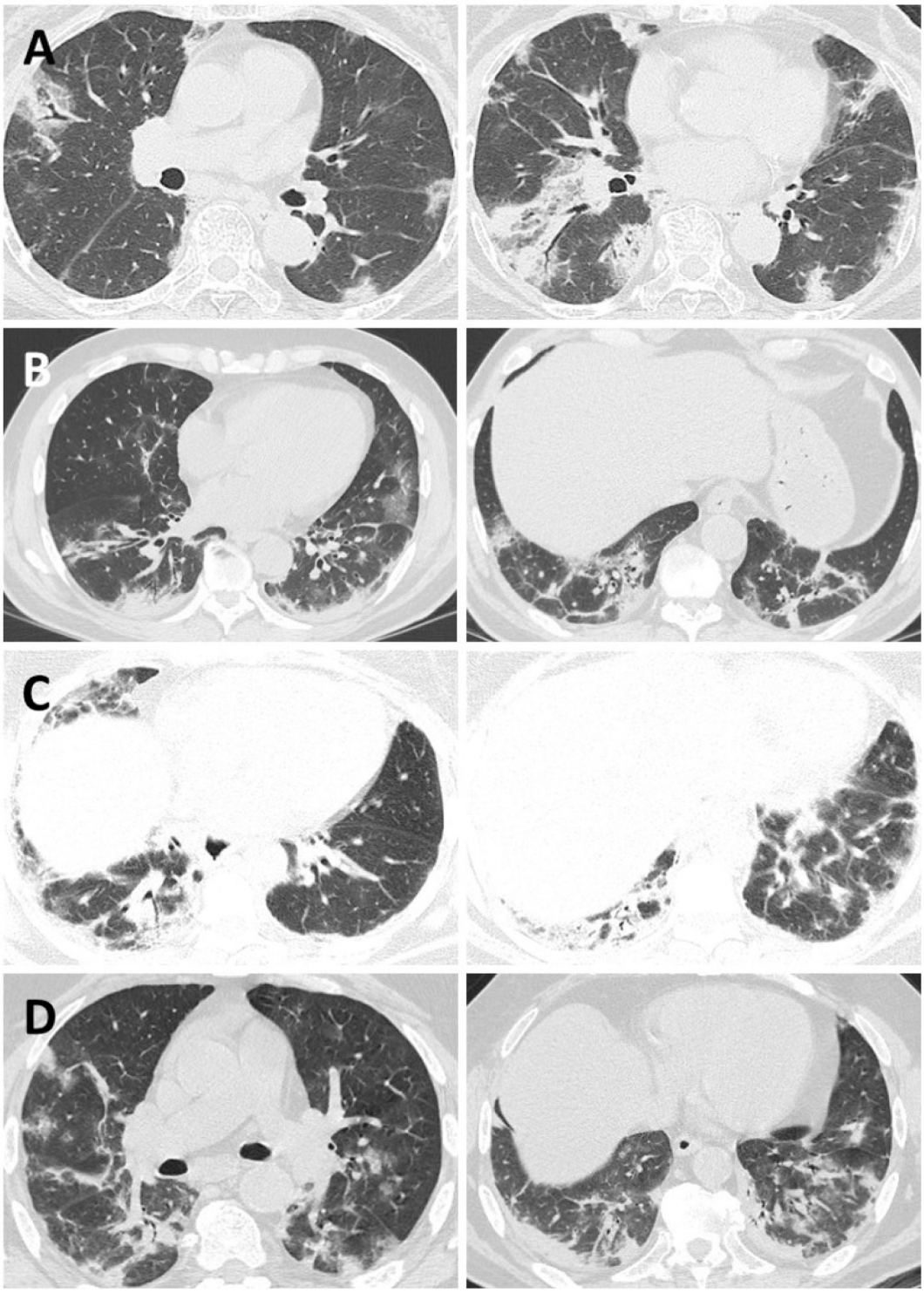

Fig. 1. Similarities in CT scans findings of two patients with anti-MDA5 dermatomyositis (A*, C**) and two patients with COVID-19 (B, D).
The images show bilateral subpleural areas of patchy ground glass opacities and consolidation accompanied by traction bronchiectasis and perilobular linear opacities.
*Courtesy of Prof. Noriho Sakamoto, Nagasaki University Graduate School of Biomedical Sciences.
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Contributorship

All the authors gave substantial contributions to the conception or design of the work, acquisition, analysis or interpretation of data, drafting the work or revising it critically for important intellectual content and final approval of the version published.

Declaration of Competing Interest

There are no competing interests for any author.

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