Similarities and differences between severe COVID-19 pneumonia and anti-MDA-5-positive dermatomyositis-associated rapidly progressive interstitial lung diseases: a challenge for the future

We read with great interest the article by Megremis *et al*,[1] who identified three immunogenic linear epitopes with high sequence identity to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) proteins in patients with dermatomyositis (DM). Speculatively, this finding could indicate that latent exposure to the Coronaviridae family might contribute to musculoskeletal autoimmune disease development.[1] Consequently, SARS-CoV-2 infection might mimic myositis and could also lead to catastrophic results in patients with DM with prior interstitial lung disease (ILD) manifestation.

COVID-19, caused by SARS-CoV-2, has rapidly spread to the whole world. Lung involvement is the hallmark of the disease, significantly associated with worse prognosis and higher mortality. The mechanism leading to acute lung injury in COVID-19 has not yet been completely elucidated. Nevertheless, immune dysfunction and cytokine dysregulation seem to play a pivotal role in this process. It is speculated that SARS-CoV-2 binds to target host cells through ACE 2, which is expressed in the airway and on type 2 pneumocytes in the lung. Subsequently, the virus triggers a storm of innate and adaptive immune response, resulting in the aberrant release of a large number of cytokines, including interleukin (IL)-1, IL-6, IL-10, granulocyte-macrophage colony stimulating factor (GM-CSF), monocyte chemotactic protein-1 and interferon gamma (IFN-γ), called 'cytokine storm' by some.[2] Abnormally high levels of these cytokines/chemokines are considered to lead to acute pulmonary interstitial tissue and alveolar damage, accounting for respiratory failure. The major high-resolution CT (HRCT) features of COVID-19 pneumonia encompass multifocal bilateral peripheral ground glass area associated with subsegmental patchy consolidations, mostly subpleural and predominantly involving the lower lung lobes and posterior segments, similar to ILD. Pathological findings in severe cases of COVID-19 pneumonia showed pneumocyte desquamation and pulmonary oedema with hyaline membrane formation, and interstitial lymphocyte infiltration.[3] Growing evidence, although uncontrolled and anecdotal, supports the prompt use of an anticytokine regimen, including IL-6 inhibitors, IL-1 blockade, GM-CSF receptor antagonist, antitumour necrosis factor alpha (anti-TNF-α), glucocorticoid and Januskinase (JAK) inhibitors, to treat this cytokine storm. If any of these medications are used during the initial time window of pulmonary involvement, they appear to dampen the inflammation, prevent the 'cytokine storm' and improve clinical outcome.[4]

Patients with antimelanoma differentiation-associated gene 5 (MDA-5) antibody-positive DM are prone to present with life-threatening, rapidly progressive ILD (RP-ILD), contributing to significant mortality. The pathogenesis of this clinical scenario is not fully understood. Given the critical role of MDA-5 in the innate immune defence against viruses by driving the production of large amounts of type I IFN, one hypothesis is that viral infection and subsequent immune response induces the manufacture of anti-MDA-5 antibodies, which in turn leads to RP-ILD.[5] The role of anti-MDA-5 antibody in ILD is supported by the finding that anti-MDA-5 concentrations correlate with RP-ILD activity as well as relapse.[6] The macrophage activation markers, ferritin and IL-18, increased in anti-MDA-5-positive RP-ILD and were associated with severity and poor outcomes. In addition, high-titre soluble macrophage-mannose receptor, sCD206, a serum marker for M2 polarisation, correlated with worse prognosis in this subset of patients.[7] These findings imply that macrophages play an important role in the pathogenesis of RP-ILD. Recent studies further revealed that multiple cytokines were involved in the pathogenesis of RP-ILD, such as IFN-α, interferon-inducible protein-10 (IP-10), IL-6, IL-8, IL-10, IL-15 and TNF-α,[8] in many ways similar to the cytokine storm of COVID-19. Organising pneumonia and non-specific interstitial pneumonia are major patterns of DM-ILD, and lower zone consolidation on HRCT correlated with RP-ILD (also similar to COVID-19 lung involvement). Although no standard treatment regimen for anti-MDA-5 antibody-positive DM-RP-ILD has been established, aggressive combination with high-dose glucocorticoid, calcineurin inhibitors and intravenous cyclophosphamide has been proposed. Plasmapheresis has been used for additional effect in intractable disease.[9] Among the many extrapulmonary manifestations of SARS-CoV-2, myalgia is prominent, although only one acute autoimmune myositis case (confirmed by muscle MRI) induced by SARS-CoV-2 has been described.[10]

The clinical similarities and differences between the two entities are summarised in table 1.

Since the association of muscle inflammation with interstitial pneumonia can be encountered in either COVID-19 or autoimmune myositis, it would be very important to be able to separate these two or three circumstances. One can only speculate as to how to do this, but our suggestions include consideration of the non-pulmonary differences between COVID-19 and DM-RP-ILD. Thus, marked change in creatine kinase (CPK) or swallowing points towards worsening DM. Marked lymphopaenia, anosmia and positive SARS-CoV-2 PCR point to COVID-19. Classic signs of infection such as changing pulmonary infiltrates, marking increase in white blood cell count, urine

Table 1 Comparison of severe COVID-19 pneumonia and anti-MDA-5 antibody-positive DM-RP-ILD

	Severe COVID-19 pneumonia	Anti-MDA5 antibody-positive DM-RP-ILD
Clinical behaviour	Acute.	Rapidly progressive.
Trigger	SARS-CoV-2.	Possible virus infection.
Ethnic and/or geographical differences	All ethnicities are susceptible and vulnerable.	More severe in Asian populations.
Typical rash	No.	Gottron's rash, skin ulceration, palmar papule.
Muscle involvement	Myalgia and myositis.	Amyopathy or hypomyopathy.
Predictive factors	Older age, male sex, comorbidities, high levels of proinflammatory cytokine.	High titre of anti-MAD5 antibody, hyperferritinaemia, high levels of proinflammatory cytokine.
Cytokine/chemokine profile	IL-1, IL-2, IL-6, IL-10, IL-18, IP-10, MCP-1, GM-CSF, IFN-γ, TNF-α.	IL-1β, IL-4, IL-6, IL-8, IL-10, IL-18, IP-10, IFN-α, IFN-γ, TNF-α.
HRCT pattern	GGO, consolidation, AIP.	NSIP, OP.
Treatment		
Glucocorticoid	Possible benefit.	Benefit.
Immunosuppressant	No data.	Benefit.
Anticytokine therapy	Possible benefit.	Benefit.
Antifibrotic agents	No data.	Probable benefit.
Plasmapheresis	Possible benefit	Probable benefit.

AIP, acute interstitial pneumonia; DM-RP-ILD, dermatomyositis-associated rapidly progressive interstitial lung disease; GGO, ground glass opacity; GM-CSF, granulocyte-macrophage colony stimulating factor; HRCT, high-resolution CT; IFN, interferon; IL, interleukin; IP-10, interferon-inducible protein-10; MCP-1, monocyte chemotactic protein-1; MDA-5, melanoma differentiation-associated gene 5; NSIP, non-specific interstitial pneumonia; OP, organising pneumonia; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; ;TNF-α, tumour necrosis factor alpha.

with signs of infection, positive cultures and so on would point to infection. This does not mean one cannot have all of COVID-19, worsening DM and infection, but the above may be hints to help rheumatologists in a difficult position.

In summary, we wish to point out that muscles and lungs are two vulnerable target organs attacked by SARS-CoV-2 and that this virus may worsen MDA-5-related DM-ILD. Thus, rheumatologists need to be particularly vigilant in MDA-5-positive patients with DM-ILD and use all laboratory resources plus good clinical judgement to separate overlapping clinical scenarios.

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Contributors YW wrote the manuscript. GD provided some evidences. GZ, DEF and MM-C revised the manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; internally peer reviewed.

To cite Wang Y, Du G, Zhang G, *et al*. *Ann Rheum Dis* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/annrheumdis-2020-218594

Received 13 July 2020
Revised 18 July 2020
Accepted 20 July 2020

Linked

► http://dx.doi.org/10.1136/annrheumdis-2020-218712

Ann Rheum Dis 2020;**0**:1–2. doi:10.1136/annrheumdis-2020-218594

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