COVID-19 shares clinical features with anti-melanoma differentiation-associated protein 5 positive dermatomyositis and adult Still's disease

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Abstract

Objective

To investigate the similarities and differences between Coronavirus disease 2019 (COVID-19) and autoimmune and autoinflammatory rheumatic diseases characterised by hyperferritinaemia, such as antimelanoma differentiation-associated protein 5 (MDA5) autoantibody-positive dermatomyositis and adult Still's disease.

Methods

We reviewed consecutive, newly diagnosed, untreated patients with COVID-19, anti-MDA5 dermatomyositis, or adult Still's disease. We compared their clinical, laboratory, and radiological characteristics, including the prevalence of macrophage activation syndrome and lung involvement in each disease.

Results

The numbers of patients with COVID-19, anti-MDA5 dermatomyositis, and adult-onset Still's disease with hyperferritinaemia (serum ferritin ≥500ng/dL) who were included for main analysis were 22, 14, and 59, respectively. COVID-19 and adult Still's disease both featured hyperinflammatory status, such as high fever and elevated serum C-reactive protein, whereas COVID-19 and anti-MDA5 dermatomyositis both presented with severe interstitial lung disease and hypoxaemia. While two-thirds of the patients in each group met the criteria for macrophage-activated syndrome that is used in systemic juvenile idiopathic arthritis, the HScore, an indicator of haemophagocytic lymphohistiocytosis, was low in anti-MDA5 dermatomyositis and COVID-19 even in severe or critical cases. The findings of chest computed tomography were similar between COVID-19 and anti-MDA5 dermatomyositis.

Conclusion

COVID-19 shared clinical features with rheumatic diseases characterised by hyperferritinaemia, including anti-MDA5 dermatomyositis and adult Still's disease. These findings should be investigated further in order to shed light on the pathogenesis of not only COVID-19 but also the aforementioned rheumatic diseases.

Key words

COVID-19, macrophage activation, dermatomyositis, interstitial lung disease, adult Still's disease

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Introduction

The coronavirus disease 2019 (COVID-19), caused by a novel corona virus named SARS-CoV-2, has emerged as a global pandemic (1, 2). Infected patients typically present with fever and respiratory symptoms in addition to showing interstitial inflammation upon computed tomography (CT) scanning (3, 4). The associated pneumonia tends to progress with a remarkable speed, leading to diffuse alveolar damage or acute respiratory distress syndrome via hyperinflammation. Intensive care and mechanical ventilation are sometimes required. An effective treatment method has not yet been established for COVID-19, although the efficacy of short-term high-dose glucocorticoids has recently been reported (5-7). At present, the main pathogenesis of severe inflammation and organ damage in patients with COVID-19 is thought to be not only the virus itself but also the hyper-inflammatory response of the host. These inflammatory process caused by SARS-CoV-2 infection involves cytokine storm along with overactivation of macrophage (8, 9). Indeed, a significant increase in inflammatory cytokines including both adaptive and innate immune cytokines such as interleukin (IL)-1β, IL-6, IL-8 and IL-18 from helper T cells or non-classical monocytes has been found in patients with COVID-19 (10-14).

On another front, cytokine storm with macrophage activation are frequently observed in various connective tissue diseases. Dermatomyositis with positive antimelanoma differentiation-associated protein 5 (anti-MDA5) autoantibodies and adult Still's disease are representative diseases that involves overactivated macrophages in their pathogenesis (15-19). Macrophage activation during inflammatory states are partially characterised by an increased serum ferritin levels (18), and both anti-MDA5 dermatomyositis and adult Still's disease present with hyperferritinaemia that reflects disease activity (15-17), which has been also increasingly reported in COVID-19 (20, 21). Furthermore, anti-MDA5-positive dermatomyositis can be complicated with fatal progressive interstitial lung disease similar to COVID-19 (22, 23), and the main features of adult Still's disease such as persistent high fever and the increase in acute phase reactants is observed in severe COVID-19 (19-21). Hyperferritinaemia and characteristics shared by the three diseases are a topic of interest to rheumatologists, however, no study has evaluated anti-MDA5-positive dermatomyositis and adult Still's disease in comparison to COVID-19 (19-23).

The aim of this study was to highlight the homology and heterogeneity of COVID-19, anti-MDA5 dermatomyositis, and adult Still's disease by comparing clinical pictures of each disease in order to discuss their respective pathogeneses.

Materials and methods

Patients

We retrospectively reviewed consecutive, newly diagnosed, untreated patients with COVID-19, anti-MDA5-positive dermatomyositis, and adult Still's disease at Keio University Hospital from April 2012 to June 2020. All of the patients with COVID-19 were found positive for SARS-CoV-2 using reverse transcription polymerase chain reaction testing, and abnormal shadowing was detected during chest CT scanning. Patients with classical or clinically amyopathic dermatomyositis were diagnosed according to the classification criteria proposed by Bohan and Peter (24) or Sontheimer (25), respectively. We measured the levels of anti-MDA5 antibodies in the patients with dermatomyositis using an enzyme-linked immunosorbent assay with recombinant MDA5 as an antigen source (26). Patients with adult Still's disease were diagnosed according to Yamaguchi's criteria (27). Interstitial lung disease was assessed based on the criteria established by the American Thoracic Society as well as a multidisciplinary assessment involving clinical, radiological, and pathological findings (28) This study was approved by the Ethics Committee of Keio University School of Medicine, and obtaining written informed consent was waived according to the Japanese regulations.

Data collection

Clinical and laboratory data were obtained from the patients' medical records. The presence of symptoms and organ involvement therein were evaluated during the clinical course. The laboratory data used in the analysis were the maximum values obtained within 14 days of being diagnosed with one of the three diseases. The images were independently assessed by an experienced rheumatologist and pulmonologist who were blind to the patients' clinical information, and their disagreements were discussed and appropriately adjusted.

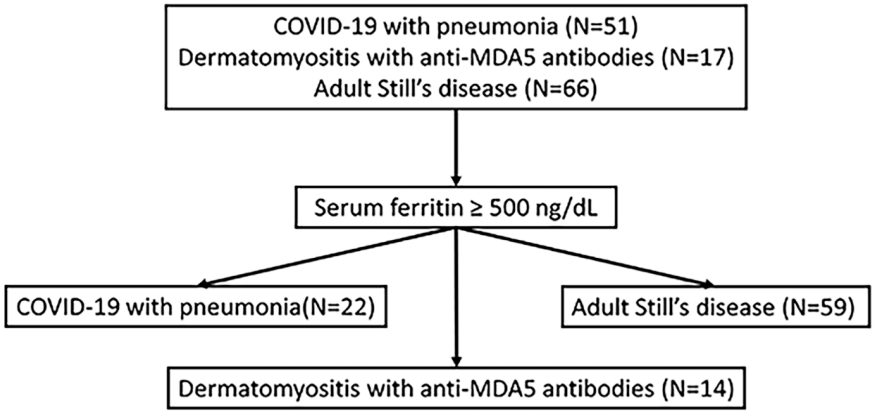

Fig. 1. Patient's flow of this study
A total of 22 patients with COVID-19, 14 with anti-MDA5-positive dermatomyositis, and 59 with adult-onset Still's disease with hyperferritinaemia were included in the analysis.

Definition

The severity of COVID-19 was categorised according to previous studies; severe COVID-19 was defined as the presence of dyspnoea, respiratory frequency ≥30/min, blood oxygen saturation ≤93%, partial pressure of arterial oxygen to fraction of inspired oxygen ratio <300, or lung infiltrates >50% within 24 to 48 hours. Critical cases were defined as the presence of respiratory failure, septic shock, or multiple organ dysfunction or failure (29, 30). Hyperferritinaemia was defined as a serum ferritin level ≥500ng/dL, using hemophagocytic lymphohistiocytosis as a reference (31). The patients' HScores were calculated according to a previously reported definition for the diagnosis of reactive haemophagocytic syndrome (32).

Statistical analysis

All statistical analyses were performed using the JMP 13 software (SAS Institute Inc., Cary NC, USA). Continuous data have been presented as the mean with standard deviation (SD) or median with interquartile range (IQR). Categorical data were compared using the Fisher's exact or Wilcoxon signed-rank test, as appropriate. Analysis of variance was used to compare the continuous data in the three groups, after which the Kruskal-Wallis test was used. The predictive accuracy was estimated using a receiver-operating characteristic curve with an area under the curve. A *p*-value of <0.05 was deemed to be statistically significant.

Results

Demographic and clinical characteristics

The numbers of patients with COVID-19, anti-MDA5-positive dermatomyositis, and adult-onset Still's disease in our hospital were 51, 17, and 66, respectively (one patient with COVID-19 with bacterial pneumonia was excluded). The demographics and clinical characteristics of all patients are shown in Supplementary Table S1. Of the patients, hyperferritinaemia (serum ferritin ≥500ng/dL) was observed in 22 COVID-19 patients (43%), 14 anti-MDA5 dermatomyositis patients (82%), and 59 adult Still's disease patients (89%) (Fig. 1). We compared disease severity and manifestations between patients with high serum ferritin levels (≥500 ng/ml) and those with low levels (<,500 ng/ml) in each three disease (Suppl. Table S2). Mostly, patients with ferritin levels ≥500 ng/ml were severer than those without.

The demographics and clinical characteristics of the patients with hyperferritinaemia are summarised in Table I. COVID-19 was male-dominant, anti-MDA5 dermatomyositis was equally distributed in terms of sex, and adult Still's disease was female-dominant. High fever was more frequently observed in patients with COVID-19 (86.4%) and adult Still's disease (76.2%) than in those with anti-MDA5 dermatomyositis (21.4%, $p<0.01$) Hypoxaemia had a higher incidence in patients with COVID-19 (86.4%) and anti-MDA5 dermatomyositis (71.4%) than in those with adult Still's disease (3.3%, $p<0.01$), reflecting lung involvement (100% *vs*. 100% *vs*. 21.5%, respectively, $p<0.01$). Rash and arthralgia were more frequent in patients with anti-MDA5 dermatomyositis and adult Still's disease than in those with COVID-19 (rash, 100% *vs*. 91.5% *vs*. 9.1%, $p<0.01$; arthralgia, 64.3% *vs*. 72.5% *vs*. 13.7%, respectively). Lymphadenopathy, hepatosplenomegaly, or both were found to be characteristic of adult Still's disease (72.9%), while thrombosis mostly occurred in COVID-19 patients (18.1%).

The laboratory findings have also been presented in Table I. We observed a decrease in lymphocytes in COVID-19 (507/μL) patients and an increase in neutrocytes in adult Still's disease (13768/μL) patients, the result of which was an increase in the neutrophil-lymphocyte ratios of both diseases (8.8 *vs*. 14.2, respectively). The platelet count was lower in the COVID-19 patients ($15.3x10^4$/μL) than in the anti-MDA5 dermatomyositis ($21.6x10^4$/μL) or adult Still's disease patients ($20.0x10^4$/μL, $p=0.04$). The D-dimer level was significantly higher in adult Still's disease patients (12.3 mg/dL) than in COVID-19 (5.3 mg/dL) or anti-MDA5 dermatomyositis patients (1.9 mg/dL, $p<0.01$). The serum C-reactive protein (CRP) levels were significantly higher in the patients with COVID-19 (10.8 mg/dL) and adult Still's disease (9.2 mg/dL) than in those with anti-MDA5 dermatomyositis (1.2 mg/dL, $p<0.01$). The serum ferritin levels were much higher in the

Table I. Patient demographics and clinical characteristics with hyperferritinaemia.

Variables	COVID-19 n=22	Anti-MDA5 dermatomyositis n=14	Adult Still's disease n=59	*p*-value			
				For three	COVID-19 *vs.* Dermato-myositis	COVID-19 *vs.* Adult Still's disease	Dermato-myositis *vs.* Adult Still's disease
Demographics							
Female, n (%)	2 (9.1%)	9 (64.3%)	48 (81.3%)	<0.01*	0.02*	<0.01*	0.21
Age	59.8 ± 14.2	56.1 ± 13.3	45.7 ± 18.9	<0.01*	0.54	<0.01*	0.04*
Died in hospital	2 (9.1%)	4 (28.6%)	0 (0%)	<0.01*	0.12	0.02*	<0.01*
Symptoms							
Fever (>37.5ºC), n (%)	22 (100%)	4 (35.7%)	58 (98.4%)	<0.01*	<0.01*	0.95	<0.01*
Fever (>38.5ºC), n (%)	19 (86.4%)	3 (21.4%)	45 (76.2%)	<0.01*	<0.01*	0.53	<0.01*
Hypoxaemia (SpO2 ≤93% on room air), n (%)	19 (86.4%)	10 (71.4%)	2 (3.3%)	<0.01*	0.64	<0.01*	<0.01*
Rash, n (%)	2 (9.1%)	14 (100%)	54 (91.5%)	<0.01*	<0.01*	<0.01*	0.88
Arthralgia, n (%)	3 (13.7%)	9 (64.3%)	44 (74.5%)				
Lymphadenopathy/ hepatosplenomegaly, n (%)	3 (13.7%)	3 (21.4%)	43 (72.9%)	<0.01*	0.41	<0.01*	<0.01*
Lung involvement, n (%)	22 (100%)	14 (100%)	8 (21.1%, n=38)	<0.01*	NA	<0.01*	<0.01*
Thrombosis, n (%)	4 (18.1%)	1 (7.1%)	1 (1.7%)	0.03*	0.35	0.01*	0.26
Laboratory findings							
White blood cell (/μL)	5250 (3900-7025)	4650 (3725-7125)	16400 (11100-19300)	<0.01*	0.81	<0.01*	<0.01*
Neutrophil (/μL)	3997 (2741-5807)	3301 (2760-5953)	13768 (9448-16622)	<0.01*	0.78	<0.01*	<0.01*
Lymphocyte (/μL)	507 (249-1018)	713 (370-968)	882 (556-1242)	0.04*	0.76	0.02*	0.12
Neutrophil/Lymphocyte ratio	8.8 (4.7-30.2)	5.6 (3.2-16.4)	14.2 (8.3-23.1)	0.02*	0.47	0.07	0.02*
Platelets (x10^4/μL)	15.3 (9.3-22.9)	21.6 (15.8-29.0)	20.0 (13.8-24.4)	0.04*	0.03*	0.04*	0.32
Fibrinogen (mg/dL)	526 (443-584)	412 (309-591)	551 (394-705)	<0.01*	<0.01*	0.56	<0.01*
D-dimer (mg/dL)	5.3 (1.1-17.0)	1.9 (1.0-3.9)	12.3 (3.3-24.1)	0.03*	0.12	0.27	<0.01*
LDH (U/L)	401 (274-510)	433 (313-694)	566 (409-792)	0.07			
AST (U/L)	59 (39.5-119)	57 (45.5-123)	87 (58-173)	0.11			
CPK (IU/L)	53 (40-75)	113 (72.5-371)	39 (26-82)	<0.01*	0.04*	0.06	<0.01*
CRP (mg/dL)	10.8 (6.8-18.6)	1.2 (0.3-2.1)	9.2 (4.7-17.1)	<0.01*	<0.01*	0.31	<0.01*
Ferritin (ng/mL)	1232 (780-2049)	1711 (967-3268)	8107 (3293-29850)	< 0.01*	0.17	<0.01*	0.01*
IgG (mg/dL)	1117 (985-1217)	1322 (1119-1516)	1340 (1084-1609)	<0.01*	<0.01*	<0.01*	0.83
Triglycerides (mg/dL)	123 (85-162)	174 (135-191)	123 (99-195)	0.21			
KL-6 (U/dL)	279 (229-526)	566 (433-924)	233 (177-318, n=34)	<0.01*	<0.01*	0.02*	<0.01*
Antinuclear antibody, n (%)	2 (15.4%, n=13)	3 (21.4%)	6 (10.2%)	0.65			
Rheumatoid factor, n (%)	1 (10.0%, n=10)	2 (15.3%, n=13)	3 (5.2%, n=57)	0.51			
Antiphospholipid antibody, n (%)	3 (20.0%, n=15)	3 (23.1%, n=13)	2 (5.1%, n=37)	0.22			
Anti-cardiolipin antibody, n (%)	0 (0%, n=15)	3 (23.1%, n=13)	2 (5.1%, n=37)	0.77			
Lupus anticoagulant, n (%)	3 (20.0%, n=15)	0 (0%, n=10)	0 (0%, n=22)	0.03*	0.15	0.02*	NA

Values are mean ± SD or median (IQR) unless otherwise specified.
COVID-19: Coronavirus disease 2019; MDA: melanoma differentiation-associated protein 5: LDH: lactate dehydrogenase; AST: aspartate aminotransferase; ALT: alanine aminotransferase; CRP: C-reactive protein; KL-6: Krebs von den Lungen-6 (sialylated carbohydrate antigen).

patients with adult Still's disease (8107 ng/mL) than in those with COVID-19 (1232 ng/mL) or anti-MDA5 dermatomyositis (1711 ng/mL, $p<0.01$), while serum IgG levels were slightly lower in adult Still's disease patients (1117 mg/dL) than in COVID-19 (1322 mg/dL) or anti-MDA5 dermatomyositis patients (1340 mg/dL, $p<0.01$).

Fulfilment of macrophage activation syndrome and secondary haemophagocytic lymphohistiocytosis criteria

We investigated the fulfilment of the criteria for macrophage activation syndrome or haemophagocytic lymphohistiocytosis in the diseases (Table II). The most recent classification criteria for systemic juvenile idiopathic arthritis, a paediatric disease known to be complicated with macrophage activation syndrome in many cases, have been proposed by the European League Against Rheumatism/American College of Rheumatology/Paediatric Rheumatology International Trials Organization (33). These criteria were fulfilled by 63.6% of patients with COVID-19, 71.4% of those with anti-MDA5 dermatomyositis, and 67.8% of those with adult Still's disease ($p=0.47$). When we focused on the patients who fulfilled the macrophage activation syndrome criteria, the difference in demographics and clinical characteristics between the three diseases remained almost the same (Suppl. Table S3).

However, the 2004 HLH criteria were fulfilled by none of the patients with COVID-19 and anti-MDA5 dermatomyositis and only by 6.8% of those with adult Still's disease. Furthermore, The HScore, an equation proposed for the diagnosis of secondary haemophagocytic lymphohistiocytosis, was 85.0 in the COVID-19 group, 76.5 in the anti-MDA5 dermatomyositis group, and 132.2 in the adult Still's disease group

Table II. Fulfilment of various criteria for macrophage activation syndrome and secondary haemophagocytic lymphohistiocytosis in patients with hyperferritinaemia.

Criteria	COVID-19 n=22	Anti-MDA5 dermatomyositis n=14	Adult Still's disease n=59	*p*-value			
				For three	COVID-19 *vs.* Dermato-myositis	COVID-19 *vs.* Adult Still's disease	Dermato-myositis *vs.* Adult Still's disease
EULAR/ACR/PRINTO criteria for MAS	14 (63.6%)	10 (71.4%)	40 (67.8%)	0.47			
HScore	85.0 ± 33.1	76.5 ± 31.5	132.2 ± 47.4	<0.01*	0.55	<0.01*	<0.01*
HScore >169	1 (4.5%)	0 (0%)	11 (18.6%)	0.02*	0.71	0.03*	0.02*
2004 HLH criteria	0 (0%)	0 (0%)	4 (6.8%)	0.28			

COVID-19: Coronavirus disease 2019; MDA: melanoma differentiation-associated protein 5; EULAR/ACR/PRINTO criteria for MAS 2016 European League Against Rheumatism/American College of Rheumatology/Paediatric Rheumatology International Trials Organisation classification criteria for macrophage activation syndrome; HLH: haemophagocytic lymphohistiocytosis.

Table III. Chest CT findings in patients with hyperferritinaemia.

CT findings	COVID-19 n=22	Anti-MDA5 dermatomyositis n=14	Adult Still's disease n=38	*p*-value			
				For three	COVID-19 *vs.* Dermato-myositis	COVID-19 *vs.* Adult Still's disease	Dermato-myositis *vs.* Adult Still's disease
Bilateral ground glass Opacity	20 (90.9%)	13 (92.9%)	3 (7.9%)	<0.01*	0.91	<0.01*	<0.01*
Consolidation	15 (68.1%)	8 (57.1%)	1 (12.5%)	<0.01*	0.85	<0.01*	<0.01*
Shrinking lung	13 (59%)	7 (50%)	0 (0%)	<0.01*	0.88	<0.01*	<0.01*
Subpleural curvilinear line	7 (35.7%)	6 (42.8%)	2 (5.2%)	0.04*	0.9	0.03*	0.04*
Diffuse alveolar damage	6 (27.3%)	4 (28.5%)	0 (0%)	<0.01*	0.78	<0.01*	<0.01*
Pulmonary thromboembolism	1 (4.5%)	1 (7.1%)	0 (0%)	0.9			
Pleural effusion	0 (0%)	0 (0%)	8 (21.1%)	<0.01*	NA	<0.01*	<0.01*

CT: computed tomography; COVID-19: Coronavirus disease 2019; MDA: melanoma differentiation associated protein.

(p<0.01, Table II). The proportion of patients whose HScore >169, which considered to be a potential indicator of haemophagocytic lymphohistiocytosis, was only 4.5% in the COVID-19 group, 0% in the anti-MDA5 dermatomyositis group, and 18.6% in the adult Still's disease group. In 19 of the patients with severe and critical COVID-19 (8 were critical cases), the mean HScore was found to be 96.5. The receiver-operating characteristic curve revealed that an HScore classified severe COVID-19 with a cut-off of 68 (area under the curve 0.77, sensitivity 79%, specificity 75%) and critical COVID-19 with a cut-off of 92 (area under the curve 0.84, sensitivity 88%, specificity 76%).

CT findings in the lungs

The findings of the chest CT scan are summarised in Table III, including bilateral random ground-glass opacities, consolidations, subpleural curvilinear line, diffuse alveolar damage, shrinking lung, pulmonary thromboembolism, and pleural effusion. The characteristics of these findings were very similar between the COVID-19 and anti-MDA5 dermatomyositis patients, except for pulmonary embolism, which was only found in COVID-19. Shrinking lungs were found in 59% of COVID-19 cases and 50% of anti-MDA5 dermatomyositis cases. Pleural effusion was the main chest CT finding in patients with adult Still's disease. (Fig. 2A-B-C).

Discussion

This study discusses the similarities and differences in clinical and laboratory features between COVID-19 and rheumatic diseases characterised by hyperferritinaemia, including anti-MDA5 autoantibody-positive dermatomyositis and adult Still's disease. The associations of the three diseases in terms of the involved organs and laboratory findings are depicted in figures 3A and 3B. The clinical pictures of lung involvement in COVID-19 were similar to those of pneumonitis complicated with anti-MDA5 dermatomyositis, and hyperinflammation was present in both COVID-19 and adult Still's disease.

The pathogeneses of these three diseases are partly common with regard to macrophage activation. On a cellular level, macrophages act as a major iron sink by directly phagocytising senescent red blood cells and secrete ferritin in accordance with their activation, resulting in an increase in serum ferritin levels (34). Significant macrophage activation can occur in various conditions such as hereditary diseases, sepsis, and other rheumatic diseases including catastrophic antiphospholipid syndrome, systemic lupus erythematosus, systemic juvenile idiopathic arthritis, and Kawasaki disease, all of which involve extremely elevated levels of inflammatory cytokines such as tumour necrosis factor-α, interferon-γ, IL1-β, and IL-6 with hyperferritinae-

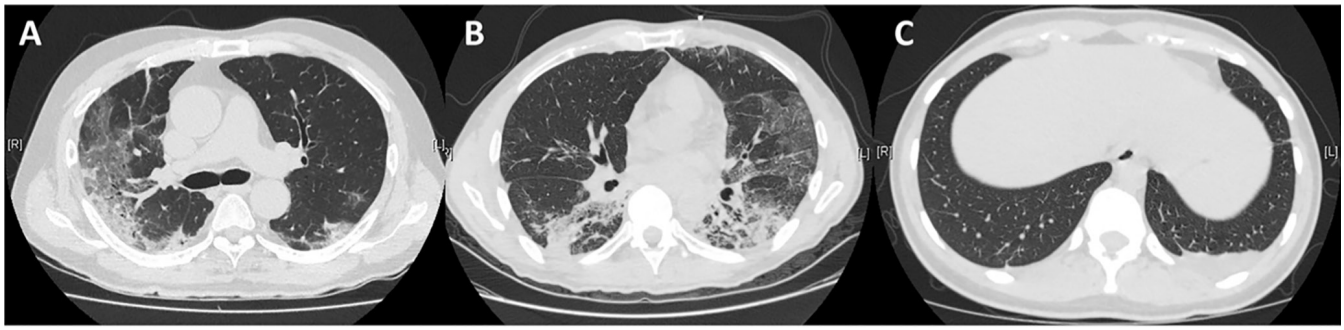

Fig. 2. Imaging characteristics of chest CT scans in patients with COVID-19, anti-MDA5 dermatomyositis, and adult Still's disease.
A: Bilateral ground-glass and consolidative opacities with peripheral distribution in COVID-19.
B: Bilateral ground-glass opacities with peripheral consolidations in anti-MDA5 dermatomyositis.
C: Pleural effusion with pleural thickening on the left side in adult Still's disease.

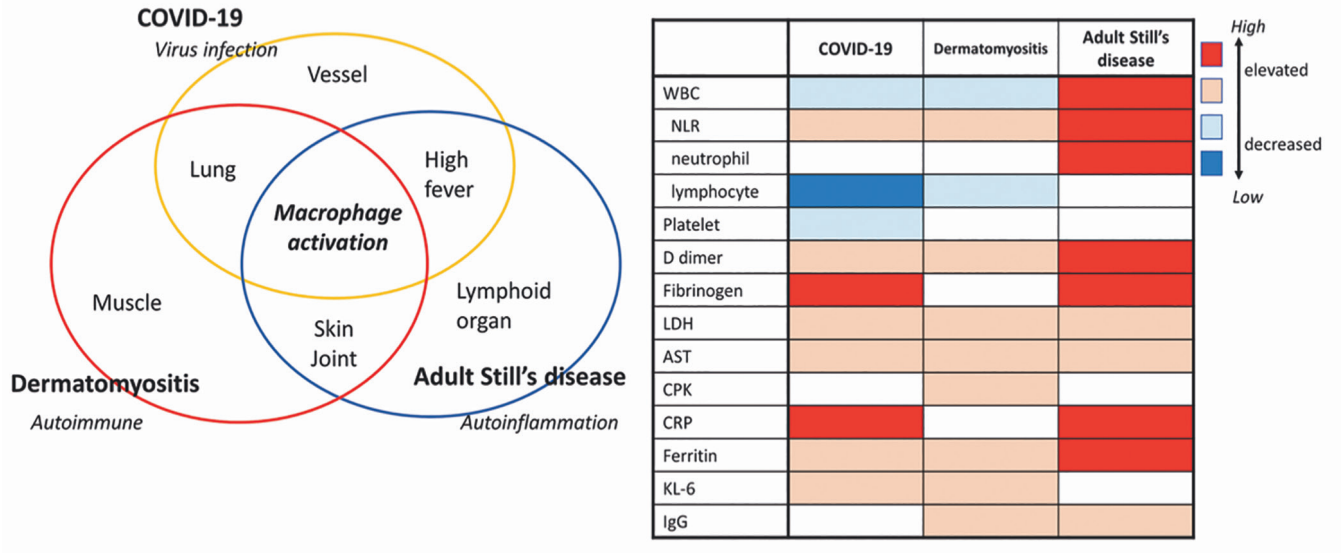

Fig. 3. The associations of the three diseases in the involved organs and laboratory findings.
A: The main affected organs in COVID-19, anti-MDA5 dermatomyositis, and adult Still's disease. COVID-19 and adult Still's disease had hyperinflammatory status, high fever, and serum inflammation markers in common, whereas COVID-19 and anti-MDA5 dermatomyositis both included severe interstitial lung disease along with similar findings observed during computed tomography.
B: Summary of changes in laboratory test results in the three diseases.

mia (18, 35). However, catastrophic antiphospholipid syndrome is very rare, and systemic lupus erythematosus with hyperferritinaemia due to macrophage activation syndrome is also infrequent and heterogeneous pathologically and clinically. Systemic juvenile idiopathic arthritis and Kawasaki disease are paediatric diseases. Therefore, we focused on anti-MDA5 dermatomyositis and adult Still's disease which are frequently related with hyperferritinaemia due to macrophage activation (15-17). The current study has shown that the criteria for macrophage activated syndrome for systemic juvenile idiopathic arthritis were fulfilled by approximately two-thirds of the patients in each disease.

We highlighted that COVID-19 and adult Still's disease both featured hyperinflammatory status such as high fever and CRP levels, although, the serum ferritin levels and the development of haemophagocytic lymphohistiocytosis were much higher in the adult Still's disease group than in the COVID-19 group. While macrophage activation syndrome is considered to be synonymous with haemophagocytic lymphohistiocytosis (36), only one of the COVID-19 patients had an HScore more than 169. Similarly, a previous study reported that only 7.5% of the patients with critical COVID-19 who were admitted to the intensive care unit had an HScore >169 (37). Furthermore, our study identified that severe or critical COVID-19 could be classified with an HScore of as low as 68 or 92, respectively. The possible explanation is that the epicentre of the COVID-19 is primarily localised to the lungs, whereas the inflammation in adult Still's disease occurs in the systemic reticuloendothelial system through IL-1β downstream inflammasome activation and dysfunctional regulation (38, 39). Additionally, this could be partly due to the nature of the HScore, as it was derived from observations in patients with haematological malignancies and bacterial infections (32).

We demonstrated that the clinical and radiological features of the lungs were very similar between COVID-19 and anti-MDA5 dermatomyositis (40, 41). Actually, bilateral ground glass opacity

and consolidation, typical radiological features of COVID-19, also appear in other connective tissue disease associated interstitial lung disease (CTD-ILD) than anti-MDA5 dermatomyositis (42, 43). However, the interstitial lung disease of anti-MDA5 dermatomyositis is distinct from other CTD-ILDs; firstly, serum ferritin levels are associated with its prognosis (15-17), second, random interstitial opacities or consolidations located under the pleura tend to be folded and shrink during recovery (40, 41). These characteristics are common with COVID-19 pneumonia. Additionally, there are several studies that could provide clues to identify the commonality of the pathological processes of these two diseases. MDA5, the corresponding antigen of anti-MDA5 antibodies, is an intracellular pattern recognition receptor for viral ribonucleic acid that activates the innate immune response and induces type I interferon signatures that are associated with biological defence (21, 22, 44-46). SARS-CoV-2 is a coronavirus consisting of a single ribonucleic acid that can be recognised by MDA5, suggesting that activation of the pulmonary reticuloendothelial system in COVID-19 is triggered through MDA5. The efficacy of glucocorticoids in severe COVID-19 has also suggested that COVID-19 is not merely infectious pneumonia but is associated with an excessive inflammatory response (5, 47). However, the difference between the two diseases is the tendency of COVID-19 to induce thrombogenesis. SARS-CoV-2 primarily infects the host via the respiratory system, leading to viraemia and the injury of peripheral vascular endothelial tissues, and its substantial damage may develop microthrombosis (48-50). Meanwhile, anti-MDA5-positive dermatomyositis is associated with autoantibodies and autoreactive lymphocytes spreading throughout the body via blood flow. The aforementioned commonalities and differences should be investigated further in order to shed light on these diseases and their respective pathogeneses.

Since COVID-19 develops various clinical symptoms and production of autoantibodies, its pathogenesis and clinical features can be shared with many rheumatic diseases other than anti-MDA5 dermatomyositis and adult Still's disease. Pro-inflammatory cytokine profiles of COVID-19 are largely common with rheumatoid arthritis, and treatment drugs for rheumatoid arthritis such IL-6 inhibitors and Janus kinase inhibitors are shown to be beneficial for COVID-19 (51). COVID-19 triggers production of various autoantibodies including antiphospholipid antibodies and type-1 interferon (52, 53), and exacerbation of pre-existing autoimmune diseases have been also reported (54). The relationship of COVID-19 and its effect on immunoregulatory disturbances is similar with virus-associated vasculitis characterised by an initial viral infection that induces a dysregulation of the immune response which in turn is responsible for tissue damages (55). Additionally, both COVID-19 and anti-neutrophil cytoplasmic antibody associated vasculitis are associated with formation of neutrophil extracellular traps, suggesting close relationship between autoimmunity and acute viral infection (56-58). While we focused on anti-MDA positive dermatomyositis and adult Still's disease to compare with COVID-19 in our study, clinical and serological features of COVID-19 are shared with other autoimmune/autoinflammatory disorders. The commonality can be a spectrum and should be investigated in future.

Our study had some limitations. First, this was a retrospective study with a small sample size. As all three diseases are relatively rare, multicentred cohort studies are needed to minimise bias. Second, we did not measure serum cytokines, which could have helped to elucidate the proinflammatory patterns of these diseases. Third, we measured anti-MDA5 antibodies in only two patients with severe COVID-19 (both negative). These limitations should be addressed in future studies.

In conclusion, our study revealed that COVID-19 have several clinical features in common with autoimmune or autoinflammatory rheumatic diseases accompanied by hyperferritinaemia, including anti-MDA5 dermatomyositis and adult Still's disease. These similarities and differences should be investigated further in future studies in order to understand the pathogenic mechanisms of not only COVID-19 but also rheumatic diseases, thereby enabling the establishment of an optimal treatment method.

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