CLINICAL SCIENCE

Lung involvement in macrophage activation syndrome and severe COVID-19: results from a cross-sectional study to assess clinical, laboratory and artificial intelligence–radiological differences

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ABSTRACT

Objectives To evaluate the clinical pictures, laboratory tests and imaging of patients with lung involvement, either from severe COVID-19 or macrophage activation syndrome (MAS), in order to assess how similar these two diseases are.

Methods The present work has been designed as a cross-sectional single-centre study to compare characteristics of patients with lung involvement either from MAS or severe COVID-19. Chest CT scans were assessed by using an artificial intelligence (AI)-based software.

Results Ten patients with MAS and 47 patients with severe COVID-19 with lung involvement were assessed. Although all patients showed fever and dyspnoea, patients with MAS were characterised by thrombocytopaenia, whereas patients with severe COVID-19 were characterised by lymphopaenia and neutrophilia. Higher values of H-score characterised patients with MAS when compared with severe COVID-19. AI-reconstructed images of chest CT scan showed that apical, basal, peripheral and bilateral distributions of ground-glass opacities (GGOs), as well as apical consolidations, were more represented in severe COVID-19 than in MAS. C reactive protein directly correlated with GGOs extension in both diseases. Furthermore, lymphopaenia inversely correlated with GGOs extension in severe COVID-19.

Conclusions Our data could suggest laboratory and radiological differences between MAS and severe COVID-19, paving the way for further hypotheses to be investigated in future confirmatory studies.

Key messages

What is already known about this subject?

- Severe COVID-19 and macrophage activation syndrome (MAS) are challenging disorders characterised by overlapping clinical pictures, and it is still matter of debate if severe COVID-19 is part or not of the haemophagocytic lymphohistiocytosis spectrum.

What does this study add?

- Although all patients showed fever and dyspnoea, MAS patients were characterised by thrombocytopaenia and higher H-score, whereas severe COVID-19 patients were characterised by lymphopaenia and neutrophilia.
- Artificial intelligence (AI)-reconstructed images of chest CT scan showed that apical, basal, peripheral and bilateral distributions of GGOs, as well as apical consolidations, were more represented in severe COVID-19 than in MAS.
- C reactive protein directly correlated with GGOs extension in both diseases, whereas lymphopaenia inversely correlated with GGOs extension in severe COVID-19.

How might this impact on clinical practice or future developments?

- Laboratory and AI–radiological differences have been shown between MAS and severe COVID-19, thus helping physicians to differentiate these patients in spite of overlapping clinical pictures.

INTRODUCTION

The COVID-19 pandemic has brought attention to a virally induced hyperinflammatory lung injury, sometimes evolving to multiple-organ failure and death.[1] This finding mirrors what has been observed in macrophage activation syndrome (MAS),[2 3] a secondary form of haemophagocytic lymphohistiocytosis (HLH), complicating rheumatic diseases, mostly adult-onset Still's disease (AOSD), rapidly evolving into multiple-organ failure and death in a large percentage of patients.[4 5] Recently, during AOSD and its juvenile counterpart, pulmonary involvement has been strictly associated with MAS and poor outcome.[3 6 7] Thus, the analysis of chest CT associated with artificial intelligence (AI) tools may be of crucial importance to assess these patients.[8 9]

A scientific debate is being raised about the possibility that severe COVID-19 may be considered part of the HLH spectrum due to overlapping clinical features.[1 10 11] To assess how similar these two diseases are, we evaluated the clinical pictures,

laboratory tests and AI imaging of patients with lung involvement, either from COVID-19 or MAS. Finally, we correlated the specific laboratory abnormalities observed in our patients with the extension of lung involvement.

PATIENTS AND METHODS

Study design, setting and patients

The present work has been designed as a cross-sectional single-centre study to compare clinical, laboratory and AI–radiological findings between patients with lung involvement either from MAS or severe COVID-19. Patients with MAS, diagnosed by previous criteria,[12] were retrospectively selected from our database. Their underlying disease was AOSD, diagnosed according to Yamaguchi criteria,[13] without documented lung involvement, and treated with glucocorticoids, 0.2–0.3 mg/kg/day of prednisone equivalent and non-steroidal anti-inflammatory drugs, on-demand, during acute flares. MAS was triggered in all patients by a new acute AOSD flare, in the context of a polycyclic disease pattern.[14] Patients with MAS were matched with consecutive patients with severe COVID-19 attending our institution and admitted to intensive or subintensive care units (online supplementary figure S1 and table S1). All patients with severe COVID-19 showed severe acute respiratory syndrome coronavirus 2 infection confirmed by reverse transcriptase-polymerase chain reaction (RT-PCR). Pulmonary and other infections were excluded in both groups by a specific diagnostic workup including blood cultures, bone marrow cultures, serology, RT-PCR analyses, chest X-rays, chest CT scan, and heart and abdominal echographies. All data were collected before starting any immunosuppressive therapy for MAS or severe COVID-19. Informed consent was obtained from each patient for the use of clinical and laboratory data for study purposes. In reporting the results, we followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (online supplementary table S2).

Table 1 Laboratory findings in patients with MAS and COVID-19

Laboratory findings	MAS	COVID-19	P value
CRP, mean±SD (mg/L)	129.74±26.58	111.937±14.24	0.564
Ferritin, mean±SD (ng/mL)	4888.83±1131.49	1207.17±171.66	**0.010**
Red blood cells, mean±SD (10^3/mL)	4.01±0.28	4.58±0.23	0.092
Haemoglobin, mean±SD, (g/dL)	9.5±1.8	12.5±2.1	**<0.0001**
Platelets, mean±SD (10^9/L)	121.90±36.34	254.53±19.51	**0.043**
Neutrophils, mean±SD (10^3/mL)	4.08±0.55	8.98±2.32	**0.044**
Lymphocytes, mean±SD (10^3/mL)	2.61±0.58	1.02±0.09	**0.005**
Monocytes, mean±SD (10^3/mL)	0.32±0.09	0.55±0.05	0.063
D-dimer>4 ng/mL, n (%)	4 (40%)	10 (21.27%)	0.076
D-dimer, mean±SD (ng/mL)	3.2±0.9	2.9±1.4	0.069
Fibrinogen, mean±SD (mg/dL)	386.6±121.4	533.4±177.9	**0.031**
aPTT, mean±SD (s)	37.7±2.2	33.8±4.9	**0.020**
INR, mean±SD	1.7±1.1	1.2±0.5	0.206
AST, mean±SD, IU/L	148.8±75.2	34.7±13.1	**0.002**
ALT, mean±SD (IU/L)	178.9±77.4	42.4±14.8	**0.001**
CK, mean±SD (IU/L)	105.2±58.9	133.3±51.9	0.605
Albumin, mean±SD (g/dL)	2.97±0.7	3.25±0.8	0.351
BNP, mean±SD (pg/mL)	100.9±40.1	170.3±65.2	0.585
Troponin I, mean±SD (ng/L)	11.8±3.2	24.11±11.9	0.164

Bolded values indicate statistically significant results.
ALT, alanine aminotransferase; aPTT, activated partial thromboplastin time; AST, aspartate aminotransferase; BNP, brain natriuretic peptide; CK, creatine kinase; COVID-19, coronavirus disease 2019; CRP, C reactive protein; INR, international normalised ratio; MAS, macrophage activation syndrome.

Table 2 Chest CT scan findings in patients with MAS and COVID-19

Chest CT scan findings	MAS	COVID-19	P value
GGOs, n (%)	6 (60)	47 (100)	**0.028**
Apical, n (%)	3 (30)	31 (65.6)	**0.006**
Middle, n (%)	6 (60)	42 (89.3)	0.149
Basal, n (%)	5 (50)	45 (95.7)	**0.022**
Bilateral, n (%)	5 (50)	46 (97.8)	**0.009**
Peripheral, n (%)	5 (50)	45 (95.7)	**0.014**
Extension of GGOs, mean±SD (cm^3)	1295.96±572.36	1529.80±448.13	0.336
Extension of GGOs, mean±SD (%)	39.39±16.19	35.80±12.59	0.561
Parenchymal consolidation, n (%)	8 (80)	29 (61.7)	0.399
Apical, n (%)	0 (0)	11 (23.4)	**0.005**
Middle, n (%)	6 (60)	19 (40.4)	0.429
Basal, n (%)	7 (70)	23 (48.3)	0.355
Bilateral, n (%)	4 (40)	23 (48.3)	0.867
Peripheral, n (%)	2 (20)	20 (42.5)	0.999
Extension of consolidation, mean±SD (cm^3)	227.26±65.91	353.31±122.19	**0.014**
Extension of consolidation, mean±SD (%)	7.15±3.14	8.43±4.43	0.477
Septal thickening, n (%)	7 (70)	39 (82.9)	0.655
Intralobular, n (%)	6 (60)	27 (57.4)	0.999
Interlobular, n (%)	7 (70)	38 (80.8)	0.759
Bronchovascular thickening, n (%)	9 (90)	33 (70.2)	0.237
Traction bronchiectases, n (%)	1 (10)	6 (12.8)	0.999
Pleural effusion, n (%)	4 (40)	6 (12.8)	0.192
Hylar lymphadenopathy, n (%)	5 (50)	30 (63.8)	0.653
Cardiomegaly, n (%)	3 (30)	14 (29.8)	0.999

GGO, ground-glass opacity; MAS, macrophage activation syndrome.

Variables to be assessed, image acquisition and analysis

CT examinations were performed using a multidetector CT scanner with a single spiral acquisition obtained from the apex to the base of the lungs, with the patient in supine position at full inspiration. Scanning parameters were as follows: 250–330 mm field of view (FOV), 512×512 matrix, 120 kV, 100–150 mAs and tube rotation time of 0.5/0.3 ms. Two radiologists, unaware of the underlying diagnoses, independently reviewed all CT examinations, with final conclusions reached by consensus. Images were reviewed using lung parenchyma (level, −600 to −700 HU; width, 1200–1500 HU) and mediastinal (level, 20–50 HU; width, 350–400 HU) window settings. Presence and distribution of lung parenchymal abnormalities were assessed according to the glossary of terms for thoracic imaging by the Fleischner Society,[15] as reported in table 1 and online supplementary table S3. An AI-based software (Myrian V.2.0, Intrasense, France) was used to obtain quantitative data about lung

parenchymal involvement, after automated segmentation, from the same CT examinations.

Data sources, study size and bias

Data were collected during scheduled examinations for each patient by reviewing the clinical charts. Institutional Picture Archiving and Communication System was searched for available chest CT examinations, which were also screened for image quality. To overcome the issue of MAS rarity, we increased the number of severe COVID-19 patients to a ratio of about 4:1 to improve the power, without a specific sample size estimation. Although this rise is not linear, an equally small number of controls would provide little ability to retrieve possible associations.[16] We minimised the effects of possible biases and missing data by a careful definition of each variable and a relatively simple study design.

Statistical methods

Data were collected, organised and analysed through XLSTAT V.2017 Data Analysis and Statistical Solution for Microsoft Excel V.2017 (Addinsoft, Paris, France). All the results are expressed as mean±SD for quantitative variables and as number and percentage for categorical variables. Student t-test was used to compare means for continuous variables, whereas Fisher exact test was used to compare proportions. Pearson correlation analyses were performed to correlate laboratory abnormalities with lung involvement extension.

RESULTS

Characteristics of assessed patients

Ten patients with MAS (age 56.20±10.58 years, 6 male patients) and 47 patients with COVID-19 (age 66.27±13.98 years, 35 male patients), before starting any immunosuppressive therapy for their conditions, underwent chest CT, which was considered of sufficient quality for AI assessment (online supplementary figure S1). Due to the specific severe pattern of COVID-19 in elderly patients, the matching for age was not reliable. All patients with MAS and COVID-19 showed fever and dyspnoea. Patients with MAS were characterised by lower platelet counts (121.90±36.34 vs 254.53±19.51 1 10^9/L, p=0.043) and more elevated ferritin levels (4888.83±1131.49 vs 1207.17±171.66 ng/mL, p=0.010), whereas patients with COVID-19 were characterised by lower lymphocyte counts (2.61±0.58 vs 1.02±0.09 10^3/mL, p=0.005) and higher neutrophil numbers (4.08±0.55 vs 8.98±2.32 10^3/mL, p=0.044). Aspartate aminotransferase (148.8±75.2 vs 34.7±13.1 IU/L, p=0.002) and alanine aminotransferase (178.9±77.4 vs 42.4±14.8 IU/L, p=0.001) levels were increased in MAS. D-dimer was increased in both groups. Other laboratory findings are summarised in table 1. Finally, higher values of H-score characterised patients with MAS than patients with severe COVID-19 (201.9±15.3 vs 88.8±48.3, p<0.0001), as detailed in online supplementary table S4.

Chest CT scan results

All 47 patients with COVID-19 showed ground-glass opacities (GGOs), whereas this finding was observed in 60% of patients with MAS (p=0.028). The proportion of basal, bilateral and peripheral distributions of GGOs was significantly higher in patients with COVID-19 than in patients with MAS (95.7% vs 50%, p=0.022; 97.8% vs 50%, p=0.009; and 95.7% vs 50%, p=0.014, respectively). No significant differences were observed in parenchymal consolidations between groups, except for the more frequent apical consolidations in COVID-19 than in MAS (23.4% vs 0%, p=0.005). Other CT findings are summarised in table 2. About 30% of patients in both groups showed cardiomegaly without any sign of infections or myopericarditis. By assessing AI-reconstructed images (figure 1), the extension of consolidation was higher in COVID-19 than in MAS (353.31±122.19 vs 227.26±65.91 cm^3, p=0.014), whereas the extension of GGOs was similar in both diseases.

In MAS, C reactive protein (CRP) directly correlated with GGOs extension (coefficient 0.75, p=0.031). Similarly, in severe COVID-19, CRP directly correlated with GGOs extension (coefficient 0.49, p=0.020), whereas lymphocytes inversely correlated with GGOs extension (coefficient −0.70, p=0.008). No further correlations were retrieved with other laboratory abnormalities and extension of both GGOs and parenchymal consolidations.

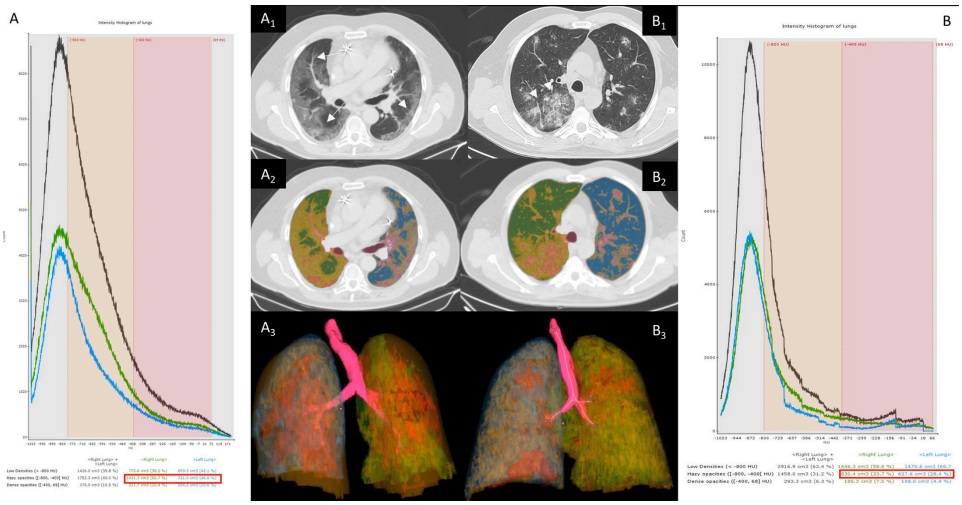

Figure 1 Multiparametric chest CT scan analysis of COVID-19 pneumonia (A,A1–A3) and MAS pneumoniae (B,B1–B3). Axial CT scans with lung window level show the prevalent peripheral distribution of parenchymal opacities (arrows) in COVID-19 pneumonia (A1) compared with MAS pneumonia (B1). The automated segmentation using the AI software (A2,B2) depicts more clearly GGOs in yellow and dense opacities in red. The quantitative histogram graphic representations (A,B) confirm the higher percentage of parenchymal involvement by GGOs (red frames) in COVID-19 pneumonia with respect to MAS pneumonia, as shown by the volumetric surface rendering (A3,B3). AI, artificial intelligence; GGO, ground-glass opacity; MAS, macrophage activation syndrome.

DISCUSSION

Severe COVID-19 and MAS are challenging disorders characterised by overlapping clinical pictures, and it is still matter of debate if severe COVID-19 is part or not of the HLH spectrum.[1 10 11]

Although all patients showed fever and dyspnoea, laboratory differences were retrieved, since MAS patients showed thrombocytopaenia, whereas severe COVID-19 patients were characterised by lymphopaenia and neutrophilia. During MAS, thrombocytopaenia may depend on haemophagocytosis and severe cytokine-mediated inflammation.[4] Differently, COVID-19 is characterised by isolated lymphopaenia, since the virus might infect lymphocytes, inducing their apoptosis.[17] Both diseases showed increased ferritin levels, with the highest levels observed in MAS, which maybe related to the magnitude of the hyperinflammation.[18] D-dimer levels were increased in both groups: in MAS, due to disseminated intravascular coagulation; and in severe COVID-19, for pulmonary intravascular coagulopathy and associated right heart strain.[19 20] All MAS patients achieved H-score diagnostic cut-off (>169) but only 10% of severe COVID-19 patients did it, suggesting the need of further studies to assess its usefulness in severe COVID-19.

AI-reconstructed chest CT images showed that apical, basal, peripheral and bilateral distributions of GGOs were more represented in severe COVID-19 patients. Furthermore, these patients showed more frequent apical consolidations, with a larger extension than in MAS. AI-quantitative assessment of lung involvement permitted to correlate these radiological findings with the specific laboratory abnormalities observed in our patients. In fact, we observed that CRP directly correlated with GGOs extension in both diseases. Furthermore, lymphopaenia inversely correlated with GGOs extension in severe COVID-19. These results may suggest the possible predictive role for some specific biomarkers and may help physicians in identifying more severe patients.

Although providing a comprehensive comparison of clinical, laboratory and radiological findings between MAS and severe COVID-19, our study is affected by some limitations due to the single-centre study design and the relatively low number of patients with MAS, which may limit the external validity. However, it must be pointed out that MAS is a rare disease, and to plan large and multicentre studies is very challenging.

In conclusion, our data showed laboratory and AI–radiological differences between MAS and severe COVID-19; the latter did not appear as being part of the HLH spectrum, thus paving the way for further hypotheses to be investigated in future and larger confirmatory studies.

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Patient consent for publication Not required.

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Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information.

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