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First report on clinical and radiological features of COVID-19 pneumonitis in a Caucasian population: Factors predicting fibrotic evolution

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ABSTRACT

Background: At the end of February, the Lombardy region (Northern Italy) was involved in the pandemic spread of the new COVID-19. We here summarize the clinical and radiological characteristics of 90 confirmed cases and analyze their role in predicting the evolution of fibrosis.
Methods: We retrospectively analyzed the clinical and radiological data of 90 patients with COVID-19 pneumonitis. All subjects underwent an HRCT study on the day of admission and eight weeks later, and were treated with lopinavir + ritonavir (Kaletra) 400/100 mg two times a day or darunavir + ritonavir two times a day, and Hydroxychloroquine 200 mg two times a day. Pulmonary fibrosis was defined according to the Fleischner Society glossary of terms for thoracic imaging.
Results: Twenty-three patients developed pulmonary fibrosis (25.5%): 15 were males, whose mean age was 75 ± 15. The majority were active smokers (60.8%) and had comorbidities (78.2%), above all, hypertension (47.8%), and diabetes (34.7%). Interestingly, in our series of cases, the "reversed halo sign" is frequent (63%) and seems to be a typical COVID-19 pneumonitis pattern. The patients showing fibrosis had a higher grade of systemic inflammation (ESR and PCR) and appeared to have bone marrow inhibition with a significant reduction in platelets, leukocytes, and hemoglobin.
Conclusions: To conclude, our data showed that the reversed halo sign associated with a ground-glass pattern may be a typical HRCT pattern of COVID-19 pneumonitis. The evolution to pulmonary fibrosis is frequent in older males and patients with comorbidities and bone marrow involvement.

Introduction

At the end of February, the Lombardy region (Northern Italy), particularly the province of Cremona, was the first European area involved in the pandemic spread of the new COVID-19. The virus was reported to utilize angiotensin-converting enzyme-2 (ACE2) of pneumocytes as the cell receptor in humans, causing first pulmonary alveolar damage and subsequently, parenchymal changes. At present, the diagnosis of COVID-19 pneumonia is based on clinical symptoms, contact history of the epidemic area, imaging diagnosis, and nucleic acid detection. However, false negatives in nucleic acid detection have been reported, and the clinical symptoms may be atypical, giving rise to misdiagnosis and the spread of contagion (Wu and Mc Googan, 2020; Pascarella et al., 2020). Therefore, imaging becomes particularly important. High-resolution contrast CT scans (HRCT) seem to play a key role in these patients' diagnosis and prognosis (Wu and Mc Googan, 2020). Bilateral distribution of ground-glass opacities (GGO) with or without consolidation in posterior and peripheral lungs was the cardinal hallmark of COVID-19. However, with the further analysis of additional cases, a variety of interesting CT imaging features have been found, including the halo sign, reversed halo sign, and crazy paving (Li and Xia, 2020; Zheng et al., 2020; Xiong et al., 2020). On the other hand, data regarding the evolution of pulmonary lesions are sparse, particularly in Caucasian populations. Lessons learned from previous experiences with other viral pulmonary infections, above all SARS (Severe acute respiratory syndrome) and influenza A (H7N9), along with preliminary reports from China, suggest that some pulmonary consequences are predictable in some phenotypes of patients with COVID 19

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infection. Different clinical factors may play a pivotal role in determining the appearance of residual fibrotic evolution: age, smoking habits, and clinical history, to mention only a few (Salehi et al., 2020a).

We herein summarize the clinical and radiological characteristics of 90 confirmed cases and analyze their role in predicting the evolution to fibrosis.

Patients and methods

We retrospectively analyzed the initial and follow-up chest CT images of 90 consecutive patients hospitalized at the respiratory medicine ward of the Istituto Figlie di San Camillo, Cremona (Northern Italy) with SARS-CoV-2 pneumonitis. Patient characteristics are reported in Table 1. The diagnosis was made by a suggestive medical history, clinical symptoms and a positive test for 2019-nCoV viral RNA in throat- nose swab specimens collected from patients, using real-time reverse transcription-polymerase chain reaction (RT-PCR) and HRCT. All subjects underwent a complete blood test and arterial blood gas (ABG) analysis on the day of admission. Spirometry was not performed at baseline because of the high risk of the virus spreading. Patients underwent global spirometry 70 days after admission (70 ± 7 days).

Because the study started during the initial phase of the pandemic, patients were treated with an off-label therapy, following the resolution of AIFA (Italian Agency on Drugs) published in the *Gazzetta Ufficiale* (March 17, 2020): lopinavir + ritonavir (Kaletra) 400/100 mg two times a day or darunavir + ritonavir two times a day plus Hydroxychloroquine 200 mg two times a day. The mean duration of therapy was 12 ± 2 days. CT examination (Philips 256 CT scanner, low dose <1mSv)) was first performed at admission within a range of one to ten days after onset of symptoms, with an average of 5.5 days. Patients were informed of the date of their follow-up CT scan on the day of discharge because all subjects presented residual pulmonary symptoms (cough, dyspnea at rest or during exercise) and clinical signs of residual disease (inspiratory squeaking and end-inspiratory crackles). The CT scan was performed 60 days after admission (60 ± 5 days). Because the study is a retrospective analysis, no standard CT protocol was applied. All CT images were reconstructed to 1.25-mm thin slices.

CT images were evaluated by two expert radiologists (with more than 30 years' experience in interpreting chest CT) and two expert pulmonologists, divided into two groups (each group was composed of a radiologist and a pulmonologist: M.M + F.F and S.R. + M.U.). They were unaware of the clinical conditions and of the laboratory tests of patients. Multiple CT scans for each individual patient were manually reviewed by the same group, and the decision was reached by consensus.

Table 1
Patients characteristics.

	Fibrosis n = 23	Non Fibrosis n = 67	p value
Age	75 ± 15	61 ± 14	p<0.0001
Sex MF	158	3234	
Comorbidities	18	10	p<0.001
Hypertension	11	6	p<0.001
Diabetes	8	2	p<0.001
COPD	4	1	p<0.001
Ashtma	2	2	n.s.
Liver disease	1	0	n.s.
Chronic renal failure	3	0	p<0.001
Smoking current	14	13	p<0.001
Smoking former	5	10	p<0.001
Symptoms onset days	5	6	n.s.
Temperature at admission °C	37.8	37.6	n.s.

Pulmonary fibrosis was defined according to the Fleischner Society glossary of terms for thoracic imaging: reticulation, architectural distortion, traction bronchiectasis, and honeycombing (Lynch et al., 2018). The study was approved by the local ethical committee; informed consent was signed by all patients on the day of the follow-up HRCT.

Statistical analysis

Continuous variables were compared with the Mann-Whitney *U* test or Wilcoxon test; categorical variables were expressed as number (%) and compared by χ^2 test or Fisher's exact test if appropriate. A two-sided α of less than 0.05 was considered statistically significant. Statistical analyses were done using GraphPad Prism 8.0.

Results

As shown in Table 1, our population included 90 pts, 60 of whom were men (66%); the mean age was 66 ± 15. Common symptoms at onset of illness were fever (72 pts-80%), cough (46 pts -51%), and myalgia/fatigue (15 pts-16.6%); less common symptoms were sore throat (ten pts-11.1%), diarrhea (eight pts-8.9%), and headache (three pts -3.3%). Also, 70 of the 90 pts (77.7%) had lymphopenia, and 30 (33%) mild anemia. The vast majority of subjects (n = 81; 90%) were treated with supplemental oxygen

Table 2
HRCT features.

	Fibrosis n = 23	Non Fibrosis n = 67	p value
Patchy GGO	0	12	p<0.001
Diffuse GGO	13	36	p<0.001
Consolidation	2	4	p<0.001
Both	10	32	p<0.001
Anatomic side			
Unilateral	0	8	p<0.001
Bilateral	20	61	n.s.
Upper	3	6	p = 0.05
Middle	7	10	p<0.01
Lower	15	25	p = 0.05
Central	7	15	p = 0.05
Peripheral	12	60	p<0.01
Reversed Halo sign	17	53	p<0.01
Halo Sign	6	15	p<0.01
Involved Lobes > 3	17	50	p<0.01
Legenda: GGO = ground glass opacity.			

Table 3
Blood chemistry and respiratory function parameters.

	Fibrosis n = 23	Non Fibrosis n = 67	p value
LDH UL	460 ± 32	430 ± 25	p<0.01
CRP mgdl	11 ± 4	7 ± 4	p = 0.001
ESR mm	90 ± 30	55 ± 30	p<0.0001
Hb	9.5 ± 2.0	12.5 ± 1.9	p<0.0001
WBC	3500 ± 1200	5.300 ± 1.400	p<0.0001
PLT	180.000 ± 100.000	250.000 ± 95.000	p = 0.018
D-dimer mcgml	5.5 ± 2.0	2.0 ± 1.5	p<0.0001
ALT UL	51 ± 15	47 ± 10	n.s.
Albumin gl	32 ± 3	34 ± 4	n.s.
FVC % pred	50 ± 11	90 ± 15	p<0.0001
DlcoVA % pred	58 ± 13	91 ± 13	p<0.0001

LDH= Lactate dehydrogenase; **CRP**: c reactive protein; **ESR**: erythrocyte sedimentation rate; **Hb**: hemoglobin; **WBC**: white blood cells; **PLT**: platelets; **ALT**: alanine aminotrasferase; **FVC**= Forced Vital capacity; **DlcoVA**: diffusion of the lung for carbon monoxideAlveolar volume.

(mean oxygen flow 6 ± 4 Lmin), six with non- invasive mechanical ventilation (four with CPAP, two with BiPAP). (Table 3)

The majority of subjects developed bilateral lung disease (90%); the others had unilateral involvement. 54.4% of patients developed diffuse GGO; 46.6% developed both GGO and consolidations. (Table 2)

The area and number of GGOs or consolidations decreased or disappeared in 50% of cases; the density of GGO increased and changed into consolidation in 20% of cases; the edge of the consolidation shadow became contracted in 15% of cases. Patients were discharged after an average hospital stay of 14 ± 5 days. All subjects were discharged after two RT-PCR nose and throat specimens tested negative.

Long term oxygen therapy (LTOT) at discharge was prescribed, following the European Respiratory Society guidelines, for sixteen subjects (17.9%) - ten at rest, the others during exercise.

"Halo sign" refers to the ground-glass shadow around the mass or nodule. The "reversed halo sign" (Atoll sign) is characterized by a focal, round, or half-moon shape with ground-glass density in the center, and almost completely (more than 3/4) surrounded by a high-density consolidation shadow (Figure 1) (Lynch et al., 2018).

Interestingly, in our series of cases, the "reversed halo sign" is frequent (70 pts; 63%) and seems to be a typical pattern of COVID-19 pneumonitis in this series of cases (Table 2). In our series of cases, only two patients had pleural effusion (one of these had pericarditis, one developed a pneumothorax that required the placement of a pleural drain), and two patients had pneumatocele. Seven patients developed localized fibrosis, usually in a localized area of GGO. Twenty-three patients developed bilateral pulmonary fibrosis (Figure 2) with a typical non-specific interstitial pneumonia (NSIP) pattern, following the Fleischner Society criteria (25.5%): 15 were males, whose mean age was 75 ± 15. The lung diffusing capacity for carbon monoxide (DLcoVa) was significantly lower in these 23 subjects than in the non-fibrosis group (58 ± 13 % versus 91 ± 13 %; $p < 0.001$). The majority were active smokers (14 patients; 60.8%) and had comorbidities (18 pts; 78.2%), above all hypertension (eleven patients; 47.8%) and diabetes (eight patients; 34.7%) (Table 3).

Patients showing fibrosis had a higher grade of systemic inflammation (ESR, PCR, and d-dimer) and appeared to have bone marrow suppression with a significant reduction in platelets, leukocytes, and hemoglobin (Table 3).

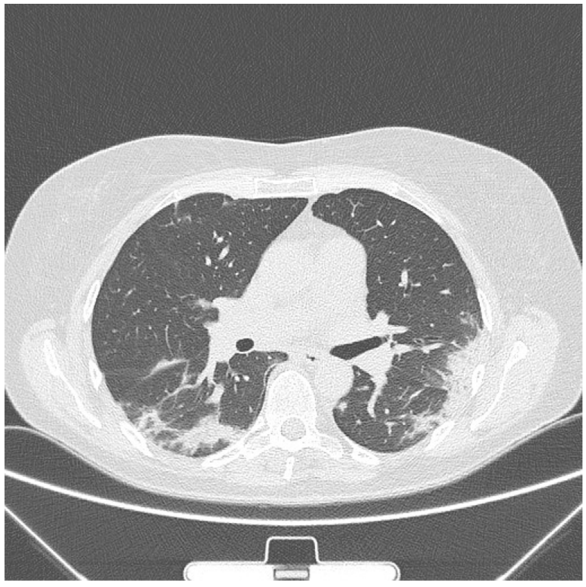

Figure 1. "Reversed halo sign." Peripheral and bilateral consolidations. In the right lung, a peripheral "reversed halo sign.".

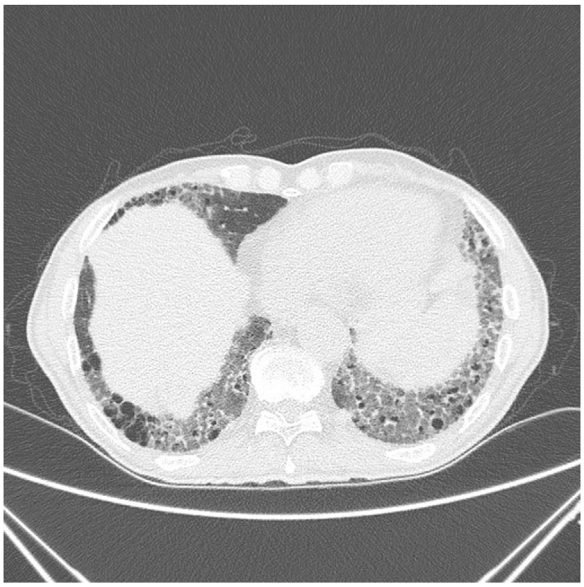

Figure 2. Fibrotic evolution. Honey combing and interstitial thickening in a patient who developed pulmonary fibrosis.

Discussion

Consistent with several recent reports regarding the CT findings of patients with 2019-nCoV infected pneumonia, our results showed that CT manifestations featured predominant ground-glass opacities that are usually peripheral and bilateral involving middle and lower lung fields (Wu and Mc Googan, 2020; Pascarella et al., 2020; Li and Xia, 2020). Jiong W, et al. studied 80 consecutive subjects and suggested that the most commonly involved lung segment was the dorsal segment of the right lower lobe (69/80, 86%), and that the most frequent CT abnormalities observed were ground-glass opacities (73/80 cases, 91%), consolidation (50/80 cases, 63%), and interlobular septal thickening (47/80 cases, 59%) (Jiong et al., 2020).

Jing Wu et al. analyzed the CT scan of 130 patients from five hospitals in China. Of these, 35 subjects underwent a follow-up chest CT scan: 40% became worse, developing consolidation with marginal contraction, bronchiectasis, subpleural line, and fibrous streak. In their series of cases, halo sign and reversed halo sign were rare (18 and six cases respectively) (Wu et al., 2020). Shy H et al. retrospectively studied 81 pts from Wuhan. Patients were grouped based on the interval between symptom onset and the first CT scan: group 1 (subclinical patients; scans done before symptom onset), group 2 (scans done ≤1 week after symptom onset), group 3 (scans done >1 week to 2 weeks), and group 4 (scans done >2 weeks to 3 weeks). In this last group, the predominant patterns were: GGO with reticulations, bronchiolectasis, and thickening of the adjacent pleura. Follow-up CT images were obtained from 57 subjects; in this small subset, 32% had a radiological deterioration with fibrosis and consolidation (Shi et al., 2020).

Recently, Salehi S et al. published a systematic review including 19 case series and eleven case reports considering the HRCT findings of 919 patients, the vast majority of whom were Chinese. In this article, data regarding follow-up changes are sparse and limited by the short time of follow-up (two weeks). In the majority of subjects, progressive transformation of GGO into multifocal consolidative opacities, septal thickening, and the development of a crazy-paving pattern were visible on day ten after symptom onset (Salehi et al., 2020b).

To our knowledge, this is the first prospective study evaluating the evolution of pulmonary lesions in a Caucasian population. More than one patient out of three (36%) was seen to develop pulmonary fibrosis in our series. The vast majority of these are male smokers with comorbidities, higher inflammatory markers (CRP and ESR), increased D-dimer, and bone marrow involvement. These data are concordant with those of Yang Z et al. that, performing a short CT follow-up (a week), evaluated some clinical parameters' prognostic value in predicting imaging progression. The white blood cells, platelets, neutrophils, monocyte-lymphocyte ratio, and age were significantly higher in imaging progression patients compared to imaging progression-free ones (Zongguo et al., 2020). Moreover, these parameters have been reported to be significant prognostic factors; a D-dimer value greater than 1 μgml could help clinicians to identify patients with poor prognosis at an early stage (Fei et al., 2020). Interestingly, in our Caucasian population, the reversed halo sign is prevalent and seems to be a pattern peculiar to COVID 19 pneumonitis.

On the one hand, our study has important limitations: first, the prospective design, the small number of patients, and the short time of follow up. On the other hand, this is the first study involving a Caucasian population. The novelty of the clinical information, and its impact on everyday clinical practice, warrant rapid disclosure to the scientific community.

At this juncture, three questions require a prompt answer. What will be the impact of pulmonary fibrosis secondary to COVID-19 infection on our patients' pulmonary function and quality of life? Why do some phenotypes show diffuse alveolar damage, mononuclear cells and macrophage infiltration in air space, and diffuse thickening of the interstitial space? Is there any role for some drugs, particularly steroids, in decreasing the risk of a fibrotic evolution? To conclude, our data showed that the reversed halo sign associated with the ground-glass pattern may be a typical HRCT pattern of COVID-19 pneumonitis. The evolution to pulmonary fibrosis is frequent in older male smokers and in patients with comorbidities and bone marrow involvement.

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Conflict of interest

We have no conflict of interest.

All authors had access to the data. All authors contributed to the writing of the text.

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