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COVID19 & FUO: A CASE OF AN INVASIVE COVID19 PRESENTED AS UNEXPLAINED PROLONGED FEVER

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Abstract
More than four years have passed upon the combat of the entire world against the rapidly spreading Corona virus disease-2019 (COVID-19) pandemic, while health care providers are still learning the disease and its progression, thus it is crucial to share.

Introduction

More than four years have passed upon the combat of the entire world against the rapidly spreading Corona virus disease-2019 (COVID-19) pandemic, while health care providers are still learning the disease and its progression, thus it is crucial to share knowledge and experience regarding the behavior of this disease and the potential treatment options. Caused by severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2), the clinical presentation of COVID-19 is now well recognized. Common symptoms include fever, cough, fatigue, dyspnea, and impaired smell and taste sensations. Typical laboratory findings include high levels of C-Reactive protein (CRP), elevated liver enzymes, and increased levels of D-Dimer and Prothrombin time. In addition, leukopenia and lymphopenia frequently occur and correlate with disease severity. Definite diagnosis is made by positive PCR testing of naso-pharyngeal swab for SARS-CoV-2 [1-6].

While fever is the most commonly reported symptom of COVID-19 [2,5], so far there were no reported cases of fever of unknown origin (FUO) related to COVID-19. However, it is appealing to assume that the occurrence of COVID-19-related FUO could be underestimated, as emerging evidence implicates COVID-19 in prolonged febrile illnesses due to deep tissue involvement, even while patients have repetitive negative results of the apparently diagnostic naso-pharyngeal swabs for the virus [7].

We here present, for the first time in literature, a case of FUO related to COVID-19. It was important to make the diagnosis, as the disease was progressive and resistant to most acceptable treatment regimens, and the cure was possible only after applying alternative treatments than the usual regimens being used in treating common COVID-19 cases.

Case Description

A 77-years-old female diagnosed with COVID-19 in the past sixteen days prior to her admission, was referred to the emergency department with high grade fever, general fatigue, shortness of breath and abdominal pain that had started in the past ten days and worsened in the last two days prior to her admission. Her medical history was remarkable for hypertension, inflammatory polyarthritis, sjorgen syndrome and follicular lymphoma that was in remission according to a PET-CT scan performed fifteen months prior to her admission with no evidence of active disease.

On physical examination, the patient looked pale and ill, with noticeable speech dyspnea, but no apparent tachypnea or use of any accessory muscles. Her temperature was 39.3^{o}c, with normal hemodynamic parameters. Oxygen saturation was 85-90% on room air (RA).

Laboratory workup revealed leukopenia of 2900 cells/μL with lymphopenia of 580×10^{9}cells/L, and CRP 4.2 mg/dL. Hemoglobin was 11 gr/dl, creatinine 1.53 mg/dl, and liver enzymes were normal. D-dimer was elevated (702 ng/ml), with normal INR, PTT and platelet count.

Chest X-ray (CXR) revealed bilateral peripheral ill-defined opacities, mainly in the lower zones [Fig 1].

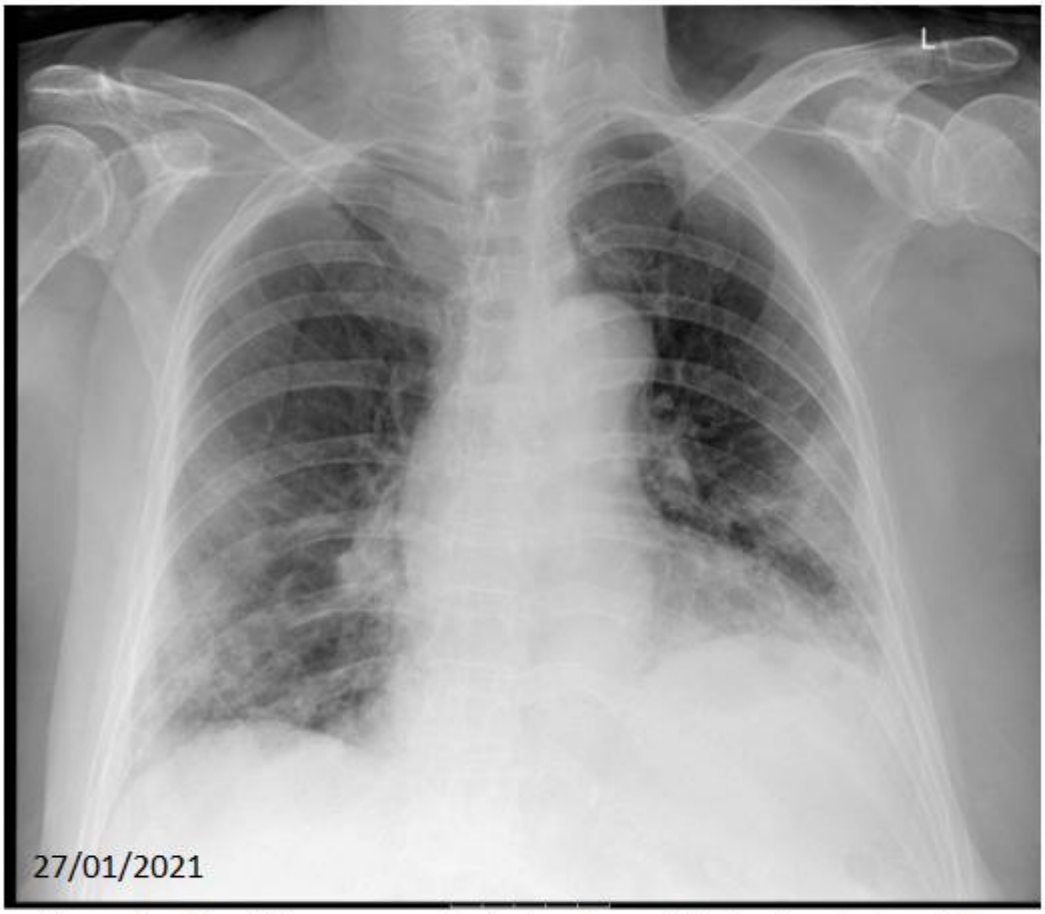

Figure 1 – Chest Xray upon admission shows bilateral peripheral ill-defined opacities, more prominent in the lower zones.

The diagnosis of severe COVID-19 pneumonia was made and the patient was treated with intravenous Dexamethasone 6 mg/d, Esomeprazole 20 mg and prophylactic dose of Enoxaparin (40 mg/d).
During the first days of hospitalization, the patient was hemodynamically stable, the oxygen saturation level was 90% while on RA, and remained febrile with daily fevers of up to 39.5°c. Serial CXRs revealed worsening bilateral pulmonary infiltratres [Fig 2]. Ceftriaxone and Azithromycin

were added. A workup for prolonged fever that included urine culture which revealed E. Coli, for which Amikacin was administered for 6 days.

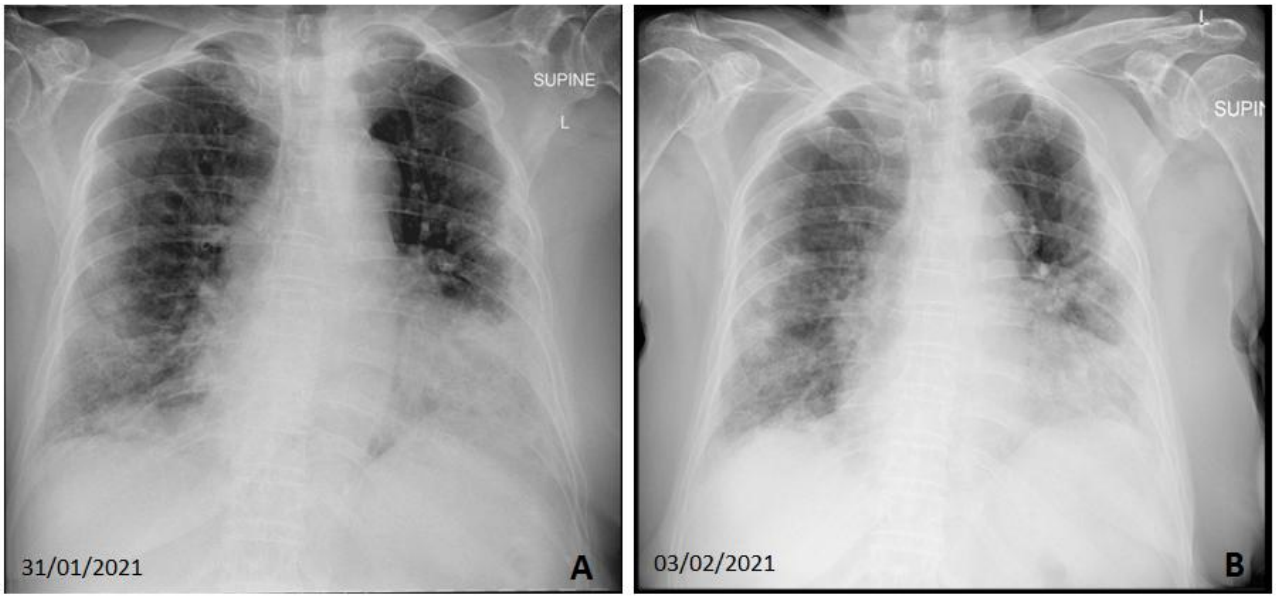

Figure 2 – Serial chest x-rays after admission, show worsening bilateral pulmonary opacities possibly obscuring the border of the diaphragm on the left. A – 4 days after admission, B – 7 days after admission

Nevertheless, the patient condition continued to deteriorate. She looked ill and repeated laboratory tests revealed an elevation of CRP values up to 39.5 mg/dL, with documentation of Bacteroides fragilis bacteremia in blood cultures sensitive to metronidazole, which was also administered for 7 days. The Bacteroides bacteremia raised suspicion of an abdominal infection, but an abdominal computerized tomography demonstrated only bilateral peripheral alveolar and ground glass opacities with curvilinear subpleural shadows that can be compatible with COVID-19 infection [Fig. 3], while no abdominal infectious process was disclosed. Repeated blood cultures showed no continued growth of pathogens, yet the patient continued to be with high fevers. Piperacillin/Tazobactam was administered for a week without any improvement in her condition. Repeated Blood tests that included rheumatological panel was also negative.

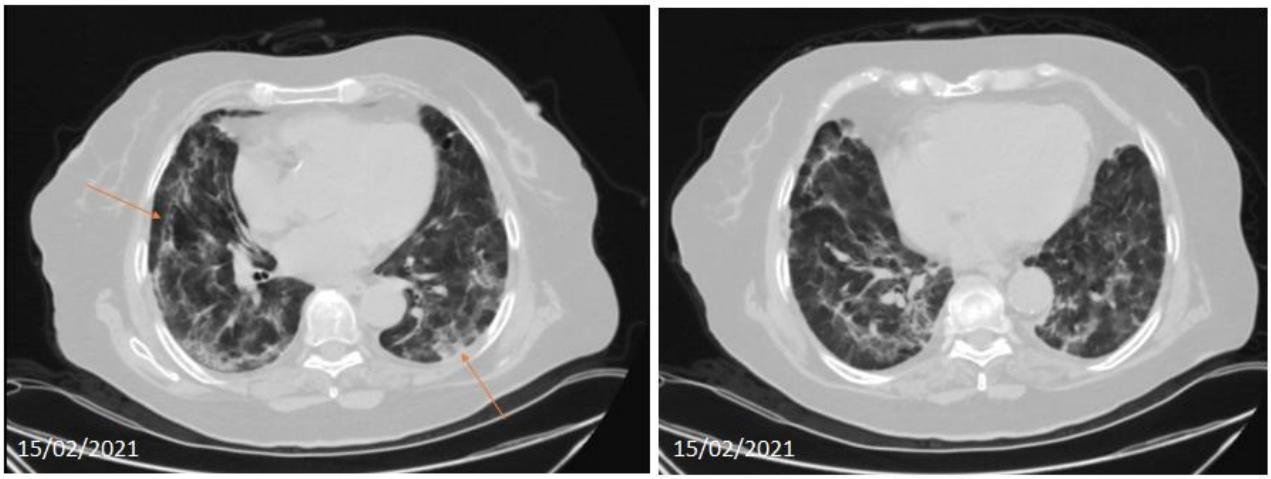

Figure 3 – abdominal computerized tomography demonstrated bilateral peripheral alveolar and ground glass opacities, curvilinear subpleural shadows, can be compatible with COVID-19 infection.

For more thorough investigation for possible etiologies for the continuous fever, the patient underwent a PET-CT scan, which was remarkable for pathological uptake in both lungs [Fig 4]. After revision and comparison of the PET-CT Scan with a number of formerly performed PET-CT scans, the conclusion was that the uptake is most likely due to an infectious process involving the lung parenchyma, a finding which could be compatible with COVID-19 infection.

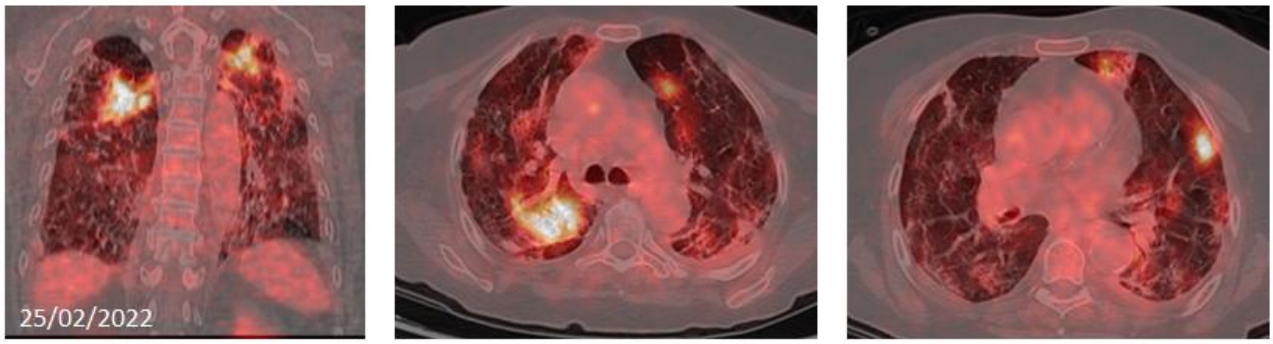

Figure 4 – PET-CT scan remarkable for pathological uptake corresponding to the alveolar and ground glass opacities in both lungs.

In light of the PET-CT scan findings, Fiber-optic bronchoscopy with bronchoalveolar lavage was conducted. The lavage fluid analysis showed numerous macrophages and lymphocytes with no findings that can indicate an infection with Aspergillus, Pneumocystis, or Legionella. Ziehl–Neelsen and Galactomannan tests were also negative. Bacterial and Fungal cultures were negative. PCR for respiratory viruses was negative with the exception of a positive COVID-19 test.

Accordingly, we concluded that an invasive pulmonary COVID-19 infection was the etiology for FUO despite a prolong course, and accordingly high dose Dexamethasone was initiated (20 mg per day). Under this therapy, an immediate clinical improvement was documented, with cessation of the high fever and reduction in inflammatory markers, as the CRP reduced to 11 mg/dL. Upon discharge, chest xray showed partial resolution of the aforementioned opacities [Fig 5]. The patient was maintained on high dose Dexamethasone for 3 weeks, after which slow tapering-down of Dexamethason dosage was applied, while the patient remained symptom free. No written consent has been obtained from the patients as there is no patient identifiable data included in this case report/series.

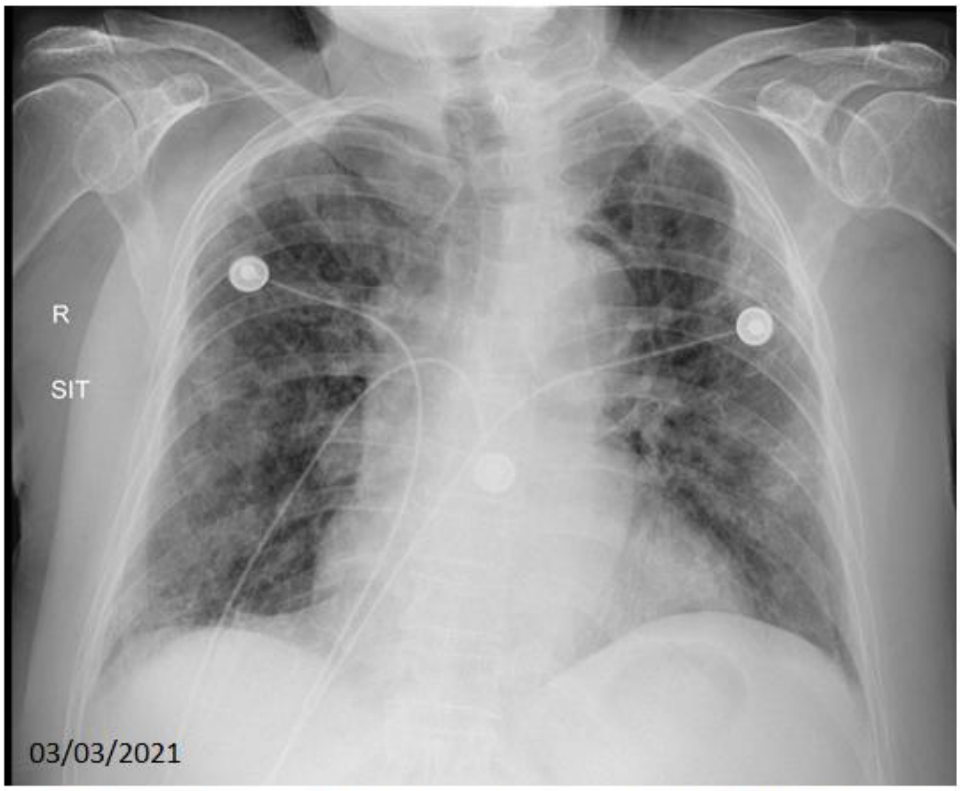

Figure 5 - partial resolution of the aforementioned opacities, bilateral gross reticular shadows appeared.

Literature review

Since the initial reports describing the outbreak of Coronavirus disease-2019 (COVID-19), it has been concluded that the disease runs its course through two phases. In the first phase, the disease lies dormant during its virus incubation period, while subtle symptoms often arise, and despite being mostly mild, patients are considered highly contagious. In the second phase, the actual clinical phase becomes apparent while the immune system is fully activated and the disease may run its course to different severities [1,3]. According to the WHO, the incubation period lasts as much as 14 days (2-14 days), with a median time of 4-5 days from the moment of exposure to the onset of symptoms [2]. The clinical progression course among patients in different studies has resolute in median time of 5-8 days from illness onset to the appearance of dyspnea. As for the median time of illness onset to full blown acute respiratory distress syndrome (ARDS), studies have showed a time period of 8-12 days; and the median time period from symptoms onset to admission to the ICU was 9.5-12 days [4,5,8,9,10]. The median time for hospitalization in patients who recovered from the disease was 10-13 days [2,5,10].

While typical symptoms of COVID-19 include fever, cough, dyspnea and fatigue, so far there are no cases in the literature describing COVID-19 as a cause of FUO, but it is worth mentioning that there are cases in which the diagnosis of COVID-19 is not easily made with regular nasopharyngeal swabs and may be done only with a deep tissue sampling like bronchoscopy [7]. Treatment is based mostly on systemic corticosteroids, with the common protocol being a dose of 6 mg Dexamethasone per day for as much as 10 days.

As we are more than two years among the worldwide combat against COVID-19, we realized that the virus acts differently on different parts of the population, as it often causes a milder disease in the young and healthy individuals compared to a life threatening disease in the old and sick patients at baseline [2,4]. There is only few data available on COVID-19 in the immunocompromised hosts, and one research that followed the disease course among transplant patients, revealed that a large proportion of those patients had no apparent epidemiological contact. In addition, many exhibit symptoms similar to the general population like fever, dry cough and fatigue, usually at the onset of the disease. All the patients developed ground glass opacities in their chest radiographs, mostly at presentation. Leukopenia and notable lymphopenia were seen in the majority of those patients, as well as increased levels of serum Lactate dehydrogenase, while the rest of the inflammatory markers' elevations were inconsistent [11, 12].

It is known that there is some variability in the progression of the disease among different groups of patients, but overall it appears to advance faster in the immunocompromised patients with higher rates of ICU admissions and death, with approximately a mortality rate of 21.4% [9,11,12]. In many of the cases, a super-infection with a bacterial or viral pathogen was observed at time of COVID-19 diagnoses and it exacerbated the course of the disease [5, 11, 12]. Many clinicians promote an approach of reducing the dose of immunosuppressive agent, while this may risk immune reconstitution and rejection of transplanted organs, it may help on the other hand in improving the viral clearance [11-14].

The clinical presentation of our patient, as well as her laboratory and radiologic findings, are in line with the commonly reported signs and symptoms in moderate-severe COVID-19 cases described in literature. Our patient was immunocompromised, the disease course was prolonged and bared bacterial super-infections, and only high dose of steroids course succeeded in achieving complete resolution of the illness.

So far, there are no cases in the literature describing FUO caused by COVID-19. As such, we have learned that it would be wise to consider COVID-19 as a potential causative of FUO, and only high dose steroids in these cases can cure the disease and relieve the symptoms.

Summary

We here report, for the first time in literature, an invasive COVID-19 pneumonia presented as a case of FUO, and only high dose Dexamethasone resulted in symptomatic relief and clinical resolution. thus, we suggest taking into account that invasive COVID-19 infection should be in the differential diagnosis of FUO in subjects with unexplained prolonged fever, and particularly in patients who present with signs and/or symptoms suggestive for COVID-19.

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