SARS-CoV-2 related pneumonia in an adult with cystic fibrosis: natural favourable clinical course or effective therapy?

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Abstract

We report the case of a man affected by cystic fibrosis who developed a severe SARS-CoV-2 related pneumonia in March 2020. In addition to lopinavir/ritonavir and hydroxychloroquine, he was treated with two doses of tocilizumab, displaying a significant clinical improvement. This is the first case described in the literature of an adult patient affected by cystic fibrosis who received tocilizumab for COVID-19, with documented total recovery, also assessed by a spirometry.

Introduction

The novel coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was first described in December 2019 in Wuhan, China, and was declared pandemic by the World Health Organization (WHO) on March 11th, 2020. The clinical spectrum varies widely, from asymptomatic infection or mild influenza-like disease to potentially fatal pneumonia with respiratory failure. Hypertension, diabetes and coronary heart disease have already been described as common comorbidities and are linked, with various degrees of importance, with a worse evolution and outcome of the infection, both in preliminary papers and in most recent evaluations. With respect to respiratory tract pathological conditions, chronic obstructive pulmonary disease (COPD) and active smoking have been reported as factors linked to more severe outcomes [1]. Spread of Covid-19 among patients with cystic fibrosis (CF) might have a severe impact on their clinical conditions. To date, few data are available on the association of these two diseases.

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Case Report

Here we report the case of a 34-years-old male with CF admitted to our Department of Infectious Disease, in Bologna, in March 2020 for a COVID-19. His CF was diagnosed during newborn screening (CFTR mutations: 2183AA->G, 1717-1G->A) and complicated by exocrine pancreatic insufficiency and CF-related diabetes, but his nutritional status was acceptable (BMI 20.31 Kg/m2). His last spirometry revealed a forced expiratory volume in 1 second (FEV1) of 75% predicted. His airways were chronically infected by *Pseudomonas aeruginosa*, Methicillin-Sensitive *Staphylococcus Aureus* and *Haemophilus* spp, in chronic treatment with azithromycin, trimethoprim -sulfamethoxazole, levofloxacin (LVX) and inhaled vancomycin. His symptoms began two days before admission, with fever and dry cough. Because of the worsening of dyspnoea, he was transported to the Emergency Room (ER). When admitted to the ER, the patient had increased body temperature (BT 39.4°C), high respiratory rate (RR, 24 acts per min), high heart rate (HR, 115 bpm) and low peripheric saturation (93% on ambient air).

Investigations

Biochemical exams showed a normal total white cell count (WBC), with no lymphopenia; C-reactive protein (CRP) was 3.96 mg/dL and interleukin 6 (IL-6) concentration was 19.6 pg/ml. An arterial blood gas (ABG) test was performed, showing respiratory failure (PaO_2 58 mmHg on air), indicating a probable respiratory alkalosis. The chest radiograph revealed bilateral interstitial thickening prevalent in lower lobes, in absence of parenchymal

consolidation. In suspicion of COVID-19, a computed tomography (CT) was performed, showing cylindrical bronchiectasis with mucous plugging and a ground-glass pattern (Figure 1). Specimens from the upper respiratory tract (nasal and oropharyngeal samples) were collected and then analysed with reverse polymerase chain reaction (RT-PCR) assay for detection of SARS-CoV-2. After the positive result for SARS-CoV-2 infection on nasopharyngeal swab, the patient was transferred to our Department.

Treatment

The patient received low flow oxygen support and rapidly started therapy with lopinavir/ritonavir 200 mg/50 mg BID and hydroxychloroquine 200 mg BID for 6 days. Besides chronic treatment based on LVX, he received piperacillin/tazobactam (TZP) for 5 days, as a prevention of bacterial superinfection. Due to the progressive clinical deterioration, it was decided to add to the current therapy two doses of intravenous IL-6 receptor inhibitor, tocilizumab (TCZ), at the standard dose of 8 mg/kg in two administrations (24 hours apart).

Outcomes

After 5 days from admission, we observed a progressive improvement of clinical and laboratory parameters (Figure 2), with removal of oxygen support a week after hospital admission along with a reduction of the consolidation area shown by a HRCT (Figure 1 C,D). Viral clearance on nasopharyngeal swabs was documented after 18 days from the first viral detection. A follow-up spirometry performed after one month from discharge showed FEV1 79% predicted, similar to the baseline value.

Discussion

To date, few data have been reported about the clinical course of COVID-19 in patients with CF compared with the general population. An international report proposed that patients with CF have neither higher mortality nor higher chance of complications [2], but no specific treatment strategies have been proposed. It has been already established that viral infections, including influenza A H1N1, are associated with higher rate of hospitalization and higher rate of severe disease in CF patients compared to non-CF patients [3]. In addition, viral infections are linked to new bacterial colonization. For these reasons, during COVID-19 pandemic, particular attention has to be given to patients with CF.

SARS-CoV-2, as many other Beta Coronaviruses, uses ACE-2 receptor, which is expressed in lung epithelial cells and many other

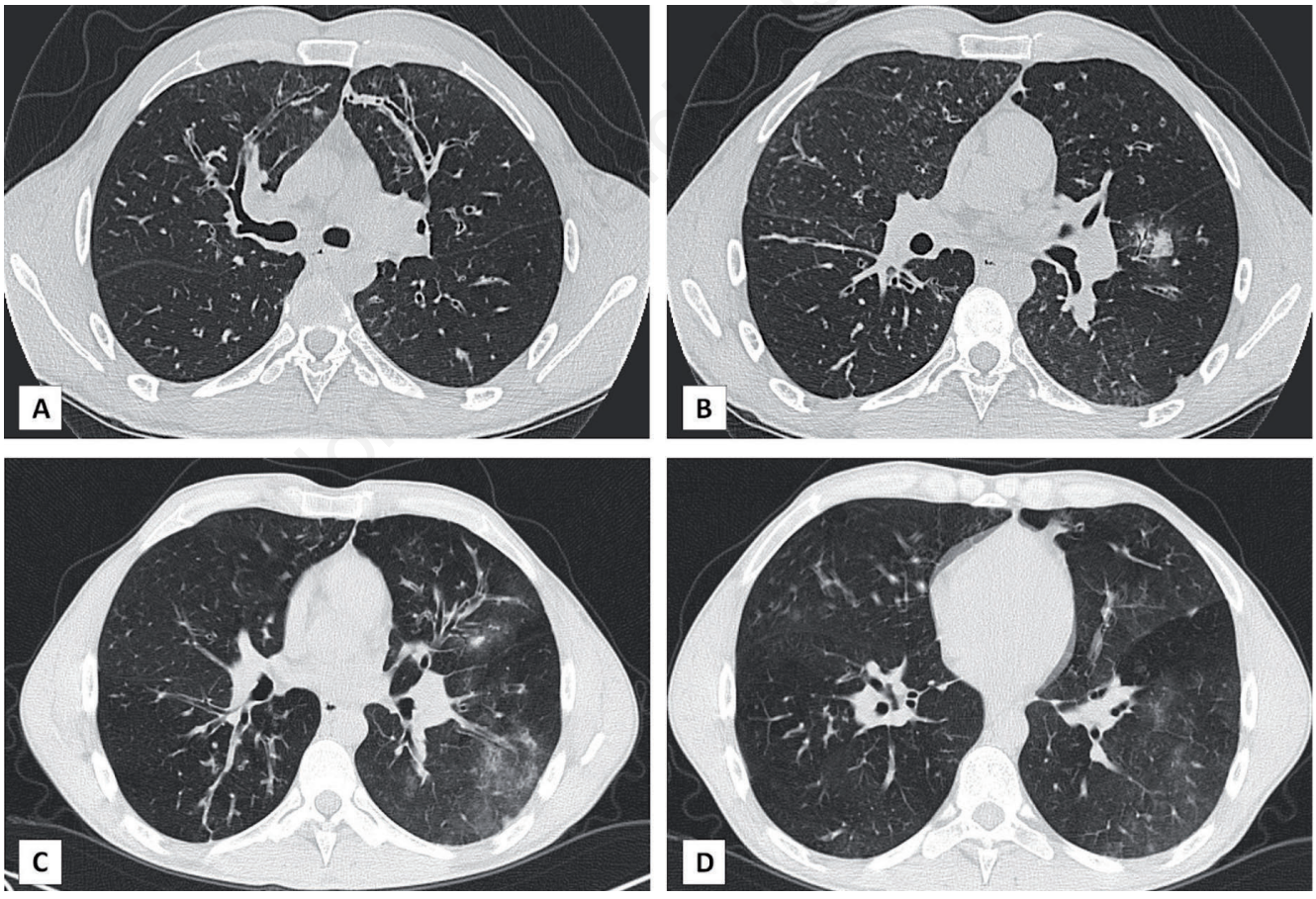

Figure 1. Chest computed tomographic images. A) Axial unenhanced chest CT performed on day of admission showed typical alterations of cystic fibrosis characterized by upper-lung-predominant cylindrical bronchiectasis with mucus plugging and bronchial wall thickening. B) CT images also confirmed a consolidation lesion in the lower left lobe and subpleural ground glass opacities. C,D) Follow-up CT scan performed after 14 days of hospitalization showed the resolution of the previous parenchymal consolidation while ill-defined patchy ground-glass opacities increased in the lower left lobe and in the lingula.

tissues to enter its targets. As ACE-2 expression is often increased in patients with lung diseases [4], it could be expected that our patient experienced a more aggressive evolution of the infection, going through a longer and more intense viral phase. Nevertheless, this was not observed in our patient, who, contrarily, achieved a rapid viral clearance assessed by the swabs.

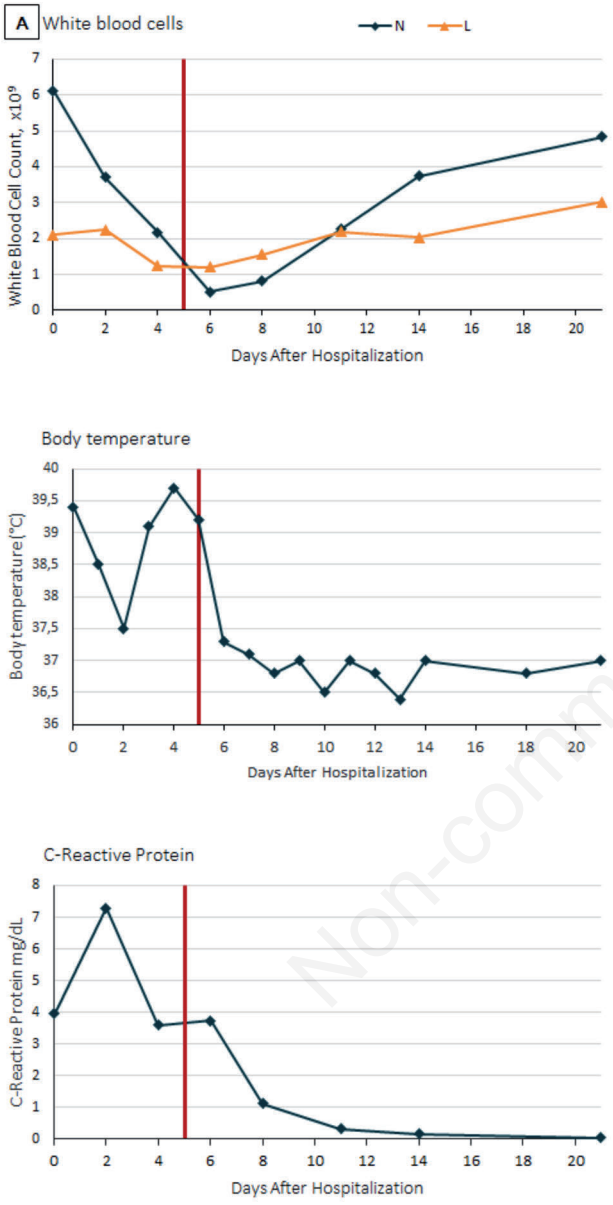

Figure 2. Timeline profile of principal laboratory and clinical parameters describing the laboratory parameters and the course of fever during hospitalization. The solid lines in red indicate the first TCZ e.v. administration. The second dose of TCZ was administered the following day. Hydroxychloroquine and LPV/r were administered from day one to day six. TZP from day one to day five. A) After an initial reduction, elevation of lymphocytes was observed; the important reduction in neutrophils could be due to a side effect of TZP. B) Course of fever during hospitalization. C) Trend of CRP during hospitalization. BT, body temperature; L, lymphocytes; LPV/r, lopinavir/ritonavir; N, neutrophils; TCZ, tocilizumab; TZP, piperacillin/tazobactam.

It has been shown that baseline levels of pro-inflammatory cytokines, such as IL-6, are elevated in patients with CF, and are even higher during pulmonary exacerbations [5]. The CF lung is, in fact, an inflammatory microenvironment where bacteria, fungi and also viruses create an insult that tends to worsen the functionality of epithelial lung cells. This could be linked to worse evolution of infections and higher rate of acute respiratory distress syndrome (ARDS) in patients with CF. SARS-CoV-2 infection is also associated with very high levels of IL-6, hallmark of the cytokine storm, which the patients with COVID-19 often experience [6]. With regard to our patient, the IL-6 level was dosed only at the entrance in ER (19.6 pg/mL), a value that is only moderately high, in particular if compared to those measured in cohorts of patients with severe disease [7]. Due to the clinical deterioration he was experiencing, it was suspected that a cytokine storm was arising, that is why it was decided to administer TCZ. Nevertheless, since no dosage of IL-6 has been made before and after the administration of the drug, this hypothesis cannot be confirmed. The man displayed a progressive improvement following the administration of TCZ. The temporal correlation between the two phenomena makes us suspect that the events were related to each other (Figure 2). However, it is not possible to determine a clear causal effect of this treatment on the patient's favourable clinical evolution, considering that the positive outcome could have been independent from therapy. In addition, he did not display any deterioration in FEV1, although in CF patients the pulmonary function often declines after virus-associated lower respiratory tract infections. Contrary to what could be intuitively expected, from the few data available it is not yet possible to determine whether patients with CF experience a more or less severe form of COVID-19 than the general population. In the latest version of the European Cystic Fibrosis Society Patient Registry database, which is continuously collecting data on patients with CF and COVID-19 across Europe, COVID-19-related mortality in these patients has been estimated around 2.06%, rate of critical patients 5.61% and of severe form 6.74% [8]. Several therapeutic strategies have been tried so far, since the scientific results reported in the literature are frequently updated: to date, as far as we know, only two CF patients in Europe received TCZ [8], as our patient did, since he was considered a severe case of COVID-19.

In conclusion, our case illustrates a positive course of a severe COVID-19 with good response to the treatment in a man affected by CF. Further investigations will be necessary to understand the real impact of SARS-CoV-2 on patients with CF, to have a better knowledge of what an appropriate therapeutic strategy in these patients may be and whether the use of an IL-6 inhibitor (also in addition to other drugs) can find its rationale here.

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