Complicated and persistent severe COVID-19 pneumonia in a recipient of allogeneic haematopoietic stem cell transplant

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SUMMARY
We describe the case of a 45-year-old man affected by T-cell acute lymphoblastic leukaemia and diagnosed with COVID-19 early after an allogeneic haematopoietic stem cell transplant. The infectious disease was characterised by a severe and prolonged course, further complicated by a spontaneous pneumomediastinum and pneumopericardium. We successfully treated this patient with the antiviral drug remdesivir associated with two courses of COVID-19 convalescent plasma. This case report represents a good example of the typical clinical course of COVID-19 in severely immunosuppressed patients and gives evidence that in this population only a prompt treatment directed towards viral clearance can face the absence of a valid immune reactivity.

BACKGROUND
SARS-CoV-2 has spread rapidly since December 2019, causing a pandemic and a global public health crisis. Infected individuals develop several symptoms, mainly affecting the respiratory system, collectively known as COVID-19. Disease course can range from mild to life-threatening based on risk factors including age, sex and comorbidities, such as cardiovascular disease or cancer. Here, we report a case of protracted and complicated COVID-19 in a recipient of allogeneic haematopoietic stem cell transplant (allo-HCT) successfully treated with COVID-19 convalescent plasma (CCP) and remdesivir.

CASE PRESENTATION
A 45-year-old man was diagnosed with high-risk T-cell acute lymphoblastic leukaemia (T-ALL) and began treatment with multiagent chemotherapy, acquiring a complete remission. A myeloablative allo-HCT from a 10/10 HLA-matched unrelated donor was performed 6 months after the initial diagnosis (figure 1); graft-versus-host disease (GVHD) prophylaxis consisted of rapamycin, mycophenolate and cyclophosphamide. Primary antimicrobials prophylaxis comprised posaconazole, cotrimoxazole, acyclovir and leteremovir. At day 41 from allo-HCT, the patient experienced skin acute GVHD overall grade II that was treated with methylprednisolone. A partial response was achieved after 2 weeks, and the patient started extracorporeal photopheresis but was able to conclude only a single session due to diagnosis of COVID-19 (day 54 after transplant). Symptoms at diagnosis were mild and consisted only of non-productive cough and low-grade fever.

INVESTIGATIONS AND DIFFERENTIAL DIAGNOSIS
At the time of diagnosis, the only abnormalities found on blood tests were a mild and stable pancytopenia and a high ferritin level, both easily explicable, respectively, by the recent allo-HCT and previous red cell transfusions. Hepatic, renal, cardiac and urinary laboratory test were normal and, notably, we observed an absence of acute-phase reactants abnormalities, including C-reactive protein, procalcitonin and interleukin 6. Coagulation parameters were also in range, with only a mildly elevated D-dimer (figure 1). A chest plain radiography showed no signs of consolidation or interstitial lung disease (ILD). Due to the COVID-19 pandemic situation at the time, we immediately performed a rapid SARS-CoV-2 antigen test that turned out to be positive, further confirmed by a molecular test (cycle threshold ORF1 a/b 17.15, cycle threshold gene E 16.79). Anyway, given the presentation with low-grade fever and the profound immunosuppressive state of our patient, we searched for other possible causes that could explain these symptoms but a nasopharyngeal swab test for other respiratory viruses was negative and we did not detect any positivity in plasma using PCR for cytomegalovirus, Epstein-Barr virus, adenovirus and human herpes virus 6. Pneumocystis jiroveci pneumonia was considered less probable because of ongoing antimicrobial prophylaxis, and pulmonary GVHD was excluded due to a time criteria.

OUTCOME AND FOLLOW-UP
The COVID-19 clinical picture persisted to be mild until day 16 from symptoms onset when respiratory failure began: oxygen saturation fell to 87% and an arterial blood gas analysis (patient supported with non-rebreather mask) showed a pO2 of 67.7 mmHg with normal pH and pCO2. Chest CT scan displayed bilateral basal lung infiltrates without other pathological signs; CT severity score1 was 64.1% at this timepoint (figure 2). He was hospitalised and treated with high-flow oxygen through a non-rebreather mask. Given the steroid-refractoriness of acute GVHD and the promising effect of JAK1/2 inhibition in COVID-19, the patient was switched to ruxolitinib and started a steroid tapering; rapamycin was continued according to plasma levels. Remdesivir could not be used at this time because in Italy it was reserved only for patients in the first 10 days after COVID-19 symptoms onset. Despite treatment modifications, SARS-CoV-2 positivity persisted with high viral load (cycle threshold ORF1 a/b 17.15, cycle threshold gene E 16.79). Anyway, given the presentation with low-grade fever and the profound immunosuppressive state of our patient, we searched for other possible causes that could explain these symptoms but a nasopharyngeal swab test for other respiratory viruses was negative and we did not detect any positivity in plasma using PCR for cytomegalovirus, Epstein-Barr virus, adenovirus and human herpes virus 6. Pneumocystis jiroveci pneumonia was considered less probable because of ongoing antimicrobial prophylaxis, and pulmonary GVHD was excluded due to a time criteria.

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threshold ORF1 a/b and gene E always around 18) on repeated nasopharyngeal swabs and the patient could not obtain an antibody seroconversion. For this reason, we decided to administer two 200mL doses of high-titre CCP on day 32 and day 33 from symptoms onset. On day 40, a follow-up chest CT scan revealed no signs of pulmonary thromboembolism but revealed a spontaneous pneumopericardium and pneumomediastinum with an associated extensive subcutaneous emphysema (figure 3). No sign of cytokine storm was present on laboratory analysis (figure 1). High-flow nasal cannula (HFNC) was introduced, and minor improvements were seen owing to mediastinal air reabsorption (figure 4); anyway, oxygen requirement was still high despite anti-SARS-CoV-2 antibody seroconversion. A bronchoalveolar lavage performed on day 58 turned out positive only for SARS-CoV-2, excluding coinfec-
tions. Therefore, starting from day 61 after symptoms onset, a 5-day course of off-label remdesivir was started and, following the recent experience of Hueso et al in haematologic patients with protracted COVID-19,3 we made a second attempt with other two 200mL units of CCP. After all these treatments, a slow weaning of oxygen therapy was started until day 73 when HFNC was definitively stopped. The patient finally achieved a negative molecular test for SARS-CoV-2 on day 75 from the onset of COVID-19 symptoms. He went through a rehabilitation programme achieving a substantial improvement in overall performance status and pulmonary function but, owing to a moderate restrictive deficit with a severe reduction in lung diffusion capacity due to fibrosis-like lesions that persisted in

**DISCUSSION**

The risk of intensive care unit (ICU) admission, invasive ventilation and death for patients with cancer infected by SARS-CoV-2 is twice that of the general population. The estimated 30-day overall survival after COVID-19 diagnosis is poor for allo-HCT recipients, and it is estimated around 68%.4 Older age, male sex, active disease, GvHD, ongoing steroid therapy and development of COVID-19 within 12 months of allo-HCT were associated with worse outcomes in recent studies.4–6 Our patient had four out of six of these risk factors and sustained a prolonged and severe form of COVID-19, which required high-flow oxygen support but no ICU admission. Hyperinflammatory laboratory abnormalities, like elevated interleukin 6 and C-reactive protein,
were absent in our case, excluding a cytokine storm commonly observed in severe COVID-19 cases. Profound B and T-cell lymphopenia combined with anti-inflammatory therapies with steroids and ruxolitinib possibly impaired the development of COVID-19 hyperinflammatory syndrome but, conversely, allowed persistent viral replication inducing extensive cytopathic effects on the pulmonary parenchyma.

Our case report outlines a couple of peculiar points to discuss and reflect on. First, as reported by Belletti et al., pneumothorax and pneumomediastinum occur frequently in patients with COVID-19 with acute respiratory distress syndrome requiring mechanical ventilation (24%) and are associated with a significant mortality rate, which can reach 60%. Contrarily, spontaneous pneumomediastinum and pneumopericardium are recognised as rare complications of COVID-19 interstitial pneumonia. Our patient had no risk factors associated with the development of these conditions, such as previous pulmonary disease, tobacco use or use of invasive or non-invasive ventilation, and did not undergo invasive procedures in the previous weeks such as positioning of a central venous line. The mechanism behind these phenomena can be explained by the Macklin effect: air released after alveolar rupture, caused by barotrauma, reach the mediastinum moving through the perivascular and peribronchial sheaths and thereafter extend into the pericardium. Increased alveolar pressure and diffuse alveolar injury in severe COVID-19 pneumonia is common, which may make the alveoli prone to rupturing. These complications are usually self-limiting and, if not massive, require no specific intervention. In our patient the air gradually reabsorbed, thanks to the low positive end-expiratory pressure provided by HFNC, and it was completely absent in a CT scan performed 2 weeks after.

Second, remdesivir treatment was able to reduce the time to recovery in adults hospitalised with COVID-19, but the analysis was not focused on immunosuppressed patients. As for CCP, its results are discordant: several trials fail to demonstrate clinical improvement compared with the placebo arm, while its results are discordant: several trials fail to demonstrate clinical improvement compared with the placebo arm, while the persistence of SARS-CoV-2 in this severely immunosuppressed patient, allowing recovery from COVID-19 pneumonia at last. The prolonged but not critical clinical course observed is probably related to the ability of antibodies to induce both viral clearance and progression to a hyperinflammatory life-threatening disease. Without a working immune system and owing to anti-inflammatory therapies, COVID-19-related hyperinflammation never appeared, and viral replication was probably the only factor responsible for a slow and steady pulmonary damage. The cytopathic effect of SARS-CoV-2 may also have been the cause of pneumomediastinum and pneumopericardium, given the absence of other typical risk factors.

Immune dysregulation during SARS-CoV-2 infection has been implicated in pathogenesis. Mathew et al. revealed the existence of three immunotypes displaying different patterns of lymphocyte responses in hospitalised patients with COVID-19. These three major patterns may each represent a different suboptimal response, ranging from a robust active CD4+ and CD8+ T-cell activity to a lack of obvious activated B and T-cell reactivity, reflecting different clinical patterns, disease severity and progression of COVID-19. All data derived from our case seem to confirm this observation, placing our patient in the immunotype without a valid immune activation, and suggesting that a timely treatment directed towards viral clearance (antiviral drugs, CCP, neutralising monoclonal antibodies anti-SARS-CoV-2) is the best option for curing COVID-19 in severely immunosuppressed patients.

Finally, post-COVID-19 ILD, an important yet not fully elucidated complication of SARS-CoV-2 infection impaired the overall beneficial effect of the treatments we administered. This pulmonary sequelae is part of the post-acute COVID-19 syndrome, a new clinical entity that affects up to 40% of long-term survivors of SARS-CoV-2 infection. Since there are still no specific guidelines for the management of these patients, according to a preliminary experience documenting a symptomatic and radiological improvement with the use of corticosteroids in a small cohort of survivors with post COVID-19 ILD, we attempted in this case to maintain a low-dose steroid therapy, obtaining only a subjective but not functional and radiologic improvement. The cytopathic effect of the virus, the prolonged hypoxia and exposure to high-flow oxygen therapy could represent the risk factors for the development of a persistent ILD in our immunosuppressed patient. As new evidence on the pathophysiology of post-acute COVID-19 syndrome emerges, further clinical trials appear, including some studies with antifibrotic therapies for ILD, with the aim not only to cure the acute phase of SARS-CoV-2 infection but also to prevent the serious long-term adverse effects of the disease.

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Case report
Case report

Patient's perspective

It was the end of November when I realized that I had the virus and, starting from there, it began a long battle between me and my lungs. Because I was coming from a hard cycle of treatments for my leukemia, I was extremely weak at that time and the COVID-19 only aggravated the situation and kept me on a hospital bed for 3 months and a half. Anyway, I never gave up and, thanks also to the wonderful help from the doctors, nurses, and all the hospital personnel, I finally managed to win the battle and return safely home.

Learning points

- COVID-19 in immunosuppressed hosts is characterised by a prolonged and complicated course, mainly driven by the cytopathic effect of the virus.
- A timely treatment with remdesivir and COVID-19 convalescent plasma is a good option for treating COVID-19 in immunosuppressed patients.
- Spontaneous pneumomediastinum and pneumopericardium are a possible rare complication of SARS-CoV-2 infection.
- Post COVID-19 intestinal lung disease is a challenging and severe long-term complication of acute SARS-CoV-2 infection.

Patient consent for publication Consent obtained directly from patient.

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