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Case Report

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Atypical Course of SarsCov-2 Infection in a Patient with Multiple Myeloma Treated with Autologous Stem Cell Transplantation

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ABSTRACT
Covid-19 infection has more relevant consequences in frail and comorbid patients, but little is known about its course in patients with hematologic malignancies. In this report, we would like to present the case of a patient with multiple myeloma treated with recent autologous bone marrow stem cell transplantation and affected by Covid-19 pneumonia, presenting with a possible reinfection or an extremely long viral shedding.

Keywords: Covid-19; Multiple myeloma; Hematopoietic stem cell transplantation

Case presentation

The patient was a 63-year-old man suffering from multiple myeloma IgG kappa. He underwent autologous bone marrow stem cell transplantation (on October 19th). His pathological anamnesis included arterial hypertension and chronic obstructive pulmonary disease (COPD) with a reduced pulmonary capacity because of a prominent kyphotic deformation of the rib cage. Due to his hematological disease, the spirometry carried out in January 2020 showed a severe restrictive pulmonary impairment (FEV1 37%), severe reduction of carbon monoxide diffusion capacity (DLCO 37%), and signs of air trapping. Before transplantation, the patient underwent a *pneumatology* evaluation (August 2020), confirming a mild restrictive pulmonary impairment and a moderate DLCO reduction compared to the spirometry of January 2020. At diagnosis, he received six cycles of induction therapy with Bortezomib, Thalidomide, and Dexamethasone (VTd), and he obtained a very good partial response. Thereafter, he received cyclophosphamide 3g/mq as mobilization regimen followed by peripheral stem cell collection. On October 17th, he was treated with a cycle of reduced dose chemotherapy with melphalan (100 mg/mq instead of 200 mg/mq because of the reduction of DLCO to the *pneumatology* examination) followed by autologous stem cell transplantation (ASCT) on October 19th. Aplasia occurred from October 25th to October 30th, and he was treated with granulocyte-colony stimulating factor (G-CSF) from October 22nd to October 31st. During the aplasia phase, he developed

fever with a suspected left maxillary abscess treated with Piperacillin/Tazobactam (4,5 g four times a day) and Daptomycin (400 mg daily) for seven days with resolution of symptoms and normalization of laboratory inflammatory indexes. He was discharged on November 3rd, and his home therapy included antiviral prophylaxis with Acyclovir 400 mg twice daily and antibacterial prophylaxis with Trimethoprim/Sulfamethoxazole twice a week while he was not taking immunosuppressive drugs.

On November 6th, the patient was admitted to the Emergency Department with a blood pressure of 125/80 mmHg, an oxygen blood saturation of 96% on room air and fever (38.1°C). The arterial blood gas analysis showed the following values: pH 7.46, pO2 80, pCO2 33, HCO3- 25.

Other most relevant blood values were: white blood cells (WBC) 12.57 cells/mm3 (neutrophils 10.38, lymphocytes 1.06), hemoglobin 10.2 g/dl, creatinine 1 mg/dl, c- reactive protein (CRP) 22.5 mg/l, procalcitonin (PCT) 0.1 ng/ml, D-dimer 1180 ng/ml, LDH 423 U/l, fibrinogen 426 mg/dl. The result of a routine Sars-CoV2 nasopharyngeal swab (obtained with FLOQSwabs- Flexile Sterile Single Wrapped, Molded bp 100 mm- and transported with Universal Viral Transport -UTM- 3 ml, Copan, Brescia, Italy) was positive.

Chest X-ray showed an area of hypodiaphany in the basal fields of both lungs (negative for pneumonia).

The patient was treated with low dose low molecular weight heparin (LMWH), and he remained clinically stable for the length of the hospitalization without oxygen supplementation or antibiotic-steroid treatment. The second nasal swab was still positive on November 13th so he was discharged on November 18th on self-quarantine. The third nasal swab of November 20th was negative.

After a period of well-being, on December 5th, the patient manifested fever again, with dyspnea (saturation was 85% on room air). He was given Levofloxacin (5 days) and oxygen supplementation in a nasal cannula by his general practitioner (GP) without benefit. On December 11th, the patient was admitted again to the Emergency Department of the same Hospital for persistent dyspnea and fever (body temperature: 38°C). At admission to the Emergency Department, he had a blood pressure of 130/90 mmHg and oxygen blood saturation was 92% on room air; the main blood values were: WBC 7.27 cells/mm3 (N 6.73, L 0.41), hemoglobin 7.8 g/dl, creatinine 0.71 mg/dl, CRP 168.2 mg/l, PCT 0.19 ng/ml, D-dimer 6605 ng/ml, LDH 329 U/l, ferritin 668 ng/ml. Nasopharyngeal swab for Sars-CoV2 was positive and arterial blood gas analysis (FiO2 27%) showed the following values: pH 7.48, pCO2 33, pO2 92, HCO3- 25.7, P/F 296. Due to the anemia, the patient underwent a blood transfusion on December 12th, with the improvement of hemoglobin levels (8.5 g/dl), and three fecal occult blood tests were performed and proved negative results (29 ng/ml on December 14th, 27 ng/ml on December 15th, 6 ng/ml on December 16th).

Chest X-ray showed an area of hypodiaphany in the superior field of the right lung confirmed by the chest CT (ground grass areas were present bilaterally in the superior fields and in the apical area of the inferior fields; in the remaining fields there were similar but smaller alterations of the parenchyma). Blood cultures were negative, but he was empirically treated with Piperacillin/Tazobactam eV (4,5 g three times a day) and fluid supplementation. During the second day of hospitalization, oxygen supplementation with Venturi Mask (FiO2 50%) and Corticosteroids (Dexamethasone 6 mg once daily) were required due to a sudden reduction of oxygen blood saturation to 90% (with the following blood gas analysis values: pH 7.44, pCO2 40, pO2 79, HCO3- 27.2, P/F 198). During the fourth day of hospitalization, since the laboratory inflammatory indexes started to increase and there were no significant clinical improvements, therapy with Piperacillin/Tazobactam was turned to Ceftobiprole eV (500 mg three times a day).

Clinical conditions gradually improved from the sixth day of hospitalization, and oxygen supplementation was progressively reduced (on December 17th, blood gas analysis, with FiO2 26%, showed the following values: pH 7.44, pCO2 46, pO2 90, HCO3- 31, P/F 438). On December 21st, oxygen supplementation was stopped. The day after, the patient was discharged with the following parameters: blood pressure 140/80 mmHg, heart rate 70 bpm, SpO2: 96% on air and body temperature 36 °C. Sars-CoV2 nasopharingeal swab was still positive.

DISCUSSION

This case report should be helpful for several reasons. Infections are a significant cause of morbidity and a leading cause of death in MM patients, and it has been shown that MM patients display a low immune response to infections. For this reason, these patients are particularly susceptible to infections[1]. B-cell immunodeficiency is the primary defect, manifested by hypogammaglobulinemia and increased risk of infections caused by encapsulated bacteria, while lymphocytopenia and neutropenia are secondary to bone marrow infiltration; T cell, dendritic cell, and NK cell abnormalities are also present[1,2].

Autologous hematopoietic stem cell transplantation (HSCT) is a major component of the treatment approach to MM, and pneumonia is a common complication during the early post-engraftment period (days 30 to 100 after HSCT); respiratory viruses may cause both upper and lower respiratory tract infections[3,4], and Sars-CoV2 is among the group of viruses that can cause pneumonia after HSCT. Prolonged asymptomatic viral shedding may also occur without the presence of clinical illness in immunocompromised patients[5].

We think this case report lends itself to multiple discussions: is this the case of a SarsCov-2 re-infection? If yes, immunodeficient patients may be exposed to the continuous risk of infection. The susceptibility of previously infected individuals to secondary infections with SARS-CoV-2 is not well understood, and cases of reinfection have been described in reports published from Hong Kong, the Netherlands, Belgium, Ecuador, and Nevada. The cases of reinfection in North America and Ecuador showed severe symptoms in their second infection. Meanwhile, the cases from Belgium, the Netherlands, and Hong Kong showed the same severity of symptoms[6]. The greater severity of symptoms could be explained by different hypothesis: the higher dose of virus, the more virulent versions of the virus or a mechanism of antibody dependent enhancement (previously seen in other beta-coronaviruses responsible of acute respiratory syndrome) may cause the second infection[6].

In contrast, in our patient, we could suspect the case of a false negative nasal swab, but longer viral positivity for specific patients with frailty should be considered as compared to not frailty ones. Moreover, the detection of pneumonia only during the second hospital admission might induce to suspect a hospital acquired pneumonia (HAP). At this point, several questions arise: how long this disease lasts in immunodeficient patients. Do the clinical and radiological manifestations start later in these patients? Do we treat them with specific protocols? How high the viral load and the contagion are in these patients? It is very difficult to answer these questions. Probably, the immunity and the inflammatory responses play a crucial role on the infection's onset, course, and resolution.

Regarding autologous stem cell transplantation, the normalization of humoral levels and cellular immunity may take more than one year[7]. Innate immunity is compromised because epithelial barriers are disrupted by chemotherapy[8]. The total number of CD19+ and CD 20+ B cell remain low in the first three months and increase gradually in the following 18 months after engraftment; however, B cell function remains inefficient because a decrease in T cell help to intrinsic B cell defects[7]. Serum Ig levels remain low in the first three months, with normalization of IgM levels during six months, of IgG levels during 12 to 18 months, and of IgA levels after years[7,9]. The quantitative and functional recovery of T cell subsets (CD3, CD4, and CD8) did not normalize for a year or more, and we observed an inverted CD4/CD8 ratio. NK cells were the first lymphocyte subset to recover, and their number and function became normal two weeks after HSCT[7].

Immunocompromised patients with Covid-19 infection have different clinical features such as viral incubation period and duration of shedding, onset and duration of clinical signs and symptoms, viral detection, and associated laboratory features[10]. Indeed, patients with profound immunosuppression after undergoing stem cell transplantation or receiving cellular therapies may shed Sars-CoV2 for at least two months[11] and may not have typical symptoms of Covid-19[12].

CONCLUSION

Further studies are required to investigate the evolution and consequences of SarsCov-2, particularly in selected patients. Protocols adopted for SarsCov-2 infection are probably valid or partially valid for most patients, but the case of recent bone marrow stem cell transplantation requires more attention.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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