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Convalescent Plasma Treatment in Patient with Multiple Myeloma and Severe Sars-Cov-2 Infection

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Abstract

Multiple myeloma (MM) is a plasma cell dyscrasia characterized by uncontrolled cell division, leading mainly to kidney and bone damage. Since it affects the cell specialized in producing antibodies, the disease can cause immunodeficiency. This can be temporarily accentuated by chemotherapy, which could explain the high mortality rate of patients with MM and COVID-19. This report describes a 63-year-old woman with relapsed MM and severe SARS-CoV-2 infection, which presents a clinical picture of progressive deterioration of respiratory function, requiring invasive mechanical intubation because there was no clinical response to the usual treatment; convalescent plasma was administered, evidencing recovery of ventilatory parameters after infusion. The patient was extubated and discharged from the Hospital in good general condition.

Keywords: multiple myeloma; convalescent plasma; COVID-19; SARS-CoV-2.

1. Introduction

MM is a neoplastic disease that derives from plasma cells, affecting humoral and cellular immunity and therefore giving patients a greater risk of mainly respiratory infections [1]. In addition, immunosuppression can be exacerbated by the combined use of antineoplastic drugs [2].

Both, the biology and treatment of MM, could affect the production of antibodies against SARS-CoV-2, which would explain the high mortality rate (24-29%) described in patients with MM and COVID-19 [3,4]. In this group, the transfer of anti-SARS-CoV-2 antibodies obtained from subjects recovered from infection [5] could be a therapeutic alternative.

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For these reasons and because MM is the second most common hematological malignancy, the clinical course of a patient with MM and COVID-19 treated with convalescent plasma (CP) in the HRLBO is described below.

2. Case report

A 63-year-old female patient with a history of type 2 diabetes mellitus (T2DM) and systemic arterial hypertension (SAH), was diagnosed with MM type IgG lambda ISS 3 in 2017. For that reason, she received CTD (Cyclophosphamide 350 mg/m^2 on days 1, 8, 15, and 22; thalidomide 100 mg/day continuous and dexamethasone 40 mg/day on days 1-4 and 15-18; every 28 days for 6 cycles) as induction treatment, achieved remission and was in maintenance with thalidomide (100 mg/day) and dexamethasone (40 mg days 1-4, every 28 days). In February 2020, she began to present bone pain, limitation for walking and asthenia, describing the presence of monoclonal component class IgG lambda type in the immunofixation of heavy and light chains of serum, Beta-2 microglobulin: 2.4 mg/L (VR: 0. 54-3. 86), IgG: 2230 mg/dL (VR: 751-1560), IgA: 236 mg/dL (VR: 82-453), IgM: 53 mg/dL (VR: 46-304); finally, a bone marrow biopsy was performed, evidencing infiltration by 80% of abnormal plasma cell.

For these reasons, and because the relapse was after >6 months, the CTD scheme was indicated again; before the beginning of the fifth cycle, the state of the disease was evaluated and a decrease in the component (paraprotein 0.3 g/dL) and hypogammaglobulinemia subclass IgM (IgA: 180 mg/dL, IgG: 1330 mg/dL, IgM: 36.2 mg/dL) was determined. While receiving the fifth cycle, she began to present non-productive cough, dyspnea and myalgia (October 20, 2020. Because of the symptoms persisted for 48 hours, she decided to go to the health center where she was evaluated, and oxygen saturation of 86% was evidenced; for these reasons oxygen therapy was indicated by nasal cannula at 2-3 L, and a nasal swab sample was taken for RT-PCR of SARS-CoV-2 whose result was positive. Due to the identification of rapid clinical deterioration, she was referred to the HRLBO where she was admitted on 10/22/2020 to the Intensive Care Unit, whose clinical characteristics are summarized in Table 1.

On admission, a pO_2 of 69.1 mmHg, pCO_2 of 51.3 mmHg, and oxygen saturation of 92.8% were documented; bilateral diffuse interstitial infiltrates with apical predominance, atelectasis band in the lower lobe of the right pulmonary field and pleural effusion were evidenced by chest x-ray (Figure 1A). Therefore, it was decided to intubate partially, thus improving ventilatory parameters (pO_2: 70.2 mmHg, oxygen saturation: 95.1%, FiO_2: 0.35; PaO_2/FiO_2: 200). The patient received supportive treatment based on dexamethasone (6 mg/day) and enoxaparin (60 mg every 12 hours).

Table 1: Clinical characteristics of this report and two cases described in the literature.

	This case	**Case 1**	**Case 2**
Age (years)	63	88	72
Sex	F	M	F
Illness	MM IgG lambda	MM IgG kappa	MM IgG kappa
GM Status	Relapse	Relapse	Relapse
Antineoplastic treatment	Yes	Yes	Yes
Type of treatment	Thalidomide and dexamethasone	Daratumumab, lenalidomide, and dexamethasone	Cafilzomib
Comorbidities	SAH, type 2 diabetes mellitus	SAH, dyslipidemia, AF, benign prostatic growth	CKD
Symptoms of COVID-19	Cough, shortness of breath, and myalgia	Shortness of breath, fever, and weakness	Shortness of breath, cough, wheezing, diarrhea, and nausea
Survival status	Alive	Alive	Alive
Leukocytes (x 10^3/mm3)	9.2	2.8	Leukopenia*
ANC (x 10^3/mm3)	6.4	2.6	ND
ALC (x 10^3/mm3)	2.8	0.08	Lymphopenia *
Hb (g/dL)	16.3	7.8	ND
Platelets (x 10^3/mm3)	182	58	ND
Paraprotein (g/dL)	0.3	ND	0.36
C-reactive protein (mg/dL)	36.37	7.8	ND
D dimer (ng/mL)	330	ND	ND
Reference	NA	Abid and colleagues [10]	Luetkens and colleagues [11]

*F= Female, M= male, MM= Multiple myeloma, SAH= Systemic arterial hypertension, AF= Atrial fibrillation, CKD= Chronic kidney disease, ANC= absolute neutrophil count, ALC= Absolute lymphocyte count, ND= Not described, NA= Not applicable, *= Absolute value not reported.*

As shown in Graph 1, the pressure and oxygen saturation were progressively worsening, requiring more supplemental oxygen and a decreasing PaO_2/FiO_2 (Days -5 to 0); given this situation, on October 28 (Day 0) she was administered 200 cc of CP supplied by the central venous catheter. Afterwards, improvement in ventilatory parameters was observed /after 24 hours (Day 1) and 48 hours (Day 2) of transfusion. Inflammatory markers were improving and no significant changes in blood count were evidenced during hospitalization (data not shown). From the radiological point of view, a decrease in infiltrate was observed 5 days after transfusion (Figure 1B).

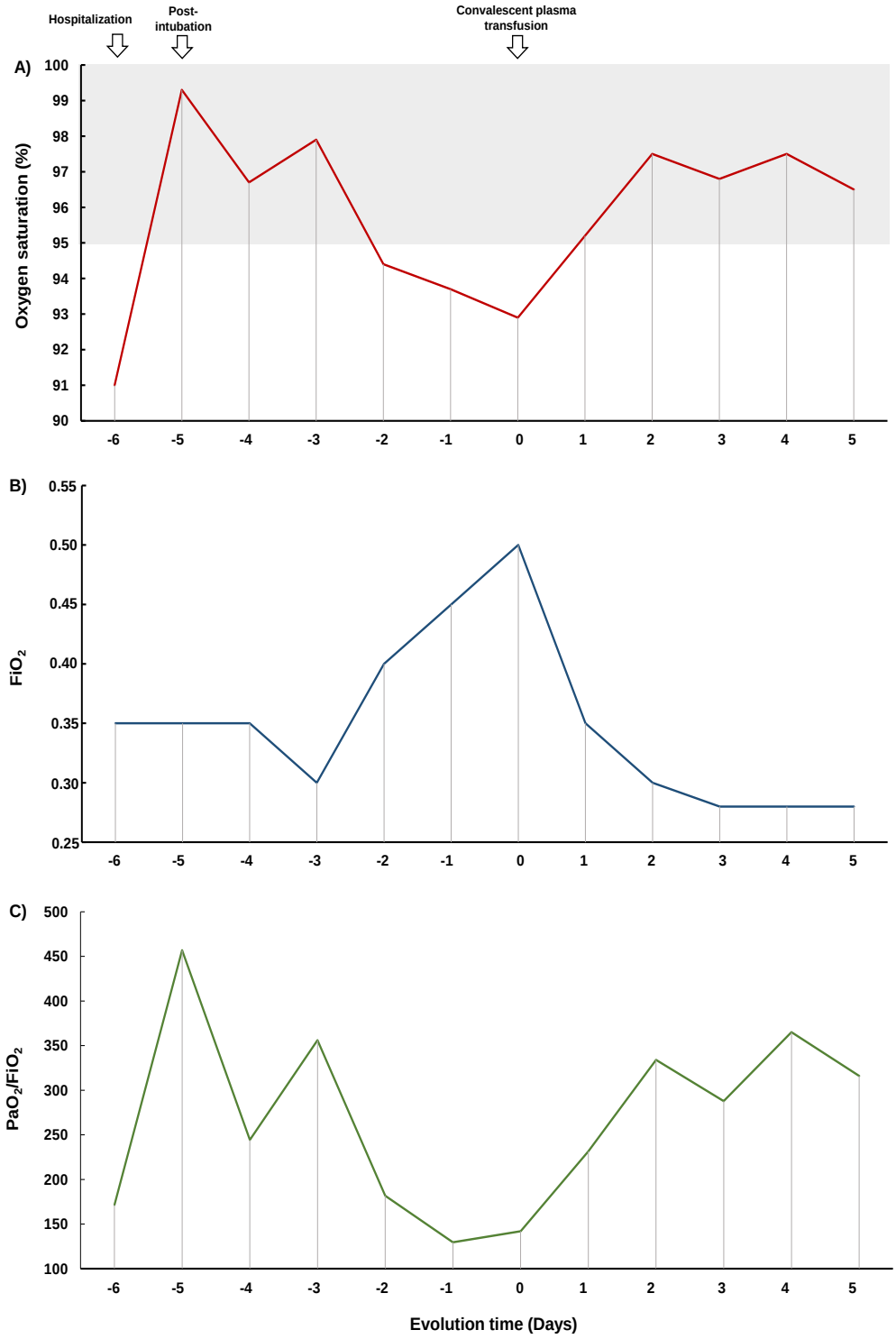


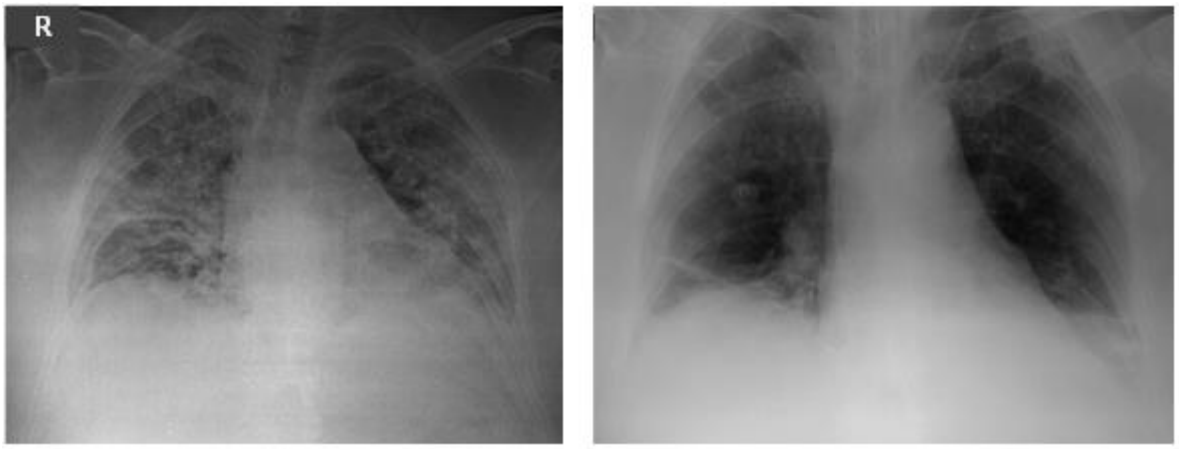
Figure 2: Evolution of ventilatory parameters before and after convalescent plasma transfusion.

FiO2= Inspired fraction of oxygen; PaO2/FiO2= Ratio of oxygen partial pressure to inspired oxygen fraction; Gray area= normal value.

Due to the stabilization of ventilatory parameters during days 2 to 5 (Graph 1), extubation was scheduled, which was successfully performed on 05-11-2020 (Day 9), then the patient was transferred to the Intermediate Care

Unit and subsequently discharged.

The report is part of a study approved by the Scientific Ethics Committee of the Eastern Metropolitan Health Service, Chile. Informed consent was obtained from the patient.



(A) (b)

Figure 1: Chest x-ray at diagnosis and post-transfusion of convalescent plasma.

Chest x-ray in bed with portable equipment. A) X-ray at diagnosis, bilateral diffuse interstitial infiltrates with apical predominance, atelectasis band in the lower lobe of the right pulmonary field, and pleural effusion; B) Image obtained on day 5 after the transfusion of convalescent plasma, where improvement of the infiltrate is evident.

3. Discussion

The impact of SARS-CoV-2 infection on MM patients remains unclear. A series of 100 subjects with MM and COVID-19 exposed the heterogeneity of treatment in this segment of patients, some being treated with hydroxychloroquine, azithromycin, IL-6 blockers, lopinavir-ritonavir and remdisivir [3].

CP has been described as effective in the treatment of patients with COVID-19 and primary or secondary immunosuppression; in this last group, the response of 54 cases with different hematological malignancies was analyzed, evidencing significant reduction in oxygen requirement and viral clearance after treatment with CP [6].

In the present report, the excellent evolution of a patient treated with CP who developed rapid deterioration of respiratory function and who had different risk factors (such as hypertension, T2DM, hypogammaglobulinemia, and cancer in chemotherapy) was described. Although the symptoms were consistent with those described in a sample of 75 patients with MM and COVID-19 [7], orotracheal intubation was necessary within 48 hours from its onset. Unlike what was described by Hultcrantz and colleagues [3] in a similar sample, in the present case, there was no evidence of lymphopenia during infection. In addition, this report observed a reduction in the

concentration of IgM prior to the diagnosis of COVID-19, like those described by Cook and colleagues who documented hypogammaglobulinemia in 90% of patients with MM and COVID-19, with the IgM subclass being affected in second place [7].

Due to the relapse of the MM, the patient was receiving the CTD protocol, which can lead to myelosuppression and, therefore, to a state of immunodeficiency. In this order of ideas, the drug thalidomide stands out, whose mechanism of action includes the inhibition of the synthesis of specific inflammatory cytokines and stimulates the production of IL-2 and interferon-gamma [8]. Although the effect of thalidomide in patients with COVID-19 is not fully established, recently Gadotti and colleagues indicated that a higher concentration of interferon-gamma is associated with an increased risk of death in patients with moderate or severe COVID-19 [9]. Due to the biology of MM, many patients are receiving antineoplastic treatment chronically, experiencing greater or lesser immunosuppression. Information obtained from 5 centers in New York indicated that 86% of patients with MM were on treatment at the time of contracting SARS-CoV-2 infection [3]. This highlights the importance of having a treatment that allows rapid control of infection in subjects with MM, as well as other types of cancer, making PC transfusion a safe alternative.

To date, only a few cases have been published describing the clinical benefit of CP in patients with MM [4,10,11]. Table 1 summarizes the characteristics of the present report, as well as some published clinical cases such as those described by Abid and colleagues [10] and Luetkens and colleagues [11], in the cases the disease was active, and all were receiving salvage chemotherapy, this situation could accentuate the humoral immunodeficiency; however, convalescent plasma was administered in all case reports, and clinical improvement of SARS-CoV-2 infection was evidenced. Wang's group described their experience with 58 patients with plasma cell dyscrasia, where one patient was treated with CP (details are not shown in the publication) [4].

In the present case, no transfusion reactions were evidenced, and a notable reduction in supplemental oxygen requirement and an increase in oxygen saturation after PC transfusion were determined (Figure 1). Our patient, like the others described in the literature with baseline characteristics and similar treatment [4,10,11], recovered from the infection and are alive. A recently published meta-analysis that included 1560 participants with immunodeficiencies demonstrated that transfusion of COVID-19 convalescent plasma was associated with a decrease in mortality (risk ratio: 0.63; 95% CI: 0.50-0.79) [12].

Although anecdotal cases are available so far, there is information suggesting that individuals with hematological malignancies may have a different clinical course. Baang and colleagues described the case of a patient with refractory mantle lymphoma in which the persistence of viral replication and its infectious capacity for 119 days was documented through viral culture and, and the patient required analysis of genetic material 3 hospitalizations related to COVID-19 in a period of 4 months [13]. It has also been determined that patients with MM and hypertension (such as this report) have a significantly higher risk of death, requiring intensive therapy or mechanical ventilation (OR: 3.5; 95% CI: 1.5-8.1) [3].

Although mass vaccination will allow greater control of infection, there are data that have shown that the

effectiveness of vaccines in patients with MM is lower; therefore, the *European Myeloma Network* has recommended to measure the titer of protective antibodies and/or repeat immunization [14]. In addition, the description of SARS-CoV-2 variants with mutations in E484 can cause reinfection [15], because its neutralization is 35-60 times lower than the wild type [16].

For all of the above reasons, there is a need to continue investigating the effectiveness of CP transfusion in more vulnerable segments of the population, such as immunosuppressed individuals.

4. Limitation

This study had a limitation in that it was impossible to determine the titer and type of transfused antibodies and quantify the SARS-CoV-2 burden as a response marker.

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