Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Transfusion and Apheresis Science 59 (2020) 102921

Contents lists available at ScienceDirect

Transfusion and Apheresis Science

journal homepage: www.elsevier.com/locate/transci

No transmission of SARS-CoV-2 in a patient undergoing allogeneic hematopoietic cell transplantation from a matched-related donor with unknown COVID-19

ARTICLE INFO

Keywords
Hematopoietic stem cell transplantation
Transfusion-transmitted disease
Blood safety
COVID-19
SARS-CoV-2

ABSTRACT

The Hematology Department and its Hematopoietic Cell Transplantation (HCT) program implemented several measures during COVID-19 outbreak in order to keep clinical activities with the maximum security for both donors and recipients. Nevertheless, there was a lack of evidence whether blood products and specifically bone marrow can cause transfusion-transmitted infection. Initially, there were many uncertainties and did not exist formal recommendations.

Before official statements were available, we performed an allogeneic HCT in a 57-year-old male from a related matched donor in the incubation period of COVID-19 where the patient did not develop the disease.

Actual epidemiology data suggest that transmission may occur early in the course of infection, even from asymptomatic patients in the incubation period. In our knowledge this is the first case report of an adult hematopoietic cell donor with COVID-19 in the incubation period where the transplant is successfully completed with no transmission of SARS-CoV-2. The low concentration of viral RNA in plasma of patients with COVID-19 could support the safety of blood products, including peripheral blood hematopoietic cells.

In conclusion, blood products including hematopoietic stem cells are safe in the context of COVID-19 pandemic.

1. Case description

We report the case of a 57-year-old male diagnosed with a relapsed mantle cell lymphoma, who started conditioning on March 7th for a matched related donor HCT from his sister. His donor, who was living in Brazil, traveled to Spain in order to start mobilization. She was asymptomatic during the medical examination before mobilization and prior to the apheresis.

The apheresis was successful, collecting 6.45 $\times$ 10^6/kg of CD34+ cells, and no ex vivo manipulation of the graft was performed. A reduced intensity conditioning regimen was preferred due to comorbidities and previous autologous HCT. There were no adverse effects during chemotherapy except grade 1 nausea and no significant complications were reported during infusion.

The medical team were alarmed from the patient himself on day +3 that the donor had a positive nasopharyngeal PCR SARS-CoV-2 test on arrival to Brazil, which was performed considering Spain a risk area for COVID-19. Because of the pandemic, visitors were banned in our Hematopoietic Transplantation Unit, so the patient had not received visits from his sister since admission. SARS-CoV-2 nasopharyngeal PCR tests were subsequently performed every 48 h even though the receptor was asymptomatic, and all of them resulted negative. On day +11, the patient had febrile neutropenia. Blood and urine cultures, serology test for *Mycoplasma pneumoniae*, *Chlamydophila pneumoniae*, urine antigen test for *Legionella pneumophila*, and a new nasopharyngeal swab were negative. Chest X-ray showed a small left pulmonary infiltrate, not suggestive either of COVID-19. He did not require oxygen supplementation and completed antibiotic treatment with Cefepime and Levofloxacin for 7 days. After that, he remained afebrile and 2 consecutive PCR of SARS-CoV-2 were negative. Neutrophil and platelet engraftment occurred on day +18 and +16, respectively. He was discharged on day +24, and no other transplant-associated complications were reported. In the day +100 evaluation he remained in complete response, with a complete graft function and full chimerism. Serology test for SARS-CoV-2 were negative both for IgM and IgG.

2. Discussion

At the beginning of the COVID-19 outbreak, there was a lack of evidence about the capacity of transmission of SARS-CoV-2 in blood products, including hematopoietic cells from peripheral blood.

In our knowledge this is the first case report of an adult hematopoietic cell donor with COVID-19 in the incubation period where the transplant is successfully completed. Recently, Anurathapan et al. published a similar case on a 7-year-old where transmission through bone marrow did not occur [1], but they counted with a tested negative bone marrow for SARS-CoV-2 by RT-PCR prior to infusion. In our case, we did not perform a SARS-CoV-2 PCR in the donor due to the lack of symptoms and formal recommendations at the time of apheresis. However, the capacity of infection during asymptomatic incubation period in COVID-19 has been consistently documented. This period has been shown to be of 5 days approximately (5.2 days, 95 % confidence interval, 4.1–7) [2], suggesting that 3 days before diagnosis, our donor was very likely already infected. In addition, viral load in upper respiratory specimens from symptomatic and asymptomatic patients were similar in an analysis [3]. All this data suggests that transmission may occur early in the course of infection.

Initially, there was also a lack of practical experience about the impact this new virus may have in patients undergoing HCT. The Hematology Department and its Hematopoietic Cell Transplantation program implemented several measures in order to keep the clinical

https://doi.org/10.1016/j.transci.2020.102921
Received 28 July 2020; Received in revised form 4 August 2020; Accepted 4 August 2020
Available online 24 August 2020

activities with the maximum security for both donors and recipients. Diverse recommendations about the safety of blood products were lately incorporated [4]. In Spain, the first official statement about HCT and COVID-19 was made by the Spanish National Organization of Transplants (ONT), on March 11th [5]. Parallel to other international recommendations [6] it advocates to exclude donors if COVID-19 is suspected, to test the donor prior mobilization and to cryopreserve the product at least 14 days. The Spanish Hematopoietic Stem Cell Transplantation Group (GETH) also advised about the safety of cryopreservation and need of keeping the product in the center facilities prior to conditioning, on March 18th [7]. Therefore, when the conditioning was initiated in our patient, there were no formal recommendations about cryopreservation of bone marrow products. Nevertheless, from this case we implemented a strict protocol consisting in test donors twice: first, prior to mobilization and second, prior to apheresis. Even though transmission through blood products is not demonstrated, a positive result should exclude the donor.

Theoretically, many conclusions can be taken from SARS-CoV-2 similarity to SARS-CoV and MERS-CoV. There are several reports that confirm that both viruses can be detected in blood. Also, viral RNA could be isolated in plasma or serum from COVID-19 asymptomatic patients in a very low concentration [4]. It has been reported that ACE2, which has been described as the main receptor for SARS-CoV-2, is expressed in hematopoietic stem and progenitor cells especially under hypoxia situations [8]. In 2004 it was found that lymphocytes have higher concentration of SARS-CoV than plasma and that it can replicate inside them [4]. This could mean that blood products containing lymphocytes (like peripheral blood hematopoietic cells) would be more infectious than plasma. By contrast, this statement could not be demonstrated with MERS-CoV which induces T-cell apoptosis causing lymphopenia but cannot replicate inside T lymphocytes [9]. SARS-CoV-2 is also known for causing lymphopenia, suggesting a similar pathogenic mechanism to MERS-CoV, though it has not been yet demonstrated.

Currently, the AABB, FDA, and centers for disease control do not require any action on blood collection and testing because there is no data suggesting a risk of transfusion-transmitted infection of SARS-CoV-2. However, in case of individuals diagnosed with COVID-19 or who are suspected of having COVID-19, donation should be deferred at least 14 days since resolution of the symptoms or the date of the positive test. AABB also recommends to consider retrieval and quarantine of blood products if donors report fever or respiratory symptoms within 48 h after their donation [10].

Lastly, applied to our case, the low concentration of viral RNA in plasma of asymptomatic patients with COVID-19 [5], and a theoretical inefficacy of SARS-CoV-2 to replicate inside lymphocytes could support the safety of blood products, including peripheral blood hematopoietic cells.

3. Conclusion

In conclusion, this case report illustrates that HCT from a donor with positive SARS-CoV-2 nasopharyngeal PCR in the asymptomatic incubation period does not cause COVID-19 in the recipient. We could conclude that our case supports the current evidence about blood products safety in donors with asymptomatic COVID-19.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

CRediT authorship contribution statement

P. Lázaro del Campo: Conceptualization, Methodology, Writing - original draft. **A. Ramírez López:** Writing - review & editing. **B. de la Cruz Benito:** Writing - review & editing. **R. de Paz Arias:** Conceptualization, Methodology, Resources. **K. Humala Barbier:** Resources. **I. Sánchez Vadillo:** Resources. **A. López de la Guía:** Resources. **T. de Soto Álvarez:** Resources. **V. Jiménez Yuste:** Conceptualization, Methodology, Supervision. **M. Canales Albendea:** Conceptualization, Methodology, Writing - review & editing, Supervision.

Acknowledgments

The authors wish to thank all the Hematology staff for its immense work during this period taking care of our patients. We would like to thank also Aurora del Campo and Elena Garrido who provided writing assistance.

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