

Post-Allograft Anti-Phospholipid Antibody (APLA) Syndrome – A Case Report

Beddou G^{1*}, Skalli H¹, Raissi A², Yahyaoui H¹, Benjelloun I¹, Ait Ameer M¹, Chakour M¹¹Biological Hematology Department, Military Hospital Avicenne, Marrakech, Morocco²Clinical Hematology Department, Military Hospital Avicenne, Marrakech, MoroccoDOI: [10.36347/sjams.2020.v08i01.030](https://doi.org/10.36347/sjams.2020.v08i01.030)

| Received: 08.01.2020 | Accepted: 15.01.2020 | Published: 22.01.2020

*Corresponding author: Beddou Ghita

Abstract

Original Research Article

The production of autoantibodies after a hematopoietic stem cell allograft is a fact observed in hematology and often observed during graft versus host disease (GVHD) following an immune disturbance, however studies have shown the possibility of transferring B cells memory from a donor to the recipient and be responsible for autoimmune manifestations similar to that observed in the donor. We present here an extremely rare case of a manifestation of an isolated anti-phospholipid syndrome, 7 years after allograft in a patient whose donor is always asymptomatic. The appearance of autoantibodies was preceded by the appearance of chronic GVHD and the patient posed a management problem in the face of her persistent thrombocytopenia. The distinction between the manifestation of chronic GVHD and adoptive immunity is necessary due to the prognostic and therapeutic differences between these two entities.

Keywords: hematology, (GVHD), allograft, thrombocytopenia.

Copyright @ 2020: This is an open-access article distributed under the terms of the Creative Commons Attribution license which permits unrestricted use, distribution, and reproduction in any medium for non-commercial use (NonCommercial, or CC-BY-NC) provided the original author and source are credited.

INTRODUCTION

Allogeneic hematopoietic cell transplantation is based on the destruction of the future recipient's (host) bone marrow, secondarily replaced by that of the donor (graft) [1]. The main complication after this transplant is the graft versus host disease (GVHD). It manifests mainly by: cutaneous and/or mucous, but sometimes digestive and respiratory symptoms [2]. However, certain autoimmune or inflammatory pathologies after bone marrow transplantation (MO) can be signs of chronic graft against host disease (GVHD), by production of self-reactive B cells from naive B cell precursors with immunological help. non-tolerance of alloreactive T cells or passive transfer of a pool of B cells with self-reactive memory of the donor (adoptive immunity) [3, 4,17].

A few cases illustrating the transmission of autoimmune disease by hematopoietic stem cell transplantation have been reported in the literature.

PATIENTS AND METHODS

We describe the case of a patient presenting after 7 years of allogeneic bone marrow transplantation, thromboembolic episodes diagnosing an anti phospholipid syndrome. This case report discusses the

diagnoses of chronic GVHD and adoptive immunity [17].

OBSERVATION

We report on a 28-year-old female who developed a bone marrow aplasia of idiopathic origin diagnosed in 2011, treated with a geno-identical allograft in 2012. She presented a chronic GVHD with cutaneous manifestations (sclerodermiform and alopecic), as well as hepatic, pulmonary and ocular manifestations, treated by corticosteroids, anticalcineurin, photopheresis, rituximab, and ibrutinib. Since the diagnosis of chronic GVHD, there was also a chronic pancytopenia which did not respond to changes in therapy with a bone marrow smear showing a reactionary marrow.

In April 2017, during a plane trip the patient had intense headache, vomiting and diplopia, arrived in the emergency room with a general tonic-clonic crisis. The brain scan with injection showed a subarachnoid hemorrhage without parenchymal hemorrhage and the angio-MRI encephalic revealed a thrombosis of the upper longitudinal sinus.

A diagnosis of venous thrombosis was retained, but the patient presented with a difficulty of management of the subarachnoid hemorrhage and the depth of the associated thrombocytopenia. We established an anticoagulation by Low molecular weight heparin (LMWH) at curative doses during 74 hours after diagnosis and after stabilization of the patient, combined with antiepileptic treatment (Oxcarbazepine 600 mg per day) and nimodipine. Heparin was relayed by a vitaminK antagonist (VKA) with a targeted INR between 2 and 3 for an expected duration of 6 months. Symptoms, especially headache, were improved the next day and the venous sinuses were rechecked on the angio-MRI two months later.

5 months after the episode, the patient went to the emergency room for pain in the right iliac fossa with painful edema of the right calf. The curative anticoagulation had been stopped a few days earlier for undetermined causes. A doppler showed an iliac venous thrombosis with deep distal venous thrombosis of the left lower limb. The thoraco-abdomino-pelvic CT scan did not show any other thrombosis. The patient was treated with unfractionated heparin, with strict monitoring of platelets before relaying with direct oral anticoagulant (DOA). The thrombophilia assessment at that time before taking DOA made it possible to eliminate a deficiency in Protein C, Protein S, antithrombin, a mutation of V or II factors, or an increase in factor VIII. The DRVVT found a circulating anticoagulant. The anti-beta2GP1 IgM antibodies were positive at 132 MPL-U / mL (> 7) and persisted in 2019 (54 MPL-U / mL). The diagnosis of post-allograft antiphospholipid antibody (APLA) syndrome was based on persistent immunological biological arguments and a thrombotic history. However, the donor did not represent any clinical symptoms and his immunological assessment was not carried out.

DISCUSSION

Passive transfer of B cells matures from the donor occurs between donor and recipient of hematopoietic stem cells [5, 6]. However, the functional recovery of these cells after the transplant is slow and incomplete, causing often a seronegativity against previous vaccinations despite the immunological status of the donor, indicating that passive transfer alone is insufficient and that reactivation of B lymphocytes is essential for protective immunity [7].

Monitoring of clonal B cells transferred before and after vaccination has shown that the production of antigen-specific plasma cells from the donor memory B cell pool requires additional exposure to the antigen and leads to the production of antibodies. Identical affinity to that produced in the donor [8].

Passive transfer of autoimmune diseases, most commonly autoimmune thyroiditis [9-10] and psoriasis [11], from an affected donor to a stem cell transplant

recipient has been reported in several studies. However, the post-allograft APLA syndrome is an exceptional situation. In the literature, some cases of post-allograft acquisition of circulating anticoagulant, or of positivation of antiphospholipid antibodies (APL) are described, but the cases of APLA syndrome, the respondents to international criteria are extremely rare [12, 13].

The production of autoantibodies and their persistence despite intensive immunosuppression in our patient is compatible with the hypothesis of passive transfer of auto-reactive memory B cells. It is unlikely that the production of autoantibodies is generated in post-transplantation from naive B cells of self-reactive B cells even with extensive chronic GVHD [14, 15] especially that the production of high titer antibodies is rare in patients with chronic GVHD. Furthermore, to our knowledge, APLA syndrome has only been described once in the context of chronic GVHD [16]. However, the absence of APLA syndrome and a thrombotic antecedent in the donor as well as the time of onset of the thromboembolic event seems rather in favor of a de novo production by the self-reactive B lymphocytes of the donor, integrating into a form of GVHD.

Our observation supports the hypothesis that passive transfer of donor immunity occurs, but the expression of this immunity (protective or pathological) depends on additional stimulation of the memory B cell population. The relationship between the appearance of GVHD and the development of autoantibodies would suggest that GVHD provides the B cell stimulus necessary to unmask the latency auto-immunity derived from the donor [18].

CONCLUSION

The post-allograft APLA syndrome is an exceptional situation, its etiology can be explained by the production of self-reactive B cells or adoptive immunity, the latter falls within the framework of manifestations of chronic GVHD, but remains an extremely rare manifestation. The distinction between these two mechanisms is essential because of the prognostic and therapeutic differences between these two entities.

REFERENCES

1. Vinzio S, Lioure B, Grunenberger F, Schlienger JL, Goichot B. Auto-immune-like disease post-bone marrow transplantation. *La revue de médecine interne*. 2004 Jul;25(7):514-23.
2. Magro L, Forcade E, Giraud C, Granata A, Parquet N, Röhrlich PS, Terriou L, Yakoub-Agha I, Beguin Y. Prise en charge de la maladie du greffon contre l'hôte chronique: recommandations de la Société francophone de greffe de moelle et

- de thérapie cellulaire (SFGM-TC). *Bulletin du Cancer*. 2017 Dec 1;104(12):S145-68.
3. Ritchie DS, Sainani A, D'Souza A, Grigg AP. Passive donor-to-recipient transfer of antiphospholipid syndrome following allogeneic stem-cell transplantation. *American journal of hematology*. 2005 Aug;79(4):299-302.
 4. Molrine DC, Guinan EC, Antin JH, Wheeler C, Parsons SK, Weinstein HJ, McGarigle C, Blanding P, Phillips NR, Ciamarra A, George S. Haemophilus influenzae type b (HIB)-conjugate immunization before bone marrow harvest in autologous bone marrow transplantation. *Bone marrow transplantation*. 1996 Jun;17(6):1149-55.
 5. Storek J, Saxon A. Reconstitution of B cell immunity following bone marrow transplantation. *Bone marrow transplantation*. 1992 Jun;9(6):395-408.
 6. Haddad E, Le Deist F, Aucouturier P, Cavazzana-Calvo M, Blanche S, De Saint Basile G, Fischer A. Long-term chimerism and B-cell function after bone marrow transplantation in patients with severe combined immunodeficiency with B cells: a single-center study of 22 patients. *Blood*. 1999 Oct 15;94(8):2923-2930.
 7. Molrine DC, Guinan EC, Antin JH, Wheeler C, Parsons SK, Weinstein HJ, McGarigle C, Blanding P, Phillips NR, Ciamarra A, George S. Haemophilus influenzae type b (HIB)-conjugate immunization before bone marrow harvest in autologous bone marrow transplantation. *Bone marrow transplantation*. 1996 Jun;17(6):1149-1155.
 8. Lausen BF, Hougs L, Schejbel L, Heilmann C, Barington T. Human memory B cells transferred by allogeneic bone marrow transplantation contribute significantly to the antibody repertoire of the recipient. *The Journal of Immunology*. 2004 Mar 1;172(5):3305-18.
 9. Aldouri MA, Ruggier R, Epstein O, Prentice HG. Adoptive transfer of hyperthyroidism and autoimmune thyroiditis following allogeneic bone marrow transplantation for chronic myeloid leukaemia. *British journal of haematology*. 1990 Jan;74(1):118-9.
 10. Karthaus M, Gabrysiak T, Brabant G, Prahst A, Link H, Soudah B, Geissler RG, Diedrich H, Ganser A, Hertenstein B. Immune thyroiditis after transplantation of allogeneic CD34+ selected peripheral blood cells. *Bone Marrow Transplantation*. 1997 Oct;20(8):697.
 11. Snowden JA, Heaton DC. Development of psoriasis after syngeneic bone marrow transplant from psoriatic donor: further evidence for adoptive autoimmunity. *British Journal of Dermatology*. 1997 Jul;137(1):130-2.
 12. Söhngen D, Heyll A, Meckenstock G, Aul C, Wolf HH, Schneider W, Specker C, Withold W. Antiphospholipid syndrome complicating chronic graft-versus-host disease after allogeneic bone marrow transplantation. *American journal of hematology*. 1994 Oct;47(2):143-4.
 13. Kasamon KM, Drachenberg CI, Rapoport AP, Badros A. Catastrophic antiphospholipid syndrome: atypical presentation in the setting of chronic graft versus host disease: case report and review of the literature. *Haematologica*. 2005 Jan 1;90(3):ECR17.
 14. Lister J, Messner H, Keystone E, Miller R, Fritzier MJ. Autoantibody analysis of patients with graft versus host disease. *Journal of clinical & laboratory immunology*. 1987 Sep;24(1):19-23.
 15. Rouquette-Gally AM, Boyeldieu DE, Prost AC, Gluckman EL. Autoimmunity after allogeneic bone marrow transplantation. A study of 53 long-term-surviving patients. *Transplantation*. 1988 Aug;46(2):238-40.
 16. Söhngen D, Heyll A, Meckenstock G, Aul C, Wolf HH, Schneider W, Specker C, Withold W. Antiphospholipid syndrome complicating chronic graft-versus-host disease after allogeneic bone marrow transplantation. *American journal of hematology*. 1994 Oct;47(2):143-144.
 17. Eldin C, Sautereau N, Guemas A, El Cheikh J, Ebbo M, Schleinitz N, Bernit E, Harle JR. Manifestations auto-immunes et inflammatoires après greffe de moelle osseuse: maladie du greffon contre l'hôte ou immunité adoptive?. *La Revue de medecine interne*. 2014(35):A133-4.
 18. Ritchie DS, Sainani A, D'Souza A, Grigg AP. Passive donor-to-recipient transfer of antiphospholipid syndrome following allogeneic stem-cell transplantation. *American journal of hematology*. 2005 Aug;79(4):299-302.