Allergy & Rhinology
Volume 11: 1–3

DOI: 10.1177/2152656720915701
journals.sagepub.com/home/aar
SAGE

Post Autologous Bone Marrow Transplant Associated With a Resultant Mixed Polyclonal/Monoclonal Hyper-IgG3

Lauren Fill, DO[1], Marija Rowane, OMS-II[2], Kelsey Graven, DO[3], Neha Sanan, DO[3], Shan Shan Wu, DO[3], and Robert W. Hostoffer, DO[3]

Abstract

There have been few studies illustrating the post immunological phenotype of patients receiving autologous bone marrow transplant (ABMT) for the treatment of diffuse large B-cell lymphoma. High-dose chemotherapy and autologous bone marrow transplantation have been shown to be the only potential curative treatment modalities for B-cell lymphoma. Autologous bone marrow transplantation, although widely utilized in patients with non-Hodgkin lymphoma recurrence, does have an association with immunologic side effects, although serologic changes where rarely reported unless accompanied by recurrent infections. We report the first case of a 62-year-old female patient who experienced recurrent infections, namely, sinusitis and pneumonia, after receiving an ABMT with subsequent hyper-IgG3 phenotype

Keywords

autologous stem cell transplantation, large B-cell lymphoma, monoclonal gammopathy, hyper-IgG3 phenotype

Introduction

The mainstay of treatment for diffuse large B-cell lymphoma is a high-dose chemotherapy regimen and/or autologous bone marrow transplant (ABMT).[1,2] ABMT is a therapeutic option for patients who have relapsed.[3] Few studies illustrate the post immunological phenotype of patients receiving ABMT for the treatment of diffuse large B-cell lymphoma.[4] We report the first case of a polyclonal/monoclonal hyper-IgG3 phenotype with recurrent respiratory infections, sinusitis, and pneumonia, following ABMT.

Case Report

A 62-year-old female with a medical history of diffuse large B-cell lymphoma, nongerminal cell type was diagnosed in 2004. The patient received 2 salvage therapy lines. She was given 6 cycles of R-CHOP (rituximab, cyclophosphamide, doxorubicin, hydrochloride, vincristine sulfate, prednisone) in March 2004 with remission. She experienced a recurrence in February of 2017 and was given 4 unsuccessful cycles of R-GCD (rituxan, gemzar, cisplatin, dexamethasone). As a second-line therapy, she received an ABMT, which was not T-cell depleted. The patient's stem cell collection was performed in July 2017, 5 months after receiving her second round of high-dose chemotherapy with R-GCD. The patient did not receive any other unusual chemotherapy regimens, nor any investigational drugs prior to her graft. Prior to her transplant, the patient received BEAM conditioning [carmustine (bis-chloroethylnitrosourea, BCNU), Etoposide, Ara-C, and Melphalan]. The patient was placed in remission after receiving ABMT July 2017. The patient was not on any immunosuppressive therapy following ABMT. She

[1]Internal Medicine, University Hospitals St. John Medical Center, Westlake, Ohio
[2]Ohio University Heritage College of Osteopathic Medicine, Athens, Ohio
[3]Cleveland Medical Center, University Hospitals, Cleveland, Ohio

Corresponding Author:
Lauren Fill, Internal Medicine, University Hospitals St. John Medical Center, Westlake, Ohio, USA.
Email: lauren.fill@uhhospitals.org

has not experienced recurrence since receiving her ABMT.

During the first year after her ABMT, the patient experienced recurrent sinusitis and was treated with antibiotic therapy approximately once every 2 to 3 months, with temporary resolution of symptoms between recurrences. During the second year after her ABMT, she developed pneumonia twice, the second of which required hospitalization for sepsis secondary to *Streptococcus pneumonae*. Prior to receiving her ABMT, the patient was not subject to recurrent infections.

Serum immunoglobulins (Igs), Ig subclasses, antibody responses, lymphocyte subsets, complete blood cell count, and immunofixation were performed 2 years post-transplant. Tables 1 and 2 demonstrate the results of the patient's initial testing. As described in Table 1, the Ig levels demonstrated an elevated total IgG with IgG1, IgG2, and IgG4 subclass deficiencies. IgG3 was found to be significantly elevated >220 g/dL. The immunofixation demonstrated a monoclonal IgG without light chain detected at 0.4 g/dL (Table 2). Antipneumococcal titers were unresponsive to both *Pneumovax* and *Prevnar* vaccinations. Lymphocyte subsets were within normal limits.

Table 1. Ig Levels.

Value	Result, g/dL	Reference Range, g/dL
IgA	21	20–320
IgA subclasses		
IgA1	16	60–294
IgA2	2	6–61
IgM	25	50–300
IgE	<2	0–150
IgD	<1.34	<14.11
IgG	1636	600–1540
IgG subclasses		
IgG1	80	382–929
IgG2	<2	241–700
IgG3	>220	22–178
IgG4	0.80	4–86

Abbreviation: Ig, immunoglobulin.

Table 2. Protein Electrophoresis and Immunofixation.

Value	Result, g/dL	Reference Range, g/dL
Total protein	5.9	6.4–8.2
Albumin	3.6	3.4–5
Alpha 1 globulin	0.3	0.2–0.6
Alpha 2 globulin	0.6	0.4–1.1
Beta globulin	0.5	0.5–1.2
Gamma globulin	0.5	0.5–1.4

Immunofixation interpretation: monoclonal IgG without light chain detected at 0.4 g/dL.

The patient received intravenous immunoglobulin (IVIG) diagnosis of hyper-IgG3 gammopathy with total IgG deficiency and IgG1, IgG2, and IgG4 subclass deficiencies. This therapy successfully decreased the frequency and quantity of recurrent infections.

Discussion

Diffuse large B-cell lymphoma, a subtype of non-Hodgkin lymphoma (NHL), is a devastating disease for which there are several options for treatment.[3] High-dose chemotherapy and ABMT have been shown to be the only potential curative treatment modalities.[3] High-dose chemotherapy continues to be first-line therapy with the goal of complete remission.[1] Bone marrow transplantation, both allogenic and autologous, is considered a reasonable second-line therapeutic option for patients who relapse from complete remission as the cure rate with chemotherapy alone is oftentimes less than 10%.[1]

ABMT, although widely utilized in patients with NHL recurrence, is associated with immunologic side effects, although serologic changes have rarely been reported unless accompanied by recurrent infections.[4] Pretreatment of the graft may cause cellular abnormalities.[4] Purification, which involves depleting the graft of non-CD34+ tumor cells to limit posttransplant relapse, has been postulated to delay immune reconstitution. This procedure may result in a higher infectious morbidity and relapse rate posttransplantation, potentially neutralizing the beneficial effects of stem cell selection.[4] A potentially deleterious consequence of the purification process that has been documented is transient, severe combined immunodeficiency after bone marrow transplantation.[5] Anderson et al. demonstrated that patients who had undergone T-depleted ABMT had a profound immunodeficiency posttransplant that was not reflected in the phenotypic reconstitution of their T and Natural killer (NK) cells posttranplant.[6] However, this patient's graft in this report did not undergo T-cell depletion, nor does the literature describe immunodeficiency post-non-T-cell-depleted ABMT.

Serum Ig deficiencies of IgG isotypes do not always predispose individuals to recurrent infections. Depiero et al. observed lack of infection in a 50-year-old male patient with high titers of IgG3 but lack of detectable IgG1, IgG2, IgG4, and IgA1 levels during routine medical examination.[7] This case report aimed to elucidate the immunological mechanism of protection from pneumococcal infection in patients with large-spanning deletions of the Ig heavy chain loci as attributable to IgG3 antibodies production of pneumococcal polysaccharide capsule serotypes 8, 9, and 51.[7] Other antibody deficiencies, such as heterogenous humoral defects in primary immunodeficiencies, also typically manifest with recurrent infection but have been associated with inability of

increase antibody affinity during an immune response, inability to generate non-IgM isotypes, and a complete absence of B cells.[7] Hyper-IgG subclasses with IgG isotype deficiency may be attributable to diverse immunological mechanisms, with or without clinical manifestation of recurrent infection, such as the present secondary immunodeficiency attributable to ABMT.

We acknowledge the limitation that this patient did not have any immunologic testing prior to transplant or salvage therapy. Thus, the immunologic findings cannot be solely attributed to immunoregulatory dysfunction due to transplant but may have been an undiagnosed primary immunodeficiency. The patient did not clinically present with recurrent infections until after the transplant, indicating immunoregulatory dysfunction.

Despite other immunologic side effects of bone marrow transplantation described in the literature, hyper-IgG3 gammopathy has not been documented. We report the first case of an isolated polyclonal/monoclonal hyper-IgG3 following ABMT. Clinicians are advised to consider this information and an investigation of IgG subclass deficiencies in patients presenting normal IgG levels and recurrent infections following ABMT.

Authors' Contribution

All authors were involved in the conception and design of the study, data generation, analysis and interpretation of the data as well as preparation and clinical revision of the manuscript.

Ethical Approval

This study was approved by our institutional review board.

Statement of Human and Animal Rights

This article does not contain any studies with human or animal subjects.

Statement of Informed Consent

There are no human subjects in this article and informed consent is not applicable.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

ORCID iDs

Lauren Fill https://orcid.org/0000-0001-8540-5944
Marija Rowane https://orcid.org/0000-0002-6500-8279

References

1. Armitage JO. Bone marrow transplantation in the treatment of patients with lymphoma. *Blood*. 1989;73:1749–1758.
2. Gribben JG, Goldstone AH, Linch DC, et al. Effectiveness of high-dose combination chemotherapy and autologous bone marrow transplantation for patients with non-Hodgkin's lymphomas who are still responsive to conventional dose therapy. *J Clin Oncol*. 1989;7:1621–1629.
3. Freedman AS, Takvorian T, Anderson KC, et al. Autologous bone marrow transplantation in B-cell non-Hodgkin's lymphoma: very low treatment-related mortality in 100 patients in sensitive relapse. *J Clin Oncol*. 1990;8:784–791.
4. Steingrimsdottir H, Gruber A, Bjorkholm M, Svensson A, Hansson M. Immune reconstitution after autologous hematopoietic stem cell transplantation in relation to underlying disease, type of high-dose therapy and infectious complications. *Haematologica*. 2000;85:832–838.
5. Bomberger C, Singh-Jairam M, Rodey G, et al. Lymphoid reconstitution after autologous PBSC transplantation with FACS-sorted CD34+ hematopoietic progenitors. *Blood*. 1998;91:2588–2600.
6. Anderson K, Soiffer R, DeLage R, et al. T-cell depleted autologous bone marrow transplantation therapy: analysis of immune deficiency and late complications. *Blood*. 1990;76:235.
7. Depiero A, Kaminski DA, Halsey JF, BRiles D, Burrows PD, Hostoffer RW. Immunologic compensation in a patient with a large IgH constant region deletion. *J Allergy Clin Immunol*. 2001;107(6):1051–1055.0