A Case of Autoimmune Haemolytic Anaemia After Allogeneic Stem Cell Transplantation in Adult Patient: A Refractory and High Mortality Outcome

Erişkin Hastada Allojenik Kök Hücre Nakli Sonrası Bir Otoimmün Hemolitik Anemi Olgusu: Refrakter ve Yüksek Mortalite Sonucu

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ABSTRACT

Autoimmune haemolytic anaemia (AIHA) is a complication arising from allogeneic haemopoietic stem cell transplantation (AHSCT), and it poses a significant challenge in patient management with poor outcome. We present the case of a 32-year-old Malay woman with chronic myeloid leukaemia who, after treatment failure with a tyrosine kinase inhibitor, was referred for AHSCT with HLA-matched peripheral blood stem cells donated by her younger brother. She suffered acute graft-versus-host disease and cytomegalovirus infection within three months post-transplant, followed by AIHA. She did not respond to multiple treatment modalities and had to be frequently admitted to hospital due to symptomatic anaemia which requiring frequent blood transfusion. Here, we highlight an AIHA case in post-AHSCT as a refractory disease due to resistance to standard treatment. This is a condition that requires close monitoring and care because it carries a high risk of morbidity and mortality for the patient, who unfortunately succumbed to her disease.

Keywords: Autoimmune haemolytic anaemia; stem cell transplantation; graft-vs-host disease; outcome; leukaemia, challenging

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ÖZET

Otoimmün hemolitik anemi (AIHA), allojenik hemopoietik kök hücre transplantasyonundan (AHSCT) kaynaklanan bir komplikasyondur ve hasta yönetiminde olumsuz sonuçlanan önemli bir zorluk teşkil etmektedir. Bir tirozin kinaz inhibitörü ile tedavi başarısızlığı sonrası, erkek kardeşi tarafından bağışlanan HLA-uyumlu periferik kan kök hücreleri ile AHSCT için sevk edilen, kronik miyeloid lösemili 32 yaşında bir Malay kadın vakasını sunuyoruz. Nakilden sonraki üç ay içinde akut graft-versus-host hastalığı ve sitomegalovirüs enfeksiyonu geçirdi, ardından AIHA geldi. Çoklu tedavi yöntemlerine yanıt vermedi ve sık kan transfüzyonu gerektiren semptomatik anemi nedeniyle sık sık hastaneye yatırılması gerekti. Burada, standart tedaviye direnç nedeniyle refrakter bir hastalık olarak AHSCT sonrası bir AIHA vakasını sunuyoruz. Bu durum hastalığına yenik düşen hasta için yüksek morbidite ve mortalite riski taşıdığı için yakın takip ve bakım gerektiren bir durumdur.

Anahtar Sözcükler: Otoimmün hemolitik anemi; kök hücre nakli; graft-vs-host hastalığı; sonuç; lösemi, zorlu

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INTRODUCTION

Allogenic haemopoietic stem cell transplantation (AHSCT) is a treatment option for some malignant and non-malignant blood diseases, in which patients would require precursor cells from a donor to produce normal blood cells again. Autoimmune haemolytic anaemia (AIHA) is a recognised complication after AHSCT, and is often refractory to treatment with a high risk of mortality. The risk is greater with the development of chronic graft-versus-host disease (GVHD) (1,2). Mismatched human leucocyte antigen (HLA) antigen and autoreactive lymphocytes (allogenic lymphocytes) targeting self-tissues are believed to be the factors that contribute to the development of AIHA after AHSCT (1).

The incidence of AIHA is estimated at between 2 % and 6 %, affecting both adults and paediatric patients alike (2,3,4). Patients who develop AIHA after AHSCT will show poor outcome as the underlying mechanism of AIHA is not well understood, thus leading to treatment resistance. Here, we highlight the challenges in managing AIHA arising from AHSCT, including difficulties faced in the transfusion therapy and eradication of autoantibodies.

CASE REPORT

The patient was a 32-year-old Malay woman with a history of diabetes mellitus and hypertension when she presented with AIHA. Previously, she had been diagnosed with BCR-ABL1 positive chronic myeloid leukaemia (CML) at age 25, and she achieved complete cytogenetic response (CCyR) within one year after being treated with oral Imatinib (400 mg daily). At the time of her diagnosis, BCR-ABL1 quantification was not available. Six years later at age 31, she lost her CCyR status while still under Imatinib treatment due to the presence of T315I mutation. She was then referred for HLA-matched (10/10) AHSCT using T cell-depleted peripheral blood haemopoietic stem cells (PBHSC) donated by her younger brother. Both donor and patient had the same blood group of AB Rhesus D positive.

Within 100 days after transplant, despite being on prophylaxis of oral cyclosporine (3mg/kg bd) and acyclovir (200mg tds), she developed acute GVHD, which manifested in the skin (generalised rashes) and liver (jaundice with elevated enzymes). Her condition was further complicated by fever, abdominal pain and diarrhoea caused by cytomegalovirus (CMV) colitis, which was diagnosed through CMV DNA quantitative assay (1,320 copies/ml) and colon biopsy. The acute GVHD was successfully treated with intravenous and oral prednisolone, with then oral cyclosporine was continued as prophylaxis. CMV colitis was treated with intravenous ganciclovir for two weeks, followed by oral valganciclovir. Treatment success was evidenced by alleviation of clinical symptoms and negative CMV DNA assay. Prophylaxis was continued with oral valganciclovir for six months post-AHSCT. Her engraftment was considered a success after four months based on serial peripheral blood count and bone marrow assessment. She also achieved complete donor chimerism based on short tandem repeat assessment at seven months post-AHSCT.

However, she began experiencing recurrent symptomatic anaemia after seven months post-transplant and was diagnosed with warm AIHA after eight months based on the following criteria: (a) peripheral blood smear showed morphological changes compatible with immune haemolysis; (b) positive indirect antiglobulin test and direct coomb test (DCT) test; (c) clinical and laboratory evidence of haemolysis (spherocytosis in blood film, increase of LDH and bilirubin levels, decrease of Hb and increase in transfusion requirements); and (d) other causes of immune haemolytic anaemia had been excluded (2). Table 1 shows the summary of her diagnostic tests.

This condition was challenging to treat as the patient failed to respond to multiple immunosuppressive therapies, including corticosteroid and cyclosporin treatment, as well as intravenous immunoglobulin (IVIG) and Rituximab. Therapeutic plasmapheresis also was performed but complicated by anaphylaxis and possible TRALI, requiring intensive care management and support. She required frequent packed red cell (PC) transfusion for a year due to symptomatic anaemia. While on immune suppression therapy, she suffered recurrent bouts of diarrhoea, severe septicaemia (which resulted in admissions into the Intensive Care Unit) and pulmonary tuberculosis. Her AIHA eventually showed positive response towards mycophenolate mofetil after eight cycles of Rituximab. Her latest Hb reading was 15.4 g/dl. However, five years after her positive response, she succumbed to ischaemic stroke and gram-negative septicaemia at age 38.

Table 1: Summary of patient's diagnostic tests

Laboratory test	Results		Comment
	1 to 6 months post- transplant	After 6 months post-transplant	
Full blood count			
Hb (g/dL)	4.5	4.5	Severe anaemia and mild thrombocytopenia due to autoimmune response.
Platelet (x10^9/L)	343	109	
Haemolytic work-up			
Sr Bilirubin (µmol/L)	10	36	
LDH (U/L)	350	812	
Retic count (%)	0.23	Not done	Haemolytic work-up is suggestive of acute autoimmune haemolysis.
Peripheral blood film	Occasional spherocytes seen with no evidence of acute haemolysis	Severe anaemia with many spherocytes, nRBC, left shift	
DCT (polyspecific)	Negative	Positive (3+)	
Haptoglobin	Not done	Not done	
Immunohaematology test			
ABO/RhD grouping	AB/RhD positive	AB/RhD positive	
Antibody screening	Negative	Positive (3+) in all screening panels	Presence of autoantibody with no specificity and no underlying alloantibodies.
Antibody identification	Not applicable	Pan-agglutination (3+)	
Auto control	Negative	Positive (3+)	
Auto adsorption	Not applicable	No reaction	
DCT (IgG/C3d)	Negative	Positive (3+/3+)	
Elution	Not applicable	Pan-agglutination (3+)	
RBC phenotype	Not done	R1R2, Kk, Kp^{a-b+}, Ss, Fy^{a+b+}, Jk (mf) MN (mf)	
Autoimmune screening			
ANA	Not done	1:40	False positive. Connective tissue diseases excluded.
dsDNA	Not done	Negative	
Anti-RNP	Not done	Negative	
Anti-Jo-1	Not done	Negative	
Anti-SM	Not done	Negative	

Hb=haemaoglobin; Sr=serum; nRBC=nucleated red blood cell; LDH=lactate dehydrogenase, DCT=direct Coombs test; RBC=red blood cell; mf=mix field; ANA=anti-nuclear antibody, dsDNA=double stranded DNA

DISCUSSION

AIHA after AHSCT is rarer than alloimmune haemolysis, and it occurs because the recipient's immune system is producing antibodies against antigens in red blood cells (RBC) that developed from the donor's PBHSC. The cumulative incidence of AIHA in three years after using PBHSC donated by a sibling was 2.6 % (2).

To the best of our knowledge, the case in this report may be the first in Malaysia, indicating the rarity of the condition. Our patient's condition involved an IgG-mediated haemolysis of her RBC. It has been reported that the median time of AIHA onset following AHSCT was four months (range two to 32 months) (5). One study revealed that IgM-mediated haemolysis could occur earlier (two to eight months after AHSCT) than IgG-mediated haemolysis (six to 18 months after AHSCT) (6). Secondary AIHA due to connective disease had been excluded. The low titre of ANA positivity (1:40), was probably a false positive as other specific tests for connective tissue diseases were negative. The transfer of autoimmunity from donor to a recipient was also unlikely as the donor's autoimmune screening was negative. Donor history and clinical examination were important in AHSCT selection, and it was suggested that they should also be screened for autoimmune disease (7).

The risks of developing AIHA in this patient was magnified by her age and the acute GVHD and CML infection that she suffered. Risk factors of AIHA post-AHSCT included chronic GVHD, T cell depletion and sourcing from an unrelated donor (2). In a few studies, CMV reactivation had been proven to contribute to the onset of post-transplant autoimmune complications (4, 8). Other possible risk factors were AHSCT of non-malignant diseases, being middle-aged, receiving from an allogenic PBHSC source and short interval between cancer diagnosis and AHSCT treatment (1).

There has been no consensus regarding transfusion management of AIHA. The most important step is to exclude the presence of clinically significant alloantibodies before selecting suitable red cells for transfusion. Patients who developed AIHA might also exhibit increased frequency of alloimmunisation to RBC antigens (1). Autoantibodies that reacted with all RBC reagents, even weakly, would be capable of masking alloantibody reactivity. In this case, auto adsorption did not show the presence of alloantibodies. If RBC transfusion is required, the best-matched RBC phenotypes and antigen-negative alloantibodies should be administered (9). However, there was difficulty in interpreting the patient's RBC phenotype and searching for the best phenotypically matched blood for transfusion as no pre-transplant RBC phenotype was available for her and her donor. The volume of transfused blood should be in the smallest amount to maintain adequate oxygen delivery and did not have to reach arbitrary haemoglobin levels. Even though resolving the serological problems is important, it should be noted that delaying transfusion in the hope of finding compatible blood might end up bringing more harm to patients.

The patient in this report also required a wide range of immune suppressive drugs and modulation therapy, which has been shown to increase morbidity (2). Such therapies should be carefully considered because she developed life-threatening infections and anaemic complications that significantly reduced her quality of life.

Patients who developed AIHA after AHSCT showed poor outcomes as the mechanism of underlying AIHA in post-transplantation patient is poorly understood due to complexity of the process, thus explain the treatment resistance.

CONCLUSION

The important lesson in this case is the need to perform RBC phenotyping for both donor and recipient prior to allogenic transplantation to mitigate transfusion management issue in post-transplant AIHA. Further study is required to understand the underlying mechanisms of this complication.

Conflict of interest

No conflict of interest was declared by the authors.

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