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Posttransplant Erythrocytosis after Allogenic Stem Cell Transplant for Acute Myeloid Leukemia: A Case Report and Review of Literature

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Abstract

Postallogenic hematopoietic stem cell transplant (post-allo-HSCT) erythrocytosis is a rare phenomenon mostly seen in cases of aplastic anemia. It is a well-known complication in renal transplant *recipients*. Clinical evaluation, serum erythropoietin (EPO) level, and Janus kinase 2 (JAK 2) mutation are important to differentiate between primary and secondary erythrocytoses. Treatment aims at normalizing the clinical, physical, and laboratory parameters and minimizing thromboembolic complications. The majority of the patients have a favorable outcome with phlebotomies and low-dose aspirin. We report a rare case of post-allo-HSCT erythrocytosis in a patient who underwent related allo-HSCT for acute myeloid leukemia.

Keywords

- erythrocytosis
- allogenic hematopoietic stem cell transplant
- acute myeloid leukemia

Introduction

Erythrocytosis is characterized by raised hemoglobin and hematocrit levels due to increased red cell mass. It can be primary (polycythemia) or secondary depending on the etiology.[1] Posttransplant erythrocytosis is a well-known sinister complication occurring in 10 to 15% of patients who receive renal transplant.[2] Erythrocytosis following allogenic hematopoietic stem cell transplant (allo-HSCT) is a rare, unexpected phenomenon mostly seen in patients with aplastic anemia.[1] We report a patient with acute myeloid leukemia (AML) who developed post-allo-HSCT erythrocytosis after related allo-HSCT.

Case Report

A 47-year-old gentleman, nonsmoker, diagnosed with AML, intermediate risk, received standard induction therapy with cytosine arabinoside and daunorubicin, but had persistent disease. He attained complete remission following salvage chemotherapy with the FLAG IDA regime. After myeloablative conditioning with the busulfan cyclophosphamide (BuCy) regime, he underwent a human leukocyte antigen (HLA) matched sibling donor allo-HSCT. Cyclosporine and methotrexate were given as standard graft versus host disease (GVHD) prophylaxis. The immediate posttransplant period was uneventful except for cyclosporine-induced hypertension, which was controlled by antihypertensives. Six months following transplant, he had chronic GVHD of moderate severity as per the National Institutes of Health (NIH) grading, involving skin, oral cavity, and eyes, which resolved on topical steroids. Immunosuppressants were tapered and stopped *24 months* posttransplant.

Two years after the transplant, he was incidentally found to have elevated levels of hemoglobin and hematocrit (►**Fig. 1**). Clinical examination was unremarkable. He was worked up to rule out secondary causes of erythrocytosis. He had no exposure to high altitudes and had normal platelet and total leucocyte counts. Peripheral smear examination was suggestive of normocytic normochromic red blood cells

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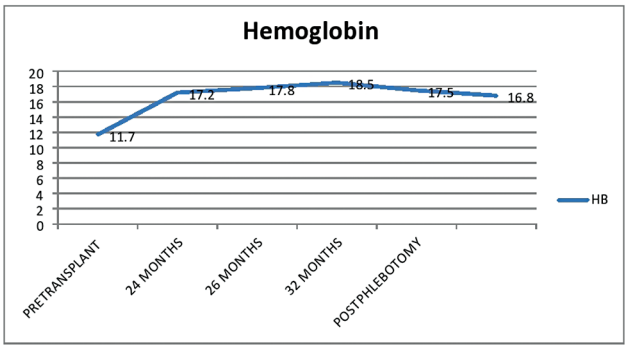

Fig. 1 Hemoglobin levels at different timelines.

with no clumping or rouleaux formation. Atypical forms were absent. His liver function tests, renal function tests, thyroid function tests, and lipid profile were normal. Chest radiograph and ultrasound of the abdomen and pelvis did not show any mass lesion or organomegaly. The Janus kinase 2 V617F (JAK 2V617F) and JAK 2 Exon 12 mutation study was negative. His serum erythropoietin (EPO) level was at *the lower limit of* normal.

Hence, a primary differential of posttransplant erythrocytosis was considered and he was started on low-dose aspirin and therapeutic phlebotomy once in 2 weeks, following which his hemoglobin showed a decreasing trend (►**Fig. 1**).

Discussion

Erythrocytosis is defined as hemoglobin level greater than 17 g/dL and hematocrit level greater than 50% in males and greater than 16.5 g/dL and greater than 48% in females respectively.[3] It can be primary or secondary. Primary erythrocytosis is rare and occurs usually due to a myeloproliferative disorder, polycythemia vera (PV) in which excess erythrocytes are produced autonomously. Patients may be asymptomatic or may show symptoms of thrombosis, vasomotor symptoms, splenomegaly, or constitutional symptoms. Any pathology causing elevated serum EPO levels resulting in physiologically appropriate response leads to more common form of secondary erythrocytosis. Differentiating between primary and secondary erythrocytoses is important in the therapeutic aspect and requires clinical evaluation, measurement of the serum EPO level, and JAK 2 mutation testing.[4]

Posttransplant erythrocytosis is classically described after renal transplant and is known to have a deleterious prognosis in transplant recipients. Postallogenic stem cell transplant erythrocytosis is a rare phenomenon with an incidence of around 1% commonly described in patients having aplastic anemia.[1,3] ►**Table 1** shows major studies on posttransplant erythrocytosis in hematological conditions. Ayas et al conducted an observational study on 17 pediatric patients with Fanconi's or acquired aplastic anemia who developed posttransplant erythrocytosis following allo-HSCT.[5] It is rarely reported in patients with AML. Atilla et al studied four patients with AML having posttransplant erythrocytosis and reported a median time to diagnosis of 56 months after transplant.[3] Our patient underwent allo-HSCT for AML and was diagnosed with *posttransplant erythrocytosis 24 months* after transplant, which is much earlier compared to that reported by Atilla et al.

Patients may present with symptoms of malaise, headache, and plethora or may be asymptomatic.[3,6] Our patient was asymptomatic and erythrocytosis was detected on routine follow-up visit after transplant. The exact pathophysiology of posttransplant erythrocytosis is not known.

Table 1 Major studies on posttransplant erythrocytosis in hematological conditions

Study	No. of patients with erythrocytosis	Median time to erythrocytosis after transplant (mo)	Disease (no. of patients)	Highest hemoglobin level (mg/dL)	Treatment
Chaudhry et al[14]	14	33 (range: 18–51)	Aplastic anemia	19.9	Phlebotomy
Ayas et al[5]	17	67 (range: 17–164): females	Aplastic anemia/ Fanconi's anemia	18.9	–
		103 (range: 23.3–206): males			
Kibirova et al[1]	12	50	Aplastic anemia (2)	19.7	Phlebotomy
			AML (3)		
			MDS (2)		
			ALL (1)		
			CML (1)		
			NHL (1)		
			HL (1)		
			HLH (1)		

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CML, chronic myeloid leukemia; HL, Hodgkin's lymphoma; HLH, hemophagocytic lymphohistiocytosis; MDS, myelodysplastic syndromes; NHL, non-Hodgkin's lymphoma.

Increased EPO sensitivity of erythroid progenitors and presence of abnormal stromal factors are possible mechanisms.[6] Our patient had negative JAK 2 mutation study and EPO levels *at the lower limit of normal*, which suggested intact feedback mechanisms.

Data on risk factors for post-allo-HSCT erythrocytosis are sparse in the literature. Risk factors for postrenal transplant erythrocytosis are smoking, male gender, transplant artery stenosis, cyclosporine, and posttransplant hypertension.[7–9] In the series by Atilla et al, 45% of patients with post-allo-HSCT erythrocytosis had liver GVHD and 36% had GVHD involving skin.[3] Evidence shows that hypoxia-inducible factor (HIF) produced during hepatocyte injury as in GVHD, promotes erythropoiesis through increased EPO production in the liver.[10] Risk factors like male gender, posttransplant hypertension, and cyclosporine use during allo-HSCT seen in our patient were similar to those reported after renal transplant. He also had GVHD involving skin, eyes, and oral cavity.

Treatment strategy for patients with erythrocytosis aims at normalizing the clinical, physical, and laboratory parameters and minimizing long-term complications.[11] A risk-adapted approach is preferred in PV in which risk factors for poor prognosis identified are age more than 60 years and past history of thrombosis. Therapeutic phlebotomies to reduce blood viscosity is the treatment approach in low-risk groups similar to this case.[12] It has been shown that incidence of thromboembolic complications and death from cardiovascular causes can be reduced with use of low-dose aspirin.[13] In the series by Atilla et al, all of them had low-risk disease well controlled on therapeutic phlebotomies and concurrent aspirin with no thromboembolic complications.[3] Ours being a low-risk patient had therapeutic phlebotomies and was started on concurrent low-dose aspirin, following which the hemoglobin levels showed a decreasing trend and the patient did not develop any thrombotic complications.

Conclusion

Post-allo-HSCT erythrocytosis is an uncommon phenomenon with a favorable prognosis. The exact pathophysiology is not known. Low-dose aspirin and phlebotomies can prevent thromboembolic complications in the majority of the patients.

Authors' Contribution

S.S.A., S.S., and A.B.A. were involved in the literature search, manuscript preparation, and editing and reviewing of the manuscript. S.G.N. was involved in the conception and design of the study, literature search, manuscript preparation, and editing and reviewing of the manuscript. All the authors have read and approved the final manuscript.

Declaration of the Patient Consent Form

For participation in the study and publication of data and any related images, written informed consent was obtained from the patient.

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Conflict of Interest

None declared.

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