Received: November 7, 2024
Accepted: November 30, 2024

Acad Med J 2024;4(3):160-163
UDC: 616.155.194.125-085.38
https://www.doi.org/10.53582/AMJ2443160t
Case report

INEFFECTIVE ERYTHROPOIESIS IN PATIENT WITH BETA-THALASSEMIA AND MYELODYSPLASTIC SYNDROME - CASE REPORT

Trajkova Sanja[1], Krstevska Balkanov Svetlana[1], Pivkova Veljanovska Aleksandra[1], Ridova Nevenka[1], Popova Labacevska Marija[1], Stojanovski Zlate[1], Stojanovska Simona[1], Cvetanovski Milche[1], Kocoski Bozidar[1], Kebakoska Mihaela[2], Paunoska Andrea[1], Angelovic Dimitrievska Rosica[1], Petrovska Savica[1], Dukovski Dushko[1], Panovska Stavridis Irina[1]

[1]University Clinic for Hematology, Faculty of Medicine, Ss. Cyril and Methodius University in Skopje, Republic of North Macedonia
[2]Faculty of Medicine, Ss. Cyril and Methodius University in Skopje, Republic of North Macedonia
e-mail: sanjatrajkovamd@yahoo.com

Abstract

Ineffective erythropoiesis and associated anemia are hallmarks of two hematological diseases - myelodysplastic syndromes and thalassemia, treated with regular blood transfusions. Erythropoiesis is a highly regulated process where functional erythrocytes are produced from hematopoietic stem cells, and defects can adversely affect the proliferation, differentiation, and survival of erythroid precursors. Treatments that directly mark the ineffective erythropoiesis are limited. There is unmet requirement for treatments that can restore effective erythropoiesis. Herein, we present a case report of a patient with beta-thalassemia and development of myelodysplastic syndrome with 5q deletion.

Keywords: ineffective erythropoiesis, beta-thalassemia, myelodysplastic syndromes, 5q deletion

Introduction

Ineffective erythropoiesis and associated anemia are hallmarks of these two hematological diseases - myelodysplastic syndromes (MDS) and thalassemia. The most common human disorders of hemoglobin synthesis are the inherited alpha- and beta-thalassemia, endemic to tropical and subtropical global regions, and which result from germline mutations, rearrangements, or deletions of the globin gene clusters and their cis-acting regulatory elements. Acquired thalassemia has also been described, primarily alpha-thalassemia due to somatic point mutations in a trans-acting regulatory factor, ATRX, or due to deletions of the alpha globin gene cluster on chromosome 16 as part of the clonal instability of myeloid neoplasia[1]. In contrast to alpha-thalassemia, cases of MDS with acquired beta-thalassemia are exceedingly rare and poorly characterized[2]. This case report describes an inherited beta-thalassemia and concurrent MDS, which can create diagnostic challenges due to their common consequence of ineffective erythropoiesis.

Case report

A 69-year-old woman, born in a part of Macedonia that borders neighboring Greece, with a reported history of chronic anemia was initially referred by her primary care physician to the University Clinic for Hematology for evaluation of elevated serum level of iron discovered during follow-up for chronic anemia. Initial laboratory report in 2011 was: Hgb 10.1 g/dl, Wbc 5.04 10^9/L, Pl 256 10^9/L, MCV 61 fL ,level of SeFe 28 umol/L. Due to the patient's reported history of beta-thalassemia in the family, hemoglobin electrophoresis was performed which revealed hemoglobin A of 93.7%, hemoglobin A2 of 5.2% [normal 3.5%] and hemoglobin F of 1.1% [normal ≤1%], consistent with heterozygote form of beta-thalassemia. The patient was treated with folic acid without need of red blood cells transfusion. But in 2022, after severe Covid 19 infection, the patient notice worsening of symptoms such as severe fatigue, weakness, intolerance to physical activity, the appearance of tachycardia. Blood analysis showed very low Hgb level of 6.3g/dl, low red blood cell count of 2.4x 10^6/ul, normal count of leukocytes and platelets, elevated level of MCV 84 fL. Iron tests revealed elevated ferritin to 1659.5 [ref: 300 ug/L], elevated iron level to 30.1 umol/L [ref: 7-26 umol/L], a lower total iron binding capacity 32.4 umol/L [ref: 46-70 umol/L) with a calculated transferrin saturation of 78%. Vitamin B12 was with normal values. The peripheral blood smear showed normal number of differentiated leukocytes and erythrocytes with macrocytic features, hypochromic cells with variation in size and shape anisocytosis and poikilocytosis, including increased target cells, elliptocytes (Figure 1). Bone marrow biopsies was performed to evaluate anemia at thalassemia patient with elevated MCV. Bone marrow core biopsy and aspirate smears revealed a mildly hypercellular marrow for the age (60% cellular), the myeloid to erythroid ratio (M: E) was moderately decreased (M: E ratio 1:3). Aspirate smears showed erythroid hyperplasia and erythroid dysmaturation including binucleated forms, nuclear irregularities, and megaloblastic changes. There was a slightly increased number of lymphocyte population with immunohistochemically analysis of positivity for CD 20+ and CD 3+ in nodose and dispersed gatherings. Immunohistochemical analysis of CD 34 was negative and of CD 117 positive in only 1-2% of cells. The constellation of morphologic findings was suggestive of myelodysplastic syndrome. A bone marrow aspirate smears are presented in Figures 2 and 3.
The molecular findings of the bone marrow aspirate pointed absence of deletions and duplications in the chromosomal regions: chromosome 3, 7q, 11q, 12p, chromosome 17, chromosome 19, 20q, absence of JAK2 V617F mutation and possible 5q deletion (on the edge of detection).

Since the immunohistochemical analysis showed positivity for CD 20 and CD 3, we performed chest and abdomen CT scan, which showed no abnormalities.

Myelodysplastic syndrome with 5q deletion is a rare form of MDS. Risk stratification was performed according to the most commonly used revised international prognostic scoring system (R-IPSS). Results showed a low risk, based on the risk of mortality and transformation to acute myeloid leukemia (AML). To establish a definitive diagnosis of MDS with 5q del, cytogenetic analysis as an essential diagnostic tool will be performed in a renowned center for cytogenetic analyses in a neighboring country. As we are waiting for the results of the chromosomal analysis, the treatment option is an iron chelate agent Deferasirox 360 mg twice a day.

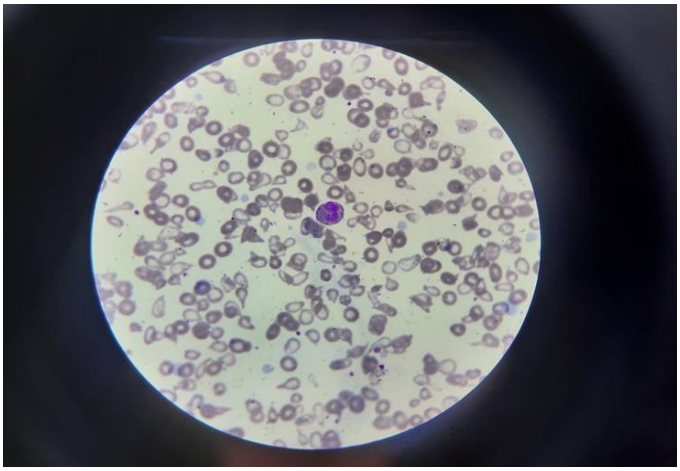

Figure 1. Peripheral blood smear from patient with beta-thalassemia and myelodysplastic syndromes (archive of University Clinic for Hematology)

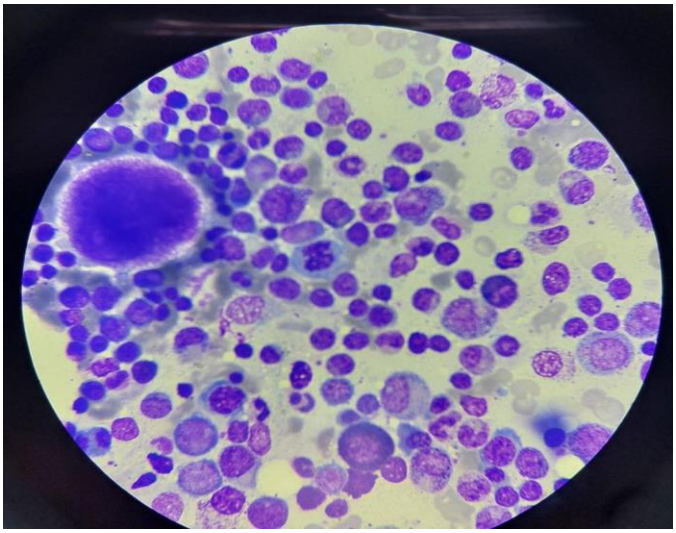

Figure 2. Bone marrow biopsy aspirate smears from patient with beta-thalassemia and myelodysplastic syndromes (archive of University Clinic for Hematology)

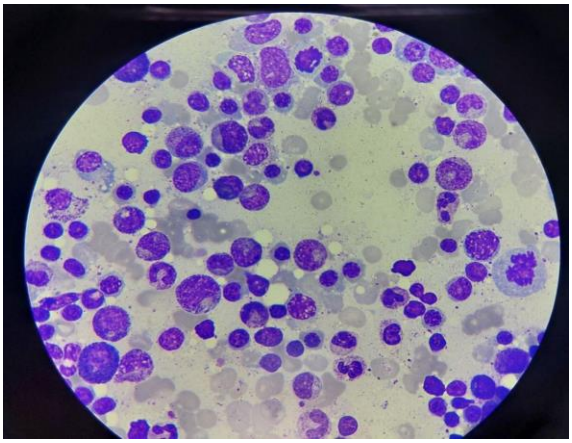

Figure 3. Bone marrow biopsy aspirate smears from patient with beta-thalassemia and myelodysplastic syndromes (archive of University Clinic for Hematology).

Discussion

Although the two entities, thalassemia and MDS, are different diseases with their own characteristics, they basically have ineffective erythropoiesis. Thalassemia with MDS can be secondary to MDS-associated cytogenetic abnormalities or occur as a separate inherited congenital disorder. Acquired beta-thalassemia in MDS is rare and only a few cases have been described in the literature[3]. This report describes an inherited beta-thalassemia and development of MDS after severe Covid 19 infection, which can generate diagnostic tasks due to their common consequence of ineffective erythropoiesis. The case presents a setting in which the patient presented with worsening of chronic anemia with a feature of macrocytic anemia which is not characteristic for chronic anemia in thalassemia. One study[4] described nine patients with similar clinical presentations; all diagnosed MDS were low-grade with an IPSS score of 0–1, all patients had simple cytogenetic abnormalities including loss of chromosome Y, loss of 20q, and trisomy 8, and genetic mutations in MDS genes were not reported in the study similar to our report.

Our patient had a Covid 19 infection with a more severe clinical picture where the infection may have caused bone marrow changes in the direction of myelodysplasia with ineffective erythropoiesis, as a hint for consideration by hematologists. A review of the literature based on this topic showed not enough data on patients with MDS and concurrent thalassemia. It would be stimulating to see if the marrow microenvironment in thalassemia patients predisposes to the development of MDS.

The presented case has a possible 5q deletion and it will be a therapeutic challenge to make a decision to carry out further treatment of MDS with a 5q deletion with a combination of corticosteroids and angiogenesis inhibitor thalidomide.

We can conclude that both entities have almost common clinical and laboratory features and represent a diagnostic and therapeutic challenge. There are no large series of patients described in the literature, and hence they remain undiagnosed.

The therapeutic decision is also a real predicament due to the fact that there are currently no clinical guidelines regarding the management of concurrent MDS and thalassemia. For us, hematologists, it is important to think about these entities, to follow-up patients affected by these diseases and to report on more such topics.

Conflict of interest statement. None declared.

References

1. Steensma DP, Gibbons RJ, Higgs DR. Acquired α-thalassemia in association with myelodysplastic syndrome and other hematologic malignancies. *Blood* 2005; 105(2): 443–452. doi: 10.1182/blood-2004-07-2792.
2. Galanello R, Perseu L, Perra C, Maccioni L, Barella S, Longinotti M, *et al*. Somatic deletion of the normal beta-globin gene leading to thalassaemia intermedia in heterozygous beta-thalassaemic patients. *Br J Haematol* 2004; 127(5): 604-606. doi: 10.1111/j.1365-2141.2004.05237.x.
3. Brunner AM, Steensma DP. Myelodysplastic syndrome associated with acquired Beta thalassemia: "BTMDS." *Am J Hematol* 2016; 91(8): E325-E327. doi:10.1002/ajh.24400.
4. Niscola P, Tendas A, Giovannini M, Scaramucci L, Perrotti A, de Fabritiis P. Diagnosis of myelodysplastic syndromes in individuals heterozygous for mutations in the α- and β-globin genes: a reminder for haematologists. *Blood Transfus* 2014; 12(Suppl 1): s158-s159. doi:10. 2450/2013.0083-13.