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Hb C/Beta thalassemia: A case report from Pakistan

Zara-tul-Ain Bashir[1]; Rabeea Munawar Ali[1]; Qurat Ul Abedin[2]*; Saima Siddiqui[2]

[1]Department of Clinical Hematology, National Institute of Blood Disease & Bone Marrow Transplantation, Karachi, Pakistan.

[2]Department of Molecular Medicine, National Institute of Blood Disease & Bone Marrow Transplantation, Karachi, Pakistan.

***Corresponding Author: Qurat Ul Abedin**
Department of Molecular Medicine, National Institute of Blood Disease & Bone Marrow Transplantation, Karachi, Pakistan.
Email: quratabedin@yahoo.com

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Abstract

Hemoglobin C (HbC) is a variant that is formed as a result of missense mutation in the coding region of HBB gene. Co-inheritance of hemoglobin C and Beta thalassemia mutations results in Hb C/ Beta thalassemia, a rare hemoglobinopathy. Usually patients with hemoglobinopathies present in early childhood, however, some are also diagnosed later in adulthood. This case report discusses a rare manifestation of HbC/Beta Thalassemia in 52 years old male with a history of transfusion dependent anemia for 4 years and moderate splenomegaly. His peripheral smear shows poikiloanisocytosis, hypochromic microcytic cells with hemoglobin crystals. Hemoglobin electrophoresis revealed a band in HbA2 region corresponding to 94.8% and an HbF fraction of 5.2%, raising suspicion of hemoglobinopathy. Genetic testing further supported the diagnosis. The patient was managed with folic acid supplementation and Hydroxycarbamide, blood transfusions were avoided as patient was maintaining hemoglobin levels. No major complications of iron over load or hemolysis were observed. This case highlights the importance of considering hemoglobinopathies in unexplained anemia in older adults. Late diagnosis of C/Beta Thalassemia may influence management strategies, preventing unnecessary interventions.

Keywords: Hemoglobinopathy; Hb C; Hb C/ beta; Thalassemia; anemia

Introduction

Thalassemia is one of the most common genetic disorders worldwide [1]. The spectrum of beta-thalassemia syndrome encompasses a wide range of disorders of the hemoglobin chain with over 350 identified mutations [2] in the beta-globin gene (HBB gene) resulting in various phenotypes including homozygous, compound heterozygous and carrier states.

The incidence of thalassemia shows considerable geographic variation, and each ethnic group has a few predominant mutations and a variable number of rare ones [3]. The highest rates of thalassemia are observed in the Mediterranean region, Middle East, and parts of Asia including India and Pakistan [4]. In contrast, hemoglobin C (HbC) defects are rare in the Indian subcontinent, with a reported prevalence of 0.32% in Pakistan [5], although it shows a higher prevalence in malaria-endemic areas such as Atlantic West Africa and Southeast Asia due to its protective effect against malaria similar to sickle hemoglobin [6]. Compound heterozygosity for Hb C/Beta thalassemia (Hb C/β0/+) is exceedingly rare accounting for 6% of all HbC defects [7] consequently it has never been reported in Pakistan. Here, we describe 52 year-old patient who was diagnosed with compound heterozygous Hb C/β thalassemia.

Case presentation

A 52-year-old male, Baloch by ethnicity and resident of Karachi presented to the Hematology Clinic with complaints of generalized weakness, palpitation and exertional dyspnea. The

given history dates to 4 years back in time with insidious onset and symptoms have been progressive over time. He was managed initially before referring to our institute with blood transfusions and iron supplements. There was an improvement in his symptoms in the early period of treatment, however, later on the symptoms stopped responding to iron replacement and transfusion requirement also increased. There was no history of hemoglobinopathy or symptomatic anemia in the siblings or extended family. He was a product of a non-consanguineous marriage. The family survey could not be carried out because of the death of both parents. Clinical examination revealed pallor and moderate splenomegaly only.

His complete blood count (CBC) revealed a hemoglobin level of 5.6 g/dL and a mean corpuscular volume (MCV) of 69 fl, while the red-cell distribution width (RDW) was within normal limits, the mean corpuscular hemoglobin concentration (MCHC) was low. A peripheral smear revealed anisocytosis, poikilocytosis, hypochromic microcytic cells, target cells, nucleated red blood cells, and Hemoglobin crystals (Figure 1).

Further investigations showed normal hepatic and lipid profiles, however, there was an increasein levels of lactate dehydrogenase (LDH), reticulocyte count, and indirect bilirubin, while haptoglobin levels were suppressed and the Direct Antiglobulin Test was negative.

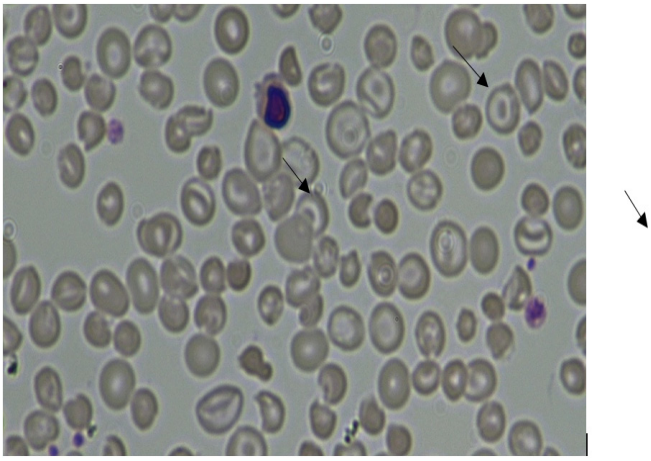

Figure 1: Peripheral smear showing anisopoikilocytosis, hypochromic microcytic cells, spherocytes, target cells, Nucleated RBC, and hemoglobin crystals (denoted by arrow).

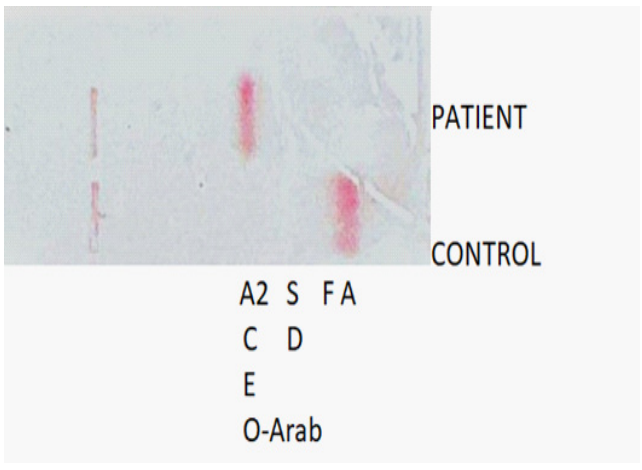

Figure 2: Hb electrophoresis of the patient along with control.

The patient's ferritin level was elevated at 780 ng/ml. Hemoglobin electrophoresis demonstrated a band in the region of HbA2 corresponding to 94.8% and an HbF fraction of 5.2% (Figure 2), raising suspicion of hemoglobinopathy.

To confirm this, the patient's blood samples were sent for genetic analysis. Beta-globin gene sequencing was performed on the ABI 3500 genetic analyzer. Two mutations were identified in the heterozygous state:

1. Mutation in Exon 1, c.19G>A (p.Glu7Lys) [Hb C].
2. Mutation in Exon 1, c.27dupG (Fr8/9+G)

These findings confirmed the diagnosis of compound heterozygosity for Hb C and beta-thalassemia.

Discussion

Hemoglobinopathies are either quantitative abnormalities, such as thalassemia, or qualitative abnormalities that result in defective hemoglobin. Thalassemia is an inherited, autosomal recessive disorder of the hemoglobin gene, characterized by reduced or absent production of the beta-globin subunit of the hemoglobin molecule [8].

Understanding the molecular basis of the HBB gene mutations elucidates the diversity of clinical manifestations. Beta (zero)-thalassemia typically has a more severe clinical presentation, causing thalassemia major in homozygous and compound heterozygous states, whereas beta (+)-thalassemia results in a milder phenotype (thalassemia intermedia) [9]. In beta-thalassemia, the common mutations are frameshift or nonsense in HBB exons 1 and 2, caused by small insertions and deletions.

HbC is a structural variant of normal adult hemoglobin caused by a missense mutation of the β-globin chain; this mutation concerns the first nucleotide of this codon, and it is the substitution of guanine by adenine (GAG→AAG). This results in the replacement of glutamic acid with lysine (βGlu-Lys, HBB:c.19G > A) at position 6. This mutation produces HbC, which has reduced solubility, leading to the formation of intracellular crystals and a shortened lifespan of red blood cells [10]. Hemoglobin C crystals can be visualized on blood smears as rhomboidal crystals with straight parallel edges in an otherwise empty red blood cell [11]. In a heterozygous state, Hb C causes no symptoms, while in a homozygous state, it results in mild hemolytic anemia [12].

In C/β-thalassemia, an individual inherits a thalassemia trait from one parent and an abnormal hemoglobin condition from the other parent. This heterozygous condition is expressed in two ways: C/β0, in which HbA is absent, and C/β+, in which HbA can reach up to 30%. β+ is more common than β0 in subjects with HbC; this compound heterozygosity is found more specifically in people of African descent and also reported in Italy (Sicily), Turkey, and South Africa [13].

Compound heterozygosity for Hb C/β is rare and clinically manifests as thalassemia intermedia [14]. Patients usually present with mild hypochromic, microcytic anemia requiring infrequent transfusions with or without splenomegaly and may present with gallstones. Characteristic blood film examination shows hemoglobin C crystal, target cells, and irregularly contracted cells; Pappenheimer bodies may also be observed [11].

Our patient also presented with a similar clinical history of hypochromic microcytic anemia and splenomegaly along with the peripheral smear findings of Hb C crystals.

The diagnosis of thalassemia is based on CBC with peripheral smear examination alongside hemoglobin electrophoresis or High performance liquid chromatography (HPLC) and thalassemia gene analysis [15]. Similarly, diagnosis of Hb C is also established on these combined modalities; however, with certain caveats. On Hb electrophoresis, the band of Hb C appears in the same region as Hb A2, Hb E, or Hb O Arab, which can make differentiation challenging. However, Hb C can be more clearly distinguished on HPLC, as it elutes separately, providing a more reliable clue for diagnosis [16]. Molecular studies for the identification of specific gene mutations are essential for the confirmation of the definitive diagnosis of thalassemia and its variants.

Thus initial diagnostic workup comprising Hb electrophoresis alone can be misleading, as was seen in our patient in whom the Hb electrophoresis was inconclusive with a major band seen in the region that corresponds to more than one hemoglobin variant. HPLC can be more helpful in this scenario as it distinguishes many more Hb variants than conventional Hb electrophoresis. The diagnosis in this patient was ultimately confirmed through gene analysis. Unfortunately, the patient was unable to provide information about their parents due to their demise, and further family screening is currently pending.

The patient was initially treated with packed red cell transfusions and supplementation of deficient nutrients, such as vitamin B12 and folic acid. Hydroxycarbamide was later initiated, resulting in symptomatic improvement and maintaining hemoglobin levels above 9 g/dL. Due to the rarity of HbC/β thalassemia, there are no established guidelines for the specific management of this disease; however, a case reported by A. Agapidou et al. described a patient with HbC/β who responded to hydroxycarbamide treatment, showing an increase in Hb F levels from 14% to 24.5% [17]. Following this precedent, we adopted a similar approach for our patient.

Iron chelation therapy will be initiated based on serial monitoring of serum ferritin levels. To assess potential disease-related complications, the patient underwent a DEXA scan for bone health evaluation, which showed osteopenia with an increased risk of osteoporotic fractures (T-score -2.4 SD); hence he was commenced on weekly alendronate. The findings of T2 MRI*, which showed a cardiac T2* value of 32 ms, and hepatic T2* value of 14 ms, ruled out organ iron overload.

Conclusion

Hb C/β-thalassemia is a rare disorder with a clinical presentation resembling thalassemia intermedia. Its rarity, particularly in certain regions, combined with the potential ambiguity of the initial diagnostic workup, makes it a diagnostic challenge. Therefore, molecular analysis is crucial for achieving an accurate and definitive diagnosis.

References

1. Quek L, Thein SL. Molecular therapies in beta thalassemia. Br J Haematol. 2007; 3: 353–65. doi: 10.1111/j.1365-2141.2006.06408.x
2. Rao E, Chandraker SK, Singh MM, Kumar R. Global distribution of β-thalassemia mutations: An update. Gene. 2023: 148022.
3. Al-Ali AK, Al-Ateeq S, Imamwerdi BW, Al-Sowayan S, Al-Madan M, Al-Muhanna F, et al. Molecular bases of beta-thalassemia in the eastern province of Saudi Arabia. J Biomed Biotechnol. 2005; 4: 322–5. doi: 10.1155/JBB.2005.322.
4. Kountouris P, Lederer CW, Fanis P, Feleki X, Old J, Kleanthous M. IthaGenes: an interactive database for haemoglobin variations and epidemiology. PloS one. 2014; 9(7): e103020
5. Ghani R, Manji MA, Ahmed N. Hemoglobinopathies among five major ethnic groups in Karachi, Pakistan. Southeast Asian J Trop Med Public Health. 2002; 33(4): 855-61. PMID: 12757239.
6. Piel, F., Howes, R., Patil, A. et al. The distribution of haemoglobin C and its prevalence in newborns in Africa. Sci Rep. 2013; 1671: 3. https://doi.org/10.1038/srep01671
7. Ouzzif Z, El Maataoui A, Oukhedda N, Messaoudi N, Mikdam M, Abdellatifi M, Doghmi K. Hemoglobinosis C in Morocco : A report of 111 cas. Tunis Med. 2017; 95(12): 229-233
8. Origa R. β-Thalassemia. Genetics in Medicine. 2017; 19(6): 609-19.
9. Asadov C, Abdulalimov E, Mammadova T, Gafarova S, Guliyeva Y, Aliyeva G. Genotype–phenotype correlations of beta-thalassemia mutations in an Azerbaijani population. Turk J Haematol. 2017; 34(3): 258–263. doi: 10.4274/tjh.2016.0427
10. Ekizoglu S. Genetic Basis and Molecular Diagnosis of Hemoglobinopathies.
11. Bain BJ. C/beta(0) thalassemia. Am J Hematol. 2009; 84(11): 749. doi: 10.1002/ajh.21534. PMID: 19790254.
12. Piel FB, Howes RE, Patil AP, Nyangiri OA, Gething PW, Bhatt S, Williams TN, Weatherall DJ, Hay SI. The distribution of haemoglobin C and its prevalence in newborns in Africa. Scientific reports. 2013; 3(1): 1671
13. Bachir DD, Galacteros F. Hemoglobin C. Orphanet Encyclopedia. 2004; 2013.
14. Weatherall DJ, Clegg JB, Knox- Macaulay HHM, et al. A genetically determined disorder with features both of thalassaemia and congenital dysery dyserythropoietic anaemia. Br J Haematol 1973;24:681-702.
15. Liu G, Sun S. The laboratory diagnosis of thalassemia: selection and evaluation of tests and methods. Chinese Journal of Laboratory Medicine. 2012: 385-9.
16. Joutovsky A, Nardi M. Hemoglobin C and Hemoglobin O-Arab Variants Can Be Diagnosed Using the Bio-Rad Variant IIHigh-Performance Liquid Chromatography SystemWithout Further Confirmatory Tests. Archives of pathology & laboratory medicine. 2004; 128(4): 435-9
17. Agapidou A, King P, Ng C, Tsitsikas DA. Double heterozygocity for hemoglobin C and beta thalassemia dominant: a rare case of thalassemia intermedia. Hematology Reports. 2017; 9(4).