Case Report

A rare compound heterozygosity of hemoglobin Siriraj and β-thalassemia in a 72-year-old male: A case report

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ABSTRACT

Microcytic hypochromic Anemia in elderly patients is commonly attributed to iron deficiency or chronic disease. However, hemoglobinopathies may remain undiagnosed until late adulthood. A 72-year-old male with no significant clinical symptoms, with a history of hypertension, diabetes mellitus (type 2), and peripheral neuropathy, came to our Center for blood glucose levels. High-performance liquid chromatography (HPLC) revealed an abnormal hemoglobin (Hb) pattern with an HbC fraction of 74.6% and an elevated HbA2 of 8.9%. Subsequent molecular analysis using Sanger sequencing identified compound heterozygosity for Hb Siriraj and β-thalassemia. This case highlights the importance of considering rare Hb variants and molecular testing in elderly patients with unexplained microcytic anemia. The coexistence of Hb Siriraj and β-thalassemia is rare in the Indian population.

Key words: Hemoglobin Siriraj, High-performance liquid chromatography, Microcytic hypochromic anemia, Sanger sequencing, β-thalassemia

Microcytic anemia is frequently encountered in clinical practice and is most often caused by iron deficiency or anemia of chronic disease. Hemoglobinopathies such as thalassemia and structural hemoglobin (Hb) variants are typically diagnosed in childhood or early adulthood. However, rare variants and compound heterozygous states may remain clinically silent and present later in life.

In our case, the patient went for monitoring of glycated Hb (HbA1c) and was incidentally found to have an unknown window with a retention time of 3.7 min, indicating the possibility of abnormal Hbs. Monitoring and follow-up of diabetes mellitus by measurement of HbA1c has become a routine and standard practice worldwide. In the process of utilising this test for the said purpose, it at times yields results indicating the presence of abnormal Hbs that are otherwise clinically silent in the patients.

As of academic interest, and the rare occurrence of the condition, we did Sanger sequencing in this case, which revealed a compound heterozygous state of Hb Siriraj and beta thalassemia.

Hb Siriraj is a rare β-globin variant with limited reported cases in the literature [1,2]. In India, it is very rare, and the prevalence of Hb Siriraj is very low; one case was identified among 23,000 tests in a study done in Morocco [3,4]. Its coexistence with β-thalassemia is extremely uncommon.

We report a rare case of compound heterozygosity for Hb Siriraj and β-thalassemia diagnosed in a 72-year-old male. Hb G Siriraj overlaps in a window of retention time similar to HbC, Hb O-Arab, and Hb Q-India in the TOSOH G11 high-performance liquid chromatography (HPLC) analyzer in our laboratory. Given the reduced solubility of red blood cells and intracellular crystal formation in the presence of the HbC mutation, co-existence of Beta thalassemia along with the same has definite clinical outcomes by presenting like Beta thalassemia intermedia, thus there is a need for accurate categorization of the Hb variant [5]. Thus, we have performed sequencing as the next step for the same. Hb Q India is an uncommon alpha-chain structural Hb variant observed in North and West India. Patients are mostly asymptomatic and often present in the heterozygous state or co-inherited with beta-thalassemia. When presented as a compound heterozygous condition with Beta-thalassemia or Alpha-thalassemia, it may cause hematological manifestations [6]. Due to the same

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retention time of Hb O Iran as that of Hb G Siriraj, it also needed to be excluded. Hb O Arab, when present as a double heterozygous state along with sickle Hb or Beta thalassemia, can produce moderate anemia [7]. Due to this wide overlap of these variant Hb in a single retention time window, there is a need for further genetic workup in cases with this type of presentation, and thus, we opted for further evaluation by sequencing.

CASE PRESENTATION

A 72-year-old male presented with high blood pressure and found to have hypertension, peripheral neuropathy, Diabetes mellitus (type 2), and peripheral neuropathy. As a part of the workup, he came for testing of blood glucose levels at our Centre.

On evaluation of HbA1c, the chromatogram showed an unknown window, and HbA1c was non-reportable (Fig. 1). He was advised to undergo Hb variant analysis and alternate methods to monitor glycemic control. The chromatogram pattern showed a peak of 74.6% with retention time 3 min.77 s and HbA2 of 8.9% (Fig. 2). There was no history of blood transfusions, chronic bleeding, or known hematological disorders. Family history was not contributory.

Physical examination was unremarkable. There were no signs of jaundice, hepatosplenomegaly, or lymphadenopathy.

Investigations, namely complete blood picture and HbA1c testing, were done initially. Complete blood count (CBC) revealed Hb of 14.7 g/dL and red blood cell count of 7.79 million/cu.mm. PCV was 47.9, MCH was 18.9 pg, and mean corpuscular Hb concentration was 30.7 g/Dl. Mean corpuscular volume was 61.4 fL. Calculated red cell distribution width (CV%) was 20.2, indicating a microcytic hypochromic picture and erythrocytosis. Peripheral blood smear showed microcytosis and hypochromia without significant anisopoikilocytosis. HbA1c was not reportable, and further HPLC was performed for Hb variants, which revealed the presence of 74.6% of HbC, HbA2 of 8.9%, and reduced HbA. The elevated HbA2 raised suspicion of an underlying β-thalassemia, while the predominant HbC-like peak suggested Hb variant HbC, and together suggested a compound heterozygous HbC–beta thalassemia.

To confirm the diagnosis, we performed molecular analysis by Sanger sequencing of the β-globin gene. Sequencing identified a mutation consistent with Hb Siriraj and a pathogenic mutation associated with β-thalassemia (Fig. 3). Based on these findings, a diagnosis of compound heterozygosity for Hb Siriraj and β-thalassemia was established.

DISCUSSION

Hemoglobinopathies constitute a group of genetic diseases related to structural or functional abnormalities of globin chains. Hb Siriraj is an extremely rare Hb variant; there is no significant prevalence data, and it is not listed among the common or regionally significant hemoglobinopathies in large-scale studies in India. Its identification is generally limited to rare case reports or is found during the molecular characterization of "unknown" peaks in laboratory HPLC analyses. The medical literature suggests that while the heterozygous form is asymptomatic with basic hematology parameters often within reference range, the potential clinical findings in the homozygous state (Hb Siriraj/Hb Siriraj) or in combination with other hemoglobinopathies

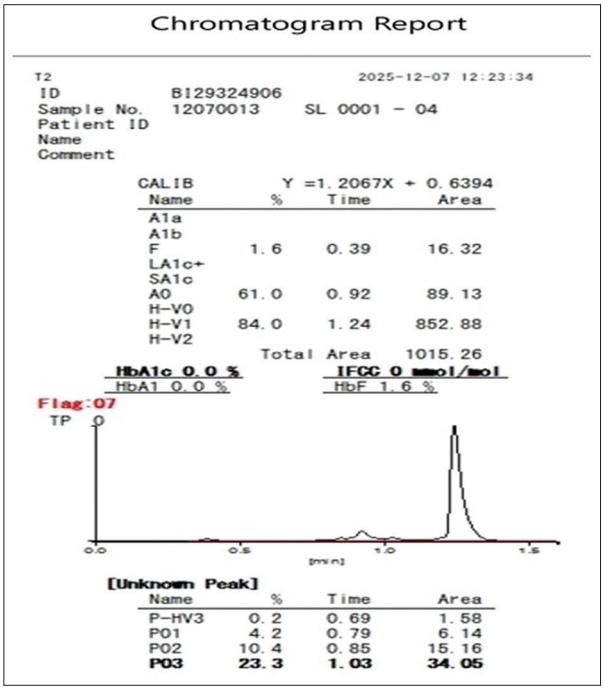

Figure 1: Glycated hemoglobin chromatogram showing unknown window

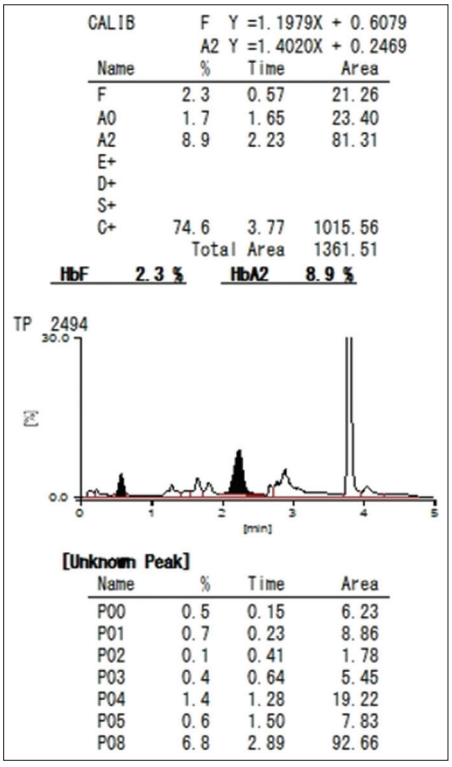

Figure 2: Hemoglobin (Hb) variant analysis showing C window and elevated HbA2

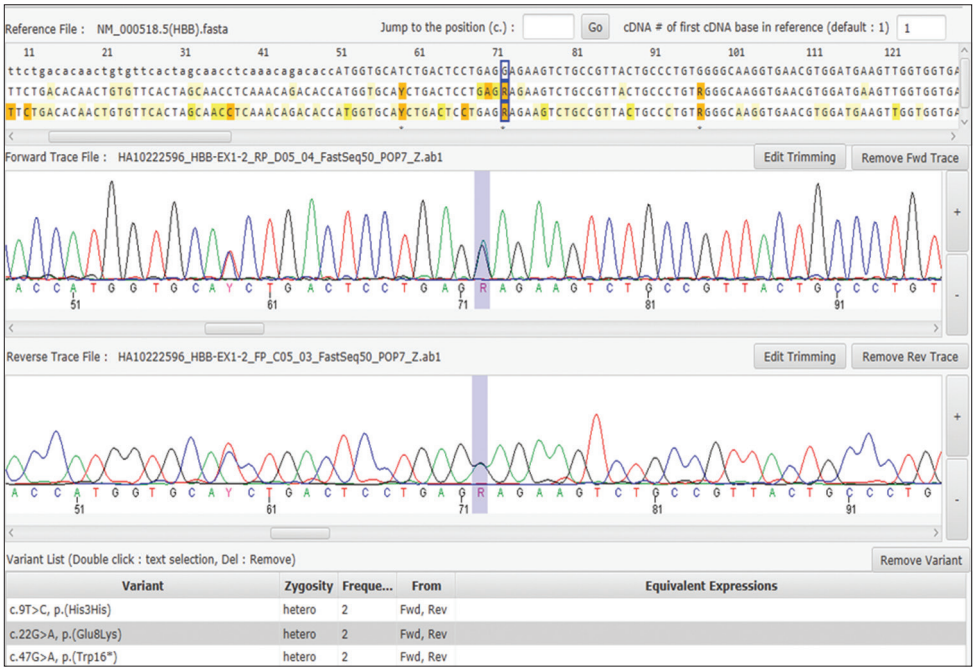

Figure 3: Sanger sequencing showing c.22G > A, p.(Glu8Lys) –Heterozygous and c.47G>A, p.(Trp16*)- heterozygous condition

(e.g., Hb Siriraj/beta-thalassemia) might involve different clinical presentations, however, due to the extreme rarity of this specific variant, large-scale studies on its clinical implications are not available. Furthermore, the correlation between genotype and phenotype can be complex, and discrepancies sometimes require extensive family studies and molecular analysis.

The Hb G-Siriraj variant is a consequence of a point mutation in the *HBB* gene (c.22G > A), which leads to a substitution of glutamic acid for lysine at position β7. It is a rare occurrence, and this variant is generally asymptomatic in the heterozygous state; carrier subjects typically present with a normal CBC, without morphological abnormalities of red blood cells or signs of hemolysis. Wang *et al*. found ten types of structural Hb variants, which were HbE compound with thalassemia, Hb G-Taipei, Hb Q-Thailand, Hb Youngstown, Hb Guangzhou-Hangzhou, Hb M-Boston, Hb G-Siriraj, Hb J-Baltimore, Hb J-Sicilia, and Hb Tamano in 1029 samples that were assessed by the Biorad variant II analyzer. One case of Hb G Siriraj was noted, which eluted in C window [8]. This presentation is similar to our case.

Hb G Siriraj was discovered in a Thai family by Tuchinda *et al*. in 1965 and in a Taiwanese family by Chang *et al*. [9,10]. It presented as a heterozygous state in the Taiwanese family. Blackwell *et al*. found a case of Hb G Siriraj in a normal Chinese individual, and the amounts of Hb Ao and Hb G Siriraj found were 67 and 33 in that case [11]. Incidence of Siriraj in Chinese subjects is low; only one subject was found among 160,000 Chinese tested according to their study. The Hb G-Siriraj variant was previously identified in Morocco by Ousguine *et al*. in a patient whose HbA1c by HPLC (ARKRAY ADAMS HA-8180V) had shown the variant as HbC, which is a similar scenario in our case also [1]. The variant window in HbA1c chromatogram prompted for Hb variant analysis, which was performed by HPLC on a Tosoh G [11]. The chromatogram pattern suggested the possibility of a compound heterozygous condition of HbC and Beta thalassemia trait. A compound heterozygous state of HbC-Beta thalassemia has clinical implications and can present as Thalassemia intermedia; thus, a clear distinction of the variants that overlap with Hb G Siriraj is crucial [5].

Guan *et al*., reported a case that showed a condition which is a combination of Hb G-Siriraj and α-thalassemia (double heterozygous), the analysis of which had mistakenly raised suspicion of β-thalassemia due to a spuriously interpreted elevation of HbA2 [2]. In our case, there is a mildly elevated A2 peak suggestive of Beta-thalassemia. This was confirmed on further sequencing.

A screening study done in a population of 23,000 subjects by Chen *et al*. showed a single case of Hb G-Siriraj, thus confirming the possibility of detection at very low prevalence [3]. This shows the rarity of this Hb variant and thus emphasizes the importance of the identification of such rare and abnormal Hbs.

There is significant overlap of the retention time of Hb G Siriraj with HbC, Hb Q–India and Hb O-Iran on HPLC-based assays of Hb variant analysis. HbC, when present as a double heterozygous condition with Beta thalassemia, can cause a significant clinical presentation due to its propensity to cause intracellular crystallization of erythrocytes [5]. Thus, a clear distinction of the same by a genetic testing is necessary to definitely confirm/exclude HbC. Hb Q India, which occurs along with beta/alpha thalassemia, can cause hematological manifestations [6]. Due to a similar retention time to that of Hb G Siriraj, it comes in the differential diagnosis, and delineating it from other Hb variants is crucial due to the clinical implications of the same. Hb O-Arab

presents with moderate anemia when it exists as a double heterozygous condition, and it also presents in a similar retention window to Hb Siriraj and has to be excluded definitively by genetic testing [7].

We emphasize that these biological manifestations can be present, in the majority of cases, without significant clinical translation, which can delay diagnosis and can cause misdiagnosis in the absence of thorough hematological investigations.

CONCLUSION

This case represents a rare instance of compound heterozygosity for Hb Siriraj and β-thalassemia diagnosed in advanced age. Comprehensive Hb analysis and molecular testing are essential for accurate diagnosis. Awareness of rare hemoglobin variants can prevent misdiagnosis and unnecessary investigations.

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