

CASE REPORT



## Blessing in disguise; a case of Hereditary Persistence of Fetal Hemoglobin

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### ABSTRACT

Fetal Hemoglobin (HbF,  $\alpha_2\gamma_2$ ) is produced from the eighth week of gestation, constitutes 60–80 % of total hemoglobin by birth, which is then replaced with adult Hemoglobin A1 (HbA1:  $\alpha_2\beta_2$ ) by 6–12 months. Hereditary Persistence of Fetal Hemoglobin (HPFH) is a rare benign asymptomatic genetic disorder where the HbF persists, and incidentally discovered on screening for other hemoglobinopathies. In adults, the variation in HbF levels could also be associated with other disease states, including hemoglobinopathies, leukemias and bone marrow failure syndromes. Here we present a case of a young asymptomatic female with the incidental finding of HPFH who was misdiagnosed as the sickle cell disease. It is important to have awareness about HPFH and should be distinguished from other causes of elevated HbF.

### ARTICLE HISTORY

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### KEYWORDS

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## 1. Case report

A 28-year-old African American female with medical history significant for asthma, ovarian cyst and endometriosis status post hysterectomy was referred to Hematology/Oncology clinic for evaluation of sickle cell disease. The patient recalled being told at young age, that she has sickle cell disease but denied any sickle cell disease related complications including vaso-occlusive crisis or requiring transfusions for that reason. Family history was positive only for sickle cell trait in her parents. She was using albuterol inhaler for asthma and her physical examination was otherwise unremarkable.

Initial investigations ruled out anemia with normal Hb/Hct & normocytic cells but hemoglobin electrophoresis showed elevated HbF levels (28.4%) with no HbS while 69.9% HbA1 and 1.7% HbA2 thus ruling out sickle cell trait or sickle cell disease. Also, thalassemia was unlikely as patient has significant elevation of HbF and cells were normocytic. The diagnosis of these hemoglobinopathies were ruled out while HPFH was further confirmed with flow cytometry; showing 30% HbF with homocellular distribution. The patient was relieved to know that she did not have sickle cell disease. She was informed that HPFH is a benign condition, which does not require transfusions under regular circumstances and would likely not impact her health and quality of life

## 2. Discussion

The persistence of HbF into adult life could be a non-pathogenic condition as in HPFH or be

associated with other diseases states. HPFH is a rare benign asymptomatic inherited disorder with persistence of HbF into adult life [1]. It is either pancellular/homocellular or heterocellular based on the hemoglobin distribution pattern. In pancellular HPFH, the level of HbF can range from 10–40 %, inherited in a Mendelian fashion, caused either by large deletions in the Human beta globin subunit gene (HBB) or by point mutations in the promoters of the gamma globin genes (non-deletion HPFH). On the other hand; in heterocellular HPFH, the inheritance pattern is not clear with only a modest increase in HbF levels and the hemoglobin is unevenly distributed among the erythrocytes.

Variable increase in HbF with heterogeneous distribution is pathogenic when associated with drugs, chromosomal disorders, hemoglobinopathies, and malignancies. Drugs like hydroxyurea and thalidomide analog pomalidomide increase HbF production. A chromosomal disorder like trisomy 13 is associated with the delayed switch of HbF to HbA and persistently elevated HbF levels [2,3]. Patients with beta thalassemia have a variable increase in HbF determined by the degree of beta chain deficiency and co-inheritance of alpha thalassemia, protecting against the deleterious effects of alpha-globin chain precipitation [4]. Elevated levels may also be found in many patients with leukemias following chemotherapy, considered to be stressed erythropoiesis as observed in juvenile chronic myeloid leukemia (JCML) [5], erythroleukemia occurring in infancy [6], acute myeloblastic leukemia,

lymphoblastic leukemia, chronic myeloid leukemia [4] and recipients of bone marrow when donor marrow proliferates [7,8]. Elevated levels of HbF can also be found after treating severe iron deficiency anemia due to acute blood loss [9]. Patients with inherited bone marrow failure syndromes (Diamond-Blackfan anemia, dyskeratosis congenita, Fanconi anemia, Shwachman-Diamond syndrome) often have increased HbF as part of their 'stressed' hematopoiesis that also includes macrocytosis and erythropoietin levels higher than predicted by their degree of anemia [10]. Rarely, increased HbF levels have been observed in solid tumors including choriocarcinoma, adenocarcinoma of the lung and hepatoma [11–14].

HPFH has beneficial effects if it co-exists with sickle cell or beta thalassemia. It can decrease the severity of sickle cell disease by reducing the concentration of HbS levels and thalassemia by decreasing the unused alpha globin chains and thus its precipitated forms.

### 3. Conclusion

An incidental finding of HbF with or without a family history of sickle cell trait should be investigated further, as it is not only associated with sickle cell but could be due to HPFH or other underlying condition including certain malignancies. Occasionally these patients are mislabelled with 'sickle cell anemia' and every little pain as 'sickle cell crisis'. In this era of opioid epidemics, it is crucial to identify, stratify and re-educate the patients to avoid inappropriate use of resources as it was done in the given case. This will minimize ER visits and unnecessary opioid use in the population with suspected 'sickle cell disease'.

### Disclosure statement

No potential conflict of interest was reported by the authors.

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