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An Undiagnosed Case of Jaundice: Who Is the Culprit, Liver Or RBC- An Interesting Case Report of HbH Disease

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Abstract

HbH disease is not an uncommon but it is an underdiagnosed entity in India. Clinically symptomatic beta thalassemia cases outnumber alpha Thalassemia in our country with ~0.01% of hemoglobinopathies being Hb H disease. We hereby present a case of Hb H disease manifesting as undiagnosed jaundice in adult male with review about clinical presentation and diagnostic modalities for same.

Keywords: Alpha thalassemia, Jaundice, golf ball inclusions, HbH disease.

INTRODUCTION

HbH disease is a type of alpha thalassemia usually caused by deletion or inactivation of three alpha-globin genes leading to underproduction of alpha-globin chains of Hemoglobin, with the formation of beta-4 tetramers (HbH).Patients with HbH disease have varied presentation from asymptomatic to mild anemia to intermittent transfusion requiring hemolytic anemia (Non transfusion dependent thalassemia). [(1)] In India the prevalence of α Thalassemia is estimated to be around 12.9%.The most common molecular abnormalities leading to alpha thalassemia in India are $(-\alpha^{3.7})$, $(-\alpha^{4.2})$ (less common than $-\alpha^{3.7}$), α $\alpha^{IVS1nt117G-A}$, $\alpha^{Koyadora}$ α .[(2,3)] Alpha thalassemia is most common in the Middle East, Southeast Asia, and certain Mediterranean countries. The incidence of HbH disease in these countries is approximately 4-20 individuals per every 1,000 births.[(4)] The prevalence of Hb H disease resulting from either 3 gene deletion or combination of deletion and mutation is ~0.01% of all hemoglobinopathies in Indian subcontinent. [(5)]

We hereby present a case of 25 yrs. old young man being evaluated and treated for jaundice of unknown origin. However interesting laboratory findings clinched the diagnosis and found the real culprit.

CASE HISTORY

A 25-year-old male presented with complaints of generalized weakness and jaundice in the last one month. He gave history of consumption of some ayurvedic medication in the last fifteen days. On general examination pallor, icterus, mild hepatosplenomegaly was noted. On Complete Blood Count Hemoglobin was 10 g/dl, MCV-59.8 fl, MCH-18.8pg, MCHC- 31.5 g/dl, RDW-25.8%, TLC-5,890/mm3 and platelet-1.4 lacs/mm3. Peripheral smear showed microcytic hypochromic cells with marked anisopoikilocytosis, tear drop cells, basophilic stippling, fragmented RBCs, hemighost cells, target cells, polychromatophils and occasional Nucleated RBCs (Figure1). Corrected reticulocyte count was 12%. With such a blood picture two possibilities were considered, first was liver disease with nutritional anemia on treatment with hematinics showing response to treatment and second possibility was Hemolytic anemia. So detailed history was derived

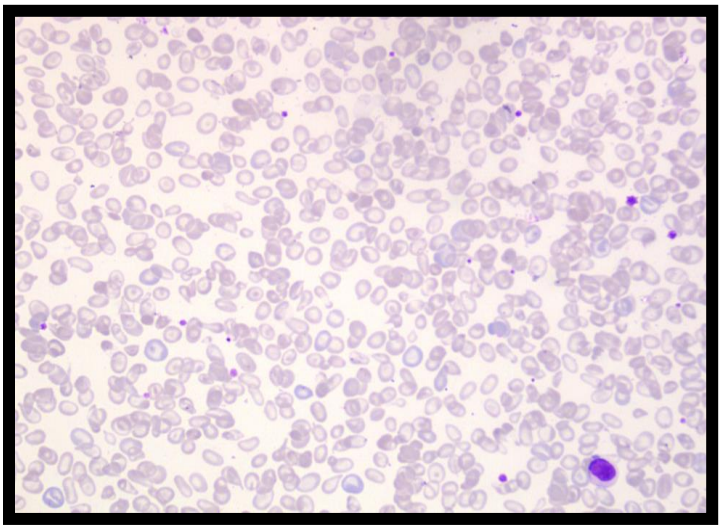

Figure 1. Peripheral smear showing anisopoikilocytosis with predominant microcytic hypochromic blood picture

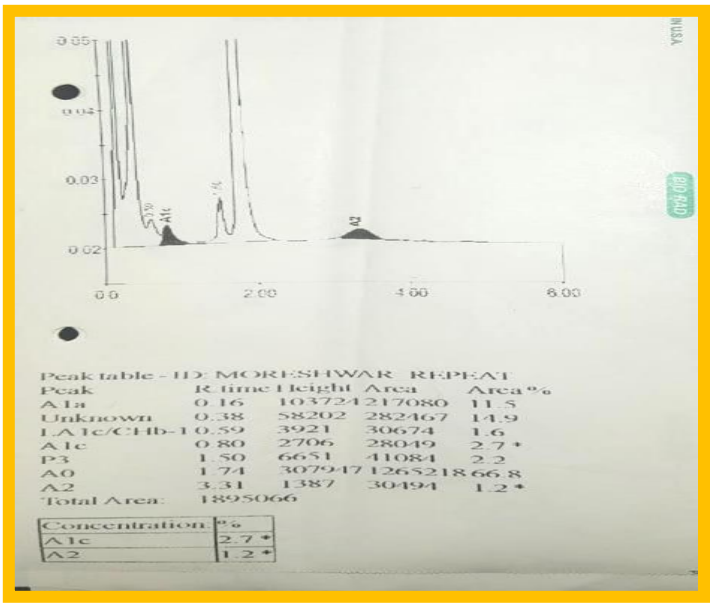

Figure 3a. Hb HPLC on Bio rad D10 showed sharp M shaped peak

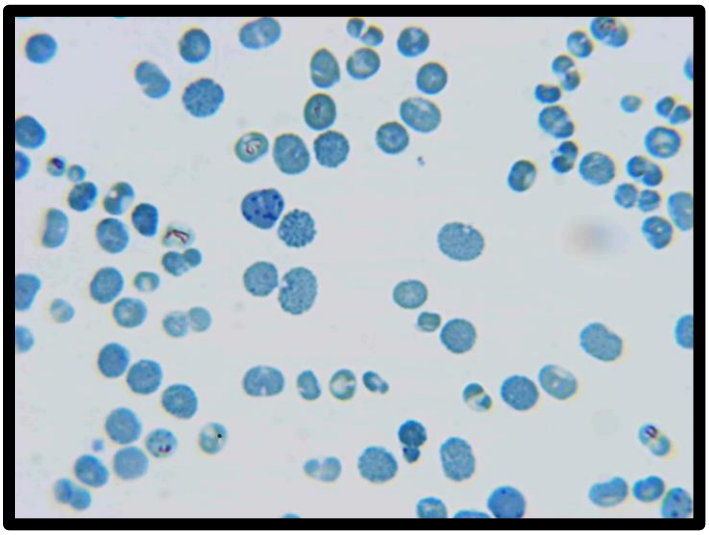

Figure 2. HbH preparation showing golf ball inclusions

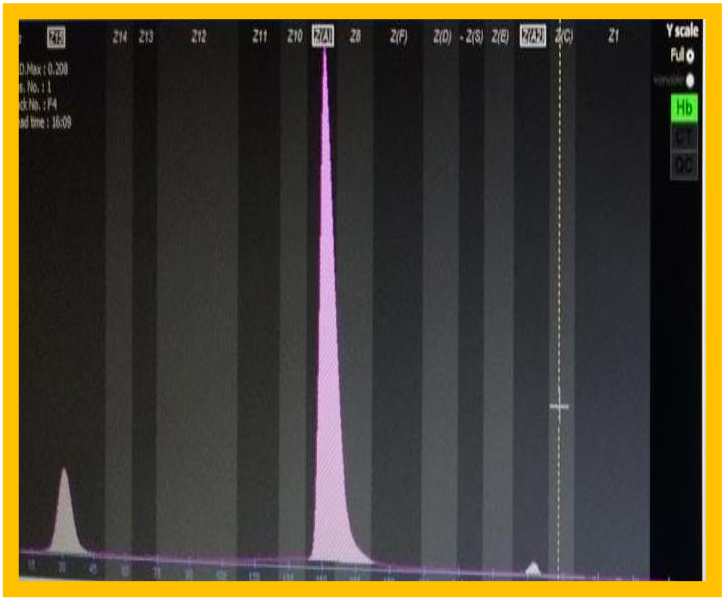

Figure 3b. Capillary zone electrophoresis showed peak in zone 15 of 14.4%

and we learned that patient was not on any nutritional supplements. But he gave past history of intermittent jaundice for the last one year, the last episode being 3 months back. He had been investigated for jaundice earlier with no previous reports available. However, he had one CBC one year back showing similar findings. None of the siblings had similar history and parents did not give history of consanguineous marriage. Biochemical investigations revealed total serum bilirubin 2.79mg%, conjugated fraction being 0.27mg%, AST 22.9 IU/L, ALT 16.7 IU/L and alkaline phosphatase 203.3 IU/L. With this history of persistent microcytic hypochromic anemia, unconjugated hyperbilirubinemia and increased retic

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count, hemolytic cause of anemia was considered. Simple test of Hb H preparation using supravital stain-new methylene blue was ordered and it showed beautiful golf ball inclusion. (Figure2). Hb HPLC on Bio rad D10 showed sharp M shaped peak of variant Hb of 14.9% with retention time less than 1 minute & reduced HbA2-1.2% (Figure3a). This indicated HbH disease. Capillary zone electrophoresis showed peak in zone 15 of 14.4% (Figure3b). Hence, confirming the rare diagnosis of HbH disease.

DISCUSSION

Alpha chain synthesis is regulated by 4 genes located on Chromosome 16. In India α+ mutations are more common than αo. Loss of function of 3 alpha genes by deletion or mutation (non deletional) leads to clinically significant alpha thalassemia called as Hemoglobin H (HbH) disease. As a result of markedly reduction in alpha chain production unstable beta tetramer is formed which is called-HbH. Hb H can precipitate in the red cells and RBC precursors, triggering cell lysis, oxidative damage, membrane dysfunction and shortened RBC survival causing hemolysis and jaundice. [6]

Clinical features of HbH disease are highly variable and generally develop in the first years of life but may not develop until adulthood in some patients. Most commonly they present with non-transfusion dependent mild anemia (NTDT). [7]

Patients have variable microcytic hypochromic hemolytic anemia, splenomegaly and less commonly hepatomegaly, mild jaundice, hypersplenism and mild-to-moderate beta-thalassemia major like skeletal changes mainly affecting the face. Initial signs may be noticed only during routine hematologic analysis. [7] Study by Au WY, Cheung WC, et al reported 50 % of cases of Hb H may present primarily with jaundice.[8] Similar to our scenario this may create confusion and delay in correct diagnosis and treatment if not approached correctly. The severity of the disease is related to its molecular basis: patients with non-deletional types of HbH disease, such as Constant Spring mutation, are more severely affected than those with the common deletion types. [9]

Simple investigation like CBC will alert the pathologist to order diagnostic testing. RBC indices are microcytic hypochromic with peripheral smear confirming above. In addition, marked Anisopoikilocytosis with codocytes, fragmented RBCs and nucleated red blood cells, basophilic stippling with variable polychromasia is noted. Together with peripheral smear findings, markers of hemolysis like high reticulocyte count, increased LDH & unconjugated hyperbilirubinemia should help to order next specific test for hemoglobinopathy i. e. Hb high performance liquid chromatography (HPLC). [3]

In absence of sophisticated equipment simple test of Hb H preparation can help us to make diagnosis. Simply prolonging the incubation with supra vital stains to 2 to 4 hrs help us to see golf ball inclusions as Hb H precipitates in those RBCs. [10] We can detect variants using HPLC, capillary zone electrophoresis, alkaline electrophoresis. When HPLC is done using Bio rad variant II program pathologist should be alerted by presence of bifid M shaped peak at the very start of graph which is not quantified and raise the possibility of Hb H disease. However, on D10 program there is bifid peak of Hb H with retention time less than 1 minute and is also quantified. Another technique called Hb capillary zone electrophoresis (CZE) is also frequently used these days. This platform identifies and quantifies both Hb H and Hb Bart in zone 15 and 12 respectively. This is one of the advantages of CZE over HPLC. However, one should be aware that Hb H comprises 1 to 40% of total Hb (usually only 8 to 10%). Along with this Hb F may be increased to 1-3% and Hb A2 is reduced to 1-2%. These are additional clues to pay attention to HPLC graph and pick up the variant peak. Hb H percentage will be higher in non-deletional type of genetic event and lower when there is coexisting heterozygosity for Hb βC, βS etc. [3]

Pathologist should be aware and interpret these findings with caution based on machine used in their lab. Supplementing it with manual technique will enable us to diagnose such cases.

CONCLUSION:

Hemolytic anemias are important differentials in a case of undiagnosed jaundice. Good CBC, peripheral smear examination with reticulocyte count is crucial in leading diagnostic evaluation in correct direction. Alpha thalassemia is a rare hemolytic anemia in our country with varied presentation. High index of suspicion and at least simple manual technique of Hb H preparation should be used to identify the inclusions.

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Hb HPLC, Hb CZE, Hb electrophoresis are different platforms available to detect and quantify the variant Hb. Pathologist should be aware of interpretation complexities of these equipment to make correct diagnosis.

Correct diagnosis of Hb H disease is important for correct management of the patient and more so for offering genetic councelling to the family and prevent occurrence of lethal state Hb Barts due to four gene deletions in coming generation.

Finally, often the culprit is not the one which appears. Take a deep dive with your diagnostic armamentarium to know the real cause and offer effective management.

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