An atypical presentation and diagnostic dilemma of sickle cell disease

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Abstract

A 5½ year old male child of a consanguineous couple presented with moderately high fever, hepatosplenomegaly and severe pain in the left upper quadrant of the abdomen for four days. On examination, the child was found severely anemic, ill-looking and mildly icteric but the abdomen was soft and non-tender. Radiological investigations and ultrasonography of the whole abdomen revealed the diagnosis of space occupying lesions which may be either due to splenic abscess/cyst or leukemia/lymphoma. However, blood film revealed the features of hereditary hemolytic anemia and later on hemoglobin electrophoresis initially commented as HbS–beta thalassemia but subsequent family screening of the patient turned out to a case of homozygous sickle cell anemia or sickle cell disease. To resolve such diagnostic dilemma, it is very much essential to analyze critically the history including family history, clinical and physical findings as well as investigational findings.

Introduction

Sickle hemoglobin variants result from the sickle mutation that substitutes thymine for adenine in the sixth codon of β gene (GAG→GTG), thereby encoding valine in place of glutamine in the sixth position of β chain. This minor change causes alterations in the erythrocyte morphology and rheology with profound changes in the molecular stability and solubility. The hemoglobin S (HbS) in deoxygenated red cells tends to undergo polymerization, that is responsible for the various sickling syndromes.[1] HbS is one of the major hemoglobinopathies that exists both in a heterozygous state called sickle cell trait, where red cells contain HbA as well as HbS and homozygous state called sickle cell disease in which erythrocytes are totally lacking HbA.[2] HbS is widespread in Africa, Middle East, parts of India and Mediterranean basin. Patients with sickle cell disease are the offspring of parents both of whom are carriers of sickle cell gene (β^S).[3]

The severity of sickle cell disease varies widely and depends on the degree of anemia, frequency of crises and extent of organ damage. Few of the sickling syndromes are devoid of serious pathologic complications, but they are easily confused with clinically aggressive conditions on the basis of physical presentations and clinical findings. Therefore, collective evaluation of clinical and laboratory findings is required for precise diagnosis which is essential both to clinical management and to appropriate, meaningful and effective genetic counseling.[2]

In this paper, we report a case of sickle cell anemia who presents clinical and radiological features of space occupying lesions in spleen as splenic abscess/cysts or leukemia/lymphoma.

Case Report

A 5½ year old male boy, second offspring of a consanguineous couple, hailing from Mymensingh presented with sudden onset of fever and pain in the left upper abdomen to a referral hospital of Dhaka Cantonment. Fever was 101^0F, continuous in nature and not associated with vomiting, chills or rigors. The pain was localized, dull aching without any radiation. There was no history of respiratory or urinary tract infection, convulsion or unconsciousness. On physical examination, the child was ill-looking, severely anemic and mildly icteric without any signs of meningitis. The abdomen was mildly distended but soft, non-tender without any muscle guard or rigidity. Spleen and liver were palpable about six and four centimeters from the left and right mid-clavicular line respectively. No other abnormality was detected in other systems. With these findings, the patient was initially diagnosed as either acute leukemia or acute intravascular hemolysis due to malaria or glucose-6-phosphate dehydrogenase deficiency.

Keeping in mind with the above diagnosis, the

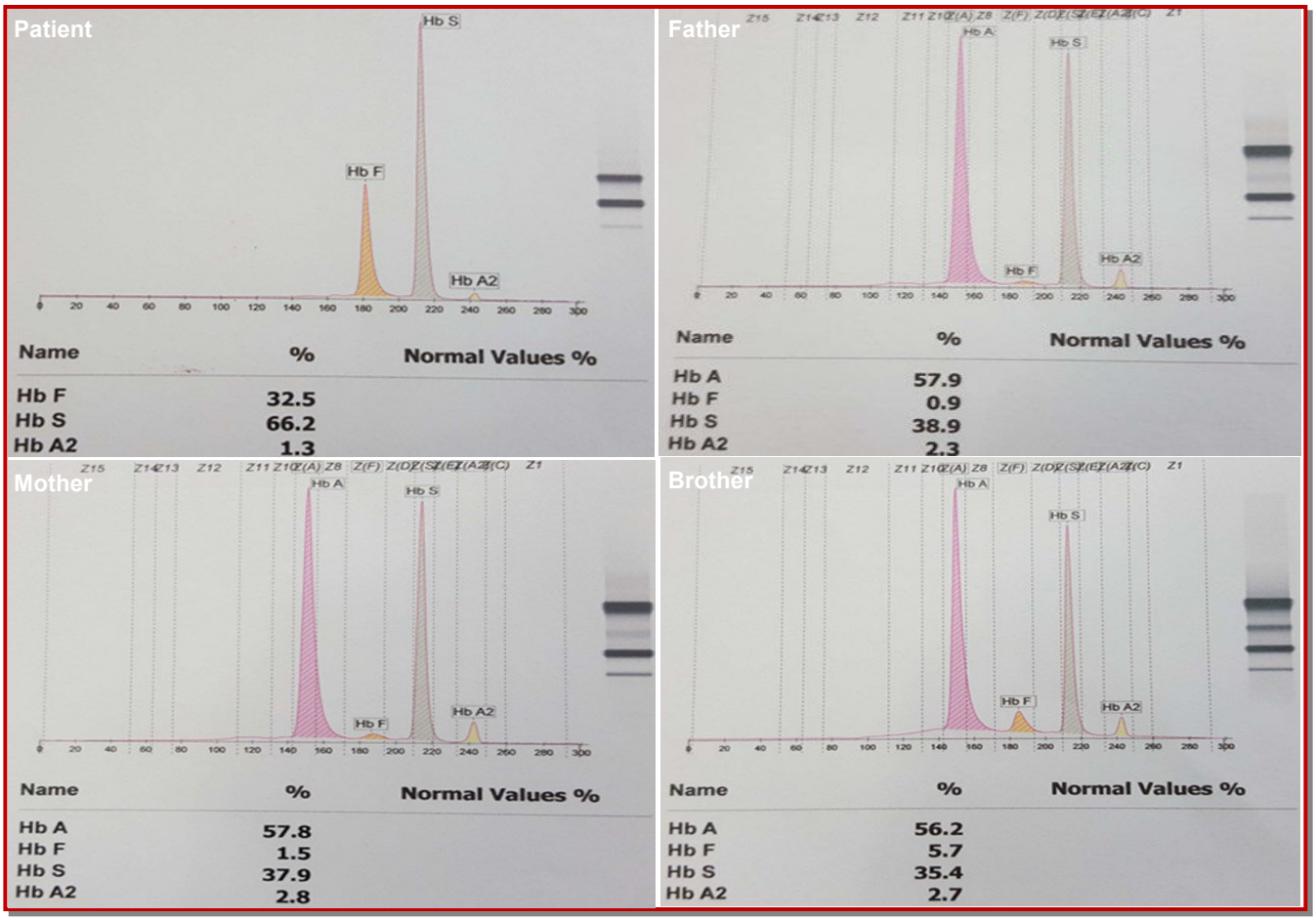

Figure 1: Hemoglobin pattern of the patient, father, brother and mother (clockwise) of the index case on capillary hemoglobin electrophoresis

patient was investigated with full blood count which revealed hemoglobin 5.0 g/dL, total leucocyte count 20.8 x 10^9/L with normal differentials and platelet count 90 x 10^9/L. Peripheral blood film examination showed features of hereditary hemolytic anemia with thrombocytopenia. Meanwhile, other investigations such as blood for malaria parasite, immunochromatographic test for malaria, G-6-PD assay, X-Ray chest, ultrasonography of the whole abdomen, serum iron, total iron binding capacity, serum ferritin, Coombs test, reticulocyte count, coagulation profile (PT, APTT, FDP and D-dimer), liver function tests (serum bilirubin, ALT and alkaline phosphatase), serum urea and createnine, serum lactate dehydrogenase, uric acid and hemoglobin electrophoresis (Hb-electrophoresis) were sent. The notable findings were hepatosplenomegaly with space occupying lesion in spleen suggestive of splenic abscess/cyst or leukemia/lymphoma on ultrasonography of abdomen, reticulocyte count was 4.0% (normal range = 0.5-2.5%), Coombs test was negative. Serum iron and total iron binding capacity were within the normal limit but serum ferritin was raised (561.8 ng/mL [normal range = 12–300 ng/mL]). Serum bilirubin was slightly raised (1.2 mg/dL) but other liver function tests were within the normal limit. Coagulation profile, serum uric acid and renal function tests were also within the reference range. But the serum lactate dehydrogenase was markedly raised (2931 U/L [normal range= up to 450 U/L]) and the hemoglobin electrophoresis showed HbF 32.5%, HbS 66.2% and HbA_2 1.3% providing the diagnosis of HbS-beta thalassemia (Figure 1). After getting such hemoglobin pattern, sickling test was done and found positive.

For confirming the diagnosis, parents and brother of the child were requested for full blood count and Hb–electrophoresis. As grandparents were not available, so it was not possible to investigate them. Hb -electrophoresis of the father, 35 years old, showed HbA 57.9%, HbA_2 2.3%, HbF 0.9% and HbS 38.9%, mother, 30 years old, revealed HbA 57.8%, HbA_2 2.8%, HbF 1.5% and HbS 37.9% and the only brother of the index case, 8½ years old, showed HbA 56.2%, HbA_2 2.7%, HbF 5.7% and HbS 35.4% almost confirming that all are suffering from the sickle cell trait. As the parents are suffering from sickle cell trait, therefore as per Mendelian law, the index case should be either sickle cell trait or sickle cell disease. But the hemoglobin pattern of the index case

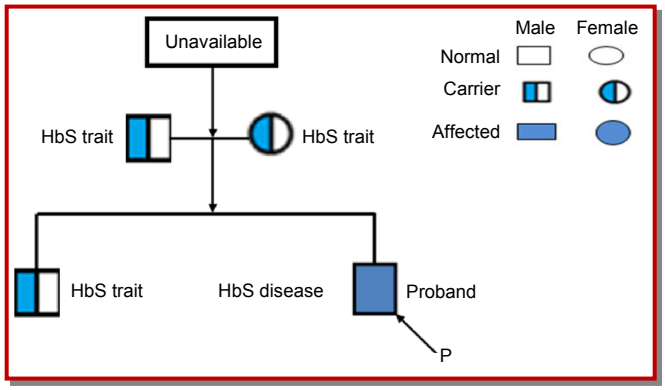

Figure 2: Pedigree of the index case

(younger son) revealed the possible diagnosis of sickle cell–beta thalassemia causing a diagnostic dilemma. Pedigree analysis of two generations of index case is shown in Figure 2. Hematological parameters of the patient and his family members are shown in Table I.

Discussion

In sickle cell disease, the predominant hemoglobin is S (90.0%) with varying concentration of HbF (7.0%) and normal HbA_2 (3.0%).[3] HbF level may be raised up to 20%.[4,6] As HbF was 32.5% in this case, so it was diagnosed as HbS-β thalassemia. In HbS–β^+ thalassemia, the usual pattern of hemoglobin is HbA 5-30, HbF 5–15, HbA_2 >3.5 and HbS 60–85%, on the other hand in HbS-β^0 thalassemia, the hemoglobin pattern is HbA 0%, HbF 5–30, HbA_2 >3.5 and HbS 70–90%.[4,5] Therefore, analyzing only the hemoglobin electrophoretic pattern of this case made it confusing for the hematologist in the interpretation of hemoglobin electrophoresis as well as concerned physicians to reach in the definitive diagnosis. Moreover, as the patient was very ill and severely anemic on presentation and had a moderate fever, excruciating pain in the left upper quadrant of the abdomen and hepatosplenomegaly on physical examination, so the concerned clinician thought that it might be a case of either acute leukemia or lymphoma. On that day, reports of full blood count and ultrasonography also revealed almost different types of diagnosis; therefore it has made the situation cloudier. However, after getting the electrophoresis result, diagnosis was almost confirmed that it is a case of HbS–beta thalassemia but subsequent family screening revealed that all members has been carrying β^S gene and suffering from HbS trait, so the patient should never be a case of HbS–beta thalassemia as per Mendelian law provided no new mutation for beta thalassemia took place which is very unlikely. More so, the hemoglobin pattern in this case was more in favor of the diagnosis of HbS-β^0 thalassemia. It is also well recognized that the interaction of HbS-β^0 thalassemia gives an electrophoretic pattern that is indistinguishable from that of homozygous sickle cell anemia[2,7] which happened in this case. Though grandparents are not available for family screening but hemoglobin electrophoresis of the parents and brother of the patient almost confirms the diagnosis of homozygous sickle cell anemia or sickle cell disease.

Conclusion

Hemoglobin electrophoresis only in many a time could not provide definitive diagnosis in a patient with varied and atypical clinical presentation where meticulous as well as critical analysis of electrophoretic pattern of hemoglobins along with family screening is mandatory to arrive at a definitive diagnosis, although hemoglobin S mutation study may be required to characterize accurately the genotypic basis for a sickling disorder.

Ethical Issue

Written and informed consent was taken from the parents for publishing this article.

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Table I

Hematological parameters of the index case and his family members

Relation	Hb (g/dL)	RBC count ($X10^9$/L)	MCV (fL)	MCH (pg)	MCHC (g/dL)	RDW (%)	HbA	HbA2	HbF	HbS	Sickling test
Patient	5.0	1.9	83.2	26.2	31.4	20.2	-	1.3	32.5	66.2	Positive
Father	12.8	4.6	81.0	27.6	34.0	14.9	57.9	2.3	0.9	38.9	Negative
Mother	11.7	4.1	86.8	28.7	33.1	13.9	57.8	2.8	1.5	37.9	Negative
Brother	13.0	4.7	91.9	27.5	30.0	15.5	56.2	2.7	5.7	35.4	Negative

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