CASE REPORT

Sickle- β^+ thalassemia with splenic calcification and bone marrow infarction: a case report

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Abstract We came across an unusual case of a 20 years old male from north India who presented with repeated episodes of pyrexia of unknown origin (PUO) and history of chronic hemolytic anemia. On investigation he was detected to have Sickle- β^+ Thalassemia and subtle features of hyposplenism. Radiological investigations revealed extensive splenic calcification and bone marrow examination to evaluate for PUO showed extensive bone marrow infarction and fibrosis. Molecular diagnosis for beta thalassemia mutation revealed heterozygosity for IVS 1-5 M and alpha globin genes were normal. This case highlights the wide variation of clinical phenotype which is encountered with Sickle- β^+ Thalassemia where genotyping can predict the clinical phenotype only partially.

Keywords Splenic calcification · Sickle- β^+ Thalassemia · Bone Marrow Infarction

Introduction

Sickle cell disease is the commonest structural hemoglobin variant which is symptomatic. Compound heterozygotes of HbS with other mutant α or β globin genes are also present in populations with a high prevalence of HbS [1]. Symptomatic sickle cell syndromes can occur due to homozygous sickle cell disease (Hb SS), compound heterozygous state for HbS and other structural hemoglobin variants like HbC (Hb SC disease) and HbD Punjab (Hb SD disease) and sickle-beta thalassemia (HbS/ β^0 or HbS/ β^+). Sickle- β thalassemia syndrome has two forms: sickle- β^0 thalassemia when there is no β globin synthesis from the affected allele and sickle- β^+ thalassemia when β globin synthesis is present but reduced. Depending on the output of the β chains, the individual patient may resemble sickle cell trait or have a clinical phenotype with hemolytic anemia and vasoocclusive complications. In general, Hb SS disease is the most severe form of the sickle syndromes followed by Hb S- β^0 thalassemia, Hb SC/SD disease and finally Hb S- β^+ thalassemia. Patients with HbS/ β thalassemia unlike those with sickle cell disease often have splenomegaly beyond the first few years of childhood [2]. Recently we came across an unusual presentation of an adult patient of HbS/ β^+ thalassemia having repeated febrile episodes who was detected to have splenic calcification and bone marrow infarction. His condition was diagnosed while investigating for pyrexia of unknown origin (PUO).

Case report

A 20-year-old male from north India, presented with a history of fever for one month, generalized myalgia and

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jaundice. Fever was high grade accompanied with chills and rigors. On examination, the patient was thin-built with moderate pallor and icterus. There was no lymphadenopathy or splenomegaly but the liver was 5 cms below the costal margin. Other systemic examination was within normal limits. His past history revealed that he had been symptomatic since ten years of age with episodes of fever off and on, anemia and jaundice. There was a history of joint pains and body aches. He was the youngest of seven siblings and neither his parents nor siblings had history of similar course of illness.

On investigation, all his blood cultures and urine culture were sterile. Widal was non reactive. Hepatitis viral serology was negative. Peripheral blood smear was negative for malarial parasites. Chest X-Ray was normal and ultrasound of abdomen showed hepatomegaly with 16.5 cm span. CT scan abdomen showed extensive splenic calcification. Hemoglobin ranged from 46 gm/l in the pre-transfused sample to 119 gm/l in the post-transfusion sample. Platelet counts and TLC were normal with counts of $183 \times 10^9/l$ and $11.6 \times 10^9/l$ respectively on one occasion. Peripheral blood showed moderate anisopoikilocytosis with hypochromic microcytes, target cells, sickle cells, occasional teardrop cells, Howell-Jolly bodies and 18–20 nRBCs/100 WBC's.

The patient's plasma hemoglobin was 20 mg% and total serum bilirubin was 7 mg/dl. G6PD screening was normal and urine hemoglobin was absent. Hemoglobin electrophoresis with 2% starch agar at alkaline pH 8.6, citrate agar at acidic pH 6 and sickling test were performed. Hb quantitation was carried out by HPLC using the Biorad-Beta Thal Short programme. Simultaneously family study for hematological evaluation was carried out (details in Table 1). The patient was found to be double heterozygous for HbS/ β^+ thalassemia while his mother was β thalassemia trait and father was sickle cell trait. Molecular characterization of β gene defect done on genomic DNA extracted from peripheral blood leucocytes showed the mutation to be IVS 1-5 M (severe β^+ mutation). GAP-PCR for alpha gene defect showed a normal pattern for the family.

A bone marrow examination for microbiological cultures for PUO work up was performed. Bilateral trephine biopsy showed hypercellular marrow spaces with marked erythroid hyperplasia, normal granulocytic and megakaryocytes lineages in one core. No evidence of any granuloma or infectious pathology was seen. The other core showed total replacement of normal marrow spaces by fibrosis and dilated vascular spaces. Scattered hemosiderin-laden macrophages and new bone formation rimmed by osteoblasts

Table 1 Blood counts and Hb electrophoresis

Parameters	Index case (20/M)	Father (60/M)	Mother (55/F)
Hb (g/L)	47	140	102
PCV (%)	14.2	40.3	31.1
Reticulocytes (%)	6.7	1	1.2
Plt count ($\times 10^9/L$)	116	168	210
TLC ($\times 10^9/L$)	18.4	10	4.6
DLC (N/L/M/E/My)	66/24/5/2/3		
18-20 nRBCS	77/13/2/8/-	80/15/3/2/-	
MCV (fl)	70.2	85.1	63.7
MCH (pg)	22.9	29.6	21.0
MCHC (%)	32.9	34.8	32.9
RBC count ($\times 10^{12}/L$)	2.03	4.74	4.88
RDW (CV%)	22.0	16.2	14.8
HbA (%)	4	84.2	50.8
HbF (%)	25.6	<1	0.7
HbA ₂ (%)	5.4	5.5	3.9
Hb S (%)	61.8	Absent	38.9
Sickling test	Positive	Positive	Negative
Hb electrophoresis (alkaline pH-8.6)	HbS+F+A ₂ bands	HbA+S bands	HbA+A ₂ bands
Hb electrophoresis (acid pH-6)	HbS band (towards anode)	HbS band (towards anode)	-
Diagnosis	HbS/ β^+ thalassemia	Sickle cell trait	β thalassemia trait

were seen in between. Both the ends of the biopsy showed large areas of infarction.

The patient received three units of blood transfusion and broad spectrum antibiotic cover for two weeks was administered after which the fever subsided.

Discussion

Sickle β thalassemia was first recognized in Italy, where β thalassemia is common and HbS is found in selected sub populations [3]. In HbS- β^0 thalassemia, the hemolysate contains only HbS, HbF and 4 to 6% HbA₂. HbA is absent unless the patient has been transfused and hence the phenotype mimics sickle cell anemia. In contrast, in HbS- β^+ thalassemia, HbA varies from < 5 to 45% of the hemolysate. Hence individuals with traces of HbA as in the index case have a disease resembling sickle cell anemia or HbS- β^0 thalassemia [2].

Among the different genotypes of HbS- β^+ thalassemia, higher levels of HbA are associated with milder phenotype. Individuals with HbS- β^+ thalassemia with very low levels of HbA are often mistaken for HbS- β^0 thalassemia. As IVS 1 position 5 G-C shows HbA to be less than 5%, four β^+ thalassemia mutations all producing severe phenotype have been described at this position and two of these have been associated with severe HbS- β^+ thalassemia, masquerading as HbS- β^0 thalassemia [4].

In all types of HbS- β thalassemia, as in sickle cell anemia higher HbF concentration decreased the clinical severity of the disease. The beneficial effect of high levels of fetal hemoglobin in sickle cell disease is due to the sparing effect of HbF on the polymerization of deoxyhemoglobin S [5]. Fully oxygenated HbS does not enter the polymer phase while partially or fully deoxygenated HbS can do so. If HbF is mixed with HbS, neither the HbF tetramer ($\alpha_2\gamma_2$) nor the $\alpha_2\beta_\gamma$ hybrid can enter the polymer phase [6].

Sickle cell anemia is characterized by vaso-occlusive episodes leading to end organ damage manifested as painful crises and splenic infarction leading to auto-splenectomy. Although co-inheritance of α -thalassemia attenuates the hemolytic severity of the disease, double heterozygosity for β -thalassemia may either ameliorate or exacerbate the hemolytic or vasoocclusive manifestations of the disease [7]. Nevertheless, auto-splenectomy is a rare occurrence in HbS/ β^+ thalassemia with few reported cases in literature showing absence of spleen [8], or splenic calcification [9]. The patient in our case also had subtle features of auto-splenectomy in the form of Howell-Jolly bodies in the peripheral blood smear, repeated episodes of febrile illness and splenic calcification on radiology. The vaso-occlusive events in this patient were reiterated by finding bone marrow infarction

and fibrosis. Although, bone marrow infarction is described in sickle cell disease [10, 11], such a finding is infrequently described in literature in double heterozygous sickle-beta thalassemia patients. Other unusual presentations like multiorgan failure [12], orbital compression syndrome [13] and fatal splenic sequestration crisis [14] etc are described in these patients.

In conclusion, this case presents another interesting facet of double heterozygous sickle β^+ thalassemia – an entity with genotypic and phenotypic variability. Since HbS- β^+ thalassemia may be confused either with sickle cell trait or HbS- β^0 thalassemia / sickle cell anemia depending on the amount of HbA found, a multifaceted approach with detailed genetic, molecular and family study is required for exact characterization of the defect. The case under discussion had been symptomatic with episodes of hemolytic anemia and fever with radiologic evidence of splenic calcification. The hematological work-up helped in arriving at a correct diagnosis.

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