

SICKLE CELL THALASSEMIA IN AN ADULT FROM CENTRAL INDIA SHOWING MASSIVE SPLENIC INFARCTION AND GAMNA-GANDY BODIES IN SPLENIC PARENCHYMA WITH CONCOMITANT PLASMODIUM FALCIPARUM INFECTION (case report)

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Background. Sickle cell thalassemia is a heterozygous state of HbS/ β^+ or HbS/ β^0 manifested clinically either as an asymptomatic carrier or have features akin to sickle cell anemia.

Objective. The aim of the study is to review the literature and discuss the varied clinical manifestations and diagnosis of a case report of haemoglobinopathy in an adult from Central India.

Methods. A case of haemoglobinopathy from central part of India is being investigated.

Results. A case of haemoglobinopathy in an adult presenting to a tertiary hospital with chronic back ache was reported. The patient was found to have massive splenomegaly with evidence of splenic infarction. Gross examination of spleen revealed multiple soft yellowish pasty areas, which on microscopic examination showed significant necrosis with presence of great amount pale amorphous yellow substance, Gamna-Gandy bodies (GGBs) and massive foreign body cell reaction in splenic parenchyma. Post-splenectomy peripheral blood smear (PBS) showed thrombocytosis and plasmodium falciparum gametocytes. The Hb electrophoresis revealed both elevation of Hb S (49.7%), Hb F (46.7%); Hb A₂ (3.0%) and (Hb A 0.7%) consistent with as Sickle Cell Thalassemia Hb S/ β^+ Thalassemia.

Conclusion. Sickle cell thalassemia with long standing huge splenomegaly, splenic infarction with GGBs deposition and concomitant falciparum malaria in clinically stable patient is rare indeed.

KEYWORDS: sickle-cell anemia; beta-thalassemia; malaria; plasmodium falciparum; Gamna-Gandy bodies.

Introduction

Hemoglobinopathies are the most common inherited RBC disorders, thalassemia and sickle cell disease – the most frequent. Co-existent both sickle cell mutation and thalassemia mutation, commonly beta thalassemia, facilitating development to a compound heterozygous state known as sickle cell beta thalassemia, was first reported and described by Silvestroni and Bianco in 1944 [1]. The incidence of this condition is very common in Mediterranean region. Its prevalence in Indian subcontinent is under-reported, perhaps due to underdiagnosis as most of these patients are normal and asymptomatic. Documented prevalence of sickle cell beta thalassemia in India is less than 1% in various studies [2].

Inherited as autosomal recessive disorder it occurs when one abnormal gene for produc-

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tion of hemoglobin S is inherited from one parent and one abnormal gene for production of beta thalassemia is inherited from the other parent. The genes for both hemoglobin and beta thalassemia are both located on chromosome 11.

Manifestation of the condition was studied in 1973 by Serjeant et al [3]. Clinical manifestations vary depending upon heterozygosity from being completely asymptomatic (Hb S/ β^+) to signs and symptoms very much akin to sickle cell anemia (Hb S/ β^0) [4].

Case Report

A 29-year-old serving soldier, the resident of central India, while being employed in high altitude area complained of chronic pain abdomen, which was found to be due to massive splenomegaly (23 cm in span) with sonographic evidence of splenic infarction. Approximately 7 years earlier, he had similar episode of abdomen pain for which he was worked up to rule

any hematological disorder. He had microcytic hypochromic anemia with normal TLC and DLC. Thrombocytosis was noted. There was no documented evidence of any organomegaly in the past. Past Hb electrophoresis reports revealed HbS – 49.7%, Hb A – 0.7%, Hb A2 – 3.0% and Hb F – 46.7%; consistent with as Sickle Cell Thalassemia (Hb S/ β^+ Thalassemia).

His general, systemic examinations were within norm during pre-anesthetic check-up. He was taken up for the splenectomy operation and specimen sent to Dept of Pathology for histopathological examination.

Lab received a grossly enlarged specimen of splenectomy weighing 1.2 kg and having apparently normal architecture externally. Serial cut section of the fresh specimen showed multiple soft yellowish areas of splenic infarction. Formalin-soaked cotton were placed in between these cut surfaces and whole specimen was put in 10 % formalin for 24 hours. Multiple sections from these necrosed soft areas were submitted along with normal appearing areas of spleen. H&E stains slides were studied by microscopy.

Histopathological examination revealed significant necrosis in infarcted area and there were multiple areas showing deposition of yellowish granular substances in splenic tissue which were Congo-red negative and birefringence negative under polarized light. Sickle cells in the sinusoids were also seen.

Post splenectomy period was uneventful with no fever, however, there was incidental findings of different forms of plasmodium falciparum including gametocytes in the peripheral blood. Thrombocytosis was also noted as expected.

Discussion

Sickle cell thalassemia, described originally as micro-drepanocytic disease by Silvertroni and Bianco [1], is a clinical condition where mutations in both HbS gene and Thalassemia gene (commonly beta gene) occur resulting in

two heterozygous states of either Hb S/ β^+ or Hb S/ β^0 . Heterogeneity in the beta thalassemia mutations leads to different beta globin synthesis and hence different amounts of HbA are synthesized which result in variable clinical manifestations ranging from nearly asymptomatic to a severe condition similar to sickle cell anemia (homozygous HbS) [4].

Laboratory investigations reveal microcytic hypochromic red cells with target cells and occasionally sickled forms. Hemoglobin electrophoresis may reveal 60-90% Hb S, 0-30% Hb A, 1-20% Hb F and an increased HbA2 level. In Hb S/ β^+ Thalassemia, as in our case, variable amounts of Hb A dilute Hb S and consequently inhibit polymerization-induced cellular damage. Increased levels of Hb A are usually associated with a milder phenotype [2, 5, 6, 7].

In our case, in the pre-splenectomy period, the patient was consistently having microcytic anemia as shown in Table 1 with leukopenia and increased LDH indirectly suggesting hemolysis. Platelet was adequate. No malarial parasite was seen in the peripheral smear. Post splenectomy, anemia improved but mild leukocytosis and thrombocytosis was evidenced as expected. LDH was found decreasing. Incidentally, peripheral smear showed numerous gametocytes of Plasmodium falciparum. Molecular tests for confirmation of sickle cell thalassemia were unavailable in the lab. Hence diagnosis was purely based on tests for sickling and Hb electrophoresis. Role of PBS examination and relevant histopathological sections could not be undermined.

Individually, both thalassemia and sickle cell trait offer protection from malarial infection, however when both occurs in the same individual protection offered by thalassemia can be reversed by another additional genetic polymorphism such as HbS mutation. The two mutations essentially cancel each other and the individual becomes susceptible to malaria [8]. Heterozygotes for the sickle gene (Hb genotype AS) are relatively protected against death due

Table 1. Relevant present investigations

Sr No.	Pre splenectomy	Post splenectomy
Hb (gm/dL)	6.6	10.1
MCV (fL)	68	69
TLC	2450	11220
DLC	P-69%, L-23%, M-07%, E-01%	P-82%, L-11%, M-04%, E-03%
Platelets ($10^5/\mu\text{L}$)	1.1	5.56
LDH (U/L)	>1000	634
PBS	No malarial parasites	Malarial parasites evidenced



Fig. 1. Gross specimen before and after fixation showing areas of infarction.

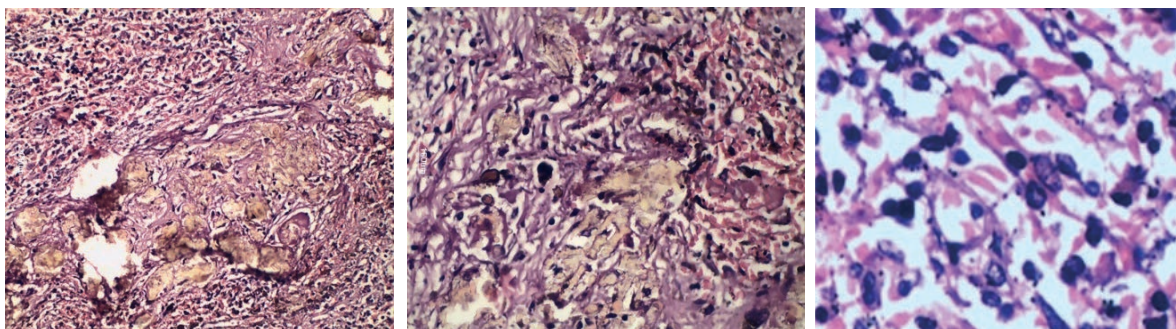


Fig. 2. Photomicrographs from H&E sections showing deposition of yellowish fine granular to amorphous (inset) substances in spleen (Gamna-Gandy bodies) and sickle cells.

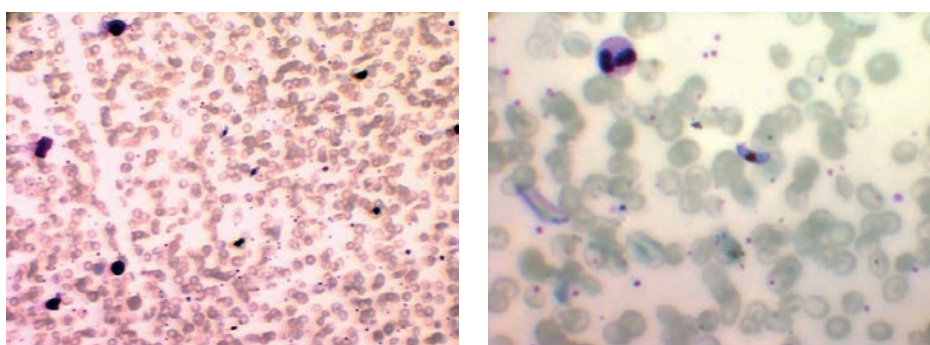


Fig. 3. Photomicrographs showing numerous gametocytes and trophozoites of Plasmodium falciparum and thrombocytosis.

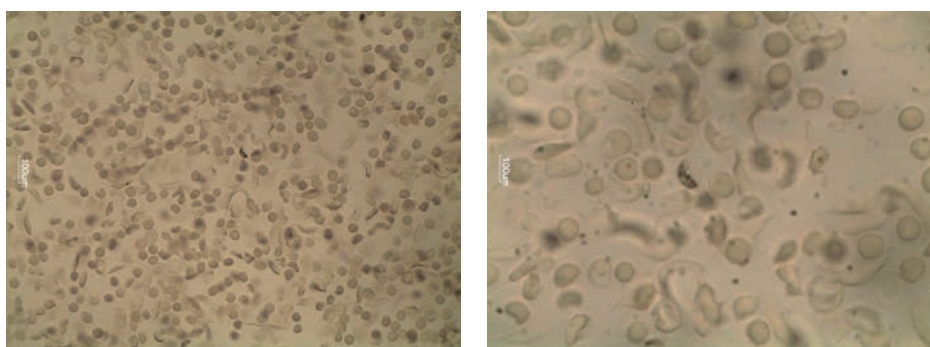


Fig. 4. Photomicrographs showing positive sickling with malarial gametocytes.

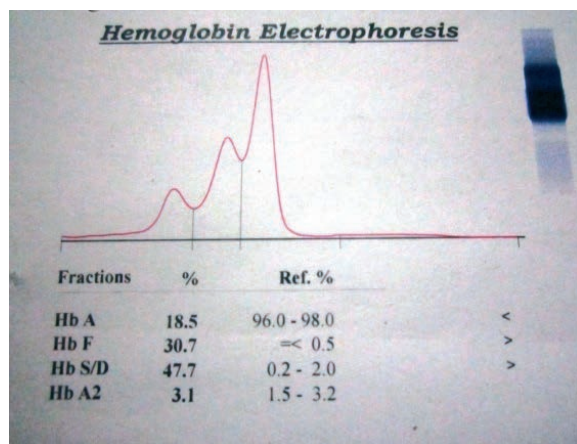


Fig. 5. Hb electrophoresis at alkaline pH showing a prominent band in SDG region, Hb F and faint band in HbA2 (Hb S – 47.7%, Hb F – 30.7%, Hb A – 18.5 % and Hb A2 – 3.1 %).

to malaria, probably through accelerated clearance by macrophages of *Plasmodium falciparum*-infected erythrocytes and by inhibiting growth of parasites in RBCs by increasing intracellular potassium, reduced PH and increasing endothelial adherence of infected cells [9]. On the other hand, homozygous (Hb SS) sickle cell anemia patients are not protected from malaria or any other infections [10,11] and, hence, there is increased chance of dying from malaria which is additionally aggravated by having dysfunctional spleen [12,13] or in the post-splenectomy period as removal of abnormal RBCs and other intracytoplasmic inclusion bodies is the primary function of spleen [14,15]. In our case, the pre-splenectomy period blood did not show any malarial parasites due to effective hyperactive enlarged spleen but once patient's spleen was removed, numerous forms of *plasmodium falciparum* were seen in the blood as the individual was devoid of major protection offered by spleen including removal of infected RBCs and other inclusion bodies.

People living in the malaria endemic areas have some degree of acquired immunity against malaria which may weaken over absence of recurrent exposures or when individuals moved to non-endemic areas [16]. This partial acquired immunity against malaria develops during the first 5 years of life and is dependent on the intensity of transmission, on exposure frequency and so it decreases with time if re-exposure does not occur [17]. In sickle cell disease, auto-splenectomy or functional asplenia occurs in early adulthood in homozygous state, however, in sickle beta-thalassemia the spleen may persist and remain enlarged

even in adults. This splenomegaly may cause massive pooling of blood in the spleen (splenic sequestration), which leads to its enlargement and resulting in severe anemia and hence a more compelling indication for splenectomy in sickle beta-thalassemia. This reduces substantially the rate of blood transfusion [18].

Also, multiple areas in splenic parenchyma with deposition of yellow-brownish fine granular to amorphous substance with associated foreign-body giant cell reaction were found [19]. They were Gamna-Gandy bodies. Initially described by Marini as siderotic nodules in 1904, French physician Charles Gandy in 1907 found it in biliary cirrhosis patient. In 1921, the etiology was better described by an Italian pathologist Carlos Gamna, who observed deposits of amorphous material composed of iron and calcium sulfate in the spleen of a patient, who died of chronic hemolytic anemia; it was named Splenogranulomatosisiderotica. The name "Gamna-Gandy bodies" has been widely used ever since [20]. It is formed in sickle cell disease (SCD) due to chronic episodes of vaso-occlusion and hemolysis in the central arteriole of the white pulp with periarteriolar hemorrhages followed by mineral elements of the blood. It can be seen as either fine granular deposits in red pulp or as perivascular deposits or subcapsular deposits. GGBs can vary in size, ranging from 10 to 49 microns [21]. The GGDs is not pathognomonic of sickle cell disease as it can be found in many other diseases and in several other organs.

Conclusion

Splenomegaly in a case of sickle cell thalassemia is an established association, however to such extent that infarction with deposition of Gamna-Gandy bodies deposition is rare indeed. Loss of protective mechanism due to splenectomy also predispose the individual to manifest subclinical malarial infection. Our case highlighted patient's high endurance and acquired immunity against all the conditions mentioned by virtue of his birth with inherited mutations in an endemic area of malaria. Diagnosis in the era of molecular tests still count on Hb electrophoresis, sickling test and peripheral blood smear.

Conflict of Interests

Authors declare no conflict of interest.

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Author's Contributions

Thongam Sachin Singh – conceptualization, methodology, formal analysis, writing – original

draft, writing – reviewing and editing; Raj Singh – data curation, writing – reviewing and editing; Rahul Pandey – investigation, formal analysis.

СЕРПОВИДНО-КЛІТИННА ТАЛАСЕМІЯ З МАСИВНИМ ІНФАРКТОМ СЕЛЕЗІНКИ ТА ВУЗЛАМИ ГАМНА-ГАНДІ В ПАРЕНХІМІ СЕЛЕЗІНКИ З СУПУТНЬОЮ МАЛЯРІЙНОЮ ІНФЕКЦІЄЮ У ДОРΟΣЛОГО З ЦЕНТРАЛЬНОЇ ІНДІЇ (клінічний випадок)

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Вступ. Серповидноклітинна анемія – це спадкова гемоглобінопатія, яка характеризується гетерозиготним станом Hb S/β⁺ або Hb S/β⁰ і клінічно може не проявлятися у гетерозиготних носіїв

Мета. Метою дослідження є огляд літератури та обговорення різноманітних клінічних проявів і діагностики клінічного випадку гемоглобінопатії у пацієнта із Центральної Індії.

Методи. Описано випадок гемоглобінопатії у пацієнта із Центральної Індії.

Результати. Ми повідомляємо про випадок гемоглобінопатії у дорослого, який звернувся до лікарні третього рівня з хронічним болем у спині. Було виявлено масивну спленомегалію з ознаками інфаркту селезінки. При загальному дослідженні селезінки виявлені множинні м'які жовтуваті тістоподібні ділянки, які при мікроскопічному дослідженні показали виражений некроз з наявністю великої кількості блідо-аморфної жовтої субстанції, тілець Гамна-Ганді (GGBs) і виражену реакцію гігантських клітин на чужорідне тіло в паренхімі селезінки. Мазок периферичної крові після спленектомії показав тромбоцитоз і гаметоцити *Plasmodium falciparum*. Електрофорез гемоглобіну виявив підвищення Hb S (49,7%), Hb F – 46,7%; Hb A2 – 3,0% & Hb A – 0,7%, що відповідає серповидноклітинній таласемії Hb S/β⁺ таласемії.

Висновки. Серповидноклітинна таласемія з тривалою спленомегалією, інфарктом селезінки з тільцями Гамна-Ганді і супутньою малярією у клінічно стабільних пацієнтів є справді рідкісним явищем.

КЛЮЧОВІ СЛОВА: серповидно-клітинна анемія; бета-таласемія; малярія; малярійний плазмодій; Тілець Гамна-Ганді.

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