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CASE REPORT

An Interesting Case Of Compound Heterozygous Sickle Cell-B^+ Thalassaemia Presenting With Acute Chest Syndrome

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ABSTRACT

Sickle cell disease is a hereditary disorder which is caused due to a mutation in the ß-globin gene. Acute chest syndrome is a rare complication which is seen in sickle cell patients in India. Here, we are presenting an interesting case of compound heterozygous Sickle cell-ß+ thalassaemia who presented at the age of 20 years with acute chest syndrome and massive hepatomegaly. The patient also typically had veno-occlusive crisis. The diagnosis was based on the presence of numerous sickle cells in the peripheral smear and also on the presence of a strong HbS (68%) band on cellulose acetate electrophoresis supported by increased HbA2>3.5% and decreased cell indices. His mother was reported to have Sickle cell trait, who was asymptomatic with HbS(35.7%) and HbF (1.1%).

Key Words: Sickle cell anaemia, Sickle cell ß+ thalassaemia, Acute chest syndrome

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Introduction

Sickle cell disease is a hereditary haemoglobinopathy resulting from the inheritance of a mutant version of the β-globin gene on chromosome 11, which is characterized by the presence of sickle haemoglobin (HbS), resulting from the substitution of glutamic acid by valine at the 6^{th} position of the β-globin chain. The heterozygous carrier state, known as sickle cell trait (SCT), results in the production of both haemoglobin A and S and has a predominantly benign clinical picture [1].

Sickle gene is widespread in the Mediterranean region, Italy, Greece and the southern coast of Turkey which is of the Benin haplotype and is of African origin [2]. Nagel and Pagnier et al have described three independent mutations, namely Senegal, Benin, Bantu and later on, Cameroon in the African continent itself [3]. In the eastern province of Saudi Arabia and in central India, there is a separate independent occurence of the HbS gene which is of the Asian haplotype[2]. The average frequency of Sickle cell disorders in India is 4.3%. The highest prevalence has been recorded in the state of Orissa (1-44.4%) and the prevalence in Karnataka is around 1-8% [3]. The beta S gene linkage to a high HbF expressing haplotype and the high incidence of α thalassemia predict a mild phenotypical expression of sickle cell anaemia in India [4]. The complications of acute chest syndrome, leg ulcer, lung blockage and priapism are either absent or rare in Indian patients with sickle cell disorder [3]. The association of β+ thalassemia is also rare, which was reported as 1.7% by Balgir [5]. Hence, we are presenting this rare case of compound heterozygous sickle cell-β+ thalassemia with acute chest syndrome.

Case

A 20 year old man was brought to the hospital with fever of 8 days duration and altered sensorium since 2 days. He had difficulty in breathing and had yellowish discolouration of the eyes.

The patient was hospitalized 4 months back with complaints of low backache and left lower limb pain. He was diagnosed to have acute intervertebral disc prolapse (L4-L5) with

left radiculopathy. Past history revealed that the patient used to have similar health problems like fever, jaundice, and weakness, on and off, since the past 10 years, for which he received some iron injections and possibly blood transfusion. His father also used to have similar episodes of illness and repeated hospitalization and he expired at the age of 45 years due to paraplegia and stroke.

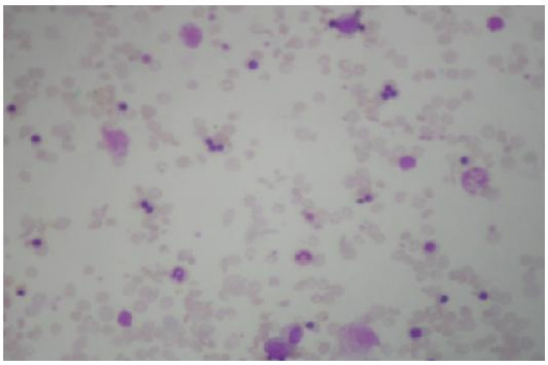
On examination, he was found to be breathless and was conscious but irritable. His lungs showed bilateral crepitations. There was massive hepatomegaly up to the umbilicus and splenomegaly. The cardia was normal.

The patient was put on intravenous fluids and mechanical ventilation. Antibiotics were administered empirically along with Deriphylline injection. He was put on ryle's tube feeding. He was maintained on an O2 saturation of 98% and FiO2 of 20%.

Chest X-ray revealed cardiomegaly with bilateral hilar congestion, with features of pulmonary hypertension, indicating that he had acute chest syndrome. Ultrasonography of the abdomen showed hepatomegaly with grade I fatty changes. The spleen was normal in size, with no focal lesions.

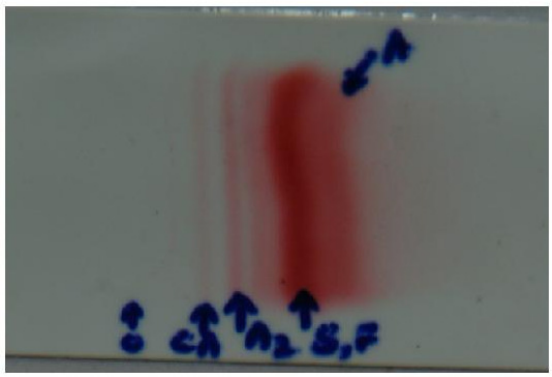
QBC (Quantitative buffy coat method) done on the 2nd day was negative for malarial parasites.

HBsAg (Hepacard) and HIV (1+2) Ab – Rapid test were negative. Laboratory investigations done on the day of admission showed Haemoglobin – 6.2 g/dl, RBS – 95 mg/dl, Blood urea – 85 mg/dl, Serum creatinine – 1.3 mg/dl, Total bilirubin – 5.2 mg/dl, Unconjugated bilirubin – 4.43 mg/dl, Conjugated bilirubin – 0.8 mg/dl, AST – 525 IU/L, ALT – 170 IU/L and ALP – 850 IU/L. Urine analysis showed traces of albumin to be present. Complete blood count showed RBC count – 2.77 million/cumm and a total WBC count of 40,000 cells/cmm, which was not in favour of leukaemia and the plateletcount was 80,000 cells /cumm. Peripheral smears showed severe anisopoikilocytosis with numerous target cells, schistocytes and also notably, the sickle shaped cells. The cells showed a severe degree of hypochromia. Numerous nucleated RBCs were seen (80/100 WBC's). WBCs showed a shift to the left in the neutrophilic series (90%). Occasional myeloblasts were seen. Then, it was reported as sickle cell anaemia with a leucoerythroblastic blood picture [Table/Fig 1].The blood indices were - MCV – 69.8fl, MCH – 21.3pg, MCHC – 31.1g% and ESR – 4 mm/1st hour.



(Table/Fig 1) Peripheral Smear Showing Sickle Cells

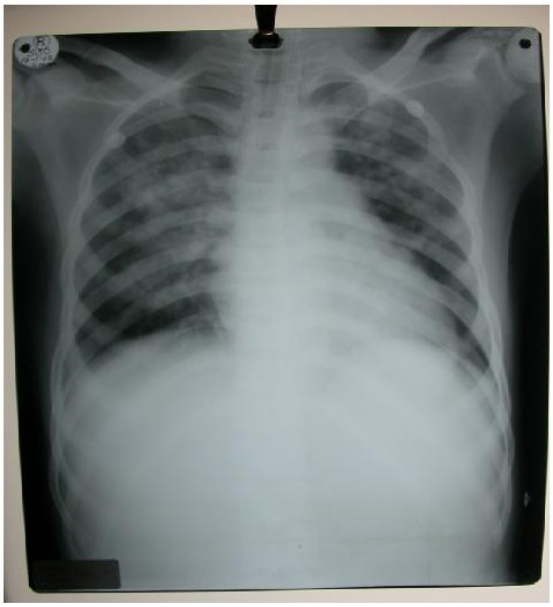
The solubility test for sickling [6] was positive. Haemoglobin electrophoresis on cellulose acetate strips [6] showed the presence of a strong HbS band in between the HbA_2 and the HbF/A bands. Quantitative analysis of HbF by modified Betke method [7] showed an increased HbF concentration of 16.2%. Further, the quantification of the HbS and HbA2 bands by the elution method [7] showed HbS - 68.2%, HbA_2 -3.9% and HbA – 11.7% [Table/Fig 2].



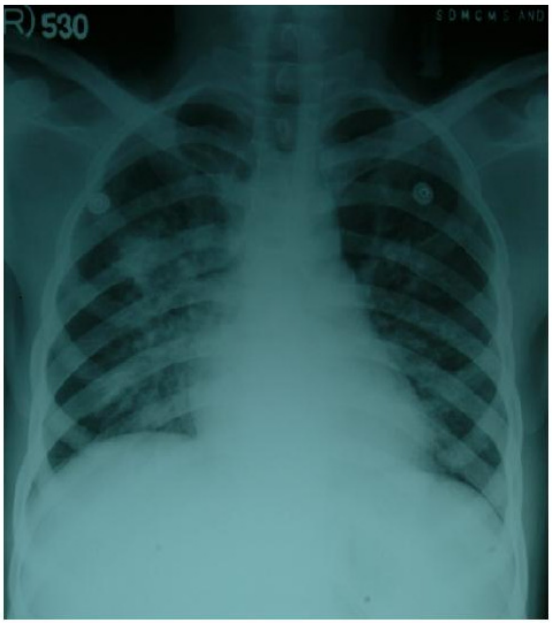
(Table/Fig 2) Hemoglobin Electrophoresis Of The Patient With HbS – 68.2%, HbF – 16.2%, HbA2 – 3.9%

On the 8th day of admission, his chest x-ray showed the evidence of dense air space consolidation on both sides [Table/Fig 3]. On the 12th day, there was evidence of ill defined

fluffy shadows which were seen in both lung fields, which were confluent in nature, on the right side, suggestive of Bronchopneumonia [Table/Fig 4].

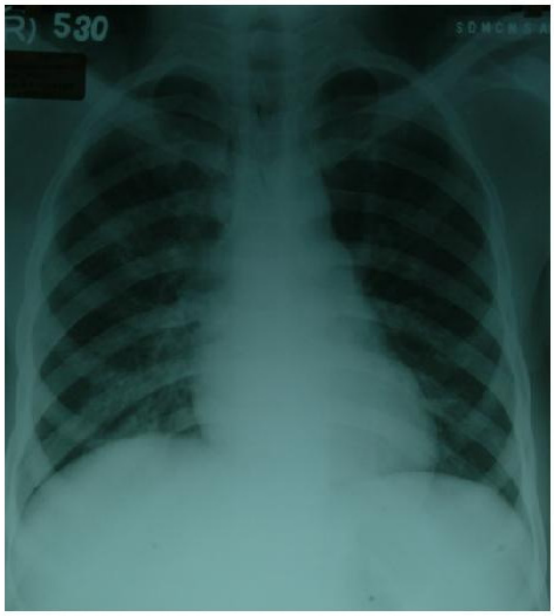


(Table/Fig 3) Chest X-Ray On The Day Of Admission Showing Pulmonary Edema With Cardiomegaly



(Table/Fig 4) Chest X-Ray Showing Ill Defined Fluffy Shadows In Both Lung Fields After 10 Days Of Admission

Then, after appropriate treatment, chest x-ray taken on the 20th day showed the resolution of earlier seen bilateral fluffy shadows, with minimal residue of the scarred lesions. The pleural spaces were clear and the heart size was within normal limits [Table/Fig 5].

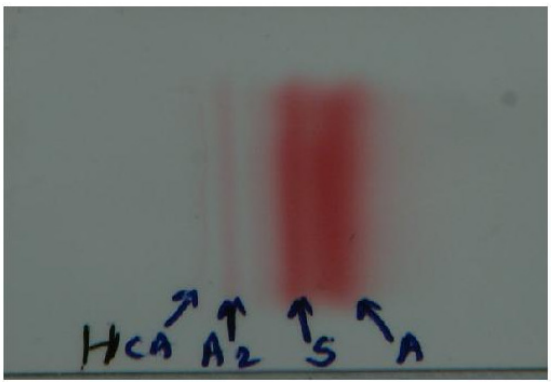


(Table/Fig 5) Chest X-Ray Showing Resolution Of Fluffy Shadows With Normal Cardia After Treatment.

The patient was transfused with 3 points of blood before discharge. After 16 days of discharge, the patient again developed fever and he had severe pain in the left small toe. He was diagnosed to have veno occlusive crisis. He was symptomatically treated and was discharged with an advice to continue to take Iron, Folic acid and vitamin supplements along with adequate hydration.

The clinical presentation and the laboratory reports strongly supported the diagnosis of the compound heterozygote of HbS-β^+ thalassemia, with acute chest syndrome and venoocclusive crisis.

With the suspicion of his family members to be carriers of the disease, all his family members were investigated for the presence of sickle cells and Haemoglobin S. Analysis of the blood samples of his 3 elder sisters revealed normal haemoglobin electrophoresis patterns and peripheral smear reports. His mother showed positive sickling test and the presence of HbS – 35.7%, HbF – 1.1%, HbA_2 – 2.9% and HbA- 60.3%. Her peripheral smears also showed the presence of sickle cells. Her haemoglobin was 12.9g%, RBC count – 4.46 million/cumm, MCV-89 fl, MCH- 28.9 pg and MCHC-32.5 g/dl. But she was asymptomatic. Based on these evidences, she was diagnosed to be having sickle cell trait [Table/Fig 6].



(Table/Fig 6) Hemoglobin Electrophoresis Of Mother Of The Patient With Hbs – 35.7%, Hbf – 1.1%, Hba2 – 2.9%

Discussion

Genetic heterogeneity of Sickle cell β thalassaemia is noticed in India. [Table/Fig 7]. The sickle cell patients in India usually do not show severe clinical manifestations unlike the African patients due to the interaction of α thalassaemia with sickle cell disease, high foetal haemoglobin levels and the maintenance of life at low haemoglobin levels. They can survive upto the 3rd to 4th decades of life [3].

(Table/Fig 7) Showing The Compound Heterozygous Sickle Cell/Beta Thalassemia Cases Reported In Literature With Different Presentations

Sl No	Author	No of Cases	Presentation	Reference
1	Aksoy M	6	1st observation of S/beta thalassemia	Blood 1963;22:757-69
2	Gilliam JC et al	1	Low back pain	Journal of the national Medical Association 1963;55(6):492-495
3	Rowley PT et al	1	Hypersplenic thrombocytopenia	The American Journal of Medical Sciences 1972;264(6)
4	Predescu C et al	6	9 Romanian Family study	Med Interne 1975;13(2):135-40
5	Hardikar JV et al	1	Absent spleen	J Postgrad Med 1983;29:251-52
6	Teckchandani SD et al	1	Mild recurrent jaundice	J Postgrad Med 1984;30(3):196-7
7	Jagtap SR et al	1	Total hip arthroplasty	Indian journal of Surgery, 1996;58(3-4):111-113
8	Yung GL	2	Pulmonary thromboendarterectomy	Am J Respir Crit Care Med 1998;157:1690-93
9	Hutchins KD et al	1	Splenic sequestration	J Forensic sciences, 2001;46(2):3
10	Adhikari RC et al	1	Hepatosplenomegaly	Journal of Nepal Medical Association 2003;42:36-38
11	Daar A	1	Colonic pseudo obstruction	The southern medical association 2003; 0038-4348/03/9601-0093
12	Connie Le	1	Acute chest syndrome	Southern Medical Journal 2004;Nov 1.
13	Dixit A et al	1	Orbital compression syndrome	Ann Hematol 2004;83:536-540
14	Kosecki SM et al	1	Bad glycemic monitoring	Ann pharmacother 2005;39(9):1557-60
15	Mussig K et al	1	Pheochromocytoma	Journal of Maternal-Fetal & neonatal Medicine 2005;18(2):145-46.
16	Costa BB et al	1	Intrahepatic cholestasis	J Natl Med Assoc 2006;98(7):1183-7
17	Johnson K et al	1	Fat embolism with asthma	Am J of Hematol 2006;46(4):354-57
19	Pinto LM et al	1	Systemic lupus erythematosis	Int J Rhematic diseases, 2008;11(1):73-76
20	Kar R et al	1	Splenic calcification & bone marrow infarction	Indian J Hematol Blood transfus 2008;24(1):31-34
21	Lynch A et al	2	Infection	The journal of Pediatrics 2009; 126(4):581-582.
22	Biedrzycki OJ et al	1	Acute chest syndrome with fatal overdosage of fentanyl patches	Am J Forensic Med Pathol 2009;30(2):188-90
23	Karunatilake H et al	1	Intrahepatic cholestasis	Ceylon Med J 2009; 54(3):95-96
24	Aisiku IP	1	Episodic pain in lower limb	Emerg Med 2009;41(2):8

Total cases of HbS/β+ thalassemia reported according to our literature search – 36

Cases presented with Acute chest syndrome - 3

The HbS level of >50%, with a positive sickling test and numerous sickle cells on the peripheral smears is suggestive of sickle cell disorder. Elevated HbA_2 >3.5% and HbF associated with decreased MCV, MCH and anisopoikilocytosis andthe presence of target cells in the peripheral smear strongly suggests the association of β^+ thalassaemia. Since HbA is 11.7%, which would have been completely absent if it were to be β^0 thalassemia, we may rule out the possibility of the coexistence of β^0 thalassemia All these findings suggested that the patient was suffering from the compound heterozygous form of sickle cell-β^+ thalassaemia [7]. The laboratory picture of the mother with HbS-35.7%, HbA-60.3% with normal HbA_2, HbF and cell indices goes in favour of the Sickle cell trait. The only possibility of the coexistence of β^+ thalassaemia in the patient could be from the father who might have had a similar disorder, who expired due to stroke in the 4th decade of life, with a history of repeated hospitalization in the past. The association of α thalassaemia may be ruled out clinically with HbA_2>3.5%, but it needs to be confirmed with genetic analysis. The A_2 values in α thalassaemia usually will be <2.5% [7].

The markedly increased but extremely variable production of haemoglobin F significantly affects the clinical effects of haemoglobin S. In contrast, the African haplotypes commonly express foetal haemoglobin concentrations of up to 15% and typical production by the Asian haplotype is even higher at 8–30%.HbF levels in our patient was 16.2%. Higher intracellular haemoglobin F concentrations ameliorate the pathological impact of haemoglobin S on the erythrocytes and are associated with a protective clinical effect [1]. The presence of HbF has an inhibitory effect on sickling, which can be attributed to the presence of glutamine residues at γ-87 of HbF. This leads to the decreased deformability of RBCs and sickling [8].

Clinically, Sickle cell disease (SCD) is characterized by chronic haemolytic anaemia,

recurrent episodes of intermittent vasoocclusion, severe painful crisis, splenomegaly, bone changes, pulmonary hypertension and chronic end organ damage [8].

Anaemia in SCD depicts an extremely complex pathophysiology. The decreased deformability of RBCs is thought to be the cause for the trapping of the rigid cells in vessels [8], leading to haemolysis and increased viscosity. Our patient also presented with severe anaemia, with haemoglobin of 6.2 g%. Recent evidence associates chronic intravascular haemolysis with a state of endothelial dysfunction that is characterized by reduced nitric oxide (NO) bioavailability. It is increasingly clear from the studies that plasma haemoglobin-mediated and oxygen free radical–mediated consumption of NO produces a state of resistance to NO in patients with sickle cell disease. Haemolysis could also release erythrocyte arginase, as suggested by recent reports that arginase activity may be increased and that the bioavailability of arginine and NO is reduced in patients with sickle cell disease[9][10].

Our patient presented with dyspnea which is a frequent complaint amongst patients with sickle cell disease, the aetiology of which is unclear and likely multifactorial. Although the chest radiograph may be normal initially, subsequent radiographs will reveal an infiltrate, which may extend rapidly, involving one or more lobes as well as the pleura [11]. Acute chest syndrome is not a common complication in India [3]. A major cause may be the altered circulation of the blood through the pulmonary circuit. At least, part of the problem may be an inability to de-sickle incoming venous blood; this would lead to an increase in viscosity, further decreasing the ability of the blood to circulate, leading to altered ventilation-perfusion [12].

In our patient, we found that initially he had features of pulmonary hypertension and cardiomegaly on chest x-ray, which gradually worsened to dense air space consolidation and development of fluffy shadows, which resolved slowly after treatment. Pulmonary hypertension is increasingly recognized as a complication of sickle cell anaemia. Retrospective studies have reported that up to 40% of patients have moderate to severe pulmonary hypertension [13]. If the anaemia is severe, children develop coexistent cardiomegaly as a result of high blood flow [11].

Vasoocclusive crisis was seen in our patient when he was admitted for the third time with fever and with severe pain in the left small toe. As adherence of sickle red cells to the vascular endothelium will impede blood flow and thereby increase capillary transit time, it has been suggested that increased cell adherence can initiate and propagate vasoocclusion. Various studies showed that both red cell membrane changes and plasma factors (increased synthesis of adhesive factors) mediate sickle cell adherence [10],[12].

From the age of a few months on, children with sickle disease have increasing splenic dysfunction as the organ is at first intermittently and then chronically occluded with sickled cells [11]. Mohanty J et al showed that splenomegaly was identified among 64% of the patients during sonological evaluation of the abdominal organs in SCD. Usually after 30 years, as age advances, the spleen undergoes progressive fibrosis and shrinkage [14].

Our patient had acute massive hepatomegaly with elevated bilirubin levels, elevated transaminases and alkaline phosphatase levels. Increased hepatic blood volume and blood flow may contribute to severe hepatomegaly. There was drastic improvement after exchange transfusion. In patients with SCD, chronic liver abnormalities are frequent and seem to be a multifactorial phenomenon, depending on overlapping factors such as cholelithiasis, viral damage, iron overload, acute/chronic hepatitis C and also the primary disease itself. It can also occur as a complication of chronic haemolysis, like the development of pigment stones with consequent cholecystitis or choledocholithiasis [15].

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