Case Report

Iron overload and Liver cirrhosis in Sickle cell disease

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ABSTRACT

Sickle cell disease is a common entity in our region and patients of sickle cell disease receive multiple blood transfusions since early part of their lives. These transfusions lead to the excess burden of iron and can lead to haemosiderosis / hemochromatosis and multiple organ dysfunction. We report a 38 year old male who developed liver cirrhosis due to iron overload as a result of multiple blood transfusions.

Key words : Sickle Cell Disease, Multiple Transfusions, Iron Overload, Cirrhosis of Liver

Introduction :

Sickle cell disease (SCD) encompasses a group of hemoglobinopathies characterized by a single amino acid substitution in the ß-globin chain. The liver can be affected by a number of complications due to the disease itself and its treatment. In addition to the vascular complications from the sickling process, patients with SCD have often received multiple transfusions, placing them at risk for viral hepatitis, iron overload, and (combined with the effects of chronic hemolysis) the development of pigment gallstones, all of which may contribute to the development of liver disease. The clinicopathological features of Liver disease are aggravated by liver iron overload that results from cumulative red cell transfusions. Nontransferrin bound iron induces reactive oxygen species, which not only directly causes cellular damage but also depletes nitric oxide levels leading to endothelial dysfunction. Iron overload ultimately results in Cirrhosis of Liver[1].

Our patient of SCD developed Cirrhosis of liver due to chronic iron overload from repeated blood transfusions. He improved after oral iron chelation therapy.

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Case Report :

A 38 year old male patient, XYZ, cable technician by occupation came with chief complaints of yellowish discolouration of eyes since 2 months, yellowish discolouration of body since 15 days, passing highcoloured urine since 15 days, and swelling overfeet since 4 days. He also had loss of appetite, severe weakness and nausea this time. Patient was diagnosed to have sickle cell disease (SCD) 'SS' pattern in childhood. He had episodes of mild jaundice off and on. He also had repeated hospitalizations for vasoocclusive crisis. Patient had received 30 blood transfusions in last 5 years. He was a non-alcoholic.

On examination patients vitals were stable. He had pallor, deep icterus, haemolyticfacies, edema feet and blackish pigmentation of skin especially over face and extremities and nails ***(Figure 1).*** On abdominal examination his liver was palpable; 3 cm, nodular, firm and tender. Spleen was not palpable. Free fluid was present in the abdomen.

His lab investigations on admission are shown in ***Table 1.***

Ultrasound examination of abdomen revealed liver parenchymal disease with ascites with bilateral pleural effusion and cholelithiasis. Chest radiograph also revealed bilateral pleural effusion. Ascitic fluid was transudate. Magnetic resonance imaging (MRI) of abdomen was done which showed nodular cirrhosis of Liver, dilated Gall bladder and a large calculus of 2.5 cm in the neck of gall bladder which was nonobstructing with mild ascites and bilateral pleural effusion ***(Figure 2).***

Patient was started on Injectable Methylcobalamin, Oral Folic acid, Oral Spironolactone, proton pump inhibitors (PPI), multivitamins and nutritionl support. He was also given 1 unit of blood transfusion as he had severe anaemia and weakness.

However his general condition did not improve and he had persistent icterus and malaise. Patient's iron profile was done in view of hyperpigmented skin and nodular liver cirrhosisand history of multiple blood transfusions . Results are shown in ***Table 2.***

Liver biopsy was not done due to severe hyperbilirubinaemia.

His Serum Ferritin levels were more than 2000 mg/dl. Considering the chronic iron overload due to multiple blood transfusions it was possible that Cirrhosis of liver was due to haemochromatosis.

Patient was then started on Tab Desferasirox and gradually his liver functions started to improve. His Serum Bilirubin decreased to 11 mg/dl. His pleural effusion and ascitis has disappeared. His general health also improved. Patient is under follow up in our Sickle cell clinic.

Discussion :

Sickle cell disease is a commonly encountered disease in our region. Patients of sickle cell disease have repeated admissions for vaso-occlusive crises and severe anaemia and receive multiple blood transfusions. These multiple blood transfusions along with the ongoing haemolysis leads to RBC breakdown and lead to release of excessive iron which gets deposited in the body.

In sickle cell disease transfusions improve blood flow by reducing the proportion of red cells capable of forming sickle hemoglobin polymer. This limits hemolysis and the endothelial damage that result from high proportions of sickle polymer-containing red cells. Additionally, transfusions are used to increase blood oxygen carrying capacity in sickle cell patients with severe chronic anemia or with severe anemic episodes. Transfusion is well-defined as prophylaxis (stroke) and as therapy (acute chest syndrome and stroke) for major complications of sickle cell disease and has been instituted, based on less conclusive data, for a range of additional complications, such as priapism, vaso-occlusive crises, leg ulcers, pulmonary hypertension, and during complicated pregnancies. The major and unavoidable complication of transfusions in sickle cell disease is iron overload[2].

Like patients of thalassemia major, patients with sickle cell disease receive repeated blood transfusions but screening for iron overload is not commonly done as compared to thalassemia major patients. This case indicates the importance of searching and treating for iron overload in SCD patients with history of repeated blood transfusions.

Transfusion of packed red blood cells (RBCs) provides 1 □ mg per mL transfused of additional elemental iron. Long-term transfusion therapy of, for instance, 20-units RBCs/year is associated with significant iron overload (20 units x 220 □ mL per unit, 1 □ mg per mL = 4400 □ mgm exogenous iron/year). With repeated transfusions, serum transferrin becomes saturated and the excess circulating iron is transported as NTBI (non transferrin bound iron). NTBI enters cells in a dysregulated fashion; a subset of NTBI, called Labile Plasma Iron (LPI), may cause end organ damage secondary to its high redox potential[3].

Both thalassemia and SCD patients suffer from of severe hemosiderosis due to multiple blood transfusions. SCD patients tend to have higher serum ferritin levels than thalaessemia patients. However, cardiac disease and endocrine dysfunction are significantly more frequent in thalassemia patients than in SCD patients[4].

Liver and biliary tract dysfunction are common complications of sickle cell anemia and its variants. Early reports described jaundice, hepatic infarcts, acute and chronic viral hepatitis, choledocholithiasis, and cirrhosis. The pathophysiology of hepatic dysfunction was attributed to the classic histologic features of Kupffer cell erythrophagocytosis and engorgement of sinusoids by aggregates of sickled cells. More recent reports have emphasized the importance of hepatic disease as a consequence of conditions not necessarily related to hemoglobinopathy.

Table1 : **Baseline investigations of the patient**

Investigation	Patient's value
Haemoglobin %	3.5 gm/dl
Complete blood count	25,800/cumm
Platelet count	1 lakh
RBC count	0.95 million
MCV	101 fl/red cell
Serum Creatinine	2.6 mg%
Blood Urea Nitrogen	62 mg%
Serum Bilirubin	33.2 mg/dl
Direct	11.2 mg/dl
Indirect	22 mg/dl
AST	110 IU/L
ALT	22 IU/L
Alkaline phosphatase	76 IU/L
Serum Proteins	7.9 gms/dl
Serum Albumin	2.5 gms/dl
INR (International Normalized ratio)	2.1
Ascitic Fluid Analysis	Transudate
Hbs Ag	Negative
Anti HCV	Negative
HIV I & II	Negative

Table No.2 : **Showing Iron studies**

Serum Iron	205.6 microgm/dl
Serum Ferritin	>2000 ng/ml
TIBC (Total Iron Binding Capacity)	225 microgram/dl
Transferrin	153.1 microgram/dl
Transferrin saturation %	91.4%

Because liver dysfunction in SCD is difficult to define, its prevalence too is difficult to document, with previous reports of; 10%. Using liver function tests to assess liver damage in SCD is confounded by abnormal liver enzymes reflecting not only intrinsic liver disease but also hemolysis. Abnormal liver enzymes should prompt a more comprehensive liver workup including laboratory and radiologic assessments, aimed at identifying true liver dysfunction and determining severity and etiology[5].

One of the rare but important cause for cirrhosis in sickle cell disease is Iron overload due to multiple transfusions as well as looking for causes of liver dysfunction unrelated to SCD, an assessment of iron

Figure 1 : **Showing Hyperpigmentation of hands, feet and nails**

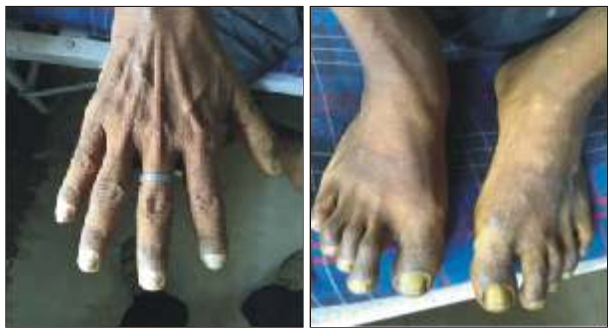
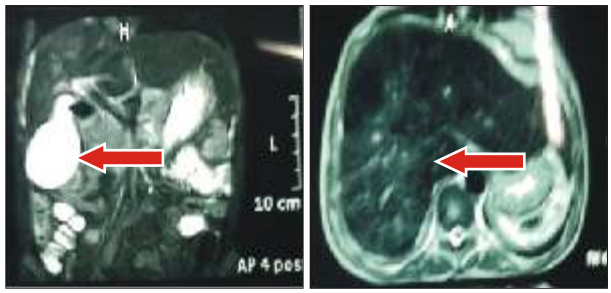


Figure 2 : **MRI Abdomen showing dilated gall bladder and cirrhotic liver**



overload must also be made, especially in view of the increasing use of blood transfusion in SCD. The risk of hepatic siderosis is further likely to escalate with the increasing life span in SCD patients and cumulative exposure to transfused red cells[6].

In a patient suspected to have iron overload, the recommended investigations are Serum ferritin levels, T2 weighted MRI and Liver Biopsy which is the gold standard. We could not do liver biopsy in our patient as he had severly compromised liver function. Serum ferritin may be relatively unreliable in SCD. The cut-off point for serum ferritin levels from which one can consider that tissue damage has already occurred is still to be determined: certainly, in cases where the values are > 1000 mg/dl, the damages to organs and tissues have already occurred and some authors defend that the utilization of chelating agents be started at levels < 500 mg/dl[7]. Our patient had Serum Ferretin levels of >2000mg/dl.

A noinvasive technique SQUID - The Superconducting Quantum Interference Device quantitatively determines Hepatic Iron

concentration (HIC) by magnetic measurement, which is a reliable predictorof HIC, but expensive and available in few institutions worldwide, mostlyfor research purposes.T2*MRI is a well-validated predictor of HIC and cardiac complications from iron overload[7].

Iron chelation for iron overload is recommended. Quantitatively, chelation is considered appropriate when liver iron concentration exceeds 7 mg Fe/g dry weight, roughly equivalent to transfusion of more than 20 units of red cells. It is also indicated if serum ferritin levels are high and patient has end organ damage. In SCD or thalassemia, phlebotomy is not done due to presence of anaemia. Deferoxamine is an oral chelating agent which chelates 10-20 mg iron/day.

This case emphasizes the importance of searching and treating for iron overload in sickle cell anaemia patients with history of repeated blood transfusions. Chronic iron overload can lead to end organ damage, as in our patient who developed Cirrhosis of Liver.

Conflicts of interest : None reported by author

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