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Original Research Paper

Pathology

COMPLICATIONS OF IRON OVERLOAD IN BETA THALASSEMIA- AN AUTOPSY CASE REPORT

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ABSTRACT Beta thalassemias are a common group of hereditary disorders that have a high incidence in south Asian countries like India. The following article presents an autopsy case report of a patient with beta thalassemia major discussing the various clinicopathological features, gross and histopathological findings. Common causes of death in patients with beta thalassemia major, various screening modalities for early detection of carriers, diagnosis and treatment have also been discussed, along with the review of literature.

KEYWORDS : Beta thalassemia, cardiac siderosis, infections, hemochromatosis.

Introduction:

Beta thalassemia major is highly prevalent in southeast Asia. Despite improvements in therapy, India continues to witness a high mortality in these patients. The common causes of death include cardiac failure, infections and liver diseases. Accumulation of iron in various parenchymal organs due to multiple transfusions leads to secondary hemochromatosis and organ damage. Here, we present an autopsy case report of a 19-year old female with beta thalassemia major discussing the various clinical features, gross and histopathological findings along with a review of literature.

Clinical history:

A 19-year old female, known case of beta thalassemia major diagnosed at the age of 5 months, came with presenting complaints of fever, ascites, bilateral pedal edema and abdominal pain since 15 days. On examination, her general condition was poor. Her pulse rate was 80/minute and blood pressure was 120/80 mm Hg. Air entry was reduced on the right side. Icterus was present over the skin and sclera. The patient was receiving regular blood transfusions since childhood.

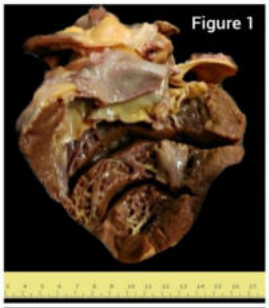
Investigations: Hemogram: Neutrophilic leucocytosis with hemoglobin: 8 g%, total leucocyte count: 15,300 cells/mm^3, platelet count: 1,13,000/mm^3. Total bilirubin: 19.1 mg/dl, direct bilirubin: 10.6 mg/dl, total protein: 6.6 g/dl, serum albumin: 2.9 g/dl, alanine transaminase(ALT): 53 units/L, aspartate aminotransferase(AST): 68 units/L, serum creatinine: 0.5 mg/dl.

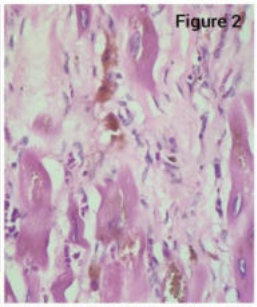
Ultrasound examination of abdomen and pelvis revealed moderate hepatomegaly, splenomegaly and ascites. A clinical impression of hepatitis in a known case of beta thalassemia major with fluid overload was given.

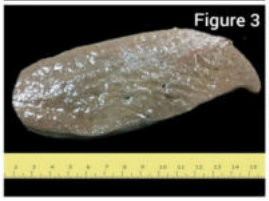
Her condition deteriorated rapidly within 26 hours of admission and despite all resuscitative measures, the patient could not be revived and was declared dead. A medicolegal autopsy was conducted.

Autopsy findings:

A complete autopsy was performed on this patient, with due permission. On external examination, icterus was present on the skin and sclera. Lower limbs showed presence of bilateral pedal edema. Internal examination revealed presence of approximately 300 milliliters of ascitic fluid. All organs were present in normal anatomical position. The heart weighed 300 grams and was dark brown in colour (figure 1). It was globular in shape with the apex formed by left ventricle. All the chambers were mildly dilated and both the ventricles showed moderate hypertrophy. Microscopy showed dense interstitial fibrosis, myofibre hypertrophy, atrophy and presence of intramyocardial golden-yellow hemosiderin pigment (figure 2). The spleen was markedly enlarged and weighed 800 grams with a dark brown to slate gray colour (figure 3). Microscopy showed a normal white pulp and a markedly dilated red pulp. The red pulp contained plenty of histiocytes with hemosiderin pigment (figure 4). The liver was markedly enlarged and weighed 3.5 kilograms. It was dark brown to bronze in colour (figure 5). Microscopy showed a partially disturbed hepatic architecture with formation of nodules surrounded by broad fibrous septae (figure 6) with marked bile ductular proliferation and moderate mononuclear infiltration. Hepatocytes showed ballooning degeneration. Hemosiderin pigment was present in the hepatocytes and Kupffer cells. There were foci of liver cell necrosis with proliferation of histiocytes containing golden yellow pigment. All these features were suggestive of secondary hemochromatosis of liver. Prussian blue stain for iron demonstrated blue granules of hemosiderin in the hepatocytes and Kupffer cells (figure 7). Gross examination of the lungs revealed presence of mildly thickened pleura at places and rubbery to firm consistency on cut surface. Microscopy showed features of brown induration of lungs with systemic hemosiderosis (figure 8). Gross examination of pancreas showed dark brown colour. Microscopy showed dense increase in interstitial fibrosis with presence of hemosiderin pigment in the pancreatic epithelial cells as well as ductal lining cells. Bone marrow examination revealed a hypercellular marrow with marked erythroid hyperplasia and presence of golden yellow hemosiderin pigment (figures 9 & 10). Microscopic examination of the kidneys, perihepatic lymph node, stomach, small intestine and large intestine also revealed deposition of golden yellow hemosiderin pigment. The final cause of death was given as congestive cardiac failure with massive iron overload.







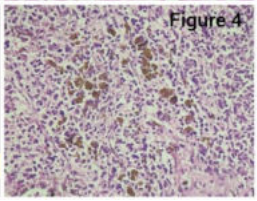


Figure 1: Gross image of the heart showing dilated left sided chambers, left ventricular hypertrophy and dark brown colour of the heart, suggestive of cardiac siderosis.
Figure 2: Microscopy of the heart showing interstitial fibrosis, myofibre hypertrophy and intramyocardial golden-yellow hemosiderin pigment (H & E, 400x).
Figure 3: Gross image of the spleen showing marked enlargement in size and dark brown to slate gray colour.
Figure 4: Microscopy of the spleen showing a markedly dilated red pulp containing plenty of histiocytes with golden-yellow hemosiderin pigment (H & E, 400x).

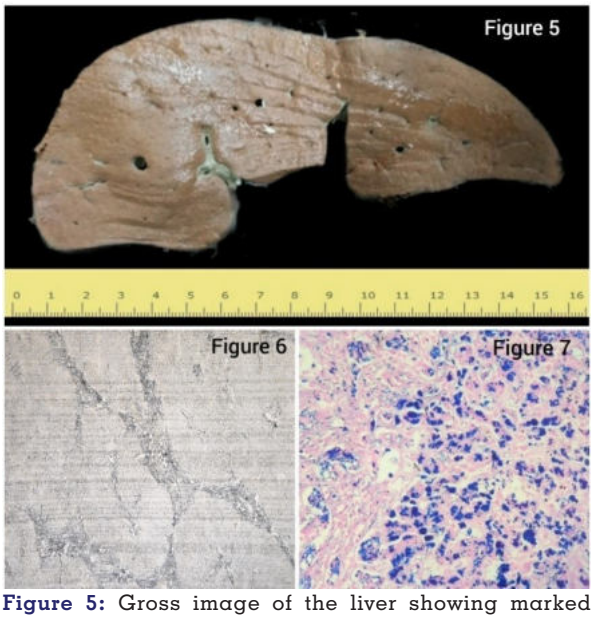


Figure 5: Gross image of the liver showing marked enlargement and a characteristic dark brown to bronze colour, suggestive of hemochromatosis.
Figure 6: Microscopy of the liver showing a partially disturbed hepatic architecture with formation of nodules surrounded by broad fibrous septae (Reticulin stain, 100x).
Figure 7: Prussian blue stain for iron demonstrating blue granules of hemosiderin in the hepatocytes and Kupffer cells (400x).

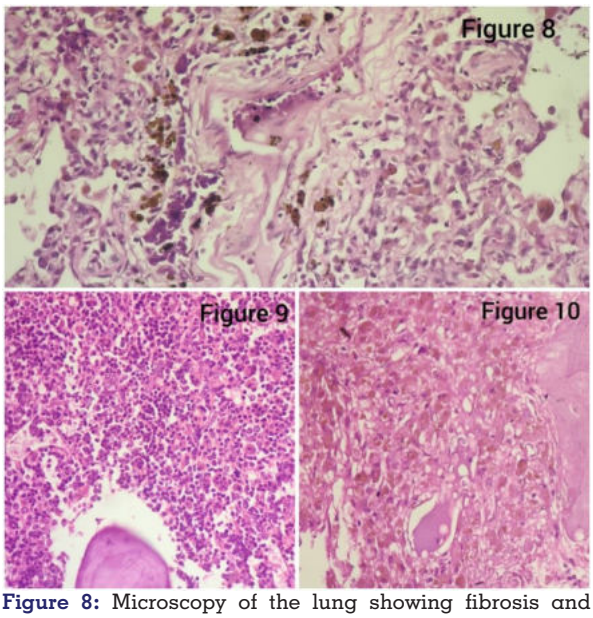


Figure 8: Microscopy of the lung showing fibrosis and presence of golden-yellow hemosiderin pigment in the alveolar lining epithelial cells and within the alveoli (H & E, 400x).
Figure 9: Microscopy of the bone marrow showing a hypercellular marrow with marked erythroid hyperplasia and secondary expansion of erythropoiesis (H & E, 400x).
Figure 10: Microscopy of the bone marrow showing presence of golden-yellow hemosiderin pigment (H & E, 400x).

Discussion:

Beta thalassemia major is a hereditary disorder caused by mutations that reduce the synthesis of beta-globin chains. It is prevalent in southeast Asia, Mediterranean countries and certain parts of Africa. The causative mutations can either be β^0 mutations, in which there is absent beta-globin synthesis or β^+ mutations, in which there is detectable but reduced beta-globin synthesis. A homozygous genotype (β^0/β^0, β^+/β^+, β^0/β^+) results in beta thalassemia major[1].

The major causes of death in patients with beta thalassemia major are congestive cardiac failure(most common cause), infections and liver diseases[2]. In past, the major cause of congestive cardiac failure was cardiomyopathy due to severe anemia. However, the improvements in management of these patients in the past few decades have led to iron overload and secondary hemochromatosis be the major cause of heart failure. A delay in cardiomyopathy due to iron overload can be done with the use of iron chelators. Some reports in literature suggest the use of combined iron chelation therapy to improve the cardiovascular function and reverse the process of congestive cardiac failure[3].

The second most common cause of death in these patients is infections. The main causes for an increased prevalence of infections are splenectomy, transfusion transmitted diseases, iron overload and iron chelation. More than 75% of documented bacterial infections in asplenic patients are caused by Streptococcus pneumoniae. Asplenic patients also have a more severe form of Babesia and Malaria with an increased risk of death. The exact mechanism of iron overload causing an increased susceptibility to infections is not well established. It is believed to be due to a variety of microorganisms being more pathogenic in the presence of excess iron. Also, the efficiency of phagocytosis is impaired in patients with iron overload as compared to normal individuals. Yersinia enterocolitica has the best described association between bacterial infection and iron/iron chelators. Iron chelators like deferoxamine can be used as a source of iron by pathogens, thereby making them more virulent[4].

Within a year of starting regular transfusions, iron deposition commences in parenchymal tissues[5]. Liver has a central role to play in the homeostasis of iron. Excessive iron deposition in the liver, pancreas, heart, joints, endocrine organs and others causes hemochromatosis. Secondary hemochromatosis is caused by iron accumulation due to parenteral iron administration, especially in the form of multiple transfusions, seen in patients with beta thalassemia major. In normal adults, the total storage pool of iron in the body is 2 to 6 grams, which may exceed 50 grams in hemochromatosis. One third of this iron is accumulated in the liver[1]. This excess iron causes direct injury to the hepatocytes leading to various pathological manifestations like cirrhosis, hepatitis B and C infections and even hepatocellular carcinoma.

In the case being discussed, the patient presented with fever and hemogram showed neutrophilic leucocytosis, suggestive of an infection. The patient also presented with bilateral pedal edema and ascites with autopsy findings suggestive of congestive cardiac failure and massive iron overload in all the major organs. In beta thalassemia major, insoluble precipitates of unpaired alpha chains cause membrane damage leading to apoptosis of red cell precursors, resulting in ineffective erythropoiesis[1]. This causes marked erythroid hyperplasia in the marrow and extramedullary hematopoiesis, leading to organomegaly, both of which were seen in the

present case. Erythroferrone secreted by erythroid precursors inhibits hepcidin production. Hepcidin plays a key role in negative regulation of iron uptake in the gut and reduces plasma levels of iron. Thus, iron overload in beta thalassemia major is because of multiple transfusions as well as an increased iron absorption in the gut.

Despite the improvements in management, India still witnesses a high rate of mortality in patients with beta thalassemia major. Significant factors include suboptimal transfusions of blood, infections transmitted via transfusions and iron chelation therapy[6]. An early start of comprehensive thalassemia care at various day-care centers may likely improve the long-term outcome. An early detection of cardiac siderosis and heart failure can be done by using magnetic resonance imaging (CMR T2*) [7]. There are nearly 42 million carriers of beta thalassemia trait in India, with Sindhis, Gujaratis, Lohanas, Bengalis, Gaurs, Kolis, Saraswats and Mahars being the commonly affected communities[8]. Screening tests like calculating the Mentzer's index using the complete hemogram report, NESTROFT(Naked Eye Single Tube Red Cell Osmotic Fragility Test) method and HbA2 estimation using HPLC(High Performance Liquid Chromatography) can help to identify carriers[9]. Early prenatal screening can be done with cells obtained from the fetus by using chorionic villus sampling or amniocentesis[8]. Bone marrow transplantation is currently the only well-established treatment of beta thalassemia major that provides a cure for the condition with excellent results in the long run[10].

Conclusion:

The common causes of death in patients with beta thalassemia major are congestive cardiac failure, infections and liver diseases such as hemochromatosis and its complications. It remains to be a common hereditary condition causing a significant morbidity and mortality in India. Awareness amongst the general population regarding the disease and various screening modalities for beta thalassemia trait can contribute in an increased rate of early detection of carriers and prevention of a full blown thalassemia major. At the same time, the availability of bone marrow transplantation in India, even in government set-ups, offering services across all strata of population is heartening and is a silver lining of cure for these patients.

References:

1) Kumar V, K Abbas A & C Aster J (2020). Robbins And Cotran Pathologic Basis Of Disease; 10th Ed: 644-850.
2) Kremastinos DT, Farmakis D, Aessopos A, Hahalis G, Hamodraka E, Tsiapras D, Keren A. Beta-thalassemia cardiomyopathy: history, present considerations, and future perspectives. Circ Heart Fail. 2010 May;3(3):451-8.
3) Karimi M, Emadmarvasti V, Hoseini J, Shoja L. Major causes of hospital admission in Beta thalassemia major patients in southern iran. Iran J Pediatr. 2011 Dec;21(4):509-13.
4) Cappellini MD, Cohen A, Eleftheriou A, et al. Guidelines for the Clinical Management of Thalassaemia [Internet]. 2nd Revised edition. Nicosia (CY): Thalassaemia International Federation; 2008. Chapter 9, Infections in Thalassaemia Major.
5) Mishra AK, Tiwari A. Iron overload in Beta thalassaemia major and intermedia patients. Maedica (Bucur). 2013;8(4):328-332.
6) Dhanya R, Sedai A, Ankita K, et al. Life expectancy and risk factors for early death in patients with severe thalassemia syndromes in South India. Blood Adv. 2020;4(7):1448-1457.
7) Kurtoğlu A, Karakuş V, Kurtoğlu E, Bozkurt S. NT-proBNP levels in □-thalassemia major patients without cardiac hemosiderosis. Turkish Journal of Biochemistry. 2017;42(1): 71-75.
8) Thiyagarajan A, Bhattacharya S, Sharma N, Srivastava A, Dhar DK. Need for a universal thalassemia screening programme in India? A public health perspective. J Family Med Prim Care 2019;8:1528-32.
9) Sharma G.K, Sharma D, Gulati R.K. Use of NESTROFT as a screening test for the carriers of thalassemia major. Int J Pediatr Res.2016;3(7):502-506.
10) Gaziev J, Sodani P, Polchi P, Andreani M, Lucarelli G. Bone marrow transplantation in adults with thalassemia: Treatment and long-term follow-up. Ann N Y Acad Sci. 2005;1054:196-205.