HAEMOCHROMATOSIS AND SIDEROBLASTOSIS COMPLICATING TUBERCULOSIS

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SYNOPSIS

A 55 year-old patient with the typical clinical features of haemochromatosis together with sideroblastosis and associated with tuberculosis is described. High serum ferritin values of between 1450 ng/ml to 2600 ng/ml were obtained in 3 consecutive samples investigated, whereas serum iron values, iron-binding capacity and percentage saturation were not helpful in establishing the diagnosis. Multiple factors acting together may have contributed to the iron overload syndrome and sideroblastosis.

INTRODUCTION

Iron overload can result from excessive absorption of either dietary or medicinal iron or it can occur from an excessive administration of parenteral iron preparations or from repeated blood transfusions.

A distinction between the conditions in which either reticulo-endothelial or parenchymal iron deposits predominate is important, since the accumulation of iron in reticuloendothelial cells is relatively innocuous, whereas parenchymal iron overload of sufficient magnitude and duration is considered to be responsible for the clinical manifestations of haemochromatosis (Cook et al, 1973) which is characterized by dysfunction of many organs in the body.

The most important mechanism in the production of parenchymal overload is the absorption of dietary iron in excess of erythropoetic requirements. Iron absorption in classical idiopathic haemochromatosis an inborn error of iron metabolism is higher than in normal subjects in relation to iron stores (Walters et al, 1975). Cirrhosis of the liver itself may contribute to iron overload (Hershko, 1977).

Reticulo-endothelial iron overload may result after repeated blood transfusions and injections of iron preparations. It may be associated with inflammatory processes or any form of tissue injury in which there is impaired release of iron from reticulo-endothelial cells (Hershko, 1977).

In the clinical setting, iron overload is never limited entirely to reticulo-endothelial cells. Some excess iron is recycled into the plasma and deposited in parenchymal cells (Cartwright & Lee, 1971).

In contrast to the above where there is little or no anaemia, iron overload may occur in conditions associated with severe anaemia, such as haemolytic and sideroblastic anaemias. The inappropriately high iron absorption in these conditions is explained by the known stimulating effect of erythroid hyperplasia and increased plasma iron turnover on the absorption of iron (Cavill et al, 1975).

We describe here a patient who primarily suffered from tuberculosis but who developed an iron loading anaemia with haemochromatosis and sideroblastosis probably as a complication of the disease, drug therapy, parenteral iron and transfusions.

CLINICAL HISTORY

A 55 year-old male Chinese was admitted to the National Tuberculosis Centre on 20.1.75 as a case of pulmonary tuberculosis with failed primary treatment. He was noticed to be pale and examination of the respiratory system showed a decrease of breath sounds bilaterally. His Haemoglobin (Hb) was 7.6 g/dl. The bone marrow was normocellular; erythropoesis was mainly megaloblastic with a Myeloid: Erythroid ratio of 2 : 1. Myeloid maturation sequence and platelet production were normal. Large amounts of stainable iron were present. Liver Function Tests (LFT), random blood sugar (RBS), fasting blood sugar (FBS), anti-human globulin test (AHGT), glucose 6-phosphate dehydrogenase (G6PD) and electrophoresis and estimation of HbF were normal. He was treated with Kanamycin, Pyrazinamide and Ethionamide and was given 430 ml of blood. His sputum became negative after two months.

He defaulted treatment in Oct. 1975. In November 1976 he was found to be infective again and treatment was changed to Refadin 600mg and Ethambutol 1,000mg. The FBP on 11.12.1976 showed a decrease in Hb concentration to 6.5 g/dl. His red cells were macrocytic; platelets and white cells were mildly reduced while neutrophils had hypersegmented nuclei.

The bone marrow biopsy on 13.1.1977 showed a mild megaloblastic erythropoesis. His liver function tests were normal and a liver scan showed an enlarged liver with left lobe hypertrophy and patchy pick-up activity, suggestive of cirrhosis. He was given 5 ml of imferon daily for 5 days. His sputum became negative for acid fast bacilli after 4 months of treatment, but he remained anaemic.

On 1.8.1978 the Hb had fallen to 5mg/dl. He had a slightly raised SGOT and SGPT of 67 and 52 RF units respectively and a serum bilirubin of 2 mg/dl. Liver biopsy showed features of haemachromatosis with early cirrhosis. The Glucose Tolerence Test (GTT) showed a diabetic curve. Alfa-feto proteins were not detected. He was transfused with 4 units of blood. At this time, he was noticed to have skin pigmentation typical of haemochromatosis.

A bone marrow biopsy done 11.10.1978 showed a mild erythroid hyperplasia with large amounts of iron stores. Many ring sideroblasts were also seen. The Hb at this time had come up to 12.6g/dl and remained steady between 10g and 11g/dl. The patient was venesected 6 times; 200 ml of blood was removed on 11.10.1978 and 24.10.1978 and 500 ml on 27.10.1978, 6.11.1978, 14.11.1978 and 8.12.1978.

RESULTS

Laboratory tests were carried on serum samples obtained from the patient on 6.11.1978, 14.11.1978 and 8.12.1978. Serum iron, TIBC and ferritin concentrations of the 3 serum samples were shown in Table 1. In all 3 samples, the serum iron and TIBC were normal but the ferritin concentrations were extremely high. Except for raised level in serum bilirubin, all LFT on the 3 samples were almost normal (Table 1). The lipid profile of the samples were also normal except for a marginally raised level of triglyceride in sample 3 (Table 1).

The results of hepatitis B antigen markers are shown in Table 1. The 3 samples were all positive for antibody to hepatitis B core antigen (anti-HB_C) and anti-body to hepatitis B surface antigen (anti-HB_S).

DISCUSSION

The patient described manifested the typical clinical features of haemochromatosis with cirrhosis of liver, diabetes and skin pigmentation. In typical uncomplicated cases of haemochromatosis, the serum iron is raised and the percentage saturation of transferrin is above the normal range. In this patient the serum iron and transferrin saturation were within normal limits in the first two serum samples but was raised in the third serum sample. Furthermore the total transferrin level was typically reduced in the third sample.

Haemochromatosis in this patient may have a multifactorial basis. It is possible that he had basically an inborn error of metabolism associated with excessive absorption of iron. However, it is also possible that iron overload was caused initially by the chronic tuberculosis infection, as inflammatory processes are associated with defective release of iron from reticulo-endothelial cells (Hershko, 1977). Increased absorption of iron associated with anaemia may also have occurred. Sideroblastic anaemia, characterized by deposition of haemosiderin in mitochondria of nucleated red cells, has been described in association with anti-tuberculosis therapy (Vermilghen et al, 1965) which this patient received over a period of several months. The iron overload was further enhanced by parenteral iron therapy and blood transfusion in attempts to improve the anaemic state. Although these procedures usually produce haemosiderosis — i.e. iron deposition in reticulo-endothelial cells predominantly, a relatively innocuous condition, excess iron deposits can spill into plasma and be carried into parenchymal cells and lead to haemochromatosis. It is possible that hepatitis B infection evident from positive tests for antibody to hepatitis B core antigen (anti-HB_C) and anti-HB_S Ag may have further contributed to increased iron deposition. This patient also had megaloblastic anaemia. It is known that nutritional deficiency and megaloblastic anaemia are often associated with cirrhosis and may be responsible for increased iron deposition (Graville & Dameshek, 1958; Mac Donald et al, 1965).

The lipoprotein profile of the patient was normal thereby indicating that there was no metabolic abnormality of lipoprotein synthesis nor an impairment of synthesis of lipoprotein by the liver cells.

This patient had serum ferritin values of between 1450 ng/ml to 2600 ng/ml representing a marked increase of total iron content in the body of between 11.6 — 20.8 g (Walters et al, 1973) compaired to mean normal values of between 0.4 — 0.9 g. The near normal liver function tests in Table I indicates that hepatic functions were only minimally impaired though early cirrhotic changes were found in the liver biopsy. Biochemical evidence of hepatic dysfunction is usually only seen in the late stages after

several years, though clinical signs such as palmar erythema and spider naevi may manifest earlier which this patient did not show. As the patient was lost to follow up, further studies could not be carried out. The complications arising in this patient illustrate the need for careful and regular haematological profiles in the management of certain patients on anti-tuberculosis therapy. The determination of serum ferritin is of much greater value in establishing the diagnosis of iron overload than serum iron and iron binding capacity.

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TABLE I: BIOCHEMICAL PROFILES ON CASE OF HAEMOCHROMATOSIS

	Normal Range	Dates		
		6.11.1978	14.11.1978	8.12.1978
Serum Iron	60 — 160 ng/dl	127	105	160
T I B C	240 — 400 ng/dl	262	250	210
% Saturation	25 — 56	48	42	76
Ferritin	10 — 300 ng/ml	2,600	1,450	2,300
Liver Function Tests				
Serum Proteins	5.5 — 8.2 g/dl	5.3	5.9	6.1
Albumin	2.7 — 4.6 g/dl	3.0	3.5	3.5
Globulin	2.8 — 3.6 g/dl	2.3	2.4	2.6
A/G Ratio	0.9 — 1.8	1.3	1.3	1.3
Alkaline Phosphatase	3 — 13 K.A. Units/dl	3	4	4
Bilirubin	less than 1 mg/dl	1.6	2.3	2.3
SGOT	4 — 40 RF Unit/dl	14.8	15.4	12.1
SGPT	3 — 35 RF Unit/dl	17.5	5.6	8.7
Non-fasting Lipid Profile				
Total cholesterol	166 — 298 mg/dl*	185	155	180
Triglycerides	48 — 192 mg/dl*	190	140	200
β-lipoproteins	261 — 797 mg*	380	260	430
Hepatitis B Markers				
Anti — HB_C		+	+	+
HB_S		-	-	-
Anti — HB_S		++	++	+
DNA polymerase		-	-	-

*Levels for an urban Chinese males aged between 50 — 59 years (Chong & Khoo, 1975).