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TRANSFUSION HAEMOSIDEROSIS INSPITE OF REGULAR USE OF DESFERRIOXAMINE: CASE REPORT

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SUMMARY

We describe a case of a female who developed haemosiderosis, in the course of treatment for very severe unstable aplastic anaemia for fourteen years. She was 37 years old at the time of initial diagnosis. Her management consisted of regular blood transfusions aimed at haemoglobin above 8.5 g/dl, antimicrobials, oxymetholone, low dose prednisone and folate. She had received about seventy five units of blood at the start of 2 grams of desferrioxamine with every subsequent blood transfusion. Annual tests of serum ferritin showed progressive increase. She developed skin changes, diabetes mellitus, heart disease, recurrent infections, generalized joint and abdominal pains and liver failure. She died within six weeks of developing congestive heart failure coupled with liver failure due to haemosiderosis despite regular use of desferrioxamine.

INTRODUCTION

Blood transfusion is necessary to prevent death from severe anaemia in persons with chronic anaemia. However, recurrent transfusions are associated with many complications of which a serious one is transfusion haemosiderosis (1). Transfusion induced haemosiderosis is the consequence of parenteral administration of excessive amounts of iron in the red blood cells. There is no physiologic way to induce significant excretion of iron by the body. Only very small amounts, 1 mg or less per day usually is lost. Further, the haemoglobin iron administered in this way bypasses the regulatory process of the intestine and usually is sequestrated in macrophages in the marrow, spleen and later in the parenchymal cells of liver, pancreas and other organs (2,3). What makes matters worse is the fact that chronic anaemia modifies the regulation of absorption of iron with the result that greater than the normal amount of iron is absorbed from the alimentary canal.

One milliliter of red blood cells contains one milligram of iron therefore one unit of packed cells with approximately 220 ml delivers 220 mg of iron. Total body iron is about 3,500mg thus only 15 units transfusions more than double body iron.

Daily urinary excretion of not less than 115 mg of iron in this situation would be necessary to offset the amount of iron received and attain a negative iron balance(4). Currently the major drug used to increase the secretion of iron is desferrioxamine (DFO), which also has limitations. The resulting accumulation of iron leads to haemosiderosis and its clinical manifestations. The common ones include the triad of skin dyspigmentation, diabetes mellitus and hepatomegaly(5,6).

We describe a case of transfusion haemosiderosis resulting from supportive transfusion for very severe aplastic anaemia. This case is intended to highlight the emergence of transfusion induced haemosiderosis despite the use of desferrioxamine.

CASE REPORT

For fourteen years, a female who had severe, unstable aplastic anaemia was under our care for bone marrow failure. She was 37 years at the time of diagnosis, when she presented with easy bruisability, palpations, dizziness, oral sores and headaches. Physical examination revealed marked pallor of mucous membrane and petechial haemorrhages in the lips and anterior aspects of the arms. Her blood count picture showed pancytopenia. Repeated bone marrows were either dry or bloody taps. A trephine bone marrow showed a cellularity of 17% with normal cellular morphology and no increase in reticulin fibres. Other results showed reticulocytes 0.2%, neutrophils 0.3 x 10^{9}/L and platelets of less than $20x10^{9}$/L. Haemosideriurea, Coombs' and Ham's Dacie tests were negative. She was started on a transfusion regimen to maintain her haemoglobin (Hb) at between 8.5 and 10.5 g/dl. Oxymetholone and prednisone were also given intermittently. She was frequently admitted to the hospital for severe anaemia, infections, bleeding or a combination of all these. Six years later, serum ferritin was noted to be

8,420 ng/ml against upper level of 125 ng/ml. She had however been started on desferrioxamine 2gms following each transfusion. It was estimated that she had received cumulatively 75 units of blood at the time desferrioxamine was initiated. She had remission for periods of nine and eight months, in 1994 and 1996 respectively when she was transfusion independent. In 1997 she was noted to have diabetes mellitus, which was controlled on insulin having failed oral antihypoglycaemics. At which time also she had normal liver functions (LFTs), kidney functions but heart functions revealed myocardial dysfunction. Her skin had obvious dyspigmentation on the face and extremities particularly the arms, legs and feet.

Three years later she presented with severe abdominal pains and pancytopenia. The liver was noted to be enlarged, firm, slightly tender and felt nodular. Liver functions were deranged. At this time, repeated transfusions would not bring the haemoglobin to 10.5 g/dl. She developed jaundice, oedema and ascites all within three weeks. The spleen became palpable. She also had generalized pains in the abdomen, most joints in the body and severe stomach pains following eating. She lost 10 kg of weight within the six weeks and was progressively getting very weak. She developed obvious features of hepatic and heart failure and the diabetes mellitus was out of control on her usual doses of insulin. Serum, ferritin levels, was 12,000 mg/ml. She died due to heart and hepatic failure.

DISCUSSION

Our patient illustrated all the common manifestations of haemosiderosis namely the triad of skin pigmentation, diabetes mellitus, and hepatomegaly. In addition, she had other features such as joint and abdominal pains, splenomegaly, and heart failure.

It was noteworthy that the sequence of these events was in this stated order. Since most series have shown that diabetes mellitus and heart failure tend to precede other clinical features(7).

Other studies have shown that hepatomegaly is found in 90% of patients on clinical examination, and abnormalities of liver function tests have often been minimal or lacking. This particular case appears to fall in this group. In an occasional case, full-blown liver failure with ascites and partial hyperplenism has been seen. Hepatic insufficiency results from iron deposition in the liver giving a firm palpation feeling. Splenomegaly is reported in 50% while this case had a significant splenomegaly that was also firm on palpation(7).

As in our case, severe abdominal pains of sudden onset, often in association with shock are a serious complication. This complaint is of obscure aetiology but has been the apparent cause of death in several cases(8).

The initial cardiac dysfunction was quite non specific in this case. The classical chronic congestive heart failure and arrhythmias were definite only in the last six weeks. However, exertional dyspnoea at Hb above 10.5g/dl, which were the initial signs of dysfunction was noted four years before her death. Previous observations show that arrhythmias and congestive heart failure are seen in approximately 35% of cases and that these develop rapidly and unexpectedly particularly in stable patients(7,9).

Our case developed these features in the last four weeks. Generalized body weakness, weight loss and other symptoms attributable only partially to diabetes mellitus. Abdominal pains were generalized, marked over the liver and spleen. These were perhaps due to the congestion in these organs. Lack of feeding due to generalized pains and abdominal discomfort could be explained in liver disease.

Bronze pigmentation of the skin has been evident in 90% of patients at presentation. The pigmentation is most obvious in areas normally exposed to the sun and on the external genitalia. It also may be seen in scars. Purpura, spider angiomatous and loss of body hair also are common cutaneous abnormalities. This case manifested these as the first signs of sclerosis and these intensified as the level of ferritin increased.

A distinctive arthropathy has been recognized in association with haemosiderosis(10). This resembles rheumatoid arthritis in most respects and most commonly involves the metacarpophalangeal and pronounced in the interphalangeal joints particularly those of the second and third fingers. So that this case's arthropathy manifestations were consistent with the observed characteristic diabetes mellitus result from iron deposits in the pancreas. This case had this as a second complication following skin manifestations and is commonly referred to as bronze diabetes characterized by response to increasing doses of insulin and not oral hypoglycaemic agents.

Existing chelation protocols are highly imperfect, expensive and inconvenient. Desferrioxamine mesylate (Desferol DFO) despite its shortcomings, remains the treatment of choice(11). For satisfactory treatment of iron in the body, daily urinary excretion of not less than 115 mg of iron is necessary to offset the amount of iron received by way of transfusion and attain a negative iron balance. This would be equivalent to DFO given 0.5g/daily for several years(4).

Other studies have shown that an injection of 1.0 g/day DFO should decrease cardiac and hepatic size and improved cardiac function in a small group of patients treated for 2-10 years(11). Lifelong daily intramuscular injections are clearly impractical as a method for dispensing the drugs.

As was well demonstrated when DFO was available to this case, an important advance showed that iron excretion induced by DFO is markedly enhanced by slow intravenous or subcutaneous injection of the drug (12,13). However, slow infusion of DFO can achieve negative iron balance in many transfusion dependent

patients over 4-5 years of age(14,15). This involves daily 10-12 hours subcutaneous injection of about 28 of DFO using a small battery driven pump. Due to technicalities, and a huge economic burden, only post transfusion desferrioxamine was possible in this patient. Measurement of serum ferritin levels is a convenient way to assess efficacy of treatment. In compliant patients a clear drop in ferritin should occur after one year of treatment with continued decline to a level of less than 1,000 mg/ml in 3-5 years(15).

Clearly, these are difficult regimens to achieve in most of our settings. Due to economic, social and practical details, this patient could not receive more than 2 gm of DFO at intervals of less than six weeks. These may have contributed to the build up of iron and subsequently hastened the complications. Transfusion haemosiderosis is the major cause of morbidity and mortality particularly in thalassaemia majors that require regular blood transfusions (2). The same scenario existed in this case requiring the use of blood to maintain her haemoglobin.

Perhaps better and more practical ways of reducing iron overload due to transfusion would improve the quality of life of the chronically transfused. The search should be intensified towards this goal.

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