Sideroblastic anaemia secondary to chronic alcoholism: a case study and review

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Abstract
Recent literature on secondary acquired sideroblastic anaemia reports on the high prevalence of this type of anaemia in alcoholics. Studies have also shown that the sideroblastic abnormality is only seen in those alcoholics with an associated folate deficiency. Furthermore, folate deficiency in alcoholics is not only from the poor nutrition associated with a ‘liquid diet’, but also from the effect of ethanol on folate absorption, catabolism and excretion. This case study is used to review recent literature on the haematological aspects of chronic ethanol consumption and associated sideroblastic anaemia.

Key words: sideroblastic anaemia, alcohol, folate

Case history
Patient B, a 54-year-old female, presented to the emergency department in June 2006 with a moist cough and coinciding chest pain, and possible jaundice. Emergency staff noted a ‘stale alcohol smell’ on admission. Examination showed a weight of 49 kg and an enlarged liver. The patient stated that she had lost approximately 25 kg over the last two years. She was admitted to the ward and intravenous antibiotics for the treatment of pneumonia were begun. On admission, the patient had a macrocytic anaemia (MCV 108 fL and Hb 106 g/L), with target cells and toxic changes seen in the blood film. She had abnormal liver functions (using Prussian blue staining), and showing florid sideroblastic change. At the time of this bone marrow aspiration, Patient B had ferritin of 2049 g/L, with target cells and toxic changes seen in the blood film. Her folate level was 3.6 mmol/L, and she had an absolute reticulocyte count of 9x10^6/L. Siderocytes had been noted on prior blood film examinations but it was not until this time that alcoholism was suggested as a cause, and that sideroblastic anaemia could be present in this patient. In review of these results, a bone marrow aspirate was recommended. This showed mixed marrow cellularity, with iron stores 4+ (using Prussian blue staining), and showing florid sideroblastic change. At the time of this bone marrow aspiration, Patient B had ferritin of 2049 g/L and her iron saturation was 73%. Both of these extremely high results were due to her sideroblastic abnormality. A diagnosis of alcoholic liver disease with secondary acquired sideroblastic anaemia was therefore established for this patient.

The patient presented again December 2006 with symptomatic anaemia, and investigation showed that she consumed 10-15 nips of whiskey a day. Clinical investigations ruled out blood loss as a cause of her anaemia. Her folate level was 3.6 mmol/L, and she had an absolute reticulocyte count of 9x10^6/L. Siderocytes had been noted on prior blood film examinations but it was not until this time that alcoholism was suggested as a cause, and that sideroblastic anaemia could be present in this patient. In review of these results, a bone marrow aspirate was recommended. This showed mixed marrow cellularity, with iron stores 4+ (using Prussian blue staining), and showing florid sideroblastic change. At the time of this bone marrow aspiration, Patient B had ferritin of 2049 g/L and her iron saturation was 73%. Both of these extremely high results were due to her sideroblastic abnormality. A diagnosis of alcoholic liver disease with secondary acquired sideroblastic anaemia was therefore established for this patient.

Patient B finally presented in March 2007 with a H of 70 g/L. She had dramatically reduced her alcohol intake and had been on folate and vitamin B6 therapy. Her MCV had returned to within normal range (96 fL), and no siderocytes were seen in her blood film.

Sideroblastic anaemia
The sideroblastic anaemias are a heterogeneous group of disorders with the unique characteristic of amorphous iron deposits in erythroblast mitochondria (1). These iron deposits are the result of ineffective insertion of iron into the developing haem molecule. To understand the causes of sideroblastic anaemia, the pathway of haem synthesis is described in Figure 1.

Figure 1. Simplified diagram of haem synthesis, occurring both within and outside the mitochondrion. Note that the cofactor for ALA-synthase is pyridoxal phosphate. ALA: 5-aminolevulinate. Modified from Bridges, and Wiley & Moore (2,3).

There are three forms of sideroblastic anaemia: hereditary, primary acquired, and secondary acquired. The hereditary form is caused by a mutation on the X-chromosome, resulting in a defect in ALA-synthase (Figure 1). Primary acquired sideroblastic anaemia, which involves abnormal haematopoesis, is idopathic, as it is not clear what the cause of defective haem synthesis is in the abnormal erythroid clone (3) This type of sideroblastic anaemia is the one most commonly seen in the haematology laboratory, as it is part of the myelodysplastic syndromes – a series of clonal haematopoietic stem cell diseases. The myelodysplastic syndromes are characterised by refractory anaemia and ringed sideroblasts, which can transform into a state with excess blasts and then on to acute leukaemia.

The causes of secondary acquired sideroblastic anaemia, and the mechanisms behind them, have been extensively researched. One of the most common causes of secondary acquired sideroblastic anaemia is chronic ethanol consumption, with a ringed sideroblast abnormality occurring in 25-30% of anaemic alcoholic patients (1,4,5). Consumption of over 80 g ethanol a day will lead directly to sideroblastic anaemias (1). A single 45 mL nip of whiskey contains 12 g ethanol, so to consume >80 g/day, the patient must be drinking over 6 nips a day (6).

Alcohol has two effects on haematopoiisis. Firstly, it is directly toxic to developing cells, causing an increased or high-normal MCV and vacuolation of erythroid precursors. Secondly, alcohol consumption causes lowering of the plasma concentration of pyridoxal phosphate. As shown in the pathway of haem synthesis (Figure 1), pyridoxal phosphate is a cofactor for ALAS. The product of alcohol breakdown in the liver, acetaldehyde, accelerates hepatic degradation of pyridoxal phosphate, meaning there is less cofactor for ALAS and thus the pathway of haem synthesis is disrupted (3). As a result, iron is not inserted into the
developing haem molecule, but builds up in the mitochondria. Because erythrocyte production is depressed, more iron is absorbed from the gastrointestinal tract in an attempt to increase this. Thus, the patient moves into a state of iron overload. If alcohol consumption is ceased, the sideroblastic abnormalities in these patients will resolve within 14 days (1,3,4).

Folate deficiency

Alcoholics often suffer from both primary and secondary malnutrition. Primary malnutrition is where alcohol replaces nutritious meals (a ‘liquid diet’), whereas secondary malnutrition occurs when the alcohol interferes with the absorption or metabolism of important nutrients [6]. One of these nutrients is folate. Folate is an important substrate in haematopoiesis, as it is involved with the synthesis of nuclear DNA. Without enough folate, asynchrony between the nuclear and cytoplasmic development of red cells develop, and cell division is halted. This results in megaloblastic anaemia (7).

The acquired sideroblastic abnormality is only seen in alcoholics with a corresponding folate deficiency. Chronic alcohol ingestion in patients with appropriate folate levels is not associated with a sideroblastic change (1,3). Without a deficiency in folate, a chronic alcoholic will demonstrate macrocytosis and possibly anaemia, but this anaemia will not be sideroblastic.

Originally it was assumed that folate deficiency in alcoholics was solely the result of poor nutrition. However, increased levels of ethanol, as seen in a chronic alcoholic, lead to increased urinary excretion of folate, increased catabolism of folate by the ethanol to acetaldehyde conversion, and malabsorption of folate in the jejunum by inhibiting the enzyme responsible for this. These all lead to a rapid decrease in serum folate levels of as little as 2-4 days (3). Folate deficiency itself leads to a further decrease in serum folate, by causing intestinal folate malabsorption and diarrhoea (8). The severity of folate deficiency is proportional to the amount of alcohol consumed and to the decrease in vitamin intake (8). One nutritious meal a day, however, can prevent the alcoholic from a deficiency in folate (3).

Conclusions

The case of patient B has presented an example of secondary acquired sideroblastic anaemia caused by chronic alcoholism and associated folate deficiency. Through this case and review of recent literature concerning the haematological aspects of chronic alcohol abuse, strong evidence for the requirement of folate deficiency in the development of cases of sideroblastic anaemia caused by chronic alcoholism is found.

The correlation between alcoholism, folate deficiency and secondary acquired sideroblastic anaemia is shown in Figure 3.

Figure 2. Prussian blue stain of Patient B’s bone marrow. Arrows show mitochondrial iron deposits in developing erythroid cells.

Alcohol also affects the absorption of iron directly. This is due to its direct toxic effect on the gastrointestinal tract, causing increased iron absorption. In those alcoholics without blood loss, this may result in acquired haemochromatosis (5). The characteristic mitochondrial iron loading seen in the sideroblastic state is therefore exacerbated [10]. Those alcoholics who develop haemochromatosis are at increased risk for liver cancer.

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References


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