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Pyridoxine-sensitive X-linked 'sideroblastic' anaemia in the absence of ring sideroblasts - the molecular diagnosis of congenital red cell disorders

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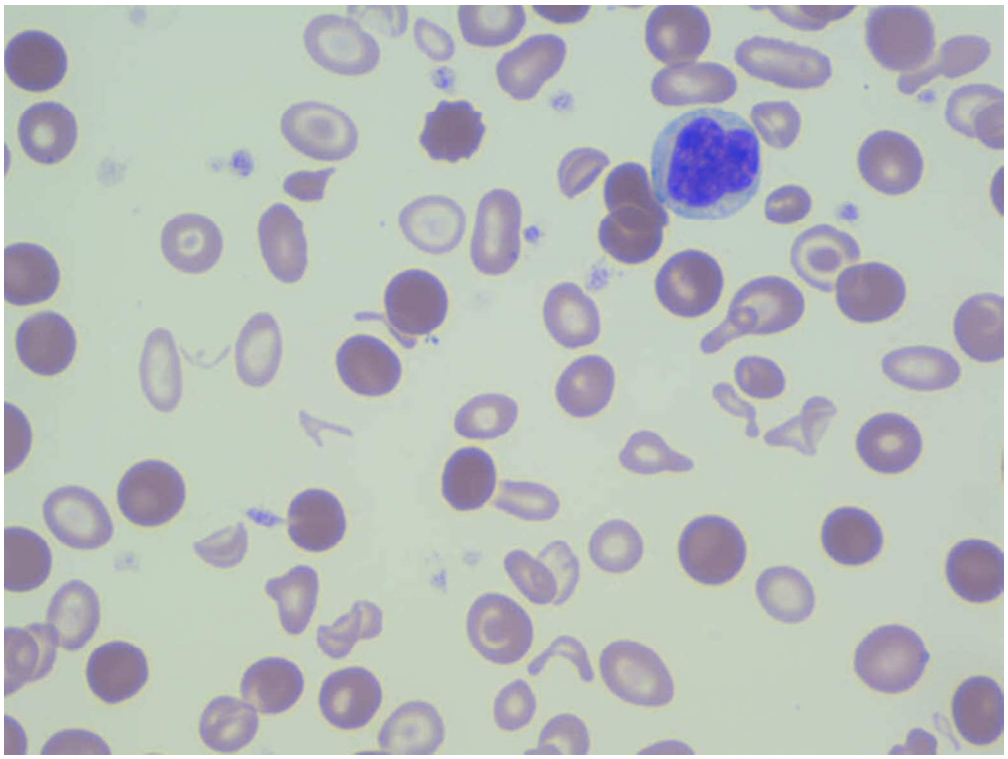

Figure 1: Peripheral blood

57x42mm (300 x 300 DPI)

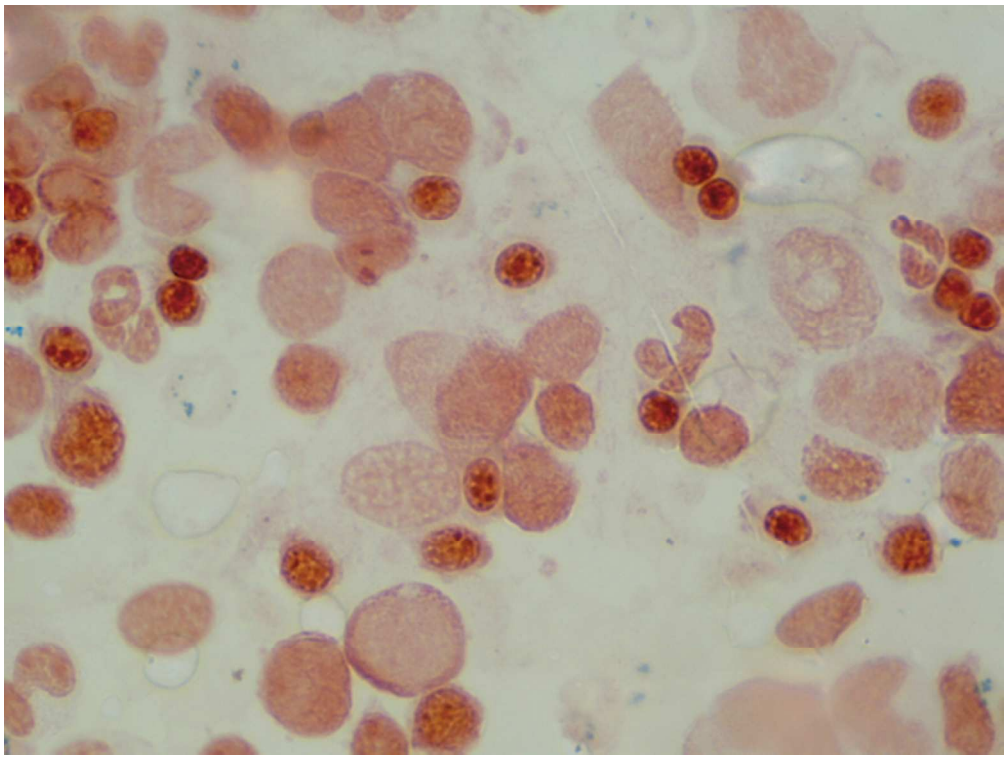

Figure 2: Bone marrow aspirate (Perls' stain)

57x42mm (300 x 300 DPI)

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A 2-year-old boy was taken to the Accident and Emergency department with a persistent productive cough. Further assessment revealed a 6-month history of worsening pallor and lethargy. He had been born by emergency Caesarean section at 41 weeks gestation for fetal distress but had subsequently been healthy. Examination revealed no hepatosplenomegaly. He was small for age with height and weight on the 2nd and 0.4th centiles respectively.

His full blood count showed a haemoglobin concentration (Hb) of 27 g/l, MCV 48 fl and MCH 13.5 pg, with reticulocytes 0.40 x 10^9/l. White cell count was 6.62 x 10^9/l, neutrophil count 2.23 x 10^9/l, platelet count 311 x 10^9/l and ferritin 262 µg/l. A peripheral blood film demonstrated dimorphic red cells with one population of normocytic, normochromic cells and a second population with marked poikilocytosis, target cells, irregular microcytes and fragmented red cells (left). Despite the dimorphic red cell morphology the clinical presentation was felt to be suggestive of hereditary pyropoikilocytosis. An eosin-5'- maleimide (EMA) binding test, however, was normal and a haemolysis screen was negative (bilirubin 6 µmol/l, lactate dehydrogenase 214 iu/l). A bone marrow aspirate showed normocellular erythropoiesis. A Perls' stain (right) showed storage iron to be present; there were very occasional ring sideroblasts, constituting less than 1% of all sideroblasts.

Both parents had normal Hb, red cell indices and EMA binding test. His mother's blood film showed occasional elliptocytes but no other abnormalities. Further enquiry into the family history revealed a maternal male cousin with congenital sideroblastic anaemia. Subsequently targeted genetic analysis identified an unusual combination of abnormalities. The patient was hemizygous for a C to A nucleotide substitution in exon 7 of *ALAS2* (c.791 C>A), which, although not previously reported, was predicted to result in

the replacement of the amino acid serine with tyrosine at residue 264 (p.Ser264Tyr) and was therefore consistent with X-linked sideroblastic anaemia, inherited from his mother. In addition, he was heterozygous for *SPTA1* (c.2608G>A; p.Val870Met) and *SPTB* (c.2519G>A; p.Arg840His) variants. Although not previously described, this digenic effect was felt to be potentially consistent with hereditary pyropoikilocytosis. The mother was a carrier of the *SPTA1* genetic variant and had some elliptocytes, suggesting a spectrinopathy.

At this stage, the predominant abnormality responsible for his phenotype was unclear. Due to the family history of congenital sideroblastic anaemia and the identification of a potential pathogenic *ALAS2* variant a trial of pyridoxine therapy was commenced. A dramatic improvement in his Hb was seen, rising to 112 g/l within 3 months without further red cell transfusion.

Despite the lack of overt sideroblastic change in his marrow aspirate, we postulate a primary diagnosis of pyridoxine-sensitive X-linked sideroblastic anaemia. Additional mutations associated with red cell membrane abnormalities may have contributed to the morphological abnormalities at presentation although this remains speculative. However, the absence of overt haemolysis and the dimorphic blood film were inconsistent with a significant pathological red cell membrane abnormality, such as hereditary pyropoikilocytosis.

This case highlights the importance of correlation between genetic and phenotypic features in the diagnosis of congenital anaemia. It suggests that the absence of significant ring sideroblasts does not preclude a diagnosis of congenital sideroblastic anaemia. A thorough family history and appropriate genetic analysis was particularly important in this patient's management.

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