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A novel mutation, Ile289Thr, in the *ALAS2* gene in a family with pyridoxine responsive sideroblastic anaemia

X-linked sideroblastic anaemia (XLSA; OMIM 301 300) is characterised by accumulation of inorganic iron in erythroblast mitochondria, visualised on staining as distinctive perinuclear rings. It arises from a deficiency of the erythroid specific isoenzyme of δ-aminolaevulinate synthase (ALAS2; E.C. 2.3.1.3.7), caused mainly by mutations affecting the catalytic or substrate-binding domains.[1 2] ALAS2 uses pyridoxal-5-phosphate as a cofactor to catalyse the first, rate-limiting step of erythroid haem synthesis and pyridoxine treatment can alleviate anaemia in many cases, although the response is variable and affected by factors such as mutation, age and iron load.[3 4]

A 40-year-old man presented with microcytic anaemia (haemoglobin 7.9 g/dl, mean corpuscular volume 58 fl, and mean corpuscular haemoglobin 15 pg), no evidence of thalassaemia, raised serum ferritin and 88% saturated transferrin. The blood film was dimorphic, with basophilic stippling and Pappenheimer bodies (fig 1A). Bone marrow cytology showed dysplastic erythropoiesis and ringed sideroblasts (fig 1B). After a 10-week course of 200 mg pyridoxine twice daily, the haemoglobin concentration rose to 12.4 g/dl. A liver biopsy, undertaken because of increased liver transaminases, showed heavy parenchymal iron deposition, but no fibrosis or cirrhosis. Screening for *HFE* gene mutations was negative. During fortnightly venesections over 8 months, haemoglobin remained stable, serum ferritin fell to 125 µg/l and liver transaminases returned to normal. The patient remains on pyridoxine and on a three-monthly maintenance venesection. Family history included a maternal grandfather and a brother (haemoglobin 13.1 g/dl, mean corpuscular volume 82 fl, mean corpuscular haemoglobin 26 pg) with microcytic anaemia.

Sequencing the coding region and intron or exon boundaries of *ALAS2* detected a T918C change on exon 7, predicting substitution of the highly conserved isoleucine by threonine at codon 289. The Ile289Thr mutation was present in the affected brother but not in an unaffected brother. Screening 150 alleles from 75 healthy women, mostly of northern European ancestry, and 45 alleles from 34 (11 women, 23 men) unrelated patients with congenital or inherited sideroblastic anaemia excluded *ALAS2*T918C as a common (≥5%), but not rare, north European polymorphism.

The novel mutation Ile289Thr is therefore probably responsible for the development of sideroblastic anaemia in this family, despite a variable associated phenotype not uncommon for this disorder.[3] Ile289 is located in a highly conserved region close to previously reported mutations, Gly291Ser and Lys299Gln, also associated with marked responses to pyridoxine,[4] and to His285, predicted by homology to have an important steric relationship with bound pyridoxal-5-phosphate.[4 5]

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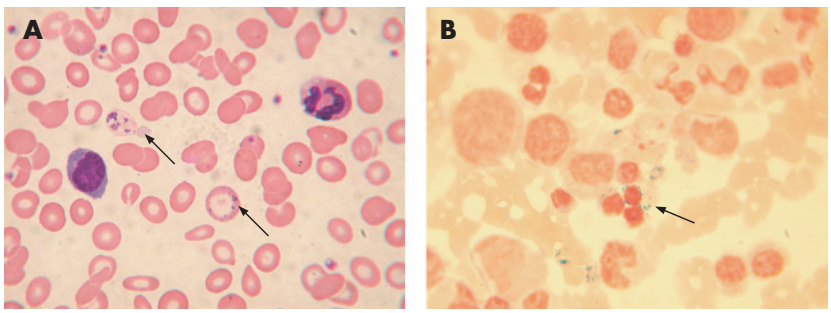

Figure 1 Blood film and bone marrow smear from the index case. (A) Wright–Giemsa stain of the peripheral blood showing dimorphic red cells and the presence of Pappenheimer bodies (indicated by arrows). (B) Perls's stain of the bone marrow aspirate showing the presence of ringed sideroblasts (indicated by the arrow).

Cystic dysplasia of testis: a case report

Cystic dysplasia of the testis is a rare congenital defect that results in the formation of numerous irregularly shaped cystic spaces in the mediastinum testis. The clinical presentation of such a disorder usually occurs in the paediatric age group as an asymptomatic scrotal swelling that can mimic testicular tumours. The case presented in this paper is the first identified and diagnosed case of cystic dysplasia in Kashmir, India.

A 2-year-old boy presented with a history of scrotal swelling since birth and was admitted to the Department of Surgery, Shri Mahraja Hari Sirgh Hospital, Srinagar, Kashmir, associated with Government Medical College, Srinagar, Kashmir, India.

On examination, the scrotum showed an enlarged right testis with a cystic feel. A trans-illumination test was positive. Scrotal ultrasound also showed cystic spaces in the testis. The testis was 7 × 3 cm with all three coverings and had a cystic feel, with small cystic spaces ranging in size from 0.2 to 1.5 cm on the cut section, affecting the whole testicular mass. Microscopic examination showed that the cysts were lined by low cuboidal flattened epithelium resembling the epithelium of the rete testis, separated from each other by fibrous septae with a complete replacement of normal testicular tissue.

Cystic dysplasia of the rete testis is a rare abnormality often associated with ipsilateral agenesis of the kidney. This malformation is due to a developmental defect of the mesonephric duct, which is the cause of both the dilatation of testicular rete testis and renal agenesis.[1] It is characterised by multiple irregular cystic spaces in the mediastinum of the testis that may affect the whole gonad and is associated with renal malformations (agenesis or cystic dysplasia[2]).

Embryologically, when the duct system of the testis is formed, seminiferous tubules anastomose with one another to form the rete testis. The rete testis in turn establishes contact with persisting mesonephric tubules, which form vasa-efferentia, the cranial part of the mesonephric duct becomes highly coiled on itself to form the epididymis and the distal part becomes the vas deferens. The seminal vesicle arises on either side of the mesonephric duct as a diverticulum. The part of the mesonephric duct between the opening into the prostatic urethra and the origin of the diverticulum forms the ejaculatory duct.[3]

A defect in the connection between efferent ductules derived from the mesonephric epithelium and the rete testis and seminiferous tubules seems to be the most likely explanation for the pathogenesis of cystic dysplasia of the testis.[3 4]

In our patient, teratoma was clinically suspected and orchidectomy was carried out