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CASE REPORT

Pearson syndrome: a rare inborn error of metabolism with bone marrow morphology providing a clue to diagnosis

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ABSTRACT

Pearson syndrome is a rare disorder of mitochondrial metabolism presenting in infancy with transfusion dependent refractory anaemia and multisystem involvement. We report a case of a 3-month-old infant presenting with anaemia requiring multiple transfusions. The presence of lactic acidosis, hyperglycaemia and cytoplasmic vacuoles in erythroid precursors on bone marrow aspiration study helped to suspect the diagnosis. However, the baby succumbed to metabolic crisis before he could be offered definitive therapy. This case report aims to emphasise the typical bone marrow aspiration finding which serves as a useful marker for establishing the diagnosis of this rare disorder, which is mostly fatal without bone marrow transplantation.

KEYWORDS

Mitochondrial disorders; Pearson marrow-pancreas syndrome; Refractory anaemia; Infants.

INTRODUCTION

Pearson syndrome (PS) is a mitochondrial cytopathy, first described in 1979 by Pearson et al. [1] in infants who presented with refractory anaemia and a variable degree of neutropenia and thrombocytopenia in addition to multisystem dysfunction, such as pancreatic insufficiency, proximal renal tubular acidosis and metabolic acidosis. Peripheral blood picture shows macrocytic anaemia and reticulocytopenia with ringed sideroblasts and marked vacuolisation of erythroid precursor cells on bone marrow examination. The incidence of PS is unknown, with only about 100 patients described in the literature [2]. Single mitochondrial DNA deletions causing the disease have a non-uniform tissue distribution leading to variability in clinical phenotype and is called heteroplasmy [3]. Due to diverse phenotypic manifestations of the disease and a lack of awareness, such cases are likely to be overlooked and underdiagnosed. We report a case of Pearson syndrome with fatal metabolic acidosis and anaemia.

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CASE REPORT

A 3-month-old, exclusively breastfed, male infant presented with history of progressive pallor since 1 month of age for which he had required blood transfusions on two occasions. He was born at term to a second degree consanguineous parentage by normal vaginal delivery with a birth weight of 3 kg. There was a significant family history of deaths of three previous siblings, involving both sexes, with only one surviving healthy girl child (Figure 1). All three babies died between 20 to 30 days of life, following brief episodes of excessive cry and poor feeding, even before medical help could be sought.

On examination, he was found to be lethargic with severe pallor, scanty scalp hair and periungual hyperpigmentation. Anthropometry was appropriate for age with a weight of 5 kg (−1.19 *z*-score), length of 57 cm (−1.38 *z*-score) and head circumference of 39 cm (−1.62 *z*-score). Systemic examination revealed a soft hepatomegaly (liver span 7 cm) without splenomegaly. He was found to have hypotonia with normal reflexes. Preliminary investigations revealed pancytopenia and reticulocytopenia with haemoglobin 6.6 g/dl, total leukocyte count 9 × 10^3/µl and a differential count of 16% polymorphs, 77% lymphocytes, 5% eosinophils, 2% monocytes and platelet count 46 × 10^3/µl. Vitamin B12 levels were 337 ng/ml (Normal: 150 – 450 ng/ml). In view of previous sibling deaths and pancytopenia, an inborn error of metabolism (IEM) was considered. Work up for inborn errors of metabolism revealed persistent hyperglycaemia (286–301 mg/dl) requiring insulin, absence of urine ketone bodies, high anion gap metabolic acidosis with elevated lactate levels of 15.4 mmol/l (Normal: 0.9–1.6 mmol/l). Plasma ammonia levels and tandem mass spectrometry for detection of IEM were normal. Bone marrow aspiration and biopsy were done at this point which showed decreased erythroid precursors, prominent cytoplasmic vacuolisation of proerythroblasts and early normoblasts (Figure 2) with grade 6 iron stores. Hence, a diagnosis of Pearson syndrome with endocrine pancreatic insufficiency was made. Molecular study could not be performed due to lack of availability.

The child's clinical condition initially improved following red blood cells transfusion. A few days later, during the course of hospital stay, he developed sudden onset of poor feeding and decreased activity. His condition abruptly deteriorated thereafter, with the onset of shock, hyperglycaemia and metabolic acidosis. He

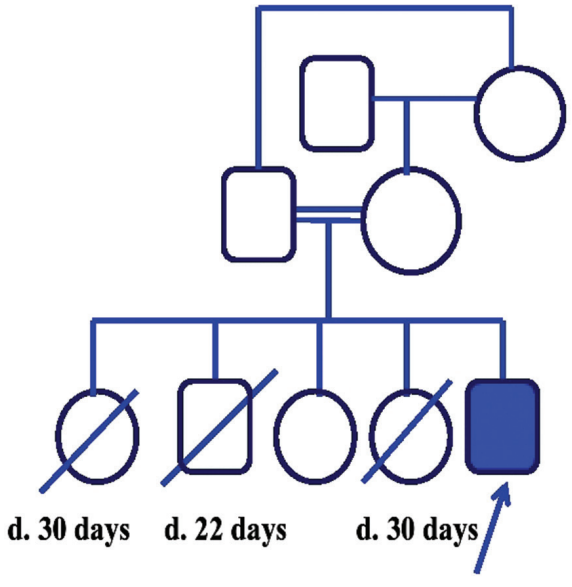

Figure 1. Pedigree of the family. The arrow points to the proband. *d* = *Died*.

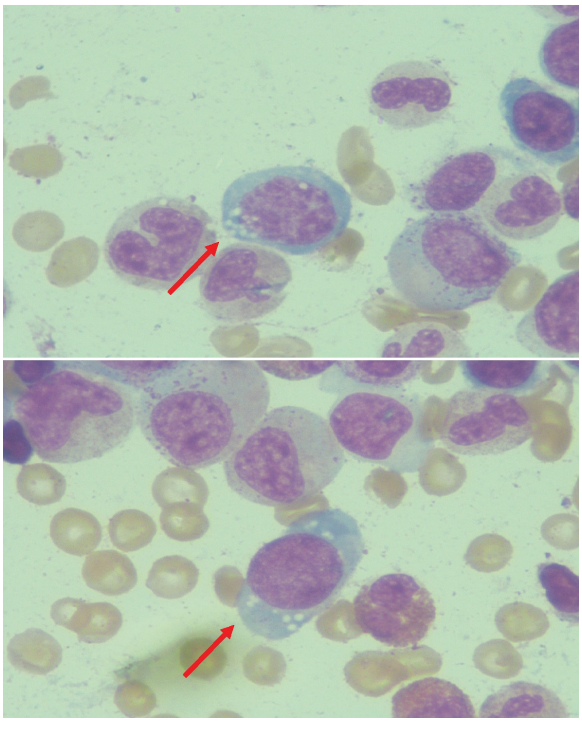

Figure 2. Cytoplasmic vacuolations of erythroid precursors (arrows).

received supportive care with fluid resuscitation, inotropes, insulin infusion, intravenous antibiotics and bicarbonate replacement. However, the child unfortunately succumbed to this episode of metabolic crisis with refractory shock.

DISCUSSION

Pearson syndrome, caused by mitochondrial DNA deletions, is characterised by anaemia in early infancy, exocrine pancreatic dysfunction, lactic acidosis and variable neurologic, hepatic, renal and endocrine disturbances [3]. Transfusion dependent anaemia due to a refractory sideroblastic anaemia, characterised by vacuolisation of marrow progenitor cells, is often seen. Exocrine pancreatic dysfunction and ringed sideroblasts, though frequent findings, are not mandatory for diagnosis [4]. As only few may be diagnosed on clinical grounds, demonstration of mitochondrial deletions by genetic testing is essential to confirm the diagnosis in infants presenting with anaemia of unclear etiology [4].

In the present case, the child was diagnosed as Pearson Syndrome based on pancytopenia with metabolic acidosis, hyperglycaemia requiring insulin, possibly diabetes mellitus, with bone marrow aspirate showing typical cytoplasmic vacuolisation of erythroid precursors. There was no clinical evidence of malabsorption to suggest exocrine pancreatic deficiency or ringed sideroblasts in the bone marrow aspirate although iron stores were high. Cytoplasmic vacuoles may be seen in various other disorders, such as childhood myelodysplastic syndrome, zinc toxicity, copper deficiency and acute parvovirus B19 infection [5,6]. However, it remains a useful marker for suspecting this diagnosis, especially as genetic evaluation is not easily accessible in resource-limited settings, like in this case.

Therapy is largely supportive with packed cell transfusions, treatment of metabolic acidosis and granulocyte colony-stimulating factor [7]. Despite supportive care, the prognosis is grave and most infants succumb to the illness within the first 3 years of life, most commonly due to persistent metabolic acidosis, sepsis or acute hepatic failure. A complete recovery of bone marrow and pancreatic function may be achieved in those children who survive infancy with appropriate supportive care. However, disease transformation from Pearson syndrome into a phenotypically different mitochondrial disease, namely, Kearn–Sayre Syndrome (KSS) may be seen in these survivors. KSS is characterised by the presence of ophthalmoplegia, ataxia, cardiac conduction defects, dementia and sensori-neural hearing loss [8]. Haematopoietic stem cell transplant can correct the haematological manifestations of the disease but is associated with unique toxicities. such as encephalopathy, renal tubular dysfunction and second malignancies [9].

Single mtDNA deletions such as in Pearson syndrome usually occur as sporadic events in isolated members of a family, although they can be transmitted through the germline in rare cases and has been reported in literature [10,11]. The index case, despite supportive care, had an acute deterioration following a short history of poor feeding and lethargy, in a fashion similar to his siblings. The possibility of Pearson syndrome, as a cause of recurrent neonatal deaths in the family, is hypothesised but due to lack of facilities the molecular tests were not conducted. Genetic counselling should aim to inform families of the sporadic nature of disease as well as the rare possibility of maternal transmission. Prenatal testing for subsequent pregnancies, though is theoretically possible, cannot predict the outcome of a specific pregnancy as there could be considerable variation in the mutated DNA inherited by the offspring, and also the clinical features correlate with the ratio of mutated to non-mutated mtDNA [12].

CONCLUSION

Pearson syndrome should be considered in the differential diagnosis of severe anaemia in infancy. It carries a poor prognosis and requires a high index of suspicion. In resource-limited settings where access to molecular analysis is not easily available, supportive evidence for diagnosis in the form of lactic acidemia, pancreatic insufficiency as well as the typical cytoplasmic vacuolisation of erythroid precursors should be looked for. Robust supportive care is required to tide over metabolic and infectious complications that can result in

death of these children. Hematopoietic stem cell transplantation may be offered as a therapeutic measure.

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CONFLICTS OF INTEREST

None.

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ETHICAL APPROVAL

Ethics committee approval has been granted by our Institution. Signed informed consent for participation and publication of medical details were obtained from the guardian of the patient. Confidentiality was ensured at all stages.

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