Early View Article: Online published version of an accepted article before publication in the final form.

Journal Name: Journal of Case Reports and Images in Pathology

doi: To be assigned

Early view version published: February 6, 2018

How to cite the article: Jyothi M. Pearson syndrome: A fatal inborn error of metabolism presenting with anemia. Journal of Case Reports and Images in Pathology. Forthcoming 2018.

Disclaimer: This manuscript has been accepted for publication. This is a pdf file of the Early View Article. The Early View Article is an online published version of an accepted article before publication in the final form. The proof of this manuscript will be sent to the authors for corrections after which this manuscript will undergo content check, copyediting/proofreading and content formatting to conform to journal’s requirements. Please note that during the above publication processes errors in content or presentation may be discovered which will be rectified during manuscript processing. These errors may affect the contents of this manuscript and final published version of this manuscript may be extensively different in content and layout than this Early View Article.
TYPE OF ARTICLE: Case Report

TITLE: Pearson syndrome: A fatal inborn error of metabolism presenting with anemia

AUTHORS:
Dr. Jyothi M

AFFILIATIONS:
Senior resident, Department of Pediatrics, St John’s Medical College Hospital

CORRESPONDING AUTHOR DETAILS
Dr. Jyothi M
Senior resident, Department of Pediatrics, St John’s Medical College Hospital
Email: jyothimunireddy@yahoo.co.in

Short Running Title: NOT GIVEN

Guarantor of Submission: The corresponding author is the guarantor of submission.
ABSTRACT

Pearson syndrome is a mitochondrial disorder presenting in infancy with refractory anemia and multisystem involvement. Due to the variable phenotype of the disorder and lack of awareness, such cases are likely to be underdiagnosed. There have been no cases reported from India so far. We report one such case of a three month old infant presenting with anemia requiring multiple transfusions. The presence of cytoplasmic vacuolisation of erythroid precursors on bone marrow aspiration study clinched the diagnosis. However, the baby succumbed to metabolic crisis before he could be offered bone marrow transplantation. This case report aims to emphasize the typical bone marrow aspiration finding which serves as a useful marker for establishing the diagnosis of this rare disorder which is uniformly fatal without bone marrow transplantation.

Keywords: Mitochondrial diseases, Pearson marrow-pancreas syndrome, Anemia, Refractory
INTRODUCTION
Pearson syndrome (PS) is a mitochondrial cytopathy, first described in 1979 by Pearson et al, [1] in infants who presented with refractory anemia with variable degree of neutropenia and thrombocytopenia, marked vacuolization of bone marrow cells and pancreatic insufficiency. The incidence of PS is unknown, with only about 100 patients described in literature and none reported from India till date. [2] 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 anemia.

CASE REPORT
A 3 month old, exclusively breast fed, male child presented with history of progressive pallor since 1 month of age for which he had required blood transfusion on 2 occasions. He was born to a second degree consanguineous parentage at term by normal vaginal delivery with a birth weight of 3 kg. There was significant family history of 3 previous sibling deaths affecting both sexes with only one surviving healthy girl child. All 3 babies died between 20 to 30 days of life, following a brief period of illness characterized by 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. Systemic examination revealed a soft, hepatomegaly (Liver span 7cm) without splenomegaly. He was found to have hypotonia with normal reflexes. Anthropometry was appropriate for age. Preliminary investigations revealed pancytopenia and reticulocytopenia with hemoglobin 6.6 g/dL, total leukocyte count 9 x 10^9/µL and a differential count of 16% polymorphs, 77% lymphocytes, 5% eosinophils, 2% monocytes and platelet count 46 x 10^9/µL.
Vitamin B12 levels were 337 pg/ml (Normal: 150 – 450pg/ml). In view of previous sibling deaths and pancytopenia, an inborn error of metabolism (IEM) such as organic acidemia, was considered. Work up for inborn errors of metabolism revealed persistent hyperglycemia (286-301mg/dL) requiring insulin, absence of urine ketone bodies, high anion gap metabolic acidosis with elevated lactate levels of 15.4mmol/l (Normal: 0.9 – 1.6 mmol/L). Plasma ammonia levels and tandem mass spectrometry
for detection of IEM was normal. Bone marrow aspiration and biopsy was done at this point which showed decreased erythroid precursors, prominent cytoplasmic vacuolation of proerythroblasts and early normoblasts (Figure 1) with grade 6 iron stores.

Hence a diagnosis of Pearson syndrome with endocrine pancreatic insufficiency was made. However, the child succumbed to an episode of metabolic crisis.

DISCUSSION

Pearson syndrome, caused by mitochondrial DNA deletions, is characterized by pallor in early infancy, frequently transfusion dependent, due to refractory sideroblastic anemia with vacuolization of marrow progenitor cells, exocrine pancreatic dysfunction, lactic acidosis and variable neurologic, hepatic, renal and endocrine disturbances [3]. Exocrine pancreatic dysfunction and ring 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 anemia of unclear etiology [4].

In the present case, the child was diagnosed as Pearson Syndrome based on pancytopenia with metabolic acidosis, hyperglycemia 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 vacuolations 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 G-CSF [7]. Despite supportive care, the prognosis is grave and most infants die before age 3 years, often due to unremitting metabolic acidosis, infection, or liver failure. Those who survive infancy with supportive care may experience a full
recovery of marrow and pancreatic function. However, these individuals eventually undergo a phenotypic transformation from Pearson's syndrome to Kearns-Sayre syndrome, with the development of ptosis, incoordination, mental retardation and episodic coma. Cardiac conduction abnormalities and hearing loss can also develop [8]. Hematopoietic stem cell transplant (HSCT) can correct the hematological manifestations of the disease but is associated with unique toxicities such as encephalopathy, renal tubular dysfunction, second malignancies etc [9].

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 hypothesized. 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 [10].

CONCLUSION

Pearson syndrome should be considered in the differential diagnosis of severe anemia in infancy and supportive evidence for diagnosis in the form of cytoplasmic vacuolation of erythroid precursors should be looked for. Hematopoietic stem cell transplantation may be offered as a therapeutic measure in these children.

CONFLICT OF INTEREST

NOT GIVEN

AUTHOR’S CONTRIBUTIONS

NOT GIVEN

REFERENCES


FIGURE LEGEND

Figure 1: Cytoplasmic vacuolations of erythroid precursors
Figure 1: Cytoplasmic vacuolations of erythroid precursors