Case Report

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mtDNA Deletion in an Iranian Infant with Pearson Marrow Syndrome

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Abstract

Background: Pearson syndrome (PS) is a rare multisystem mitochondrial disorder of hematopoietic system, characterized by refractory sideroblastic anemia, pancytopenia, exocrine pancreatic insufficiency, and variable neurologic, hepatic, renal, and endocrine failure.

Case Presentation: We describe a six-month-old female infant with Pearson marrow syndrome who presented with neurological manifestations. She had several episodes of seizures. Hematopoietic abnormalities were macrocytic anemia and neutropenia. Bone marrow aspiration revealed a cellular marrow with marked vacuolization of erythroid and myeloid precursors. Analysis of mtDNA in peripheral blood showed 8.5 kb deletion that was compatible with the diagnosis of PS.

Conclusion: PS should be considered in infants with neurologic diseases, in patients with cytopenias, and also in patients with acidosis or refractory anemia.

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Key Words: mtDNA; Mitochondrial DNA; Pearson Marrow Syndrome; Exocrine Pancreatic Insufficiency; Pancytopenia

Introduction

Pearson's marrow syndrome (PS) is a rare, often fatal disorder of infancy, characterized by impaired bone marrow, exocrine pancreatic, hepatic and renal function. Large-scale rearrangements of mitochondrial DNA (mtDNA) are present in blood or other tissues[1,2,3].

Children with PS characteristically present in early infancy with pallor, failure to thrive, pancytopenia, diarrhea, and markedly increased serum and/or cerebrospinal fluid lactate[4].

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Additional manifestations often include progressive external ophthalmoplegia, proximal myopathy with weakness, and neurologic disturbances (seizures, ataxia, stroke-like episodes)[4,5,6]. The extent of multiple organ involvement is quite variable.

PS can now be redefined as refractory sideroblastic anemia (or refractory anemia with ring sideroblasts) with vacuolated marrow precursors and deletion of mtDNA. Other findings, such as pancreatic insufficiency, acidosis, or renal tubular insufficiency, are common but not mandatory for diagnosis[7].

Most infants die before the age 3, often due to unremitting metabolic acidosis, infection, or liver failure[8]. Those few individuals who can be medically supported through infancy may experience a full recovery of marrow and pancreatic function. However, these individuals eventually undergo a phenotypic transformation from PS to Kearns-Sayre syndrome with the development of ptosis, incoordination, mental retardation, and episodic coma. Cardiac conduction abnormalities and hearing loss can also develop. The major problem is acidosis. The arm of specific therapy is to bypass the deleted respiratory enzymes through the use of thiamine, riboflavin, L-carnitine, and coenzyme Q.

A mtDNA deletion was reported in patients with PS[9], which is a mitochondrial disease that can be inherited only maternally[10]. Treatment of PS is symptomatic, majority of the patients received transfusions. The patients can benefit from G-CSF (granulocyte colony stimulating factor) and EPO (erythropoietin) [11,12]. PS is probably misdiagnosed as of rare condition. Here we describe an infant with PS who had presented with neurological manifestations.

Case Presentation

A six month-old female infant was referred to our hospital with seizure disorder and pancytopenia. She is the first child of healthy parents who were not relatives. Perinatal and neonatal periods were without any serious problem except for a mild jaundice during the first month.

Birth body weight was 2950 gr and head circumference 34 cm. Growth and development of the patient were normal until the age of 4 months, when she started neuro-developmental regression. She lacked tonic neck and showed attention deficit.

She experienced seizure attacks as sucking and eye movement just 10 days before hospitalization in our center; she was treated with phenobarbital and phenytoin in another center, but was referred to our center for further follow-up as of increased frequency of seizures and pancytopenia. She was lethargic and pale at the time of admission; body weight was 6500 gr (10th percentile for age) and head circumference was 42 cm (50th percentile for age). Hepatomegaly was detected in physical examination, but the spleen was not palpable. The patient was febrile (axillary temperature 38.5°C).

Complete blood count (CBC) revealed pancytopenia: white blood cell (WBC): 1100/µL, polymorphoneuclear (PMN): 34%, red blood cell (RBC): 2870000/µL, hemoglobin (Hb): 8.8 g/dl, mean corpuscular volume (MCV): 91 fl, mean corpuscular hemoglobin (MCH): 30 pg, mean corpuscular Hb concentration (MCHC): 33 g/dl, Platelet count: 125000/µL, Reticulocyte count: 1.4%. Other chemical laboratory test results (blood suger, blood urea nitrogen, ctartinie, sodium, potassium, phosphor, calcium, liver function tests, triglyceride, cholesterol and lactate dehydoganase) at the first day of admission were normal. Arterial blood gas, serum lactate and pyrovate, serum and urine aminoacid chromatography, TORCH study, thyroid function tests, serum folate, and serum B_{12} levels were normal. Treatment with anticonvulsant drugs and antibiotics continued.

She experienced an episode of status epilepticus and loss of consciousness two days after hospitalization. The status epilepticus was controlled by midazolam. Brain computed tomography scan demonstrated marked brain atrophy, and visual evoked potential revealed bilateral cortical blindness. The cerebro spinal fluid analysis was in normal range.

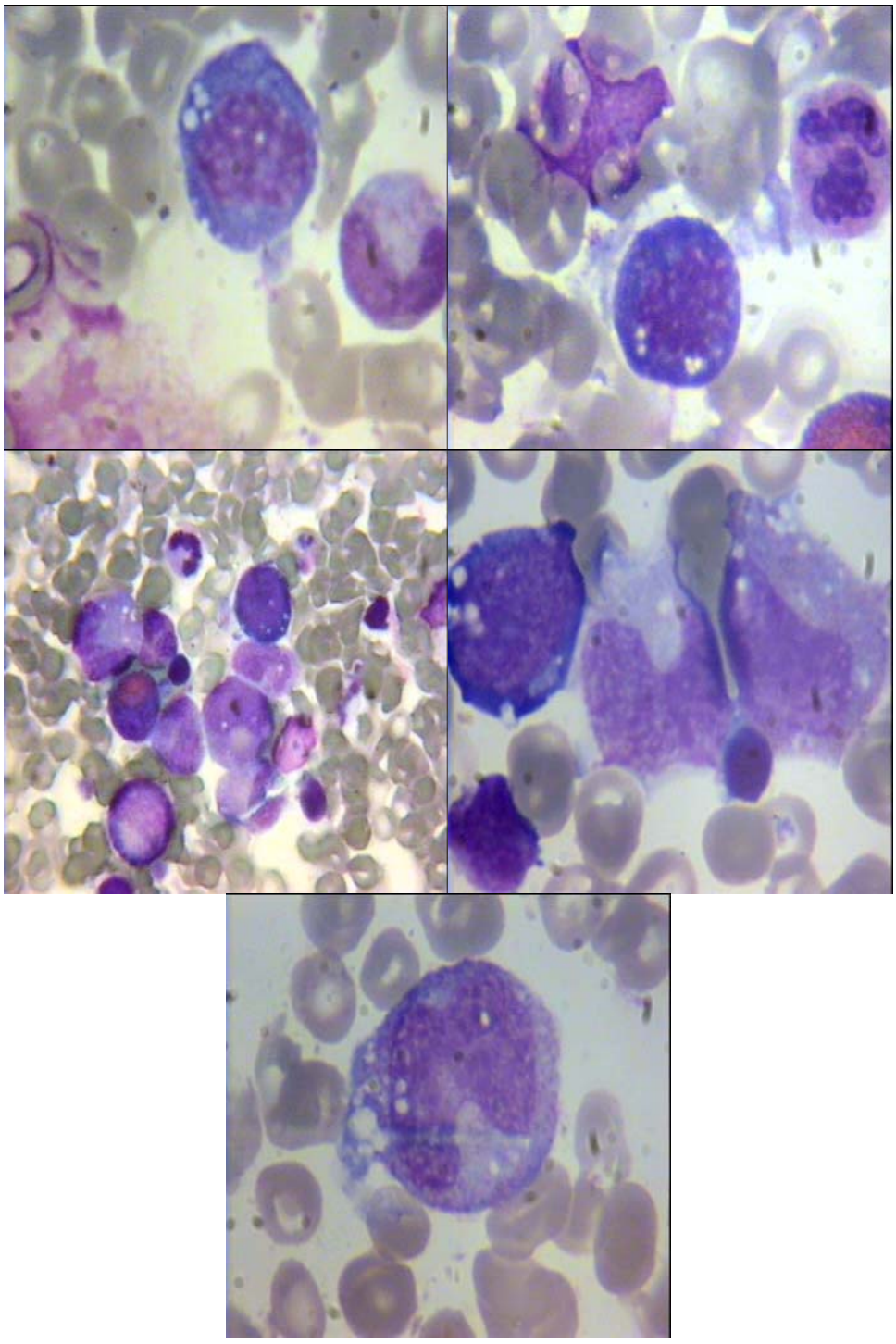

Fig. 1: Characteristic vacuolization of a hematopoietic precursor in the bone marrow (Light microscopy; 100x; Wright-Giemsa stain)

Electroencephalography of the patient displayed slow background activity. Abdominal sonography revealed mild hepatomegaly, and mild osteopenia was reported in skeletal survey.

CBC, which was performed 7 days after hospitalization still showed bicytopenia: WBC:1600/µL, RBC: 2270000/µL, Hb: 7.2 g/dl, MCV: 95 fl, MCH: 31 pg, MCHC: 33 g/dl, Plt: 190000/µL. Bone marrow aspiration revealed a cellular marrow with marked vacuolization of erythroid and myeloid precursors (Fig 1).

The bone marrow cell differentiation and percentage of different developmental stages of the cells were as follow: myeloid/erythroid ratio 3/1, myeloblast 2%, promyelocyte 15%, myelocyte 20%, metamyelocyte 15%, band 10%, PMN 8%.

Iron staining of bone marrow showed markedly ring sideroblasts (Fig 2). Percentage of ring sideroblasts in iron staining of bone marrow was 22%. Patient received 100 cc packed cell transfusion and also Granulocyte colony-stimulating factor (G-CSF) 5 µg /kg/day sub-cutaneously.

On the day of 15 after hospitalization, the results of her CBC were as follow: WBC: 4100/µL, PMN: 22%, Lymphocyte: 78%, Hb: 8.2 g/dl, Plt: 234000/µL. Blood transfusion was repeated.

Being suspicious to Pearson marrow syndrome, study on mitochondrial DNA from peripheral blood sample of the patient was performed, which indicated mtDNA deletion (8.5 kb deletion, 39.5% mtDNA deletion and 60.5% wild type). So, the diagnosis of PS was confirmed for this patient.

Discussion

Pearson syndrome was primarily explained by Pearson et al in 1979[1], while the patho-gnomonic deletion of mtDNA was identified by Rotig et al in 1990[13]. The mitochondropathies consist of a number of syndromes, such as PS, Kearns-Sayre syndrome (KSS) and the mitochondrial myopathies, caused by mutations of mtDNA[14-16]. PS has a distinct phenotype with prominent involvement of bone marrow and exocrine pancreas, which could be due to several factors such as differences in the tissue-specific distribution of abnormal mtDNA and the effects of tissue-specific nuclear modifier genes[17].

Rotig et al reported 21 patients with PS in which mtDNA abnormalities were detected in all patients[17]. The most common abnormality was 4.9 kb deletion, which was seen in 9 patients. Macrocytic sideroblastic anemia is one of the most common findings of PS, which could be refractory. Neutropenia and thrombocytopenia may also occur.

Exocrine pancreatic insufficiency is one of the main clinical manifestations of patients with PS[17]. History of low birth weight and metabolic acidosis is also reported in a number of patients with PS, while physical anomalies are rare[11,18]. Renal involvement is also common and could manifest as tubulopathy[13,19]. Hepatic failure and impaired glucose tolerance were other clinical findings of these patients. Twelve patients died by the age of 3.5 years[17].

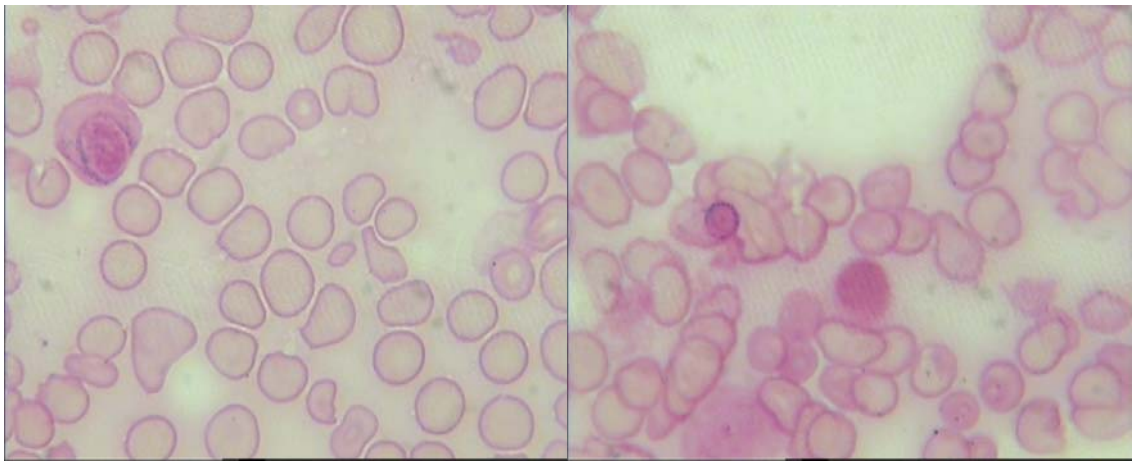

Fig. 2: Ring sideroblasts in the bone marrow (Iron stain)

Our patient presented with anemia and neutropenia in infancy; she also experienced neurological involvement such as seizures, developmental delay, and bilateral cortical blindness. Other manifestations such as pancreatic involvement and renal tubular dysfunction have not been detected in this patient till the time of this report but this findings are not mandatory for diagnosis of Pearson marrow syndrome[7]. In the study of Rotig et al, seven of 21 PS patients did not experience dysfunction of the exocrine pancreas[17]. The endocrine pancreas usually remains functional, while a number of patients develop diabetes mellitus. The neurological features of PS have potential evolution changes that are from normal, mild neurological deficits to special mitochondrial syndromes such as KSS and Leigh syndrome[20,21].

DNA deletion is complicated: patients with KSS may have identical deletions without hematologic signs, and patients with bone marrow findings as seen in PS may not have DNA deletions although they may have abnormal mitochondrial enzymes. Still other mitochondrial disorders may be due to point mutations or to deletions smaller than those that can be detected by Southern blotting[22,23].

While intellectually challenging to the clinician and researcher, a diagnosis of PS results in an extremely grave prognosis for the patient. Unfortunately, at this point, treatment can only be directed toward symptomatic relief.

In our patient the main manifestations were neurological features (seizures, developmental regression, brain atrophy), and hematologic (macrocytic sideroblastic anemia, vacuolization of hematopoietic precursors and neutropenia). The diagnostic clue in our patient was vacuolization of marrow precursors. Although certain drugs can also be associated with vacuolization of marrow precursors, mtDNA deletion is not seen in this condition. The final diagnosis of our patient was made by such finding. The cells have different amount of mitochondria in their cytoplasm and each mitochondrion has its own DNA. Thus when a mutation occurs in the mitochondria, some of the DNA in the mitochondria carry the mutation and some other function as wild type without mutation, a condition called heteroplasmy. In our patient, mtDNA deletion was found in 39.5%, while the remaining 60.5% were wild type.

The amount of the mutant mitochondrial DNA in a cell is an important factor for the determination of the level of mitochondrial dysfunction, which is crucial for the disease severity. Mitochondrial mutations such as deletion of a big portion of the DNA, which is the case in this patient, could have certainly considerable effect on the respiratory chain and energy household of the cells. In the presented patient lactic acidosis and renal involvement were not seen. Exocrine and endocrine functions of pancreas and the function of liver were also intact.

Conclusion

PS should be considered in infants with neurologic diseases, in patients with cytopenias, and also in patients with acidosis or refractory anemia. Due to the heteroplasmy, it is very important to know the percentage of mutant mitochondrial DNA in the analyzed cells to try to find a correlation between the percentages of mutated DNA and the clinical data..

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