Pediatrics & Therapeutics
ISSN: 2161-0665

Kitano and Yoshida, Pediatr Ther 2018, 8:1
DOI: 10.4172/2161-0665.1000341

Case Report Open Access

Pearson Syndrome as a Rare Cause of Failure to Thrive, Anemia and Exocrine Pancreatic Insufficiency: A Case Report

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Received date: Jan 24, 2018; **Accepted date:** Feb 02, 2018; **Published date:** Feb 05, 2018

Abstract

Pearson syndrome is a rare mitochondrial disorder. We present a 1-year-old girl with Pearson syndrome confirmed by the deletion of mtDNA (a 2.7-kb deletion, m.11244_13981del2738). She presented with failure to thrive, anemia, exocrine pancreatic insufficiency and severe liver failure. She also had elevated serum lactate and alanine level and renal tubular dysfunction. She required multiple packed red blood cell transfusions, which led to iron chelation therapy due to her elevated serum ferritin level. Nutritional management including vitamin supplement was performed, which did not help save her life.

In conclusion, although Pearson syndrome is a rare disorder, we need to consider the possibility of Pearson syndrome in case of failure to thrive in addition to multiple organ involvement such as bone marrow, liver, kidney and pancreatic insufficiency.

Keywords: Pearson syndrome; Liver failure; Sideroblastic anemia; Exocrine pancreatic insufficiency

Introduction

Pearson syndrome was first reported as a disorder associated with bone marrow failure and exocrine pancreatic insufficiency [1]. In almost all cases, patients with Pearson syndrome are involved with failure to thrive. A variety of organs, such as bone marrow, pancreas, liver and kidney, are often affected. The prognosis of Pearson syndrome is poor and it is very difficult for the patients to live to be adults. The incidence of Pearson syndrome was estimated approximately 1/1,000,000 live birth in a previous report from Italy [2]. In this case report, we present a case of Pearson syndrome with failure to thrive and refractory anemia.

Case Presentation

A 19-month-old Japanese girl presented with nasal discharge, cough, wheezing and decreased appetite for a week. When she was 10 months old, she visited a previous hospital where she was found to have a pancytopenia (white blood cell count 7,200/μl, hemoglobin 8.6 g/dl, mean corpuscular volume 101 fl and platelets 52,000/μl). She had a bone marrow aspiration, which revealed vacuolated erythroid and myeloid precursors and ringed sideroblasts without myelodysplasia (Figure 1). She had a first red blood cell transfusion at 13 months and had required it regularly approximately every other month since then due to refractory anemia. In a previous hospital, she had had a history of multiple admissions due to infections, including gastroenteritis, pharyngitis, bronchitis and pneumonia. In addition, she had a history of diarrhea and greasy-looking stool on and off over the past year. She also had had a failure to thrive. Her body weight was 7.3 kg (-1.3SD) at 10 months of age and it became 6.6 kg (-3.3SD) at 19 months of age.

She was born at 38+4 gestational weeks. Her birth height was 47.2 cm (-0.7SD) and her birth weight was 2732 g (-0.5SD). Her perinatal history was unremarkable. Her developmental milestones were appropriate for age. None of her family members, including her 5-year senior brother, had not had a history of any genetic disorder.

Physical examination at the time of presentation to our hospital revealed her temperature to be 38.5, blood pressure to be 92/58 mmHg, heart rate to be 140/minute and respiratory rate to be 32/minutes. She was pale and feeble. Her conjunctivas were severely anemic and not icteric. Her pharynx was not erythematous or swollen. Inspiratory coarse crackles were heard on auscultation. Her abdomen was soft and flat without hepatosplenomegaly. No rash was seen. Her skin was dry. Capillary refilling time was within normal limits.

The result of her blood test is shown in Table 1. Blood and urine amino acid analyses showed that she had elevated serum alanine level and generalized aminoaciduria. Tandem mass spectrometry was performed, which revealed that she had a hypocarnitinemia (17.18 mmol/l; normal 25-100 mmol/l). Irregular liver echogenicity and dilation of kidney calix were confirmed on the abdominal ultrasonography. Cardiac echo and electrocardiogram did not reveal any abnormality. MRI of her brain and abdomen did not show any significant results. Pancreatic function diagnostant test showed that 59.2% of N-benzoyl-l-tyrosyl-para-aminobenzoic acid (BT-PABA) was excreted (normal>71%). This test was conducted when her laboratory liver and kidney tests were the results in Table 1. Fecal fat study (Oil red O stain) of her stool was positive even though she had had little oral intake for 1 week before the test.

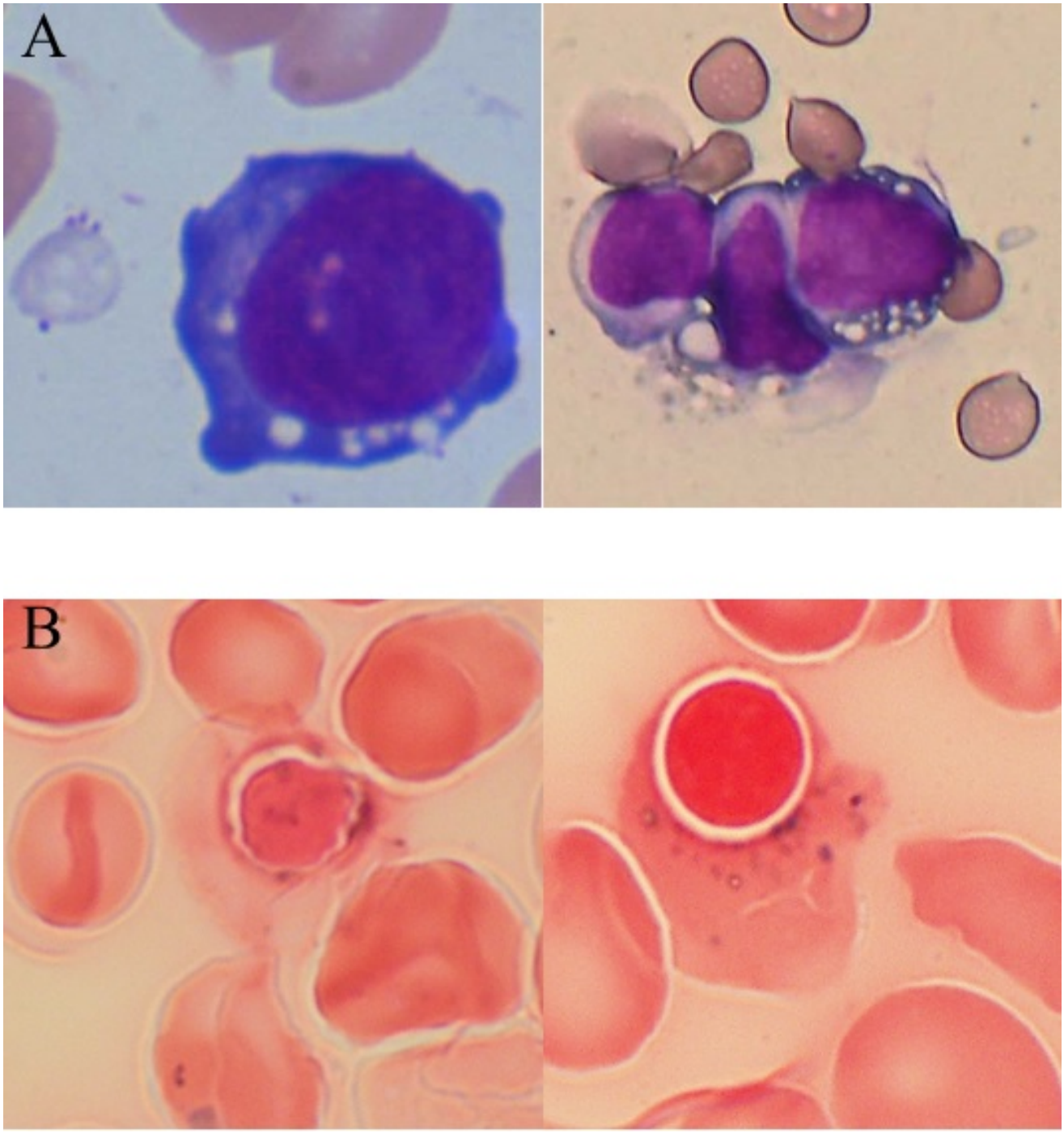

Figure 1: Bone marrow aspiration (A) Vacuolated erythroid and myeloid precursors are seen on Hematoxylin-Eosin stain (x 1000); (B) Ringed sideroblasts are confirmed by iron stain (x 1000).

Component	Quantity
WBC	5500/μl
Band	4%
Seg	32%
Lympho	64%
Mono	2%
Hb	5.5 g/dl
MCV	97 Fl
Ret	0.05%
PLT	17.6 × 10^4/μl
pH	7.39
CO_2	34.8 mmHg
HCO^{3-}	20.7 mmol/L
Base excess	-3.1 mmol/L
Lactate	7.3 mmol/L
Pyruvate	4 mg/dl
Carnitine	17.18 mmol/l
Alanine	758.6 nmol/l
Citrulline	6.3 nmol/l
Total ketone bodies	1274 μmol/L
Acetoacetic acid	162 μmol/L
β-hydroxybutyric acid	1112 μmol/L
Vitamin B1	17.7 ng/ml
Transferrin	120 mg/dl
Zinc	48 mg/dl
C3	52 mg/dl
C4	15 mg/dl
CH50	12/ml
Insulin	8 μU/ml
C-peptide	1 ng/ml
Anti-GAD Ab	-
Anti-IA-2 Ab	-
Anti-insulin Ab	-
TP	5.8 mg/dl
Alb	3.7 mg/dl
Pre-Alb	9.9 mg/dl

AST	167 U/L
ALT	138 U/L
LDH	300 U/L
T-Bil	0.7 mg/dl
Amy	38 U/L
CK	35 U/L
Glu	80 mg/dl
BUN	12.3 mg/dl
Cre	0.26 mg/dl
Na^+	136 mEq/l
K^+	4.6 mEq/l
Cl^-	103 mEq/l
Calcium	8.7 mg/dl
Phosphorus	5.3 mg/dl
Iron	159 μg/dl
UIBC	17 μg/dl
TIBC	176 μg/dl
Ferritin	935 ng/dl
Ammonia	40 μg/dl
IgG	861 mg/dl
BNP	19.5 pg/dl
PCT	0.2 ng/dl
CRP	0.03 mg/dl
HbA1c	6.50%
TSH	2.25 μIU/ml
Free T3	2.4 pg/ml
Free T4	0.85 pg/ml

WBC: White Blood cell Count; MCV: Mean Corpuscular Volume; PLT: Platelets; GAD: Glutamate Decarboxylase; IA-2: Islet Antigen 2; TP: Total Protein; Alb: Albumin; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; LDH: Lactate Dehydrogenase, T-bil: Total bilirubin; Amy: Amylase; CK: Creatinine Kinase, BUN: Blood Urea Nitrogen; UIBC: Unsaturated Iron Binding Capacity; TIBC: Total Iron Binding Capacity; BNP: Brain Natriuretic Peptide; PCT: Procalcitonin, CRP: C-Reactive Protein; TSH: Thyroid Stimulating Hormone.

Table 1: Laboratory tests.

She was admitted and ceftriaxone and symptomatic treatments were administered for her respiratory infection. She had enteral and parenteral nutrition with pancreatic enzyme supplementation. However, we had to stop enteral nutrition and pancreatic enzyme supplementation because of her refractory vomiting and strong refusal of feeding tube. Nutrition support team had actively been supporting from the beginning of our treatment course. We tried complementary foods, including medium-chain triglyceride oil, medium-chain triglyceride powder and ketone formula. For the entire course of the treatment, the component of her total calorie intake was adjusted to 10-15% protein, 50% fat and 35-40% carbohydrate. However, her fat intake had to be temporarily decreased because her serum triglyceride level had sharply risen. We administered the following nutritional supplements as a conservative treatment; carnitine 100 mg/kg, ubiquinone 5 mg/kg, vitamin B1 10 mg/kg, vitamin C 100 mg/kg, vitamin E 10mg/kg and biotin 0.5 mg/kg. Liver function was exacerbated and she was placed on ursodeoxycholic acid, glycyrrhizic acid and taurine. We discussed her indication of liver transplantation

with surgery departments in other hospitals and it was concluded that she was not a candidate of liver transplantation because of her general condition and expected poor prognosis. Because she had needed multiple red blood cell transfusions and her ferritin level had risen up, we started the treatment with deferoxamine for iron chelation therapy. After her oral intake had improved, she was discharged on Day 30. However, she had another episode of respiratory infection and decreased oral intake 8 days after 1st discharge from our hospital, which made her be readmitted. Her appetite was improved again during her 2nd admission for 20 days. Seven weeks after her 2nd discharge, she had another episode of gastroenteritis with exacerbated liver function and severely decreased oral intake. She was transferred to another hospital because of her exacerbated general condition and severe liver failure. She died at 23 months of age due to liver failure (on Day 144 after 1st admission to our hospital). The treatment schedule is presented in Figure 2.

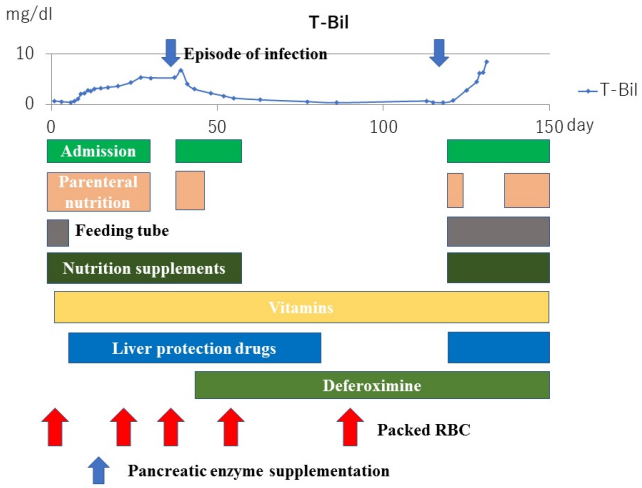

Figure 2: Treatment schedule (T-Bil: Total bilirubin; RBC: Red Blood Cell).

The component of her total calorie intake from enteral and perenteral nutrition was adjusted to 10-15% protein, 50% fat and 35-40% carbohydrate. Complementary food included medium-chain triglyceride oil, medium-chain triglyceride powder and ketone formula. Nutrition supplements included carnitine 100 mg/kg, ubiquinone 5 mg/kg, vitamin B1 10 mg/kg, vitamin C 100 mg/kg, vitamin E 10 mg/kg and biotin 0.5 mg/kg. Liver protection drugs were ursodeoxycholic acid, glycyrrhizic acid and taurine.

Informed consent was provided for DNA testing. The targeted gene sequencing test was performed on Day 10 and it revealed a 2.7-kb deletion, m.11244_13981del2738, which was consistent with mitochondrial DNA deletion. No autopsy was performed in the case.

Discussion

Pearson syndrome was first reported as a disorder associated with bone marrow failure and exocrine pancreatic insufficiency [1]. In almost all cases, patients with Pearson syndrome are involved with failure to thrive. A variety of organs, such as bone marrow, pancreas, liver and kidney, are often affected. The prognosis of Pearson syndrome is poor and it is very difficult for the patients to live to be adults. The incidence of Pearson syndrome was estimated approximately 1/1,000,000 live birth in a previous report from Italy [2].

This case presented with failure to thrive, sideroblastic anemia, exocrine pancreatic insufficiency, hyperlactatemia and progressing liver failure. All of these findings were consistent with the clinical diagnosis of Pearson syndrome. According to the previous report of 11 cases from Italy, common findings were elevated serum lactate (10 cases), elevated serum alanine (9 cases), transfusion dependency (8 cases), severe infections (8 cases), hepatomegaly (8 cases), failure to thrive (7 cases), neurological symptoms (7 cases) and eye involvement (6 cases) [2]. Sepsis was the most common cause of death. Although our patient needed packed red blood cell transfusions regularly, some case reports indicated that those who survived past 2 years tended to decrease the frequency of transfusions [3].

There are several tests to evaluate pancreatic exocrine function, including fecal elastase test, fecal chymotrypsin tests and BT-PABA test. In Japan, BT-PABA test is the only pancreatic function diagnostant test reimbursed by the national medical insurance. However, the accuracy of the test is sometimes questionable, especially in cases with liver or renal failure. Although our case finally had severe hepatic failure, we assume that the patient had exocrine pancreatic insufficiency to some extent because she preserved her liver function when the test was performed and because of her history of steatorrhea with the positive result of her fecal fat stain test. Like our case, hepatic involvement was common in Pearson syndrome though its severity varies on each patient [2,4]. Patients with Pearson syndrome were often involved with insulin dependent diabetes, which our patient did not experience [5].

Some previous cases reported that elevated serum alanine was useful to make an early diagnosis [6]. Our case also had elevated serum alanine. Although it was a sign of the mitochondrial dysfunction though elevated alanine was not specific. Her elevated serum lactate and alanine were resulted from the impaired tricarboxylic acid cycle. In addition, her decreased serum citrulline level was consistent with the previous case report of Pearson syndrome and other mitochondrial disorders [7,8]. Regarding that she had a generalized aminoaciduria, we assume that she had a renal tubular dysfunction which was often reported in other cases [3]. Although she had a decreased level of serum carnitine, we assumed that it was not derived from congenital hypocarnitinemia but from Pearson syndrome because the level was not severely decreased and her history did not fit with congenital hypocarnitinemia.

In terms of genetic diagnosis, some studies reported that the increased length of deletion in the mtDNA was related to the earlier onset and more severe form of the disease while others did not find any significant correlation between the length of deletion and the phenotype [2,9-11].

Because there is a lack of fundamental treatment of Pearson syndrome, a nutritional management and supportive treatments are main-stream of the management of Pearson syndrome. Regarding a nutrition management, large doses of vitamins and other nutritional supplements are often administered to patients with mitochondrial disorders [12]. For example, coenzyme Q, l-carnitine, thiamin, riboflavin, niacin, pantothenic acid, pyridoxine, vitamin B12, folic acid, biotin, vitamin C, vitamin E, beta-carotene, zinc, selenium, magnesium and *N*-acetyl cysteine are the candidates of supplements; however, these evidences are limited [13,14]. Likewise, ketogenic diet is another nutritional intervention widely implemented for patients with

mitochondrial disorders. Although several studies revealed that it could be efficacious for the seizure prevention [15,16]. Its long-term safety and efficacy have yet to be researched. Therefore, it was difficult to conclude that our nutritional management for this patient was efficacious for the better patient outcome. The evidence based-approach considering cost-effectiveness in nutritional management needs to be established. Evidence of fundamental treatments, such as genetic treatment is limited, which needs to be developed in the future.

Conclusion

This case highlights that Pearson syndrome is a rare cause of failure to thrive, anemia and exocrine pancreatic insufficiency. Among these typical symptoms of Pearson syndrome, anemia tends to get less severe as patients grow up; however, the prognosis of the disease is poor. This case illustrates the difficulty of the management of Pearson syndrome. Although a variety of nutritional managements have been tried, the fundamental treatment has yet to be found.

Acknowledgement

We gratefully acknowledge Dr. Hideki Muramatsu, Dr. Yusuke Okuno and Dr. Seiji Kojima, Department of Pediatrics, Nagoya University, Nagoya, Japan for genetic analysis and Dr. Ritsuo Nishiuchi, Department of Pediatrics, Kochi Health Science Center, Kochi, Japan and Takafumi Sakakibara, Department of Pediatrics, Nara Medical University, Kashihara, Japan for the managements of the patient.

Authors' Note

Identifying patient information has been removed to protect patient privacy.

Authorship statement

All authors meet the ICMJE authorship criteria.

Author Contributions

Kitano T and Yoshida S collected case information. Kitano T wrote the manuscript. Kitano T and Yoshida S edited the manuscript.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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