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CLINICAL INSIGHTS

Atypical presentation of Pearson syndrome in an infant with suspected myelodysplastic syndrome

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Abstract

Background Anemia exhibits complex causation mechanisms and genetic heterogeneity. Some cases result in poor outcomes with multisystemic dysfunction, including renal tubulopathy. Early diagnosis is crucial to improve management.

Case–diagnosis/treatment A 21-month-old female patient was admitted with severe anemia. Persistent neutropenia and dysplastic signs suggested myelodysplastic syndrome, but targeted gene panel results were negative. After multiple transfusions, spontaneous hematologic recovery was observed. At 4 years old, she presented failure to thrive, renal Fanconi syndrome, and severe metabolic acidosis. Differential diagnosis included Pearson syndrome (PS), a life-threatening condition associated with mitochondrial DNA (mtDNA), featuring anemia and pancreatic insufficiency. Further analysis revealed a ~ 7.5 kb mtDNA deletion. Until the age of 5, supportive care has been provided, without pancreatic insufficiency.

Conclusions This PS case highlights the importance of genetic testing, even in the absence of typical features. Understanding the nature of mitochondrial disorders enables treatment tailoring and counseling about the prognosis.

Keywords Anemia · Myelodysplastic syndrome · Fanconi syndrome · Mitochondrial DNA · Pearson syndrome

Case report

A Chilean female had no reported genetic disorders in her family, including her older brother. She remained healthy until the age of 21 months when she was admitted to hospital with pallor, fatigue, and decreased appetite. Complete blood cell count indicated non-regenerative severe macrocytic anemia, moderate neutropenia, and normal platelet count. Blood examination revealed anisocytosis, poikilocytes, schistocytes, elliptocytes, and anisochromia. Direct antiglobulin test was negative, and PCR ruled out leukemia-specific translocations. Bone marrow aspiration displayed vacuolated erythroid and myeloid precursors, but no signs of myelodysplasia were observed in the biopsy. Hemoglobin electrophoresis demonstrated a normal distribution. Antibody serologies for common infections and parasitology stool tests yielded negative results. Additionally, transglutaminase and anti-endomysial antibodies were negative. B12 vitamin level was found low and treatment with cobalamin, folic acid, and oral iron was initiated.

At 22 months of age, the white cell count dropped and multiple filgrastim doses were administered. Up to 5 erythrocyte transfusions were required due to refractory anemia. A panel targeted to 364 genes related to leukemia, myelodysplastic syndromes, and bone marrow failure syndromes was considered. The patient experienced spontaneous hematologic recovery, with the last transfusion administered at 2.2 years of age. Subsequent bone marrow aspiration

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revealed dysplastic changes in the ringed sideroblasts and vacuolated erythroid and granulocytic precursors (Fig. 1A). By the age of 3.5 years, the neutrophil count improved partially. Notably, the patient did not experience severe infections throughout this period.

The patient's growth and developmental skills were within the normal range until the age of 3 years. She began to experience failure to thrive, leading to malnutrition at the age of 4. Additionally, bilateral convergent strabismus was observed, prompting an MRI to rule out any brain masses. Around the same time, the results of the targeted panel became available, but no causative variants were reported. Laboratory testing revealed severe decompensated metabolic acidosis with a high anion gap, hyperlactatemia, mild hypokalemia, hypocalcemia, and hypophosphatemia. Urine analysis showed significant glycosuria and increased renal

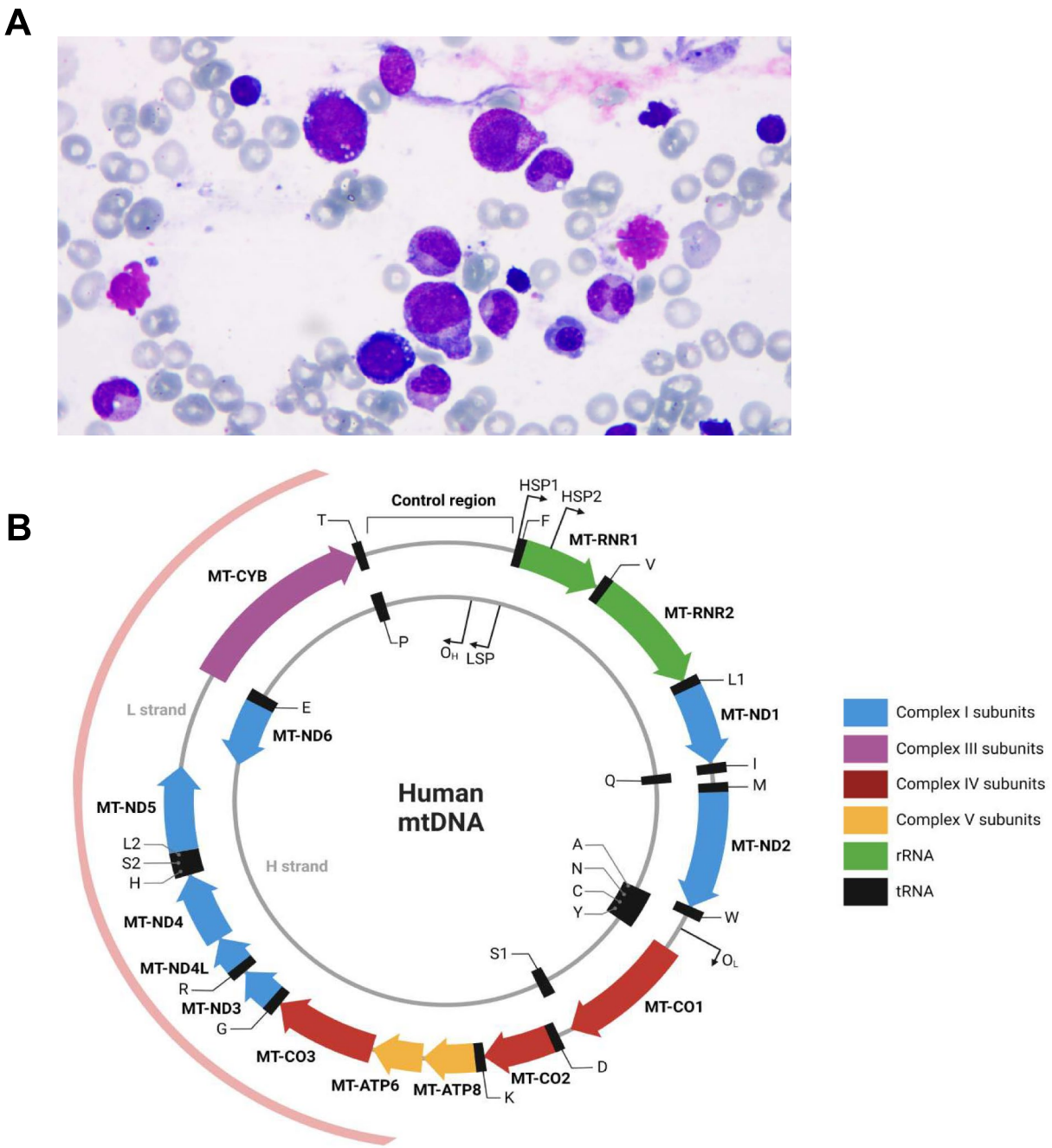

Fig. 1 **A** In the bone marrow, cytoplasmic vacuoles are observed in the granulocytic series. **B** Human mitochondrial DNA and its genes. The location of the ∽7.5 kb deletion identified in the patient is shown as an external pink semi-circle. Created with biorender.com

losses of electrolytes, indicative of Fanconi syndrome. The patient also exhibited reduced levels of parathyroid hormone, suggesting primary hypoparathyroidism. Additional tests, including echocardiogram, electromyogram, fundoscopy, and audiometry, all yielded normal results. Exocrine pancreatic function was assessed, and the fecal elastase was within the normal range.

Considering this evidence, Pearson syndrome (PS) was suspected, despite normal pancreatic function. mtDNA testing was performed, revealing a ∽7500 bp deletion, affecting *ATP6*, *COX3*, *ND3*, *ND4*, *ND5*, *ND6*, *CYB*, and *TP* genes that account for nearly half of the mtDNA (Fig. 1B). Until the patient's last visit at the age of 5 years, she has been closely monitored and received supportive care. No evidence of pancreatic insufficiency has been detected thus far.

Discussion

PS is a rare disease caused by single large-scale mtDNA deletion syndromes (SLSMDs), reported in approximately 100 cases worldwide, with no reported cases in Chile. The global prevalence of childhood-onset mitochondrial disease ranges between 5 and 15 patients per 100,000, but the possibility of delayed or missed diagnoses cannot be excluded [1].

The mitochondrial nature of PS contributes to the variability in the onset of symptoms. While anemia and exocrine pancreatic insufficiency are the most common characteristics, additional features such as failure to thrive, renal Fanconi syndrome, hypotonia, and endocrinopathies have been described. Anemia in PS is typically early onset and refractory to transfusions. Marrow aspiration reveals vacuolization of progenitor cells and ring sideroblasts, without the presence of blasts [2]. Spontaneous hematologic recovery is a known phenomenon in PS.

The prevalence of kidney dysfunction in PS may be underestimated as the most noticeable manifestations typically occur in other organs. However, since cells of the proximal tubule, distal convoluted tubule, and connecting segments are rich in mitochondria, tubular dysfunction is commonly observed in mitochondrial disorders [3]. Patients may present with partial defects, such as isolated or a combination of renal tubular acidosis, aminoaciduria, low molecular weight proteinuria, and non-diabetic glycosuria. Phenotypes associated with kidney dysfunction in PS include Fanconi syndrome, the most severe form of tubulopathy, and reflect a global impairment of proximal tubule cells, leading to decreased reabsorption of various filtered solutes [3].

Identifying children with PS can be challenging due to the variable multisystemic manifestations. While sideroblastic anemia and exocrine pancreatic dysfunction are suggestive findings, they can also be present in other non-mitochondrial syndromes, such as Diamond-Blackfan anemia [1]. Most mitochondrial diseases exhibit evident clinical manifestations in cells with high energy demand. However, these diseases are difficult to diagnose due to the absence of specific features during the first months of life.

The SLSMDs diagnosis is confirmed through genetic testing, which identifies a mtDNA deletion ranging from 1.1 to 14 kb, with a ~ 4.9 kb deletion being the most common [1, 4]. In our patient, a larger deletion was observed, but it overlaps with the common deletion, affecting the region between *ATP6* and *ND5* genes. This region encodes the complexes required for mitochondrial oxidative phosphorylation, as well as tRNA genes. The relationship between a specific mtDNA deletion and the phenotype is still undetermined, and factors such as mitochondrial heteroplasmy, deletion size, and location within the mitochondrial genome are not definitive predictors of disease severity and progression. Furthermore, the regulation of mtDNA gene expression is still poorly understood [1, 5].

There is currently no specific or unique treatment for PS; however, therapies are being developed to address the underlying mitochondrial dysfunction. It is crucial to establish an early and definitive diagnosis in patients to enable personalized management and avoid unnecessary tests or invasive procedures. Symptomatic management is possible in PS. Severe anemia and low white blood cell count can be managed through supportive measures such as blood transfusions and close monitoring. However, certain medications with direct mitochondrial toxicity, such as chloramphenicol, aminoglycosides, valproate, and reverse transcriptase inhibitors, should be avoided.

Despite supportive care, the prognosis for PS patients is generally poor. Approximately half of the patients do not survive beyond 4–5 years of life, with the most common causes of death being persistent metabolic acidosis, sepsis related to neutropenia, or acute hepatic failure [1]. However, for those who survive infancy, there is a possibility of complete recovery of pancreatic and bone marrow function. Unfortunately, there have been no reported cases of kidney function recovery in PS patients to date.

Conclusion

This genetically diagnosed case exhibits phenotypic characteristics consistent with PS rather than the other SLSMDs. Due to the low incidence and potential underdiagnosis of mitochondrial cytopathies, the limited knowledge about these conditions highlights the need of raising awareness to facilitate their early diagnosis.

When encountering severe refractory anemia, lactic acidosis, Fanconi syndrome, or cytoplasmic vacuolization of erythroid precursors in infancy, PS should be considered in the differential diagnosis. DNA testing including

mitochondrial genes is necessary to confirm the diagnosis. Despite the poor prognosis associated with PS, early diagnosis plays a crucial role in improving survival rates. It enables the implementation of multidisciplinary management and strict supportive care, which can help anticipate complications and prevent early death.

Summary

What is new?

- Introduces a novel large mtDNA deletion
- Normal pancreatic function until 5 years
- Absence of severe infections
- Surpassing median survival age, suggestive of a more favorable outcome

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Declarations

Ethical approval Signed informed consent for publication of medical details was obtained from the mother of the patient.

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