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LETTER TO THE EDITOR

Pearson Syndrome: Diagnostic Challenges and a Case of Successful Haploidentical Hematopoietic Stem Cell Transplantation

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To the Editor:

Pearson syndrome (PS), first reported by Howard Pearson et al. in 1979, is a mitochondrial cytopathy. Three overlapping phenotypes include PS, Kearns–Sayre syndrome (KSS), and progressive external ophthalmoplegia [1]. The prevalence is approximately 1 in 1,000,000 [2], with approximately 150 patients described in the literature [3]. Only six successful transplants have been reported, none of which were haploidentical.

A 10-month-old female infant, firstborn of African origin, born prematurely (35 weeks) to a non-consanguineous marriage, birth weight 3.2 kg, presented with a history of progressive pallor from 3 months of age. There were no sibling deaths. Preliminary investigations revealed pancytopenia with hemoglobin 6.9 g/dL, a total leukocyte count of 2.15 × 10^3/μL; a differential count of 5% polymorphs, 92% lymphocytes, 1% eosinophils, and 2% monocytes; a platelet count of 28 × 10^3/μL; and a reticulocyte count of 30 × 10^9/L. The patient had mildly elevated levels of transaminases and normal pancreatic function. Workup for inborn errors of metabolism revealed normoglycemia, normoacidosis, and normal serum ammonia levels. Bone marrow aspiration showed a lack of erythroid cells, significant vacuolations in, erythroid and lymphomonocytoid cells, and significant dysgranulopoiesis. Bone marrow biopsy showed hypocellular marrow (20%–30%) cellularity and significant dysmegakaryopoeisis (shown in Figure 1). Next generation sequencing testing for inherited bone marrow failure genes was negative, and multiplex ligation-dependent probe amplification for mitochondrial DNA revealed pathogenic heteroplasmic deletions in *MTND4*, *MTND5*, *MTND6*, and *MT-CYTB* probes with deletion in 80% of all mitochondrial copies, suggestive of KSS (shown in Figure 2). She had a normal 2D echocardiogram, ophthalmologic screening, hearing, renal ultrasound, and a normal DTPA scan. With no sibling availability and no unrelated donor, the patient was planned for a haploidentical hematopoietic stem cell transplant (HLA typing, 10/12 match—mismatched loci A and DPB1) from the

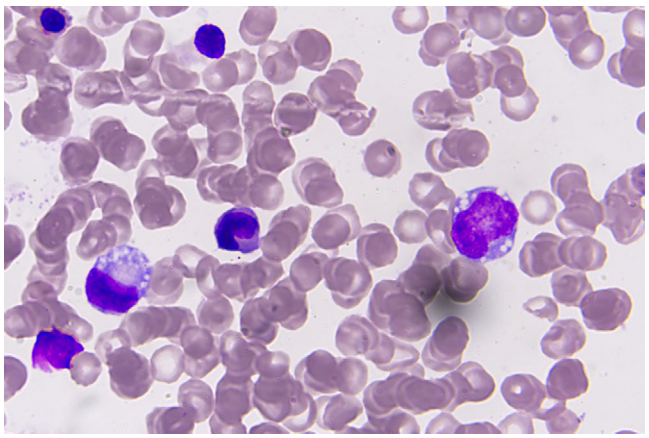

FIGURE 1 | Bone marrow in Pearson syndrome showing vacuolations.

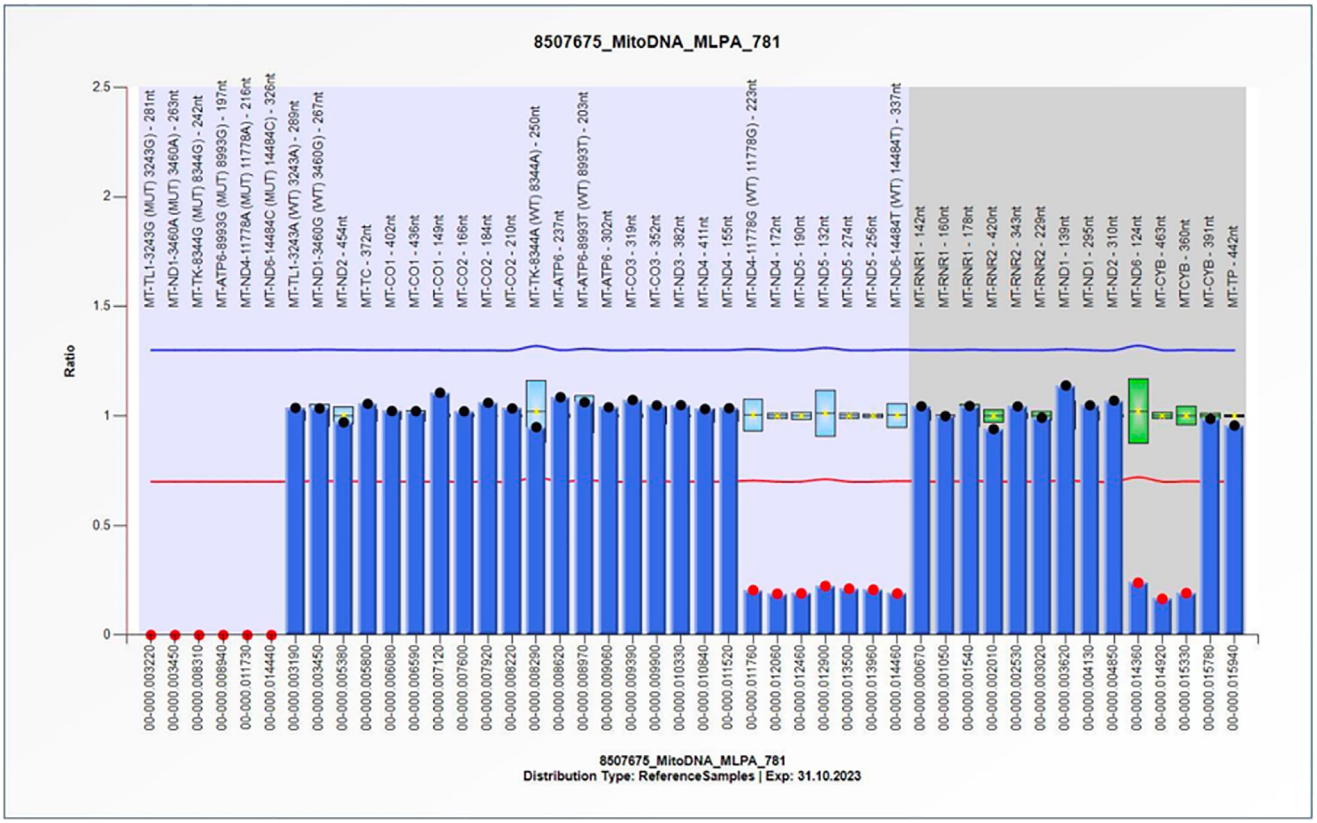

FIGURE 2 | Multiplex ligation-dependent probe amplification for the diagnosis of Pearson syndrome.

mother. She received conditioning with thymoglobulin (1.5 mg/kg × 3 doses Day −6, −5, −4)/fludarabine (40 mg/m^2 Day −5, −4, −3, −2)/thiotepa (5 mg/kg Day −2)/treosulfan (10 mg/m^2 Day −5, −4, −3) with posttransplant cyclophosphamide (50 mg/kg Day +3 and +4) cyclosporine and MMF as GVHD prophylaxis. She received seizure prophylaxis, antiviral, antifungal, and anti-PJP (*Pneumocystis jirovecii*) prophylaxis as per institutional protocol. Peripheral blood stem cells were transfused with a dose of 5.0 million/kg. Her transplant stay went majorly smoothly with some issues such as culture-negative febrile neutropenia, Clostridium difficile toxin-positive diarrhea, and PICC-line-associated thrombosis.

The patient is now 1 year and 4 months old, with around 180 days post-transplant. She has been transfusion-independent and on regular follow-ups with CMV PCR and growth monitoring. She has maintained her full chimerism (100% on day +30, +60, and +90) and is gaining weight. She developed mild skin graft-versus-host disease, managed with topical steroids. She is closely followed up for new manifestations of the disease.

The most common presenting feature of PS is refractory anemia, with the median age of presentation being 5 months [4]. Around 10% of children are born with intrauterine growth retardation; our case had adequate birth weight [5]. Patients with PS show peripheral blood findings of macrocytic or normocytic anemia, neutropenia, and thrombocytopenia in approximately 75%–80% of patients [1]. The typical bone marrow findings of PS include dysplastic features in all cell lineages, vacuolization in myeloid and erythroid precursors, and iron staining revealing ring sideroblasts [6]. Some patients have elevated lactate [2], an elevated ratio of lactate to pyruvate greater than 20 [7], elevated excretion of 3-methylglutaconic acid [8], ketonuria, and elevated alanine. However, none of these abnormalities are specific to PS and can be present in mitochondrial diseases. PS is associated with endocrine or exocrine pancreatic insufficiency in 6% to 63% in studies [9].

The diagnosis is confirmed by mutation analysis of the mitochondrial DNA in peripheral blood, buccal swabs, and/or urinary epithelial cells [1] and is documented in almost all cases [4]. Deletions are common, as in our case the commonly reported genes *MTND4*, *MTND5*, *MTND6*, and *MT-CYTB*. Single mtDNA deletions usually occur as sporadic events, and there are a few reports of mothers with PS. In the largest reported series of 139 cases reported in the literature, only 57 cases had a family history provided [4]. Genetic counseling was done to inform families of the sporadic nature of the disease as well as the rare possibility of maternal transmission. Prenatal testing for subsequent pregnancies, though 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.

Hematopoietic stem cell transplant can correct the hematological manifestations of the disease. Only six transplants have been reported in the literature, with one patient undergoing two transplants. The outcomes reported are that two children died,

two children are alive, and one child progressed to KSS [10–14] Supplemental Table 1.

To the best of our knowledge, this is the seventh transplant reported in the literature for PS and the first case of PS undergoing a haploidentica l transplant.

Consent

The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.

Supplemental Table 1: Reported HSCT of Pearson Syndrome