

MITO 101 –Hematology

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Key points

- Although mitochondrial diseases can cause symptoms in any organ or tissue, as a rule hematological abnormalities are unlikely as the initial presentation¹.
 - The marrow's ability to expand and compensate for functional impairment provides a strong selective mechanism against pathogenic mitochondrial DNA mutations.
 - Pearson Syndrome, a pediatric disorder characterized by a profound and clinically significant anemia, is a notable exception in that it is caused by a high mutant mtDNA load (specifically, a single large-scale mtDNA deletion) in hematopoietic cells².
- While hematologic abnormalities are rarely the primary manifestation of mitochondrial diseases, the selective involvement of the bone marrow in Pearson Syndrome makes it prudent to evaluate marrow function in all patients with mitochondrial diseases.

Well characterized mitochondrial marrow syndromes

- Pearson marrow–pancreas syndrome (PS)²
- Kearns Sayre syndrome (KSS)³
- Mitochondrial Myopathy with Sideroblastic Anemia (MLASA)⁴
- Barth Syndrome (BS)⁵

Aging-related bone marrow diseases

- Some common aging-related disorders of the bone marrow may be the result of somatically acquired alterations in mitochondrial function⁶⁻⁹.
- These largely geriatric disorders are known as the myelodysplastic syndromes (MDS)¹⁰.
 - The hematologic disorder MDS has been associated with mutations and deletions, but not complete loss, of mtDNA, and so should not be confused with mtDNA depletion syndromes, which are also referred to as MDS¹¹

Mechanisms of hematopoietic dysfunction in mitochondrial disease

- Ringed sideroblasts
 - Synthesis of sufficient heme for cellular needs is an essential function of mitochondria in all tissues, but given the vast quantities of hemoglobin required for the production of $\sim 2 \times 10^{11}$ red blood cells (RBCs) in the average adult male DAILY, heme synthesis takes on additional importance during erythropoiesis¹².
 - 70% of all body iron is utilized by the mitochondria of erythroid precursors (erythroblasts) in the production of hemoglobin¹³.
 - The pathognomonic finding of Pearson Syndrome, the ringed sideroblast, results from the accumulation of iron in the mitochondria of erythroblasts¹⁴.
 - When sufficient iron accumulation occurs in erythroblasts to allow detection by light microscopy, the iron-laden mitochondria typically cluster in a ring around the nucleus.
 - Erythroblasts with this characteristic appearance are referred to as "ringed sideroblasts," and an anemia in which ringed sideroblasts are detected is referred to as a "sideroblastic anemia."
- Abnormal remodeling of cardiolipin
 - Cardiolipin is an integral component of the inner mitochondrial membrane.
 - For reasons that are still unclear, defective remodeling of cardiolipin, as seen in Barth syndrome, results in cardioskeletal myopathy, neutropenia, and abnormal mitochondria¹⁵.
- Pyrimidine nucleotide synthesis
 - An enzyme necessary for *de novo* pyrimidine synthesis, dihydroorotate dehydrogenase (DHODH), is located in the inner mitochondrial membrane and utilizes coenzyme Q as its electron acceptor¹⁶.
 - Inhibition of the respiratory chain impairs pyrimidine synthesis and affects DNA replication and repair¹⁷.
 - Impaired pyrimidine synthesis may contribute to the megaloblastic changes that are frequently seen in the marrow of patients with MDS¹⁸.

- While supplementation with exogenous uridine is an attractive therapy for future investigation¹⁹, no data exist to support its routine clinical use.

Molecular bases of mitochondrial defects affecting the bone marrow

- mtDNA single deletions
 - Pearson's marrow pancreas syndrome (pediatric)²
 - Kearns Sayre syndrome (pediatric)²⁰
- mtDNA point mutations
 - tRNA^{leu(CUN)} - Sideroblastic anemia (adult)²¹
- Recessively inherited nuclear defects
 - COX 10 – transfusion dependent macrocytic anemia (pediatric)²²
 - Pseudouridine synthase 1 gene (*PUS1*) – deficient pseudouridylation of mitochondrial tRNA with resultant decreased activities of the mtDNA encoded subunits, resulting in MLASA^{4, 23, 24}
 - Tafazzin (*TAZ* gene) – Barth syndrome (pediatric)^{5, 15}

Clinical investigation

- CBC – megaloblastic anemia, neutropenia, thrombocytopenia, inappropriately low reticulocyte count
 - Also obtain differential, peripheral blood smear, and reticulocyte count
 - Elevated MCV (macrocytosis) would suggest presence of megaloblastic anemia.
 - Reticulocyte count should increase in response to anemia, so look for inadequate increase given the level of the anemia
 - In addition to anemia, patient may have neutropenia, thrombocytopenia, or both.
- Bone marrow aspiration/biopsy – Ring sideroblasts, vacuolization
 - Obtain Wright-Giemsa (or similar) and iron stains of marrow aspirate, H&E of biopsy
 - Stain iron on aspirate, as decalcification of biopsy samples will also remove iron.
 - Prominent cytoplasmic vacuolization of marrow cells seen in Pearson Syndrome².
- Analysis of mtDNA
 - While in most cases mtDNA for diagnosis can be obtained from other tissues, if a primary marrow disorder such as Pearson Syndrome is suspected, it may be necessary to perform these studies on cells obtained during bone marrow aspiration.

Medical Care

- Patients with hematologic manifestations of mitochondrial disease often need transfusions to manage anemia, and many become dependent on transfusions.
- Although there have been concerns recently regarding the overuse of erythropoietin in some patient populations, its use in MDS remains justified²⁵.
- Evaluate fever promptly.
 - In the setting of febrile neutropenia, treatment with broad-spectrum antibiotics must be initiated promptly, preferably within six hours²⁶.
 - Granulocyte colony-stimulating factor (G-CSF) has been used in some patients to prevent or treat severe neutropenia²⁷.
- While allogeneic bone marrow transplantation (BMT) has been effective in the treatment of a number of inherited bone marrow disorders, the multisystem manifestations of the mitochondrial disorders makes BMT, as a treatment for hematologic disease, less appealing in most patients.
 - One notable use for BMT is in treatment of MNGIE (mitochondrial neurogastrointestinal encephalomyopathy), where partial allogeneic transplantation has been shown to improve the biochemical abnormalities in the blood of these patients²⁸.
- Some patients may benefit from an indwelling venous catheter to facilitate frequent transfusions or infusions.

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