Bone marrow failure

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The term bone marrow failure refers to any condition in which the bone marrow fails to fulfil its primary function which results in decreased production of one or more blood cell types. These conditions could be inherited/ congenital or acquired. While malignancies can effectively be a cause of secondary bone marrow failure, the term generally is usually used to describe non-malignant disorders whether or not they have the potential for malignant transformation. There has been more effort in the past decades to recognize and characterize many of the inherited marrow failure syndromes as they may sometimes present with a leukemia for the first time, but still, the treatment and outcome is different from a de-novo leukemia. The term also applies to disorders mainly affecting the myeloid cell line. In other words, conditions as severe combined immunodeficiency where patients have severe lymphopenia are not bone marrow failure syndromes.

The term used to describe acquired bone marrow failure is aplastic anemia. In other words, aplastic anemia is bone marrow failure where no inherited cause. Potential causes include radiation exposure, chemicals and drugs (alcohol, benzene, antipsychotics, anti-epileptics, etc.), viruses (CMV, HIV, HHV6, EBV, seronegative hepatitis and others) or it could be idiopathic. Aplastic anemia can be associated with other conditions such as autoimmune disorders, malignancies, MDS or paroxysmal nocturnal hemoglobinuria. The theory is that in most cases of aplastic anemia (with exceptions as the ones caused by irradiation) the rise of this disorder is triggered by an abnormal immune response to an infection or an event leading to the generation of anti-stem cell cytotoxic T lymphocytes. This is supported by the association with autoimmune, other immune system disorders and rheumatologic disorders.

This means aplastic anemia has under its umbrella a multitude of heterogenous disorders. Aplastic anemia is subdivided into severe and non-severe. To qualify as severe, we need 2 of the following three criteria: ANC less than 500 per cubic millimeter, platelet count less than 20,000 per cubic millimeter and a corrected retic count of less than 1%. Also, the bone marrow needs to demonstrate less than 25% cellularity on biopsy. To diagnose aplastic anemia, in addition to meeting the criteria above, we need to show that this hematologic picture is not secondary to other entities. Studies to do so include: Cytogenetics (from the bone marrow, to rule out MDS), chromosome breakage studies (to rule out Fanconi anemia), telomere length studies (rule out dyskeratosis congentia) and flow cytometry (rule out PNH). Complete workup should include viral serologies or PCRs and evaluation of renal and hepatic function in addition to thyroid function studies (severe hypothyroidism can be a cause of pancytopenia).

Once the diagnosis is established, the treatment will depend on the availability of a suitable sibling donor. What follows applies to severe aplastic anemia. Management of non- severe aplastic anemia is less standardized and depends on many individualized factors. If a matched sibling donor is available, the first line of therapy will be stem cell transplant. More recent literature supports this approach with matched unrelated donors given the advancements in transplant methods over the recent years. If no such donor is available, the treatment of choice is immune suppression with anti-T cell therapy since the process is mostly T cell driven. The main drugs used for this purpose are anti-thymocyte globulin (ATG) and cyclosporine. Immune suppression is every effective in most patients in the short term but up to a third of patients relapse after discontinuation of therapy and may need to go back on immune suppression or proceed with stem cell transplant. Immune suppression gives better outcomes on the short term since its less toxic than a stem cell transplant but has a higher failure rate in the long term. Transplant has a better long-term outcome but more toxicity and early mortality.

A description of aplastic anemia is never complete without the discussion of Paroxysmal nocturnal hemoglobinuria, PNH, a rare but associated disorder that can sometimes make the diagnosis of aplastic anemia more challenging. PNH is an acquired clonal stem cell disorder. This means a specific cell clone that may naturally represent a very small fraction of the stem cells, disproportionately expands to form a significant fraction or a majority. This clone is characterized by the lack of a surface protein, PIG-A. this clone is characterized by sensitivity to the action of the complement system. So, PIG-A deficient RBCs can hemolyze very easily giving this disorder its characteristic presentation (hemolysis, hematuria, and

thrombosis). Thrombosis is the leading case of death in this disorder. In the past, diagnosis was done using the ham's test, but nowadays it's done with flow cytometry for GPI anchored proteins CD55/59. PNH may sometimes present as and can be mixed with aplastic anemia and may be responsive to immune suppressive therapy but this won't address the underlying problem. The only cure is stem cell transplant which was the first line of therapy until recently when eculizumab, a monoclonal antibody (anti-C5) became available. Eculizumab improves the clinical picture of the disease by blocking the complement pathway abolishing hemolysis and decreasing the risk of thrombosis. It doesn't cure the disease, however.

In contrast, congenital or inherited bone marrow syndromes don't usually present with cytopenias upfront, they are usually associated with other congenital anomalies and most of them carry an increased risk for future cancers. In fact, the presenting feature sometimes be the malignancy.

The classical example is Fanconi's anemia (differentiate from renal Fanconi, an unrelated entity) where patients usually have normal counts initially and progress to pancytopenia over the years. Macrocytosis usually precedes the development of cytopenias. The most common associated physical features in these individuals include café a lait spots, short stature, absent or abnormal thumbs, other skeletal anomalies, genital anomalies and renal anomalies. These anomalies may or may not be present so are not needed for the diagnosis of Fanconi's anemia. Patients are predisposed to many cancers, commonly AML, squamous cell carcinoma, brain tumors, Wilms tumor and others. The main culprit is a DNA repair defect, particularly increased chromosome breakage so diagnosis relies on chromosome breakage studies in addition to specific mutation analysis. Detection of the specific mutation is not always possible since many mutations have been implicated (FANC-A mutation in 60% of cases). Different mutations explain different spectrums and presentations of this disease. Treatment relies on supportive therapy as long as possible. If severe refractory anemia or leukemia develops, referral to stem cell transplantation is warranted. Supportive measures include transfusions, myeloid growth factors, androgen therapy (slows count decline) and monitoring and treatment of solid tumors that may develop. Risk of malignancy in these patients is about 1000 times higher than the general population. By adulthood, about a third of patients develop cancer. The risk of malignancy increases after receiving a stem cell transplant.

Dyskeratosis congentia is another DNA repair defect that results in ectodermal dysplasia. The classical triad is reticulated hyperpigmented skin, dystrophic nails and mucous membrane leukoplakia. About half the patients develop aplastic anemia by their third decade of life. High risk for solid organ cancers and leukemias. Typical solid tumors include those of the head and neck area, skin, pancreas and GI tract. Associated anomalies include dental anomalies, microcephaly, deafness, cognitive impairment, hypogonadism, ataxia, hair loss and early greying of hair. It can follow multiple modes of inheritance depending on the mutation involved (most common mutation involves the gene DKC1 and is inherited in an X-Linked recessive pattern). The hallmark of this disorder is short telomeres, so diagnosis relies on telomere length studies in addition to clinical features and family history. Gene testing can be helpful if the mutation is among the identified ones. Treatment is initially supportive and androgen therapy may be considered. Stem cell transplant is the curative option for the hematologic component of this disorder.

Diamond Blackfan anemia is a disorder the hallmark of which is pure red cell aplasia. Macrocytic anemia presents before the age of 1 year (required for diagnosis) along with reticulocytopenia and hypoplasia of erythroid precursors in the bone marrow. Diagnosis is supported by family history and isolation of a specific mutation in addition to the presence of associated anomalies such as glaucoma, bicolored hair, cardiac anomalies, genitourinary anomalies or upper extremity anomalies (triphalangeal thumb). It's inherited in an autosomal dominant pattern and caused by mutations in ribosomal proteins. The anemia is usually responsive to steroid therapy but some patients are steroid refractory. For these patients, chronic transfusion is an alternative. About a quarter of patients eventually self-limit. But for the rest, anemia may be persistent, and they may develop complications of chronic transfusion. Stem cell transplant is a recommended option for those with a suitable sibling donor. The most common cancers associated with DBA are MDS/AML and osteosarcoma, but others also may develop. DBA needs to be differentiated from transient erythroblastopenia of childhood that is an acquired self-limiting condition were no mutations or other congenital anomalies are identified and does not carry a higher risk for malignancies. DBA tends to have elevated levels of erythrocyte adenosine deaminase while transient

erythroblastopenia of childhood does not and is much more likely to be associated with macrocytosis and elevated fetal hemoglobin levels.

Pearson Syndrome presents with refractory sideroblastic anemia by the age of 6 months in addition to exocrine pancreatic insufficiency and mild anemia and thrombocytopenia. It's a typically severe clinical entity where children pass away in early childhood usually due to refractory acidosis, liver/ renal failure and sepsis. It's a mitochondrial disease so its characterized by a maternal inheritance pattern.

Shawchman-Diamond syndrome, congenital Amegakaryocytic thrombocytopenia and TAR syndrome are covered in the platelet/ white blood cell section.