Bone marrow and bone marrow failure

See the related separate Aplastic anaemia article.

What is bone marrow?

Bone marrow consists of a matrix of sinusoids lined with epithelial cells interspersed with islands of erythropoietic cells encapsulated by reticulin cells. The bone marrow is composed of red marrow and inactive adipose tissue (yellow marrow) in about equal quantity.

Bone marrow is mainly found in the pelvis, ribs and ends of the long bones of the axial skeleton. At birth, 100% of marrow is of the active red type, and this is gradually replaced by adipose tissue as an individual ages.

Some erythropoietic cells are stem cells. Pluripotent stem cells are able both to renew themselves and to differentiate into various cell types, depending upon the growth factors acting upon them:[1]

- They first differentiate into either lymphoid stem cells or myeloid stem cells.
- Lymphoid stem cells can only develop into B, T or NK lymphocytes.
- Myeloid stem cells undergo a series of stages as progenitor and precursor cells to form erythrocytes, platelets (via megakaryocytes), basophils, polymorphonuclear leukocytes, monocytes/macrophages and eosinophils.

The differentiation process is extremely complex and involves haematopoietic growth factors (HGFs) in regulating production of blood cells. There are many HGFs including erythropoietin, thrombopoietin, granulocyte colony-stimulating factor, macrophage colony-stimulating factor, interleukins and stem cell factor. Recombinant HGFs are used in a number of treatment settings.

Bone marrow failure[2] [3]

Bone marrow failure can affect red blood cells (RBCs), white blood cells (WBCs) and platelets. Single line deficiencies or pancytopenia may occur. Broadly speaking, it can be divided into two categories, inherited or acquired. These underlying causes can result in damage or defects of haemopoietic cells. Causes include:

- **Inherited**, due to inherited or spontaneous gene mutations - eg:
  - Fanconi's anaemia.
  - Diamond-Blackfan anaemia.
  - Dyskeratosis congenita.
  - Shwachman-Diamond syndrome.
  - Congenital amegakaryocytic thrombocytopenia.
  - Reticular dysgenesis.
- **Acquired**:
  - Autoimmunity (as in most cases of aplastic anaemia).
  - Antineoplastic agents (chemotherapy), and other pharmacological agents (eg, steroids, NSAIDs, allopurinol, anti-thyroid medication, chloramphenicol, gold) and poisons (eg, benzene).
  - Malignancy causing bone marrow infiltration - eg, lymphoma, multiple myeloma, carcinoma, hairy cell leukaemia.
  - Myelodysplasia.
  - Ionising radiation (including therapeutic radiotherapy).
  - Viruses (hepatitis B virus, Epstein-Barr virus, parvovirus B19).
  - Paroxysmal nocturnal haemoglobinuria (PNH).
  - Vitamin B12 or folate deficiency causing maturation defects of the cells.

How common is bone marrow failure? (Epidemiology)[3]

Inherited causes account for 10-15% of cases of bone marrow failure, but for 30% of cases presenting in children. It can occur at any age, with a peak for inherited syndromes in pre-school children.

Acquired causes are more common in older adults. Inherited bone marrow failure syndromes are rare - Fanconi's anaemia is the most common with an incidence of 1-5 in a million, although it is much more common in certain populations. The annual incidences of paroxysmal nocturnal haemoglobinuria and myelodysplastic syndrome are estimated to be 0.13 and 7 per 100,000 population per year respectively.[4] The incidence of aplastic anaemia is 2-3 per million per year in Europe, although it is higher in East Asia.[5]

Bone marrow failure is also a frequent iatrogenic side-effect of radiotherapy and chemotherapy.

Those with inherited bone marrow failure syndromes have an increased risk of future malignancy, particularly acute myeloid leukaemia and myelodysplastic syndrome as well as some solid tumours.[2] [6]

Symptoms of bone marrow failure (presentation)

Whatever the cause, the patient presents with signs and symptoms of:

- Anaemia - tiredness, weakness, pallor, breathlessness, tachycardia.
- Neutropenia - recurrent or severe bacterial infections.
- Thrombocytopenia - easy bruising, petechiae, bleeding from the nose and/or gums.

The inherited syndromes may have other clinical features typical of the condition, such as skin or skeletal abnormalities. Other specific acquired causes may have specific clinical findings such as enlarged liver and/or spleen and/or lymphadenopathy.

Differential diagnosis

- Systemic lupus erythematosus and hypersplenism - can cause pancytopenia with a normal bone marrow.
- Other causes of anaemia.

Diagnosing bone marrow failure (investigations) [3] [7]

The starting point is FBC, reticulocyte count and blood film; from there investigation will be guided by findings from history, examination and that report. Further investigation will be in the hands of the specialist.

- FBC:
    - Normocytic, normochromic anaemia with low reticulocyte count in aplastic anaemia and myelodysplasia.
    - WBC count and differential.
    - Thrombocytopenia.
    - Blood film examination findings may include macrocytosis and anisopoikilocytosis. Neutrophils may show toxic granulation. There may be dysplastic neutrophils, abnormal platelets, blasts or other abnormal cells, such as hairy cells.
- Further blood tests may include U&E, LFT, CRP, immunoglobulins, ferritin, B12, fibrinogen, folate, virus serology, and serum erythropoietin (EPO).
- Bone marrow aspiration and biopsy to look for myelodysplastic morphology or clonal cytogenic abnormalities.
- Imaging - ultrasound may be used to look for liver, spleen or lymph node enlargement suggestive of malignancy. Radionucleotide scans, MRI or positron-emission tomography (PET) scans are sometimes used to look at bone marrow activity.
- Flow cytometry should be performed according to established guidelines to screen patients with suspected haematopoietic malignancies, including myelodysplastic syndrome. Flow cytometry also for GPI-anchored proteins to detect PNH clone.

- Diagnosis of Fanconi's anaemia depends upon the detection of chromosomal aberrations (breaks, rearrangements, radials, exchanges) in cells after culture with a DNA interstrand cross-linking agent such as diepoxybutane (DEB) or mitomycin C (MMC).[8]
- Gene sequencing may be required to confirm inherited conditions. The choice to postpone treatment while awaiting genetic testing can result in significant delay in definitive therapies in patients with severe pancytopenia. Additionally, the misdiagnosis of inherited bone marrow failure can expose patients to ineffective, expensive and toxic treatment regimes. A machine learning model correctly predicted inherited or likely immune aetiology in 79% and 92% of cases, respectively.[9]

Management of bone marrow failure[3] [10]

The management will depend on the underlying cause and the degree of bone marrow failure. It will be undertaken by specialist haematologists.

Transplants

Definitive treatment for inherited marrow failure, and for some acquired causes, is with bone marrow transplant. Improvements in outcome have been in part due to better HLA tissue typing to identify better matched donors. Haematopoietic stem cell transplantation using fludarabine-based protocols has significantly improved outcomes, particularly in patients with Fanconi's anaemia.[11]

Transfusions

Transfusions of blood or specific blood components such as platelets may be required.

Pharmacological

- Febrile neutropenia is a medical emergency and aggressive antibiotic treatment may be required. Some may require prophylactic antibiotics/antifungals/antivirals.
- Immunosuppression: where transplant is not an option, intensive immunosuppressive therapy is used. A gold standard for severe aplastic anaemia, ineligible for allogenic transplant, is antithymocyte globulin (ATG) and ciclosporin.[5]

- Androgens are used in some inherited syndromes such as Fanconi's anaemia and dyskeratosis congenita.
- Corticosteroids have a role in some inherited syndromes or in combination with other immunosuppressive agents.

Gene cell therapy may be an option for treatment of inherited bone marrow syndromes in the future.

Further reading

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