Aplastic anaemia is a rare and heterogeneous disorder. It is defined as pancytopenia with a hypocellular bone marrow in the absence of an abnormal infiltrate or marrow fibrosis. To diagnose aplastic anaemia there must be at least two of the following:

- Haemoglobin concentration below 100 g/L.
- Platelet count below 50 x 10^9/L.
- Neutrophil count below 1.5 x 10^9/L.

**Epidemiology**

- The incidence is 2-3 per million per year in Europe, but higher in East Asia.
- There is a biphasic distribution, with peaks at 10-25 years and over 60 years.
- Certain histocompatibility locus specificities, especially HLA DR2, are associated with an underlying predisposition to acquired aplastic anaemia.

**Causes**

The majority (70-80%) of cases are idiopathic. The remainder mainly consist of inherited bone marrow failure syndromes. Environmental triggers include drugs, viruses and toxins.

- Congenital or inherited - eg, Fanconi’s anaemia, Diamond-Blackfan syndrome: congenital aplastic anaemia is very rare, the most common type being Fanconi’s anaemia (inherited as an autosomal recessive disorder).
- Acquired:
  - Idiopathic.
  - Infection: 5-10% of severe acquired cases are preceded by seronegative hepatitis.
  - Epstein-Barr virus, HIV, parvovirus and mycobacteria.
  - Toxic exposure: radiation, chemicals (eg, benzene).
  - Drugs - eg, chloramphenicol, sulfonamides, gold, penicillamine, indometacin, diclofenac, naproxen, piroxicam, phenytoin, carbamazepine, carbimazole, thiouracil, dosulepin, phenothiazines, chlorpropamide, chloroquine.
  - Transfusional graft-versus-host disease.
  - Pregnancy.
  - Sickle cell anaemia: aplastic crisis associated with parvovirus infection.
  - Genetic factors influencing the capacity for bone marrow to regenerate have been identified.

**Presentation**

- A family history of cytopenias should raise suspicion of an inherited disorder even when no physical abnormalities are present.
- In children and young adults, short stature, café au lait spots and skeletal anomalies suggest the possibility of a congenital form of aplastic anaemia.
- A preceding history of jaundice, usually 2-3 months before, may indicate a post-hepatitic aplastic anaemia.
- The history should include drug exposure and occupation (exposure to chemicals or pesticides).
- Aplastic anaemia can present abruptly over, or insidiously over, weeks to months. Clinical manifestations are proportional to the peripheral-blood cytopenias and include:
  - Patients with aplastic anaemia most commonly present with symptoms of anaemia (pallor, headache, palpitations, dyspnoea, fatigue, or ankle oedema) and thrombocytopenia (skin or mucosal haemorrhage, visual disturbance due to retinal haemorrhage, petechial rashes).
  - Infection - a less common presentation.
  - There is no lymphadenopathy or hepatosplenomegaly (in the absence of infection).

**Differential diagnosis**

- **Hypersplenism.**
- **Hypocellular myelodysplasia, acute myeloid leukaemia.**
- **Hypocellular acute lymphoblastic leukaemia.**
- **Hairy cell leukaemia.**
- **Lymphoma.**
- **Mycobacterial infections.**
- **Anorexia nervosa** or prolonged starvation.
- **Myeloma.**
- **Systemic lupus erythematosus.**

**Investigations**

- FBC, reticulocyte count, blood film.
- HbF estimation in children.
- Bone marrow aspirate and trephine biopsy, including cytogenetics.
- Peripheral blood cytogenetics to exclude Fanconi's anaemia if under 35 years old.
- Flow cytometry has to a large extent replaced Ham's test to exclude paroxysmal nocturnal haemoglobinuria (PNH) clones (50% of patients with aplastic anaemia have small PNH clones).
- Ham's test was used for the diagnosis of PNH. Red blood cells are added to a mild acid. The test is positive (increased red cell fragility) in PNH. The test is rarely used now because of low sensitivity and specificity.
- Urine haemosiderin if Ham's test is positive or there is phosphatidylinositol glycan-anchored protein deficiency.
- Vitamin B12 and folate.
- LFTs.
- Viral studies: hepatitis A, B and C, Epstein-Barr virus, cytomegalovirus (CMV).
- Antinuclear antibody and anti-dsDNA.
- CXR: to exclude infection.
- Abdominal ultrasound scan: an enlarged spleen and/or enlarged lymph nodes raise the possibility of a malignant haematological disorder as the cause of the pancytopenia. In younger patients, abnormal or anatomically displaced kidneys are features of Fanconi's anaemia

**Associated diseases**

There is high incidence of concomitant myelodysplastic syndrome and paroxysmal nocturnal haemoglobinuria.

**Classification of acquired aplastic anaemia**

- A wide range of disease activity from very mild to severe.
- The risk of morbidity and mortality from aplastic anaemia correlates better with the severity of the cytopenias than with bone marrow cellularity.
- Acquired aplastic anaemia is classified as non-severe, severe, or very severe on the basis of the degree of peripheral-blood pancytopenia:
  - **Non-severe:**
    - Hypocellular bone marrow but the cytopenias do not meet the criteria for severe disease.
  - **Severe:**
    - Bone marrow cellularity <25%, or 25-50% with <30% residual haemopoietic cells.
    - Two out of three of the following:
      - Neutrophils <0.5 x 10^9/L
      - Platelets <20 x 10^9/L
      - Reticulocytes <20 x 10^9/L
  - **Very severe:**
    - As for severe but neutrophils <0.2 x 10^9/L.

**Management**

The course of non-severe aplastic anaemia is variable. The majority of cases have a relatively indolent and mild course requiring no treatment. However, in one study 18.8% of patients with non-severe disease progressed to severe disease.

- Treatment should be based on the degree of cytopenia, not the marrow cellularity. Patients with asymptomatic cytopenias probably need no treatment.
- Indications for haemopoietic stem cell transplant (HSCT):
  - HLA identical sibling donor: severe aplastic anaemia in young and adult patients who have a matched sibling donor.
  - Unrelated donor: severe aplastic anaemia after failure to respond to one course of immunosuppressive therapy.
  - Alternative donor using either cord blood, a haploidentical family donor or a 9/10-matched unrelated donor may be considered, among other treatment options, after failure to respond to immunosuppressive therapy and in the absence of a matched sibling donor and a suitably matched unrelated donor.
  - Syngeneic donor (identical twin): in the rare situation where there is a syngeneic donor available, HSCT should be considered in all patients regardless of age.

- Immunosuppressive therapy is recommended first-line therapy for:
  - Non-severe aplastic anaemia requiring treatment.
  - Severe or very severe aplastic anaemia patients who lack a matched sibling donor; and
  - Severe or very severe aplastic anaemia patients aged over 35-50 years.

The first-line immunosuppressive therapy is horse antithymocyte globulin (ATG) combined with ciclosporin. Other agents such as alemtuzumab are also used.

**Supportive care**

- Blood transfusions should be given to improve quality of life. The threshold haemoglobin concentration should be individualised according to comorbidities. Phenotype (Rh and Kell) matched blood should be considered to reduce the risk of alloimmunisation.
Prophylactic platelet transfusions should be given to stable aplastic anaemia patients receiving active treatment. A threshold pre-transfusion platelet count of 10 x 10^9/L should be used. In patients judged to have additional risk factors for bleeding, such as fever or sepsis, a higher prophylactic transfusion threshold of 20 x 10^9/L is recommended. Routine prophylactic platelet transfusions are not recommended for stable aplastic anaemia patients not on active treatment.

Prior to administration of ATG, a daily threshold (pre-transfusion) platelet count of 20 x 10^9/L should be used for the duration of the ATG course.

All patients undergoing treatment with immunosuppressive therapy (ATG or alemtuzumab) and those undergoing haemopoietic stem cell transplantation (HSCT) should receive irradiated blood products.

The need for iron chelation therapy should be decided on an individual patient basis. Patients with iron overload after successful HSCT should undergo venesection.

Aplastic anaemia patients who are severely neutropenic should be given prophylactic antibiotics and antifungal therapy according to local policies.

Aplastic anaemia patients receiving immunosuppressive therapy should also receive prophylactic antiviral agents, although routine prophylaxis against *Pneumocystis jirovecii* is not necessary.

Complications

- The major causes of morbidity and mortality from aplastic anaemia include infection and bleeding.
- Complications of bone marrow transplantation - eg, graft-versus-host disease, graft failure.
- Complications of immunosuppressive therapy.
- Paroxysmal nocturnal haemoglobinuria, acute myeloid leukaemia and myelodysplastic syndrome may arise in patients with aplastic anaemia.

Prognosis

- Aplastic anaemia has a varied clinical course; some patients have mild symptoms that necessitate little or no therapy, whereas others present with life-threatening pancytopenia representing a medical emergency[7].
- Non-severe aplastic anaemia is seldom life-threatening and in most cases no therapy is necessary.
- The two-year mortality rate with supportive care alone for patients with severe or very severe aplastic anaemia is about 80%; invasive fungal infections and overwhelming bacterial sepsis are the most common causes of death[6].
- Improvements in bone marrow transplantation and immunosuppression have increased the number of long-term survivors of patients with aplastic anaemia.
- One review reported that, in general, elderly patients have an inferior outcome following immunosuppressive therapy and stem cell transplantation[8].

Prevention

If a drug trigger can be identified, the patient should be advised never to take the drug again. If a drug is linked with the development of aplastic anaemia this should be reported through the Yellow Card Scheme. An electronic version is also available online at www.mhra.gov.uk/yellow card.

Further reading & references


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