Aplastic Anemia

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- Aplastic anemia (AA) is a rare disorder characterized by pancytopenia with a markedly hypocellular bone marrow. This disease was first described in 1888 by Paul Ehrlich, who observed that autopsy bone marrow specimens from a young woman who died of severe anemia and neutropenia were extremely hypoplastic.
- Later studies demonstrated that patients with severe AA possessed only a fraction of normal pluripotent stem cell numbers despite normal functional marrow stromal cells and normal or even elevated levels of stimulatory cytokines.

- The incidence of AA ranges from 1 to 5 cases per million people in the general population.
- It occurs predominantly in young adults (20 to 25 years old) and older adults (60 to 65 years old).
- The incidence is threefold higher in developing countries (e.g., Thailand and China) compared with industrialized Western nations (e.g., Europe and USA), a fact that is not explained by differences in drug or radiation exposure.
- A few AA cases occur in the context of a congenital bone marrow failure disorder, such as Fanconi's anemia, Shwachman-Diamond syndrome, and dyskeratosis congenita.
- The most common congenital AA, Fanconi's anemia, is an autosomal recessive disorder arising from mutations in genes encoding DNA repair proteins.

Primary idiopathic acquired aplastic anaemia

- This is a rare disorder in Europe and North America, with 2–4 new cases per million population per annum. The disease is much more common in certain other parts of the world, e.g. east Asia. The basic problem is failure of the pluripotent stem cells because of an autoimmune attack, producing hypoplasia of the bone marrow with a pancytopenia in the blood. The diagnosis rests on exclusion of other causes of secondary aplastic anaemia and rare congenital causes, such as Fanconi's anaemia.

Secondary aplastic anaemia

- That is occur secondary to ecposure to an offending drug or chemical.
- It is important to check the reported side-effects of all drugs taken over the preceding months.
- In some instances, the cytopenia is more selective and affects only one cell line, most often the neutrophils. Frequently, this is an incidental finding, with no ill health. It probably has an immune basis but this is difficult to prove.

Causes of secondary aplastic anaemia

- Drugs:
  - Cytotoxic drugs
  - Antibiotics – chloramphenicol, sulphonamides
  - Antirheumatic agents – penicillamine, gold, phenylbutazone, indometacin
  - Antithyroid drugs – carbimazole, propylthiouracil
  - Anticonvulsants
  - Immunosuppressants – azathioprine
- Chemicals:
  - Benzene, toluene solvent misuse – glue-sniffing
  - Insecticides – chlorinated hydrocarbons (DDT), organophosphates and carbamates
- Radiation
- Viral hepatitis
- Pregnancy
- Paroxysmal nocturnal haemoglobinuria

Pathology

- The known causes of acquired AA are numerous and range from myeloablative radiation exposure to common viruses and medications. Prior bone marrow toxicity from drugs, chemicals (e.g., benzene, cyclic hydrocarbons found in petroleum products, rubber glue, insecticides, chemical dyes), or radiation predisposes to AA because these agents directly injure proliferating and differentiating HSCs by inducing DNA damage.
- In contrast, cytotoxic chemotherapy (especially with alkylating agents) and radiation therapy target all rapidly cycling cells and often induce reversible bone marrow aplasia.
- Despite the many causes of acquired AA, most cases are idiopathic.

- Acquired and congenital AAs appear to be etiologically linked through abnormal telomere maintenance. Telomeres are repeated nucleotide sequences that cap and protect chromosome ends from degradation. Cell division leads to normal telomere erosion;
- when telomeres reach a critically short length, cells cease to proliferate, senesce, and undergo apoptosis, often with accompanying DNA damage and genomic instability. Telomerase enzyme in normal HSCs preserves long telomeres and promotes quiescence and a prolonged cellular lifespan. Patients with autosomal dominant dyskeratosis congenita have mutations in the genes for telomerase complexes, predisposing to premature aging and enhanced marrow failure in the setting of accelerated telomere shortening. One third of patients with acquired AA also have short telomeres, likely due to a combination of genetic, environmental, and epigenetic factors.

- Autoreactive host lymphocytes can destroy normal hematopoiesis in AA. Bone marrow stromal cells and cytokine levels in patients with AA are normal.
- The fact that AA also occurs in diseases of immune dysregulation and after viral infections further suggests an immune-mediated mechanism for the disease. One hypothesis is that drug or viral antigens presented to the immune system trigger cytotoxic T-cell responses that persist and destroy normal stem cells.
- Only 1 in 100,000 patients develops severe AA as an idiosyncratic drug reaction. Whether these individuals have a genetically predisposed sensitivity to common exposures (e.g., nonsteroidal anti-inflammatory drugs, sulfonamides, Epstein-Barr virus) is unknown.

Clinical Presentation

- The clinical onset of AA can be insidious or abrupt. Patients often complain of symptoms related to their cytopenias: weakness, fatigue, dyspnea, or palpitations resulting from anemia; gingival bleeding, epistaxis, petechiae, or purpura caused by low platelet counts; or recurrent bacterial infections caused by low or nonfunctioning neutrophils.
- Results of the physical examination are often normal except in patients with congenital AA, who may have various abnormalities.

Diagnosis

- Patients present with symptoms of bone marrow failure, usually anaemia or bleeding, and less commonly, infections.
- An FBC demonstrates pancytopenia, low reticulocytes and often macrocytosis.
- Bone marrow aspiration and trephine reveal hypocellularity. The severity of aplastic anaemia is graded according to the Camitta criteria

Camitta criteria

Severe AA (SAA)

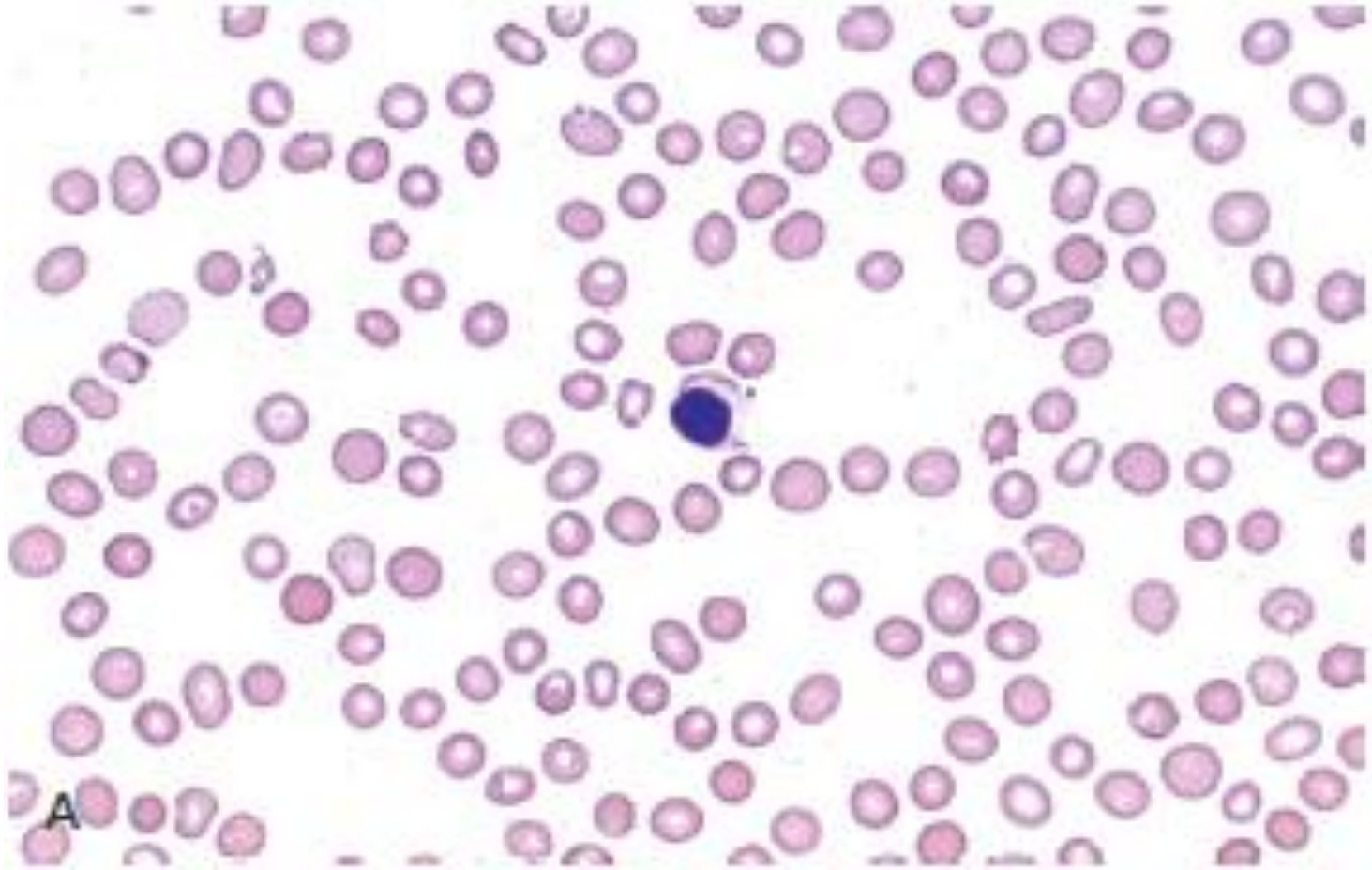
- Marrow cellularity <25% (or 25–50% with <30% residual haematopoietic cells), plus at least two of:
  - Neutrophils $<0.5\times10^9$/L
  - Platelets $<20\times10^9$/L
  - Reticulocyte count $<20\times10^9$/L

Very severe AA (VSAA)

- As for SAA but neutrophils $<0.2\times10^9$/L

Non-severe AA (NSAA)

- AA not fulfilling the criteria for SAA or VSAA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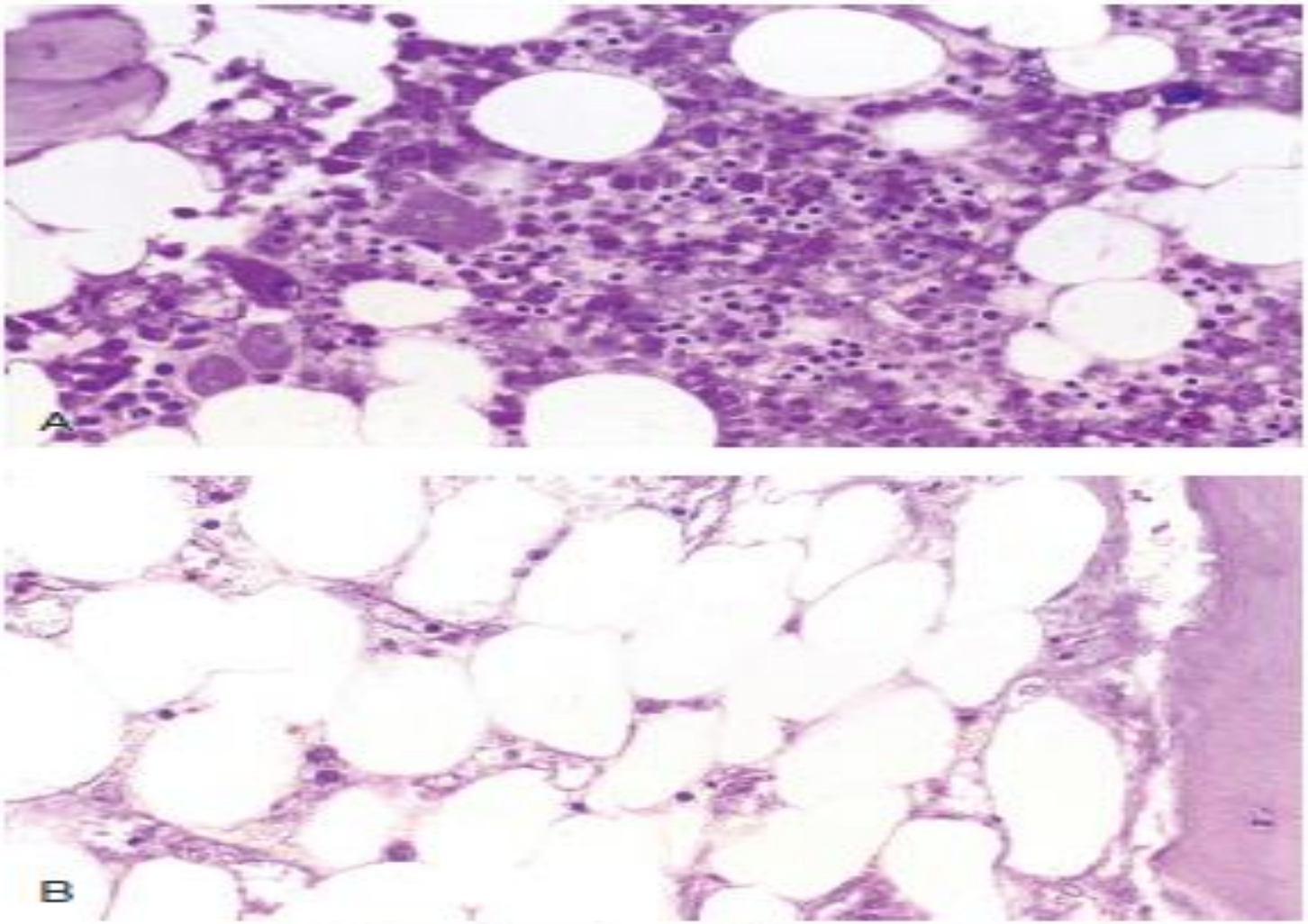
- Diagnostic confirmation of AA requires bone marrow biopsy to confirm hypocellularity and to rule out other marrow processes.
- Normal bone marrow cellularity ranges from 30% to 50% up to age 70 years and is less than 20% after 70 years of age.
- In contrast, bone marrow cellularity in patients with AA usually ranges from 5% to 15%, with increased fat accumulation and few or no hematopoietic cells (primarily plasma cells and lymphocytes)



Comparison of normal bone marrow (**A**) with empty bone marrow characteristic of aplastic anemia (**B**). Notice the differences in overall marrow cellularity. **A,** In the normal marrow biopsy, the fat-to-cell ratio is 50:50. Myeloid cells and megakaryocytes are positive for periodic acid–Schiff (PAS) stain, whereas hemoglobin-containing erythroid precursors are negative. The myeloid-to-erythroid ratio is 2:1. An iron-laden phagocyte *(upper right)* stains rust-brown. A small fragment of bone trabecular is seen (PAS stain, ×100). **B,** In the aplastic marrow biopsy (i.e., aplastic anemia), the fat-to-cell ratio is 95:5. Trilineage hematopoiesis is virtually absent, but rare lymphocytes remain.

- In AA, hematopoietic progenitor and precursor cells are morphologically normal but number less than 1% of normal levels, and they are markedly dysfunctional, with a decreased ability to form differentiated progenitor cell colonies in vitro.

Management

- Treatment of AA is based on the severity of disease. Patients with mild cytopenias can be monitored expectantly. However, patients with severe AA based on peripheral blood cells counts (i.e., neutrophil count <500/μL, platelet count <20,000/μL, anemia with corrected reticulocyte count <1%, and marrow cellularity of 5% to 10%) have a poor median survival of 2 to 6 months without treatment.
- Because most of these patients die of overwhelming infections, supportive care with broadspectrum antibiotics, antifungal agents, and antiviral agents is warranted for those with advanced neutropenia. Red blood cell and platelet transfusions can help patients who are profoundly symptomatic, along with care given to patients eligible for transplantation.

- The curative treatment for patients under 35 years of age with severe idiopathic aplastic anaemia is allogeneic HSCT if there is an available sibling donor. Older patients (35–50) may be candidates if they have no comorbidities. Those with a compatible sibling donor should proceed to transplantation as soon as possible; they have a 75–90% chance of long-term cure.
- Although long-term survival is excellent for patients younger than 30 years transplanted from a sibling donor (75% to 90%), morbidity due to the transplant itself and the management of long-term complications are continuing problems.
- Outcomes for patients older than 40 years or patients without an HLA-matched related donor are poor.

- In older patients and those without a suitable donor, immunosuppressive therapy (IST) with anti-thymocyte globulin (ATG) and ciclosporin is the treatment of choice and gives 5-year survival rates of 75%.
- Unrelated donor allografts are considered for suitable patients who fail immunosuppressive therapy .
- Side effects of ATG include anaphylaxis and serum sickness as a result of foreign antigens in the antisera, but these adverse effects usually are self-limited.

- Patients often relapse, and recurrence of disease may warrant retreatment with ATG, androgens, and newer immunosuppressive agents. Alemtuzumab, a humanized monoclonal antibody directed against the CD52 protein found on lymphocytes and which has efficacy in other autoimmune diseases, has been as effective as rabbit ATG and cyclosporine in relapsed and refractory severe AA.
- Eltrombopag, an oral thrombopoietin receptor agonist (TPO) mimetic drug that stimulates platelet production by binding to MPL receptors on megakaryocytes, is an exciting agent for the treatment of severe AA patients. Almost one half of patients treated with eltrombopag exhibited clinically significant responses in all three hematopoietic lineages, with normalization of bone marrow cellularity and trilineage hematopoiesis.

- Treatment of AA with traditional chemotherapy such as highdose cyclophosphamide usually has proved too toxic.
- Because endogenous cytokine production is usually high in patients with AA, the routine use of growth factors such as G-CSF, EPO, or stem cell factor typically is ineffective. However, in patients with refractory disease, long-term administration of combination cytokines may have some effect in sustaining blood cell counts.

- Non-transplanted patients may relapse and patients who survive initial treatment of AA remain at increased risk for the emergence of other primary hematologic disorders, such as myelodysplasia, leukemia, and paroxysmal nocturnal hemoglobinuria (PNH) for unknown reasons.
- Patients with aplastic anaemia must be followed up long-term.

- THANKS