Abstract

Two patients presented with pancytopenia due to two different causes. The first was a patient of drug-induced pancytopenia who ultimately had good recovery and the second was a patient of viral hepatitis-induced pancytopenia who ultimately succumbed to the disease. The discussion pertains to details of aetiology and pathogenesis, diagnostic work-up, supportive and specific management.

Introduction

Pancytopenia is an important clinical-haematological entity encountered in our day-to-day clinical practice. There are varying trends in its clinical pattern, treatment modalities, and outcome. Our report describes two patients who presented with pancytopenia due to bone marrow failure.

Case report 1

A 44 year old lady presented in the emergency of a private hospital with severe pallor, intermittent high fever, bleeding gums, and oral ulcers. There was history of unsupervised intake of oral methotrexate (2.5 mg) continuously for past 2½ months for the treatment of rheumatoid arthritis. Physical examination revealed severe anaemia, sinus tachycardia (122/min), puffiness of face, and oral temperature 34.8°C. Chest, cardiovascular, and abdominal examinations were normal. Examination of oral cavity revealed whitish patches of mucosal candidiasis and oral mucosal haemorrhages. There were generalised purpuric spots all over the body. There was no sternal tenderness. Emergency haematological investigations revealed: haemoglobin 6.8 g/dl, total leucocyte count 2,100/mm³ (N 46 L48 M6), platelet count 38,000/mm³, reticulocyte count was 3% and bleeding time was 3'5". Biochemical parameters were normal.

The patient was thus diagnosed to be suffering from drug-induced pancytopenia. Bone marrow examination revealed hypoplastic marrow with increased fat spaces and depression of all series of haematopoietic cells. Stoppage of oral methotrexate, improvement in oral hygiene, and supportive care with transfusion of blood and blood components, and judicious use of antimicrobials and antifungals led to the gradual improvement of the patient and ultimately complete recovery of all the cellular components in blood. Bone marrow examination later became normal.

Case report 2

A 19 year old young male presented in the haematology department with progressive pallor, effort intolerance, weight loss, recurrent sore throat, cough, irregular episodes of intermediate to high grade fever, and epistaxis for past 6 months. There was history of jaundice 11 months back which persisted for nearly 2 months. Physical examination revealed severe anaemia, pharyngeal infection, and swollen bleeding gums. There was no evidence of peripheral lymphadenopathy, cutaneous rashes, or purpura. Chest and cardiovascular examinations were non-contributory. Abdominal examination revealed mild hepatomegaly without splenomegaly or ascites. Haematological investigations showed-haemoglobin 5.2 g/dl, total leucocyte count 1100/mm³, platelet count 21,000/mm³. Absolute neutrophil count was 250/µl and reticulocyte count was 0.4%. Biochemical parameters were normal except for raised hepatic transaminases (SGPT 198 IU/L and SGOT 154 IU/L). Viral markers revealed HBsAg and HBeAg positivity. Hepatitis C virus markers were negative.

The patient was thus diagnosed to be suffering from hepatitis B virus associated aplastic anaemia. Bone marrow examination revealed hypoplastic marrow with depression of all components of haematopoietic cells.

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components he succumbed to intracranial bleeding.

Discussion

What is pancytopenia?

Cytopenia is a reduction in the number of each type of peripheral blood cell. A reduction in all 3 types of cellular components in peripheral blood is termed pancytopenia and this involves anaemia, neutropenia, and thrombocytopenia.

Initially, mild impairment in marrow function is inapparent and pancytopenia may become apparent only during times of stress or increased demand (e.g., bleeding or infection). More severe degrees of cytopenias affect the peripheral blood count even in the steady state. Severe pancytopenia is defined as follows:

- Absolute neutrophil count < 500/mm³
- Platelet count < 20,000/mm³
- Corrected reticulocyte count < 1%

What is normal marrow activity?

The normal adult marrow produces about 1.7 x 10¹¹ RBC, 1.0 x 10¹¹ neutrophils, and 2 x 10¹¹ platelets each day and thus it has a tremendous capacity to substantially increase the output of these cells when necessary with the help of growth factors and other cytokines. All peripheral blood cells arise from common progenitor cells known as pluripotent stem cells which have enormous capacity of self renewal that ensures their continuous supply throughout the lifetime of the individual. Whenever necessary, a pluripotent stem cell can begin to differentiate (thus gradually losing its capacity of self renewal) leading to individual clone of differentiated cells. The circumstances that lead to pancytopenia due to bone marrow failure include both defects in the stem cells (i.e., seed) or defects in the stromal cells or micro-environment (i.e., soil). However, quite obviously majority of the defects are in the stem cells.

What is the aetiopathogenesis of pancytopenia?

Aplastic anaemia is one of the most serious causes of pancytopenia. Marrow failure leading to pancytopenia may result from immune-mediated or non-immune mediated damage or suppression of either pluripotent stem cells or committed progenitor cells. Fortunately, serious damage to pluripotent cells are less common because these cells are relatively resistant to the effects of most cytotoxic agents (notable exceptions are radiation and the drug busulphan which mainly affect pluripotent stem cells). Interestingly, most cytotoxic drugs used in the treatment of malignancies exert their major effects on committed progenitor cells. Ablation of these cells result in marrow hypoplasia but recovery is still possible by regeneration from the pluripotent stem-cell compartment.

Pancytopenia from bone marrow failure is also an important feature of acute leukaemias, the later stages of chronic leukaemias, myeloproliferative disorders, and myelodysplasias. The mechanisms of marrow failure in these diseases is unclear but probably involves active suppression of normal haematopoiesis as well as bone marrow infiltration by these abnormal cells.

The different causes of pancytopenia due to bone marrow failure are enumerated in Table I.

Table I : Causes of pancytopenia.

<table>
<thead>
<tr>
<th>Primary</th>
<th>Secondary</th>
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<tbody>
<tr>
<td>Idiopathic</td>
<td>Drugs</td>
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<td>Congenital/Familial</td>
<td>Viral infections</td>
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<td></td>
<td>Mycobacterial infections</td>
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<td></td>
<td>Autoimmune disorders</td>
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<td></td>
<td>Chemicals (benzene, arsenic)</td>
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<td>Cytotoxics</td>
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<td></td>
<td>Malignant infiltration</td>
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<td></td>
<td>Paroxysmal nocturnal haemoglobinuria</td>
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</table>
What are the drugs causing pancytopenia?

Drugs are the commonest, though quite often less well recognised, cause of pancytopenia. Their effects may be predictable (i.e., dose-dependent) or unpredictable (possibly immune mediated or idiosyncracy). Some drugs like chloramphenicol can cause pancytopenia by both the mechanisms. The common list of drugs that may be associated with pancytopenia is enumerated in Table II.

Table II: Drugs causing pancytopenia.

A. Cytotoxics (by bone marrow suppression)
B. Chloramphenicol (by dose related effects)
C. Idiosyncratic response (immune mediated)
   a. NSAIDs
   b. Colchicine
   c. Chloramphenicol
   d. Sulfonamides
   e. Phenothiazines
   f. Thiazides
   g. Anti-thyroid drugs
   h. Anti-epileptics
   i. Anti-diabetics

What are the viral infections causing pancytopenia?

Pancytopenia is commonly caused by Hepatitis B and C viruses, occasionally by cytomegalovirus, Epstein – Barr Virus, HIV, and rarely by Hepatitis A virus. Interestingly, 5% of adult aplastic anaemia and 1% of paediatric aplastic anaemia follow an episode of hepatitis. Hepatitis associated pancytopenia and hypoplastic anaemia has a high mortality rate of 89%. Other rare causes are rubella, influenza, parainfluenza, measles, and mumps.

What are the clinical features of pancytopenia?

The cardinal signs of moderate to severe pancytopenia are anaemia, bleeding, and infection. Red blood corpuscles survive much longer than platelets or neutrophils. Thus, anaemia develops slowly (unless there is significant bleeding) and the typical symptoms of tiredness, fatigue, puffiness of face, oedema, lassitude, and effort intolerance may not be striking in the initial phase.

The platelet count is first to be affected. Mucocutaneous bleeding is typical of thrombocytopenia with petechial haemorrhages in skin and mucous membranes (commonest being epistaxis, haematuria, GI bleeding, menorrhagia, and only rarely intracranial bleeding). The presence of spontaneous bleeding with platelet count <20 x 10^9/l indicates severe marrow failure. Retinal bleeding is common and may lead to blindness, but interestingly its presence correlates more with the presence of anaemia than with thrombocytopenia.

Next to be affected is the myeloid series. Infections usually occur with commensal organisms of the skin or gastrointestinal tract. Early manifestation of neutropenia is often a sore throat or chest or soft tissue infection which typically show incomplete response to antibiotics. Thus a complete blood count should immediately be performed if any such sign of infection develops in a patient taking drugs that are known to induce pancytopenia. Unfortunately, patients with pancytopenia may develop overwhelming septicaemia without any focal sign of infection; the only clinical features being malaise and fever. The commonest offending organisms include coliforms, klebsiella spp, pseudomonas species, and staphylococci.

What investigations must be done?

The basic investigations in a suspected case of pancytopenia include demonstration of the following:

A. Pancytopenia and morphological changes
in peripheral blood

i) RBC changes:
Reticulocytes are markedly reduced or absent.
Stress in erythropoiesis may result in an increase in Haemoglobin F.
Increase in iron overload from multiple transfusions (increased serum iron and transferrin saturation).
Increase in serum folate and vitamin B12 levels excludes other causes of macrocytic anaemia.

ii) WBC changes:
Blast cells may be evident in bone marrow of patients in whom pancytopenia is due to malignant infiltration.
Morphological changes in neutrophils (absent granulation, nuclear abnormalities) suggest preleukemia/myelodysplastic states.

iii) Platelet changes:
Mean volume of platelets (MVP) is normal.

B. Bone marrow examination:
It is indicated in all cases of pancytopenia where the underlying cause is not quite obvious. This is particularly needed to exclude leukaemia or other malignant infiltration. Routine aspiration smears may have to be combined with trephine biopsies as quite often aspiration might yield dry or bloody tap. Bone marrow examination shows diminished cellularity with increased fat cells, reticulin cells, plasma cells, mast cells, and relative increase in lymphocytes. Trephine biopsy better demonstrates increased fat spaces, elements of dyserythropoiesis, megaloblastosis, and nuclear cytoplasmic asynchrony.

What is the approach to management of these patients?
The basic management of patients with pancytopenia involves identification and reversal of the underlying cause and adequate supportive care until normal counts are restored. It must be emphasised that bleeding and infection due to cytopenias is a medical emergency.

A. Supportive care:
This is the most important aspect of management of pancytopenia. Anaemia is corrected by transfusion of packed red cells to maintain haemoglobin (Hb) level above 8-9 gm/dl. It has been observed that retinal haemorrhage is likely to occur below this level. Blood should be administered cautiously to avoid circulatory overload. The previous concept of maintaining Hb below 7 gm/dl to facilitate bone marrow stimulation is no longer valid. Intramuscular injections and teeth brushing should be avoided in thrombocytopenic patients. Active bleeding should be promptly managed with the help of infusion of platelet concentrates in the form of platelet packs from random donors (5.5 x 10¹⁰ platelet/unit) or single donor (3 to 4 x 10¹¹ platelet/unit). It has been observed that each random donor platelet unit increases the platelet count by 10,000/mm³ at 1 hour after infusion. Platelet concentrates prepared from single donors using leukocyte filter is the ideal treatment with the aim to maintain platelet count around 20,000/mm³. Bleeding in thrombocytopenic patients may be decreased by oral administration of e-aminocaproic acid 50 mg/kg every 6 hours.

In patients receiving large volumes of blood/blood component transfusions, irradiation of blood or blood products is ideal to prevent transfusion-induced graft versus host disease (GVHD). Moreover, for multiple transfusions (>50 transfusions) or when there are indications of iron overload
(serum ferritin >500 mg/dl), iron chelation is needed.

The scope of granulocyte transfusions for the management of neutropenia is very limited as well as controversial because of inconsistent rise in leucocyte count, prohibitive cost, unreliability in the homing of infused granulocytes at the sites of infection, possibility of allosensitisation, and GVHD. Its role has been further undermined with the availability of very effective and potent antimicrobials and growth factors. Granulocyte transfusions are now only confined to desperate situations in which proven infection does not respond to appropriate antibiotic therapy.

B. Prevention of infection:
Reverse barrier isolation is one of the most cost-effective measures in the management of pancytopenia. Careful maintenance of skin hygiene, good dental care, and rectal hygiene is absolutely essential. Severe neutropenia by itself is not an indication for hospitalisation as with each admission in the hospital the patient is exposed to the risk of becoming colonised with antibiotic resistant micro organisms. Strict isolation in a sterile environment (equipped with laminar flows) together with measures for skin and gastrointestinal tract decontamination and consumption of sterile food have been shown to reduce the episodes of infection but generally have little impact on the eventual outcome of the underlying disorder.

For the past few years some centres are routinely using prophylactic oral antibiotics, such as ciprofloxacin or norfloxacin to reduce the incidence of gram negative sepsis. Both these drugs are very effective but carry the risk of inducing antibiotic resistance. Scrupulous hand washing by medical and health care personnel routinely before examining any patient of pancytopenia is a simple modality for infection prophylaxis.

What are the other management strategies?
The availability of recombinant growth factors like granulocyte colony stimulating factor (G-CSF) or granulocyte macrophage colony stimulating factor (GM-CSF), and recombinant erythropoietin (rhu EPO) have enabled more specific management with improved outcome of the pancytopenic patients7,8. The exact role of newer cytokines like recombinant human interleukin – 3 (IL-3) and interleukin-6 will gradually become better established in near future. Although at present they are very expensive, yet may ultimately prove to be cost effective, by reducing the cost of antimicrobials as well as transfusion requirements, thus reducing the total cost of supportive care9.

Immunosuppressive therapy with anti lymphocyte globulin (ALG) and/or cyclosporin has proved to be effective in achieving remission in aplastic anaemia10. Bone marrow transplantation (BMT) is a therapeutic option for suitable subsets of younger patients who have HLA matched siblings donors11.

References


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