Clinical Medicine 24 (2024) 100235

Contents lists available at ScienceDirect

Clinical Medicine

journal homepage: https://www.sciencedirect.com/journal/clinical-medicine

Approach to pancytopenia: From blood tests to the bedside

Shaun Chew*, Majeed Kamangar

Croydon Health Services NHS Trust, United Kingdom

ARTICLE INFO

Keywords:
Pancytopenia
Haematology
Anaemia
Thrombocytopenia
Neutropenia

ABSTRACT

Pancytopenia is an uncommon abnormality detected on a full blood count. Features of presentation tend to be non-specific, and are due to impaired functions of the cell lines involved. These can include fatigue, infection and bleeding. However, the aetiology of pancytopenia is extensive. This narrative review aims to provide a minimally invasive diagnostic algorithm for generalist clinicians to approach pancytopenia, including investigations into the underlying aetiology, and when a referral to the haematologist is warranted for further investigations such as bone marrow aspiration and trephine biopsy.

Key Take Home Messages:

- The most common causes of pancytopenia include haematinic deficiency, aplastic anaemia, hypersplenism and haematological malignancies, although sepsis and medication causes should also be considered.
- Rare but life-threatening causes of pancytopenia include haemophagocytosis syndromes, acute promyelocytic leukaemia causing disseminated intravascular coagulopathy, and paroxysmal nocturnal haemoglobinuria.
- Blood film and reticulocyte count should be done as part of the initial workup once pancytopenia is confirmed.
- Blood films with features suspicious for malignancy (such as circulating blast cells with or without Auer rods, leucoerythroblastic film, teardrop cells) should prompt an early haematology referral for further investigations.
- Further workup of pancytopenia should include liver function tests, coagulation screen, haematinics, viral serology, haemolysis screen, autoimmune screen, and ultrasound of the spleen.

Introduction

Pancytopenia is defined as haemoglobin less than 10 g/dL, total white cell count less than 4×10^9/L or absolute neutrophil count less than 1.5×10^9/L, and platelet count less than 100×10^9/L.[1] Features arise due to impaired functions of the cell lines involved, and include fatigue, infection and bleeding.[2] However, pancytopenia is often only identified on blood testing due to its non-specific presentation. Causes of pancytopenia can largely be stratified into disorders of peripheral cell destruction, or impaired bone marrow production. However, most conditions tend to exhibit features of both, as pancytopenia can arise from multiple different pathophysiological mechanisms. Based on the study by Vargas-Carreto *et al*[3] on the pancytopenia aetiology in the adult population categorised by continent, the most common causes include megaloblastic anaemia from vitamin B12 deficiency, aplastic anaemia, hypersplenism, or malignancies including myelodysplastic syndrome and acute myeloid leukaemia. Other noteworthy causes of pancytopenia include infections, medications and autoimmune conditions. Rare but life-threatening conditions such as haemophagocytic lymphohistiocytosis (HLH), disseminated intravascular coagulopathy (DIC) and paroxysmal nocturnal haemoglobinuria (PNH) should also be considered in unwell patients.

Peripheral cell destruction

Pancytopenia can arise due to peripheral cell destruction by the reticuloendothelial system, such as the spleen in hypersplenism. Hypersplenism occurs due to splenomegaly and subsequent splenic sequestration of red blood cells, white blood cells and platelets.[4] This may be driven by portal hypertension secondary to chronic liver disease (of which alcohol, hepatitis B or hepatitis C may be causative).

Less common causes of hypersplenism includes infections (such as malaria, Epstein–Barr virus (EBV), cytomegalovirus, schistosomiasis and leishmaniasis), autoimmune conditions, chronic haemolytic diseases and malignancies.[5] Specific autoimmune conditions such as systemic lupus erythematosus, rheumatoid arthritis and Felty syndrome, and sarcoidosis cause pancytopenia,[6] due either to hypersplenism or autoimmune destruction of cell lines by autoantibodies.

* Corresponding author.
E-mail address: shaun.chew@nhs.net (S. Chew).

https://doi.org/10.1016/j.clinme.2024.100235
Received 13 May 2024; Received in revised form 29 July 2024; Accepted 10 August 2024

Impaired bone marrow production

Impaired bone marrow production can lead to pancytopenia, either due to nutritional deficiency leading to impaired cell line production, bone marrow infiltration by malignancies, or hypocellular bone marrow. This usually presents with low reticulocyte count, indicating poor marrow response.

Nutritional deficiencies such as vitamin B12 deficiency leads to defective DNA synthesis, leading to pancytopenia with megaloblastic anaemia,[7] which can be identified by macrocytosis or hypersegmented neutrophils on blood film,[8] and reticulocyte count is expected to be low. Folate deficiency and medications that inhibit dihydrofolate reductase such as methotrexate and trimethoprim can also lead to megaloblastic anaemia, through a similar mechanism. However, isolated macrocytosis should be interpreted with caution, as reticulocytosis can lead to spurious macrocytosis, except with a high reticulocyte count. Less common nutritional causes of pancytopenia include copper deficiency[9] or zinc excess,[10] and may present with associated neurological deficits.

Malignancies infiltrate and displace normal haematopoietic cell lines, impairing bone marrow production. Common haematological malignancies presenting with pancytopenia include acute myeloid leukaemia, acute promyelocytic leukaemia (APML) and myelodysplastic syndrome. Common blood film morphologies include macrocytosis, the presence of circulating blast cells with or without Auer rods, or a leucoerythroblastic blood film. Presence of granular bilobed blast cells on blood film indicates APML. Additionally, myelofibrosis presents with massive splenomegaly, tear drop cells on blood film and a characteristic inability to aspirate bone marrow ('dry tap'). Further investigations by the haematologist including bone marrow aspiration and trephine biopsy are usually warranted, and may reveal a hypercellular or hypocellular bone marrow. Suspected APML should be referred to the haematologist urgently for treatment with all-trans-retinoic acid and chemotherapy, due to the high risk of DIC. Uncommonly, non-haematological malignancies such as metastatic disease from the thyroid, kidney and prostate can also displace bone marrow haemopoietic cells, leading to pancytopenia.

Aplastic anaemia presents with pancytopenia due to hypocellular bone marrow, with reduced production of all three cell lines.[11] Other differentials to consider, especially in younger patients, include inherited causes of bone marrow failure, such as Fanconi anaemia, Shwachman–Diamond syndrome and dyskeratosis congenita.[12] The presence of splenomegaly or anisocytosis, or lack of mild macrocytosis makes the diagnosis of aplastic anaemia unlikely. Lymphadenopathy would also be unusual in aplastic anaemia, and an infection should be considered instead. Aplastic anaemia is diagnosed by bone marrow aspirate and trephine biopsy.[13]

Iatrogenic causes such as alcohol, radiotherapy and medications can also cause pancytopenia due to bone marrow suppression (see Table 1). Certain infections such as parvovirus B19 and human immunodeficiency virus (HIV) can also impair bone marrow production, thus causing pancytopenia. Genetic conditions such as Gaucher disease, an autosomal-recessive inherited disease that leads to glucocerebrosidase deficiency in lysosomes, can also cause pancytopenia through bone marrow infiltration and hypersplenism.

Table 1
Iatrogenic causes of pancytopenia.

Alcohol and associated alcoholic liver disease
Antibiotics (eg chloramphenicol, trimethoprim, linezolid)
Chemotherapy
Radiotherapy
Immunosuppressants (eg azathioprine, methotrexate)
Anti-epileptic medications (eg carbamazepine, valproate)
Drug interactions (eg allopurinol and azathioprine, methotrexate and trimethoprim)

Life-threatening causes of pancytopenia

Sepsis uncommonly presents with pancytopenia, and aforementioned micro-organisms mentioned should be considered and excluded. However, in pancytopenia-driven sepsis, DIC should be considered if patients present with a petechial rash and bleeding from three or more unrelated sites. These patients will have a raised internationalised ratio (INR) $\geq$ 1.3 on their clotting screen, and blood film will show schistocytes. Probability of DIC can also be calculated by the International Society on Thrombosis and Haemostasis (ISTH) DIC score.

HLH is a rare but life-threatening cause of pancytopenia that can mimic sepsis. It may be familial, or acquired from an infection, autoimmune condition, or malignancy.[14] HLH should be considered in patients with unremitting fevers and hyperferritinaemia $\geq$ 2,000 ng/mL. The probability of HLH can be calculated via the H-score,[15] and a score of $\geq$ 169 would warrant urgent referral to the haematologist and rheumatologist for immunosuppressive treatment.

Lastly, patients presenting with pancytopenia and thrombotic disease should raise suspicion for PNH, which presents similarly to aplastic anaemia. PNH occurs due to deficiency of complement inhibitors CD55 and CD99, leading to complement-mediated red cell destruction.[16] Patients may present with abdominal pain, dysphagia, erectile dysfunction, chronic intravascular haemolysis, haemoglobinuria worse in the morning, renal impairment, and thrombosis in unusual sites like cerebral, splenic and hepatic veins. Presence of PNH clones on flow cytometry excludes hereditary aplastic anaemia.

Approach to pancytopenia

Once pancytopenia has been confirmed on initial full blood count, initial non-invasive investigations should comprise reticulocyte count and blood film. Reticulocyte count is a good surrogate indicator of bone marrow response, where a low reticulocyte count would point towards a disease of impaired marrow production, while a raised reticulocyte count would indicate peripheral destruction.[17] Blood film would also offer insight into cell morphology, and would be helpful for diagnosing haematological malignancies or megaloblastic anaemia. Early referral to haematology is warranted for further imaging and bone marrow biopsy if suspicious features for haematological malignancies are detected.

The patient's history should also be revisited to assess for possible disease aetiologies. This should include assessing for associated symptoms such as fatigue, jaundice, easy bruising or recurrent bleeding, recurrent infections, constitutional symptoms of fever more than 38 °C, drenching night sweats, or unintentional weight loss of more than 10% in the last 6 months. Past medical history including drug or toxin exposure should be elicited, to assess for alcohol or iatrogenic causes of pancytopenia. Travel history may raise suspicion for a tropical infection causing hypersplenism. Family history of genetic conditions should also be checked. A full body examination, including for unusual bruising, petechiae or purpura, and examination of lymph nodes and abdomen for hepatomegaly or splenomegaly should be done. Useful signs for assessing splenomegaly include percussion dullness in Traube's space, and eliciting Castell's sign.[18] An ultrasound should be considered to determine the size of the spleen, which should not be larger than 13 cm. The presence of a massive spleen more than 20 cm should raise suspicion for chronic myeloid leukaemia, myelofibrosis, malaria, schistosomiasis, leishmaniasis or Gaucher disease. Splenomegaly is unlikely in aplastic anaemia, megaloblastic anaemia, and most cases of myelodysplasias.

Based on clinical findings, further workup should be focused on elucidating common disease aetiologies, including liver disease (including liver function tests and clotting screen), viral (including hepatitis B, hepatitis C, EBV, cytomegalovirus, parvovirus B19 and HIV) and parasite infections (including malaria, schistosomiasis and leishmaniasis), haemolytic screen for cell destruction (including haptoglobins and direct antiglobulin testing), autoimmune screen for rheumatic diseases (including erythrocyte sedimentation rate and autoantibody testing),

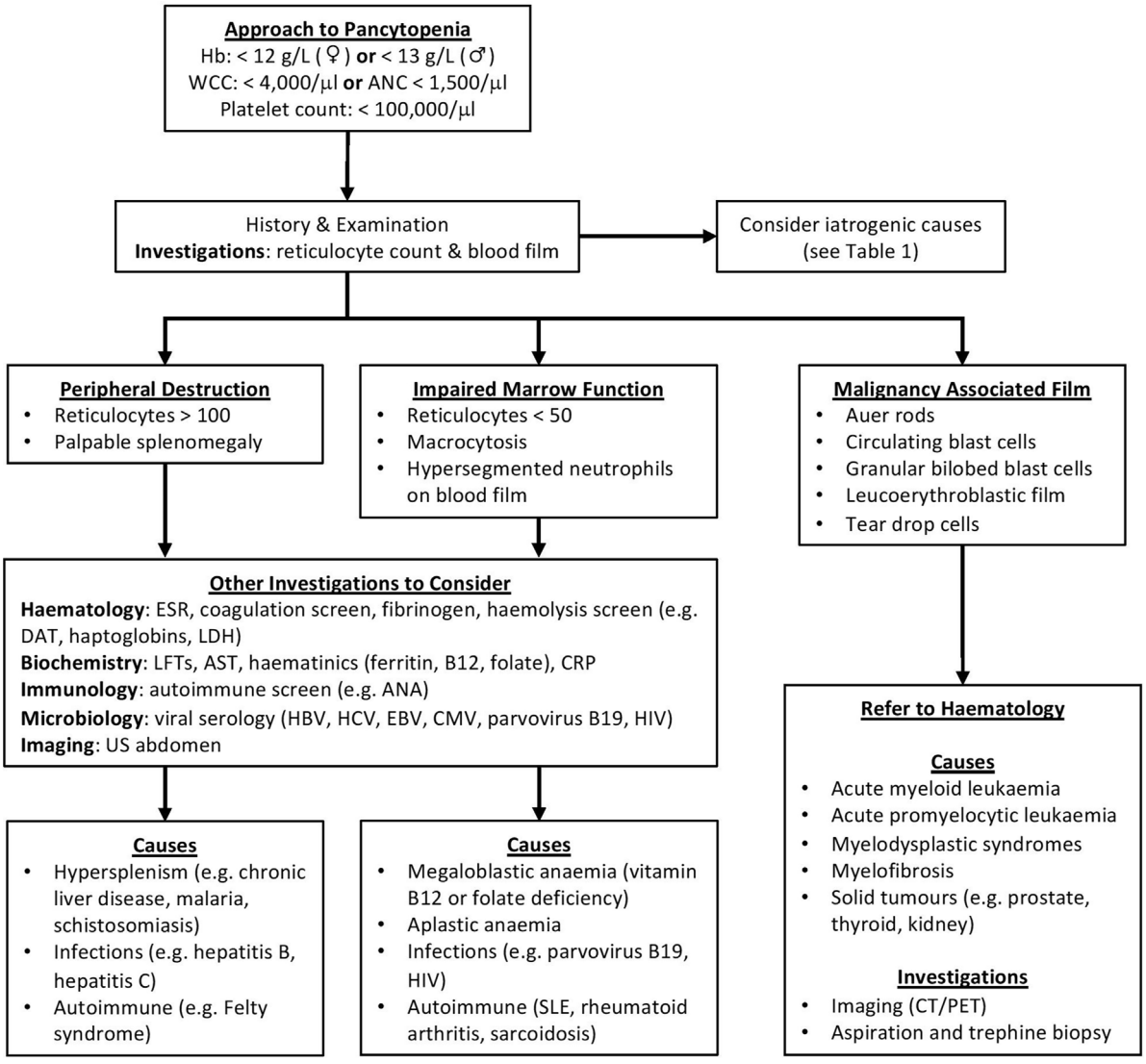

Fig. 1. Algorithm for approaching pancytopenia. ANA: anti-nuclear antibody, ANC: absolute neutrophil count, AST: aspartate aminotransferase, CMV: cytomegalovirus, CT: computed tomography, DAT: direct antiglobulin test, EBV: Epstein–Barr virus, Hb: haemoglobin, HIV: human immunodeficiency virus, LDH: lactate dehydrogenase, PET: positron emission tomography, SLE: systemic lupus erythematosus, US: ultrasound, WCC: white cell count.

and nutritional deficiencies (including haematinics, serum copper and ceruloplasmin) (See Fig. 1).

Management of pancytopenia is usually directed at the underlying cause, with supportive adjuncts such as antibiotics for severe neutropenia and restricted blood transfusion strategies to maintain haemoglobin above 7 g/dL.[19]

In unwell patients where common causes have been excluded, clinical gestalt of rarer causes should be considered. Specific investigations include flow cytometry for PNH, and aspartate aminotransferase, ferritin, triglyceride and fibrinogen levels for calculation of H-score for HLH. Involvement of the haematologist and/or rheumatologist may be warranted for further management.

Conclusion

Pancytopenia can be stratified into causes of peripheral destruction or causes of impaired marrow production, although in reality most conditions present with a combination of both. With such a broad differentials list in mind, non-invasive testing should be sought to exclude the common causes. Initial investigations should include a reticulocyte count and a blood film to help distinguish cell morphology. Further investigations should be tailored to clinical history and examination findings, and comprise liver function tests, coagulation screen, viral serology, autoimmune testing, and haematinics to exclude common pathologies. Management is usually targeted at the underlying cause. Malignancy-associated blood films should prompt referral to the haematologist for further imaging and biopsy.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Shaun Chew: Writing – original draft, Conceptualization, Methodology, Writing – review & editing. **Majeed Kamangar:** Writing – original draft, Conceptualization, Writing – review & editing.

Funding

Not applicable.

Patient consent

No patient data was involved in the preparation of the manuscript and informed consent is not applicable.

Acknowledgement

The authors would like to thank the Haematology Department at Croydon Health Services NHS Trust for their guidance and advice.

References

1. Greenberg P, Cox C, LeBeau MM, *et al*. International scoring system for evaluating prognosis in myelodysplastic syndromes. *Blood*. 1997;89(6):2079–2088.
2. Gajbhiye SS, Karwa AR, Dhok A, Jadhav SS. Clinical and etiological profiles of patients with pancytopenia in a tertiary care hospital. *Cureus*. 2022;14(10):e30449.
3. Vargas-Carretero CJ, Fernandez-Vargas OE, Ron-Magaña AL, Padilla-Ortega JA, Ron-Guerrero CS, Barrera-Chairez E. Etiology and clinico-hematological profile of pancytopenia: experience of a Mexican Tertiary Care Center and review of the literature. *Hematology*. 2019;24(1):399–404.
4. Peck-Radosavljevic M. Hypersplenism. *Eur J Gastroenterol Hepatol*. 2001;13(4):317–323.
5. Lv Y, Lau WY, Li Y, *et al*. Hypersplenism: history and current status. *Exp Ther Med*. 2016;12(4):2377–2382.
6. Nikolopoulos D, Adamichou C, Bertsias G. Suspected systemic rheumatic diseases in patients presenting with cytopenias. *Best Pract Res Clin Rheumatol*. 2019;33(4):101425.
7. Wadood Khan ZA, Vidyasagar S, Bekur R, Belurkars S, *et al*. Subhyaloid haemorrhage in a patient with vitamin B12 deficiency: a unique presentation. *J Clin Sci Res*. 2013;2:161–164.
8. Andrès E, Affenberger S, Zimmer J, *et al*. Current hematological findings in cobalamin deficiency. A study of 201 consecutive patients with documented cobalamin deficiency. *Clin Lab Haematol*. 2006;28(1):50–56.
9. Tahir N, Ashraf A, Waqar SHB, *et al*. Copper deficiency, a rare but correctable cause of pancytopenia: a review of literature. *Expert Rev Hematol*. 2022;15(11):999–1008.
10. Rowin J, Lewis SL. Copper deficiency myeloneuropathy and pancytopenia secondary to overuse of zinc supplementation. *J Neurol Neurosurg Psychiatry*. 2005;76(5):750–751.
11. Young NS. Aplastic anemia. *N Engl J Med*. 2018;379(17):1643–1656.
12. Park M. Overview of inherited bone marrow failure syndromes. *Blood Res*. 2022;57(S1):49–54.
13. Kulasekararaj A, Cavenagh J, Dokal I, *et al*. Guidelines for the diagnosis and management of adult aplastic anaemia: A British society for haematology guideline. *Br J Haematol*. 2024;204(3):784–804.
14. Janka GE. Hemophagocytic syndromes. *Blood Rev*. 2007;21(5):245–253.
15. Fardet L, Galicier L, Lambotte O, *et al*. Development and validation of the HScore, a score for the diagnosis of reactive hemophagocytic syndrome. *Arthritis Rheumatol*. 2014;66(9):2613–2620.
16. Hill A, DeZern AE, Kinoshita T, Brodsky RA. Paroxysmal nocturnal haemoglobinuria. *Nat Rev Dis Primers*. 2017;3:17028.
17. Poorana Priya P, Subhashree AR. Role of absolute reticulocyte count in evaluation of pancytopenia-a hospital based study. *J Clin Diagn Res*. 2014;8(8):FC01–FFC3.
18. Grover SA, Barkun AN, Sackett DL. The rational clinical examination. Does this patient have splenomegaly? *JAMA*. 1993;270(18):2218–2221.
19. Carson JL, Stanworth SJ, Dennis JA, *et al*. Transfusion thresholds for guiding red blood cell transfusion. *Cochrane Database Syst Rev*. 2021;12(12):CD002042.