Novel Developments in Leukopenia and Pancytopenia

Chisom Onuoha, MD[a], Junaid Arshad, MD[a], John Astle, MD, PhD[b,c], Mina Xu, MD[b], Stephanie Halene, MD[d,*]

KEYWORDS

• Leukopenia • Neutropenia • Pancytopenia • Clonal hematopoiesis
• Hemophagocytosis • Aleukemic leukemia • Large granular lymphocytosis

KEY POINTS

- Pancytopenia and leukopenia are caused by several hematopoiesis intrinsic and extrinsic processes; their duration and the company they keep (white blood cell differential, mean corpuscular volume, red cell distribution width, reticulocyte count, mean platelet volume, liver function tests) can shed light on their cause.
- A careful history and examination and review of medications are essential in determining the first steps to be taken.
- Severity of the cytopenias and concurrent symptoms determine acute management, and whenever in doubt consult a hematologist.
- Inherited disorders of childhood, such as the bone marrow failure disorders and familial hemophagocytic lymphohistiocytosis, provide mechanistic insights into acquired disorders in the adult.
- The 2 life-threatening causes of pancytopenia, acute promyelocytic leukemia (APL) and hemophagocytic lymphohistiocytosis (HLH), should be suspected in patients with fever, bleeding or bruising, and fatigue (APL) or fever, malaise, splenomegaly, hyperferritinemia, altered mental status, with or without a possible underlying rheumatologic disease (HLH).

INTRODUCTION

Cytopenias are generally discovered during investigation for causes of abnormal clinical findings, such as fatigue, bleeding, or fever, or incidentally when blood is drawn for routine checkups or other reasons. Cytopenias are not a disease entity in and of

Disclosure: The authors declare no relevant conflict of interest.
[a] Department of Medicine, St. Mary's Hospital, Waterbury, CT, USA; [b] Department of Pathology, Yale University School of Medicine, New Haven, CT, USA; [c] Department of Pathology and Laboratory Medicine, Hospital of the University of Pennsylvania, Philadelphia, PA, USA; [d] Section of Hematology, Department of Internal Medicine, Yale Comprehensive Cancer Center, Yale University School of Medicine, 300 George Street, 786E, New Haven, CT 06511, USA
* Corresponding author.
E-mail address: Stephanie.halene@yale.edu

Prim Care Clin Office Pract 43 (2016) 559–573
http://dx.doi.org/10.1016/j.pop.2016.07.005
primarycare.theclinics.com

themselves; rather, they are the expression of various underlying disease processes and may even be normal, as in the case of ethnic neutropenia. Pancytopenia is defined as the simultaneous presence of anemia, leukopenia, and thrombocytopenia on complete blood count. The parameters that define the cytopenias are given in Table 1.

The differential diagnosis for the causes of cytopenias is very broad. Thus, rather than going into depth for each disease, the authors here seek to provide the clinician with an approach toward identifying the underlying cause and first steps in their management. The authors concisely discuss a few causes of pancytopenia and isolated leukopenias while referring the reader to other articles in this issue for detailed discussions on isolated anemia, thrombocytopenia, leukemia, lymphoma, and plasma cell dyscrasia, each of which can cause cytopenias.

CAUSE

The processes that cause cytopenias are hematopoiesis intrinsic or extrinsic. Hematopoiesis intrinsic processes arise in hematopoietic stem or progenitor cells, such as in bone marrow failure syndromes, myelodysplasia (MDS), leukemia, lymphoma, and others. Hematopoiesis extrinsic processes include destructive processes, such as autoimmune processes, immune dysfunction such as hemophagocytic lymphohistiocytosis, hypersplenism due to liver disease, and others. These processes may primarily affect the bone marrow or may affect mature cells in the periphery with a compensatory response in the bone marrow. The bone marrow is a highly proliferative organ and generates more than 10^{11} red cells, platelets, and neutrophils every day. All cells arise from the hematopoietic stem cell (HSC), a rare, multipotent cell that resides in the bone marrow stem cell niche. HSCs have the unique ability to self-renew. HSCs give rise to one progenitor cell and one stem cell with each cell division, thereby maintaining hematopoiesis for the life span of the individual. The hematopoietic progenitors commit to either myeloid differentiation (ultimately giving rise to erythrocytes, megakaryocytes, granulocytes, and monocytes) or lymphoid differentiation (ultimately giving rise to B cells, T cells, or natural killer [NK] cells).[1] Hematopoiesis is highly regulated, and hematopoietic stem and progenitor cells depend on the complex bone marrow microenvironment that is intricately woven by mesenchymal stromal cells, macrophages, fat cells, endosteal cells, endothelial cells, and the sympathetic nervous system.[2,3]

Table 1
World Health Organization's criteria for cytopenia

Category	HB g/dL	ANC × 10^9/L	Platelets × 10^9/L
Normal	≥12 (f), ≥13 (m)	≥1.8	≥150
Cytopenic	<12 (f), <13 (m)	<1.8[a]	<150
MDS	<10	<1.8	<150
ICUS (1)	<11	<1.5	150

Abbreviations: ANC, absolute neutrophil count; f, female; HB, hemoglobin; ICUS, idiopathic cytopenias of unknown significance; m, male; MDS, myelodysplasia.

[a] In the white population, absolute neutrophil count values are higher than in people of African descent. See ethnic neutropenia.

Adapted from Valent P. Low blood counts: immune mediated, idiopathic, or myelodysplasia. Hematology Am Soc Hematol Educ Program 2012;2012:485–91.