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Review

Approach to pancytopenia: Diagnostic algorithm for clinical hematologists

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ABSTRACT

Pancytopenia is a relatively common phenomenon encountered in clinical practice. The evaluation of a patient with pancytopenia requires a comprehensive approach and identifying the underlying cause can be challenging given the wide range of etiologies including drugs, autoimmune conditions, malignancies, infections, hemophagocytosis, and inheritable conditions. Recent advances in molecular hematology which include genomic profiling and next-generation sequencing have helped gain major insights into various hematological conditions and can guide diagnosing specific diseases in a shorter time at lower costs. However the approach to manage patients with pancytopenia in the current era of genomics is not well defined in the literature and is widely variable in practice. Herein, we conducted a systematic review to help devise an algorithm and management approach for pancytopenia, which serves as a general consultative approach.

1. Introduction

Pancytopenia is defined as a decrease in all three blood cell lines and it could manifest with symptoms resulting from anemia, leukopenia or thrombocytopenia; patients may however be asymptomatic. Pancytopenia may also be diagnosed incidentally especially if mild or it can be present in some critically ill states such as in sepsis. It is a relatively common phenomenon in daily medical practice and one of the most common reasons for consultation from hematologists. A survey of primary care physicians showed that about 9 out of 10 times a hematologist is consulted when pancytopenia is found on lab studies [1]. It is not a disease in itself but rather a finding due to an underlying disease process affecting the bone marrow or the peripheral cell lines.

Although there are studies reviewing the underlying pathologies and the bone marrow findings in pancytopenia, only few are published on the approach to pancytopenia in clinical practice [2–4]. Internists, psychiatrists, obstetricians, pediatricians, and intensivists encounter the majority of cases and these are frequently referred to hematologists for further workup. The differential diagnoses in a patient presenting with pancytopenia are broad and extensive. These are only reviewed in textbooks and a literature gap is identified regarding the management of pancytopenia. In this review, we propose a common management approach to pancytopenia, which is essential for hematologists who perform consultative service in academic and community settings.

2. Methods

We conducted a comprehensive electronic literature search from January 1990 to July 2016. We followed the guidelines of PRISMA statement for systematic reviews for collecting the data. Only human studies published in English language were included. We searched the following electronic databases: PubMed, Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Review. MeSH Terms “Pancytopenia” was combined with “Diagnosis”, “Drug Therapy”, “Epidemiology”, “Physiopathology” and “Therapy” using Boolean Language (“OR”, “AND”). We included all studies including Controlled Trials, prospective and retrospective observational studies, case reports and systematic reviews. Case reports describing pancytopenia from unusual causes were excluded.

3. Results

Our systematic search identified many causes of pancytopenia as well as a wide variety of treatments given for conditions causing

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Table 1
Common causes of pancytopenia.

Impaired production	Peripheral destruction	Impaired production and peripheral destruction
Aplastic anemia – acquired and congenital	Autoimmune hemolytic pancytopenia	Paroxysmal nocturnal hemoglobinuria
Bone marrow infiltrating disorders	Splenic Sequestration	SLE
- Malignancy		Drugs
- Primary and autoimmune myelofibrosis		Leukemia
- Granulomatous disorders		Hemophagocytic Lymphohistiocytosis (HLH)
- Metabolic disorders		
Nutritional deficiencies		Transfusion-associated Graft-versus-host disease
- Vitamin B12		Infections
- Folic acid		
- Copper		
Myelodysplastic syndrome		

pancytopenia (Supplementary Table S1). We summarize our results below categorizing pancytopenia into three broad categories (Table 1):

- Impaired production which encompasses both bone marrow failure disorders and marrow infiltration disorders
- Peripheral destruction of different cell lines (includes splenic sequestration)
- Combination of above.

These three processes can be distinguished from one another by hematologic testing but the crucial first steps of evaluation must include a hemogram (called complete blood count [CBC] or complete picture [CP] in various countries), peripheral blood smear, reticulocyte count and comprehensive history and a meticulous physical examination. The reticulated platelet count or the immature platelet fraction, though not used commonly, can also help distinguish if the pancytopenia is due to impaired production or increased consumption.

3.1. Impaired production

3.1.1. Acquired aplastic anemia

Aplastic anemia is caused by failed hematopoiesis either due to an acquired or a congenital cause. Several observational studies from South East Asia looking for the causes of pancytopenia by bone marrow examination point to aplastic anemia and leukemia being the most common cause in children [5,6] and aplastic anemia and megaloblastic anemia among the general population [7]. Congenital causes of bone marrow failures are far less common compared to acquired causes.

3.1.1.1. Idiopathic. Although the cause of aplastic anemia (AA) is not clear, it is thought to be due to autoimmune destruction of pluripotent hematopoietic stem cells (HSC) by T lymphocytes [8–11]. Unregulated lymphocyte activation, impaired regulatory T cells and increased activity of IL-17 have also been proposed as causes for the autoimmune mechanism [12,13]. Evaluation starts with a reticulocyte count and a peripheral smear. The absolute reticulocytes are reduced and sometimes totally absent. The peripheral blood smear may show macrocytic red blood cells with other cell lines having a normal morphology. The diagnosis is established by bone marrow aspiration and biopsy, which show reduced cellularity with absence of fibrosis and malignant cells. In order to conclude the diagnosis of AA, besides drugs and infections, one must exclude the absence or co-existence of paroxysmal nocturnal hemoglobinuria (PNH), inherited bone marrow failure syndromes and myelodysplastic syndrome, as the management of the latter disorders may be different. In the current genomic era, besides obtaining cytogenetics, we prefer a directed panel for use of severe AA (SAA) using the next-generation sequencing (NGS), since patients with mutations in ASXL1 or DNMT3 typically have a poorer response to immunosuppressive therapy (IST) and a greater propensity for clonal evolution development thus prompting a referral to a hematopoietic stem cell transplant (HSCT) center. Generally, for SAA, the treatment for patients under the age of 50 is by HSCT (matched related or alternative donor) but for those over 50 without a fully matched donor, IST (with or without eltrombopag) may a reasonable option [14].

3.1.1.2. Drugs and radiation. Many drugs can cause aplastic anemia. Toxins like benzene, chemotherapeutic drugs, NSAIDs, antiepileptic drugs, steroids, and chloramphenicol are commonly known to cause AA. The mechanism of aplasia is either by direct toxic effect on the stem cells or from autoimmune mechanisms. Studies have shown that activity of P – Glycoprotein in the cells is decreased among patients with AA [15]. Reduced activity of P – Glycoprotein can cause accumulation of the drugs in the cytoplasm leading to toxic levels. In some occasions, as in the idiosyncratic reaction seen in chloramphenicol, effects of the drugs on the bone marrow can be irreversible, which led consequently to a marked decline in its use. Most conventional chemotherapeutic agents cause pancytopenia by direct bone marrow toxicity. Specifically, fluropyrimidines such as flurouracil and capecitabine can cause severe and sometimes fatal toxicities if administered in patients with deficiency of dihydropyrimidine dehydrogenase, an enzyme involved in the metabolism of uracil and thymine. Biological agents such as inhibitors of TNF and IL-6 can cause neutropenia but pancytopenia is rare.

Alcohol abuse can affect all the three cell lines. There are several ways how alcohol can cause these hematological toxicities. Alcohol can cause direct bone marrow toxicity as evidenced by hypoplastic bone marrow in some of these patients. Excess alcohol consumption can also increase the absorption of iron from the gastrointestinal tract leading to iron overload, which in turn can contribute to hepatitis and cirrhosis. Other possible mechanisms are interference with folate absorption and acetaldehyde forming adducts with cell membrane phospholipids [16,17].

Radiation therapy can also damage the HSC and result in pancytopenia [18]. Bone marrow hypoplasia develops at cumulative doses > 5 Gy. The cytopenia reaches a nadir 1 to 4 weeks after the treatment and can persist for months. Having a more ventral exposure and sparing the dorsal bone marrow (in spine, ribs and pelvis) during the radiation might protect a significant percent of bone marrow activity. This is an important aspect of radiation biology for hematologists, as some cancer patients (particularly gynecologic cancers) receive radiation to the pelvic bones and may develop profound and prolonged pancytopenia but it is generally reversible.

3.1.1.3. Infections. Infections, mostly viral, are another cause of cytopenias in both adults and children. A prospective study among children by Alexandropoulo et al. showed that an infectious agent was identified in about 63.8% of febrile non-cancer patients with cytopenias [19]. About 45% of these were due to viral infection and the cytopenia was transient in 83% of the cases. Parvovirus B19 can directly attack proerythroblasts whereas aplasia caused by other viruses is usually due to T cell mediated mechanisms [20], however, parvovirus more commonly causes anemia only and patients with chronic hemolytic anemias are usually the most vulnerable. The pancytopenia caused by the viruses is usually transient and reversible with resolution of the infection. In a hematology consultation for pancytopenia, if a viral infection is suspected, then the common agents which should be evaluated include infectious hepatitis (Hepatitis A, B, and C), cytomegalovirus (CMV), Epstein-Barr virus (EBV), Human HerpesVirus 6 (HHV-6), Parvovirus B19, and human immunodeficiency virus (HIV). Pancytopenia associated with hepatitis