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CLINICAL CHALLENGES AND MANAGEMENT OF HYPERLEUKOCYTOSIS AND LEUKOSTASIS IN HEMATOLOGIC CANCERS

Miguel Angel Diaz Diaz MD. Unidad Central del Valle del Cauca

ABSTRACT Hyperleukocytosis is defined as a white blood cell (WBC) count exceeding 100,000/microL in patients with leukemia, particularly acute myeloid leukemia (AML). Leukostasis, or symptomatic hyperleukocytosis, results in microvascular occlusions causing respiratory distress, central nervous system abnormalities, and organ dysfunction. The epidemiology varies, with hyperleukocytosis frequently observed in AML, affecting up to 20% of newly diagnosed patients, and less commonly in other leukemias. The pathophysiology involves increased blood viscosity and endothelial adhesion, leading to tissue hypoxia. Clinical manifestations include neurological and respiratory symptoms, necessitating early recognition and intervention. Treatment involves cytoreductive therapy, supportive care, and monitoring, aiming to reduce the high initial mortality associated with leukostasis.

KEYWORDS : Hyperleukocytosis, Leukostasis, Acute Myeloid Leukemia, Microvascular Occlusions, Cytoreductive Therapy.

INTRODUCTION

Hyperleukocytosis, defined as a white blood cell (WBC) count exceeding 100,000/microL, is a significant and potentially life-threatening complication commonly seen in patients with hematologic malignancies, particularly acute myeloid leukemia (AML). The condition can lead to leukostasis, a medical emergency characterized by symptoms resulting from decreased tissue perfusion due to the high WBC count. These symptoms often include respiratory distress, central nervous system abnormalities, and other organ dysfunctions. The pathophysiology of leukostasis involves the increased blood viscosity caused by a large population of leukemic blasts, which are less deformable than mature leukocytes. This can lead to microvascular occlusions and decreased tissue perfusion, exacerbated by additional factors such as endothelial damage and cytokine release. The rapid recognition and management of hyperleukocytosis and leukostasis are crucial, given their association with high mortality rates (1,2).

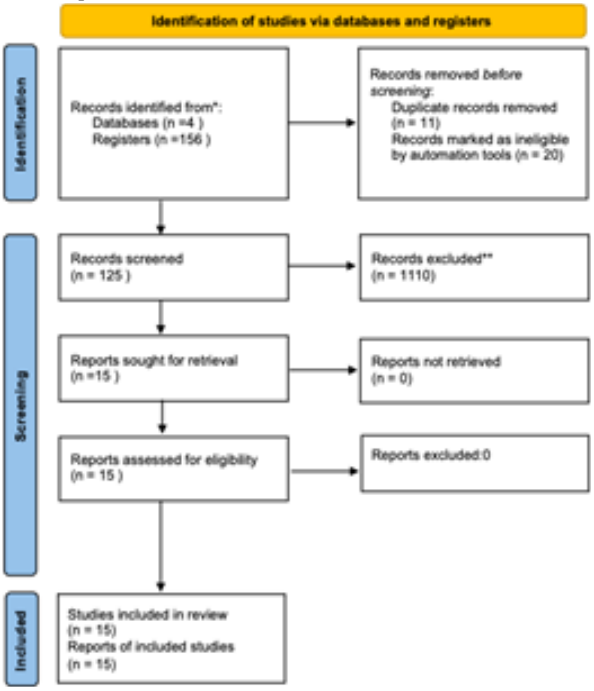

Figure 1. PRISMA.

METHODS

The methodology of this narrative review involved a comprehensive search across four databases: PubMed, Scopus, Web of Science, and Cochrane Library. Keywords used in the search included "hyperleukocytosis," "leukostasis," "hematologic malignancies," "acute myeloid leukemia," and "management." Inclusion criteria were studies and reviews published in English that focused on the clinical challenges and management of hyperleukocytosis and leukostasis in hematologic cancers. After screening and assessing the relevance of the search results, a total of 15 references were selected to provide a detailed overview and insights into the topic.

Definition

Hyperleukocytosis is defined as a white blood cell (WBC) count exceeding 100,000/microL in patients with leukemia, most commonly seen in acute myeloid leukemia (AML). Leukostasis, or symptomatic hyperleukocytosis, is a clinical condition where high WBC counts cause microvascular occlusions, leading to respiratory distress, central nervous system abnormalities, and organ dysfunction. Leukostasis is prevalent in AML and is associated with a poor prognosis if not properly managed. Accurate diagnosis and early intervention are critical for improving clinical outcomes in patients affected by these conditions (3).

Epidemiology

The epidemiology of hyperleukocytosis and leukostasis varies significantly across different hematologic malignancies. Hyperleukocytosis is most frequently observed in acute myeloid leukemia (AML), affecting up to 20% of newly diagnosed patients. Among these, approximately one-quarter develop leukostasis, characterized by symptomatic microvascular complications. Acute lymphoblastic leukemia (ALL) also presents with hyperleukocytosis in 10-30% of cases, particularly in infants and adolescents. However, leukostasis is less common in ALL compared to AML. Chronic lymphocytic leukemia (CLL) and chronic myeloid leukemia (CML) frequently show elevated WBC counts, but symptomatic leukostasis is rare, except in cases of blast crisis in CML, where WBC counts exceed 400,000/microL. The incidence of hyperleukocytosis is influenced by genetic factors, with certain cytogenetic abnormalities, such as FLT3 and KMT2A mutations, being associated with higher WBC counts. Early detection and management are crucial due to the high mortality risk associated with untreated leukostasis in these malignancies (4).

Pathophysiology

The pathophysiology of leukostasis in hematologic malignancies is complex and multifactorial, leading to significant morbidity and mortality if not promptly managed. Hyperleukocytosis, defined as an extremely high white blood

cell (WBC) count, predominantly involves large, rigid leukemic blasts that significantly increase blood viscosity. This hyperviscosity impairs microcirculation, causing microvascular occlusions and reducing tissue perfusion, which results in tissue hypoxia and subsequent organ dysfunction. Leukemic blasts tend to adhere to endothelial cells, exacerbating vascular congestion and promoting local inflammation (5).

Endothelial damage is further intensified by the release of cytokines and other inflammatory mediators from leukemic cells, which contributes to the disruption of normal blood flow. The high metabolic activity of these malignant cells increases local oxygen consumption, compounding the hypoxic conditions and leading to tissue ischemia, especially in critical organs such as the lungs and central nervous system. Additionally, red blood cell transfusions and dehydration can further elevate blood viscosity, worsening the condition (5,6).

The clinical manifestations of leukostasis often include respiratory distress, neurological deficits, and other organ-specific symptoms due to compromised microvascular perfusion. This complex interplay of increased blood viscosity, endothelial adhesion, and inflammatory response underscores the critical need for early recognition and prompt intervention. Effective management strategies are essential to mitigate the severe complications associated with leukostasis, emphasizing the importance of timely and appropriate therapeutic approaches in affected patients (6).

Clinical Manifestations

The clinical presentation of leukostasis is characterized by symptoms arising from microvascular occlusions caused by extremely high white blood cell (WBC) counts. These symptoms can vary depending on the organ systems affected but commonly involve the central nervous system (CNS) and the respiratory system. Neurological symptoms are frequently observed due to the high metabolic demand and susceptibility of the CNS to hypoxia. Patients may present with headaches, dizziness, visual disturbances, confusion, ataxia, and, in severe cases, altered mental status or coma. Intracranial hemorrhage is also a risk due to the compromised integrity of cerebral vessels and the effects of coagulopathies that often accompany leukostasis (7).

Respiratory symptoms are another hallmark of leukostasis, as leukemic blasts occlude the pulmonary microcirculation, leading to impaired gas exchange. Patients may experience dyspnea, hypoxia, and diffuse alveolar or interstitial infiltrates on chest imaging. In severe cases, acute respiratory failure can occur, necessitating urgent intervention (7,8).

Other organ systems can also be affected. Cardiovascular manifestations may include myocardial ischemia or infarction due to impaired coronary perfusion. Renal involvement can lead to acute kidney injury, characterized by decreased urine output and elevated serum creatinine levels. Gastrointestinal symptoms might include abdominal pain, bowel ischemia, or gastrointestinal bleeding. Systemic symptoms such as fever, night sweats, and weight loss are often present, reflecting the underlying malignant process and the body's inflammatory response. The presence of disseminated intravascular coagulation (DIC) can further complicate the clinical picture, leading to bleeding or thrombotic events (8).

Diagnosis

The diagnosis of leukostasis involves a combination of clinical assessment and laboratory findings. Hyperleukocytosis, characterized by an extremely high white blood cell (WBC) count, typically exceeding 100,000/microL, is a key laboratory indicator. However, the diagnosis of leukostasis is primarily clinical, based on the presence of symptoms attributable to microvascular occlusions and tissue hypoxia (8,9).

Patients presenting with respiratory distress, central nervous system abnormalities (such as headaches, confusion, or visual disturbances), and other organ dysfunctions should prompt suspicion of leukostasis. Imaging studies, including chest X-rays or CT scans, can reveal diffuse alveolar or interstitial infiltrates indicative of pulmonary involvement. Brain imaging may show signs of intracranial hemorrhage or ischemia. Blood tests often reveal leukocytosis, along with other abnormalities such as elevated lactate dehydrogenase (LDH), indicating high cell turnover, and evidence of tumor lysis syndrome, such as hyperuricemia, hyperkalemia, and hyperphosphatemia. Coagulation studies may show disseminated intravascular coagulation (DIC), complicating the clinical scenario (9).

A peripheral blood smear can provide visual confirmation of leukemic blasts, and bone marrow aspiration or biopsy can further characterize the hematologic malignancy. Prompt recognition of leukostasis through these diagnostic steps is crucial, as it guides the immediate initiation of treatment to reduce WBC counts and alleviate symptoms, thereby improving patient outcomes in this life-threatening condition (9,10).

Treatment

The treatment of leukostasis is a medical emergency that requires immediate and aggressive intervention to reduce the white blood cell (WBC) count and mitigate the associated microvascular complications. The primary goals of treatment are to rapidly decrease the leukocyte burden, manage symptoms, and prevent further complications. Cytoreductive therapy is the cornerstone of treatment. Hydroxyurea is often used as an initial agent due to its ability to quickly reduce WBC counts. The typical starting dose ranges from 50 to 100 mg/kg per day, adjusted based on response and tolerance. For more rapid cytoreduction, leukapheresis can be employed. This procedure involves the mechanical removal of WBCs from the blood and can quickly lower WBC counts, providing symptomatic relief, particularly in patients with severe symptoms or when chemotherapy cannot be initiated immediately (11).

Chemotherapy should be initiated promptly, tailored to the underlying hematologic malignancy. In acute myeloid leukemia (AML), for instance, induction chemotherapy with an anthracycline (such as daunorubicin or idarubicin) plus cytarabine is standard. The initiation of definitive chemotherapy not only reduces the leukocyte count but also targets the malignant clone responsible for the disease (11,12).

Supportive care is essential to manage complications associated with leukostasis and its treatment. This includes aggressive hydration to promote renal function and prevent tumor lysis syndrome, prophylaxis with allopurinol or rasburicase to manage hyperuricemia, and correction of electrolyte imbalances. Platelet transfusions may be necessary to manage thrombocytopenia and prevent bleeding, particularly in patients with disseminated intravascular coagulation (DIC) (12).

Monitoring and follow-up are critical to assess the effectiveness of treatment and manage any emerging complications. Patients should be closely observed for signs of improvement in symptoms and reduction in WBC counts, as well as potential adverse effects of therapy, such as myelosuppression, infection, or organ dysfunction (12,13).

Prognosis

The prognosis of patients with leukostasis depends on several factors, including the type of underlying hematologic malignancy, the promptness of diagnosis, and the efficacy of treatment. Acute myeloid leukemia (AML) with leukostasis is

associated with a high initial mortality rate, estimated between 20-40%. Prompt initiation of cytoreductive therapy and supportive care can significantly improve outcomes. However, patients who survive the acute phase may still face a lower overall survival due to complications and the aggressive nature of their underlying disease. Early and aggressive management is crucial for improving the prognosis and reducing mortality associated with leukostasis (14,15).

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