Pulmonary leukostasis as a complication of leukemia

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Abstract

Multiple acute pulmonary complications occur in patients with hematologic malignancies. They might be associated with the disease itself, with complications from treatment, or with the consequences of an impaired immune status. Pulmonary leukostasis is one of the most common life-threatening complications in patients with hyperleukocytosis. The risk of this condition is higher in myeloid leukemia with white blood cell counts greater than 100,000 /µL. Leukostasis is a diagnostic challenge for clinicians due to non-specific symptoms and radiographic presentation. Definitive treatment of pulmonary leukostasis is still controversial; however, early detection and treatment by cytoreduction may improve outcomes.

Key words: *leukemia, hyperleukocytosis, leukostasis, respiratory complications*

Introduction

Hyperleukocytosis is often defined as a white blood cell (WBC) count > 100,000/µL and is associated with increased morbidity and mortality. It can induce leukostasis, tumor lysis syndrome, and disseminated intravascular coagulopathy (DIC). Hyperleukocytosis is present in 10-20% of patients with newly diagnosed acute myelocytic leukemia (AML) and 10-30% of patients with acute lymphoblastic leukemia (ALL).[1, 2] However, the importance of the absolute number depends on the underlying hematological disorder. Most patients with chronic lymphocytic leukemia or ALL remain asymptomatic even with WBC counts > 500,000/µL, while in AML a WBC count ≥ 50,000/µL can cause severe symptoms.[3] Leukostasis occurs more frequently in AML, especially in the microgranular variant of acute promyelocytic (FAB-M3) leukemia, myelomonocytic (FAB-M4) leukemia, and monocytic (FAB-M5) leukemia, and in chronic myelogenous leukemia (CML) in blast crisis.[4] In ALL hyperleukocytosis occurs more frequently in patients with cytogenetic subtype t (4, 11) and t (9:22).[2] A WBC count >10,000/µL is considered in the hyperleukocytosis range in acute promyelocytic leukemia.[3] Leukostasis is a serious manifestation of hyperleukocytosis because vascular occlusion by leukemic blasts causes tissue hypoxia.[3]The respiratory and central nervous systems are the most frequently affected systems by leukostasis.

This review focuses on pulmonary leukostasis in hyperleukocytosis and describes the pathophysiology, clinical presentation, differential diagnosis, and management of this condition.

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Pathophysiology

The pathophysiology of hyperleukocytosis and leukostasis is not well established. The pathogenesis likely involves both changes in blood viscosity and the deformability of leukemic cells (the ability of the cells to change shape when passing through blood vessels). Marked elevations in WBCs lead to an increased fractional volume of leukocytes (leukocrit), and this leads to an increased blood viscosity. In addition, blast cells are less deformable than normal mature WBCs, and these rigid blast cells cause occlusion of the microvasculature and decrease blood flow resulting in tissue hypoxia.[5]

The viscosity of leukocyte suspensions in vitro increases dramatically when the leukocrit exceeds 12-15 ml/dL.[5] But the leukemic blast concentrations necessary to reach a leukocrit of 12-15 mL/dL (300,000-450,000/μL for AML and 6,000,000-8,000,000/ μL for ALL) are rarely seen.[5] Leukostasis has also been described with blast counts of less than 50,000/μL.[6] This indicates that hyperleukocytosis itself is not enough to cause leukostasis, and other factors, like the presence of circulating blasts or the attachment of the blast cells to the endothelium, may contribute.[7] The expression and function of adhesion receptors in leukemic cells and the up and down regulation of adhesive molecules are important causes of leukostasis.[8] Myeloblasts are larger than lymphoblasts and lymphocytes. Hence, leukostasis is more common in AML than in ALL. Thornton, et al.[9] demonstrated that genetic mutations, such as the FLT3 mutation in AML, could be associated with hyperleukocytosis and leukostasis. Differences in expression of these adhesive molecules on myeloblast and lymphoblast cell surfaces may explain leukostasis without hyperleukocytosis and the higher incidence of leukostasis in AML than in ALL.[10-12] Sturki and coworkers suggested that cytokines, including ILβ and TNF-α, produced by blast cells cause activation of endothelial cells and this blast-endothelial cells interaction is enhanced by adhesion molecules, like selectins and vascular adhesion molecules.[11]

Clinical presentation and diagnosis

The clinical presentation of leukostasis is usually nonspecific. The respiratory and nervous systems are often involved, and this can result in death.[2, 4, 13] The differential diagnosis of pulmonary opacities in patients with hematological malignancies is broad and includes pneumonia, pulmonary hemorrhage, edema, and leukostasis (Table). Infection is the most common pulmonary complication in acute leukemia, and most patients with respiratory infections have either bacterial pneumonia or fungal pneumonia. Pulmonary leukostasis and leukemic infiltration are uncommon but should be considered in the differential diagnosis in these patients. Rare drug complications also occur and include tyrosine kinase inhibitor induced pulmonary complications, retinoic acid syndrome, and hemophagocytic lymphohistiocytosis.[14]

Pulmonary complications, including leukostasis, occur in up to 80% of all leukemia patients and are a major cause of death in these patients.[16] Pulmonary leukostasis has been identified as the single worst prognostic factor in patients presenting with hyperleukocytosis with either AML or CML in myeloid blast crisis.[13] Patients with pulmonary leukostasis present with fever, dyspnea, tachypnea, and hypoxia; symptoms range from mild shortness of breath to acute respiratory failure and death. Chest radiographic findings usually include varying degrees of alveolar and interstitial infiltration. However, the chest x-ray can be normal, even in patients with severe respiratory distress.[17] Computed tomography of the chest may demonstrate thickening of the bronchovascular bundles, prominence of the peripheral pulmonary arteries, and ground glass opacities. The arterial blood gas should be interpreted skeptically as the PaO_2 can be falsely decreased (pseudohypoxemia) in patients with hyperleukocytosis due to rapid oxygen consumption by the high number of WBCs. Complete assessment of patients, searching for other signs and symptoms of leukostasis, and close frequent monitoring are critical and can help to differentiate between pseudo and true hypoxemia. In addition, monitoring pulse oximetry can more accurately assess oxygenation status.[18] Clinicians should identify patients with pulmonary leu-

Table Pulmonary complications in patients with hematologic malignancies

Pulmonary complication	Clinical setting	Finding
Infectious		
Bacterial pneumonia	Fever, cough, sputum, and/or neutropenia	Segmental or lobar consolidation
Fungal pneumonia	Post chemotherapy with neutropenia, fever, hemoptysis	Halo sign, segmental or subsegmental pleura-based consolidation, cavitation-centrilobular nodules, fungal ball, peribronchial or peribronchiolar consolidations
Pneumocystis jiroveci pneumonia (PJP)	Impaired cellular immunity, usually post hematopoietic stem cell transplant	Bilateral perihilar ground glass opacities
CMV-induced pneumonia	Same as PJP	Ground glass opacities, micronodules, or airspace consolidation
Non-infectious		
Leukostasis	Hyperleukocytosis with AML or ALL	Varying degrees of interstitial and/or alveolar opacities. Ground glass opacities
Pulmonary hemorrhage	Thrombocytopenia, sudden onset of pulmonary symptoms, rare hemoptysis	Rapid progression of diffuse ground glass opacities and/or consolidation
Pulmonary edema	History of positive fluid intake, multiple transfusion, cardiotoxic medication, and renal failure. Edema and high jugular venous pressure.	Cardiomegaly, redistribution of blood flow toward the upper lobes, increase in vasculature, ground glass opacities and/or consolidation, increased interstitial markings
Retinoic acid syndrome	History of treatment with ATRA for acute pro- myelocytic leukemia (AML subtype M3)	Diffuse ground glass opacities and/or consolidation
Effects of tyrosine kinase inhibitor therapy	History of imatinib therapy with a median duration of 49 days (range, 10–282 days), interstitial pneumonia	Varying degree of interstitial pneumonia, ground glass opacities, nodular, or reticular infiltration

AML-acute myeloid leukemia, ALL-acute lymphocytic leukemia, ATRA- all-trans–retinoic acid, PJP-Pneumocystis jiroveci pneumonia

kostasis as quickly as possible since early diagnosis and treatment should improve outcomes.

Extrapulmonary signs and symptoms in the central nervous system can range from headache to mild confusion to somnolence to coma. Patients may have focal neurologic deficits due to intracranial hemorrhage. Other manifestations include acute limb ischemia, priapism, retinal hemorrhage, retinal vein thrombosis, renal vein thrombosis, disseminated intravascular coagulation, and spontaneous tumor lysis syndrome.

Management

Leukostasis is a medical emergency with a mortality rate up to 40%; the principles of management are similar to hyperleukocytosis.[15] Every effort should be made to reduce the WBC number and stabilize the patient. Leukapheresis, low dose chemotherapy, or hydroxyurea can achieve the cytoreduction. Supportive care should include hydration, transfusion, and oxygen support to prevent complications. The treatment of pulmonary leukostasis requires the same approach as with the patient with hyperleukocytosis.

Leukapheresis can reduce the peripheral WBC quickly and is a necessary adjunct to chemotherapy. The main indication for leukapheresis is leukostasis and possibly asymptomatic hyperleukocytosis. During leukapheresis, the WBCs are concentrated and removed from the blood and other constituents are infused back into the patient. A single leukapheresis procedure can reduce the peripheral WBC count by 20-50%. Most patients require one leukapheresis session, but some patients need additional procedures. This maneuver can decrease symptoms of leukostasis, prevent the development of leukostasis in patients with hyperleukocytosis, and might decrease the severity of tumor lysis syndrome.[3] However, it is unclear if there is an early survival benefit from this treatment.[19] The complications of leukapheresis include blood loss, hypocalcemia, and complications from venous catheter placement, including bleeding and thrombosis at the catheter insertion site. Anticoagulation therapy is also required during leukapheresis to prevent thrombosis of the circuit. When the anticoagulant is citrate, this requires the administration of calcium, which may cause calcium-phosphate precipitation and worsen tumor lysis syndrome.[20] Leukapheresis is not recommended in patients with acute promyelocytic leukemia due to the possibility of increasing the risk of coagulopathy.[20]

In 2014, Oberoi, et al. conducted a meta-analysis and systematic review to compare the effect of leukapheresis versus hydroxyurea/low dose chemotherapy on the early mortality (deaths during first induction) in AML hyperleukocytosis. The study results did not identify a preferred treatment; neither had an impact on the early mortality.[21] Bug, et al. studied two groups of AML patients with WBC counts >100,000 /μL who either underwent leukapheresis (N=34) or did not (N=28) and found that leukapheresis significantly reduced the early death (P=0.015) but had no impact on the long term survival.[22] Piro, et al. reported an example of life-threatening pulmonary leukostasis secondary to hyperleukocytosis (110,000/μL) in a 27-year-old man with AML who was successfully treated with leukapheresis and low dose chemotherapy of cytarabine and etoposide followed by induction chemotherapy, which led to a complete remission.[23]

Induction chemotherapy is an essential treatment for patients with hematologic malignancy. In the setting of leukostasis or hyperleukocytosis, induction chemotherapy can rapidly decrease the circulating WBC count and target leukemic cells in bone marrow. However, starting with conventional induction chemotherapy increases the tumor lysis syndrome and DIC and can worsen leukostasis compared to low dose chemotherapy followed by induction chemotherapy. Imatinib mesylate was reported to be effective in the treatment of pulmonary leukostasis in CML. Imatinib mesylate is an inhibitor of tyrosine kinase bcr/abl; it reduces the WBC count safely in patients with CML myeloid blast crisis, resulting in marked improvement of respiratory disease and prevention of the life threatening complications.[24] Hydroxyurea is reserved for the patient with asymptomatic hyperleukocytosis who is unable to receive chemotherapy immediately. The side effects with hydroxyurea are minimal and typically occur in patients who take hydroxyurea for prolonged periods.

Supportive care is necessary in all patients with leukostasis. Adequate hydration is a key management step for this condition since it reduces blood viscosity and prevents and/or treats tumor lysis syndrome. Other supportive measures include oxygen support, ventilator management, blood component transfusion as indicated, and serum uric acid level control.

Prognosis

The prognosis of leukostasis depends upon the type of hematologic malignancy and the presence of symptoms. The initial mortality rate for patients with AML and leukostasis ranges from 20 to 40 percent.[15, 25, 26] Poor prognostic factors based on a retrospective study are coagulopathy, respiratory distress, and neurologic symptoms.[26]

Conclusions

Pulmonary leukostasis is a life threatening condition that leads to respiratory failure. It should be considered in the differential diagnosis of patients with hematologic malignancy presenting with shortness of breath, desaturation, and elevated WBCs. Patients with AML, especially M5, have the highest risk. Leukapheresis and targeted therapy with intensive supportive care should be started promptly since these measures can improve survival. However, the mortality rate is still high in this condition. More research on optimal management is necessary to improve outcomes.

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