REVIEW

NAVNEET S. MAJHAIL, MD
Department of Hematology, Oncology, and Transplantation, University of Minnesota, Minneapolis

ALAN E. LICHTIN, MD
Department of Hematology and Medical Oncology, The Cleveland Clinic Foundation

Acute leukemia with a very high leukocyte count: Confronting a medical emergency

ABSTRACT

From 5% to 30% of adult patients with acute leukemias present with hyperleukocytosis—very high white blood cell counts (> 100,000 cells/mm^3)—and symptoms of leukostasis. These conditions are a medical emergency that needs prompt recognition and initiation of therapy to prevent respiratory failure or intracranial hemorrhage. Patients should be referred as soon as possible for induction chemotherapy and leukapheresis.

KEY POINTS

Risk factors associated with hyperleukocytosis include younger age, certain types of leukemia, and cytogenetic abnormalities.

Symptoms of hyperleukocytosis are primarily due to leukostasis, a clinicopathologic syndrome caused by the sludging of circulating leukemic blasts in tissue microvasculature.

Patients can present with symptoms ranging from exertional dyspnea to severe respiratory distress. Neurologic manifestations can range from mild confusion and somnolence to stupor and coma.

Initial management includes aggressive hydration; use of allopurinol and hydroxyurea; correction of abnormalities of metabolism, coagulation, and electrolytes; and prevention of tumor lysis syndrome.

Definitive treatment consists of leukocytoreduction (via cytotoxic chemotherapy), hydroxyurea, and, in some cases, leukapheresis.

MOST PATIENTS WITH ACUTE leukemias first present to a general internist because of nonspecific symptoms of fatigue, weight loss, and fever. In such cases, if the peripheral blood count and other indices suggest acute leukemia, the patient is referred to an oncology center.

However, from 5% to 30% of adult patients with acute myeloid leukemia or acute lymphoblastic leukemia present quite differently: they have hyperleukocytosis (white blood cell counts > 100,000/mm^3),[1–4] they are acutely ill, and they have metabolic abnormalities, coagulopathy, and multiple organ failure.[1,2] The clinical picture often mimics infectious and hemorrhagic complications of acute leukemia.

This presentation is characteristic of acute hyperleukocytosis and leukostasis and should be considered a medical emergency. If it is not recognized and treated quickly, the mortality rate can be up to 40%.[1,5] Management must be started before the patient can be referred for treatment of the underlying leukemia.

This article reviews the clinical manifestations of acute hyperleukocytosis and leukostasis and discusses options for its management.

ETIOLOGY AND RISK FACTORS

Hyperleukocytosis

Hyperleukocytosis is more common in acute leukemias than in chronic leukemias. Its incidence ranges from 5% to 13% in adult acute myeloid leukemia (AML) and 10% to 30% in adult acute lymphoblastic leukemia (ALL).[1–4] The clinical presentation depends largely on

the lineage and the number of circulating leukemic blasts. Despite a higher incidence and degree of hyperleukocytosis in ALL vs AML, clinically manifest hyperleukocytosis is not commonly seen in ALL.[1,2]

Risk factors for hyperleukocytosis include younger age (it is most commonly seen in infants), certain types of leukemia (microgranular variants of acute promyelocytic leukemia [AML-M3v], acute myelomonocytic leukemia [AML-M4], acute monocytic leukemia [AML-M5], and T-cell ALL), and cytogenetic abnormalities (11q23 translocations or presence of the Philadelphia chromosome).[1,2]

Leukostasis

Symptoms of hyperleukocytosis are primarily due to leukostasis (FIGURE 1), a clinicopathologic syndrome caused by the sludging of circulating leukemic blasts in tissue microvasculature.[5,6] It is usually associated with a very high number of circulating blasts (ie, hyperleukocytosis), but leukostasis has also been described with blast counts of less than 50,000/mm^3.[5,7]

Its pathophysiology is not fully understood. Earlier hypotheses suggested a critical "leukocrit" (fractional leukocyte volume) and an increase in whole blood viscosity as putative mechanisms of leukostasis.[8]

Treatment must begin before the patient can be transferred to a tertiary care center

Leukostasis without hyperleukocytosis indicates that other factors may be involved in its development. There is increasing evidence to suggest that interactions between leukemic blasts and the surface of endothelial cells might be responsible for the aggregation of blasts in the microcirculation. Also, a difference in the expression of adhesion molecules on lymphoblast and myeloblast cell surfaces may explain the higher incidence of leukostasis in AML vs ALL.[9–12]

PRESENTATION AND EVALUATION: EARLY DEATHS DUE TO PULMONARY AND INTRACRANIAL COMPLICATIONS

Although leukostasis can affect any organ system, symptoms usually arise from involvement of the pulmonary and cerebral microvasculature, and most early deaths are due to respiratory failure and intracranial hemorrhage.

Pulmonary

Patients can present with symptoms ranging from exertional dyspnea to severe respiratory distress. However, chest radiography may be normal or may reveal varying degrees of diffuse interstitial or alveolar infiltrates.[13]

Arterial blood gas samples should be interpreted cautiously, as a spuriously low arterial oxygen tension (pseudohypoxemia) can result from rapid consumption of plasma oxygen by the markedly increased number of white blood cells.[14]

Pulse oximetry can more accurately assess oxygenation status in this setting.[15]

Neurologic

Neurologic manifestations can range from mild confusion and somnolence to stupor and coma. Focal central nervous system deficits may herald intracranial hemorrhage.

Vascular

Retinal hemorrhage, retinal vein thrombosis, myocardial infarction, acute limb ischemia, and renal vein thrombosis have all been described with leukostasis and acute hyperleukocytosis.

Disseminated intravascular coagulation (DIC) occurs in 30% to 40% of patients with AML and in 15% to 25% of patients with ALL.[1] Though more common in AML-M3 (also known as acute promyelocytic leukemia), DIC can occur in all subtypes of acute leukemia.

Laboratory

Laboratory evaluation should include careful assessment for thrombocytopenia, coagulopathy, and tumor lysis syndrome. Platelets may have to be counted manually, since a spurious elevation of the automated platelet count can occur due to the presence of fragments of white and red blood cells.[1,16,17]

Fever is common. Although fever can be traced to infection in very few (< 5%) of these patients,[2] infection needs to be ruled out, since acute hyperleukocytosis can mimic several viral, bacterial, and fungal syndromes.

Prognosis based on the presentation

In acute hyperleukocytosis due to AML, predictors of a poor prognosis are renal failure,

Hyperleukocytosis, leukostasis, and sludging

Symptoms of hyperleukocytosis are mainly due to leukostasis, a clinicopathologic syndrome caused by the sludging of circulating leukemic blasts in tissue microvasculature.

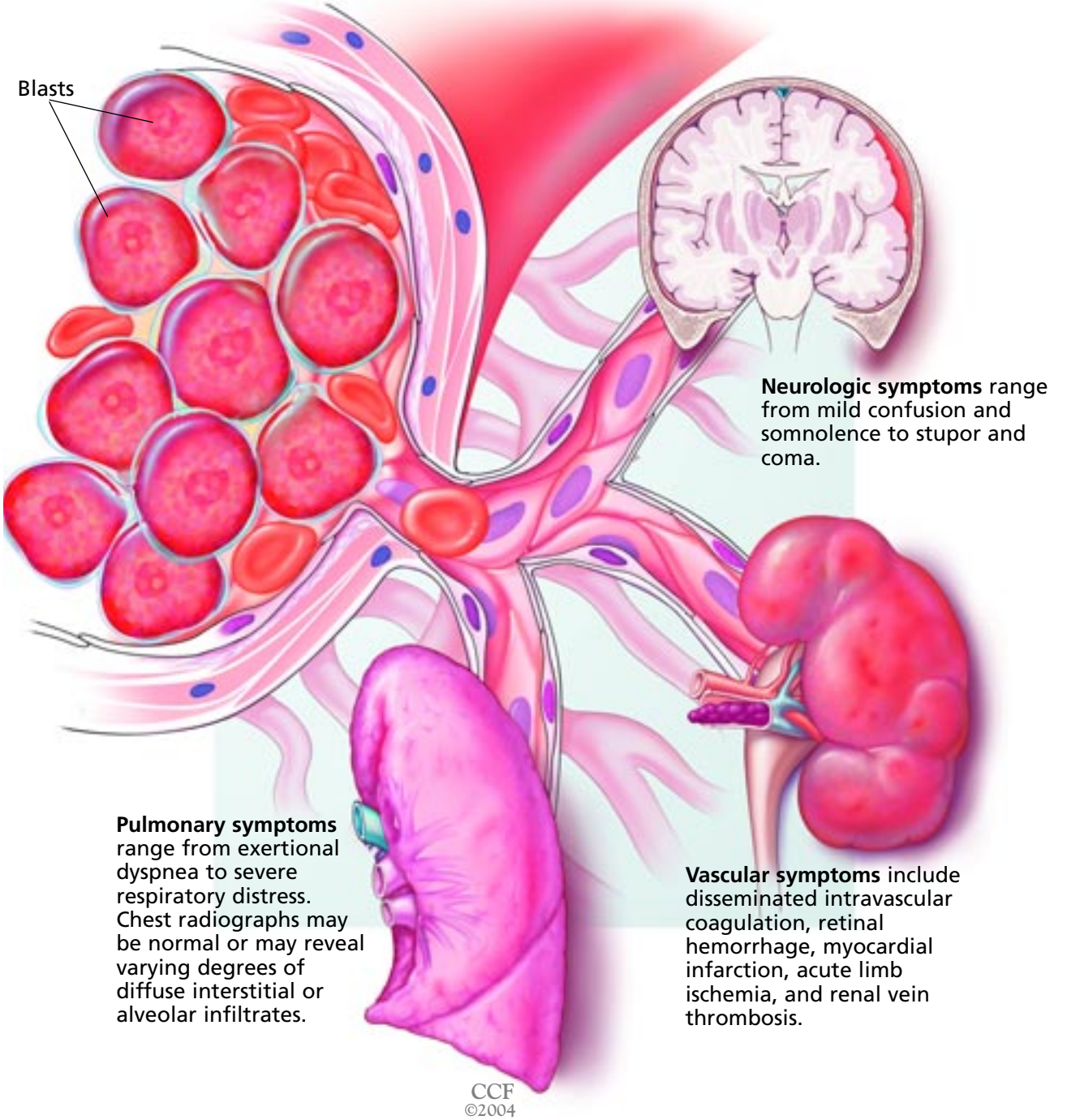

FIGURE 1

respiratory distress, neurologic symptoms, or coagulopathy; in ALL, adverse indicators are white blood cell counts more than 250,000/mm^3 or neurologic compromise.[1,2,18]

TREATMENT

The management of acute hyperleukocytosis and leukostasis involves supportive measures and reducing the number of circulating leukemic blast cells.

Supportive measures

Supportive measures should include:

- **Vigorous hydration with intravenous fluids.** Intravenous fluids should be used judiciously, however, with careful monitoring of the fluid balance in patients with coexisting cardiopulmonary comorbidities who might be prone to pulmonary decompensation in the setting of leukostasis.
- **Alkalinization of the urine with sodium bicarbonate.**
- **Prevention of tumor lysis syndrome.** Allopurinol should be given orally or intravenously (in cases of intractable nausea and vomiting) to prevent tumor lysis syndrome. Recombinant urate oxidase (rasburicase) is an alternative drug to prevent tumor lysis and manage hyperuricemia in patients who cannot tolerate allopurinol. Rasburicase converts uric acid to allantoin, which is 5 to 10 times more soluble than uric acid and therefore is rapidly excreted by the kidneys.
- **DIC or thrombocytopenia, if present, should be corrected.**

Transfusions should be avoided unless the patient has symptoms of anemia and the hemoglobin is less than 7 to 8 g/dL. Increasing the erythrocrit (fractional erythrocyte volume) and, consequently, the whole blood viscosity can lead to the development and worsening of leukostasis if the leukocrit is already high in patients with acute hyperleukocytosis.

Management involves supportive measures and reduction of blast cells

Leukocytoreduction

Prompt reduction in the number of circulating blast cells (leukocytoreduction) is essential to prevent leukostasis in patients with acute hyperleukocytosis and to treat or halt the progression of established leukostasis. Still, clinical deterioration and death can occur despite a significant reduction in the white blood cell count.

Leukocytoreduction can be achieved by induction chemotherapy, hydroxyurea, and leukapheresis. Prompt initiation of induction chemotherapy remains the mainstay of treatment of acute hyperleukocytosis and leukostasis. In patients with acute promyelocytic leukemia, treatment with all-trans-retinoic acid should be initiated as soon as possible; all-trans-retinoic acid stimulates the maturation of the myeloblasts of acute promyelocytic leukemia with a rapid reduction in the white blood cell count. Hydroxyurea given at dosages of 50 to 100 mg/kg/day in three or four divided doses has been shown to reduce the leukocyte count by 50% to 60% within 24 to 48 hours and should be started at the time of initial diagnosis and continued until the count has decreased to safer levels.[1,19,20]

Radiation

Cranial radiation has been used to control neurologic symptoms secondary to leukostasis, especially in patients with ALL.[18,21] However, lack of controlled trials and the significant toxicity associated with whole-brain irradiation preclude its routine use for the treatment of this syndrome.[22]

Leukapheresis

Leukapheresis involves the removal of circulating blast cells with re-infusion of leukocyte-poor plasma. Although there are no evidence-based guidelines for when to start leukapheresis, it is usually started in patients with AML when the blast count is more than 100,000/mm^3 or in the presence of symptoms of leukostasis, irrespective of the blast count.[23–25] In ALL, leukapheresis is usually not done unless symptoms of leukostasis develop or the blast count exceeds 100,000 to 200,000/mm^3.[26–28]

Advantages. A single session of leukapheresis decreases the white blood cell count by 20% to 50%. It immediately removes circulating blasts, and it may also recruit marginated leukemic cells into the intravascular space.[1] It also permits the infusion of blood products (eg, platelets) and correction of metabolic abnormalities.

Disadvantages. The placement and main-

tenance of central venous catheters may cause complications. Also, the treatment requires specialized equipment and trained personnel, and it is not widely available.

TREATMENT CONTROVERSIES

Though leukapheresis lowers blast counts, it has not been shown to consistently improve outcome or mortality in patients with AML and leukostasis. In addition, despite a higher incidence of hyperleukocytosis in patients with ALL, the role of leukapheresis in these patients is even more controversial because of the low rate of early mortality and a low incidence of leukostasis.

A lack of controlled clinical trials evaluating the role of leukapheresis with or without induction chemotherapy has largely contributed to the controversy regarding its role in acute hyperleukocytosis. Moreover, hyperleukocytosis might correlate with the presence of other adverse prognostic factors, and mechanisms other than "leukemia cell burden" might influence the poorer outcome observed in this group of patients.

Future therapies that specifically target cytokines and cell membrane adhesion molecules that mediate blast-blast and blast-endothelium interactions may improve the outcome in patients with acute hyperleukocytosis.

REFERENCES

1. **Porcu P, Farag S, Marcucci G, Cataland SR, Kennedy MS, Bissell M.** Leukocytoreduction for acute leukemia. Ther Apher 2002; 6:15–23.
2. **Porcu P, Cripe LD, Ng EW, et al.** Hyperleukocytic leukemias and leukostasis: a review of pathophysiology, clinical presentation, and management. Leuk Lymphoma 2000; 39:1–18.
3. **Hoelzer D, Thiel E, Loffler H, et al.** Prognostic factors in a multicenter study for treatment of acute lymphoblastic leukemia in adults. Blood 1988; 71:123–131.
4. **Dutcher JP, Schiffer CA, Wiernik PH.** Hyperleukocytosis in adult acute nonlymphocytic leukemia: impact on remission rate and duration, and survival. J Clin Oncol 1987; 5:1364–1372.
5. **van Buchem MA, te Velde J, Willemze R, Spaander PJ.** Leucostasis, an underestimated cause of death in leukaemia. Blut 1988; 56:39–44.
6. **McKee LC, Collins RD.** Intravascular leukocyte thrombi and aggregates as a cause of morbidity and mortality in leukemia. Medicine (Baltimore) 1974; 53:463–478.
7. **Soares FA, Landell GA, Cardoso MC.** Pulmonary leukostasis without hyperleukocytosis: a clinicopathologic study of 16 cases. Am J Hematol 1992; 40:28–32.
8. **Lightman MA.** Rheology of leukocytes, leukocyte suspensions, and blood in leukemia. Possible relationship to clinical manifestations. J Clin Invest 1973; 52:350–358.
9. **van Buchem MA, Hogendoorn PC, Bruijn JA, Kluin PM.** Endothelial activation antigens in pulmonary leukostasis in leukemia. Acta Haematol 1993; 90:29–33.
10. **Stucki A, Rivier AS, Gikic M, Monai N, Schapira M, Spertini O.** Endothelial cell activation by myeloblasts: molecular mechanisms of leukostasis and leukemic cell dissemination. Blood 2001; 97:2121–2129.
11. **De Waele M, Renmans W, Jochmans K, et al.** Different expression of adhesion molecules on CD34+ cells in AML and B-lineage ALL and their normal bone marrow counterparts. Eur J Haematol 1999; 63:192–201.
12. **Cavenagh JD, Gordon-Smith EC, Gibson FM, Gordon MY.** Acute myeloid leukaemia blast cells bind to human endothelium in vitro utilizing E-selectin and vascular cell adhesion molecule-1 (VCAM-1). Br J Haematol 1993; 85:285–291.
13. **van Buchem MA, Wondergem JH, Kool LJ, et al.** Pulmonary leukostasis: radiologic-pathologic study. Radiology 1987; 165:739–741.
14. **Fox MJ, Brody JS, Weintraub LR.** Leukocyte larceny: a cause of spurious hypoxemia. Am J Med 1979; 67:742–746.
15. **Loke J, Duffy TP.** Normal arterial oxygen saturation with the ear oximeter in patients with leukemia and leukocytosis. Cancer 1984; 53:1767–1769.
16. **Armitage JO, Goeken JA, Feagler JR.** Spurious elevation of the platelet count in acute leukemia. JAMA 1978; 239:433–434.
17. **Hammerstrom J.** Spurious platelet counts in acute leukaemia with DIC due to cell fragmentation. Clin Lab Haematol 1992; 14:239–243.
18. **Flasshove M, Schuette J, Sauerwein W, Hoeffken K, Seeber S.** Pulmonary and cerebral irradiation for hyperleukocytosis in acute myelomonocytic leukemia. Leukemia 1994; 8:1792.
19. **Grund FM, Armitage JO, Burns P.** Hydroxyurea in the prevention of the effects of leukostasis in acute leukemia. Arch Intern Med 1977; 137:1246–1247.
20. **Berg J, Vincent PC, Gunz FW.** Extreme leucocytosis and prognosis of newly diagnosed patients with acute non-lymphocytic leukaemia. Med J Aust 1979; 1:480–482.
21. **Gilchrist GS, Fountain KS, Dearth JC, Smithson WA, Burgert EO.** Cranial irradiation in the management of extreme leukemic leukocytosis complicating childhood acute lymphocytic leukemia. J Pediatr 1981; 98:257–259.
22. **Butler RW, Hill JM, Steinherz PG, Meyers PA, Finlay JL.** Neuropsychologic effects of cranial irradiation, intrathecal methotrexate, and systemic methotrexate in childhood cancer. J Clin Oncol 1994; 12:2621–2629.
23. **Porcu P, Danielson CF, Orazi A, Heerema NA, Gabig TG, McCarthy LJ.** Therapeutic leukapheresis in hyperleucocytic leukaemias: lack of correlation between degree of cytoreduction and early mortality rate. Br J Haematol 1997; 98:433–436.
24. **Giles FJ, Shen Y, Kantarjian HM, et al.** Leukapheresis reduces early mortality in patients with acute myeloid leukemia with high white cell counts but does not improve long-term survival. Leuk Lymphoma 2001; 42:67–73.
25. **Thiebaut A, Thomas X, Belhabri A, Anglaret B, Archimbaud E.** Impact of pre-induction therapy leukapheresis on treatment outcome in adult acute myelogenous leukemia presenting with hyperleukocytosis. Ann Hematol 2000; 79:501–506.
26. **Basade M, Dhar AK, Kulkarni SS, et al.** Rapid cytoreduction in childhood leukemic hyperleukocytosis by conservative therapy. Med Pediatr Oncol 1995; 25:204–207.
27. **Bunin NJ, Pui CH.** Differing complications of hyperleukocytosis in children with acute lymphoblastic or acute nonlymphoblastic leukemia. J Clin Oncol 1985; 3:1590–1595.
28. **Eguiguren JM, Schell MJ, Crist WM, Kunkel K, Rivera GK.** Complications and outcome in childhood acute lymphoblastic leukemia with hyperleukocytosis. Blood 1992; 79:871–875.

ADDRESS: *Alan E. Lichtin, MD, Department of Hematology & Medical Oncology, R35, The Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, OH 44195; e-mail lichtia@ccf.org.*