ScientificScholar®
Knowledge is power
Publisher of Scientific Journals

https://ijrsms.com

International Journal of Recent Surgical and Medical Sciences

Case Report

Leukostasis Due to Acute Myeloid Leukemia with Monocytic Differentiation that Resolved after Leukapheresis

Tom L Enright[1], Anthony H Bui[1], William N Rose[1]

Department of [1]Pathology and Laboratory Medicine, University of Wisconsin Hospital, Madison, Wisconsin, United States.

***Corresponding author:**
Dr. William N. Rose,
Department of Pathology and Laboratory Medicine, University of Wisconsin Hospital, Madison, Wisconsin, United States.

wrose@uwhealth.org

Received: 5 February 2022

Accepted: 11 April 2022

EPub Ahead of Print: 6 September 2023

Published: 22 December 2023

DOI
10.25259/IJRSMS-2022-2-6

Quick Response Code:

ABSTRACT

Even though the stakes of leukostasis are high, the data regarding the efficacy of leukapheresis for leukostasis is meager. We report a patient with leukostasis due to acute myeloid leukemia with monocytic differentiation who improved clinically after therapeutic leukapheresis, a rarely performed variation of therapeutic apheresis.

Keywords: Acute myeloid leukemia, Leukapheresis, Leukostasis, Therapeutic apheresis

INTRODUCTION

Leukostasis represents a rare but serious complication of acute leukemias associated with a high risk of early mortality. Leukostasis is a clinicopathologic diagnosis characterized clinically by signs of neurologic, respiratory, or renal compromise. It is sometimes seen in patients with acute leukemias and a total leukemia blood cell or blast count > 1,00,000/μL. Acute myeloid leukemia (AML), particularly AML with monocytic features, is a morphologic subtype of acute leukemias in which hyperleukocytosis and leukostasis occur more commonly.[1] It may also occur in patients with acute lymphoblastic leukemia (ALL), although the white blood cell (WBC) counts in ALL patients with leukostasis are usually much higher than those of AML patients with leukostasis.[2] Leukostasis has also been reported in patients with chronic myeloid leukemia (CML) and chronic myelomonocytic leukemia (CMML).[1] Untreated, leukostasis has a 40% one-week mortality rate.[2]

Despite the high risk of early mortality due to leukostasis, optimal treatment strategies remain unclear. The pathophysiologic mechanism of leukostasis is postulated to involve end organ hypoxia due to a combination of factors including hyperviscosity, decreased cellular deformity of leukemic cells, cytokines secreted by blasts tumor necrosis factor (TNF), interleukin-1 beta (IL-1b) causing increased expression of endothelial adhesion molecules, and high metabolic activity causing high oxygen uptake of rapidly dividing leukemic cells.[1,2] Rapid leukoreduction remains the mainstay of treatment for leukostasis. The strategies by which rapid leukoreduction can be achieved include chemotherapy or leukapheresis. A single treatment of leukapheresis can drop WBC counts by as much as 30–60%.[2] On the other hand, leukapheresis confers non-trivial risks of possible complications such as apheresis catheter-associated complications (pain, bleeding,

This is an open-access article distributed under the terms of the Creative Commons Attribution-Non Commercial-Share Alike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms.
©2023 Published by Scientific Scholar on behalf of International Journal of Recent Surgical and Medical Sciences

infection and accidental injury), acquired coagulopathy, hypocalcemia from citrate toxicity, potential delays in chemotherapy induction, and higher costs.[3,4]

Current guidelines from the American Society for Apheresis offer a Grade 2B recommendation for rapid cytoreduction with leukapheresis among patients with symptomatic leukostasis.[2] The evidence supporting this recommendation relies on retrospective, observational studies that have reached conflicting conclusions regarding the benefit of leukapheresis on early mortality.[5-7] Moreover, the retrospective methodology of these studies introduces a significant risk of selection and confounding biases as the decision to pursue leukapheresis remains highly dependent on center policy, physician preferences and patient characteristics. Thus, the optimal role of leukapheresis in the setting of leukostasis remains unclear. It is currently not well understood whether certain morphologic subtypes of leukemia or specific patient characteristics predict a better response to leukapheresis. In this report, we present a case of a 79-year-old patient presenting with hyperleukocytosis due to AML with monocytic differentiation and signs of leukostasis who was successfully treated with therapeutic leukapheresis.

CASE REPORT

A 79-year-old female with a past history of myelodysplastic syndrome with excess blasts-2 (MDS-EB2) on azacitidine and peripheral T cutaneous lymphoma stage IIB presented to the emergency department with complaints of cough, rhinorrhea, chest pain worse with inspiration, and bilateral hip/pelvic pain for several days. On arrival, her vital signs were significant for a fever of 38.0°C, blood pressure of 81/52 mmHg and a heart rate of 124 bpm. A physical exam revealed injected conjunctiva bilaterally, dry mucous membranes, a white patch on the right buccal region, soft crackles in the R lower lung field, a friction rub on cardiac auscultation, splenomegaly with the spleen tip palpable several centimeters below the costal margin, and diffuse bruising.

Laboratory findings were significant for a WBC count of 116 K with an absolute monocyte count of 58,300, blast count of 5,830, and the majority of the remainder as immature monocytic cells. Of note, a hematopathologist review stated the peripheral blood had a predominance of monocytic precursors. An image of the peripheral smear is not available. Hgb = 9.5 g/dL, platelets = 32 k/uL, Cr = 1.19 mg/dL (baseline Cr = 0.6), lactate = 4.7 mmol/L and troponin = 0.09 ng/uL. Electrocardiogram (EKG) was significant for diffuse ST elevations, compatible with pericarditis in the setting of positional, substernal chest pain. A chest X-ray showed mild pulmonary oedema. Urinalysis was consistent with a urinary tract infection (UTI). She was given 500 mL of intravenous (IV) fluids and started on cefepime prior to being admitted to the inpatient oncology service.

The patient was started on hydroxyurea for leukoreduction and allopurinol for tumor lysis syndrome (TLS) prophylaxis. A bone marrow biopsy revealed 23% blasts with marked monocytic hyperplasia and met the diagnostic criteria for acute myeloid leukemia with monocytic predominance. Of note, the aspirate showed marked monocytic hyperplasia including significant monoblasts, promonocytes and mature monocytes. Flow cytometry of the bone marrow aspirate showed a predominance of abnormal monocytic cells (60%), including increased blasts. A markedly expanded population of atypical monocytes with a spectrum of maturation was detected that included CD34 positive blasts as well as atypical immature monocytes.

Her WBC count increased from 116 K on admission to 197 K the following day despite hydroxyurea therapy. She also developed worsening tachypnea with increased oxygen requirements on the night of admission. Additionally, despite allopurinol prophylaxis, her phosphate was elevated to 4.9 and uric acid climbed to 8.5 mg/dL, diagnostic for tumor lysis syndrome. She received one dose of rasburicase, and uric acid levels normalized to 4.9 mg/dL. Creatinine peaked at 1.90, likely due to a combination of leukostasis, TLS and prerenal azotemia from suspected urosepsis.

Given her increasing WBC count, acute kidney injury (AKI), TLS and acute hypoxemic respiratory failure due to suspected leukostasis-associated pulmonary distress syndrome, transfusion medicine was consulted to do therapeutic leukapheresis. The leukapheresis was performed via centrifugal apheresis using the Spectra Optia with a processing volume of two times the patient's total blood volume as the endpoint. The procedure was performed without complications.

Her WBC count decreased by 60% from 197 K before leukapheresis to 79 K the day after it. Her respiratory status also improved significantly the day after leukapheresis. She tolerated weaning off supplemental oxygen without complications. With continued hydroxyurea therapy, her WBC count decreased to 25 K two days after the leukapheresis and to 5 K three days after the leukapheresis. Hydroxyurea was discontinued prior to discharge. She was discharged in stable condition to the care of her primary hematologist/oncologist.

Further work-up revealed an unbalanced translocation between chromosomes 1 and 9 resulting in an extra copy of 1q. *Feline McDonough sarcoma (FMS)-related receptor tyrosine kinase 3 (FLT3), cytosine-cytosine-adenosine-adenosine-thymidine (CCAAT)/enhancer-binding protein*

alpha (CEBPA), Nucleophosmin 1 (NPM1) and KIT (D816V) mutations were absent.

DISCUSSION

Patients with acute myeloid leukemia presenting with leukostasis syndrome have a poor prognosis with a high incidence of early mortality due to pulmonary failure, intracerebral hemorrhage, tumor lysis syndrome and disseminated intravascular coagulation (DIC). We present a case of a 79-year-old female with features of leukostasis due to acute myeloid leukemia treated successfully with therapeutic leukapheresis. In our case, a bone marrow biopsy revealed monocytic hyperplasia, and flow cytometry showed a predominance of abnormal monocytic cells. The rationale for starting therapeutic leukapheresis relied on her increasing WBC count despite hydroxyurea therapy, tumor lysis syndrome and worsening acute hypoxemic respiratory failure. After leukoreduction, the patient had a rapid improvement in clinical symptoms and lab counts. However, the imputability of cause and effect cannot be definitively established solely based on this sequence of events.

The nuances of the patient's diagnosis should be discussed. The monocytic subtype of AML predisposes to hyperleukocytosis, and it is believed that unique characteristics of blast cells appear to play a role in the development of leukostasis.[1] In our case, the peripheral blast count on presentation was only 5,380 compared to a total WBC count of 116 K and an absolute monocyte count of 58,300. On the surface, this may seem like a low blast count that would be inconsistent with the argument that the patient's signs and symptoms were explained by leukostasis due to leukemic blasts.

Classifying peripheral WBCs into precise stages of monocytic maturation solely based on morphology can be difficult. Importantly, the hematopathologist review stated the peripheral blood had a predominance of monocytic precursors. In addition, the bone marrow biopsy met criteria for AML with monocytic differentiation, including by flow cytometry. In sum, the abundance of evidence makes it highly likely that the predominant phenotype of the peripheral WBCs were immature leukemic cells of monocytic lineage that included but were not limited to blasts. Thus, it is likely that a significant cause of the patient's acute clinical status at that time was leukostasis due to leukemic cells.

Currently, there is no consensus in the literature regarding the benefit of leukapheresis for leukostasis due to AML. Multiple single institutional retrospective studies have reported a lower risk of early death among patients with AML with hyperleukocytosis receiving chemotherapy with leukapheresis versus chemotherapy alone.[8,9] Of note, these single institutional studies showed no significant benefit of leukapheresis on either complete remission or long-term survival. A large, retrospective, multinational study by Stahl *et al*. found statistically significant improvements in 30-day mortality and overall survival with leukapheresis in unadjusted analysis among patients with investigator-adjudicated clinical leukostasis.[5]

On the other hand, several single-center or dual-center retrospective studies have reported no benefit in early mortality for patients receiving leukapheresis versus other available treatment strategies.[3,10-13] In a propensity-score matched study, Choi *et al*. similarly reported no benefit of leukapheresis on survival outcomes, as well as no benefit for the incidence of tumor lysis syndrome and DIC.[14] A multi-center, international study by Stahl *et al*. including 12 centers showed no significant impact on early death and overall survival for patients receiving leukapheresis.[15] Oberoi *et al*. and Bewersdorf *et al*. both conducted systematic reviews and meta-analyses including 21 studies and 13 studies, respectively, that did not show the benefit of leukapheresis for early death on meta-regression, arguing against the routine use of leukapheresis for leukostasis associated with AML.[6,7]

In addition to the conflicting nature of the current evidence for leukapheresis for leukostasis, the retrospective, observational nature of the studies introduces a considerable risk of confounding bias. As such, the American Society for Apheresis offers a Grade 2B recommendation for rapid cytoreduction with leukapheresis in the setting of symptomatic leukostasis.[2] The role of prophylactic leukapheresis in the setting of hyperleukocytosis remains even more controversial, with multiple single-institution studies finding no benefit and the American Society for Apheresis offering a Grade 3B recommendation for its practice.[2,14,16]

An additional argument against leukapheresis is its lack of wide availability, as a center would not only have to have a clinical service that performs therapeutic apheresis but also one that is proficient at the rarely performed procedure of leukapheresis in particular. As an indication of its rarity, the transfusion medicine service at our 600-bed comprehensive cancer center university hospital reports that they perform therapeutic leukapheresis about 1–2 times per decade.

Given the lack of consensus, the overall low quality of current evidence and the lack of availability, practice patterns among physicians for the treatment of hyperleukocytosis and the utilization of leukapheresis remains highly variable.[17,18] The importance of patient-specific factors such as the co-occurrence of tumor lysis syndrome, AML with monocytic morphologic predominance, and history of MDS-EB2 in the pathophysiology and treatment of leukostasis remain unknown. Although grading scores for leukostasis do exist,

they reflect current evidence on the topic in that they do not account for more granular, patient-specific factors like degree of hyperleukocytosis, cytogenetics, peripheral blast count, gene mutations, morphologic subtype of AML and co-occurrence of DIC and TLS.[19,20] It is possible that many of these are independent risk factors for the development of leukostasis or independent predictors of mortality benefit from leukapheresis.

In sum, given the relative safety of leukapheresis, the rationale of the mechanism of benefit via direct removal of leukemic cells, and the potentially high stakes of leukostasis, it is plausible that leukapheresis may benefit some patients with leukostasis. To better elucidate these questions, more investigation is required to clarify pathophysiologic mechanisms for leukostasis as these investigations may elucidate new therapeutic targets related to blast adherence, endothelial activation and soft tissue infiltration. Ultimately, a controlled trial involving leukapheresis is most likely the best way to determine its efficacy.

CONCLUSION

Leukostasis is a complication of acute leukemia with a high mortality burden. Because of the lack of high-quality evidence for therapeutic leukapheresis for leukostasis and the lack of consensus regarding its benefit, the utilization of the therapy remains highly dependent on physician preferences and patient characteristics. The significant cost and potential complications of leukapheresis mean better clinical evidence and an improved pathophysiologic understanding of leukostasis are needed to clarify which patients are likely to benefit from leukapheresis.

Acknowledgement

None.

Ethical approval

The research/study complied with the Helsinki Declaration of 1964.

Declaration of patients consent

The authors certify that they have obtained all appropriate patient consent.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

REFERENCES

1. Ali AM, Mirrakhimov AE, Abboud CN, Cashen AF. Leukostasis in adult acute hyperleukocytic leukemia: a clinician's digest. Hematol Oncol 2016;34:69–78.
2. Padmanabhan A, Connelly-Smith L, Aqui N, Balogun RA, Klingel R, Meyer E, *et al*. Guidelines on the use of therapeutic apheresis in clinical practice – evidence-based approach from the writing committee of the American Society for Apheresis: The eighth special issue. J Clin Apher 2019;34:171–354.
3. Hambley B, Gehrie E, Webster J, Showel MM, Gondek LP, Dalton WB, *et al*. Coagulopathy, hypoxemia, and mortality outcomes in newly diagnosed acute myeloid leukemia with hyperleukocytosis treated with large volume leukapheresis. Blood 2019;134:3841.
4. Stenzinger M, Bonig H. Risks of leukapheresis and how to manage them—A non-systematic review. Transfus Apher Sci 2018;57:628–34.
5. Stahl M, Shallis RM, Wei W, Montesinos P, Lengline E, Neukirchen J, *et al*. Management of hyperleukocytosis and impact of leukapheresis among patients with acute myeloid leukemia (AML) on short- and long-term clinical outcomes: a large, retrospective, multicenter, international study. Leukemia 2020;34:3149–60.
6. Oberoi S, Lehrnbecher T, Phillips B, Hitzler J, Ethier MC, Beyene J, *et al*. Leukapheresis and low-dose chemotherapy do not reduce early mortality in acute myeloid leukemia hyperleukocytosis: A systematic review and meta-analysis. Leuk Res 2014;38:460–8.
7. Bewersdorf JP, Giri S, Tallman MS, Zeidan AM, Stahl M. Leukapheresis for the management of hyperleukocytosis in acute myeloid leukemia—A systematic review and meta-analysis. Transfusion 2020;60:2360–9.
8. Bug G, Anargyrou K, Tonn T, Bialleck H, Seifried E, Hoelzer D, *et al*. Impact of leukapheresis on early death rate in adult acute myeloid leukemia presenting with hyperleukocytosis. Transfusion 2007;47:1843–50.
9. Giles FJ, Shen Y, Kantarjian HM, Korbling MJ, O'Brien S, Anderlini P *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.
10. Malkan UY, Ozcebe OI. Leukapheresis do not improve early death rates in acute myeloid leukemia patients with hyperleukocytosis. Transfus Apher Sci 2017;56:880–2.
11. Rinaldi I, Sari RM, Tedhy VU, Winston K. Leukapheresis does not improve early survival outcome of acute myeloid leukemia with leukostasis patients – a dual-center retrospective cohort study. J Blood Med 2021;12:623–33.

12. Kuo KHM, Callum JL, Panzarella T, Jacks LM, Brandwein J, Crump M, *et al*. A retrospective observational study of leucoreductive strategies to manage patients with acute myeloid leukaemia presenting with hyperleucocytosis. Br J Haematol 2015;168:384–94.
13. Chang M-C, Chen T-Y, Tang J-L, Lan Y-J, Chao T-Y, Chiu C-P, *et al*. Leukapheresis and cranial irradiation in patients with hyperleukocytic acute myeloid leukemia: no impact on early mortality and intracranial hemorrhage. Am J Hematol 2007;82:976–80.
14. Choi MH, Choe H, Park Y, Nah H, Kim S, Jeong SH, *et al*. The effect of therapeutic leukapheresis on early complications and outcomes in patients with acute leukemia and hyperleukocytosis: a propensity score-matched study. Transfusion 2018;58:208–16.
15. Stahl M, Wei W, Montesinos P, Lengline E, Shallis RM, Neukirchen J, *et al*. Impact of leukapheresis and time to chemotherapy on outcomes of newly diagnosed patients (pts) with Acute Myeloid Leukemia (AML) presenting with hyperleukocytosis: An analysis from a large international patient cohort. Blood 2018;132:1428.
16. Pastore F, Pastore A, Wittmann G, Hiddemann W, Spiekermann K. The role of therapeutic leukapheresis in hyperleukocytotic AML. PLoS One 2014;9:e95062.
17. Stahl M, Pine A, Hendrickson JE, Litzow MR, Luger S, Stone RM, *et al*. Beliefs and patterns of practice in the management of hyperleukocytosis and leukostasis among health care providers for patients with acute leukemia: A large north american web-based survey. Blood 2017;130:1129.
18. Shallis RM, Stahl M, Bewersdorf JP, Hendrickson JE, Zeidan AM. Leukocytapheresis for patients with acute myeloid leukemia presenting with hyperleukocytosis and leukostasis: a contemporary appraisal of outcomes and benefits. Expert Rev Hematol 2020;13:489–99.
19. Novotny JR, Müller-Beissenhirtz H, Herget-Rosenthal S, Kribben A, Dührsen U. Grading of symptoms in hyperleukocytic leukaemia: a clinical model for the role of different blast types and promyelocytes in the development of leukostasis syndrome. Eur J Haematol 2005;74:501–10.
20. Piccirillo N, Laurenti L, Chiusolo P, Sorà F, Bianchi M, De Matteis S, *et al*. Reliability of leukostasis grading score to identify patients with high-risk hyperleukocytosis. Am J Hematol 2009;84:381–2.

How to cite this article: Enright TL, Bui AH, Rose WN. Leukostasis Due to Acute Myeloid Leukemia with Monocytic Differentiation that Resolved after Leukapheresis. Int J Recent Sur Med Sci. 2023;9:117–21. doi: 10.25259/IJRSMS-2022-2-6