Therapeutic Leukapheresis in Acute Leukaemia with Hyperleukocytosis: A Series of Three Cases

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ABSTRACT

Acute Myeloid Leukaemia (AML) is a haematological malignancy marked by uncontrolled proliferation of immature myeloid cells, impairing normal blood cell production. Hyperleukocytosis, defined as a leukocyte count >100,000/µL (4000-11,000 cells/µL), increases blood viscosity and causes leukocytes to clump, leading to reduced blood flow and stasis. This leukostasis can result in complications like end-organ damage, tumour lysis syndrome, and disseminated intravascular coagulation. Chemotherapy may exacerbate these issues by triggering tumour lysis syndrome and other severe complications. Therefore, therapeutic leukapheresis can be the treatment of choice in such situations. In this case series, we share our experience in managing three AML cases that presented with life-threatening symptoms. All three patients presented to our centre with signs and symptoms of leukostasis, with hyperleukocytosis evident in their complete blood cell counts. If left untreated, these cases could have led to severe complications and even death. After evaluating the clinical and laboratory parameters, therapeutic leukapheresis was initiated to reduce leukocyte counts, leading to significant improvement in the patient's condition. This case series emphasises the critical role of leukapheresis as a potentially life-saving intervention.

INTRODUCTION

Leukostasis is a life-threatening complication of AML with a mortality rate of 20-40%. It is caused by abnormal increase in the leukocyte count. Blood viscosity increases due to the high volume of less deformable leukaemic blasts, which can obstruct microvessels and reduce blood flow, especially in AML due to the larger size of myeloblasts [1]. Most commonly obstructed microvessels were pulmonary and central nervous system. After obstruction, interaction between blasts and endothelial cells occurs, where cytokine release and adhesion molecules promote blast cell attachment to blood vessel walls. This interaction, along with increased oxygen consumption by leukaemic blasts, can lead to vascular occlusion and ischaemic tissue damage, causing complications like haemorrhages and respiratory failure [2]. Early recognition and appropriate treatment are crucial to minimise complications, with the primary goal is to reduce the White Blood Cell (WBC) count [3]. Hyperleukocytosis is a major contributor to early mortality in both adults and children with acute myeloblastic leukaemia or other hyperleukocytic leukaemias, mainly due to complications like pulmonary or central nervous system haemorrhages [4].

Leukapheresis is an invasive procedure preferred for its immediate cytoreductive effect. During this process, WBCs are mechanically separated from the patient's blood using a machine. The WBCs are concentrated and extracted, while other blood components- such as red blood cells, plasma, and platelets- are reinfused into the patient [5]. Therapeutic leukapheresis has proven to be an effective intervention to reduce the leukaemic cell count, thus enhancing patient outcomes.

This case series includes three patients who were admitted to our hospital over a span of seven years, (from 2018 to 2024), demonstrating the successful application of therapeutic leukapheresis in treating acute leukaemia with hyperleukocytosis and related complications. They offer valuable lessons in clinical decision-making and multi-disciplinary management.

Case 1

A 56-year-old male weighing 85 kg, with a history of AML (AML M4 with monocytic differentiation) for the past year, was admitted due to severe breathing difficulties and disorientation lasting for 6 hours. His SpO_2 was low (89%), so Non-Invasive Ventilation (NIV) was initiated. Baseline investigations showed haemoglobin 7.3 g/dL (13-17 g/dL), total leukocyte count 1,28,640/µL (4000-11,000 cells/µL), neutrophil 13% (40-60%), monocyte 32% (2-8%) and platelet count 29,000/cu.mm (1.5-4.5 lakhs/cu.mm). Peripheral blood smear demonstrated hyperleukocytosis [Table/Fig-1]. Computed Tomography (CT) thorax indicated right sided pleural effusion along with collapse and consolidation of underlying lung parenchyma [Table/Fig-2,3].
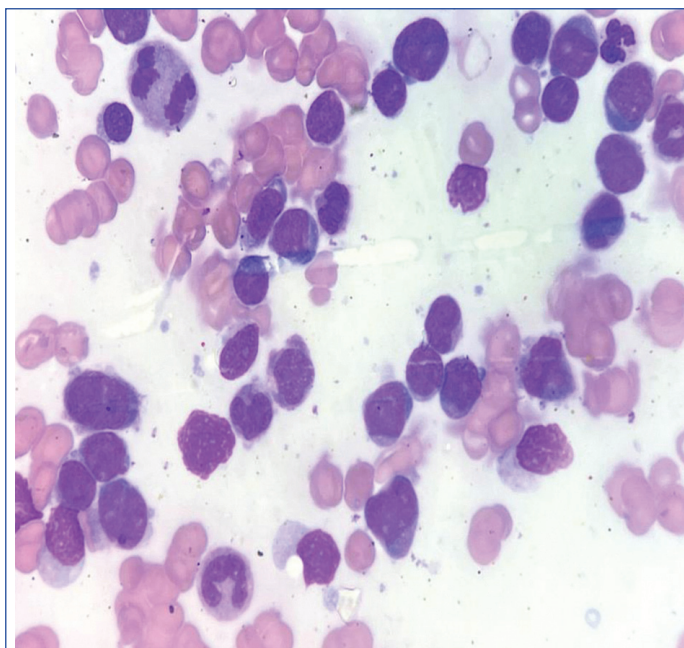
[Table/Fig-1]: Peripheral blood film stained with Giemsa reveals an elevated leukocyte count, with 70% of the cells being blasts. These blasts are large, with moderate cytoplasm, vesicular nuclei, and prominent nucleoli. Additionally, there is decreased red blood cell and platelet count.

Patient was subsequently transferred to Intensive Care Unit (ICU) for further management. Bone marrow aspiration results showed
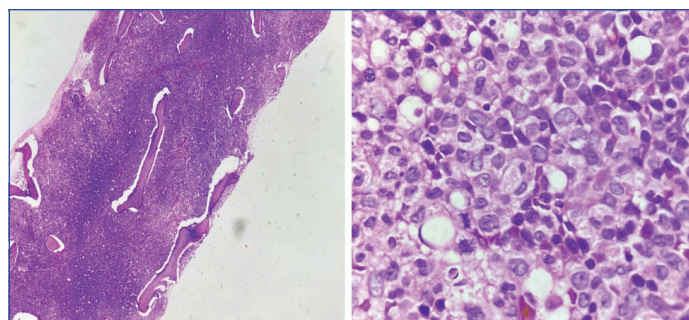
[Table/Fig-2,3]: Axial and coronal view of chest computed tomography demonstrating right sided pleural effusion with associated subsegmental atelectasis of dependant basal segment of the right lower lobe. (Images from left to right)

[Table/Fig-4,5]: These are bone marrow biopsy-stained images revealing hyperleukocytosis, marked by an elevated count of White Blood Cells (WBCs), predominantly consisting of blasts or immature cells. The presence of immature granulocytes suggests active haematopoietic activity, which may be a response to leukaemia. The high number of blasts indicates blast crisis. (4x, 40x). (Images from left to right)

hypercellular marrow containing abnormal cells. In view of hyperleukocytosis induced leukostasis, therapeutic leukapheresis was planned immediately and central line was secured in the right internal jugular vein. Informed consent was obtained for the high-risk procedure and which was then initiated. Apheresis machine used for the procedure was COMTEC Fresenius Kabi. A total blood volume of 10 litres was processed, with each cycle handling 300 mL of blood. The procedure consisted of 34 cycles, and at the end of the process, 325 mL of WBCs with plasma was removed. Duration of the procedure was three hours. To prevent hypocalcaemia induced by the Acid Citrate Dextrose (ACD) anticoagulant, intravenous calcium gluconate was administered during the procedure. The patient tolerated the procedure well, and there were no adverse reactions. Postprocedure, the total leukocyte count decreased to 65,180/μL. Patient showed symptomatic improvement, with reduced breathing difficulty and regained orientation. Following haematologist opinion, patient was started on chemotherapy. During chemotherapy, multiple Packed Red Blood Cells (PRBC) and Single Donor Platelet (SDP) transfusions were given to improve haemoglobin level and platelet counts. After improvements in symptoms and blood counts, the patient was discharged on day 14.

Case 2

A 72-year-old male weighing 65 kg presented with shortness of breath for two hours. The patient had a history of fever, cough, and expectoration for the past three days that did not improve with conservative management elsewhere. Upon admission, his blood pressure was low (70/40 mmHg). The patient had a SpO_2 of 94% and was noted to be tachypnoeic, with a respiratory rate of 32 breaths per minute. Intravenous noradrenaline was administered, and the patient was transferred to the ICU for further management. Baseline investigations revealed a haemoglobin level of 5.9 g/dL (13-17 g/dL), a total leukocyte count of 130,400/μL (4000-11,000 cells/μL), with 76% lymphoblasts, and a platelet count of 27,000/cu.mm (1.5-4.5 lacs/cu.mm). The peripheral blood smear showed an increased number of blast cells. Bone marrow aspiration results were suggestive of AML with blast crisis [Table/Fig-4,5]. CT-thorax revealed left-sided pleural effusion with collapse and consolidation of the underlying lung parenchyma [Table/Fig-6].

Due to the elevated total leukocyte count and the presence of blast crisis, therapeutic leukapheresis was planned, and a central line was secured in the right internal jugular vein. After obtaining informed consent for the high-risk procedure, which was then initiated. The apheresis machine used for the procedure was the COMTEC Fresenius Kabi. A total blood volume of 5.8 litres was processed with each cycle handling 300 mL of blood. Procedure consisted of 25 cycles, and at the end of the procedure, 175 mL of WBCs with plasma was removed. The duration of the procedure was two hours. To prevent hypocalcaemia induced by ACD, intravenous calcium gluconate was administered during the procedure. The

[Table/Fig-6]: This is an axial view of chest computed tomography demonstrating left-sided moderate pleural effusion with collapse and consolidation of the underlying lung parenchyma.

patient tolerated the procedure well, and no adverse reactions were noted. Post-procedure, the total leukocyte count was found to be 128,030/μL. Since the leukocyte count was maintaining at same level and no clinical improvement was seen, another cycle of therapeutic leukapheresis was planned. In the subsequent procedure, a total blood volume of seven litres was processed with each cycle handling 300 mL of blood. A total of 35 cycles were performed, and at the end of the procedure, 280 mL of WBCs with plasma was removed. The duration of this procedure was three hours. No adverse reactions occurred during the second procedure. Post-procedure, the total leukocyte count was reduced to 82,880/μL. Total leukocyte counts after each cycle were mentioned in [Table/Fig-7]. The patient later showed symptomatic improvement and was transferred to the ward. Following haematologist opinion chemotherapy was initiated for seven days. After chemotherapy, the patient remained stable and was subsequently discharged.

Laboratory value	Baseline (Pre-procedure)	Therapeutic leukapheresis	
		After cycle 1	After cycle 2
Total leukocyte count (4000-11,000 cells/μL)	130,400/μL	128,030/μL	82,880/μL
[Table/Fig-7]: Total leukocyte counts after each cycle.			

Case 3

A 46-year-old male weighing 70 kg, presented with high grade fever lasting for 10 days which was intermittent and associated with chills and rigour, and not improved with conservative management elsewhere. Patient was admitted and baseline investigations showed elevated total leukocyte count 1,36,000/μL (4000-11,000 cells/μL), haemoglobin 9.4 g/dL (13-17 g/dL), platelet count 61,000/cu.mm (1.5-4.5 lacs/cu.mm), along with deranged renal parameters with creatinine level of 7 mg/dL (0.5-0.9 mg/dL) and hyperuricaemia with uric acid level of 14 mg/dL (2.4-5.7 mg/dL). Bone marrow aspiration and biopsy results revealed hypercellularity which suggests acute leukaemia with 82% blasts [Table/Fig-8].
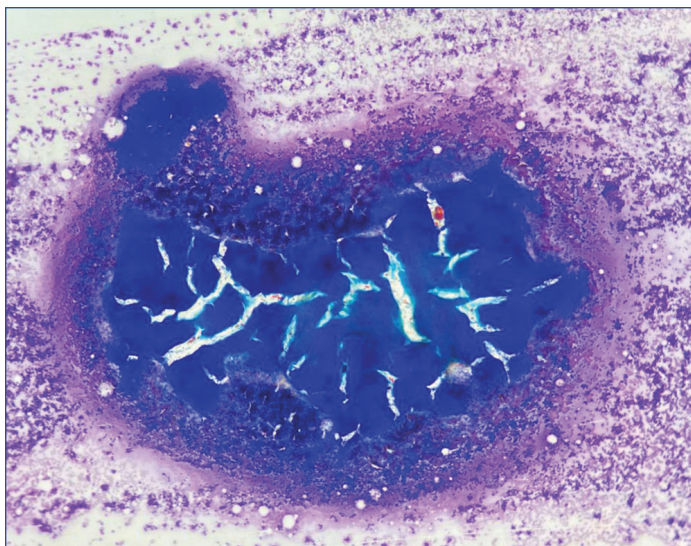
[Table/Fig-8]: Bone marrow aspirate microscopic examination with Giemsa stain indicating hypercellular marrow with highly cellular trails (4x).

In view of worsening respiratory failure and high total leukocyte count, therapeutic leukapheresis was planned and central line was secured. After obtaining informed consent, for high-risk procedure, leukapheresis was initiated. Total blood volume processed was 11.5 litres with each cycle handling 300 mL of blood. Procedure consisted of 39 cycles and at the end, 380 mL of WBCs with plasma was removed. Duration of the procedure was 5 hours. To prevent hypocalcaemia induced by ACD, intravenous calcium gluconate was administered during the procedure. The patient tolerated the procedure well, and no adverse reactions were noted. Post-procedure, the total leukocyte count was reduced to 75,300/µL. Chemotherapy was initiated according to the haematologist's recommendation. The patient developed pancytopenia and received multiple transfusions of PRBC, SDP, and Random Donor Platelets (RDP). Patient later showed improvement in symptoms and blood count, and was subsequently discharged.

DISCUSSION

All the three patients in this study presented with symptoms including breathing difficulties, disorientation, high fever, cough, and expectoration. These manifestations are attributed to elevated leukocyte counts, which cause vascular congestion. If not addressed, this condition can result in severe, life-threatening complications. In patients with AML, hyperleukocytosis is closely associated with prognosis: higher leukocyte counts correlate with a poorer survival rate. A study conducted by Jin Y et al., at Zhongnan Hospital of Wuhan University, China looked at factors before leukapheresis to see how they affected the overall survival of patients with hyperleukocytic leukaemia [6]. The analysis showed that higher the total leukocyte count is the strong predictor of poor survival for these patients.

In our study, to reduce the leukocyte count, therapeutic leukapheresis was initiated and carried out. All three patients tolerated the procedure. It resulted in significant reduction of total leukocyte count. All three patients also showed significant symptomatic improvement like reduced difficulties in breathing immediately (6-24 hours) after the procedure. A similar finding is seen in the study conducted by Zhang D et al., concluded that leukapheresis effectively reduces leukocyte counts and improves circulation with fewer side effects than chemotherapy, but its complexity and cost limit widespread use [7]. It shows short-term survival benefits, though long-term effects are unclear.

Berber I et al., analysed 31 AML patients with hyperleukocytosis and concluded that single leukapheresis session typically lowers the WBC count by 20%-50%, with additional sessions depending on the patient's symptoms and WBC count [8]. In our study, percentage reduction of leukocyte count after single session of leukapheresis was 49.33% in first case, 1.81% (first cycle) and 35.26% (second cycle) in second case and 44.63% in third case (mean=32.75%).

In case 2, despite therapeutic leukapheresis, the post-procedure total leukocyte count, measured 16 hours later, was 128,000/µL (percentage leukocyte reduction was 1.81%). This shows only a minimal reduction from the pre-procedure count.

The probable reason is discussed below:

1. **Ongoing leukocyte production:** In AML blast crisis, rapid production of leukaemic blasts by the bone marrow affects effectiveness of reduction in WBC count achieved by leukapheresis [9].

2. **Rebound effect:** The rebound effect can minimise leukapheresis effectiveness by causing increased bone marrow activity, resulting in surge of new leukocyte production following the procedure [10].

A large systematic review and meta-analysis of 13 studies on leukapheresis for AML patients with hyperleukocytosis found no significant reduction in early mortality compared to non-leukapheresis treatments [11]. Limitations of that study include variability in diagnosis and treatment protocols. Stahl M et al., conducted a survey to explore perceptions on the use of leukapheresis in the management of hyperleukocytosis in AML [12]. Most respondents believed that leukapheresis was beneficial for reducing early mortality only when leukostasis symptoms were present. Regarding long-term survival, 64% of responders felt leukapheresis had no benefit. The survey revealed significant variability in how hyperleukocytosis is defined and managed, with differing views on the indications and outcomes of leukapheresis. Leukapheresis often requires multiple sessions to reduce leukaemia cell burden, but challenges such as limited availability, need for central line access, and delay in chemotherapy hinder its effectiveness [13]. The lack of randomised trials and inconsistent study results leaves its role in cytoreduction unclear. While this procedure may offer symptomatic relief, it does not seem to affect early mortality or long-term survival, especially with severe organ damage [14].

More research trials should be conducted in multiple centres to clarify the role of leukapheresis.

CONCLUSION(S)

Hyperleukocytosis with symptomatic leukostasis is a category II indication (second line of therapy) for therapeutic leukapheresis according to the American Society of Apheresis (ASFA) guidelines. Prophylactic indication is included under category III.

Ongoing leukocyte production and potential rebound effects are key factors influencing the effectiveness of the procedure.

In conclusion, therapeutic leukapheresis, in combination with chemotherapy and adequate transfusion support, reduces mortality and provides significant clinical improvement in patients with hyperleukocytosis-induced symptomatic leukostasis.

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