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CASE REPORT

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A young adult patient with Philadelphia positive acute lymphoblastic leukemia presenting with extreme hyperleukocytosis

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Key Clinical Message

Extreme hyperleukocytosis (Leukocyte count >200 $\times 10^9$/L) in an adolescent young adult (AYA) patient with B-ALL could result in mild symptoms of leukostasis. Hyperleukocytosis requires prompt initiation of therapy with adequate hydration, cytoreduction and prevention of tumor lysis. Ph + B-ALL may present with extreme hyperleukocytosis and may be resistant to initial pre-phase therapy. In such cases, leukocytapheresis is beneficial in reducing the leukocyte count as well as controlling the symptoms.

KEYWORDS

acute lymphoblastic leukemia (ALL), case report, hyperleukocytosis, leukocytapheresis, leukostasis, Philadelphia (Ph+)

1 | INTRODUCTION

Hyperleukocytosis, described as increased peripheral blood leukocyte count >100 $\times 10^9$/L, is one of the adverse clinical prognostic factors of acute leukemias. At the initial presentation, it is a medical emergency because it can lead to fatal complications such as leukostasis, disseminated intravascular coagulation and the development of tumor lysis syndrome (TLS).[1] In the long term, it has been associated with decreased survival.[2] The incidence of hyperleukocytosis ranges from 10% to 30% in ALL with a higher incidence rate in T-ALL than B-ALL.[3,4] Increased leukemic blasts may cause occlusion in the microvasculature leading to leukostasis. Thus, oxygen and nutrients for the tissue requirement to sustain their viability cannot be maintained. Production of proinflammatory cytokines by blast cells results in endothelial dysfunction which facilitates perivascular infiltration by blast cells as well as the tendency to bleeding.[5]

Extreme hyperleukocytosis, defined as leukocyte count >200 $\times 10^9$/L is a relatively rare presentation. More than 50% of the children with leukocyte count >400 $\times 10^9$/L reportedly develop leukostasis syndrome with signs and symptoms mainly involving the lungs and the central nervous system, which mandates rapid reduction of leukocyte counts.[6] Central nervous system involvement occurs in up to 30% of patients with leukostasis and symptoms range from confusion, somnolence, dizziness and headache to delirium, coma and focal neurological deficits. Impaired vision and retinal hemorrhage are common findings.[5,7]

Since the incidence of complications increases with the increasing blast count, special consideration should be given to predisposing risk factors and treatment approaches in patients presenting with extreme hyperleukocytosis. In

Ph + B-ALL, the resistance of Ph + lymphoblasts to initial steroids has long been recognized. Extreme hyperleukocytosis and steroid-resistant phenotype may be associated with tyrosine kinase activation. While prompt initiation of disease specific treatment together with prophylaxis against TLS is utmost important, resistance to pre-phase corticosteroids may increase the risk of morbidity and mortality in patients presenting with leukostasis.

Although still controversial, leukocytapheresis is an effective way of cytoreduction if signs and symptoms of leukostasis are present.[8–11]

2 | CASE HISTORY

A 22-year-old male university student with no known disease or medication history was admitted to the dermatology clinic with complaints of persistent local swelling in the foot after a recent insect bite. The patient was immediately referred to the Hematology Clinics of Ankara Bilkent City Hospital due to hyperleukocytosis on the complete blood count (CBC). The patient had associated complaints of fatigue and hair loss. The personal and family history did not reveal any relevant findings while the physical examination showed an enlarged spleen and liver.

2.1 | Differential diagnosis, investigations and treatment

In the CBC, the patient had a total leukocyte count of 542 $\times 10^9$/L, hemoglobin 10.2 g/dL and a platelet count of 99 $\times 10^9$/L. The biochemistry values were in normal ranges except for a moderately increased lactate dehydrogenase to 425 u/L and there were no signs of tumor lysis. Peripheral blood smear consisted of 80% lymphoblasts and the bone marrow aspiration revealed diffuse blast cell infiltration. Immunophenotypically, these cells were nuclear Terminal deoxytidyl Transferase (nTdT), CD19, CD10, CD34, CD79a, CD58, CD9, CD81(partial), CD22, HLA-DR positive, which was compatible with B-ALL. Bone marrow pathology revealed a hypercellular bone marrow with diffuse TdT, CD34 and PAX5 positive blast cell infiltration (Figure 1).

A pre-phase treatment with methylprednisolone and vincristine was started immediately. Since the patient had mildly increased uric acid and normal creatinine and urea levels, prophylaxis against TLS was done with adequate hydration and allopurinol. Additionally, he did not develop TLS after treatment with chemotherapy. However, the desired response to pre-phase treatment could not be obtained.

Moreover, an ophthalmoscopic examination performed due to the symptoms of somnolence and blurred vision revealed dilatation of bilateral retinal venous structures, increased tortuosity, and scattered punctate retinal hemorrhages which were compatible with leukostasis syndrome.

Therefore, leukocytapheresis was performed on two consecutive days, by Fresenius (v. OAZT1591, Comtec, Germany) using continuous flow apheresis and processing 1.5–2 times the total blood volume. A total volume of 623 mL anticoagulant citrate dextrose solution-A (ACD-A) was used with a ratio of 1:8 and a sedimenting agent was not used. On each day, respectively 400- and 550-ml product were collected and discarded.

At the end of the two sessions of leukocytapheresis, a decrease of the leukocyte count by slightly more than 50% to 211 $\times 10^9$/L could be achieved, which was accompanied by the alleviation of symptoms.

Induction protocol according to Linker 1A with daunorubicin, vincristine and dexamethasone was started. Despite the 18th day of treatment, lymphoblasts were not cleared on the peripheral blood smear. Imatinib was added to the patient's treatment after the real-time polymerase chain reaction analysis revealed positive for t (9;22) (q34; q11) p190 and the treatment was switched to Dasatinib 140 mg/day after necessary approvals were obtained. The initial molecular and cytogenetic analysis was positive for t(12;21) (p13;q22) ETV6/RUNX1 and negative for t(1;19) TCF3(E2A)-PBX1 and t(4;11) AFF1(AF4)-KMT2A(MLL;KMT2A).

Peripheral blood blast clearance was achieved 1 week after starting the tyrosine kinase inhibitor. The changes in the patient's leukocyte count and the graphic showing the treatment protocol are shown in Figure 2. On the 23rd day of treatment, the fundus examination ruled out the presence of papilledema, which permitted prophylactic administration of intrathecal methotrexate 12 mg. Cerebrospinal fluid was acellular with no lymphoblasts detected on cytology. The patient recovered from neutropenia on day 24 and the bone marrow biopsy performed on day 28 was compatible with an incomplete hematological response with 9% residual blasts.

Complete hematological remission was obtained at the end of the second cycle of ALL induction therapy (Linker 1 B; cytarabine and etoposide). After the 4th cycle, the patient was still in complete hematological remission with both immunophenotypic and molecular MRD positivity.

Since the patient did not have a suitable sibling donor, an unrelated donor HSCT after an appropriate bridging treatment is planned.

3 | DISCUSSION

Acute lymphoblastic leukemia presenting with extreme hyperleukocytosis with a leukocyte count higher than 500 $\times 10^9$/L is extremely rare. High leukocyte count can lead

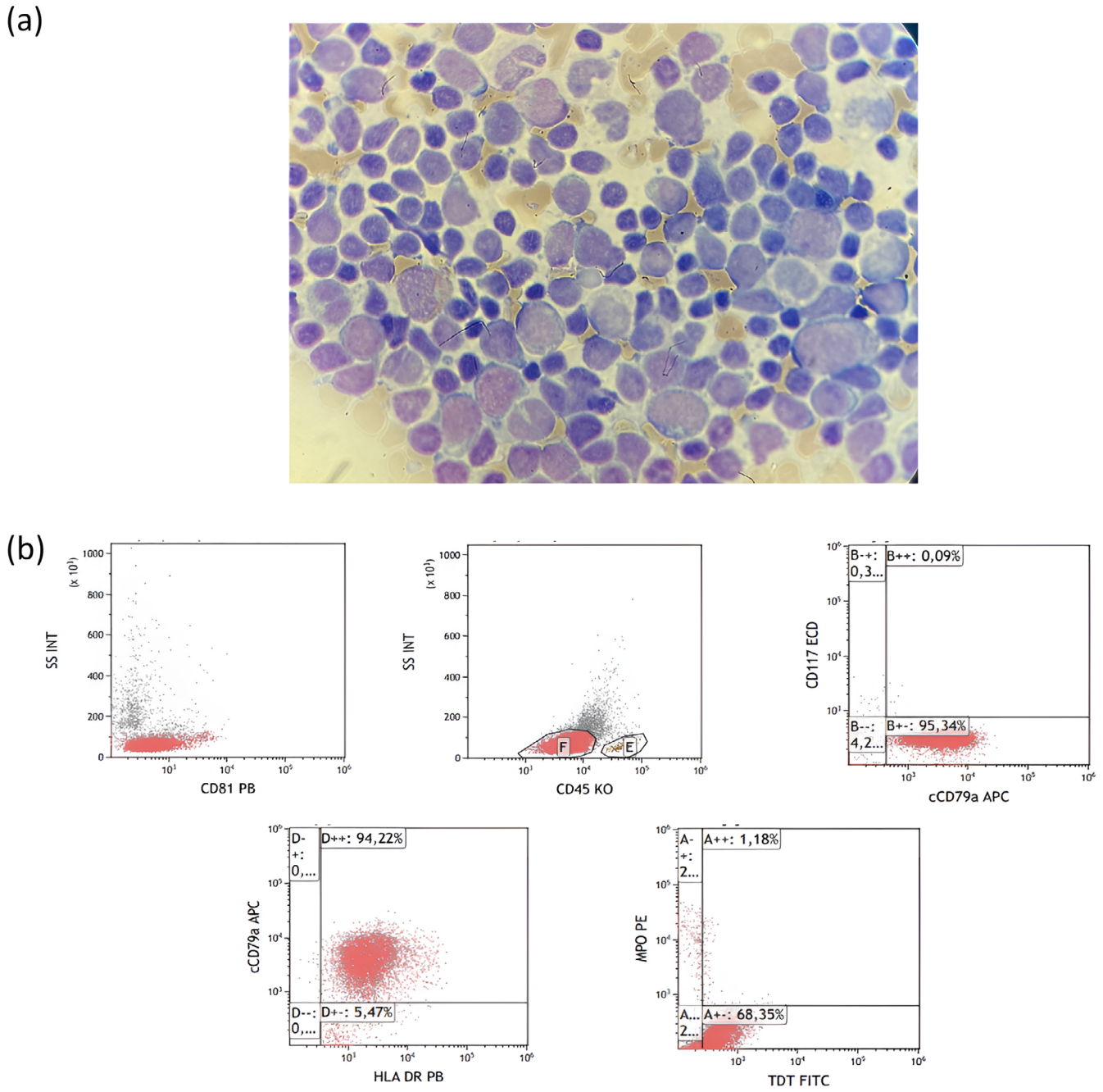

FIGURE 1 (A) Flow cytometry analysis shows positivity for CD45, TdT, HLA-DR, CD79a and CD81. (B) Bone marrow aspiration shows diffuse blast cell infiltration.

to many fatal complications such as, leukostasis, disseminated intravascular coagulation, and TLS. Leukostasis symptoms can occur in different organ and systems.

While neurologic symptoms vary from confusion to coma, pulmonary symptoms can range from dyspnea to respiratory distress.[1–3] It should be noted that clinical findings of leukostasis may not be apparent in younger patients. Even a slight somnolence or blurred vision should alert for a fundoscopic examination for papilledema and specific features of leukostasis in the retinal vasculature. Our case was an AYA presenting with extreme leukocytosis and neurological symptoms. Hyperleukocytosis requires prompt initiation of therapy with adequate hydration, cytoreduction and prevention of tumor lysis.[1–3] Intially, we started a pre-phase treatment to test the sensitivity of ALL blasts and also to be able to manage the early signs of TLS. However, besides presenting with extreme hyperleukocytosis and leukostasis, he was resistant to initial pre-phase treatment and had to undergo daily leukocytapheresis for 2 days before an adequate cytoreduction of 50% could be achieved. Both initially and with the subsequent therapy, the patient did not have any signs or symptoms of TLS.

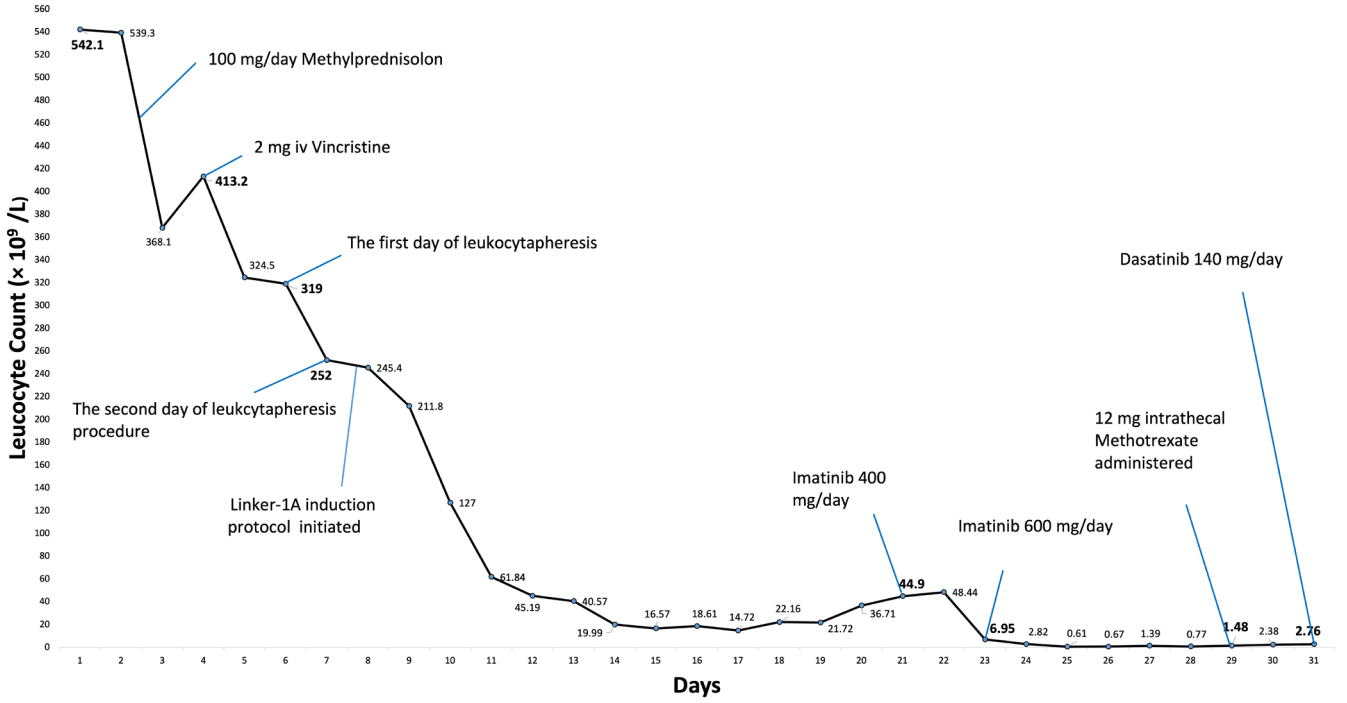

FIGURE 2 The changes in the leukocyte count during the pre-phase and induction therapies.

Although its role in short-term mortality and overall survival is still controversial, leukocytapheresis is an effective way of cytoreduction if signs and symptoms of leukostasis are present.

It should be noted that the non-randomized trials which could not demonstrate the survival benefit of leukapheresis mainly accumulated patients with AML.[12,13]

Thus, the recently published American Society for Apheresis consensus guidelines recommends leukocytapheresis as a category III grade 2B therapeutic approach for patients with symptomatic hyperleukocytosis, who do not respond to first-line cytotoxic chemotherapy.[14] Leukocytapheresis may be useful in ALL cases presenting with hyperleukocytosis especially if the patient has leukostasis and Ph chromosome positivity. Tyrosine kinase activation seems to be associated with extreme hyperleukocytosis and renders the patients insensitive to steroids, which may be associated with the poor prognostic nature of the Ph + ALL.[8,9]

Besides presenting with hyperleukocytosis, responses of our patient to conventional chemotherapeutics were also suboptimal.

The patient could achieve peripheral blood blast clearance only after initiation of a tyrosine kinase inhibitor. Moreover, at the end of the first course of therapy, he recovered with residual blasts in the bone marrow. The patient achieved complete hematological remission without molecular remission only after 2 courses of therapy. It is also noteworthy that even after 4 courses, he still had immunophenotypic and molecular MRD. Since attaining complete molecular remission is desired before Allo HSCT, novel therapies such as targeted monoclonal antibody-drug conjugates or bispecific T-cell engagers will be integrated before proceeding to transplantation.[15,16]

4 | CONCLUSION

This case demonstrates a very rare case of extreme hyperleukocytosis (leukocyte count of 542 $\times 10^9$/L) in an AYA patient with Ph + B-ALL. The patient had disproportionately mild symptoms of leukostasis such as mild somnolence and blurred vision. Hyperleukocytosis requires prompt initiation of therapy with adequate hydration, cytoreduction and prevention of tumor lysis. However, it should be kept in mind that Ph + B-ALL, as in our case, may be resistant to initial pre-phase therapy. In such conditions, leukocytapheresis may be beneficial in reducing the leukocyte count as well as controlling the symptoms of leukostasis.

AUTHOR CONTRIBUTIONS

Gulten Tikit: Investigation; visualization; writing – original draft; writing – review and editing. **Elif Yucesu:** Writing – review and editing. **Aliye Serpil Sarıfakıoglu:** Writing – review and editing. **Imdat Dilek:** Writing – review and editing. **Sule Mine Bakanay:** Conceptualization; supervision; visualization; writing – original draft; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

There are no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

Our case report is exempt from ethical approval in our institution. The reason is, it is case report only.

CONSENT

Written informed consent was obtained from the patient for publication of this case report and accompanying data.

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