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The Role of Plasmapheresis and Exchange Transfusion in Pediatric Acute Leukemia - Case Report of an Infant with Extreme Hyperleukocytosis

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Abstract

Hyperleukocytosis in children with acute lymphoblastic leukemia is a rare and potentially life-threatening complication that has to be treated promptly with chemotherapy, hydroxyurea, leukapheresis or exchange transfusion. Many different studies gave conflicting results considering the best approach in patients with extremely high white blood cell count. We present a case report of an infant with MLL rearranged acute lymphoblastic leukemia, who presented with extreme hyperleukocytosis (white blood cell count of 2,000 × 10^9/L), and severe anemia (hemoglobin level of 3.9 g/dL), who was successfully treated with exchange transfusion, followed by chemotherapy according to Interfant 2006 protocol. The case report presents a successful treatment of an infant with extreme hyperleukocytosis and anemia and highlights the indications for exchange transfusion and leukapheresis.

Keywords: Hyperleukocytosis; Leukostasis; Pediatric ALL; Exchange transfusion

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Introduction

Hyperleukocytosis is a life-threatening condition in acute leukemia, usually defined as a White Blood Cell (WBC) count of >100 × 10^9/L. We present a case of an infant with extreme hyperleukocytosis with a WBC count of 2,000 × 10^9/L and concomitant severe anemia with Hemoglobin (Hb) level of 3.9 g/dL due to acute lymphoblastic leukemia, who presented with leukostasis and respiratory symptoms and was treated with Exchange Transfusion (ET).

Case Presentation

The 11-month-old girl without a relevant family history or any previous medical conditions was admitted to the Pediatric Clinic of University Medical Centre Ljubljana due to fatigue and paleness. Upon admission, she was clinically stable and marked hepatosplenomegaly was present. The first laboratory test showed extreme leukocytosis with a WBC count of 2,000 × 10^9/L, Hb level of 3.9 g/dL, Platelet (PLT) count of 26 × 10^9/L, lactate dehydrogenase level of 29.76 µkat/L and uric acid level of 431 µmol/L (Figure 1: Blood sample tube). There was no major electrolyte imbalance and arterial blood gas analyses were normal. Coagulation tests revealed increased Prothrombin Time (PT) and activated Partial Thromboplastin Time (aPTT). No mediastinal mass was found on a chest X-ray, but diffuse pulmonary infiltrates were present. The girl had no cardiocirculatory or neurological manifestation of leukostasis but the signs of respiratory failure developed on the day of admission. She was sedated, orally intubated and mechanically ventilated. RBC transfusion was not given despite severe anemia due to extreme hyperleukocytosis. She received hyperhydration, rasburicase, PLT transfusion and vitamin K to ensure optimal coagulation. Due to the combination of extreme hyperleukocytosis, severe anemia and low body mass of 10 kg, ET was performed manually with reconstructed whole blood at a rate of 25 ml every 4 min to 5 min. Over 4.5 h 1,250 ml or 1.5 of total blood volume was exchanged, causing a substantial drop in WBC count. During the procedure, the patient did not develop any adverse events. First laboratory results after the ET demonstrated a WBC count of 522 × 10^9/L, a Hb level of 7.1 g/dL and a PLT count of 43 × 10^9/L. Since blasts

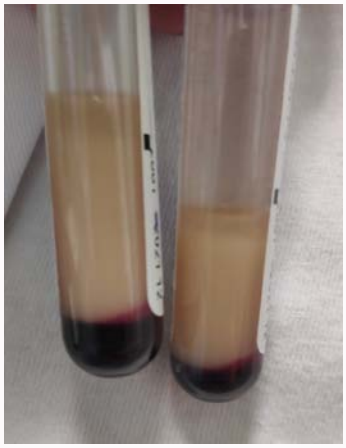

Figure 1: Blood sample tube.

in the peripheral blood were defined as lymphoblasts, therapy with steroids was started immediately after ET, still within the first 24 h after the admission. Bone marrow aspiration confirmed B-cell ALL with Mixed-Lineage Leukemia (MLL) rearrangement and since the girl was just under one year of age, she was treated according to the Interfant 2006 protocol. The girl responded well to chemotherapy and is currently in remission and receiving maintenance therapy.

Discussion

Hyperleukocytosis is a life-threatening condition in acute leukemia, usually defined as >100 × 10^9 WBC/L, and can be seen in 5% to 20% of patients [1,2]. It can lead to leukostasis syndrome, Tumor Lysis Syndrome (TLS) with metabolic abnormalities, severe coagulopathy and multiorgan failure, with a possible evolution of clinical signs from mild to life-threatening within hours [3]. Leukostasis, a potentially deadly complication of hyperleukocytosis, is a result of increased blood viscosity due to the high number of rigid large blasts. Since myeloblasts are bigger than lymphoblast's, leukostasis in Acute Myeloblastic Leukemia (AML) develops at a lower WBC count compared to Acute Lymphoblastic Leukemia (ALL). The risk factors of hyperleukocytosis and leukostasis in children with AML are age below one year, FAB M1, M4 and M5 and genetic alterations such as inv(16) and presence of FLT3-ITD$^+$ [4]. In ALL hyperleukocytosis is associated with age below one and above nine years, male sex, T-cell immunophenotype and genetic alterations such as KMT2A rearrangement or BCR-ABL fusion [3-5]. Hyperleukocytosis can present with the pulmonary, Central Nervous System (CNS) and metabolic complications. Severe pulmonary complications present with hypoxia, tachypnea, dyspnea, diffuse alveolar hemorrhage, respiratory failure and changes on chest X-ray [1,2,6]. The need for mechanical ventilation usually develops in patients with a WBC count of >650 × 10^9/L and >200 × 10^9/L in ALL and AML respectively [7]. Central nervous system signs of leukostasis are blurred vision, tinnitus, dizziness, headache, papilloedema, confusion, delirium, somnolence and coma [1,2]. Lowe reported that CNS complications in children with ALL developed in 3,6% of those with WBC count <400 × 10^9/L and in 17.9% when WBC count was >400 × 10^9/L [8]. Metabolic complications include hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia [3,4]. The coagulation disorders with Disseminated Intravascular Coagulation (DIC) develop as a result of extrinsic pathway activation due to high levels of tissue factor from WBC and due to high cell turnover [9]. Leukostasis can also cause priapism, congestive heart failure and peripheral vascular occlusion [1,2]. The diagnosis of leukostasis is based on clinical signs. A grading score to help evaluate the risk for leukostasis and indication for leukapheresis was proposed by Novotny et al. and is based on the severity of pulmonary, CNS and other symptoms. So defined leukostasis was graded as not present (group 0) in case of no symptoms and possible (group 1), when mild pulmonary or CNS symptoms with tinnitus, headache or dizziness are present. Hyperleukocytosis is probable (group 2) in case of limitations due to pulmonary or CNS manifestations with visual disturbances, severe tinnitus, headache or dizziness, and highly probable (group 3), in case of dyspnea at rest or need for additional oxygen or mechanical respiratory support and if severe visual disturbances, confusion, delirium, somnolence, intracranial hemorrhage, myocardial infarction, priapism or ischemic necrosis develop [10]. Since hyperleukocytosis is a potentially life-threatening condition, treatment should be started promptly with chemotherapy, hydroxyurea or leukapheresis, the optimal approach still being unknown. To reduce the WBC count and blood viscosity induction chemotherapy or hydroxyurea can be used, the last being especially suitable for treating the patient with not yet identified hematological malignancy [3]. These approaches can be effective, but metabolic complication with TLS has to be prevented by using allopurinol or rasburicase. Other options for reducing WBC count and blood viscosity as well as reducing the severity of TLS and DIC are leukapheresis and ET. Leukapheresis is a procedure primarily used in AML but has been used also for ALL, chronic myeloid leukemia and chronic lymphocytic leukemia. It is contraindicated in Acute Promyelocytic Leukemia (APL) due to the increased risk of fatal hemorrhage. It enables the removal of WBCs with a reduction of blood viscosity, whereas RBC, PLT and plasma are returned to the patient. Additionally, by giving FFP before leukapheresis, the risk of bleeding complications can be further reduced. During leukapheresis, PLT transfusion is usually given to keep the PLT count above 30 × 10^9/L. Red blood cell transfusion is usually withheld until after the first leukapheresis [10]. Leukapheresis was studied by many authors. A large meta-analysis by Orbeiar et al. showed no difference in early death rate in 1,500 adult and pediatric patients with AML and WBC count >100 × 10^9/L who were treated with leukapheresis, hydroxyurea or chemotherapy [11]. COG study which included 256 children with AML and WBC count >100 × 10^9/L also showed that leukapheresis did not reduce induction mortality [4]. Another study published by Nguyen et al. [5] concluded that children with ALL and WBC count >200 × 10^9/L have no benefit from leukapheresis, and Chen et al. [12] have shown that high-dose chemotherapy in children with AML and hyperleukocytosis reduces mortality rate if it is started within hours, making leukapheresis, hydroxyurea and low-dose chemotherapy not needed in a routine manner. Porcu analyzed the results of 48 patients who were treated with leukapheresis due to hyperleukocytosis and found out that there was no correlation between the degree of leukoreduction and early mortality rate [13]. On the other hand, a high WBC count was associated with an increased risk for hypoxia, coagulopathy with pulmonary and CNS hemorrhage, renal failure and early death [4,13]. Despite controversial results, some authors suggest using leukapheresis in the case of WBC count of >400 × 10^9/L and >100 10^9/L in ALL and AML respectively [14]. According to the 2019 Guidelines on the Use of Therapeutic Apheresis in Clinical Practice, which was published by the American Society of Apheresis, symptomatic hyperleukocytosis secondary to AML or ALL is a category II (accepted as second-line therapy, either as a standalone

treatment or in conjunction with other modes of treatment) and grade 2B recommendation (weak recommendation, moderate-quality evidence) [15]. Prophylactic leukapheresis is a category III (optimum role of apheresis therapy is not established and decision making should be individualized) with grade 2C recommendation (weak recommendation and low-quality or very low-quality evidence) [15]. Novotny published a grading score to evaluate the risk for leukostasis and concluded that leukapheresis had a definitive effect on the improvement of symptoms if patients had probable or highly probable leukostasis (grade 2 or 3) [10]. When leukapheresis is performed, 1.5 to 2 blood volumes are usually processed and total WBC can be reduced by 30% to 60%, followed by the rapid improvement of clinical condition [15]. It should be repeated as long as the WBC count does not drop below 50-100 × 10^9/L and 400 10^9/L in AML and ALL patients respectively and as long as symptoms persist [15]. Giving FFP before leukapheresis and keeping the PLT count above 30 × 10^9/L reduce the risk of bleeding complications. Red blood cell transfusion is usually withheld until after the first leukapheresis [10]. Importantly, the decision to perform leukapheresis should in no way postpone the start of the treatment with chemotherapy or hydroxyurea. The important limitation during leukapheresis in small children is the proportion of extracorporeal volume which should not exceed 15% of total blood volume [16]. In children weighing less than 10 kg, whole blood ET can be used instead of automated cell separators. Since transfusion of RBC is not indicated in the hemodynamically stable child with hyperleukocytosis due to a risk of a further increase in the blood viscosity, ET is an option that enables a drop in WBC count and a rise in Hb level [17]. Clinical studies comparing apheresis and ET are lacking. Kurnaz et al. also published a retrospective study in which 29 adult patients with hyperleukocytosis were treated with leukapheresis with or without volume replacement. There was no difference in overall survival between patients with and without volume replacement but the early mortality rate was lower in the group of patients who had volume replacement, probably due to a greater reduction of WBC count and removal of cytokines [18]. Importantly leukapheresis and ET can also lead to the delay in the initiation of induction chemotherapy, and to prevent the rebound in WBC count after finishing leukapheresis, chemotherapy or hydroxyurea should be given as soon as possible. In patients with hyperleukocytosis coagulation disorders including DIC are common and supportive therapy with transfusion of PLT, Fresh Frozen Plasma (FFP) and fibrinogen are often indicated. Since a large tumour burden leads often to TLS, adequate hydration and allopurinol or rasburicase should be started promptly. Red Blood Cell (RBC) transfusion increases blood viscosity and should be avoided in patients with hyperleukocytosis [19,20]. In case of a need for RBC transfusion, it should be given after leukapheresis or with an ET.

Conclusion

Hyperleukocytosis and leukostasis are life-threatening conditions in patients with leukemia demanding prompt treatment. The role of leukapheresis and ET in the treatment of hyperleukocytosis is not clear despite the effective reduction of WBC count but can contribute to a rapid improvement of symptoms of leukostasis. Even though published studies included mostly adult and pediatric patients with hyperleukocytosis due to AML and despite their conflicting results, some authors suggest leukapheresis in case of hyperleukocytosis with WBC count of >400 × 10^9/L and >100 10^9/L in ALL and AML respectively. According to Novotny leukapheresis is effective in case of symptomatic hyperleukocytosis of grade 2 or 3. In case of low body mass or concomitant severe anemia, ET could replace leukapheresis. The presented case of an infant with ALL and clinical signs of leukostasis due to extreme WBC count confirms that ET is a feasible alternative to leukapheresis which enables the reduction of WBC, safe correction of anemia and improvement of clinical status.

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