OLGU SUNUMU / *CASE REPORT*

Acute Myeloid Leukemia (M4)/Myeloid Sarcoma Presenting with Hyperleukocytosis, 47,XX + mar Case

Akut Miyeloid Lösemi (M4)/Hiperlökositoz ile Kendini Gösteren Miyeloid Sarkom, 47,XX + mar Vakası

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ABSTRACT

Hyperleukocytosis is defined as a blood blast count >100.000/mm3 and may occur most commonly in monocytic (M4) acute myeloid leukemia (AML). Hyperleukocytosis is a medical emergency associated with lung and central nervous system leukostasis. An 18-month-old female patient was brought to our clinic with anemia, thrombocytopenia, and leukocytosis with bilateral palpebral swelling/proptosis, a palpable mass in the midline, and lymphadenopathy in the neck. Myeloid sarcoma was suspected. The patient had AML M4 morphological features, and 47,XX + mar was detected in bone marrow karyotype analysis. She had complications such as hyperleukocytosis, leukostasis (blurring of consciousness, tachypnea/tachycardia), tumor lysis syndrome, and disseminated intravascular coagulation. In addition to low-dose cytoreduction chemotherapy, leukocyte apheresis was performed. All symptoms and complaints of the patient disappeared. Therefore, myeloid sarcoma should be considered in young children with orbital swelling/proptosis, an abdominal mass, high leukocyte count at diagnosis, AML M4 morphological features, and diffuse intravascular coagulation.

Keywords: acute myeloid leukemia; myeloid sarcoma; hyperleukocytosis; disseminated intravascular coagulation

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ÖZET

Hiperlökositoz 100.000/mm3'ten yüksek bir kan blast sayısı olarak tanımlanır ve en sık olarak monositik (M4) akut miyeloid lösemi (AML)'de meydana gelebilir. Hiperlökositoz, akciğerlerde ve santral sinir sisteminde lökostaz ile ilişkili olduğu için tıbbi bir acil durumdur. On sekiz aylık kız hasta kliniğimize anemi, trombositopeni, lökositoz, bilateral palpebral şişlik/proptozis, orta hatta ele gelen kitle ve boyunda lenfadenopati şikâyetleri ile getirildi. Akut miyeloid lösemi M4 morfolojik özelliklere sahip olan hastada miyeloid sarkom düşünüldü ve kemik iliği karyotip analizinde 47,XX+mar tespit edildi. Hiperlökositoz, lökostaz (bilinç bulanıklığı, takipne/taşikardi), tümör lizis sendromu ve yaygın damar içi pıhtılaşması gibi komplikasyonları vardı. Düşük doz sitoredüksiyon kemoterapisine ilaveten, lökosit aferezi yapıldı. Hastanın tüm semptom ve şikâyetlerinin kayboldu. Sonuç olarak; orbital şişlik/proptozis ve batında kitle ile gelen, tanı anında yüksek lökosit sayısı, AML M4 morfolojik özelliklere sahip, yaygın damar içi pıhtılaşması olan ve küçük yaştaki bir çocuk hastada miyeloid sarkom akla gelmelidir.

Anahtar Kelimeler: *akut miyeloid lösemi, miyeloid sarkom, hiperlökositoz, yaygın damar içi pıhtılaşması*

Introduction

Hyperleukocytosis is defined as a blood blast count >100,000/mm^3 and may occur most commonly in monocytic (M4) acute myeloid leukemia (AML). Hyperleukocytosis is a medical emergency associated with lung and central nervous system leukostasis. It causes respiratory failure and often rapidly fatal intracerebral hemorrhage[1,2]. Acquired coagulation disorders are a common complication in patients with AML. Although it is common in acute promyelocytic leukemia (APL), coagulation abnormalities occur in other subtypes of AML, particularly myelomonocytic differentiation, and may present with both hemorrhagic and thromboembolic events. While hemorrhage occurs in 60% of patients with AML at first admission, venous thromboembolism (VTE) develops in 10%. Bleeding in patients with AML may result from disease or treatment-related thrombocytopenia and complex systemic coagulation disorders such as excessive fibrinolysis, disseminated intravascular coagulation (DIC), or nonspecific proteolysis. In this context, abnormal

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tissue factor (TF) expression by transformed myeloblasts or proinflammatory monocytes may contribute significantly to the procoagulant state[3].

An 18-month-old female patient who presented to our clinic with bilateral orbital swelling and proptosis, abdominal mass, hyperleukocytosis, disseminated intravascular coagulation, and bone marrow karyotype analysis 47,XX, + mar was diagnosed with acute myelomonocytic leukemia (M4) and treated.

This report aimed to present a patient with a positive bone marrow karyotype analysis of 47,XX, + mar, diagnosed with acute myelomonocytic leukemia (M4), who presented to our clinic with bilateral orbital swelling and proptosis, abdominal mass, hyperleukocytosis, and disseminated intravascular coagulation.

Presentation of the Case

An 18-month-old female patient was referred to us with the suspicion of malignancy, as anemia, thrombocytopenia, and leukocytosis were detected as a result of the examinations performed at the health center they went to due to swelling on her face. In the physical examination of the patient, pallor, clouding of consciousness, tachypnea/tachycardia, swelling and proptosis in the bilateral palpebral region, diffuse distention in the abdomen, and a palpable mass of approximately 8×8 cm in the midline, lymphadenopathy of 1.5×1 cm in the right submandibular and 2×1.5 cm in the left submandibular were present. The patient's laboratory results were as follows: leukocytes, 153.75×103/μL; hemoglobin, 8.0 g/dL; hematocrit, (%), 23.5; mean corpuscular volume, 80.5 fL; platelet, 74×103/μL; lactate dehydrogenase, 1,513 U/L (135–214); uric acid, 14.2 mg/dl (2.4) -5.7; total protein, 5.15 g/dL (6–8); albumin, 2.61 g/dL (3.8–5.4); sodium, 138 mEq/l (136–145); potassium, 4.1 mEq/l (3.5–5.1); calcium, 7.9 mg/dL (8.8–11); phosphorus, 6.28 mg/dL (2.5–4.5); D-dimer, 2,325 ng/ml (0–500); PT, 38.7 sec (12–16); activated partial thromboplastin time (aPTT), 43.9 sec (25–35); and fibrinogen, 40 mg/dl (245–400). In the abdominal ultrasonography performed urgently, a mass of approximately 11×13×9 cm was observed in the midline. In the peripheral smear, blasts with monocyte character were seen at a rate of 50%. Considering acute myelomonocytic leukemia, allopurinol was started at 10 mg/kg (3 doses) by adding 3,000 cc/m^2/day fluid + 40 mEq/L $NaHCO_3$. Erythrocyte and platelet suspension, 2×15 ml kg/dose fresh frozen plasma (FFP), and 5 mg vitamin K were administered.

The patient was transferred to the pediatric intensive care unit because of tachypnea/tachycardia and the need for leukapheresis. A catheter was inserted through the femoral vein, and leukapheresis was performed once under intensive care. Multiple FFP infusions were performed because of low fibrinogen levels and a long PT and aPTT. Bone marrow aspiration was performed in the patient with blasts in a peripheral smear. Flow cytometry findings were HLA-DR 53%, CD11C 95%, CD 64 97%, CD11B 93%, CD 4 94%, CD 13 79%, CD 14 30%, CD 15 26%, CD 33 98%, and Anti-MPO 18%. Disseminated intravascular coagulation laboratory findings (PT and aPTT length, low fibrinogen, increase in fibrin degradation products) were observed in the patient, and AML (M4) myeloid sarcoma was suspected together with clinical, morphological, and flow cytometry findings. Because the leukocyte count was >100.000 x 103/μL, 20 mg/m2 cytarabine, 2 x 20 mg/kg hydroxyurea, and 20 mg/m2 thioguanine were administered as pre-phase treatment according to the BFM AML-2019 protocol. The patient underwent leukapheresis once, and leukocyte count decreased below 100 x 103/μL (65 x 103/μL), fibrinogen and PT/aPTT values returned to normal, and then was transferred to the ward. Acute myeloid leukemia (M4) myeloid sarcoma was suspected, and the first induction was initiated according to the BFM AML-2019 protocol. Meanwhile, thrombosis developed in the femoral vein of the patient from which the catheter was removed. Enoxaparin at 2 x 100 μ/kg was administered to the patient for 14 days, and it was observed that the thrombosis resolved. After the second induction, swelling/proptosis in the bilateral palpebral region, abdominal distention, midline mass (11×13×9 cm), and lymphadenopathy completely disappeared. The patient's genetic result at the time of diagnosis (47,XX, + mar) was 46,XX after induction therapy. Before all chemotherapy cycles, a blast count <5% was considered for remission. The maintenance treatment was initiated according to the BFM AML-2019 protocol.

Discussion

Acute myeloid leukemia is a highly aggressive hematological malignancy characterized by clonal expansion of transformed myeloblasts. Patients with AML are at high risk for hemorrhagic and thromboembolic

complications. In addition to disease or treatment-induced thrombocytopenia, patients with AML may suffer from complex systemic coagulation disorders such as overt disseminated intravascular coagulation, excessive fibrinolysis, or nonspecific proteolysis[4].

Disseminated intravascular coagulation is more common in AML than ALL and is most common in APL. Almost all patients with APL have DIC at presentation. The incidence of DIC in AML other than APL is between 10% and 30%. Disseminated intravascular coagulation is thought to be caused by the release of tissue factor-like procoagulants from azurophilic granules within leukemia cells. Disseminated intravascular coagulation presents clinically with bruising and, when severe, bleeding from multiple sites. Laboratory findings include thrombocytopenia, hypofibrinogenemia, elevated fibrin breakdown products, and deficiency of clotting factors, including factor V and factor VIII. Other mechanisms, such as excessive fibrinolysis and secretion of interleukin (IL)-1 by AML cells, may contribute to bleeding[1]. Our patient was diagnosed with AML-M4. Due to the PT and aPTT length, low fibrinogen, and increase in fibrin degradation products, treatment for disseminated intravascular coagulation was arranged. It was observed that disseminated intravascular coagulation improved with both supportive treatment and chemotherapy.

While 60% of patients with AML experience bleeding at first admission, 10% have been reported to develop VTE[3]. Thrombosis that developed after catheter removal from our patient's femoral vein responded dramatically to subcutaneous enoxaparin treatment in addition to chemotherapy, and it was observed that the thrombosis disappeared in 14 days. The fact that our patient had AML M4 (myelomonocytic) and that thrombosis was observed in the femoral vein, albeit associated with DIC and catheter, is consistent with the literature regarding its dramatic response to treatment.

Hyperleukocytosis was defined as a blast count >100.000/mm^3. This condition is associated with increased morbidity and mortality and can induce leukostasis, tumor lysis syndrome, and DIC, especially in patients with acute leukemia. In some leukemias, hyperleukocytosis is more common in certain subsets of patients. Hyperleukocytosis in AML appears to be associated with monocytic differentiation[5]. The fact that our patient had AML M4 and hyperleukocytosis was consistent with the literature.

The exact prevalence of hyperleukocytosis in acute leukemia is unknown, but it probably occurs in 5–10% of patients with AML and is slightly higher (>20%) in acute lymphoblastic leukemia. However, acute complications of hyperleukocytosis are closely linked to leukostasis and are most pronounced in cells that show signs of myeloid differentiation. The organs most frequently affected are the central nervous system (CNS), including the lungs and retina[5]. Hyperleukocytosis is a medical emergency associated with leukostasis in the lungs and CNS, causing respiratory failure and often rapidly fatal intracerebral hemorrhage. Pulmonary leukostasis manifests as dyspnea, tachypnea, rales, interstitial infiltrates, and respiratory failure. Central nervous system leukostasis manifests as headaches, blurred vision, somnolence, obtundation, ischemic stroke, and intracerebral hemorrhage[6]. Therefore, the main goal of the initial treatment of hyperleukocytosis and/or leukostasis is to reduce the number of circulating leukemia cells, thus preventing the development of organ failure. The most common method for rapid cytoreduction is leukapheresis, which can be combined with chemotherapy[5]. Interventions with more universal support include coagulation, hyperhydration, optimization of urate oxidase administration, and avoidance of red cell suspension transfusions, which can increase blood viscosity. However, initial treatment with hydroxyurea or low-dose chemotherapy and other interventions involving exchange transfusion or leukapheresis are controversial. Low-dose chemotherapy with hydroxyurea, cytarabine, etoposide, and 6-thioguanine has been used to achieve more gradual cytoreduction. In contrast, leukapheresis has been used to achieve faster cytoreduction, potentially reducing tumor lysis syndrome[7]. Our patient received low-dose chemotherapy with hyperhydration, allopurinol, hydroxyurea, cytarabine, and thioguanine. Since our patient had symptoms, a more gradual cytoreduction was achieved with leukapheresis once, in addition to chemotherapy, to avoid complications of hyperleukocytosis.

Myeloid sarcoma (MS), also known as chloroma, refers to the accumulation of myeloid blasts outside the bone marrow that can cause the destruction or compression of normal tissue. Myeloid sarcoma sites commonly include the CNS, skin, orbit, and bone. The incidence of MS in pediatric patients with AML is approximately 10%. Myeloid sarcoma is more common in patients with high leukocyte counts, younger age, t (8; 21), and AML M4/M5 morphological features at diagnosis[8,9]. Some studies in adults have shown higher relapse rates

and lower survival rates in patients with MS. In children, the prognostic impact of MS appears to depend on its site of involvement[8–10]. Pediatric patients with MS and CNS or orbital involvement showed better survival than those without CNS or orbital involvement and patients without MS. In contrast, relapse rates are higher in children with chloromatous skin involvement. Extramedullary relapses are more common in patients with extramedullary disease at diagnosis[8,11]. Our patient was 18 months of age. She had hyperleukocytosis, AML M4, bilateral proptosis, an abdominal mass, and 47,XX, + mar positivity. However, no t (8; 21) chromosomal translocations were observed. Bilateral proptosis and the abdominal mass disappeared completely after induction treatment. We believe that myeloid sarcoma may be due to the complete disappearance of orbital and abdominal masses with chemotherapy.

Marker chromosomes are defined in the International System for Human Cytogenetic Nomenclature (ISCN=International System for Human Cytogenetic Nomenclature) as an "abnormal chromosome of unknown origin, often found in the karyotype of patients with cancer and patients with structural genetic disorders"[12]. Genetic results of our patient at the time of the first diagnosis: 47,XX, + mar came in as 46,XX after induction therapy.

Therefore, myeloid sarcoma should be considered in young children with orbital swelling/proptosis, abdominal mass, high leukocyte count at diagnosis, AML M4 morphological features, and diffuse intravascular coagulation.

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