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Case Report / *Olgu Sunumu*

Megaloblastic Anemia Due to Intrathecal Methotrexate

İntratekal Metotreksata Bağlı Megaloblastik Anemi

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We diagnosed to the patient as primary mediastinal CD20 positive diffuse large B-cell lymphoma two years ago. The patient received R-CHOP chemotherapy. Complete remission was obtained from chemotherapy. After 18 months, headache, nausea and vomiting occurred. Cranial magnetic resonance imaging showed mass lesions. Cranial radiotherapy was applied. Then intrathecal methotrexate (MTX) was administered at a dose of 12 mg via lumbar puncture twice weekly for 6 weeks. Pancytopenia was detected after ten days of the discontinuation of intrathecal MTX. There were apparent megaloblastic changes on the bone marrow aspiration and biopsy. The biochemical parameters were folic acid 6.22 ng/ml (N:4.2-19.99) and cobalamin 803 pg/ml (N:197-866). The patient was treated with oral folic acid 5 mg/day. Hematological parameters were hemoglobin 10.2 g/dl, platelet count 432 000/mm^3, and leukocyte count 5100/mm^3 at the 14th day. In conclusion, the patients treated with intrathecal MTX should be followed-up and folic acid prophylaxis may be considered.

Key words: Intrathecal methotrexate; lymphoma; megaloblastic anemia.

İki yıl once primer mediastinal CD20 pozitif yaygın büyük B hücreli lenfoma tanısı koyduğumuz hasta, R-CHOP kemoterapisi aldı. Kemoterapiden sonra tam yanıt elde ettik. On sekiz ay sonra baş ağrısı, bulantı ve kusma şikayetleri başladı. Kraniyel magnetik görüntülemede kitle tespit edildi. Kraniyel radyoterapi uygulandı. Haftada 2 kez 6 hafta süreyle lumbar yolla 20 mg intratekal methotrexate (MTX) verildi. Intratekal methotrexate kesildikten 10 gün sonra pansitopeni gelişti. Kemik iliği aspirasyon ve biyopsisinde megaloblastik değişiklikler gözlendi. Biyokimyasal değerlerinde folik asid 6.22 ng/ml (N:4.2-19.99) ve kobalamin 803 pg/ml (N:197-866) idi. Oral folik asit 5 mg/gün başlandı. Ondördüncü günde hemoglobin 10.2 g/dl, platelet sayısı 432 000/mm^3 ve lökosit sayısı 5100/mm^3 idi. Sonuç olarak intratekal methotrexate ile tedavi edilen hastalarda takip ve folik asit profilaksisi düşünülebilir.

Anahtar sözcükler: İntratekal metotreksat; lenfoma; megaloblastik anemi.

Megaloblastic anemia is usually caused by a deficiency or defective absorption of either vitamin B_{12} or folic acid. The most common cause is cobalamin or folic acid deficiency. It usually occurred in advanced ages and is very rare in young patients. But it reported in some patients received with antineoplastic and immunosupressive drugs such as methotrexate, hydroxyurea, nucleoside analoges and aminopterin. Methotrexate (MTX), inhibits dihydrofolate reductase, is frequently used in the prevention of graft versus host disease (GVHD), the treatment of autoimmune diseases like rheumatoid arthritis, psoriasis, and hematological malignancies.

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Synthesis of purine and pyrimidine deteriorates upon the decrease of tetrahydrofolate. Deoxyribonucleic acid (DNA) synthesis is inhibited and cell death takes place. [1] When used intravenously, orally and intrathecal MTX can cause depletion of intracellular tetrahydrofolate, leading to megaloblastic anemia.[2]

Here we report that megaloblastic anemia is due to intratechal MTX in a patient with primary mediastinal CD20 positive diffuse large B-cell lymphoma and central nervous system (CNS) involvement.

CASE REPORT

Twenty-four-year old female suffered from chest pain and dyspnea two years ago. We diagnosed to the patient as primary mediastinal CD 20 positive diffuse large B cell lymphoma. There were pericardial and pleural involvements, while the bone marrow or CNS were normal. According to Ann Arbor Staging System, the patient was accepted in stage IV. R-CHOP chemotherapy (rituximab 375 mg/m2 for 1 day, vincristin 1.4 mg/m2 for 1 day, cyclophosphamide 750 mg/m2 for 1 day, doxorubicin 50 mg/m2 for 1 day, and prednisone 100 mg/day for 1-5 days) was given every 21 days for 8 courses. Complete remission was obtained from chemotherapy. After 18 months, headache, nausea and vomiting occurred. Cranial magnetic resonance imaging showed mass lesions on right frontal and left posterior parietal lobes (Fig. 1). Serological and histopathological assessments and whole blood counts of cerebrospinal fluid were normal. Intrathecal 20 mg MTX twice a week for 6 weeks followed by cranial radiotherapy 46 Gy dose was applied to the patient. The patient did not receive any medication except of dexamethasone. After ten days of the discontinuation of treatment, fatigue occurred in the patient. Pallor and alopecia were detected. Hematological parameters were hemoglobin level 7.8 gr/dl, hematocrit 23%, platelet count 27 000/mm^3, leukocyte count 1000/mm^3, neutrophil count 100/mm^3, and mean corpuscular volume 97.5 fl, reticulocyte index 1%. Iron parameters were serum iron 95 μ g/dl, total serum iron binding capacity 228 mg/dl, percentage of iron 42%, and ferritin 432 ng/ml. Vitamin B_{12} and folic acid levels were 803 pg/ml (N:197-866) and 6.22 ng/ml (N:4.2-19.99), respectively. Biochemical analyses were normal. On peripheral blood smear, decreased platelets and macrocytosis and aniso-poikilocytosis in erythrocytes were seen. On the bone marrow aspiration and biopsy, there were erythroid hyperplasia (erythroid/myeloid ratio:1/1), apparent megaloblastic changes in erythroid precursors, and arrested maturation in myeloid precursors (Fig. 2). We started 5 mg/day folic acid to the patient. Reticulocyte crisis was seen at the 10th day of treatment and fatigue decreased. After 14 days, hematological parameters were hemoglobin level 10.2 g/dL, hematocrit 31.6%, platelet count 432 000/mm^3, leukocyte count 5100/mm^3, and neutrophil count 2500/mm^3. Folic acid was given for 3 months. Then, we performed peripheral autologous stem cell transplantation to the patient. She is alive and followed-up.

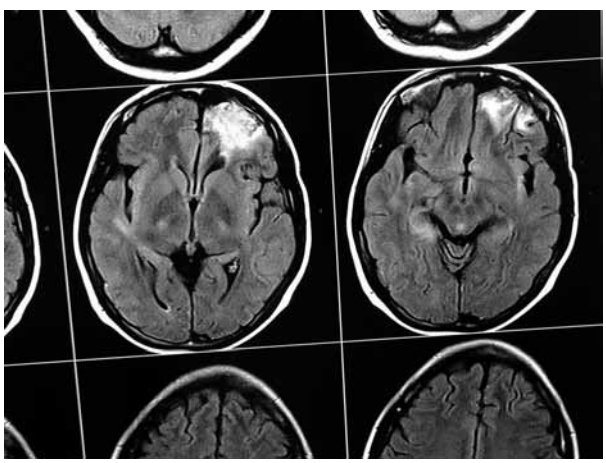

Fig. 1. *Magnetic resonance imaging, mass lesions were detected in right frontal and left posterior parietal lobes.*

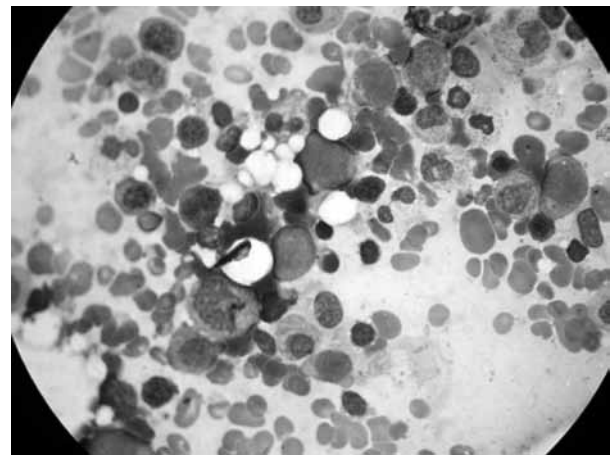

Fig. 2. *On the bone marrow aspiration, there were erythroid hyperplasia (erythroid/ myeloid ratio: 1/1), significant megaloblastic changes in erythroid series, and arrested maturation in myeloid precursors.*

DISCUSSION

Folic acid is essential for DNA synthesis. Folic acid antagonists such as aminopterin, methotrexate (MTX), pyrimethamine, trimethoprim, and triamterene may cause folic acid deficiency.[1] Tetrahydrofolate level is decreased with in the cell by intravenous and oral MTX treatment.[2] The efficacy and adverse effects of MTX such as myelosuppression, diarrhea, mucosal toxicity, and infection depend on dosage. Leukopenia, thrombocytopenia, pancytopenia and megaloblastic anemia are frequently seen in folic acid deficiency. Pretreatment levels of plasma or red cell folic acid were not useful in predicting of toxicity.[1-3]

High-dose (2 to 8 g/m2) intravenous MTX is necessary for adequate cerebrospinal fluid penetration in the patients with CNS lymphoma. Moreover MTX is usually applied for CNS prophylaxis of leukemia and lymphoma. In the treatment of CNS involvement of non-Hodgkin's lymphomas, intrathecal MTX administration is effective treatment modality.[4,5] We used intrathecal 20 mg MTX for CNS lymphoma. After ten days, fatigue and pancytopenia appeared in the patient. We diagnosed to the patient as megaloblastic anemia, because of pancytopenia, macrocytosis, megaloblastic changes in the peripheral blood and bone marrow. Serum folic acid level was normal. Erythrocyte folic acid levels were more valuable for the assessment of folic acid, but we could not examine. Hematological parameters were improved with folic acid treatment after 14 days. Use of the Naranjo ADR Probability Scale[6] indicated a probable (numerical score=7) relationship between megaloblastic anemia and MTX therapy in this patient.

Sallah et al.[2] reported megaloblastic anemia due to intrathecal MTX in three patients with acute leukemia. While folic acid level was normal in one patient, both serum and erythrocyte folic acid levels in 2 patients were low. All the patients were benefited from 5 mg/day folic acid treatment. Bleyer et al.[7] emphasized that tissue accumulation with intrathecal administration might be seen more than systemic MTX treatment in autopsy assessment of patients with leptomeningeal metastases of lung cancer. High MTX levels were detected in CNS as well as liver, kidney, lymph node, spleen, and bone. But MTX was not detected in myocardium, besides minimal accumulation in muscle tissues. So high bone levels may show bone marrow toxicity.[7] In another study, plasma MTX levels with intrathecal application might be 20-30 times higher than systemic administration, despite being applied in similar doses.[8] Cohen et al.[9] was reported that pancytopenia might develop after 25 mg single dose of intradermal MTX administration. Some authors showed that concomitant cranial irradiation and chronic intrathecal MTX reduced folic acid levels.[10] We applied intrathecal MTX and cranial radiation to our patient. Cranial radiation may be an additional factor in the development of megaloblastic anemia in our patient.

In conclusion, megaloblastic anemia may appear after intrathecal MTX in patients with CNS lymphoma. So the patients treated with intrathecal MTX should be followed-up and folic acid prophylaxis may be considered.

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