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Occurrence in a Case of Philadelphia Negative Acute Lymphoblastic Leukemia following Treatment for Ewing's Sarcoma

Ewing Sarkom Tedavisi Sonrası Gelişen Philadelphia Negatif Akut Lenfoblastik Lösemi Olgusu

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Abstract

Therapy-related leukemias are 10-20% of all acute leukemia cases. Therapy-related acute lymphoblastic leukemia (ALL) is less frequent than therapy-related acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS). In this paper, we present a patient with Ewing's sarcoma (ES) in the soft tissue of his right breast cured by chemotherapy and radiotherapy. He developed Philadelphia negative (Ph(-)) ALL four years following the therapy. *(Marmara Medical Journal 2012;25:100-2)*

Key Words: Ph(-) ALL, Secondary leukemia, Ewing's sarcoma

Özet

Tedavi ilişkili akut lösemiler tüm akut lösemili olguların %10-20'sini oluşturur. Tedavi ilişkili akut lenfoblastik lösemi (ALL) görülme sıklığı akut miyeloid lösemi (AML) veya akut myelodisplastik sendrom (MDS)'a göre daha nadirdir. Bu yazıda dört yıl önce sağ memedeki kitleden Ewing sarkom (ES) tanısı alan kemoterapi ve radyoterapi ile tam kür sağlanan olguda gelişen Philadelphia negatif (Ph(-)) ALL olgusu sunulacaktır. *(Marmara Üniversitesi Tıp Fakültesi Dergisi 2012;25:100-2)*

Anahtar Kelimeler: Ph(-) ALL, Sekonder lösemi, Ewing sarkom

Introduction

Long term survival has been recently achieved by evolution in treatment strategies for many solid neoplasms. In particular, patients treated with chemotherapy regimens commonly including alkylating agents and anthracyclines, and further exposed to radiotherapy, are at increased risk of developing leukemia. Therapy-related leukemias are 10-20% of all acute leukemia cases[1,2]. Therapy-related acute lymphoblastic leukemia (ALL) is less frequent than therapy-related acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS). In one series it is shown that therapy-related ALL occurs in 1-2% of all ALL patients[3]. In this paper, we present a patient with Ewing's sarcoma (ES) in the soft tissue of his right thorasic wall, cured by chemotherapy and radiotherapy. He developed ALL four years following the therapy. We obtained written informed consent from the patient.

Case Report

A 19-year old male was admitted to the oncology clinic with a painless, hard 7.5x3.4 cm mass in his right hemithorax lateral wall in August 2004. He was diagnosed by thorax magnetic resonance

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imaging (MRI) as having hemangioma, and partial embolization was applied. During the follow up, he was readmitted with enlargement of the mass to 17x15 cm. No metastasis was detected in the thorax-abdomen and cranial computerized tomography (CT) screening. However, there was an increased uptake in the 6th costal arcus in the bone scintigraphy, evaluated as bone invasion. The incisional biopsy of the mass, revealed ES in February 2005. There was no invasion of the bone marrow He was classified as high risk extraosseous ES (tumor>100mL) and chemotherapy regimen etoposide, vincristine, dactinomycin, ifosfamide, doxorubicin (EVAIA) was initiated as in the European Intergroup Cooperative Ewing's Sarcoma Studies (EICESS-92) protocol. He received three courses of etoposide of 150 mg/m^2 each 1.5 vincristine 0.5 mg/m^2 dactinomycin, 2,000 mg/m^2 ifosfamide and 30 mg/m^2 doxorubicin. There was more than 50% regression in the tumour size in the control thorax CT in June 2005, when radiotherapy was arranged. He received 54 Gy/25 fractions over 5 weeks radiotherapy fort the primary region and 45Gy/25fractions over 5 weeks radiotherapy fort the right hemithorax. 2 courses of EVAIA chemotherapy protocol were administered before he had total resection of the mass in December 2005. During the postoperative period he received two more courses of EVAIA protocol, which was completed in April 2006. He was followed in complete remission until March 2010. He was referred to the hematology clinic with a complete blood count reported as platelets: 20.000 µL, WBC: 8.800 µL (69.6% neutrophil, 16.9% lymphocytes, 1.1% monocyte, 1.8% eosinophil, 0.1% basophil) hemoglobin: 11 gr/dL. In his periferic blood smear analysis, rare platelets, schistocytes and lymphoblasts (35% of all leukocyte) was detected. The blood lactate dehyrogenase (LDH) level was increased to 862 U/L (normal: 125-243 U/L). Bone marrow aspiration was hypercellular and 55% of the cells was established as blasts. The blasts were positive in periodic acid schiff (PAS) stain, but negative in myeloperoxidase (MPO) or esterase stain. In the bone marrow flow cytometric analysis, the dominant cells that match the blastic cell morphology were sorted by forward scatter and side scatter detectors. The mature granular cell population was excluded in sorting. The flow cytometric expressions in immature lymphoid cells were determined as CD 10 (98 %), CD 19 (98%), CD 22 (96%), CD 34 (89%) ve HLA-DR (98%). T cell surface antigen and BCR-ABL gene were not detected with quantitative reverse transcriptase-polymerase chain reaction (QRT-PCR) in all nuclear cells. In the cytogenetic studies, 20 metaphases were examined by giemsa stain without cytogenetic anomaly. According to the findings, he was diagnosed as precursorcell Ph(-) ALL in April 2010. Alternating hyper-CVAD chemotherapy courses A and B were initiated. Course A consisted of 300 mg/m^2 cyclophosphamid, 25 mg/m^2 doxorubicine, 4mg vincristin, and 280mg dexaemethason. Course B consisted of 1 g methotrexate and 6 g/m^2 cytarabine. After the first A and B courses, a complete (morphologic) remission was achieved in the bone marrow aspiration analysis. In the next courses, we rearranged the protocol with etoposide instead of doxorubicine because the cumulative dose of anthracyline was totally 390mg/m^2. He completed 4 courses of Hyper-CVAD A and B protocol and 6 courses of prophylactic intrathecal chemotherapy: (12,5 mg methotrexate and 40 mg cytarabine) in December 2010. After 15 months of maintenance therapy with 100mg 6-mercaptopurine daily, 25mg methotrexate weekly and 1mg vincristine plus 100mg prednisolon monthly, he was followed up and still in remission. With no HLA-matched donor, he was consequently included in a non-relative allogeneic donor transplantation list .

Discussion

ES is a neuroectodermal tumor occuring mostly in the second decade and originating from bone or soft tissue[4]. Even though two over three patients with the localized disease are followed in remission by current treatment approaches, the prognosis of metastatic disease is still very poor[5]. Secondary malignancy risk increases significantly in ES cases. There are two major hypothesis explaining the occurrence of ES: the genetic predisposition may play a role as in other cancers, or it may be caused by effects of chemotherapeutic agents used for treatment[6].

It has been stated that secondary leukemias are induced after treatments with alkylating agents and topoisomerase inhibitors. The detection of leukemias secondary to topoisomerase inhibitors occurs shortly after chemotherapy for primary tumours (average of 14 months) however, alkylating agents have a longer leukemia latent period[7]. Our case was treated with both etoposide and doxorubicine and the leukemias was diagnosed 4 years after the temination of the ES treatment, which is compatible with other studies.

Sultan et al.[8] described 35 secondary malignancy cases from metaanalysis of all ES patients (1166 cases) who were diagnosed between January 1973 and December 2005 in the USA. Twenty-three of 35 were solid tumors and the remaining were hematological malignancies. One ALL case was reported 5 years after ES detection.

In general, secondary ALL is rare. In a metaanalysis of 3934 acute leukemia patients (2964 AML, 901 ALL and 69 acute biphenotypic leukemia) secondary ALL was established in 2.3% of the patients compared with secondary AML in 6% of the patients. 10.5% secondary ALL patients in the secondary malignancy group was reported[9].

Many chemotherapeutic agents are thought to cause secondary ALL. Some studies in secondary ALL pointed out the relation with chromosomal anomalies. In alkylating agent induced ALL, myelodysplasia is more frequent, the latent period is long and cytogenetic anomalies in chromosome 5 and/or 7 are detected. On the other hand, topoisomerase II inhibitor induced ALL occurs with chromosome 11q23 translocations with a short latent period[7]. In our case, treatment with both agents did not cause any cytogenetic anomaly.

In summary, secondary ALL due to chemotherapeutic agents account for 2-3% of all ALL's. Our patient is one of the rare ALL

patients occurring after the treatment of ES. The latent time period until the determination of ALL varies from 13 months to 8 years. The latent period is longer in alkylating agents compared to topoisomerase II inhibitors. The latent period was 4 years in our case where the patient was treated by both regimens which is compatible with other studies. Treatment-related malignancies should be considered in the routine follow-up of patients treated with alkylating agents and topoisomerase II inhibitors.

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