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Address for Correspondence/Yazışma Adresi: Xudong WEI, M.D., The Second Affiliated Hospital of Zhengzhou University, Department of Hematology, Zhengzhou, P.R. China
Phone : +8613837169301
E-mail : weixudong63@126.com ORCID: orcid.org/0000-0002-6753-8265

Received/Geliş tarihi: February 18, 2019
Accepted/Kabul tarihi: June 24, 2019
DOI: 10.4274/tjh.galenos.2019.2019.0071

Successful Outcome of a Case of Acute Myeloid Leukemia with t(8;21)/AML-ETO Following Langerhans Cell Histiocytosis

Langerhans Hücreli Histiositozunu Takiben Gelişen t(8;21) Akut Myeloid Lösemi Olgusunun Başarılı Tedavisi

Guangqiang Meng, Jingshi Wang, Jiancheng Huang, Yini Wang, Na Wei, Zhao Wang

Beijing Friendship Hospital, Capital Medical University, Beijing, China

To the Editor,

The occurrence of Langerhans cell histiocytosis (LCH) and acute myeloid leukemia (AML) in the same case has been reported occasionally. We report a new case of AML with t(8;21)/AML-ETO in an adolescent after LCH. To our knowledge, this is the first description of AML with t(8;21)/AML-ETO after LCH diagnosis and therapy.

A 15-year-old boy was diagnosed with LCH in October 2010. He presented with a 1-year history of a skull mass. After 9 cycles of ifosfamide, vincristine, etoposide, and prednisone, the skull mass disappeared. Two years later, the patient presented to the Hematology Department of Beijing Friendship Hospital with progression of his disease in the form of lumber fracture. The mutation BRAF V600E was negative. After relapse of LCH, he received 6 cycles of etoposide and prednisone and 1 cycle of etoposide, prednisone, cyclophosphamide, and vincristine. On 12 March 2013, he received an autologous hematopoietic stem cell transplant. When he came to the clinic with complaints of dizziness on 20 November 2017, a routine blood examination was performed with the following results: white blood cell count, $6.3x10^9$/L; hemoglobin, 60 g/L; and platelet count, $12x10^9$/L. Bone marrow biopsy showed 69% myeloblasts, and Auer rods were found. The immunophenotype profile of the blast cells was CD34 (++), CD13 (+), CD33 (++), CD117 (++), CD38 (+), CD15 (+), HLA-DR (++), MPO(+). Cytogenetic analysis revealed 46, XY, t(8;21)(q22;q22)[20]. The *AML-ETO* and *WT1* genes were positive. The patient responded well to induction chemotherapy. Standard DA chemotherapy (daunorubicin and cytarabine) was given and the boy achieved complete response (CR) after one cycle. After an additional cycle of DA consolidation chemotherapy, he received an HLA-identical sibling allogeneic hematopoietic stem cell transplant (HSCT). He received a conditioning protocol composed of busulphan and cyclophosphamide, and he was given fluconazole and acyclovir as infection prophylaxis and cyclosporine and mycophenolate mofetil as graft-versus-host disease prophylaxis. Up to 30 March 2019, the patient was in a state of persistent CR for 16 months after the diagnosis of the AML, and the *AML-ETO* and *WT1* genes were negative.

There is an association between LCH treatment and subsequent development of AML; however, the reason why AML develops in patients treated for LCH is not entirely understood. The chemotherapy for LCH and genetic predisposition may be explanations. Previously, 27 such cases have been reported [1], and lymphomas, solid tumors, and other hematologic malignancies have been associated with chemotherapy for LCH [2]. Most patients develop AML at least 2 years (mean: 5.5 years) after LCH treatment [3]. LCH treatment agents, together with the genetic predisposition of the patient, might therefore be the reason for AML development. Etoposide, a DNA-topoisomerase II inhibitor, is commonly employed in LCH treatment and is primarily related to therapy-related AML (t-AML) [4]. A safe dose of etoposide does not truly exist; between 2 and 20 years after exposure to etoposide, 1%-5% of patients may develop t-AML [5]. Etoposide-associated AML has been described after its usage for a wide spectrum of diseases, including non-Hodgkin lymphoma [6], acute lymphoblastic leukemia [7], solid tumors [2], and hemophagocytic lymphohistiocytosis [5]. The cytogenetic abnormalities of t-AML reported in patients with LCH include t(15;17), 11q23, +16, and +21 [8,9,10]. The finding of t(8;21)(q22;q22) in a t-AML patient with LCH has not been reported previously, although it was reported in t-AML patients with other malignant neoplasms, including solid tumors, lymphomas, and other hematologic malignancies [11]. Most of the t-AML cases with t(8;21) reported are t(8;21)(q22;q22); other breakpoints of t(8;21) are rare. However, the current findings indicate a worse outcome for t-AML with t(8;21) compared to de novo AML with t(8;21)(q22;q22) [11]. Throughout the treatment process, the case is more likely to be that of t-AML.

Additionally, previous studies have suggested common neoplastic precursors for LCH and AML [12]. Recent molecular analysis of human LCH samples and mouse models showed that the origin cell may be a myeloid-derived precursor [13]. Furthermore, genomic screening has revealed the presence of BRAF, ARAF, and somatic MAP2KI mutations in the majority of LCH and AML patients' specimens [14,15]. Cases in which LCH occurred concurrently and after AML have also been reported [10,16,17]. Xu et al. [17] reported a case where LCH evolved into AML without chemotherapy including etoposide for LCH. Therefore, researchers have accepted the possibility of genetic predisposition to facilitate the development of pathogenic molecular abnormalities. Yohe et al. [10] reported four patients who presented with acute leukemia of myeloid or ambiguous lineage in association with LCH. One patient had trisomy 21 in both the leukemic blasts and LCH cells, indicative of a clonal relationship. Another patient expressed CD2, CD13, and CD117 on both the LCH cells and the leukemic blasts, suggesting a possible clonal relationship. These reports suggest that LCH and AML might have a common neoplastic stem cell.

In our case, successful allogeneic HSCT not only controlled the patient's AML but also had a long-lasting effect on his relapsed LCH. For these patients, induction chemotherapy combined with allogeneic HSCT is a good choice.

Keywords: Langerhans cell histiocytosis, Acute myeloid leukemia, Allogeneic hematopoietic stem cell transplant

Anahtar Sözcükler: Langerhans hücreli histiositozu, Akut myeloid lösemi, Allojenik hematopoietik kök hücre transplant

Conflict of Interest: The authors of this paper have no conflicts of interest, including specific financial interests, relationships, and/or affiliations relevant to the subject matter or materials included.

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Address for Correspondence/Yazışma Adresi: Zhao WANG, M.D., Beijing Friendship Hospital, Capital Medical University, Beijing, China
Phone : 010-80838339
E-mail : wangzhao@ccmu.edu.cn ORCID: orcid.org/0000-0003-1067-4589

Received/Geliş tarihi: March 24, 2019
Accepted/Kabul tarihi: July 03, 2019
DOI: 10.4274/tjh.galenos.2019.2019.0126

Breast Implant-Associated Anaplastic Large-Cell Lymphoma: A Case Report

Meme İmplantı ile İlişkili Anaplastik Büyük Hücreli Lenfoma: Olgu Sunumu

Hakan Kalyon[1], Erman Öztürk[2], Sıtkı Tuzlalı[3], Olga Meltem Akay[4], Burhan Ferhanoğlu[4]

[1]American Hospital, Clinic of Hematology, İstanbul, Turkey
[2]Medeniyet University Faculty of Medicine, Department of Hematology, İstanbul, Turkey
[3]Tuzlalı Pathology Laboratories, İstanbul, Turkey
[4]Koç University Faculty of Medicine, Department of Hematology, İstanbul, Turkey

To the Editor,

Breast implant-associated anaplastic large-cell lymphoma (BIA-ALCL) is a rare type of peripheral T-cell lymphoma, also recognized as a specific disease in the 2016 revision of the World Health Organization classification of tumors of the hematopoietic and lymphoid tissues [1]. Although BIA-ALCL has an indolent course, infiltrative forms may be life-threatening and 9 deaths have been reported [2]. The annual incidence is estimated as 0.1 to 0.3 per 100,000 women with implants [3]. The median age is 53, with the disease being detected after a median of 8 years following implantation [4]. Herein, we report a rare case of BIA-ALCL, the first from Turkey.

A 40-year-old Caucasian female presented to our clinic with right-sided breast swelling and asymmetry. Five years ago, she was diagnosed with left-sided invasive ductal carcinoma. She received neoadjuvant chemotherapy, followed by mastectomy and axillary lymph node dissection of the left side and nipple-sparing mastectomy of the right side. Macro-textured anatomical silicone gel implants and fat grafting were applied, followed by adjuvant chemotherapy. Five years later, breast ultrasound and MRI revealed effusion in the fibrous capsule surrounding the breast implant (Figures 1A and 1B). Initial evaluation of the effusion was benign and the implant was replaced by another one after partial capsulectomy. However, the seroma recurred. In the third sampling, the immunochemical analysis revealed typically large and pleomorphic CD30-positive so-called hallmark cells (Figures 1C and 1D). She was diagnosed with BIA-ALCL. The Ann Arbor stage was IE and the TNM stage was IA. Complete excision of the breast implant and capsule was performed and no capsule invasion was reported upon pathological evaluation. Neither further surgery nor chemotherapy was applied. She has remained in remission to date, at the 18th month after the surgery.

Although it is a very rare entity, detection and diagnosis of BIA-ALCL is an emerging topic. BIA-ALCL is surgically treated and it has an indolent course, with the risk of death being 0.4 micromorts per patient [5]. Most cases are unilateral; however, rare bilateral cases have been reported. Patients mainly present with malignant effusions associated with the fibrous capsule surrounding the implants [6]. Lack of ALK expression and strong membranous expression of CD30 constitute the main immunochemical profile. The largest series published in the literature are summarized in Table 1.

The pathogenesis of BI-ALCL is still unclear. Textured implants are likely to induce a marked local T-cell immune response compared to smooth implants. Textured implants are known