A rare cause of breast masses in childhood: ALK positive anaplastic large cell lymphoma

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ABSTRACT

Objective: Non-Hodgkin’s lymphomas (NHLs) are the result of malign proliferation of lymphoid cells. According to the morphological, immunological and genetic characteristics of childhood NHLs, they are classified as Burkitt lymphoma (BL), Lymphoblastic lymphoma (LL), diffuse large B-cell lymphoma (DLBCL) and anaplastic large cell lymphoma (ALCL). Anaplastic large cell lymphoma is a distinct form of non-Hodgkin lymphoma (NHL) which accounts for 15% of all childhood lymphomas. We report a girl presented with a breast mass and diagnosed with systemic ALCL.

Case: A 14-year-old girl was referred to our hospital with without a painless mass in the left breast. Physical examination, it was seen two painless masses was found in the left breast. Also, a 2x2 cm, painless lymphadenopathy was found in the left axilla. She had no systemic symptoms In laboratory tests; hemoglobin, white blood cell count, platelet count, liver and kidney function tests, LDH, and uric acid levels were normal. In the imaging and metastasis screenings made to the patient; ultrasound and computed tomography (CT) showed two masses breast region. A large number of lymphadenopathies were detected in the left axillary, which surrounded the paraaortic, the paracaval, and the celiac truncus. She was found to have a hypermetabolic two masses in the breast (SUVmax=33.05) and lymphadenopathies (SUVmax=27.04) in the left axillary, paraaortic, the paracaval, and the celiac truncus on Fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography (¹⁸F-FDG PET/CT) scan. Excisional biopsy of the tumor mass in the breast was done and immunohistochemical analysis showed CD30 and anaplastic lymphoma kinase (ALK) positive ALCL. The patient was diagnosed with stage III anaplastic large cell lymphoma with systemic involvement and she began chemotherapeutic treatment, according to the NHL BFM 1995 protocol. Bone marrow aspirate was normal, and no malignancy was observed in the cerebrospinal fluid. After V-phase, AM block, and BM block treatments evaluation were performed with ¹⁸F-FDG PET/CT according to protocol. In ¹⁸F-FDG PET/CT, it was seen that the lymph nodes in the abdominal and the small mass in the breast were completely retracted, and another lymph nodes had no detected. These results showed that the response to the treatment was complete and the patient's chemotherapy was completed by continuing with the protocol. ¹⁸F-FDG PET/CT taken after the completion of chemotherapy revealed no evidence of mass or lymph node. The patient's controls continue smoothly.

Conclusions: Anaplastic large cell lymphoma should also be considered in the differential diagnosis of children presented with a breast mass. Treatment procedures should be planned according to the involvement site and spread of the disease.

Keywords: Children, Breast, anaplastic large cell lymphoma

INTRODUCTION

Non-Hodgkin's lymphomas (NHLs) are the result of the malign proliferation of lymphoid cells. Malignant lymphomas although usually seen in lymphoid structures such as lymph nodes, Peyer’s patches and spleen, can involve the central nervous system, bone marrow and bone. Constitutes for 8-10% of all childhood malignancies and 60% of all lymphomas (1).
According to the morphological, immunological and genetic characteristics of childhood NHLs, they are classified as Burkitt lymphoma (BL), Lymphoblastic lymphoma (LL), diffuse large B-cell lymphoma (DLBCL) and anaplastic large cell lymphoma (ALCL) (2). Anaplastic large cell lymphoma is a distinct form of non-Hodgkin lymphoma (NHL) which accounts for 15% of all childhood lymphomas. Anaplastic large cell lymphoma is a T or null cell lymphoma characterized by the malignant cell expression of CD30 (Ki-1) (3). The World Health Organization divides ALCL into a systemic form and a primary cutaneous form (4). Systemic ALCL is more common than the cutaneous form and most frequently occurs in the first three decades of life. Clinically, systemic ALCL is characterized by advanced disease at presentation with a high incidence of nodal involvement, frequent association with B symptoms, and frequent extranodal involvement including skin, lung, bone and liver (5). Breast involvement of ALCL in children has not been previously reported in the English literature. We report a girl presented with a breast mass and diagnosed with systemic ALCL.

**CASE**

A 14-year-old girl was referred to our hospital with about 2-month history of a growing over time without painless mass in the left breast. She was informed that an excisional biopsy was performed at the center she referred to. During the physical examination, it was seen that the left breast was bigger than the right, an 8x5 cm sized, hard, mobile, and painless mass was found in the region of the left breast covering the lateral and middle region (Figure 1).

In addition, the 2x2 cm dimensions of the second mass was palpated which have the same properties as the first mass in the sublateral region. A 2x2 cm, painless, moderately hardened lymphadenopathy was found in the surrounding areas of the left axilla. Hepatosplenomegaly in the case was not detected. She had no specific history including drug or family history. She showed no systemic symptoms such as fever, weight loss or night sweating. Her vital signs were stable and were within the normal range (blood pressure, 100/55 mmHg; heart rate, 96 beats/minute; respiratory rate, 26 breaths/minute; body temperature, 36 C°).

In laboratory tests; Hemoglobin: 14.8 gr/dl, white blood cell count: 6240 / mm3, platelet count: 347000 / mm3, liver and kidney function tests, LDH and uric acid levels were normal. In the imaging and metastasis screenings made to the patient; ultrasound and computed tomography (CT) showed two masses measuring 74x56 and 30x17 mm in the middle and lateral breast region. A large number of lymphadenopathies were detected the largest 25x25 mm size in the left axillary, that surrounded the paraaortic, the paracaval, and the celiac truncus. She was found to have a hypermetabolic two masses in the breast (SUVmax=33.05) and lymphadenopathies (SUVmax=27.04) in the left axillary, paraaortic, the paracaval, and the celiac truncus on Fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography (¹⁸F-FDG PET/CT) scan.

It was learned that the fine needle biopsy was performed at the external center and it was reported as malignant cytology, followed by excisional biopsy. Excisional biopsy of the tumor mass in the breast showed frequent mitoses and pleomorphic atypical cells with vesicular chromatin, prominent nucleoli, and pale cytoplasm (Fig. 2a).

**Figure 1:** Mass in the region of the left breast covering the lateral and middle region

**Figure 2a:** Neoplastic lymphoid cells, frequent mitoses and pleomorphic atypical cells with vesicular chromatin, prominent nucleoli, and pale cytoplasm. (HE)
Immunohistochemical analysis showed the neoplastic cells were positive for CD30 (Fig. 2b), anaplastic lymphoma kinase (ALK) (Fig. 2c), CD43, CD4 and CD7. Stains were negative for CD20, CD15, CD2, CD3, CD5, CD8, and EBV.

Figure 2b: CD30 positive neoplastic cells

Figure 2c: Anaplastic lymphoma kinase (ALK) – 1

These immunohistochemical findings corroborated the diagnosis of ALK positive ALCL. Cytogenetically, karyotype t(2;5) could not be studied due to technical reasons. The patient was diagnosed with stage III anaplastic large cell lymphoma with systemic involvement and she began the induction phase of the chemotherapeutic treatment, according to the NHL BFM 1995 protocol. Bone marrow aspirate was normal, and no malignancy was observed in the cerebrospinal fluid. After V-phase (dexamethasone 5 mg/m²/d on day 1+2, 10 mg/m²/d, on days 3–5; cyclophosphamide 200 mg/m²/d i.v. (intravenous) infusion with cystitis-prophylaxis: MESNA 70 mg/m² i.v. each 0, 4, 8 hours after start of cyclophosphamide infusion; doxorubicin 25 mg/m²/d i.v. infusion, on day 4 and 5) treatments evaluation were performed with ¹⁸F-FDG PET/CT according to protocol. In ¹⁸F-FDG PET/CT, it was seen that the lymph nodes in the abdominal and the small mass in the breast were completely removed, and that the lymph nodes in the left axillary region had an SUVmax value of 2.02 and the large mass had a SUVmax of 2.80. These results showed that the response to the treatment was complete and the patient's chemotherapy was completed by continuing with the protocol. ¹⁸F-FDG PET/CT taken after the completion of chemotherapy revealed no evidence of mass or lymph node. The patient's controls continue smoothly.

**DISCUSSION**

Lymphoma is the third most common pediatric neoplasm, preceded only by leukemias and brain tumors. Non-Hodgkin lymphoma accounts for about 6% of childhood cancer and nearly half of the lymphoma cases in patients younger than 19 years. Patients typically present with widespread disease. Generally, NHL occurring in children includes Burkitt lymphoma, lymphoblastic lymphoma, diffuse large B-cell lymphoma, and anaplastic large cell lymphoma. Staging and assessment of therapeutic response are based on imaging of the involved sites, bone marrow aspiration and biopsy and examination of cerebrospinal fluid (6). Anaplastic large cell lymphoma is uncommon in children, accounting for approximately 15% of all cases of childhood non-Hodgkin lymphoma. It commonly involves nodal as well as a wide variety of extra nodal sites, as skin, soft tissue, bones, lungs and even esophagus (7, 8). The long-term event-free survival for children with ALCL is approximately 70 %. Novel biological agents, including those that target CD30 or ALK, may hold promise for improving treatment results (9).

Treatment recommendations differ considerably in patients with ALCL. Different chemotherapeutic regimens are used for systemic ALCL, whereas surgical excision and/or radiotherapy are adequate for some patients with extranodal involvement. Han et al (8) evaluated the laboratory findings, involvement sites and treatment outcomes of 28 children with ALCL. They reported that about 80% of patients had lymph node and 64% had extranodal (most commonly mediastinal) involvement at presentation. More than half of the patients were treated with CCG-5941, a T-cell lineage lymphoblastic leukemia-type chemotherapy regimen, and the 88% of five-year overall survival was estimated.

Gajendra et al (5) presented a 14-year-old girl with extensive bone involvement of ALCL. The diagnosis of ALCL was made by examination of the axillary lymph node biopsy samples showing CD30, ALK, epithelial membrane antigen (EMA) and Ki 67 (80%) positivity. She was planned to treat with CHOP protocol (combination of cyclophosphamide, doxorubicin, vincristine, and prednisone) followed by radiotherapy to bulky sites of disease.

In the literature, surgical excision is applied only for single lesions. Oschlies et al (3) reported six children with a single skin lesion of ALK-positive anaplastic large cell lymphoma.
The lesion was completely resected in four of these patients and no further therapy was needed in three. The remaining two patients received additional local radiotherapy and one chemotherapy. Gould JW et al (10) presented a 4-year-old girl with primary cutaneous CD30 positive large cell lymphoma who has been treated by surgical excision and followed for 44 months without the disease.

Tokuyama et al (11) presented a 5-year-old girl with ALK positive ALCL forming a solitary skin tumor on the forearm. She was treated by ALCL-99 trial protocol (combination of dexamethasone, cyclophosphamide, methotrexate, ifosfamide, cytarabine, etoposide and doxorubicin) leading to marked improvement although there was no evidence of systemic dissemination.

On the light of the cases mentioned above, chemotherapy was the only choice for our case with systemic involvement besides of breast mass. She was treated with NHL-BFM 1995 protocol, a chemotherapy regimen designed for mature B-cell lymphomas, and reached complete remission.

CONCLUSION

In conclusion, ALCL should also be considered in the differential diagnosis of children presented with a breast mass. Treatment procedures should be planned according to the involvement site and spread of the disease.

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