Case Report

Non-implant associated primary breast anaplastic large cell lymphoma in a postpartum female

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ABSTRACT

Anaplastic large cell lymphoma (ALCL) is an aggressive peripheral T-cell non-Hodgkin lymphoma. Breast implant-associated ALCL is a rare subtype of ALCL, now designated as a separate entity under the latest 5th edition of the World Health Organization classification of hematolymphoid tumors. ALCL of the breast in a patient without a breast implant is an even rarer subtype. We here report a case of pathologically proven primary ALCL of the breast diagnosed during the postpartum period. The patient achieved a complete metabolic response after six cycles of rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone. It is essential to recognize this entity because the management is completely different from the more common adenocarcinoma, which is treated with surgery and radiation, unlike lymphoma, which is treated with chemotherapy alone. We reviewed the literature and identified 30 cases of non-implant-associated Primary Breast ALCL. Our case was unique in being postpartum in presentation and involving bilateral breasts.

Key words: Anaplastic, Chemotherapy, Large cell, Lymphoma, Postpartum

Anaplastic large cell lymphoma (ALCL) is a rare and aggressive peripheral T-cell non-Hodgkin lymphoma [1]. Primary breast-ALCL (PB-ALCL) is the most common T-cell-derived primary breast lymphoma (PBL) [1]. Most cases of PB-ALCL arise in association with textured breast implants; <50 cases of ALCL arising in the breast in the absence of implants have been reported [2].

We here report a case of pathologically proven primary ALCL of the breast diagnosed during the postpartum period. To the best of our knowledge and literature search, 30 such cases have been reported since 1993 [3]. Our case was unique in being postpartum in presentation and involving bilateral breasts. Furthermore, the patient responded well to chemotherapy alone.

CASE REPORT

A 34-year-old woman in her 1st week of the postpartum period presented with heaviness and pain in both breasts. She had no history of fever, weight loss, and night sweats. She gave no history of any lump in the body. She had similar complaints in the third trimester of her pregnancy when she was evaluated by her obstetrician. At that time, a physical examination and mammogram did not reveal any lump in either breast. She improved with oral analgesics, so fine needle aspiration cytology was deferred. Thereafter, she had a full-term delivery by lower-segment cesarean section and presented with the complaints mentioned above. She had a history of infertility and underwent laparoscopic ovarian drilling for polycystic ovarian disease. She gives no history of hormonal therapy or breast implants. She had breastfed her first child for 3 years. There was no family history of breast or any other malignancy.

Physical examination this time revealed the presence of well-defined lumps in both breasts. The right breast had a lump in the upper lateral quadrant measuring 4 cm × 5 cm. The left breast had multiple lumps, the largest in the central area measuring 3 cm × 2 cm. There was no lymphadenopathy or organomegaly. Apart from mild pallor, rest was within normal limits.

Mammography showed multiple well-defined heterogeneous, predominantly cystic lesions in both breasts. Few of these cysts showed solid components with peripheral vascularity. The largest lesion on the right side was at the 12 O'clock position and measured 5.1 × 4.2 × 3.7 cm. The largest lesion on the left was at the retroareolar position and measured 3.4 × 2.7 × 2.5 cm. Few axillary lymph nodes were seen. A core needle biopsy from the right breast lump was performed in an outside institution, which was inconclusive.

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The patient thereby was referred to us for further management. Meanwhile, the left breast lesion ruptured to form an ulceration with serosanguinous discharge. A repeat core biopsy was performed on the left breast lump.

Histopathology revealed a diffuse infiltrate of monomorphic small to medium sized atypical lymphoid cells with irregular nuclear membrane, fine chromatin, prominent nucleoli and moderate amount of pale eosinophilic cytoplasm (Fig. 1). Mitotic activity is brisk. The background was polymorphous composed of small lymphocytes, histiocytes, eosinophils and plasma cells. Overall histology favoured atypical lymphoproliferative disorder.

In addition, immunohistochemistry showed positivity for leukocyte common antigen, CD30, CD3, CD5, CD8, anaplastic lymphoma kinase (ALK-1), and MIC2. The tumor cells were negative for CD4, CD20, PAX5, CD79a, MUM1, TdT and EMA. Ki-67 expression was approximately 70% in the viable tumor cells. Immunohistochemistry was suggestive of ALK-positive (ALK+) anaplastic large-cell lymphoma. Staging positron emission tomography/computed tomography (PET-CT) scan showed hypermetabolic breast parenchymal masses, SUVmax 14.5. Axillary masses were inactive. Few discrete hypermetabolic enlarged supra and infra diaphragmatic nodes, maximum diameter 1 cm, suggestive of lymphomatous involvement were noted. Hypermetabolic multiple bilateral pulmonary nodularity, subcutaneous/intramuscular nodules, and omental nodularity, as part of the same disease were noted. The liver, spleen, and marrow were not involved.

Considering 75–80% of the tumor bulk localized to the breast, a diagnosis of PB-ALCL expressing ALK1, stage III was made. She was treated with six cycles of cyclophosphamide, doxorubicin, etoposide, vincristine, and prednisone chemotherapy. Her interim and end-of-treatment PET-CT was suggestive of a complete metabolic response. She is currently following every 3 months and remains in remission for 2 years.

DISCUSSION

Cancers of the breast affect millions of women worldwide and are a major cause of premature death. Breast cancer mostly arises from either the epithelial or stromal cell components of the breast parenchyma. Adenocarcinoma is the most common malignant neoplasm involving the breast [4]. The other types of malignant neoplasms affecting the breasts are exceedingly rare [5]. Non-Hodgkin lymphomas involving the breast are divided into primary lymphoma of the breast and systemic lymphoma, although the distinction could sometimes be challenging [6]. PBL is diagnosed based on criteria proposed by Wiseman and Liao, which highlights that the primary site of lymphoma presentation (75% of tumor bulk) should be limited to the breast, the lymphoma should be in close association with the breast tissue, and the patient should have no history or evidence of disseminated disease within 6 months of diagnosis, whilst the simultaneous involvement of axillary lymph nodes is considered to be part of the spectrum of PBL [7]. These criteria exclude secondary breast lymphomas, i.e., those which arise elsewhere but manifest in the breast as part of secondary involvement. PBL can present as one of many different histological variants [8]. Over 90% of reported PBL cases are of a B cell origin, of which over 50% are diagnosed as diffuse large B-cell lymphomas, while follicular B-cell lymphoma, extranodal marginal zone lymphoma and Burkitt lymphoma are among the less common B-cell variants [2].

PB-ALCL is the most common T cell-derived PBL [2]. Other T-cell lymphomas, including peripheral T-cell lymphoma and follicular T-cell have been described in the breast. Most cases of PB-ALCL arise in association with textured breast implants; <50 cases of ALCL arising in the breast in the absence of implants have been reported. In general, PB-ALCL, such as systemic/nodal ALCL, is characterized by the presence of large pleomorphic “hallmark” cells with irregular nuclear contours, enlarged and misshapen nuclei, and prominent Golgi bodies. Immunohistochemically, PB-ALCL almost invariably expresses CD30, as well as an unusual variety of cell surface markers. Owing to the frequent cell surface expression of mature T cell characteristic proteins, such as CD4, CD8, and CD45RO, and the presentation of ALCL outside of the thymus, ALCL is thought to arise from mature peripheral T-cells [9]. Like systemic/nodal ALCL, PB-ALCL is characterized by the presence or absence of aberrant ALK expression and activity, which gives rise to both ALK+ and ALK-negative (ALK−) ALCL entities. Of the ALCL cases arising in the absence of breast implants (PB-ALCL), both ALK+ and ALK− presentation have been reported. PB-ALCL, ALK+ is characterized by the presence of the t(2;5) (p23;q35) translocation juxtaposing the tyrosine kinase encoding domain of ALK to the nucleolar protein gene NPM1, resulting in the constitutive activation of ALK signaling and the upregulation of signaling pathways associated with cell proliferation and

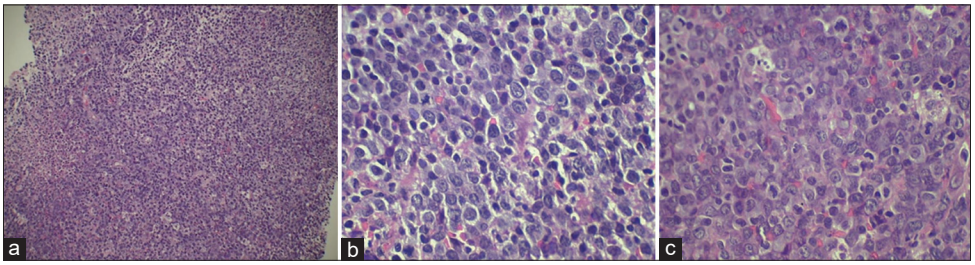

Figure 1: (a) Lymph node biopsy: Effaced architecture with a diffuse infiltrate of neoplastic cells (H and E, ×40); (b) Lymph node biopsy: the neoplastic cells are large and pleomorphic with moderate amount of cytoplasm, irregularly contoured nuclei, vesicular chromatin and prominent nucleoli. Mitotic activity is very brisk (H and E, ×400); (c) Polymoprhous background containing small lymphocytes, histiocytes, eosinophils and plasma cells (H and E, ×400)

Table 1: Summarizing various studies of ALCL breast without breast implants

Study	Age in year/Sex	Breast (L/R/bilateral)	ALK	Treatment	Outcome
Sathyanarayanan *et al*. (2013) [3]	19 y/F	R	+	CHOP	EFS (23 months)
Talwalkar *et al*. (2009) [6]	61 y/F	L	-	RCHOP+anti CD 30 ab	Alive with disease (2 years)
Ivashkevich *et al*. (2019) [11]	45 y/F	L	-	BV CHP	EFS (2 years)
Aguilera *et al*. (2000) [14]	13 y/F	L	+	Excision of mass	Died after 5 months of diagnosis
Daneshbod *et al*. (2010) [15]	16 y/F	R	+	CHOP	Succumbed to disease
Kelten *et al*. (2009) [16]	33 y/F	L	-	CHOP+DHAP+SCT	Alive with disease (30 months)
Pereira *et al*. (2002) [17]	92 y/F	L	-	Excision of lump+CHOP/Mtx	Died after 3 months of diagnosis
Krishnan *et al*. (2009) [18]	33 y/F	R	+	Chemotherapy	Alive with disease (30 months)
Bergsten *et al*. (2019) [19]	70 y/F	L	-	Excision of lump	Alive
Present case (2022)	34 y/F	bilateral	+	CHOEP	Alive (EFS 18 months)

ALCL: Anaplastic large cell lymphoma, Alk: Anaplastic large cell kinase, cHop: Cyclophosphamide, doxorubicin, vincristine, prednisolone, cHoep: Cyclophosphamide, doxorubicin, vincristine, prednisolone, etoposide, DHAp: Dexamethasone, cyctosine arabinoside, cisplatin, eFS: Event-free survival, F: Female, MtX: Methotrexate, L: Left; R-cHop: Rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone, R: Right, SCT: Stem cell transplantation, Y: Year

survival [10,11]. Systemic/nodal ALCL and ALK+ mostly affect the pediatric population, although cases arising in pregnant women have also been reported. Systemic/nodal ALCL, ALK+ primarily presents within the lymph nodes, while PB-ALCL, ALK+ usually presents as an enlarging breast lump; both often occur in combination with type-B symptoms and axillary lymph node and/or extra-nodal involvement [10,11].

PB-ALCL and ALK+ have variable treatment outcomes. It has been successfully treated with surgery and cyclophosphamide, hydroxydaunorubicin, oncovin, prednisone (CHOP) [12] chemotherapy, or CHOP chemotherapy in combination with brentuximab vedotin (BV), even with bone marrow involvement [13]. BV is an antibody-drug conjugate consisting of a monoclonal antibody targeting CD30 linked to the cytotoxic compound monomethyl auristatin E [14]. However, there are cases where PB-ALCL and ALK+ have been fatal; this mainly includes cases in young adolescents where systemic spread occurred despite the intensive chemotherapeutic regimens used [15].

This case highlights the risk of postpartum PBL. The patient achieved remission with chemotherapy alone and has been doing well for 2 years. It is essential to recognize this entity because the management is completely different from the more common adenocarcinoma, which is treated with surgery and radiation, unlike lymphoma, which is treated with chemotherapy alone. Though breast implant-associated ALCL is gaining recognition in this current era, it is important to realize that ALCL is not limited to implants itself and should be a differential in suspicion of breast lumps. We reviewed the literature and identified 30 similar cases of PBL with no prior history of breast implant placement involving breast tissue [6,16-19]. The following table summarizes our patient versus various case reports published to date of similar cases (Table 1) [1,3,6,14-19].

In the 30 cases described in case reports dating from 1993, 28 were females and 2 were males, 8 were in the age group of 10–30 years, 9 were in the age group of 30–50 years, 6 were in the age group of 50–70 years, and 3 were in the age group of 70–90 years. The age of 4 patients was not known. Of the 19 cases whose ALK status was known, 10 ALK− and 9 ALK+. Among the 11 patients whose treatment details were known, 1 underwent excision of mass only, and the rest underwent anthracycline-based chemotherapy with or without rituximab. The details of ALCL breast with no breast implant case reports published are summarized in Table 1. Our case was unique in being postpartum in presentation and involving bilateral breasts. The patient responded well to chemotherapy alone and leading event-free survival from 18 months till the date of this case report.

CONCLUSION

Although breast implant-associated ALCL is currently receiving increasing attention, it is important to realize that ALCL involving breast tissue is not limited to the ones associated with breast implants. This case also highlights the importance of having a high index of clinical suspicion to diagnose breast lymphomas, especially PBL, during pregnancy and the postpartum period.

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