Primary Non-Hodgkin Breast Lymphoma (PNHBL)

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I s r a e l

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Keywords:
Palpable mass
Well defined borders
B-cell lymphoma
Lumpectomy, chemotherapy, irradiation

Report of a case

A 36 years old woman presented to our clinic with a 4 months history of an enlarging left breast mass. No pain, fever or chills. On physical examination a long firm mobile 5x6cm mass that extended to the left axilla was found. No nipple discharge or axillary lymph nodes were present.
Mammography (fig. 1) well defined borders of a mass 5x6 cm on left breast. Ultrasonography detected a large heterogeneous hypoechoic mass. Ultrasound – guided core needle biopsy of the tumor showed: diffuse large B-cell lymphoma, high grade. Immunohistochemical staining for B-cell and LICA were strongly positive.
CA-30 focally- positive, CA-15 AMA and cytokeratin straining were negative.

Abstract

Primary breast lymphomas (PBL), which accounts for between 0.04% - 0.5% of all malignant Non-Hodgkin's breast tumors and 2.2% of all extra-nodal Non-Hodgkin's lymphomas.
The clinical profile of the patients with PBL is a middle-aged woman with painless intramammary palpable mass and most by no systemic symptoms.
Mammography shows the lesion to have well-defined borders.
The majority of primary breast lymphomas are high-grade B-cell tumors without accompanying low-grade component.
The therapeutic approach to the cases recorded in the literature varies widely. High-grade lymphomas treated with combination chemotherapy with or without radiation and low grade lymphomas (including MALT lymphomas) treated with local excision and/or radiotherapy.

Primary Non-Hodgkin's Breast Lymphoma (PNHBL)

Introduction

Primary breast lymphomas, which accounts for between 0.04% - 0.5% of all malignant Non-Hodgkin's breast tumors and 2.2% of all extra-nodal Non-Hodgkin's lymphoma [1-4].

Freeman et al. [5] reported only 2.2% of breast lymphoma among 1,467 patients of Primary Non-Hodgkin Breast Lymphoma (PNHBL) localized extra-nodal NHL. Wiseman and Liao[6] proposed the criteria for PNHBL: (a) technically adequate specimens; (b) mammary tissue and lymphomatous infiltrate in close association; (c) no evidence of concurrent widespread disease; and (d) no prior diagnosis of extra-mammary lymphoma[7].

The modification by Hugh et al. [8] included (i) adequate pathologic material available for review, (ii) signs and symptoms referable to the breast with the major tumor located in it, (iii) absence of a similar histologic type of lymphoma elsewhere, except for axillary lymph nodes or bone marrow involvement, shown in subsequent staging investigation[9-13].

Most of the published reports on PNHBL included a relatively small number of patients, and many of them also included patients that did not meet criteria of PNHBL e.g. extensive involvement of disease outside the breast.

Clinical Features

The clinical profile of the patients with PBL is a middle-aged woman with painless intra-mammary palpable mass and most by no systemic symptoms.

Differential diagnosis included infiltrating breast carcinoma, sarcoma, fibroadenoma, cystosarcoma phylloides and mammary dysplasia.

It mostly appears as a unilateral disease of the right breast. Bilateral breast lymphomas having been reported with a frequency of 5% to 25%.

The tumor tends to enlarge rapidly and the lead time is less than 2 months unlike sarcomas, lymphomas often adhere to the skin. Nipple discharge is rare observed. Ipsilateral axillary lymph node involvement is approximately 50%.

The clinical staging evaluation is according to the Ann Arbor classification system [14] [15] including a history and physical examination, complete blood count, liver and renal function, LDH tests, tumor markers, chest x-rays, mammograms and bone marrow biopsy. Imaging studies include computed tomography, Gallium scan, lymphangiogram, detection with Tc-99m tetrofosmin scintigraphy [16], F-18 FDG position emission tomography (PET) [17] and others.

The International Prognostic Index and the Working Formulation has to be done to allow for comparison with the results of other published studies.

Mammography shows the lesion to have well-defined borders. The findings of imaging resemble this to be either medullary or mucinous carcinoma, cystosarcoma phylloides, giant fibroadenoma, or lymphoma.

The mammographic appearance of lymphoma varies from discrete nodules with marginal irregularity to multiple thickenings, similar to those of dysplastic lesions, to diffuse increase in density and thickening of the skin; calcifications are absent. The discrepancy between the radiographic appearance and clinical signs should suggest the possibility of a lymphoproliferative lesion [18].

Sonography reveals a hypoechoic lesion of mostly homogeneous echo texture with lobulated well-delineated margins. No definitive acoustic shadowing or posterior enhancement is seen [19].

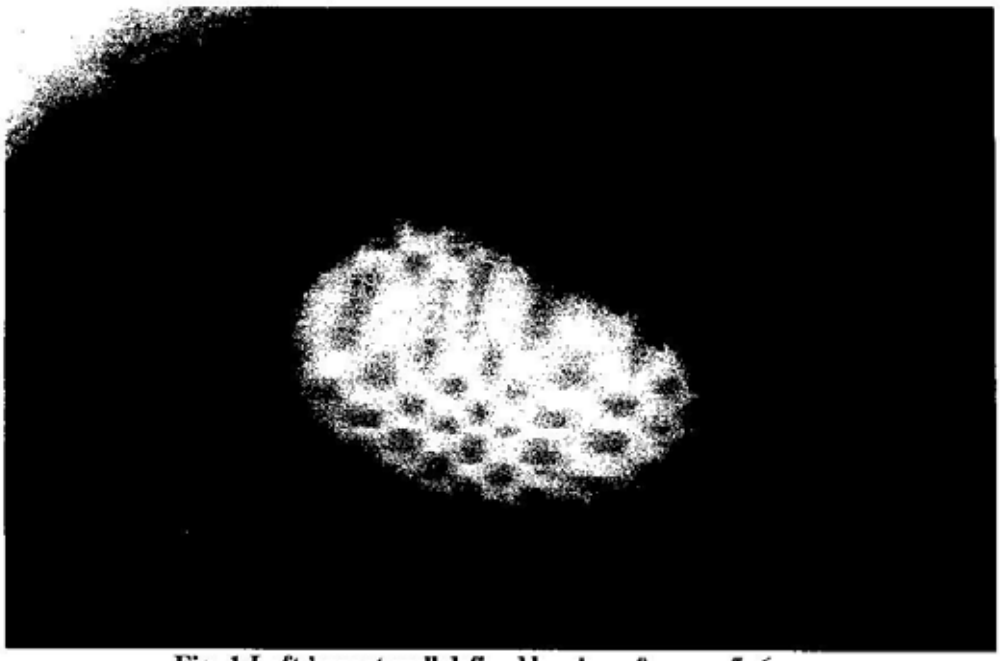

Fig. 1 Left breast well defined borders of a mass 5x6 cm.

Histopathology and Immunohistochemistry

The majority of primary breast lymphomas are high-grade B-cell tumors without accompanying low-grade component. The mucosa-associated lymphoid lymphoma has been described as a distinctive type of lymphoma arising from organs possessing mucosa-associated lymphoid tissue (MALT) as defined by Bienenstock and Befus [20]. The MALT includes gut-associated lymphoid tissue (GALT), and bronchus-associated lymphoid tissue (BALT).

The breast in one of the sites where this tissue is also present with intraepithelial lymphocytes as one component. It has been shown that B-cells from intestine and mesenteric nodes migrate to different mucosal sites, and also to the breast. In this way various mucosal sites are immunologically integrated [21].

The neoplastic component of MALT lymphomas consists of B-cells surrounding the follicles and selectively infiltrating epithelium to form the characteristic lympho-epithelial lesions and, in many cases, differentiated plasma cells [22-24]. The follicles themselves, although a characteristic feature of the lymphomas, are reactive in nature, as is the considerable population of T-cell. A case of pregnancy associates anaplastic large cell lymphoma of the breast is described [24].

The infiltration of the mucosal glands by lymphoma cells is characteristically seen in several lymphomas of MALT type. This morphological feature is considered to be of primary importance in diagnosing an extranodular lymphoma as a MALT lymphoma and is called a lymphoepithelial lesion. Another characteristic of MALT lymphomas, although not a prerequisite for diagnosis, is plasma cell differentiation of lymphoma cells which may show immunological monotypia. Plasma cells tend to displace but not invade epithelial cells, which is done by the less differentiated cells.

In keeping with other low-grade B-cell lymphomas, the cytological features of MALT lymphoma cells are not uniform. The most characteristic cells are small to medium sized with a moderate account of cytoplasm, which is sometimes pale staining, and a nucleus with an irregular outline. The cytology of MALT lymphoma may vary both between cases and, less commonly, within a single case. Remnants of ducal and lobular structures may persist inside the tumor.

Since a uniform lymphoma classification system has not been used in the rare primary breast lymphomas, the frequency of various types is indeterminable. Microscopically, lymphoma cells

infiltrate among the quite normal breast lobules and ducts. In histiocytic lymphoma, the cells are of moderate size and are uniform, although pleomorphism, giant cells, and atypia are also found. The well-differentiated lymphocytic lymphomas are composed of small, mature, monotonous lymphocytes. The poorly differentiated lymphocytic lymphomas demonstrate marked nuclear pleomorphism and cellular immaturity, sometimes with sheets of pure lymphoblasts. Occasionally, the primary breast lymphoma may be difficult to differentiate from pseudolymphoma, granulocytic sarcoma, and, less often, from medullary or poorly differentiated carcinomas. Electron microscopy is particularly helpful in the last case [25].

At a low power the lymphoma shows a well developed marginal zone growth pattern characteristic for lymphomas of the mucosa-associated lymphoid tissue (MALT lymphoma). At high power the lymphoma cells have a characteristic "monocytoid" appearance. The cytoplasm is pale and relatively broad. The nuclei are rounded, ovoid, or sometimes have a "reniform" shape. Immunostaining for kappa light chains is positive for lymphoma cells. Other immunostaining CD 20+, be 16+, CD 10+, be 12+. Bone marrow biopsy has to be performed.

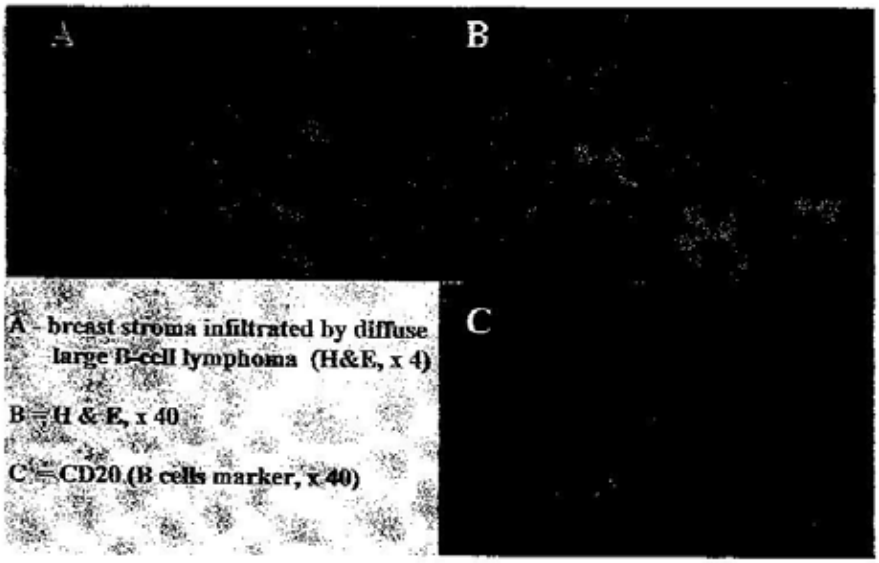

Fig. 2 Left breast B-cell lymphoma diffuse large cell type, high grade
Immunohistochemical stains for B-cell and LCA are strongly positive. CA-30 focally positive, CA-15, AMA and cytokeratin negative.

Treatment and Prognosis

The therapeutic approach to the cases recorded in the literature varies widely. High-grade lymphomas treated with combination chemotherapy with or without radiation and low grade lymphomas (including MALT lymphomas) treated with local excision and / or radiotherapy.

Treatment

Lumpectomy with free margins.

Chemotherapy: 4-6 cycles of cyclophosphamide, hydroxydoxorubicin, vicristine and prednisone.

Irradiation isocentrically with two opposite 6-megavolt (MeV) photon beams delivered from the linear accelerator (tangential fields) using asymmetric collimator opening [26]. The total irradiation dose is 44 Gy delivered in singly daily doses of 2 Grays (Gy).

Prognosis

5 year survival rate: 35% - 50%.

Discussion

The Mayo clinic experience is quoted for primary breast lymphoma [25].
Between 1973 and 1998, 25 women and 1 man with the diagnosis of primary breast non-Hodgkin lymphoma (PNHLB) were seen at Mayo Clinic Rochester and Mayo Clinic Scottsdale. Patient characteristics, treatment methods, and outcome were analyzed. The median follow-up for surviving patients was 6.6 years (range: 1.8 - 22.1 years). There were 11 low-grade NHL, 13 intermediate-grades NHL, and 2 high-grade NHL. Three patients underwent mastectomy while 23 had local excision.

A search for lymphoma elsewhere may include chest x-ray, bipedal lymphangiography, computerized tomography, and bone marrow aspiration/biopsy, and chest tomography, isotope scanning of bone or liver, and biopsy of equivocal adenopathy. Treatment of primary breast lymphoma should be performed by an experienced hematologist according to the treatment of the same lymphoma occurring elsewhere. Such treatment will probably include adequate open biopsy with material for touch prep, cell surface markers, and possibly for electron microscopy. Further treatment of breast lymphoma, depending on the cell of origin, will usually involve radiation or chemotherapy or both.

Conclusions

The management of PNHLB should be based on histologic grade. Patients with low-grade disease may be managed with local therapy alone i.e. the role of chemotherapy in this group is unclear. Patients with intermediate or high-grade disease have better outcome if chemotherapy is included. An unusual site of distant dissemination for these patients is the CNS. The only significant prognostic factor for survival is Ann Arbor stage.

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