Primary breast lymphomas

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Abstract

The diagnosis, prognostic factors, and optimal management of primary breast lymphomas (PBL) is difficult. Seven patients recorded at the Geneva Cancer Registry between 1973-1998 were reviewed. Five patient had diffuse large B-cell lymphoma, one a follicular lymphoma and one a MALT-lymphoma. All patients had clinical and radiological findings consistent with breast cancer and underwent mastectomy, which is not indicated in PBL. Diagnosis should be established prior to operative interventions, as fine needle aspiration missed the diagnosis for one patient and intra-operative frozen sections for 3 patients in our study. Five-year and 10-year overall survivals were 57% and 15%, respectively. Of the 3 patients who died from PBL, 2 had tumors that were Bcl-2 positive but Bcl-6 negative. All 3 surviving patients have positive Bcl-2 and Bcl-6 immunostaining, which could be important prognostic factors if confirmed by a larger study.

Introduction

The breast is one of the least common primary extranodal sites for malignant lymphomas. A variety of pathological subtypes have been reported. The frequency with which the different subtypes of primary lymphoma of the breast occur is difficult to determine, because both terminology and classification vary among the relatively small case series that have been reported. There is general agreement, however, that these lymphomas are usually of Non-Hodgkin's lymphoma (NHL) histology.[1] They account for 0.04-0.5% of all breast neoplasms and less than 1% of all NHL.[2]

NHL is a potentially systemic disease; therefore, appropriate management must take this into account.[1] Clinically and pathologically, primary lymphomas of the breast must be distinguished from both benign lymphoid infiltrates and non-lymphoid neoplasms of the breast. Since the breast normally contains some lymphoid tissue and functions during lactation as part of the mucosal immune system, lymphomas in this site may be related to lymphomas of mucosa-associated lymphoid tissue, so-called MALT lymphoma. Primary breast lymphoma (PBL) can still be misdiagnosed as carcinoma, a particular point of interest for pathologists and clinicians. In addition, there is a lack of consensus about its treatment and prognostic factors. The purpose of this study is to evaluate clinical presentation and pathological features, diagnostic difficulties and potential prognostic markers of this rare tumor.

Materials and Methods

The data were derived from the Geneva Cancer Registry, which includes information regarding all cases of malignant neoplasms occurring in the population of the region (approximately 420,000 inhabitants). The registry collects information from various sources and is considered accurate, as attested by its very low percentage (<2%) of cases recorded from death certificates only.[3] Individual clinical files from all university public hospitals are systematically consulted and inquiry forms are addressed regularly to physicians for patients treated in the private sector. Trained registrars systematically abstract data from medical and laboratory records. Physicians regularly receive questionnaires to secure missing clinical and therapeutic data. Death certificates are consulted systematically. Recorded data include sociodemographic information, method of discovery, type of confirmation, tumor characteristics (coded according to the International Classification of Diseases for Oncology),[4] stage of disease at diagnosis, treatment during the first six months after diagnosis, survival status, and cause of death.

The registry regularly assesses survival rate index. In brief, it refers to the date of confirmation of diagnosis or the date of hospitalization if it preceded the diagnosis and was related to the disease. In addition to passive follow-up (routine examination of death certificates and hospital records), an active follow-up is performed routinely each year using the files of the Cantonal Population Office in charge of the registration of the resident population. Finally, cause of death is established from clinical records and coded according to the World Health Organization's classification.[5]

In this study we included all cases of PBL diagnosed between January 1973 and December 1998 among the resident population. Additional clinical information was obtained from a retrospective review of all the patient charts.

Pathological diagnosis of primary breast lymphoma was based on the following strict criteria as described by Wieseman and Liao in 1972: 1) an adequate pathological specimen; 2) a close association of mammary tissue and lymphomatous infiltrate; 3) no evidence of disseminated lymphoma at the time of diagnosis; and 4) the presence of ipsilateral axillary nodes was acceptable if they occurred concomitantly with the primary lesion. Staging was based on the WHO classification 2001.[6] In all patients, the pathological diagnosis was established on excisional biopsy or mastectomy specimen. Original hematoxylin-eosin-stained sections and formalin-fixed, paraffin-embedded tissue were available in all cases. Histological review of the microscopic slides was performed by some of the authors (MFP/ATV). Extensive immunohistochemical studies were performed.

Histology and immunohistochemistry

Conventional histology included hematoxilin eosin, Giemsa, and silver stain of all available tissue blocks. Immunostaining was performed using the listed antibodies with a streptavidine-biotin peroxidase system. Antigen retrieval, if necessary, was carried out either by microwaving or pressure cooking in ethylenediamine tetraacetic buffer (pH 2.5).

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Table 1. Clinical staging under presumption of carcinoma.

N.	Age yr	Working classification	Clinical presentation	Side	Location	Size cm	TNM staging	Primary treatment	Secondary treatment	CR	Time to death	D F S years	Cause of of death
1	86	MALT	Periartritis	R	All breast	6.5	T4d N2 Mx	Patey	Rx refused	Yes	5 years	5	PBL
2	78	Follicular	Breast mass	R	UO+I	NA	T3 N1 Mx	Patey	Ch refused	No	2 months	progression	PBL
3	74	DLBCL	Breast mass	L	UO	5	T3 N0 Mx	Mastectomy	No	No	15 days	progression	PBL
4	62	DLBCL	Breast mass	L	UO	3	T2 N0 Mx	Patey	No	Yes	5 years	5	Cardiac
5	71	DLBCL	Breast mass	R	UO+I	5.4	T3 N1 Mx	Patey	Ch: CHOP	Yes	/	*7,5	Alive
6	39	DLBCL	Breast mass	R	NA	2	T2 N0 Mx	LAND	Rx	Yes	/	*16,5	Alive
7	44	DLBCL	Breast mass	L	LO	5	T3 N0 Mx	Patey	Ch: CHOP	Yes	/	*4,5	Alive

UO: upper outer quadrant; UI: upper inter quadrant; LO: lower outer quadrant; R: right; L: left; TNM: classification by Tumor Node Metastasis; Age: years; MALT: MALT lymphoma; Follicular: follicular lymphoma; DLBCL: diffuse large B-cell lymphoma; LAND: lumpectomy and axillary dissection; Pathey: mastectomy and axillary dissection; DSF: disease free survival; CR: complete response.*

Table 2. Pathological characteristics including immunochemical studies.

N.	Age yr	Working classification	Keratine	LCA	CD3	CD20	CD79	MiB1	Bcl-2	Bcl-6	MiB1
1	86	MALT	+	+	-	+	+	60%	+	-	60%
2	78	Follicular	-	+	-	+	+	30%	-	+	30%
3	74	DLBCL	+	+	-	+	+	50%	+	-	50%
4	62	DLBCL	+	+	-	+	+	/	-	-	/
5	71	DLBCL	-	+	-	+	+	80%	+	+	80%
6	39	DLBCL	-	+	+	+	+	80%	+	+	80%
7	44	DLBCL	+	+	-	+	+	90%	+	-	90%

UO: upper outer quadrant; UI: upper inter quadrant; LO: lower outer quadrant; R: right; L: left; TNM: classification by Tumor Node Metastasis; Age: years; MALT: MALT lymphoma; Follicular: follicular lymphoma; DLBCL: diffuse large B-cell lymphoma.*

The work-up included CD3, CD4, CD5, CD8, CD20, CD21, CD23, CD30, CD45, CD68, CD79a, MIB1, pan-cytokeratine, Bcl-2 and Bcl-6. If not otherwise mentioned, these antibodies were from Dako, Copenhagen. The SPSS software (SPSS 10 version Inc., Chicago, IL.) was used for statistical analysis. Descriptive statistics were performed to assess the frequency distribution. We calculated disease-specific and disease-free interval probabilities using the Kaplan-Meier method.[7]

Results

Since its creation in 1970, the registry has recorded over 7,800 women with breast malignancies. Only 9 patients were initially diagnosed and recorded as primary breast lymphoma, representing less than 0.1% of all malignant breast tumors. However, there were only 7 true PBL after histological review. In 2 women, clinical investigations performed at diagnosis were insufficient to definitively conclude that the lymphoma occurred primarily in the breast.

Patients' characteristics

Patients' and tumor characteristics are described in Table 1. The median age at diagnosis was 65 years (range 39-86); most were in the seventh decade of life (4 patients, 57%).

Three patients (43%) had left-breast involvement and 4 (57%) right-breast involvement. None had bilateral involvement. Clinical lesions were located predominantly in the upper outer quadrant (UOQ) in 2 (29%) patients, in the upper outer and inner quadrant in 2 (29%), in the lower outer quadrant (LOQ) in one (14%) and involved the whole breast in one patient (14%). Four patients (57%) had no clinical axillary involvement. All patients sought consultation for breast related symptoms and presented with a palpable mass. Only one patient reported pain, described as located in the homolateral shoulder; however, the whole breast was involved in this case. No malignant lymphoma was suspected on clinical examination, nor in complementary investigations. In particular, mammography examination before surgery was suggestive of breast carcinoma in all cases (100%).

First diagnosis was breast carcinoma in 6 out of 7 cases (86%) and inflammatory breast carcinoma in one case (14%). Fine needle aspiration (FNA) was performed in 2 (29%) cases, both suggestive of breast carcinoma. Primary breast lymphoma was diagnosed after surgical excision in all cases, with frozen section diagnosis for 3 cases. Frozen section diagnoses revealed lymphoma in 2 cases and a malignant non-differentiated tumor.

Pathology

Table 2 summarizes pathological characteristics among primary breast lymphoma patients. The average tumor size at diagnosis varied from 2 cm to 6.3 cm in the greatest diameter (mean, 4.5 cm) (Table 1). The section presented with homogeneous fish-flesh surface with occasional hemorrhagic or necrosis foci. For small tumors, margins were regular and pushing, for larger, irregular and stellate. Fibrosis or sclerosis surrounding the tumor mass may suggest a medullary carcinoma of the breast or a benign process. Under light microscopy, the tumor masses were poorly circumscribed, infiltrating the mammary lobules, and surrounded mammary ducts. Diffuse large B-cell lymphoma, or DLBCL, was the most common entity, (5 cases; 71%). Large blastic B cells replaced the normal architecture of the underlying breast in a diffuse pattern and broad or fine bands of sclerosis were observed. The morphological variant was centroblastic lymphoma for all of the masses. The most common DLBCL were composed of medium-sized to large lymphoid cells with generally basophilic cytoplasm. Nuclei were characterized by oval to round vesicles, fine chromatin and 2-4 membrane bound nucleoli. In some cases, the cells were multilobated. Centroblastic variant of diffuse large B-cell lymphoma was monomorphic in one case and polymorphic in the remaining cases. One case was diagnosed with grade III follicular lymphoma (Figure 1). The remaining case was an extranodal marginal zone B-cell lymphoma MALT lymphoma. The characteristic marginal zone B cells had small to medium-sized, slightly irreg-

ular nuclei with moderately dispersed chromatin and inconspicuous nucleoli, resembling those of centrocytes. They had a relatively abundant, pale cytoplasm. The glandular-epithelium was invaded and destroyed by aggregates of lymphoma cells resulting in so-called lymphoepithelial lesions (Figure 2).

Four DLBCL showed additional histological features of MALT (lymphoepithelial lesions) (Figure 3). Our last 2 cases showed no lymphoepithelial lesions but clearly showed ductal invasion by lymphoma cells (Figure 4).

Immunophenotype

Immunohistochemical studies are reported in Table 2. As expected, DLBCL expressed the pan-B markers CD20 and CD79. Bcl-2 was positive in 4 cases (80%) and nuclear expression of Bcl-6 in 2 cases (40%). MiB1 was highly expressed indicating a high proliferative rate (up to 90%) in all cases. The follicular lymphoma expressed the pan-B markers CD20 and CD79 as well as Bcl-6. Bcl-2 protein was expressed in the majority of the reported cases, ranging from nearly 100% in grade I to 75% in grade III however, cutaneous follicular lymphoma is frequently Bcl-2 negative. MiB1 was expressed in 30% of the cells. The MALT lymphoma expressed CD20 and CD79 as well as Bcl-2.

Treatment

Various treatment strategies were used according to available data. Treatments are reported in Table 1. Surgery was initially performed because of the initial clinical impression of mammary carcinoma. Surgeries consisted of mastectomies associated with an axillary lymph node dissection for 6 patients and a breast conserving surgery for one patient with a small size (2 cm) lesion. The Levels I and II axillary lymphatics were included within the breast or chest-wall fields; 3 of the 6 performed were positive (50%).

The treatment proposed after surgery was chemotherapy in 3 cases (43%), of whom one (14%) refused and radiotherapy in 2 cases (29%), which was also refused by one patient (14%). The last 2 cases (29%) were treated with surgery alone. One patient had a mastectomy and axillary dissection. The second patient had a simple mastectomy and did not receive adjuvant therapy because of her poor condition. None of the cases received combined modality approaches.

Outcome

Median follow-up was 5.8 years (range: 0.15-16). Of the 7 patients, 5 achieved complete response after therapy (Table 1). Two patients never achieved complete response and died of disease progression. In one of these patients progression was observed to the brain and skin. The other, because of her poor medical condition, died two weeks after surgery. One relapsed after five years (skin) and subsequently died of lymphoma. At time of the last follow-up, 3 were alive. One died of other causes (cardiovascular disease). Five and 10-year overall survival rates were 57% and 15%, respectively. Of the 3 patients who died from their PBL, 2 had positive Bcl-2 immunostaining (66%) but negative Bcl-6 immunostaining (66%). On the other hand, of the 3 patients still alive, all had positive Bcl-2 immunostaining and 2 positive Bcl-6 immunostaining (66%). Treatment modalities and their corresponding effect on mortality are presented in Table 1.

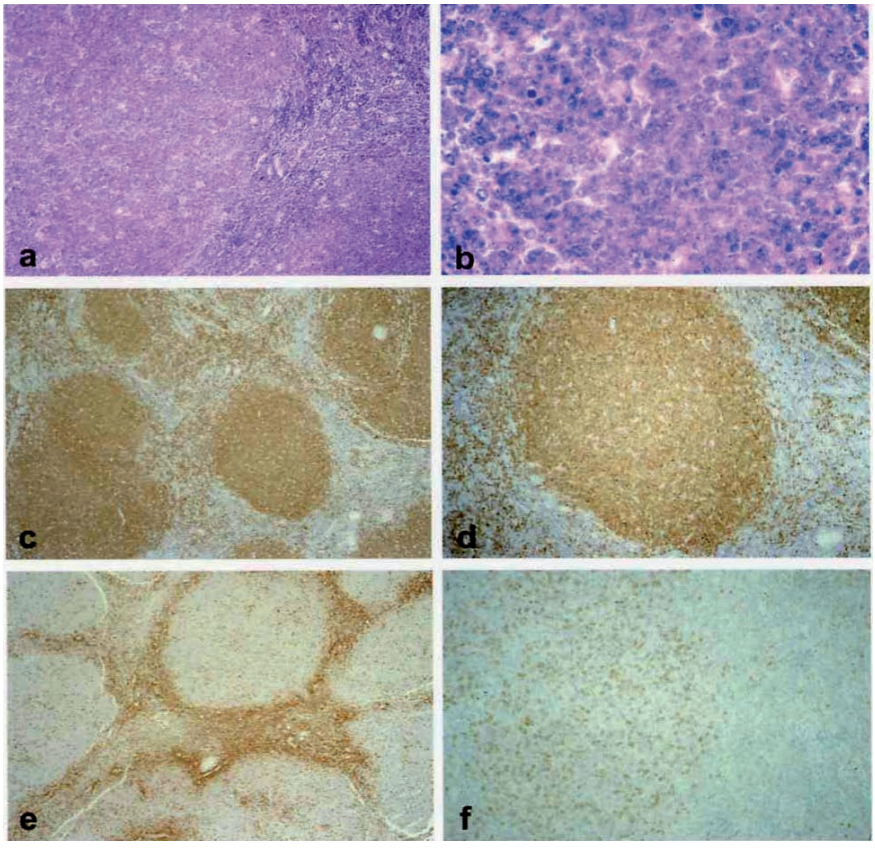

Figure 1. Follicular lymphoma. (a) Follicular aspect: HE (x100); (b) large transformed cells with one to three peripheral nucleoli: Giemsa (x200); (c) B cells with follicular arrangement: CD79 (x50); (d) B cells with follicular arrangement: CD79 (x100); (e) reactive T cells surrounding the B cells with follicular arrangement: CD3(x50); (f) Bcl-6 staining (x200).

Discussion

In the present study we evaluated all patients who presented with primary lymphomatous involvement of the breast over a 26-year period at our institution. Only the patients who satisfied the strict criteria of PLB according to Wiseman and Liao were analyzed for this study to avoid the potential inclusion of patients with secondary breast involvement of NHL.[2] The most frequent clinical scenario is that of a unilateral breast mass presenting in a middle-aged woman (median age: 55-60 years).[1,8-10] In our series we found an older median age: 65 years (39-86 years), as already described, whereas some authors find a younger median age.[11] The right breast was reported to be most frequently involved.[1,8-11] Only a few series report the opposite and another had no predominant site.[12] Five to 25%[2,13] of reported cases were simultaneously bilateral at presentation,[8,10,12] nevertheless no such case is reported in our series. We were particularly interested in the method by which these tumors were detected and hypothesized that increased knowledge and the current widespread use of mammography as a screening method for breast carcinoma may increase the detection of breast lymphoma. Hematopoietic neoplasms involving the breast, although less common than breast carcinoma, are often clinically indistinguishable from other breast tumors. Microscopically, these tumors can mimic primary carcinoma of the breast, especially in limited material such as fine needle aspirations (FNA). In 2 patients with FNA in our series, cytology was interpretated as carcinoma. In the 3 patients with frozen section diagnosis, only one (the follicular lymphoma case) was

diagnosed correctly. FNA misdiagnosis has been reported by several authors.[12]

However, breast carcinoma is not the only pitfall. Diabetic mastopathy (DM) may be over-interpreted as lymphoma. DM, which has been described in both diabetic patients and non-diabetic patients, generally demonstrates fibrocystic change with dense stromal fibrosis and an extensive perivascular infiltrate of small B-lymphocytes. However, there is no current evidence that DM is a precursor lesion to PBL.[8,13] Traditionally a surgical approach to the treatment of patients' PBL has been adopted,[2] even if mastectomy could be avoided in most patients,[15] and treatment confined to chemotherapy and radiation therapy appropriate for the histological type. In our series, all patients underwent a surgical treatment. It is important to underline that all mastectomies in our series were performed due to the initial clinical and/or pathological diagnosis impression (frozen section or FNA) of adenocarcinoma. Similarly, although there have been reports of radiation therapy alone for patients with PBL,[16] patients with intermediate-grade and high-grade lymphomas of the breast are best treated with chemotherapy or with combined chemotherapy and radiation therapy.[10]

Published reports on the treatment outcome for PBL range from equivalent to worse prognosis for PBL compared to other non-Hodgkin's lymphomas (NHL).[1,2] Confounding the matter are the different definitions of PLB used by different authors. Some consider the lymphoma to be PBL if the patient presents with complaints relating to the breast or if the main tumor mass is in the breast.[1,12] Others use more strict definitions of PBL.[2,16] Different pathological types of breast lymphoma have also been reported by different investigators at least partially because of different histological criteria used.[9,12]

Cohen *et al.* studied both primary and secondary breast lymphomas with a broad panel of T- and B-cell markers using paraffin-embedded tissue and the avidin-biotin immunoperoxidase method. Cases of PBL were further tested to determine light and heavy chain type. Thirty-five cases were analyzed, including 16 primary lymphomas. Diffuse large cell lymphoma was present in 10 of 16 primary and 14 of 18 secondary cases. Lymphoepithelial lesions in ducts and lobules and frequent vascular involvement were found in both primary and secondary cases. Immunohistochemistry studies on 13 tumors revealed all of the primary tumors to be B-cell in origin, except for one case of primary T-cell lymphoma; to the authors' knowledge, this represents the first description of this entity. Fifteen of 17 secondary tumors exhibited B-cell markers and one of 17 exhibited T-cell markers; in only one case could lineage not be determined.[17] Among primary B-cell cases, IgM was found to be the

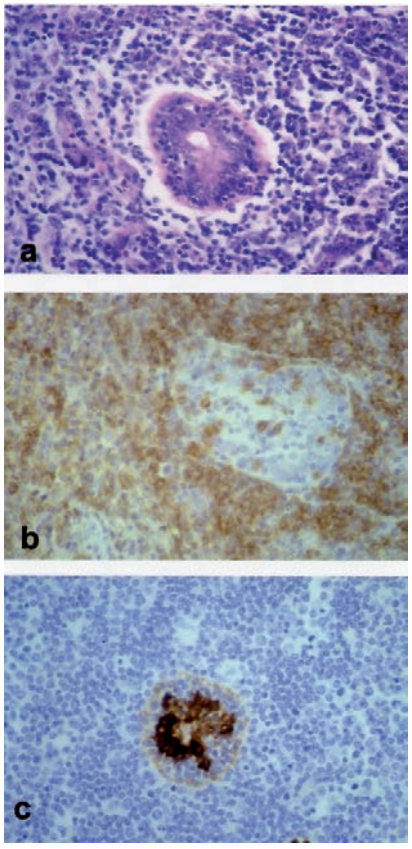

Figure 2. Destruction of the glandular tissue epithelium by aggregates of lymphoma cells. (a) Mammary gland infiltrated by lymphoma cells: HE (x400); (b) mammary gland infiltrated by B cells: CD20 (x400); mammary gland: Keratin (x400).

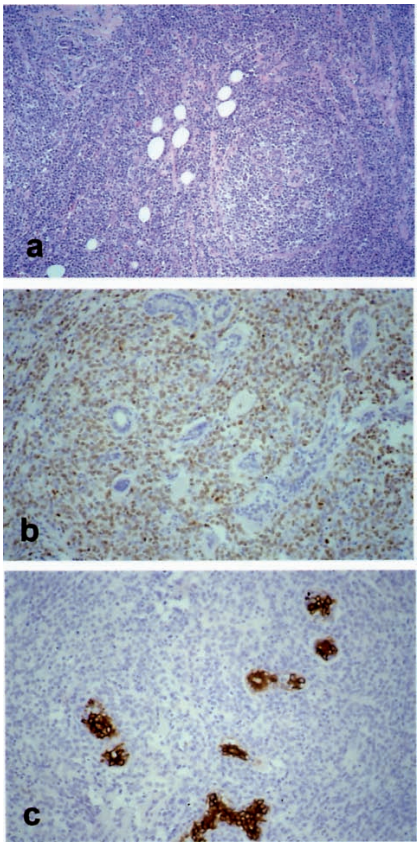

Figure 4. Primary breast lymphoma without lymphoepithelial lesion. (a) Proliferation index: MiB1 (x200) (80% positive); (b) HE (x100); (c) mammary gland: keratin (x200).

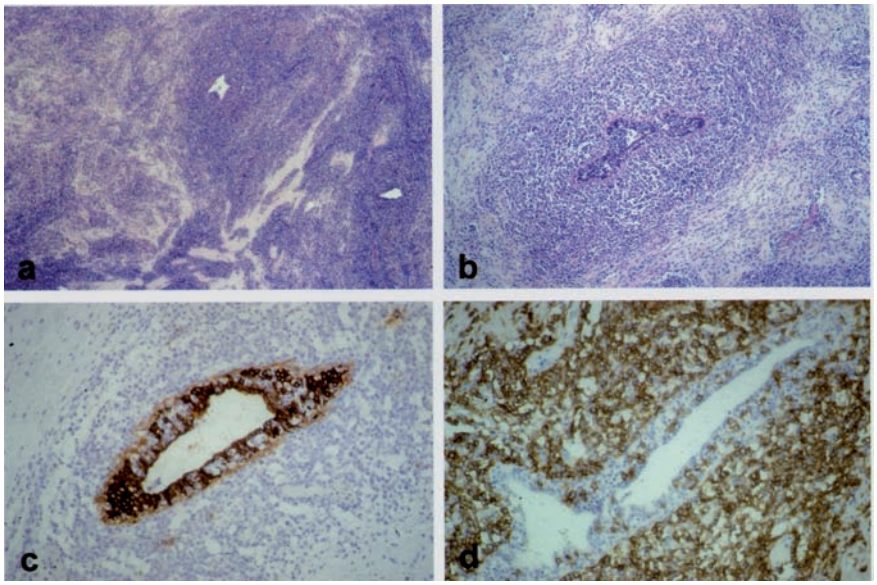

Figure 3. Lymphoepithelial lesions. (a) Lymphoepithelial lesion: HE (x50); (b) lymphoepithelial lesion: HE (x100);(c) mammary gland: keratin (x200); (d) mammary gland infiltrated by B cells: CD20 (x200).

most frequent heavy chain type; IgA reactivity was found in one case only.[18]

In our series, the World Health Organization Classification of Tumors was used.[6] Diffuse large B-cell lymphoma (DLBCL) was the most common diagnosis (71%) and all cases were of B-cell phenotype. Although there was some variation in histological appearance from patient to patient, the characteristics of large B-cell breast lymphoma were not distinctive and resembled DLBCL occuring at other sites. In addition, we reported a follicular lymphoma and a MALT lymphoma. Lamovec and Jancar first reported that some PBLs had features of MALT lymphoma. Subsequently, several series have reported MALT lymphoma as part of the spectrum of PBL, comprising 0-64% of all PBL.[9,10,18,19]

DLBCL are a heterogeneous group of tumors, varying in cellular content, phenotype, cytogenetics, site of presentation and natural history of disease. They represent the most frequent type of NHL, accounting for 30-40% of adult NHL.[20] Although approximately half of the patients with DLBCL can be cured by conventional chemotherapy, the remainder will die of their disease. Identification of patients at presentation who are unlikely to be cured by standard therapy is a key step in developing new treatment strategies. At present, the most effective tool for the identification of prognostic subgroups is the International Prognostic Index (IPI),[21] which is calculated using age, Ann Arbor Stage, number of extranodal sites, performance status (Eastern Cooperative Oncology Group (ECOG) scale) and serum lactate dehydrogenase (LDH), all of which are independent risk factors. Several molecular abnormalities, such as Bcl-2[22] and survivin[23] expression and p53 mutations,[24] were identified as prognostic indicators of DLBCL. Bcl-2 expression was reported to correlate with reduced disease-free survival (DFS),[22] but it only predicted reduced overall survival (OS) for patients with DLBCL in one of the reported studies.[22] The Bcl-2 protein is expressed in a significant proportion of DLBCLs, either as a consequence of, or independently of, the translocation-t(14;18).[21,22] This has been shown in a number of studies to have an adverse effect on survival[21,22] and is the most widely accepted cellular prognostic factor. In our study, Bcl-2 was expressed in 5 cases (71.4%). In a strange way it was expressed in 3 cases of the surviving patients but only in 2 of the 3 (66%) cases who died from PBL.

Recently, it has been suggested that the expression of a germinal center (GC) phenotype may be a favorable prognostic factor.[21] Rearrangement of the Bcl-6 locus at 3q27 seems to occur more frequently in extranodal DLBCL than in node-based disease and to be an independent poor prognostic factor in nodal diffuse large B-cell lymphoma.[21]

Expression of Bcl-6 protein has been reported to have an antiapoptotic effect in GC B cells[21] and, by analogy with Bcl-2, it may be expected that expression of Bcl-6 protein would be a poor prognostic factor. However, Bcl-6, alone and in the context of a GC phenotype, appeared to be associated with a favorable prognosis. Although not statistically significant, it is consistent with recent observations, using gene expression and microarray technology, that Bcl-6 expression and GC differentiation are favorable prognostic factors.[21] It is of particular interest that a significant proportion (32%) of the cases with a Bcl-6 gene rearrangement lacked expression of Bcl-6 protein using immunocytochemistry. This lack of correlation has been reported previously[21] and suggests that rearrangement of the Bcl-6 gene does not directly lead to Bcl-6 protein expression in every case.

Our results are difficult to extrapolate due to the small number of cases. In this study, we used immunohistochemistry to define Bcl-2 and Bcl-6 expression. Bcl-6 was negative in patients who died of PBL, but positive in 2 of 3 surviving patients. These results indicate that Bcl-6 could serve as a surrogate predictor for overall survival of patients with PBL. This should be investigated in a large scale study on PBL.

Conclusions

For patients with primary lymphomatous involvement of the breast who will classically present with a palpable mass, screening mammography appears to contribute little to their diagnosis, and FNA or frozen section can lead to misdiagnosis. The results of therapy did not appear to differ significantly from the results seen for lymphomas occuring in other sites.

Lymphomas of the breast are uncommon, present generally in elderly patients and have a bad prognosis. This potentially curable neoplasm with a stage-for-stage clinical outcome similar to that of patients with other lymphomas of similar histological type[25] is, however, often misdiagnosed. Despite a number of recent articles on lymphomas of the breast, it appears that these tumors continue to be confused with carcinomas.

As no pathognomonic clinical, pathological or radiological findings differentiate PBL completely from adenocarcinoma, pathologists must be attuned to the possibility of lymphoma, especially if the frozen section diagnosis of adenocarcinoma is questionable in the operating room.[10] This could save patients from unnecessary mastectomies.

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