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CLINICAL CASE

Lymphoma of the breast – case report and review of the literature

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We present a case of diffuse large B-cell NHL presenting as a solitary breast lump. It was not possible to establish whether the breast was the primary site of involvement. We use the issues raised in this case as a basis to review the literature concerning the diagnosis and management of NHL of the breast.

Key words: breast, non-Hodgkin's lymphoma

Introduction

The breast is an uncommon site of involvement by non-Hodgkin's lymphoma (NHL). This involvement can be primary, or as a secondary site in systemic disease. Differentiating between the two can be very difficult, but may have implications regarding prognosis and treatment.

Case presentation

A 71-year-old post-menopausal lady presented with a 6-week history of a central lump in her right breast. Clinical examination revealed a discrete, partially mobile 5 cm palpable lump with indrawing of the right nipple and areola and no evidence of deep fixation. There was no axillary lymphadenopathy. Relevant past medical history included type 2 diabetes mellitus and essential hypertension.

Mammography identified a 5 cm, partially well-defined, retroareolar mass. Ultrasound demonstrated this lesion to be heterogeneous and predominantly well-defined. The radiographic appearances were reported as being consistent with a malignancy, or, conceivably, a phyllodes tumour. Core biopsy of the mass confirmed infiltration with a pleomorphic population of cells of lymphoid appearance. A diagnosis of extranodal NHL of diffuse large B-cell type (DLBCL) was made. Immunostaining was positive for CD45 (confirming lymphocytic origin), and the atypical cells stained strongly for CD20, CD79a and CD43. Focal positive staining for CD10 and Bcl-6 was also found, and the cell population stained weakly positive for Bcl-2 throughout (Figures 1,2).

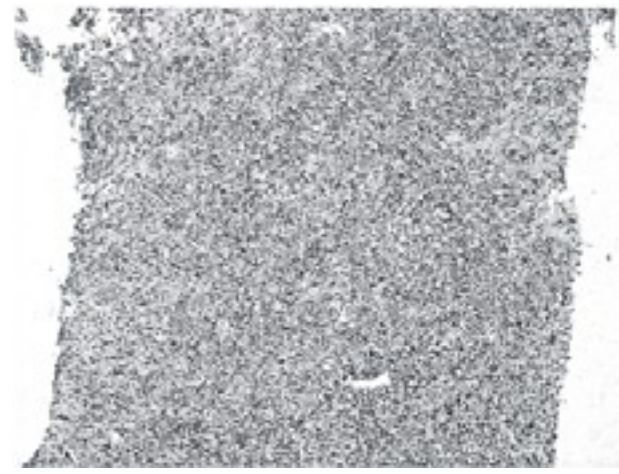

Figure 1. Core biopsy of primary breast lymphoma (H&E ×10).

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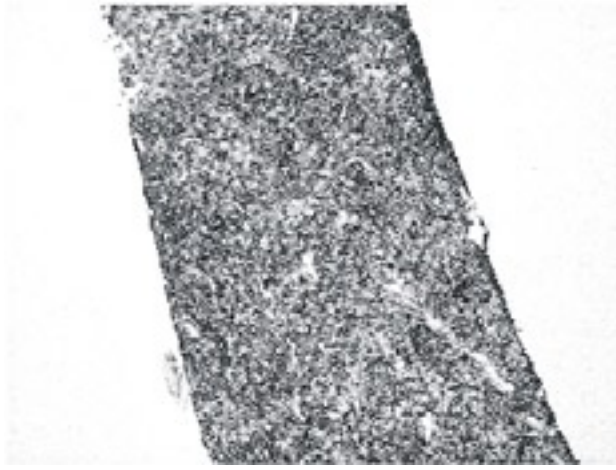

Figure 2. Core biopsy of primary breast lymphoma – Immunohistochemical staining for CD20 (×10).

A CT scan of the abdomen and thorax demonstrated multiple small glands in the region of the coeliac axis; therefore the lymphoma was a stage IV DL-BCL with low tumour bulk.

The patient was treated with the CHOP-R regimen (cyclophosphamide, doxorubicin, vincristine, prednisolone and rituximab) to be given 3-weekly for 6 courses.

Discussion

The breast is an uncommon, but recognised site to be affected by NHL. As a primary site of involvement it constitutes 1.7-2.2% of all extranodal NHL, representing 0.04-1.1% of all breast tumours [1-4]. Although secondary breast lymphomas are also rare, they represent the largest group of metastatic tumours of the breast [5]. Women are almost exclusively affected, and the median age at diagnosis is 55 years [6]. In 85% of the cases, the initial clinical presentation is with a discrete breast lump [7].

Diagnosis and staging

In 1972 Wiseman and Liao established clinical diagnostic criteria for primary breast lymphoma (PBL) [1]. They defined it as occurring if the following held true: 1) presence of technically adequate pathological specimens; 2) close association of mammary tissue and lymphomatous infiltrate; 3) no prior diagnosis of an extramammary lymphoma; and 4) no evidence of concurrent widespread disease (concomitant, ipsilateral axillary nodes excepted). Lymphomas involving the breast but not fulfilling these criteria are, by exclusion, secondary. Applying the Ann Arbor classification system PBL will correspond to stages IE and IIE (the suffix E denoting an extranodal focus). Secondary breast lymphomas, by contrast, will usually be stage III and IV.

Unlike Hodgkin's disease, which typically has a predictable pattern of spread, NHL is less predictable in its behaviour, involving organs apparently devoid of lymphatic tissue (e.g. testicle and brain). Since Wiseman and Liao developed their criteria, staging investigations for NHL have improved; the incidence of true stage I or II disease may only be of the order of 10-15% [6]. A general observation in NHL is that clinically indolent lymphomas are frequently widely disseminated at diagnosis, whereas aggressive lymphomas tend to be more localised at presentation. Domchek et al. observed this pattern in NHL of the breast; the majority of PBL are of intermediate or high grade [7]. Determining whether malignant NHL originated in the breast or is of systemic origin, is of therapeutic and, potentially, prognostic importance [8], as discussed below.

Histopathology

A number of different types of lymphoma can involve the breast. The REAL classification of NHL (1994) [9] has been widely accepted and recently updated for the current WHO classification of haematological malignancies (1999) [10]. Modern immunophenotyping methods enable the different disease entities to be differentiated with great accuracy. For the sake of discussion, they can be grouped according to their cell of origin (B-cell *versus* T-cell/NK cell) and their biological behaviour (aggressive *versus* indolent).

The cell of origin of PBL is still unknown. The normal histological architecture of the breast features intraepithelial lymphocytes dispersed within the stroma and around venules [3], and these have been regarded as part of the mucosa-associated lymphoid tissue (MALT). Lymphoma of MALT is known to affect the breast as a primary site [11]. It is an indolent, B-cell lymphoma with an incidence, in the larger series, of around 15% of all PBL [12]. Gholam et al. noted that none of a series of 16 cases of DL-BCL had associated low-grade MALT lymphoma, and they speculate this may indicate that this disease arises *de novo* [13].

The most common type of indolent NHL in adults is follicular lymphoma [14]. This disease is found far less commonly in the breast, with a range of incidence from 2 to 12% in the larger reported series [4,7,12].

The sporadic form of Burkitt's lymphoma, an ag-

gressive B-cell lymphoma, can present in extranodal locations, including the breast. Typically, this affects younger patients, and presentation with bilateral disease is not uncommon [3]. It is very rare for T-cell lymphoma to affect the breast [1,7].

Imaging

There are few reports about the radiological features of NHL of the breast. The most common mammographic appearance is as a solitary, non-calcified soft-tissue mass. Ultrasound appearances are similarly non-specific; heterogeneity of echotexture and variable definition of lesion borders may be useful in differentiating lymphoma from fibroadenoma [15].

Recently the role of MR in imaging PBL has been investigated. Ill-defined, hypointense lesions on T1W that show rapid and strong contrast enhancement, most marked peripherally, have been found consistently, but these features cannot reliably differentiate NHL from carcinoma [16]. MR imaging is better at demonstrating the extent of local involvement than conventional mammography, and as such may be helpful in the evaluation and follow-up of patients with previous history of NHL [17].

Gallium 67 scintigraphy remains the standard for radionuclide imaging of NHL. However, as there are no pathognomic features of breast lymphoma on conventional imaging, biopsy is essential for definitive diagnosis.

Treatment and prognosis

NHL are a heterogeneous group of diseases. The subset of NHL of the breast is similarly diverse, and this makes classification of these patients a challenge. It is essential to do this, however, as it has important implications for treatment.

The parameters that determine the clinical evolution of NHL can be divided broadly into those intrinsic to the tumour (aggressive *versus* indolent), and those factors related to the host. In addition, with breast NHL the primary site of the disease itself may be of importance.

Patient-related characteristics are incorporated in the International Prognostic Index (IPI) [18], the currently accepted model of clinical assessment. Taking those patients with aggressive NHL, the IPI identifies 5 parameters that, if present, are predictors of a poorer prognosis: age (>60 years), physical status (not fully ambulatory), serum LDH (elevated), Ann Arbor stage (III or IV) and number of extranodal sites involved at presentation (2 or more). These markers are regarded as equivalent; compared with Hodgkin's disease Ann Arbor stage is of less prognostic importance. It may be that the tumour bulk, or burden, is a more pertinent measure. The latter 3 parameters in the index can be considered to correlate with the presence of "bulky" disease. Prognostic indicators specific to PBL have not been extensively analysed. As by definition it is a localised lymphoma the IPI may prove to be of less importance.

One interesting and clinically relevant property of PBL is their propensity to involve the central nervous system (CNS). Ribrag et al. observed CNS involvement in 4 of 20 cases of PBL, and confirmed this propensity by analysis of relapse data in other published series [19]. This frequency of CNS relapse differs from that seen in nodal lymphomas and extranodal lymphomas at other sites from which they are histologically indistinguishable [20]. This feature, interestingly, is also a feature of primary testicular lymphoma [21]. Although no biological explanation for this behaviour has yet been identified, clinically PBL appears a distinct disease entity. Such findings have led to the conclusion, by numerous research groups, that CNS prophylaxis should be instituted in addition to systemic chemotherapy in PBL of the DLBCL type [8,13,19], and reinforces the importance of determining, where possible, whether involvement of the breast is as a primary or as a secondary site.

There is currently no specific treatment modality for lymphoma of the breast. Mastectomy is of no value in the management of the disease [22]. Patients with aggressive breast lymphomas are best managed with chemotherapy, with some evidence to suggest that in PBL radiotherapy to the breast, axilla and supraclavicular nodes may improve local control [23].

For patients with aggressive NHL the standard treatment is with the CHOP regimen of combination chemotherapy. Originally developed in the late 1970s, CHOP has repeatedly produced complete remission rates of 45-53% and has consistently produced results comparable to newer, more aggressive treatment regimens, with a more acceptable side effect profile [24,25]. However, therapy with CHOP is unsatisfactory in certain patient groups, namely those with a raised IPI score (specifically in the elderly), and those positive for the anti-apoptotic protein Bcl-2. This is presumed to be due to chemotherapeutic resistance as cells are relatively protected from apoptotic stimuli.

Mounier et al. showed that the addition of the monoclonal anti-CD20 antibody rituximab to standard chemotherapy in Bcl-2-positive patients can overcome this adverse prognostic factor [26]. Furthermore, combination of rituximab with various chemotherapy protocols has been shown to provide higher and more prolonged response rates without additional toxicity

[27]. As rituximab is so well tolerated, it is particularly useful in elderly patients who would not tolerate aggressive chemotherapy. The CHOP-R regimen has been shown to reduce both the risk of treatment failure and death in an elderly population [28].

The role of rituximab in the treatment of CNS relapse remains unclear. Whilst there are some reports in the literature to suggest it has a beneficial effect [29], Feugier et al. found no reduction in CNS recurrence in systemic NHL with the addition of rituximab to standard CHOP chemotherapy [30]. Whether it proves effective in PBL, with its comparatively greater risk of CNS involvement, is yet to be investigated.

For the minority of indolent breast lymphomas opinions differ as to the optimum management. Local excision of MALToma alone, can produce prolonged remission in stage IE disease, whereas follicular lymphoma has a 50% relapse rate if systemic therapy is not given [13].

Conclusion

Non-Hodgkin's lymphoma of the breast is a rare disease that can be very difficult to differentiate from other forms of breast disease on clinical and radiological grounds. NHL can involve the breast as a primary or a secondary site, and it is often difficult to differentiate between these two patterns of disease. This distinction, however, is an important one to make, as primary lymphomas exhibit unique and distinctive patterns of spread, and frequently involve the CNS. A biological explanation of this phenomenon has not been found, but elucidation of an underlying molecular mechanism may ultimately provide a method to distinguish between primary and secondary breast involvement.

The benefits of adding rituximab to conventional chemotherapy for NHL have been proven in a number of adverse prognostic groups. Its role specific to NHL of the breast has not been investigated, and, given the equivocal evidence regarding the effectiveness of rituximab in CNS disease, this is an area in which further work is required.

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