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Primary Breast Lymphoma (PBL): A Literature Review

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ABSTRACT Primary breast lymphoma is a rare disease. It is mainly found in female patients, the right breast in more frequently involved. The majority of PBL are diagnosed by biopsy or post-operative pathological findings. The combined therapy regimen, the main part of which is CHOP chemotherapy, is the main stream. Radical surgery is to be avoided.

KEY WORDS: breast, lymphoma, diagnosis, clinical characteristics, treatment, prognosis.

Introduction

Lymphoma is a malignant tumor mainly occurring in lymph nodes and lymphoid tissue, especially in the lymph nodes. Lymphoma in the breast is rare, which may be primary or secondary malignant lymphoma. Primary breast lymphoma (PBL) is a rare extranodal lymphoma, which has rarely been reported in the literature. This review outlined PBL in the following aspects: epidemiology, criteria of PBL diagnosis and PBL staging, clinical characteristics, approaches of diagnosis and treatment, and prognostic factors.

Epidemiology

PBL, a rare extranodal lymphoma, accounts for about 0.04%–0.74% of all malignant breast tumors, and for 0.7% of extranodal non-Hodgkin's lymphomas (NHLs)[1]. Domchek et al.[2] showed in their report that PBL was only 0.05%–0.53% of all malignant breast tumors, and 2.2% of primary extranodal lymphoma.

PBL is mainly found in female patients, accounting for 95%–100% of all the PBL patients[3]. It is very rare in men and only a few cases have been reported in the literature so far[4,5]. The age distribution of the PBL patients ranges widely from 17 to 95 years, and the age of the patients is from 55 to 62 in western countries[6,7], and 45–47 in China[8,9]. The range of the age is broad, therefore, this kind of tumor can occur in teenagers as well as in patients in their 90s. The age of onset in female PBL patients in China is younger than that of those in western countries, where the age of onset in most white PBL patients is 60 or more[6,10]. PBL is commonly found in only one breast, i.e. the right breast, and especially in the upper quadrant of the right breast. And there are also cases with bilateral breast lymphomas[11], which account for 1%–14% of all PBL[12]. PBL has been divided into 2 groups[11]: unilateral (the onset age of PBL is the same as that of breast cancer) and bilateral (mostly occur in the period of child-bearing, pregnancy or lactation).

The criteria for PBL diagnosis and for PBL staging

The diagnostic criteria for PBL were defined by Wiseman et al.[13] in 1972, which are rigid. According to the criteria, very few cases in the early studies could be diagnosed as PBL, and as a result, few reports concerning PBL have been found in the literature both in China and in western countries. Recently, International Extranodal Lymphoma Study Group (IELSG) has redefined a more loose definition of extranodal lymphoma, that is ''with extranodal lesions as the main symptom, and with or without regional lymph nodes involved''[14,15], or ''the tumor limited to unilateral or bilateral breasts, and with or without regional lymph nodes involved''. The specific criteria for the diagnosis of PBL include[12]: *i*) The tumor site is the breast. *ii*) A history of previous lymphoma or evidence of widespread disease are absent at diagnosis. *iii*) Lymphoma is demonstrated to have close association with breast tissue shown in the pathologic specimens. *iv*) Ipsilateral lymph nodes may be involved if they develop simultaneously with the primary breast tumor. This definition of PBL indicates that PBL comprises only tumors in stage I (lymphoma limited to the breast) and stage II (lymphoma limited to the breast and ipsilateral axillary lymph nodes), excluding those originating outside of the breast. All breast lymphomas which don't meet all these criteria are considered secondary breast lymphomas.

Just like other lymphomas, the malignancy of PBL is measured with NHL and the Ann Arbor Classification for PBL, which has been developed based on the above criteria[16], and the clinical stages are defined as stage I (tumor is limited to breasts), stage II (tumor is limited to breasts and ipsilateral mobile axillary nodes are palpable), stage III (tumor is limited to breasts and metastasizes to the both sides of diaphragm), and stage IV (tumor is limited to breasts and metastasizes to extranodal lymphoid tissue). According to its symptoms, PBL can be classified as type A (without typical symptoms) and type B (with fever, night sweat, weight loss of 10% within half a year).

Clinical characteristics

The typical clinical characteristic of PBL is an ever-increasing mobile mass in unilateral breast, and the mass grows rapidly. The typical clinical manifestation of PBL is a painless breast mass, most frequently located at the outer quadrant of the breast. As lymphomas of the breast are uncommon, and the clinical manifestation is hard to distinguish from that of breast cancer, therefore, they don't usually cause doubt about the diagnosis of breast cancer prior to biopsy. Breast lymphomas tend to be larger in size at diagnosis than breast cancer, but it cannot be regarded as a distinguishable feature. In breast lymphomas, skin retraction, erythema, peau d'orange appearance and nipple discharge rarely present[12,17]. Since the symptoms of the breast lymphoma are atypical and thus it is usually misdiagnosed as breast cancer or benign lesion. It is difficult to make PBL diagnosis before operation, and PBL diagnosis is mainly based on pathological biopsy and immunohistochemical staining[2]. The cases with rapid growth of mass in the breast should be first considered as PBL.

Pathological features

The lump usually has a round shape, clear surface texture, without obvious membrane wrapping up the tumor, observed with naked eyes. The slice of the specimen is subtle like fish and presents gray or pink color. When diagnostic mammography is obtained, PBL often appears as a well defined mass with benign characteristics. These tumors usually have smooth margins with a homogeneous appearance. Other signs of breast malignancy are not commonly found by mammography. Calcifications, spiculation, or distortion of surrounding tissue are usually absent. On physical examination, PBL frequently appears as a benign or less suspicious lesion. PBL usually presents as a single palpable mass that is mobile and nontender. Clinical signs of advanced breast malignancy are rare, such as inflammatory changes, nipple involvement, skin retraction, or tumor fixation. Most of the tumor cells diffusely infiltrate into surrounding tissues. They completely lose normal orginazational structure, and the tumor cells gather around the ductor in the breast.

Almost all PBLs have a B-cell lineage, and 40%–70% of breast lymphomas are diffuse large B-cell lymphoma (DLBCL)[18]. Mucous membrane on the edge of lymphoid tissue with B cells lymphoma is about 0–44%, and the young pregnant women or lactating women with breast lymphoma are usually burkitt's lymphoma or burkitt-like lymphoma. In addition, there are reports of cases with follicular lymphoma, lymphoblastic lymphoma, lymphoplasmacytic lymphoma, peripheral T-cell lymphoma, and true histiocytic lymphoma[19]. There are also reports of cases with anaplastic larger cell lymphoma (ALCL), and the cases caused by the breast implant capsules used for reconstruction after the treatment of breast cancer[20]. DLBCL, the most common type of PBL, usually has the feature of non-generating central cells[21,22].

Diagnosis

The diagnosis procedures of breast lymphoma include 3 parts: *i*) radiation inspection (such as breast imaging, ultrasound inspection, magnetic resonance imaging, molybdenum target scan, positron emission tomography, etc), *ii*) fine needle aspiration biopsy, and *iii*) pathological examination, etc[23]. Type-B ultrasonic and X-ray of the breast show no typical changes, and the latter shows no calcification.[18] Preoperative Ultrasound-guided core needle biopsy and the frozen biopsy are significant for diagnosis, and fine needle aspiration cytology (FNAC) is one way to diagnose PBL[24,25], which can save time and offer guidance for early treatment. In the cases with small lump located deeply in the breast, the operation for frozen biopsy is difficult, therefore, FNAC is the first choice for diagnosis because it is time-saving, simple, less trauma,

painless, less implications, and less cost. However, because of the limited samples, with the above 3 ways,breast lymphoma may be misdiagnosed and treated incorrectly as breast cancer or other benign tumors, therefore, one principle should be adhered to in PBL diagnosis: if a certain diagnosis can not be made, just leave it until the result of pathological examination is available. The final diagnosis of PBL should be based on the pathological examination[26], which is very important in recognition of the nature of tumors and the staging. It would be accurate to classify lymphomas based on immune tissues, ant it is especially important to distinguish the tumors originated from hematopoietic lymphatic system and from epithelial system.

Cause of NHL

As to the cause of NHL, Schwartz et al.[26] described that it may be associated with immune diseases in breasts, such as hardening of the small lymphocyte, etc., But most researchers demonstrated that it might be originated from the malignant progression of lymphomatoid disease around duct or in lobular[27].

Identification and diagnosis of PBL

Clinically, primary breast lymphoma most commonly presents as a solitary palpable mass. Less common manifestations include unilateral or bilateral diffuse breast enlargement. The radiographic image of breast lymphoma most commonly shows a mass with clear margin and without calcification in the tumor. Other radiographic patterns include the following: multiple amorphous or poorly circumscribed noncalcified masses; diffusely increased parenchymal density with or without skin thickening; spiculated masses; or, rarely, miliary densities on mammography. Because the imaging features of breast lymphoma are nonspecific, the diagnosis of primary breast lymphoma cannot be determined on the basis of mammographic findings alone. Lesions such as primary breast cancer, fibroadenoma, phyllodes tumor, and metastatic disease must be included in the list of differential diagnoses.

Intramammary lymph nodes are often encountered in routine mammography. Benign intramammary lymph nodes are characterized by their well-circumscribed borders, lobulation, and central radiolucency, which represents fatty replacement. Intramammary nodes are considered abnormal if they have become enlarged, lost their well-defined borders, increased in density, or lost their fatty hilum. These features are encountered in both benign and malignant processes. The differential diagnosis of an abnormal intramammary lymph node includes inflammation, infection, and neoplasia. More specific conditions include dermatitis, psoriasis, lymphadenitis, sarcoidosis, lymphoma, HIV, and metastatic disease.

Sonographically, breast lymphoma lesions are commonly hypoechoic and may be so significantly hypoechoic that they can be mistaken for simple cysts if careful technique is not used. Biopsy is necessary to establish a diagnosis. Treatment regimens for primary breast lymphoma may include surgery, radiation therapy, and chemotherapy. Mammography can be used to monitor a patient's response to the therapies.

Treatment

The optimal treatment of PBL, mostly with DLBCL histology, has not been defined. Several studies have suggested that the addition of radiotherapy following an extensive course of chemotherapy improves local control. However, in other studies (Babovie[28] and Ghazawy[29]), the most common site of recurrence of PBL was the contralateral breast regardless of radiotherapy. Similarly, a recent study (Lin et al.[30]) found that recurrence occurred more frequently in the contralateral than that in the ipsilateral breast of the patients with primary DLBCL of the breast, and recurrence also occurred in the contralateral breast, in which cancer had progressed over a longer period (13.3 years *vs.* 2.6 years). Most patients in that study received combination therapy, including surgery plus systemic chemotherapy and/or radiotherapy. These findings suggest that the additional use of radiotherapy for localised PBL following surgery or chemotherapy can decrease ipsilateral locoregional recurrence, and further treatment to reduce contralateral recurrence warrants further investigation.

Although some studies have suggested that central nervous system (CNS) as well as breast is the most frequent site of progression for PBL, the risk of CNS relapse is relatively low (less than 3% in two recent series). In LIN et al's[30] report, one patient presented with a progressing CNS tumor (an intraocular lymphoma) 2–3 years after complete remission of PBL. But further analysis indicated that this tumor was actually a second primary CNS lymphoma unrelated to the original breast lymphoma. To determine the biologic significance of relapsed breast lymphoma, study involving the identification of clone analysis patterns and gene expression patterns is needed. Miller et al.[31] reported that Patients treated with three cycles of a doxorubicincontainingregimen such as cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) plus radiotherapy had significantly better progression free survival and overall survival than patients treated with CHOP alone. And they came to the conclusion that three cycles of CHOP followed by involved-field radiotherapy are superior to eight cycles of CHOP alone for the treatment of localized intermediate- and high-grade non-Hodgkin's lymphoma. More cases of NHL have been effectively treated by radiotherapy or chemotherapy[32]. And use of rituximab plus CHOP has been shown to increase survival when compared with CHOP for treatment of diff use, large B-cell lymphoma in elderly patients[33].

Prognosis

In the past, prognosis of the PBL patients was poorer than that of the patients with primary breast cancers, mainly because there was not enough knowledge about

PBL, therefore, PBL was usually misdiagnosed as primary breast cancers,and only small dose of chemotherapeutic medicine was offered after operation. Some scholars deem that the prognosis of PBL is not associated with the size of tumor, or whether lymphoma occurs in unilateral or bilateral breasts, or whether palpable mobile axillary nodes can be found. What is important are histologic type and clinical stage of the tumor[11]. But Guo et al.[34] reported that bilateral lymphomas are a poor prognostic factor of PBL patients, which is linked to high risk of metastasis to CNS. Jeanneret–Sozzi et al.[35] reported that young age is a poor prognostic factor of PBL, and disease in stage II was also a poor prognostic factor in PBL. The most frequent recurrence region of PBL is lateral or bilateral breasts and distant metastasis parts are commonly seen in bone marrow and CNS[36], with the metastasis to CNS accounting for 12%–27%. Ribrag et al.[37] reported that malignant PBL was usually a diffuse pattern, and metastasize to CNS, therefore, the dynamic observation should be strictly followed during the course of treatment for PBL. Chemotherapy drugs given through intrathecal injection can improve the prognosis of the PBL patients[16], and may prevent CNS metastasis. Some scholars even think that the preventive treatment of CNS metastasis should be applied at the beginning of the treatment for all patients with PBL[38].

Conflict of interest statement

No potential conflicts of interest were disclosed.

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