Case Report

Primary marginal zone lymphoma of the breast associated with hepatitis C virus infection: A rare case report and review of literature

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ABSTRACT

Primary non-Hodgkin's lymphoma of the breast is a rare entity, comprising <0.5% of all malignant tumors of the breast. They are mainly of the diffuse large B cell lymphoma, while marginal zone B cell lymphomas (MZLs) are exceedingly rare. Links between hepatitis C virus (HCV) infection and several non-Hodgkin lymphomas have been suggested by epidemiological studies. We herein report the first case of low grade MZL of the breast associated with HCV infection showing disease free recurrence following incomplete surgery and antiviral therapy. Nevertheless, the combination of chemotherapy and radiation therapy has been proposed as the gold standard treatment for primary breast lymphoma right now.

Key words: Antiviral therapy, breast, hepatitis C virus, indolent B cell lymphomas, marginal zone B cell lymphoma

INTRODUCTION

Breast lymphoma, either a manifestation of primary extra-nodal disease or secondary involvement by systemic disease, is a rare malignancy, comprising only 2% of localized extra-nodal non-Hodgkin lymphoma (NHL) presentations and the literature addressing this subject is sparse.[1] Available information regarding primary breast lymphoma (PBL) are difficult to analyze and to compare due to the small number of publications. Moreover, almost all papers are focused on diffuse large B cell lymphoma (DLBCL), thus information regarding marginal zone B cell lymphomas (MZL) subtypes are scarce.[2] The prognosis is generally better and varies, as do the applied treatment modalities, which include surgery, radiotherapy and chemotherapy used alone or in combination. Recently, epidemiological studies have indicated links between hepatitis C virus (HCV) infection and several types of malignant lymphomas and have proved the effectiveness of antiviral therapy especially in indolent subtypes.[3] Our objective is to report a case of primary MZL of the breast associated with HCV infection, which has not been reported yet to our best of knowledge in literature and in order to assess the clinical features, incidence, therapy, prognosis of PBL and to emphasize the role of antiviral therapy in HCV-associated NHLs.

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CASE REPORT

A 64-year-old female patient presented with a 4-month history of a palpable mass in the right breast. A physical examination revealed an elastic and mobile mass occupying the upper outer quadrant of her right breast. Overlying skin was normal and examination of the axilla and neck was negative for enlarged lymph nodes. During surgery a 2.2 × 2 × 1 cm mass was excised. A frozen section was positive for malignancy. Histopathology supplemented by immunohistochemistry was compatible with MZL; immunostaining profile showed positivity for CD20 [Figures 1 and 2], CD23 and Ki67 at 40% and absence of staining for CD10, CD5, CD3 and cyclin D1. The patient was infected with the HCV genotype 1b, liver function test results showed abnormal concentration of alanine amino transferase. Staging computerized tomography of her chest and abdomen was performed and was found

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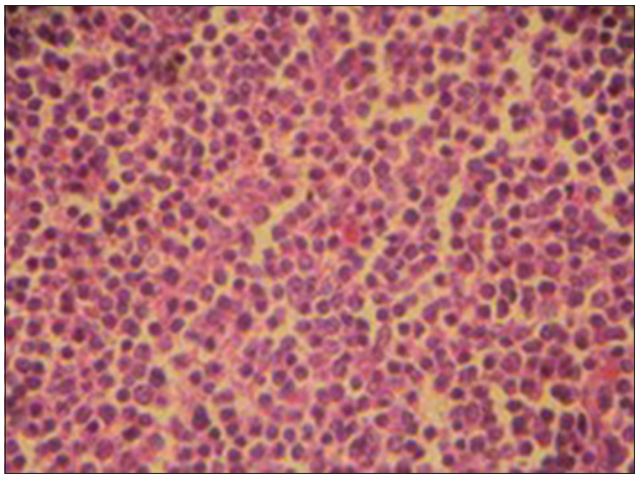

Figure 1: Histologic examination revealed a diffuse proliferation of small and intermediate lymphocytes (H and E, G×10)

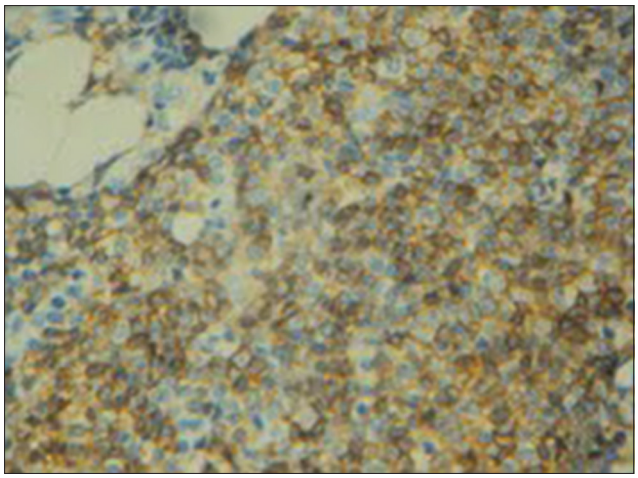

Figure 2: Immunohistochemical study showing diffuse positivity for CD20 (Avidin-Biotin, G×20)

to be normal. A bone-marrow biopsy resulted negative for lymphomatous infiltration. And thus the patient was diagnosed as stage I_E according to the Ann Arbor staging system and it was graded into the low risk group with an International Prognostic Index score of 1. Thus, she was referred for pegylated interferon-α2a and ribavirin combination therapy followed by chemotherapy (R-CHOP regimen) and central nervous system (CNS) prophylaxis. Unfortunately, the patient received 8 weeks only of antiviral therapy, because of the high cost of antiviral drug. The serum HCV RNA was detectable, but liver function test results were within normal ranges and refused further treatment, including chemotherapy and radiotherapy. Follow-up demonstrated durable remission 23 months after surgery and 17 months of antiviral combination therapy.

DISCUSSION

Primary lymphoma of the breast is a rare entity ranging from 0.04% to 0.05% of all malignant tumors of the breast and accounts for 2.2% of extra-nodal lymphomas.[1] The criteria for the diagnosis of PBL were suggested by Wiseman and Liao in 1972 and include: Adequate pathologic evaluation, close association between lymphomatous infiltrate and mammary tissue and exclusion of either systemic lymphoma or extra mammary lymphoma, except simultaneous ipsilateral axillary node involvement.[4] The characteristics of this disease, such as natural history, prognostic factors, and impact of treatment have not been yet well-established because the literature comprises many small retrospective series with just one prospective study and one large retrospective study conducted on histologically low grade PBL.[2] Most studies reported a preponderance of right-sided presentation in breast lymphoma occurring in the middle-aged and elderly, which is similar to that reported in our patient.[5] All histological types of lymphoma have been described, but approximately one-half are DLBCL, while low grade histological subtypes are a minority, comprising 14% for follicular lymphomas and 9% only for MZL.[6]

These patients must benefit from a multidisciplinary approach, after accurate diagnosis on the basis of excisional biopsy or aspiration cytology because there is no general agreement on the appropriate treatment of PBL. Surgical treatments are seldom reported in literature, this approach is presently not indicated neither in case of lesions unresponsive to chemo and radiotherapy nor for relapsing disease.[7] Currently, several retrospective studies suggest that treatment of PBLs follows treatment recommendations for lymphomas of the same stage and histology in other locations.[8] A prospective study confirmed this opinion and showed that combined therapy with radiotherapy and chemotherapy (R-CHOP regimen every 21 days) is the best treatment in this special setting of patients; with improvement in event-free survival and overall survival without acute or severe late side-effects. Prophylaxis to the CNS will be considered in the initial treatment to improve outcome because the most common site of relapse was the CNS.[9] Although PBL is poorly represented in rituximab-containing trials in DLBCL patients, the addition of this drug improves the outcome of all clinical and molecular subtypes of CD20-positive DLBCL.[10]

In the last two decades, HCV has been shown to play a role in the development of B-cell indolent lymphomas, especially marginal zone lymphomas, as well as with aggressive lymphomas, mainly DLBCLs. It has been suggested that HCV infects not only hepatocytes but also mononuclear

lymphocytes including B cells that express the CD81 molecule, a putative HCV receptor.[11] Hence, the chronic antigenic stimulation of B-cell immunologic response by the virus is the likely cause of B-cell dysregulation disorders such as B-cell lympho-proliferative disorders that may evolve into NHL. Similarly to the well-characterized induction of gastric mucosa-associated lymphoid tissue lymphoma development by *Helicobacter pylori* chronic infection.[12]

In addition, the lymphoma regression observed in some patients with interferon based treatment is strongly in favor of a causative role of HCV in a subset of patients with indolent NHL. The data from literature demonstrate that anti-HCV treatment seems to be indicated for indolent B cell NHL subtypes that not need immediately conventional immune-chemotherapy.[13] Conversely, the role of antiviral therapy in aggressive B cell lymphomas seems to be less efficacious. Although, anecdotal cases treated with antiviral therapy and obtaining remission have been reported.[14]

It appears that patients with PBL have a better prognosis than patients with carcinoma of the breast and patients with other extra nodal lymphomas. The 5-year survival reported in some series varied from 50% to 82%, respectively. The median time to local relapse and to systemic relapse was 17 and 22 months respectively. Similarly, indolent lymphomas are described as scarcely symptomatic lymphomas, growing and spreading slowly with indolent behavior. The PFS for MZL PBL was 72% and 56% at 3 and 5 years, respectively. The overall survival was 100% and 92% at 3 and 5 years, respectively.[6,15]

CONCLUSION

Finally, the effect of surgery and antiviral therapy in addition to the indolent character of the primary marginal zone lymphoma of the breast had probably operate and synergistically contribute to the disease control in the present case.

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