Hepatitis C leading to Extra Nodal Marginal Zone Lymphoma of Breast: A Rare Case

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Abstract

Background: Primary breast lymphomas account for less than 1% of all non-Hodgkin lymphomas, 1.7%-2.2% of all extranodal non-Hodgkin lymphomas, and 0.04%-0.5% of all malignant breast neoplasms. The etiology of Extranodal Marginal Zone Lymphoma (EMZL) in breast tissue has not been identified. We herein report a case of breast EMZL with the most likely etiology being hepatitis C virus.

Case report: We report a case of an asymptomatic 60-year-old of breast tissue. The lesions were excised and the patient is on active surveillance with clinical examination every 3 months-6 months and annual mammograms. Comprehensive history and evaluation yielded chronic hepatitis C infection as the etiology of the breast lymphoma seen in our patient.

Conclusions: Our case raises awareness that HCV might be a common etiological factor for B cell NHLs in the breast. More cases of breast EMZL caused by HCV should be identified and reported. The efficacy of anti-HCV therapies should be explored in HCV-induced breast EMZL.

Keywords: Extranodal marginal lymphoma breast hepatitis C • Hepatitis C virus

Introduction

Non-Hodgkin Lymphomas (NHLs) can be classified based on the type of cell they involve, B cells or T cells. Depending on their activity level, they can also be categorized as indolent or aggressive [1]. One example of a low-grade (indolent) B-cell NHL is Extranodal Marginal Zone Lymphoma (EMZL). EMZL most commonly affects the gastrointestinal mucosa but can involve any mucosal tissue in the body, including the salivary glands, thyroid, orbit, lungs, and breast tissue [2]. There are several established risk factors for Marginal Zone Lymphoma (MZL) and its subtypes, including a family history of Non-Hodgkin Lymphoma (NHL), genetic loci in the HLA region, and Helicobacter pylori infection (associated with gastric Mucosa-Associated Lymphoid Tissue (MALT) lymphoma [3]. Additionally, several autoimmune diseases—such as Sjogren syndrome, systemic lupus erythematosus, and Hashimoto's thyroiditis—are also risk factors. There is strong, though not definitive, evidence linking Chlamydia psittaci (ocular adnexal MALT lymphoma), Borrelia burgdorferi (cutaneous MZL), hepatitis C virus, human immunodeficiency virus, and solid organ transplantation to MZL [3]. When EMZL occurs in the breast, it is called Primary Breast Lymphoma (PBL) [3].

PBL accounts for approximately 1 % of all NHLs and less than 1 % of all breast cancers [4-6]. They represent about 3 % of all extranodal marginal zone lymphomas [7]. The etiology of PBL is not well understood. While infections such as Helicobacter pylori have been linked to EMZL of the gastric mucosa, no similar association between PBL and infectious agents has been reported [8]. Hepatitis C Virus (HCV) has been associated with some B cell NHLs, although a direct causative relationship has not been established. This association is particularly noted in regions with high HCV prevalence [9]. EMZL, mainly the non-gastric type, is among the B cell NHLs most frequently linked with HCV. Although a cumulative study demonstrated that patients with HCV infection were at a 1.38-fold higher risk of the development of breast cancer than the healthy population, no specific correlation between HCV and PBL is present [10].

To date, only one case report in the literature attributes HCV as a causative factor for EMZL [11]. We are reporting this case to raise awareness that HCV might be a common etiological factor for EMZL in breast tissue and should be considered when no other cause can be identified. Testing for HCV antibodies and RNA levels in such patients could be beneficial. Additionally, literature on the prevalence of EMZL in individuals with HCV infection is sparse, and many cases may remain undiagnosed due to their asymptomatic nature. The treatment options include surgical resection, chemotherapy, and radiotherapy, with resection being performed on our patient.

Case Presentation

An asymptomatic 60-year-old hypertensive female with a smoking history of 92 pack years was incidentally found to have a right lower lobe lung nodule on routine low-dose Computed Tomography (CT) screening prompting further evaluation with Positron Emission Tomography (PET/CT). PET/CT revealed low-level nonspecific Fludeoxyglucose (FDG) activity in the region of the prominent lung nodule in addition to a nodular density in the upper-inner quadrant of the left breast having mild to moderate FDG uptake requiring further assessment.

The patient did not complain of night sweats, fatigue, or weight loss (B symptoms). She has no history of oral contraceptive pills or hormone replacement therapy use. The patient has a history of chronic Hepatitis C infection contracted 18 years ago after receiving a platelet transfusion for chronic thrombocytopenia. She received interferon therapy which did not yield a complete resolution as her most recent lab investigations indicate seropositivity for Hepatitis C. Her physical examination was unremarkable for any palpable breast lump, visible skin changes, nipple discharge, or cervical, axillary, infraclavicular, or supraclavicular lymphadenopathy. The family history was negative for ovarian, colon, prostate, pancreatic, or gastric cancer. Her serum alkaline phosphatase and lactate levels were normal. A diagnostic bilateral screening mammogram showed an 8 mm nodule and a 1.7 cm mass in the upper inner quadrant of the left breast. The right breast was normal. Left breast ultrasound confirmed the presence of two lesions classified as BIRADS 4 requiring tissue biopsy for further diagnosis. Histologic evaluation of both the lesions revealed an atypical lymphoid infiltrate and immunohistochemistry raised the possibility of low-grade B-cell lymphoma. She subsequently underwent excision of both masses. The final histopathologic examination revealed a low-grade extranodal marginal zone B cell lymphoma. The neoplastic cells were positive for CD20, PAX- 5, and BCL-2 rearrangement (Table1).

Table 1. The immunohistological staining of the excised breast lesions.

Stain	Result
CD20	Positive
CD3	Negative (stains admixed T-cells)
CD5	Negative (stains admixed T-cells)
CD10	Negative
CD23	Highlights follicular dendritic meshwork
Cyclin D1	Negative
BCL-2	Positive
BCL-6	Negative
Ki-67	Approximately 20%
PAX-5	Positive

She was determined to be clinically stage 1B EMZL given the absence of distant metastatic disease. As per NCCN guidelines, she is currently under active surveillance with clinical examination every 3-6 months for 5 years and annual mammograms. She was also encouraged to perform self-monthly breast exams. She was not given any radiotherapy/ chemotherapy treatment.

Discussion

PBL is a rare entity with a prevalence of 0.07% to 0.4% [12]. It comprises less than 1% of all non-Hodgkin's lymphoma and accounts for less than 0.5% of all breast malignancies [13]. The most common type of PBL is Diffuse large B cell lymphoma [7]. Primary EMZL of the breast is rare and not often encountered. EMZL is a subtype of Marginal Zone Lymphoma (MZL) and accounts for 50%-70% of MZL. MZL comprises three subtypes mainly: Splenic MZL, Nodal MZL, and EMZL. EMZL most commonly affects the gastrointestinal tract (50%), ocular adnexa (5-10%), lungs (7%), thyroid (5%), liver (3%) and salivary glands. Breast EMZL is quite rare accounting for less than 3% of all cases of EMZL [7].

The etiology of primary breast EMZL is not well studied due to its rare incidence. Patients with breast implants have been diagnosed with an anaplastic variant of primary breast lymphoma. Autoimmune diseases like Hashimoto thyroiditis and Sjogren syndrome have been linked to EMZL of the thyroid and salivary gland respectively. Infectious triggers like H pylori are associated with gastric MZL [1]. Our patient has a history of chronic hepatitis C infection. Even though she completed a full course of interferon therapy, it did not yield a complete resolution which can be explained by the fact that the clearance rate of interferon/ribavirin therapy is 50%-60% [14]. Since there is no other history indicating other etiologies for EMZL in our patient such as infectious causes, autoimmune, genetic, or environmental exposure, there is a strong suspicion that her active hepatitis C infection resulted in an EMZL of the breast. In recent times, HCV has been identified as a culprit playing an integral role in developing indolent as well as aggressive B cell lymphomas, particularly marginal zone lymphomas, and DLBCLs respectively. HCV is known to infect hepatocytes primarily, but it has also been suggested that the virus can infect mononuclear lymphocytes, including cells that express CD81 receptors, which play a crucial role early in the HCV lifecycle. This chronic stimulation can result in B cell lymphoproliferative disorder ultimately evolving into NHL. The pathogenesis is similar to one seen in the development of gastric MALToma due to Helicobacter pylori infection [11].

EMZL of breasts is generally indolent. They majorly present as an asymptomatic mass on routine screening and sometimes occur as a painful palpable mass. All the available studies indicate that EMZL presents in middle-aged and elderly patients. The mammographic appearance of breast lymphomas can be attributed to noncalcified, iso-to-hyperdense, circumcised oval mass seen in roughly 70%-80% of cases in addition to axillary lymphadenopathy and skin changes like edema and thickening [15]. One of the major tools to diagnose EMZL is biopsy and immunohistochemistry which reveals a positive stain for CD20 and BCL2 with a low Ki-67 proliferation index and absence of CD10 and MALT1 gene (Figures 1-6).

The treatment for this lymphoma involves a multidisciplinary approach. Due to its rarity, there are no defined treatment protocols and guidelines. The management plan is determined by the grading and staging of the disease based on biopsy and IHC reports. Patients can either opt for a lumpectomy or chemotherapy with localized radiation therapy. A study reported concomitant radiotherapy and R-CHOP regimen every 21 days (chemotherapy) having favorable outcomes for patients [16]. Studies have shown that HCV-induced lymphomas respond to anti-HCV therapy therefore there is a likelihood that HCV-induced EMZL might respond to anti-HCV treatment as well [17]. More cases of HCV-induced breast EMZL should be identified and reported and a trial of anti-HCV therapy should be done to understand the efficacy and long-term reliability of anti-HCV therapy in such cases.

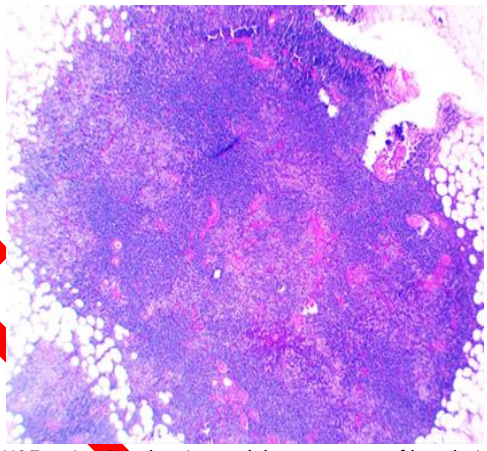

Figure 1. H&E stain 10X, showing nodular aggregate of lymphoid tissue in fat.

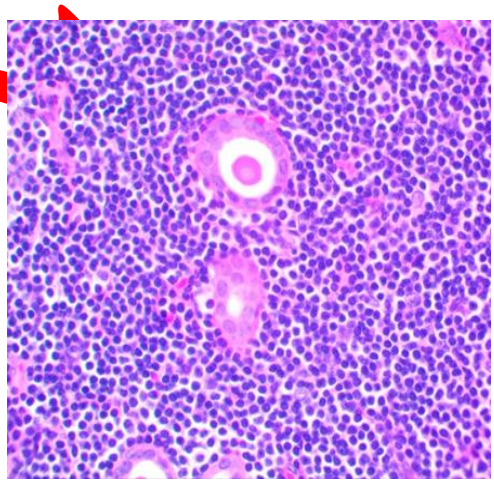

Figure 2. H&E stain 40X, showing neoplasm comprised of small to medium sized lymphocytes, surrounding benign breast ductal elements.

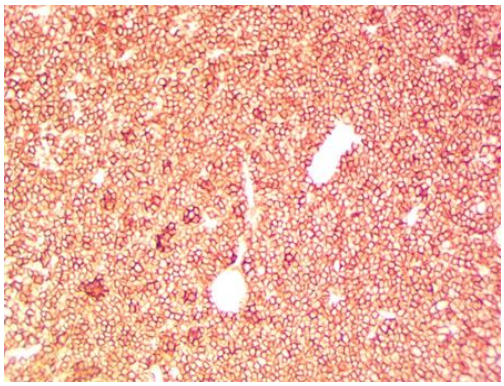

Figure 3. CD20 immunohistochemical stain highlights neoplastic B-lymphocytes.

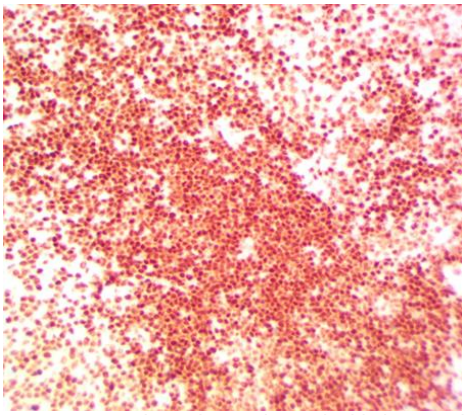

Figure 4. PAX5 immunohistochemical stain highlights neoplastic B-lymphocytes.

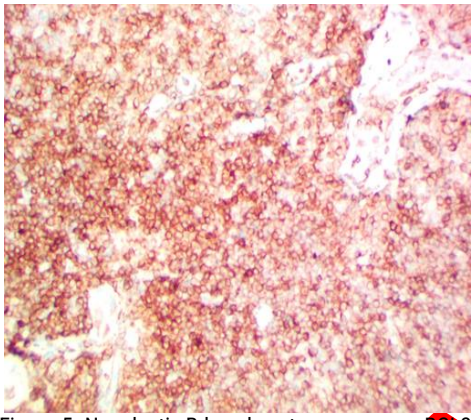

Figure 5. Neoplastic B-lymphocytes co-express BCL2.

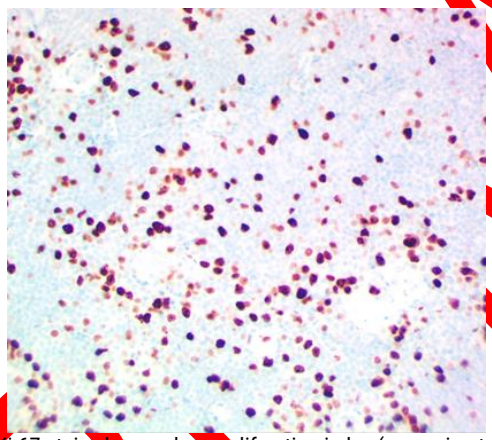

Figure 6. Ki-67 stain shows a low proliferation index (approximately 20%).

Conclusions

Our case raises awareness that HCV might be a common etiological factor for B cell NHLs in the breast. More cases of breast EMZL caused by HCV should be identified and reported. The efficacy of anti-HCV therapies should be explored in HCV-induced breast EMZL.

Note: The Publisher and Editor regretfully retract the article titled "Hepatitis C leading to Extra Nodal Marginal Zone Lymphoma of Breast: A Rare Case" "Oncology and Cancer Case Reports" Volume 10, Issue 04, and Page no. 01-04. Following an investigation which found that the author violated the Journal's policy and putting false allegations towards to the journal. This is contrary to the ethical standards of the journal and unacceptable. The author denied to support open access. The authors have been notified of this decision. The Publisher and Editor apologize to the readers of the journal for any inconvenience this may cause.

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