PRIMARY BREAST EXTRANODAL MARGINAL ZONE LYMPHOMA IN PRIMARY SJÖGREN SYNDROME: CASE PRESENTATION AND RELEVANT LITERATURE

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Abstract: The association between autoimmune diseases, mostly rheumatoid arthritis, systemic lupus erythematosus, celiac disease and Sjögren syndrome, and lymphoma has been widely demonstrated by several epidemiologic studies. By a not yet entirely elucidated mechanism, chronic activation/stimulation of the immune system, along with the administration of specific treatments, may lead to persistent stimulation of both of B- and T-cells, and to the onset of different types of lymphoma in such patients. Specifically, patients affected by may develop lymphomas may years after the original diagnosis. Several epidemiologic, hematologic and histological factors may anticipate the progression from Sjögren syndrome into lymphoma but, to the best of our knowledge, a definite pathogenetic mechanism for such progression is still missing. In fact, while the association between Sjögren syndrome and non-Hodgkin lymphoma, mostly diffuse large B-cell and extranodal marginal zone lymphomas is well established, many other variables, such as time of onset, gender predilection, sites of occurrence, subtype of lymphoma and predictive factors still remain unclear. We report on a rare case of primary breast lymphoma occurring three years after the diagnosis of Sjögren syndrome in a 57 y.o. patient. The diagnostic work-up, including radiograms, core needle biopsy and histological examination are discussed, along with emerging data from the recent literature, thus highlighting the usefulness of breast surveillance in Sjögren syndrome patients.

Keywords: Autoimmune diseases; Sjögren syndrome; minor salivary glands; B-cell lymphoma; extranodal marginal zone lymphoma; MALT lymphoma; primary breast lymphoma

1. Introduction

Sjögren’s syndrome (SS) is the second most common autoimmune disease; it is usually classified as primary or secondary to rheumatoid arthritis and other autoimmune diseases, such as lupus erythematosus, scleroderma, vasculitis, etc., mainly involves exocrine glands (salivary and lacrimal glands) and is characterized by progressive infiltration by B-lymphocytes, [1,2] The common detectability of hyper-gamma-globulinemia and different autoantibodies (such as rheumatoid factor, anti-Sjögren’s syndrome A and B antibodies) in the blood of SS patients underlines the relevance of B-cell hyperactivity in the pathogenesis. [2,3] Common clinical findings in SS patients are keratoconjunctivitis sicca, xerostomia, angular cheilitis and, adjunctively, all general symptoms related to the qualitative and quantitative reduction of secretions. [3] Along with dryness, SS patients may show
disabling symptoms such as fatigue and pain, but also develop systemic manifestations in up to 30-50% of cases, including renal, lung or neurological involvement. [4,5] In addition, SS patients have an increased risk of lymphoma, mostly diffuse large B-cell lymphoma (DLBCL), either as a primitive form or following transformation from a lower-grade non-Hodgkin lymphoma (NHL), such as marginal zone lymphoma (MZL) or mucosal-associated lymphoid tissue (MALT) lymphoma. [7-11] The World Health Organization in 2016 classified MZLs into three distinct types, according to the involved sites: extranodal MALT lymphoma, nodal MZL, and splenic MZL. [13]

The worldwide incidence of SS can be hardly assessed as many cases remain undiagnosed for years. [14,15] In general, extranodal MALT lymphomas more frequently affect the stomach, spleen, thyroid, ocular adnexal tissues and salivary glands, while they are rare in the breast (1.7%-2.2% of primary breast lymphomas), possibly due to the anecdotic presence of MALT tissue at this site. [16,18]

Also, SS patients may be affected by NHL over the course of the disease, especially of the MALT type and most commonly arising in the oral cavity, pharynx, stomach, small intestine, and thyroid, with an incidence about 10-44 times higher than in the general population. [5,9-12,19]

We report on a case of an extranodal marginal zona lymphoma of MALT, occurring in the breast of a Caucasian woman, with a three-year history of Sjögren’s syndrome; also, data from literature on this topic have been collected and reviewed.

2. Case Presentation

A 57-year-old Caucasian female was referred to the breast care unit of the Hospital of the University of Bari Aldo Moro for a small mass in her right breast. The patient had been suffering from persistent and severe dry eyes and moderate dry mouth for several years, and a biopsy of minor salivary glands, along with presence of anti-Sjögren’s syndrome A and B (anti-SSA/SSB) antibodies lead to the diagnosis of primary SS, in the absence of adjunctive autoimmune disease, as detected by clinical examination and serological tests. The revision of the original histopathological preparations confirmed the diagnosis of lymphocytic sialadenitis with a focus score >1/4mmq, grade 4 according to Chisholm & Mason. (Fig 1, A and B).

Figure 1. Low power magnification of minor salivary gland biopsy (A: hematoxylin and eosin, original magnification X100); at higher magnification small lymphocytes and plasma cells aggregates (i.e. more than one lymphocytic focus) associated with mild collagenized stroma are detectable (B: hematoxylin and eosin, original magnification X200).

Immediately after the diagnosis, the patient received methotrexate and prednisone; currently, she still is on antihypertensive and hydroxychloroquine therapy, and shows no relevant signs of SS (e.g. parotid enlargement or eye/mouth dryness). As to the breast lesion, a painless swelling of small size was detected on palpation; conventional mammography showed a small radiolucency with regular and well-defined margins of the lower inner quadrant (Fig. 2 A and B), while digital tomosynthesis highlighted a round opacity with regular edges (Fig. 3 A-D).
Figure 2. (A) Digital cranio-caudal mammographic view and (B) digital breast tomosynthesis mediolateral oblique scan. The lesion appears as a round opacity with regular edges located in the lower inner quadrant of the right breast (arrows).

Figure 3. Automated breast ultrasound scan on coronal (A-C) and axial planes (B-D). The lesion appears as an oval hypoechoic nodule with regular edges, mimicking ductal ectasia (arrows).

Regardless of the benign appearance on both imaging investigations, a US-guided core needle biopsy of the lesion was performed; unexpectedly, the subsequent histopathological examination showed a diffuse proliferation of small to medium-sized lymphoid cells, with slightly irregular nuclei, without plasmacytic differentiation, accompanied by stromal sclerosis and residual atrophic ducts.

Adjunctive immunohistochemical investigations became mandatory to confirm the purportedly monoclonal lymphoproliferative disorder; in fact, the vast majority of infiltrating lymphocytes were of the B phenotype and distinctly immunoreactive for CD20, CD79a and bcl2, while no immunoreactivity for CD3, CD5, CD23, cyclin D1, CD10, bcl6 and LEF1 was detected in small mature lymphoid neoplastic cells. Less than 10% tumor cells displayed nuclear anti-Ki 67 (MIB 1) positivity. MALT gene rearrangement, involving the MALT1 locus at chromosome 18q21, using MALT FISH
DNA Probe Split Signal, could not be demonstrated. All such findings lead to the final by exclusion diagnosis of primary extranodal MZL of MALT (MALT lymphoma) (Fig. 4 A-D). No lymphadenopathy, spleen enlargement, bone marrow involvement or other sites of disease were detected at general staging. Newly executed blood test revealed persistent presence of anti-SS A and B (anti-SSA/SSB) antibodies, cryoglobulins and low level of C4 and C3.

This study was performed in accordance to the principles of Declaration of Helsinki and has been approved by our internal ethical committe (Study n°4652, Prot. 66/C.E.; informed consent was obtained by patient at the time of hospitalization both on diagnostic, therapeutic procedures and possible use of biologic samples for research purposes.

Figure 4. Primary breast MALT lymphoma accompanied with stromal sclerosis and residual atrophic ducts (A: hematoxylin and eosin, original magnification X40). Primary breast marginal zone NHL is characterized by diffuse proliferation of small to medium-sized lymphoid cells (B: hematoxylin and eosin, original magnification X200). The neoplastic lymphocytes are strongly immunoreactive for CD20 (C: original magnification X200). The immunohistochemical stain for ki67 shows a very low proliferative index, pointing at an “indolent” lymphoma (D: original magnification X100).

4. Discussion

Primary breast lymphomas (PBL) represent approximately 1% of all NHL, 1.7–2.2% of all extranodal NHL and 0.04–0.5% of all malignancies of the breast. [20-23] About 9% of all primary breast lymphomas are MZLs of MALT and usually manifest a classic “indolent” behavior. [23-25]

It is generally accepted that chronic infection and inflammation (such as SS and Hashimoto thyroiditis, Borrelia Burgdorferi in cutaneous MZL, gastric MALToxa in Helicobacter pylori infections, viral-associated lymphomas of HCV, HHV8, EBV and HTLV-1) may play a role in lymphoma development, resulting from the transition from polyclonal B cell activation into monoclonal expansion of B-lymphocytes. The transition to B-cell NHL only affects a minority of the aforementioned chronic patients, but it has been associated with a surplus in the overall disease mortality rate. [5-10,13]

As for chronic inflammation, Bizjak et al. in 2015 [26] extensively reviewed the role of inflammation related to breast silicone implants and not-breast silicone prostheses (such as cardiac pacemakers and defibrillators, cardiac valvular and testicular/penile prostheses) in lymphoma development. They assumed that the pathogenic mechanism of chronic inflammation in predisposed individuals, though not well understood but possibly related to the severe scarring of peri-implant
tissues with persistent inflammation, could lead to chronic activation of the local/systemic immune system, with polyclonal and possibly monoclonal lymphocytic activation. Such mechanism was postulated for a distinct type of NHL, namely breast implant-associated anaplastic large T-cell lymphoma (BI-ALCL). The underlying pathogenetic base might be very similar to the one involved in the development of NHL in SS patients.

Patients with autoimmune diseases represent 5% of NHL patients, but lymphoma surely is the most severe complication occurring during SS patients’ follow-up. [5-11]

As widely discussed by Vasaitis et al. in a recent population-based study,[27] data available in the literature on lymphoma subtypes in SS patients, such as as gender differences in lymphoma risk and prevalence in comparison with the general population, are not uniform at all. [27] Also, median time from SS diagnosis until the development of breast lymphoma is related to the observational period, which rarely exceeds 10 years in almost all studies, thus distorting the overall epidemiological data. In addition, several studies (epidemiologic, single-center experiences and reviews, etc.) have reported on large case series of (primary and not) breast lymphomas without focusing on such association with SS. [27-31]

Nevertheless, although the association between SS (and other autoimmune diseases) and NHL is nowadays well defined, its true biological mechanism has not been fully elucidated yet. [1-7,10,11,13,27]

In an update on prognostic markers of lymphoma development in SS patients, Retamozo et al. (2019) [32] stated that such patients show a 7-fold increased risk of lymphoma than systemic lupus erythematosus patients, 4-fold than rheumatoid arthritis patients, and globally >10 folds than the general population. [5,32]

The same Authors listed, point-to-point evaluated and discussed the different prognostic/predictive factors emerging from previously published studies: epidemiologic markers (age and sex); clinical markers (parotid enlargement, dry mouth and eyes, arthralgias, splenomegaly, lymphadenopathy, skin purpura/vasculitis); laboratory markers (systemic activity, hypergamma/raised IgG, CD4/CD8 ≤ 0.8, raised beta2-microglobulin, raised B-cell activating factors, anemia, leukopenia, lymphopenia, neutropenia, ANA, rheumatoid factor, Anti-Ro/La, low C4, C3 and CH 50 levels, cryoglobulins, mlgs); histological markers (focus score and ectopic mesenteric lymph nodes).

They concluded that, although a wider association of risk factors surely increases the risk of NHL, such prediction still remains imperfect; therefore, SS patients need an overall closer follow-up with assessment of all possible associated predictive factors, and surely including cryoglobulin-related markers and increase EULAR SS disease activity index (ESSDAI). [32,33]

Beyond all predictive factors, what really matters in specifically diagnosing primary breast lymphoma (PBL) is both the clinical-radiological appearance and the histopathological diagnosis, the latter being mostly obtained by needle core biopsy. Generally, PBL clinically manifests as palpable masses, associated or not with axillary lymph node enlargement, thus mimicking breast carcinoma or other breast neoplasms;[34] also, although several attempts have been made throughout the years to differentiate benign from malignant breast lesions on radiograms, no specific radiologic or imaging pattern has nowadays still been reported for breast lymphomas. [35-38] Radiologically, as for the case reported herein, PBL usually resembles inflammatory lesions, such as lymphocytic mastitis,[39] IgG4-related sclerosing mastitis,[38] and cutaneous lymphoid hyperplasia.[41]

The diagnosis of breast MZL of MALT essentially is based on cytologic and histopathologic findings. Fine needle aspiration cytology is the most common technique used to non-invasively achieve the diagnosis, but quite often the sampled tissues may result insufficient for immunohistochemical investigations, and mostly aimed at distinguishing neoplastic lymphoid cells from reactive lymphocytes.

Expertise both in performing adequate tissue sampling and in evaluating histopathological and immunohistochemical features is of paramount importance. In general, regardless of the localization, the presence of small/medium sized lymphocytes with irregularly shaped nuclei, scattered blast cells and lympho-epithelial lesions are conventionally pathognomonic of MZL, along with
immunohistochemical positive staining for pan B-cell markers and negative reaction for T-cell markers.

On the bases of data available in the literature about PBL-SS association, [42,43] the single case clinical reports,[44-46] the current theories about lymphoma occurrence in immune-privileged sites (as recently reviewed by King et al. in 2020) [47] and the several attempts to predict lymphoma in SS patients, we can assume that the early diagnosis of a SS-related lymphoid proliferation, especially in the breast, is at present very challenging, and will probably remain as such in the near future, due to the wide clinical-epidemiological and histopathological scenario. Close monitoring of SS patients, including clinical observation and serologic investigations (for palpable purpura, low C4, mixed monoclonal cryoglobulinemia) along with breast surveillance, should be strongly advised in such patients.

**Author Contributions:** “conceptualization, SC, GLE, GF; methodology, GFA and, PT; validation, MM, MGM, SC, EM; investigation, GI, EM, MGM, MM; resources, PT and GFA; writing—original draft preparation, SC and GI; writing—review and editing, EM and GF; visualization, VDR, GF, LL; supervision, GI, SC, EM, GF.

**Funding:** “This research received no external funding

**Conflicts of Interest:** “The authors declare no conflict of interest.”

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