Sjögren syndrome diagnosis in a cohort of patients with breast cancer: a single-center experience

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Abstract

The association between estrogen receptor (ER) positive breast cancer (BC) and autoimmune disorders has been recently recognized. In particular exposure to aromatase inhibitors is associated with a significant increased risk of rheumatological autoimmune disorders. The purpose of this study was to investigate Sjögren syndrome (SjS) occurrence in patients with ER-positive BC. This is a prospective study analyzing 110 consecutive patients with ER-positive BC treated with anti-hormonal therapy. New 2016 American College of Rheumatology/European League against Rheumatism (ACR-EULAR) classification criteria were used to identify patients with SjS. Ultrasonography of salivary glands (SG) was used to screen patients with negative disease biomarkers, to candidate them to SGs biopsy. Sicca syndrome was detected in 51 patients (46%), whereas a true primary SjS was diagnosed in 11 patients (10%). Even if the evaluation of incidence and prevalence of primary SjS vary widely, to the best of our knowledge, the data from the present study emphasize a previously unsuspected high prevalence of defined pSjS that causes BC sicca symptoms complaints. Hypothesis, explanation of this link and even possible biases are discussed.

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Introduction

The benefit of anti-hormonal therapy in hormone receptor (ER)-positive breast cancer (BC) is nowadays well established, leading to the recommendation for his use to prevent and treat BC.[1,2] If, on one hand, anti-estrogen therapy has shown a favorable overall risk-benefit profile, on the other hand, up to 20% of patients will become non-compliant, in particular with aromatase inhibitors (AIs), because of the onset of side effects.[3-6] Hormonal manipulation may also be implicated in several immunological disorders that may have an impact on patients' quality of life.[7,8] The most recent international scientific literature reports a growing number of cases of rheumatological autoimmune disorders,[9,10] such as rheumatoid arthritis (RA), systemic sclerosis (SS), antiphospholipid syndrome (APS) in ER-positive BC patients treated with AIs[11-13] and, among others, SjS has been also described.[14-16] SjS is an autoimmune disorder that involves exocrine glands and extraglandular multiple organs. Of note, mucosal dryness, the leading symptom of SjS, crosses with iatrogenic estrogen deprivation mucosal involvement of ER-BC patients. Thus, considering the increased findings of the association between autoimmune diseases and BC and the occurrence of dryness symptoms that are reported by patients both affected by SjS and treated with anti-hormonal therapy,[17,18] we have evaluated if sicca symptoms in patients with BC, refer to SjS or are a mere consequence of estrogen deprivation.

Materials and Methods

This is a prospective study analyzing a cohort of 110 consecutive selected patients with early non-metastatic ER-positive BC, treated with adjuvant hormone therapy, from August 2019 to February 2020. These patients were evaluated in the Rheumatology clinic of the Riuniti Hospital in Foggia as part of the Institutional Breast Unit. According to standard procedures of the Breast Unit, patients usually evaluated early for the prevention of osteoporosis and are subsequently followed for occurrence of rheumatologic au-

toimmune disorders. Inclusion criteria were hormone sensitive cancer of the breast, that have been under anti-hormonal treatment for six months. Exclusion criteria were cancer recurrence, sicca symptoms (dry eyes and/or dry mouth) present at the time of cancer diagnosis, age <18 years, concurrent radio and chemotherapy, previous neck radiotherapy, estimated survival of less than 12 months, active hepatitis C infection, acquired immunodeficiency system, pre-existing rheumatological disease (*e.g.*, RA, SS). All patients were subjected to detailed clinical examination; the source of data on medical, clinical, laboratory history were represented by clinical reports of outpatients visit. Age, radiotherapy, chemotherapy, exposure to aromatase inhibitor or SERMs, the length of time between the cancer diagnosis and the onset of sicca symptoms and the start of the drug therapy were recorded. We reviewed full blood cells count, erythrocyte sedimentation rate, protein electrophoresis, aspartame amino-transferase (AST), alanine-amino transferase (ALT), alkaline phosphatase (AP), gamma-glutamyl transpeptidase (GGT), bilirubin, viral hepatitis markers (B, C), analysis of the urine, C-reactive protein. In patients complaining with sicca symptoms we evaluated antinuclear antibodies (ANA) with HEp-2 substrate, antibodies to extractable nuclear antigens (ENA), anti-dsDNA (anti-double stranded DNA), rheumatoid factor (RF), complement C3/C4. Based on the American-European Consensus Group questions, patients with at least one symptom of ocular or oral dryness were assessed for lacrimal gland function, measuring tear production using Schirmer test. Schirmer's test result was considered positive if ≤5 mm/5 min. The New 2016 American College of Rheumatology/European League against Rheumatism (ACR-EULAR) classification criteria were used to identify patients with SjS.[19] Patients lacking a clinical diagnosis and patients with an incomplete diagnostic evaluation according to the ACR/EULAR criteria were also excluded. Salivary glands (SG) ultrasonography (US) was performed in all patients with sicca symptoms,[20-22] by the same investigator, a 10 years experienced rheumatologist, using a real-time scanner (MYLab7 Esaote), with a high resolution linear probe. The OMERACT scoring system was applied in B-mode for morphological lesions.[23] The ultrasonographer was blinded for the diagnosis. Minor salivary glands (MSGs) biopsy[24] was proposed if a patient was negative for anti-Ro/SSA autoantibodies but positive on Schirmer's test and SG-US suggestive for the presence of hypoanechoic areas (grade 2-3). MSGs were excised through the mucosa of the lower lip within 3 weeks after the imaging studies. Focal lymphocytic sialadenitis with a focus score of ≥1 foci/4 mm^2 was determined on the basis of number of inflammatory cell aggregates containing >50 lymphocytes/4 mm^2 of salivary gland tissue.[25]

Statistical analysis

Data are presented as means ± standard deviation (SD) for continuous variables and as numbers with percentages for qualitative variables and analyzed using the t test. The χ^2 test was used to evaluate the relation between categorical values. All statistical tests were two tailed, and *P*-values less than 0.001 were considered to indicate statistical significance. The binary logistic regression was carried out to assess the factors associated to sicca syndrome. All statistical analysis was assessed using IBM SPSS Statistics 23.

Results

A total of 110 patients with non-metastatic ER-positive BC were recruited. Of these, 51 (46.4%) had sicca symptoms complaining, therefore meeting the inclusion criteria for the suspicion of SjS from the EULAR SjS disease activity index questionnaire. Among patients with sicca symptoms, 15 (29%) had positive Schirmer test and of these 9 (17.6%) had positive ANA (title up to 1÷160) and 7 (13.7%) also SSA antibodies, thus fulfilling the new 2016 ACR-EULAR classification criteria for the diagnosis of SjS. Above patients with sicca symptoms, 11 (21,6%) had US suggestive for salivary gland alterations grade 2-3. MSGs biopsy was suggested in patients with grade 2-3 at SGUS but negative for SSA antibodies detection: focal lymphocytic sialadenitis with a focus score of ≥1 foci/4 mm^2 was found in all patients. All of these patients were also negative for ANA detections. A true SjS, fulfilling the new EULAR/ACR criteria for the diagnosis of SjS was diagnosed in a total of 11 patients with sicca symptoms (P<0.0001). Therefore the occurrence of SjS in all BC patients was of 10%, and among these 4 were seronegative. Infiltrating ductal carcinoma was prevalent in seropositive SjS (P<0.0001). We did not find any statistically significant difference in sicca and non-sicca syndrome group regarding

Table 1. Comparison of demographic, clinical and serological characteristics between groups of patients with sicca syndrome and without.

	Sicca symptoms No. (%) 51	Non sicca symptoms No. (%) 59
Age, years (at time of cancer diagnosis)	57.8±10.6	55.2±11.9
Positive Schirmer test	15 (29%)	Not done
Rheumatoid factor	6 (11.7%)	0
ANA	9 (17.6%)	Not done
antiRo/SSA	7 (13.7%)	Not done
Leukopenia	8 (15.6%)	0
MSGs biopsy (focus score of ≥1)	4 (7.8%)	Not done
US abnormalities (grade 2-3)	11 (21.5%)	2 (3.4%)
Chemotherapy	12 (23.5%)	35 (59.3%)
Radiotherapy	23 (45%)	47 (79.6%)
SERMs	8 (15.7%)	27 (45.7%)
AIs	43 (84%)	34 (57.6%)

ANA, antinuclear antibodies; antiRo/SSA, anti-Ro/SjÖgren's syndrome antigen A; MSGs, minor salivary glands biopsy; US, ultrasound; SERMs, selective estrogen receptor modulators; Ais, aromatase inhibitors.

age, radiotherapy, chemotherapy, adjuvant anti-estrogen therapies. We did not find any sign or symptom suggestive for SjS pre-existing to the diagnosis of cancer or therapy. The mean time between anti-hormonal drug therapy start and sicca symptoms onset was 16 weeks (range 10-22). All patients with SjS had US items suggestive for SjS. Characteristic of the two groups are reported (Table 1). By binary logistic regression we noted that the onset of sicca syndrome was not influenced by the oncologic therapies (chemotherapy, radiotherapy and hormonal therapy).

Discussion and Conclusions

SjS is the second most common autoimmune rheumatic disease, affecting more women than men, with peak onset during menopause and another peak occurring between the ages of 20 and 40, with the prevalence of approximately 1% (range 0.1-4.8%) and the incidence with a risk of about 7 for every 100,000 people.[26-28] When diagnosed in an otherwise healthy individual, SjS is classified as primary SjS (pSjS). SjS is clinically characterized by the cardinal presentation of mucosal dryness, which causes inability to swallow dry food without liquids, dried and fissured tongue, cheilitis, aphthae, chronic oral candidiasis and dental cavities. Other exocrine glands may be involved and this may cause dry skin, vaginal dryness and gastrointestinal symptoms due to impaired secretion of protective mucus. Since it is a systemic disease, a range of other symptoms such as fatigue, arthralgia, immunologic and hematologic abnormalities may be present.[29] Dryness is the same symptom caused by iatrogenic estrogen deprivation in menopause.[17] Having seen the recent international literature, which has placed in evidence that there is an association between autoimmune diseases, such as SjS, and anti-hormonal therapy used in BC, we have theorized that sicca symptoms, normally attributed to induced menopause, is instead a symptom of SjS. In fact the present study emphasizes the unsuspected high prevalence of pSjS in ER-positive BC patients. To the best of our knowledge this is the first prospective cohort study evaluating pSjS among BC patients with sicca symptoms complaining. Only a few studies have reported the development of pSjS or suspected SjS under AIs treatment.[14-16] While providing insight into pSjS occurrence in BC, the present study has to be taken into consideration that there is still a lack of reliable worldly epidemiological data regarding SjS, that may have overestimated our conclusion. Besides, the variability of the prevalence and incidence of worldwide data about SjS is affected by heterogeneity in study design, inclusion criteria, ethnic origin, sample size and sex distribution among various studies. We should also consider this other bias: the general population as well as HR-positive BC patients with sicca symptoms, having trivial systemic symptoms, do not go to the specialist for check-up. In addition, we must take into consideration that the patients with sicca symptoms undergoing a rheumatologic screening, do not routinely take SGUS.[22-30] Above all, patients with seronegative SjS have phenotypic characteristics different from the seropositive ones [31]. Therefore making a SjS diagnosis might be difficult, as patients with seronegative SjS have lower frequency of hypergammaglobulinemia, rheumatoid factor and hypocomplementemia. In our study a positive SGUS, a non-invasive exam, was decisive for the diagnosis of SjS in patients without serological alteration and SS-A/Ro antibodies, as already suggested by the new EULAR/ACR criteria. Therefore suggesting a biopsy in patients with BC, with trivial symptoms and without autoantibodies, revealed to be decisive to make a diagnosis of SjS, as it has already been revealed in our cohort, where 4 of 11 SjS patients were seronegative. Moreover a routinely use of this diagnostic tool may have caused more SjS detection, which is considered to be a possible bias responsible for overdiagnosis. However, there is no way to prove whether we have improved our capacity in making a diagnosis by using SGUS, without performing a large randomized controlled study with the use of the same population, tools and investigative efforts. Several reports are emerging in the literature, which associate the use of BC anti-hormonal therapy, in particular AIs, to the appearance of rheumatic disorders.[9,10] Although the immuno-modulating effects of AIs have been extensively investigated, the mechanisms behind this link have not been clearly understood.[4-32] In published studies the association between BC and serum autoantibodies has been already confirmed in anti-thyroid peroxidase autoantibodies (TPOAb) positive patients,[33] leading to the conclusion that women with BC have a better prognosis than women lacking TPOAb.[34] Thus TPO expression in BC tissue could explain both the known association between BC and autoimmune thyroid disorder and the protective role of serum TPOAb in patients with aggressive BC.[35] As well as TPO expression in BC tissue is one possible molecular basis linking serum TPOAb to BC, SjS-associated autoantigen (SSA) is another potential molecular target linking SjS occurrence to BC, as the prognostic value of SSA in a subset of BC has already been evaluated.[36] Nevertheless SSA is an estrogen receptor coactivator that induces MYC oncogene, promotes G(1)/S transition of the cell cycle and growth capability of breast cancer cells.[37] Other hypothesis consider estrogens to protect secretory glandular acinar cells against apoptosis, whereas lack of estrogens specifically leads to increased apoptosis of the exocrine secretory cells.[38,39] In conclusion, data published in the literature, together with our results, indicate a link between BC and SjS. However, further studies with bigger sample, long-term follow-up, molecular and in vivo study are required to support the real incidence of SjS in BC patients, the link between BC and SjS, as well as eventually BC outcome in pSjS patients, will become a very interesting field of research.

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