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REVIEW

Aromatase inhibitors induced autoimmune disorders in patients with breast cancer: A review

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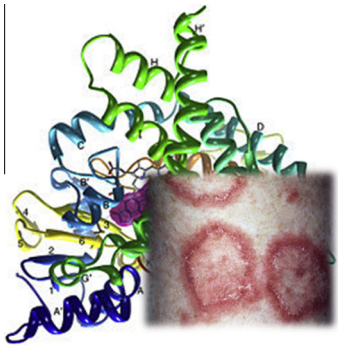
GRAPHICAL ABSTRACT



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ABSTRACT

Subacute cutaneous lupus erythematosus (SCLE) is characterized by particular cutaneous manifestations such as non-scaring plaques mainly in sunlight exposed parts of the body along with specific serum autoantibodies (i.e. antinuclear antibodies (ANA), Ro/SSa, La/SSb). It is consid-

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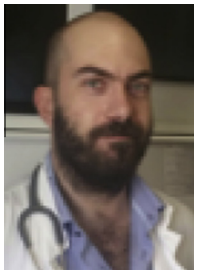
ered either idiopathic or drug induced. The role of chemotherapeutic agents in causing SCLE has been investigated with the taxanes being the most common anticancer agents. However, recent data emerging point toward antiestrogen therapies as a causative factor not only for SCLE but also for a variety of autoimmune disorders. This is a report of a case of a 42 year old woman who developed clinical manifestations of SCLE after letrozole treatment in whom remission of the cutaneous manifestations was noticed upon discontinuation of the drug. In addition, an extensive review of the English literature has been performed regarding the association of antiestrogen therapy with autoimmune disorders. In conclusion, Oncologists should be aware of the potential development of autoimmune reactions in breast cancer patients treated with aromatase inhibitors.



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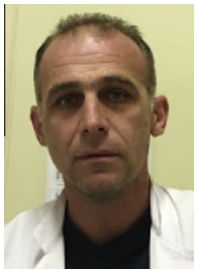

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Introduction

Aromatase inhibitors (AIs) (i.e. letrozole, anastrozole, exemestane) are used in the treatment of hormone dependent breast cancer. Their use may be complicated with cutaneous events such as increased sweating, alopecia, dry skin, pruritus, and urticaria, but also with a variety of rashes. The eruption of SCLE may begin with papules, which either coalesce or develop into annular erythematous lesions with slight scale or into scaly psoriasiform lesions. In rare cases angioedema, toxic epidermal necrolysis and erythema multiforme may be observed [1,2]. To date, there have been a number of reports of SCLE attributed to the use of antiestrogen therapy [3–7]. In addition, some chemotherapeutic agents have already been reported to induce SCLE, including cyclophosphamide, doxorubicin, paclitaxel, bevacizumab, fluorouracil or capecitabine with most prevalent the use of taxanes [8–12]. However, the accurate mechanism of SLE phenomena and various autoimmune disorders caused by antiestrogen therapy remains to be elucidated. In this article a patient with breast cancer treated with letrozole who developed SCLE is reported. An extensive search of the literature regarding the association between endocrine treatment and SCLE or autoimmune disorder development, was also attempted.

Material and methods

All published papers were obtained through the PubMed database, using the subsequent Medical Subject Heading terms: ''autoimmunity AND cancer'', ''autoimmune manifestations AND endocrine treatment AND breast cancer'', ''aromatase inhibitors AND autoimmune diseases'', ''lupus erythermatosus AND aromatase inhibitors''. Furthermore, a manual search and review of reference lists were carried out. Titles were screened and studies were excluded if obviously irrelevant. Literature up to December 31, 2015 was included.

Case presentation

A 42 year old Caucasian woman with a past medical history of heterozygous beta-thalassemia, photosensitivity and a family history of a mother with systemic lupus erythematosus (SLE), was diagnosed in December 2011 with metastatic breast cancer (estrogen receptor positive, progesterone receptor negative and HER2 positive). She was first presented with anemia and thrombocytopenia and the diagnosis was established following a bone marrow biopsy which revealed a metastatic adenocarcinoma compatible with breast cancer. She was treated with paclitaxel, trastuzumab and zoledronic acid till April 2012 with a significant improvement of her hematologic indices. Since then she continued with trastuzumab, tamoxifen, and zoledronic acid until July 2014 when progressive disease in the abdomen, brain and lungs was confirmed. Whole brain radiotherapy was provided and a second line chemotherapy with carboplatin and paclitaxel was administered until early December 2014. Partial remission in the abdomen and complete response in the chest were found, while brain metastases remained stable. She then went on letrozole, luteinizing hormone – releasing hormone (LHRH) analog and trastuzumab.

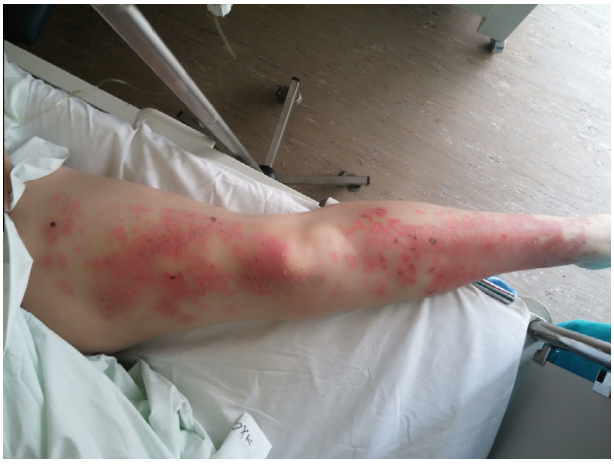

Fig. 1 Rash diagnosed as subacute lupus erythematosus in a patient with metastatic breast cancer treated with letrozole.

Within the first weeks and after the initiation of hormonal treatment, on late December 2014, an annular erythematous psoriasiform rash in the arms was noticed. During her next visits and being on the same treatment the rash deteriorated necessitating local and systematic corticosteroids. In June 2015 due to hematologic progression treatment was altered to the combination of trastuzumab, pertuzumab, and docetaxel with discontinuation of letrozole. A month later the patient was admitted to the oncology ward due to febrile neutropenia following treatment. At the time of her admission while she was kept on corticosteroids the skin rash was still persisting (Fig. 1). A skin tissue biopsy was performed revealing non-specific interface dermatitis. No vasculitis was noticed. A rheumatology consultation along with elevated serum ANA (1/640), Ro52 and Ro60 titers established the diagnosis of SCLE. The patient was then prescribed hydroxychloroquine along with a gradual tapering of the corticosteroids. She continued her medication until October 2015 when she visited the outpatient clinic. A full remission of the rash was then established and the patient had normal values on her complete blood count. A total body computed tomography (CT) was scheduled in order to further evaluate her disease and decide on her further antitumor treatment (Table 1).

Discussion

The major morphological characteristics of SCLE are annular, non-scarring, papulosquamous or psoriasiform plaques with

Table 1 Time course of reported patient since diagnosis of breast cancer.

Date	Fact
December 2011	Breast cancer diagnosis
December 2011–April 2012	Paclitaxel, Trastuzumab
April 2012–July 2014	Tamoxifen, Trastuzumab
July 2014–December 2014	Carboplatin, Paclitaxel, Trastuzumab
Early December 2014	Letrozole, LHRH, Trastuzumab
Late December 2014	Appearance of rash
January 2015–April 2015	Deterioration of rash
May 2015	Onset of corticosteroids
June 2015	Anemia, leukopenia, thrombocytopenia, persistence of rash
June 2015	Letrozole discontinuation, SCLE diagnosis and hydroxychloroquine initiation with corticosteroid tapering
October 2015	Full remission of SCLE manifestations

distribution mainly to the sunlight exposed areas of the body [13]. The autoimmune profile of SCLE may consist of positive Ro/SSA or La/SSB antibody titles while most patients test positive for antinuclear antibodies (ANA) [14]. Complete blood count tests may reveal anemia, leukopenia, and thrombocytopenia while skin tissue biopsy indicates perivascular and subepidermal inflammatory cell infiltration or vacuolar alteration of the basal cell layer. Constitutional symptoms such as malaise, fever and arthralgias may be present [8]. The diagnosis is confirmed with the conjunction of both clinical and serological profiles, while full picture of SLE may be absent. The treatment consists of therapy with corticosteroids both systematic and locally while in some cases specific drugs such as hydroxychloroquine may be prescribed depending on the severity of the manifestations. In the case of drug induced SCLE the clinical features and laboratory findings do not differentiate from typical subacute SLE [15]. Consequently, drug-induced SCLE must be of high suspicion when typical findings of SCLE onset correlate with the induction of a new drug. A mandatory discontinuation of the new drug should be considered [16].

Throughout the literature drug induced SCLE has been described and associated with the use of thiazide diuretics, angiotensin-converting enzyme (ACE) inhibitors, calcium channel blockers, and taxanes, and most recently with antiestrogen therapy [9,13,17]. The use of tamoxifen in three patients and anastrozole in one patient resulted in the appearance of SCLE [3,5]. There are also two cases in the current literature reporting the association between aminoglutethimide and SLE in cancer patients [6,7]. Etherington et al. reported a breast cancer case with a history of SLE who presented with a flair of a lupus-like syndrome and subsequent remission of her symptoms after switching her treatment from tamoxifen to aminoglutethimide [7] (Table 2).

It must be pointed out that breast cancer itself may induce the appearance of both serum autoantibodies and of clinical manifestations of autoimmune paraneoplastic syndromes [18]. The onset of the cutaneous presentations correlates with the onset of malignancy and sometimes even before the tumor is diagnosed. Complete remission of the skin manifestations can be seen following successful treatment of the underlying malignant disease [18–20].

The relationship between estrogens and rheumatic diseases has been widely investigated. There have been a number of studies showing that estrogens induce and androgens suppress the phenomena of SLE-like disease in F1 and MRL/I pr mice [21]. In addition, it has been proven that sex hormones have an immunomodulatory role in rheumatic diseases [22]. Other reports have also demonstrated that estrogens induced the production of anti-dsDNA antibodies by circulating lymphocytes in patients with active SLE and that antiestrogen therapy, in particular tamoxifen, resulted in the reduction of IgG3 autoantibodies in the sera of (NZB × NZW)F1 female mice ameliorating the course of SLE-like disease [21,23].

On the other hand, it seems that when circulating estrogen levels are higher they can inhibit the function of neutrophils. The use of AIs results in reduction of estrogen levels which in turn, increases the function of neutrophils. The cells then adhere to the blood vessel endothelium and provoke autoimmune vasculitis or vasculitis-like reactions [24,25]. To date there have been reports of cutaneous vasculitis attributed to the use of exemestane in three patients [1], while the use of letrozole seems to have been responsible for inducing necrotizing leukocytoclastic small vessel vasculitis in a number of cases [25–27]. However as Digklia et al. have reported the case of leukocytoclastic vasculitis that was attributed to the use of letrozole in a patient, did not recur when switch to exemestane took place. Thus it would be reasonable to speculate that idiosyncratic reaction of the patient rather than estrogen depletion may have induced the onset of vasculitis [26]. In addition, anastrozole was associated with the onset of pruritic micropapular eruptions in a single case and cutaneous vasculitis has also been attributed to the same medication in other patients [27,2,28] (Table 3).

Furthermore, the association between rheumatoid arthritis (RA) and the use of antiestrogen therapy has also been investigated. There are case reports of rheumatoid arthritis induction with the use of exemestane as well as accelerated cutaneous nodulosis in a patient already diagnosed with rheumatoid arthritis undergoing letrozole therapy [29–31]. Chen and Ballou have recently reported that the use of selective estrogen receptor modulators (SERMs) in women with breast cancer diagnosis results in higher incidents of both SLE and RA. The use of SERMS resulted in a statistically significant risk of SLE and RA, while the use of AIs mainly resulted in higher incidents of RA. On the contrary, the same report comes to the conclusion that the use of AIs tends to decrease the incidence of SLE although those results were not statistically significant [32]. Furthermore, third generation AIs suppress the differentiation of naïve T-cells to regulatory

Table 2 Cases of antiestrogen therapy associated SCLE or SLE.

Author	Hormonal treatment	Patient age	Type of malignancy	Clinical findings	Time of manifestations onset	Therapy
Andrew et al. [4]	Tamoxifen	40 y old female	Breast cancer	Facial eruption	Four months after initiation of tamoxifen	Discontinuation of TMX
Fumal et al. [3]	Tamoxifen	68 y old female	Hepatocellular carcinoma	Erythematosus rash arms, lower neck	Six years after initiation of tamoxifen	Discontinuation of TMX
Fumal et al. [3]	Tamoxifen	84 y old female	Breast cancer	Annular, widespread erythematous rash	Four years after initiation of tamoxifen	Discontinuation of TMX
Trancart et al. [5]	Anastrazole	73 y old female	Breast cancer	Intense annular cutaneous eruption upper trunk, face, neck	One month after initiation of anastrozole	Discontinuation of anastrozole, corticosteroids, hydroxychloroquine
McCraken et al. [6]	Aminoglutethimide	57 y old female	Breast cancer	Soft tissue swelling, severe aching in muscles	Six months after initiation of aminoglutethimide	Discontinuation of aminoglutethimide
Etherington et al. [7]	Tamoxifen and Aminoglutethimide	77 y old female	Breast cancer	Generalized joint pains, hair fall, Raynaud phenomenon	Eight years after initiation of tamoxifen	Corticosteroids and aminoglutethimide continuation

T-cells with a concomitant increase in proinflammatory cytokines interferon-γ (IFN-γ) and interleukin-12 (IL-12). Specifically, anastrozole treatment was associated with an increased expression of genes responsible for inflammatory processes in hormone receptor positive breast cancer. In addition, the use of SERMs has been associated with a reduction in the maturation and activity of autoreactive B cells and immunostimulatory dendritic cells which in turn results in alleviation of dermatomyositis symptoms [33].

The immunomodulatory function of AIs has also been reported as a potential causative mechanism leading to arthralgias and arthritis like syndromes [34]. Aminoglutethimide can result in increased natural killer (NK) cell activation whereas the use of formestane, a second generation AI, causes elevation of IL-2 and INF-γ levels. Reports of lymphocyte count reduction in patients being on exemestane, a steroidal AI, and a blockage in the balance of IgG2a/IgG1 have been described [33]. Consequently, apart from the aforementioned correlation between the use of aromatase inhibitors and SLE or SLE-like syndromes, the use of AI has been associated with the induction of arthralgias. Women on this type of antiestrogen therapy often come up with symmetrical joint pains, morning stiffness which resolves with exercise, mainly of the wrists but also in other joints of the body. Carpal tunnel syndrome is also a notable manifestation while on AI. These symptoms can lead to discontinuation of the AI therapy in a significant proportion of the patients [35,36]. Their relationship with immune disorders such as sicca syndrome, systemic sclerosis and Sjogren syndrome has also been investigated with the latter being more prevalent as reported by Laroche et al. Among twenty-four women investigated for joint pain, nineteen were found to have inflammatory pain of the joints and two had inflammatory laboratory profile. Ten patients were diagnosed with sicca syndrome of the eyes or mouth, one was diagnosed with Sjogren syndrome, one RA, and another Hashimoto thyroiditis and seven more were considered to have probable Sjogren syndrome [37,38].

Many theories have been proposed in order to explain the mechanism leading to arthritis manifestations such as the nociceptive role of estrogens and the subsequent increased sensitivity to pain stimuli following antiestrogen therapy [39]. The increased activation of vitamin D receptor attributable to antiestrogens leads to decline of vitamin D levels causing arthralgias [40]. However, the immunomodulatory theory remains a plausible explanation. It seems that the aforementioned increased plasma levels of proinflammatory cytokines have a significant role in the induction of arthritis or arthritis like syndromes. Furthermore, evidence exists concerning the expression of aromatase in synovial cells which is then inhibited by the use of AI thus resulting in high intrasynovial levels of IL-6 leading to inflammation of the joints. In addition, the upregulation of RANK ligand on osteoblasts induces the function of osteoclasts causing bone desorption. In one study, women on immunotherapy with thymosin a1, as a part of their arthralgia therapy, have been reported to measure lower serum levels of INF-γ, thus experiencing alleviation of their symptoms [41]. Furthermore recent data concerning muscoskeletal pain induced by the use of AIs have emerged. Hershman et al. have concluded that the use of omega-3 fatty acids which were speculated to have an anti-inflammatory role failed to improve the patients symptoms above placebo. The use of omega-3 fatty acids in women suffering from arthralgias while

Table 3 Other autoimmune disorders associated with antiestrogen therapy.

Author	Hormonal treatment	Type of disorder	Patient, age	Type of malignancy	Clinical findings	Time of disorder onset	Therapy
Morel et al. [30]	Exemestane, Tamoxifen	RA	64 y old female	Breast cancer	Arthritis, synovitis, ulnar deviation of fingers	Few days after switching from tamoxifen to exemestane	Methotrexate
Chao et al. [31]	Letrozole	RA, cutaneous nodulosis	71 y old female	Breast cancer	Cutaneous nodulosis	Three months after initiation of letrozole	Discontinuation of letrozole
Bertolini et al. [29]	Letrozole Exemestane Tamoxifen	RA	61 y old female	Breast cancer	Joint pains, swelling of metacarpophalangeal and proximal interphalangeal joints	Two weeks after initiation of letrozole	Hydroxychloroquine
Bertolini et al. [29]	Anastrazole	RA, sicca syndrome	61 y old female	Breast cancer	Inflammatory joint pains of hands and knees, polyarthritis, synovitis	Few weeks after initiation of anastrozole	Discontinuation of AI, sulfasalazine
Bertolini et al. [29]	Letrozole, Tamoxifen, Exemestane	RA	66 y old female	Breast cancer	Joint pains, polyarthralgia, synovitis	Four months after initiation of letrozole	Corticosteroids
Shoda et al. [28]	Anastrazole	Vasculitis	78 y old female	Breast cancer	Purpura, leg ulceration	Three months after initiation of anastrozole	Discontinuation of anastrozole
Santoro et al. [1]	Exemestane	Vasculitis	80 y old female	Breast cancer	Painful, cutaneous eruptions, palpable purpura, ecchymosis, ulceration	One week after initiation of exemestane	Discontinuation of Exemestane, corticosteroids
Wong et al. [27]	Anastrazole, letrozole	Vasculitis	63 y old female	Breast cancer	Arthralgia, skin lesions	Immediately after initiation of anastrozole	Colchicine
Digklia et al. [26]	Letrozole	Vasculitis	69 y old female	Breast cancer	Erythematous papules and plaques, petechiae, ulcerations	Five days after initiation of letrozole	Discontinuation of Letrozole, corticosteroids
Pathmarajah et al. [25]	Letrozole	Vasculitis	72 y old female	Breast cancer	Burning sensation, erythematous, violaceous rash, cough, weeze, edema	Fourteen days after initiation of letrozole	Discontinuation of letrozole
Bremec et al. [2]	Anastrazole	Pruritic eruption	68 y old female	Breast cancer	Pruritus, papules	Three months after initiation of anastrozole	Discontinuation of anastrozole corticosteroids
Pokhai et al. [38]	Letrozole, exemestane	Systemic sclerosis	61 y old female	Breast cancer	Swollen digits, synovitis, joint stiffness, pain, vasospastic phenomena	Two years after initiation of letrozole	Discontinuation of aromatase inhibitors.
Islam et al. [43]	Anastrazole	Autoimmune Hepatitis	66 y old female	Breast cancer	Abnormal liver tests	Six months after initiation of anastrozole	Discontinuation of anastrozole
Inno et al. [44]	Anastrazole	Autoimmune Hepatitis	70 y old female	Breast cancer	Abnormal liver tests, asthenia	Four months after initiation of anastrozole	Discontinuation of anastrozole
Laroche et al. [37]	Aromatase inhibitors		Among 24 females with joint pains, on AI for breast cancer, 19 found with inflammatory pain, two had inflammatory findings on laboratory tests, nine were positive for ANA, 4 were positive for rheumatoid factor, 10 had sicca syndrome of eyes or mouth, 7 possibly Sjogren syndrome, 1 definite Sjogren syndrome, 1 RA, 1 Hashimoto's thyroiditis		
Chen et al. [32]	SERMs, Aromatase Inhibitors		Among 36,720 female patients on SERM or AI for breast cancer, 1200 developed RA and 270 developed SLE. The risk was more evident for patients on SERMS for developing either RA or SLE. Patients on AI had increased risk of developing RA but not SLE				

on AIs resulted in decreased triglyceride levels while there was no difference in symptoms alleviated by the use of omega-3 fatty acids or placebo [42]. Finally, the correlation between autoimmune manifestations and AIs extends even to the induction of autoimmune hepatitis. Throughout the literature there are two case reports of female patients who developed autoimmune hepatitis with positive serum screening profile and compatible liver biopsy findings after the initiation of anastrozole for their breast cancer [43,44]. Recent data suggest a tight correlation of drug induced cutaneous lupus erythematosus with immunogenic predisposing of the patient HLA subtype. Most cases of drug induced lupus typically occur in patients with history of personal or family photosensitivity and it has been demonstrated that most of the culprit drugs usually cause photosensitivity reactions [45].

Conclusions

To our knowledge, there is a conflict regarding the use of AIs and subsequent SCLE or SLE prevalence. So far, some data suggest that antiestrogen therapy may have beneficial effects in patients with SLE, while there are studies showing increased incidence of rheumatic diseases with the use of both SERMS and AIs [33]. Consequently, more research should be conducted in order to elucidate the autoimmune adverse effects induced by hormonal agents in patients with breast cancer. Finally, clinicians must be alert of the correlation between endocrine therapy and the wide spectrum of rheumatic disorders.

This patient, who has been under surveillance and treatment since 2011, underwent sequential therapies with taxane consisting agents, anti-HER2 agents, platinum analogs, bisphosphonates without any skin disorders. As soon as letrozole was initiated, a distinct skin entity emerged which did not completely disappear despite treatment with corticosteroids. Skin rash disappeared only when letrozole was discontinued. In addition, past medical and family history of this patient must be taken into consideration regarding previous photosensitivity and mother's SLE diagnosis.

Conflict of Interest

The authors have declared no conflict of interest.

Compliance with Ethics Requirements

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008 (5). Informed consent was obtained from all patients for being included in the study.

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