**Original Article**

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# Rheumatological Findings in Patients with Breast Cancer

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**ABSTRACT**

**Objective:** Breast Cancer (BC) is the most frequently diagnosed malignancy worldwide. Not only may BC be associated with rheumatic symptoms and diseases, but also the drugs used in the treatment of this disease, including aromatase inhibitors (AIs), may lead to musculoskeletal system symptoms. In this study, we aimed to investigate the spectrum of rheumatic symptoms and diseases developing in patients with BC having no previous diagnosis of any inflammatory rheumatic disease.

**Materials and Methods:** Patients with a history of BC referring to Rheumatology Outpatient Clinics with complaints of musculoskeletal system symptoms at two centers between 2008 and 2018 were screened retrospectively. Patients with a previous diagnosis of any inflammatory rheumatic diseases before the occurrence of BC were excluded. Demographic data, onset and duration of BC, as well as onset and duration of rheumatic symptoms/diseases were recorded. Relevant laboratory tests, including autoantibodies, available imaging findings and the treatments received were also registered.

**Results:** Mean age of 128 BC patients at the time of admission was found to be 54.76±8.21 years. Mean durations of disease for BC and rheumatic disorders were 85.705±15.507 and 60.84±19.20 months, respectively. Out of 128 BC patients, nearly one third (n: 41; 32.03%), developed an inflammatory rheumatic disease, and rheumatoid arthritis was the most frequent pathology. Nonspecific arthralgia and myalgia were more frequent in patients receiving AIs than those receiving tamoxifen, despite lack of significant difference (p=0.421, p=0.411).

**Conclusion:** Given that nearly one third of the patients developed an inflammatory rheumatic disease, it should be remembered that locomotor symptoms in patients with BC may be caused not only by bone metastasis or paraneoplastic effects, but they may also suggest the presence of associated rheumatic diseases.

**Keywords:** Breast cancer, rheumatoid arthritis, systemic lupus erythematosus, Sjögren syndrome

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## Introduction

The risk of malignancy association is high in certain rheumatic diseases including dermatomyositis, polymyositis, rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), primary Sjögren Syndrome (pSS) and Systemic Sclerosis (SSc) (1, 2). On the other hand, nonspecific rheumatic symptoms such as arthralgia, arthritis, myalgia and skin lesions, or typical inflammatory rheumatic diseases may occur in patients with malignancy. The malignancies causing rheumatic symptoms most frequently are leukemias and lymphomas. The relevant symptoms may develop due to metastasis involving bones, muscles and joints, or as a paraneoplastic syndrome, or the adverse effect of chemotherapeutical drugs (1, 3). Clinical presentations such as arthritis, Coombs positive hemolytic anemia, skin rash and weight loss that are frequently seen in patients with lymphoma, may be due to associated SLE, adult-onset Still's disease or a systemic vasculitis. Some rheumatic symptoms might be the first manifestation of an occult malignancy (23%), and tumor resection may lead to a regression in rheumatic symptoms (4). It has been shown that Aromatase Inhibitors (AIs) used in breast cancer (BC) therapy increases the risk of rheumatic diseases, especially RA (5).

The most common malignancy diagnosed worldwide is BC; more than one million cases are diagnosed with BC every year. It is the most frequent cause of cancer in women and the second most frequent cause of cancer deaths in women in Unıted States (US) (6). In this study, we aimed to investigate locomotor system symptoms and the distribution of rheumatic diseases in patients with BC.

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## Materials and Methods

The data of 148 patients with BC referring to Rheumatology Outpatient Clinics due to musculoskeletal symptoms at two different centers (İzmir Katip Çelebi University Atatürk Teaching and Research Hospital and Muğla Sıtkı Koçman University Teaching and Research Hospital) between January 2008 and October 2018 were retrospectively evaluated. Twenty patients with a previous diagnosis of a certain rheumatic disease and/or with demonstrated bone metastasis were excluded. The remaining 128 patients with BC without bone metastasis or a previous diagnosis of any inflammatory rheumatic disease were included. The demographic data, onset and duration of BC, as well as presence, onset and duration of rheumatologic symptoms (Sicca syndrome, photosensitivity, alopecia, Raynaud's phenomenon, arthralgia, arthritis, sclerodactyly, ocular manifestations, muscle weakness, muscle pain, inflammatory back pain, sausage finger, aphthous ulcers, genital ulcers and specific skin lesions) were recorded. Relevant laboratory tests, including erythrocyte sedimentation rate, C-reactive protein, complete blood count, hepatic and renal function tests, hepatitis markers, calcium, thyroid function tests and autoantibodies (antinuclear antibody, rheumatoid factor, anti-cyclic citrullinated peptide antibody, anti-dsDNA and anti-extractable nuclear antigen antibodies) were noted. Available imaging findings and the treatments they received, including surgery, radiotherapy, chemotherapy and hormone therapy (particularly anastrozole and letrozole), were also recorded.

Among 128 patients with BC, those fulfilling the classification criteria of various rheumatic diseases including RA (7), pSS (8), SLE (9), SSc (10), ankylosing spondylitis(AS) (11), non-radiographic axial spondyloarthritis (nrAxSpA) (12), psoriatic arthritis (PsA) (13), Behçet's syndrome (BS) (14) and gout (15) were carefully noted.

This retrospective study was approved by the ethical board of Muğla Sıtkı Koçman University (158/180175).

### Statistical Analysis

All the statistical analyses were performed using Statistical Package for the Social Sciences software (SPSS Inc.; Chicago, IL, US). Descriptive analysis was used for the demographic and clinical characteristics. Statistical analysis of the difference between the groups with normal distribution was performed using chi-square test for qualitative data. $P<0.05$ was considered to be statistically significant.

## Results

At the time of referral, mean age of 128 patients with BC was found to be 54.76±8.21 years. Mean disease durations of BC and rheumatic disorders were 85.705±15.507 and 60.84±19.20 months, respectively. The symptoms and findings suggestive of a rheumatic problem were given in Table 1, while laboratory abnormalities including autoantibody positivity were given in Table 2. Of the patients, 18% had bilateral mastectomy and 22% unilateral mastectomy operations, while 38% had a previous history of radiotherapy. At the time of admission to rheumatology outpatient clinics, 71 patients had been using AIs and 48 patients had been receiving tamoxifen. Nonspecific arthralgia

Table 1. Frequency of rheumatic symptoms in patients with breast cancer

| Symptoms | Number (%) |
|---|---|
| Arthralgia | 77 (60.1) |
| Monoarthritis | 5 (3.90) |
| Oligoarthritis | 7 (5.46) |
| Polyarthritis | 22 (17.1) |
| Raynaud's Syndrome | 7 (5.46) |
| Photosensitivity | 2 (1.56) |
| Cutaneous vasculitis | 2 (1.56) |
| İnflammatory back pain | 4 (3.125) |
| Oral ulcerations | 8 (6.25) |
| Genital ulcerations | 4 (3.125) |
| Sicca symptoms | 22 (17.1) |
| Myalgia | 60 (46.8) |
| Dactylitis | 2 (1.56) |
| Sclerodactyly | 4 (3.125) |
| Anterior Uveitis | 4 (3.125) |

Table 2. Frequency of patients with autoantibody positivity and hypocomplementemia

| | Number (%) |
|---|---|
| Rheumatoid Factor | 12 (9.375) |
| Anti-Nuclear Antibody | 21 (16.4) |
| Anti-Scl70 | 2 (1.56) |
| Anti-Sm | 1 (0.78) |
| Anti-SSA/La | 5 (3.90) |
| Anti-SSB/Ro | 4 (3.125) |
| Anti-CCP | 5 (3.90) |
| Anti-dsDNA | 3 (2.34) |
| Anti-centromer | 2 (1.56) |
| Low C4 | 1 (0.78) |
| Low C3 | 1 (0.78) |

Table 3. Distribution of inflammatory rheumatic diseases observed in BC patients

| Disease | Number (%) |
|---|---|
| Rheumatoid Arthritis | 10 (7.81) |
| Primary Sjogren's Syndrome | 7 (5.46) |
| Psoriatic Arthritis | 6 (4.68) |
| Systemic Sclerosis | 4 (3.125) |
| Gout Disease | 4 (3.125) |
| Behçet's Syndrome | 4 (3.125) |
| Systemic Lupus Erythematosus | 3 (2.34) |
| Ankylosing Spondylitis | 2 (1.56) |
| Non-radiographic axial spondyloarthritis | 1 (0.78) |

Table 4. The histopathological types of breast cancer in all patients developing a rheumatic disease

| Disease | İnvasive Ductal Cancer | Malign Epithelial Tumor | Invasive lobular Cancer |
|---|---|---|---|
| Rheumatoid arthritis (n:10) | 4 | 4 | 2 |
| Primary Sjogren's Syndrome (n:7) | 2 | 5 | - |
| Psoriatic Arthritis (n:6) | 3 | - | 3 |
| Systemic Sclerosis (n:4) | 4 | - | |
| Gout Disease (n:4) | 2 | 1 | 1 |
| Behçet's syndrome (n:4) | 3 | - | 1 |
| Systemic Lupus Erythematosus (n:3) | 1 | 1 | 1 |
| Ankylosing Spondylitis (n:2) | 1 | 1 | |
| Non-radiographic axial spondyloarthritis (n:1) | 1 | - | - |

Table 5. Details of breast cancer management in patients developing rheumatoid arthritis

| Age at the time of breast cancer diagnosis (years) | Chemotherapy | Radiotherapy | Operation | Tamoxifen |
|---|---|---|---|---|
| 43 | + | + | + | + |
| 48 | + | + | + | + |
| 38 | - | - | - | + |
| 48 | + | + | + | + |
| 46 | + | - | - | + |
| 44 | + | - | + | + |
| 42 | + | - | - | + |
| 32 | - | - | - | + |
| 49 | + | + | + | + |
| 45 | + | - | - | + |

and myalgia were more frequent in patients receiving AIs than those receiving tamoxifen, despite lack of significant difference (p=0.421, p=0.411). Various inflammatory rheumatic diseases were diagnosed in 41 (32.03%) of the patients included in the study (Table 3). RA was the most frequent associated inflammatory rheumatic disease (n: 10; 7.81%), followed by pSS (n: 7; 5.46%) and PsA (n: 6; 4.68%). Besides, osteoporotic compression fractures were detected as the cause of vertebral pain in 3 (2.34%) patients. Three patients with vertebral fractures received AI therapy. The histopathological types of BC in all patients developing a rheumatic disease were given in Table-4. The features of those 10 patients developing RA, including their ages and details of BC management they received, were given in (Table-5). All of these patients were in pre-menopausal or peri-menopausal state with the ages ranging from 32 to 49 years (mean age±SD: 43.5±5.21years). Interestingly, all of them had a history of tamoxifen treatment.

## Discussion and Conclusion

This study is notable for investigating the locomotor system symptoms and findings, as well as rheumatic diseases in BC patients with no previous diagnosis of any inflammatory rheumatic disease. Out of 128 BC patients, nearly one third (n: 41; 32.03%) developed an inflammatory rheumatic disease after the diagnosis of BC. RA was the most frequent associated inflammatory rheumatic disease, followed by pSS, PsA, SSc, gout, Behçet's Syndrome, SLE, AS and nrAxSpA, with a decreased frequency. In consistent with literature data, we also found that nonspecific arthralgia and myalgia were more frequent in patients receiving AIs than those receiving tamoxifen, despite lack of significant difference. However, unlike Caprioli et al. (5), who reported the influence of AIs on the occurrence of RA in women with BC, we could not confirm this observation. Interestingly, all of those 10 patients developing RA had received tamoxifen treatment rather than AIs.

Tamoxifen and AIs are efficacious hormonal therapies in BC patients with hormone receptor positivity. Tamoxifen is a selective estrogen receptor modulator, while AIs suppress plasma estrogen level manifestly by preventing the conversion of androgens into estrogen by inhibiting or inactivating aromatase enzyme (16, 17). In general, tamoxifen is preferred for pre-menopausal patients, while AIs are used in post-menopausal patients. Given that occurrence of RA is more common in post-menopausal patients, there may be a bias with respect to association of AIs use and RA development in women with BC (5). Other than RA, musculoskeletal system complaints, such as arthralgia and morning stiffness, can be observed in patients using AIs. In a randomized controlled study, 21.3% of the patients receiving tamoxifen and 27.8% of the patients receiving AIs were reported to have musculo-

skeletal system symptoms (18). Crew et al. (19) observed arthralgia and morning stiffness in 47% and 44% of the patients using AIs, respectively Likewise, Presant et al. (20) reported arthralgia and/or bone pain in 61% of the patients using AIs, causing cessation of AIs in 20% of these patients . In the study of Henry et al. (21), AI treatment had to be discontinued in 10% of the patients.

Given that, in a recent nationwide study, prevalence of RA in Turkey has been reported as 0.89% for females, the frequency of patients developing RA (7.81%) fulfilling ACR 2010 criteria (7) in our series of 128 patients with BC seems to be rather high. If we make the comparison according to age groups, prevalence of RA in the Turkish female age groups of 45-54 years, and 55-64 years, which are close to mean ages of BC patients included in this study, were 0.77% and 0.88%, respectively. The increased frequency of occurrence of inflammatory rheumatic diseases, especially RA may be explained possibly by presence of common genetic pathways contributing both to malignancy and autoimmunity tendency. Besides, therapeutic agents used for management of BC may also contribute. On the other hand, patients might have skeletal symptoms due to neuropathy (caused by chemotherapy) and paraneoplastic syndromes, leading to confusion. The histopathology and stage of BC may also affect the symptoms and clinical picture (22).

As also mentioned in the previous paragraphs, AIs are at the top of the list, among therapeutic agents used for the management of BC and associated with occurrence of RA. In a previous study performed by Caprioli et al. (5) and including 10,493 patients with BC, RA risk was found to be higher in those receiving AIs, compared to those receiving tamoxifen. Why we could not confirm this association and why all of our patients developing RA had received tamoxifen treatment rather than AIs, are difficult to explain. We certainly cannot claim a causal relationship between tamoxifen use and RA development. On the other hand, we also found nonspecific locomotor symptoms to be more frequent in patients receiving AIs in our study. It may be speculated that, some of these patients treated with AIs may also develop RA in the future, if they would be followed up long enough.

With respect to other rheumatic disease, in a study of Laroche et al. (23), eight out of 24 (33%) patients with BC receiving AIs were diagnosed with SS. Guidelli et al. (24) presented three cases diagnosed as SS within the first year of AIs use, based upon autoantibody positivity and minor salivary gland biopsy findings. In our study, 7(5.46%) patients had SS diagnosis by 2016 ACR/EULAR criteria (8) and there were more patients diagnosed with SS in the tamoxifen group (3.90%) with respect to AI group (1.56%).

The pathogenesis of induction of musculoskeletal symptoms and possibly the occurrence of rheumatic diseases following treatment with AIs is not known. Interestingly, Shim et al. (25) showed the development of severe autoimmune exocrinopathy in Aromatase Knockout (ArKO) mice. Based upon this observation, it may be speculated that deficiency or inhibition of aromatase enzyme resulting in estrogen deficiency might play a role in the occurrence of rheumatic diseases in patients with BC. However, since estrogen contributes to autoimmunity itself, it needs explanation how the deficiency of estrogen facilitates the occurrence of autoimmune diseases in patients with BC. Alternatively, possible common genetic tendency may explain the later occurrence of systemic autoimmune diseases in patients with BC.

In patients with BC receiving AIs, musculoskeletal complaints due to osteoporotic bone fractures may also be observed. In contrast to tamoxifen, AIs can cause bone mineral loss by reducing endogenous estrogen levels. Perez et al. (26) studied the effects of letrozole which is an AI on bone mineral density (BMD), and observed a manifest decrease in the pelvic and vertebral BMD values of their patients after 24 months of letrozole treatment. Similarly, Muslimani et al. (27) found a higher risk of osteoporosis in their patients receiving AIs. Three patients included in our study also experienced vertebral fractures and associated pain with L2-L4 BMD T scores less than 2.5. Only one of these three patients had received AIs.

In literature, most of the studies about the association of rheumatic and malignant diseases concentrate on the development of malignant diseases in patients with rheumatic diseases. In other words, an increased risk of developing various malignancies have been reported in many systemic inflammatory rheumatic diseases including RA, SLE, SSc (28), SS (29) and AS (30). However, in the present study, the primary diagnosis is BC, and later occurrence of rheumatic diseases is discussed, which may be considered as the other side of the coin.

The main limitation of the present study is the possible failure to notice vague symptoms of the rheumatic diseases before the diagnosis of BC. Given that the appearance of autoantibodies precedes the occurrence of clinical symptoms in many systemic autoimmune diseases, the patients might have omitted vague symptoms of the rheumatic disease before the diagnosis of BC. Hence, the patient history might have misled the physicians. On the other hand, chemotherapy of BC including corticosteroids and immunosuppressive agents, generally improves the symptoms of rheumatic diseases as well. Therefore, the initial symptoms of rheumatic diseases may be realized when BC improves resulting in cessation of chemotherapy.

In conclusion, we found that nearly one third of the patients with BC developed an inflammatory rheumatic disease, mostly RA. This may implicate that not only malignant diseases may occur during the course of systemic rheumatic diseases, but also the reverse might happen in patients with BC. It should also be remembered that locomotor symptoms in patients with BC may be caused not only by bone metastasis or paraneoplastic effects, but they may also suggest the presence of associated rheumatic diseases.

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**Ethics Committee Approval:** Ethics committee approval was received for this study from the ethics committee of Muğla Sıtkı Koçman University (158/180175).

**Informed Consent:** Informed consent was not received due to the retrospective nature of the study.

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