CASE REPORT AND LITERATURE REVIEW

Rheumatology Quarterly

DOI: 10.4274/qrheumatol.galenos.2023.70299
Rheumatology Quarterly 2024;2(1):45-8

THREE CASES OF BREAST CANCER CAUSING PARANEOPLASTIC ARTHRITIS: A CASE REPORT AND LITERATURE REVIEW

Fatih Albayrak[1], Nurcihan Yavuz Savaş[2], Emrah Koç[3]

[1]Dr. Ersin Arslan Training and Research Hospital, Clinic of Rheumatology, Gaziantep, Turkey
[2]Sanko University Hospital, Clinic of Radiology, Gaziantep, Turkey
[3]University of Health Sciences Turkey, Adana City Hospital, Clinic of Rheumatology, Adana, Turkey

Abstract

There is an interesting and complex relationship between rheumatic diseases and malignancy. Paraneoplastic arthritis is caused by the effects of many hormones and cytokines secreted from the underlying hidden tumor tissue. There is no direct invasion or mechanical pressure of the tumor tissue. In particular, in the early rheumatological disease period, the diagnosis should be reconsidered in cases unresponsive to conventional treatment. It should be noted that there may be another underlying etiological factor in cases unresponsive to treatment. In this review, we discussed in detail three breast cancer cases that presented with early arthritis and were found to have breast cancer in the follow-up. In the literature, serological markers, pathological diagnosis, and imaging in breast cancer-associated paraneoplastic arthritis cases are not presented in detail. In our cases, serological markers, pathological diagnosis, and breast magnetic resonance imaging are presented in detail.

Keywords: Paraneoplastic arthritis, breast cancer, arthritis

INTRODUCTION

Paraneoplastic arthritis (PA) is a condition that develops because of mediators such as cytokines, hormones, or immunoglobulin released from the tumor tissue (1,2). The emerging arthritis condition and accompanying laboratory findings are similar to those of many rheumatological diseases. It is very difficult to distinguish them from early rheumatoid arthritis (RA). However, conditions such as older age of the patient, low steroid response, and negative autoantibodies may help in the differential diagnosis (3).

In the case series of PA we previously reported, after lung cancer, breast cancer is one of the most common solid tumors that cause PA (3). Here, we aimed to review the characteristics of 3 patients who presented with the clinical features of early RA and were later diagnosed with breast cancer, as well as the cases of PA caused by breast cancer in the literature.

CASE REPORT I

A 58-year-old female patient presented with pain, swelling, and limitation of motion in the hand, wrist, and metacarpophalangeal (MCP) joints. She said that her complaints had been for the last 3 weeks. There was morning stiffness lasting approximately 1 hour. The patient had no other complaints in the history. There were no complaints such as weight loss, fever, or night sweats. Physical examination revealed no features in other system examinations, except for the locomotor system examination. Her routine laboratory workup was unremarkable, aside from a raised

Address for Correspondence: Fatih Albayrak, Dr. Ersin Arslan Training and Research Hospital, Clinic of Rheumatology, Gaziantep, Turkey
Phone: +90 507 785 52 25 **E-mail:** drfalbayrak@yahoo.com **ORCID ID:** orcid.org/0000-0002-6052-3896
Received: 02.12.2023 **Accepted:** 27.12.2023

erythrocyte sedimentation rate (ESR) of 46 mm/hour, C-reactive protein (CRP) of 14 mg/dL, and positive antinuclear antibody (extractable nuclear antigen panel negative). Rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP) autoantibody were negative. Conventional radiographs were taken, and no pathology was detected except for soft tissue swelling. She was treated for early RA and started on hydroxychloroquine (HCQ) 200 mg twice daily and prednisolone 5 mg once daily, with good clinical response. Three months after her initial arthritis, she presented to us with complaints of right breast swelling and mass, which resulted in a breast biopsy. Breast biopsy was reported as estrogen receptor-positive invasive ductal carcinoma. She was started on neoadjuvant chemotherapy, and after chemotherapy, a mastectomy was performed. After the treatments, there were no joint complaints.

CASE REPORT II

A 56-year-old female patient was admitted with complaints of pain, swelling, and limitation of movement in her shoulders, hand proximal interphalangeal (PIF), MCP, and wrists, which lasted 1 month. The patient had no other complaints in the history. There were no complaints such as weight loss, fever, or night sweats. Physical examination revealed no features in other system examinations, except for the locomotor system examination. Her routine laboratory workup was unremarkable aside from a raised ESR of 39 mm/hour and CRP of 19 mg/dL. RF, anti-CCP autoantibody, and antinuclear antibody were negative. Conventional radiographs were taken, and no pathology was detected except for soft tissue swelling. She was treated for early RA and started on HCQ 200 mg twice daily and prednisolone 10 mg once daily. Her complaints regressed within 2 weeks. There were no joint findings. She presented to us with complaints of right breast swelling and mass, which resulted in a tru-cut breast biopsy. MRI of the patient's breast is shown in Figure 1. Breast biopsy was reported as estrogen receptor-negative invasive ductal carcinoma. The patient was referred to the oncology department, and paclitaxel and carboplatin were started as adjuvant therapy by the oncology department. There was no increase in joint complaints after chemotherapy.

CASE REPORT III

A 44-year-old female patient presented with complaints of pain and swelling in the 2nd-3rd metatarsopharyngeal (MTF) joints of the right foot and left wrist for the last 1 month. There was morning stiffness lasting about 1 hour. Examination revealed swollen and tender joints involving her left wrist andleft second-third MTF joints. There were no other significant physical findings on examination. The patient had no other complaints in the history. There were no complaints such as weight loss, fever, or night sweats. Physical examination revealed no features in other system examinations, except for the locomotor system examination. Her routine laboratory workup was unremarkable aside from a raised ESR of 44 mm/hour and CRP of 14 mg/dL. RF, anti-CCP autoantibody, and ANA were negative. Conventional radiographs were taken, and no pathology was detected except for soft tissue swelling. She was treated for early RA and started on HCQ 200 mg twice daily and prednisolone 5 mg once daily. Her complaints regressed within 1 month. After 2 months, she presented with pain that started in the right breast and a palpable mass. The patient's breast MRI image is shown in Figure 2.

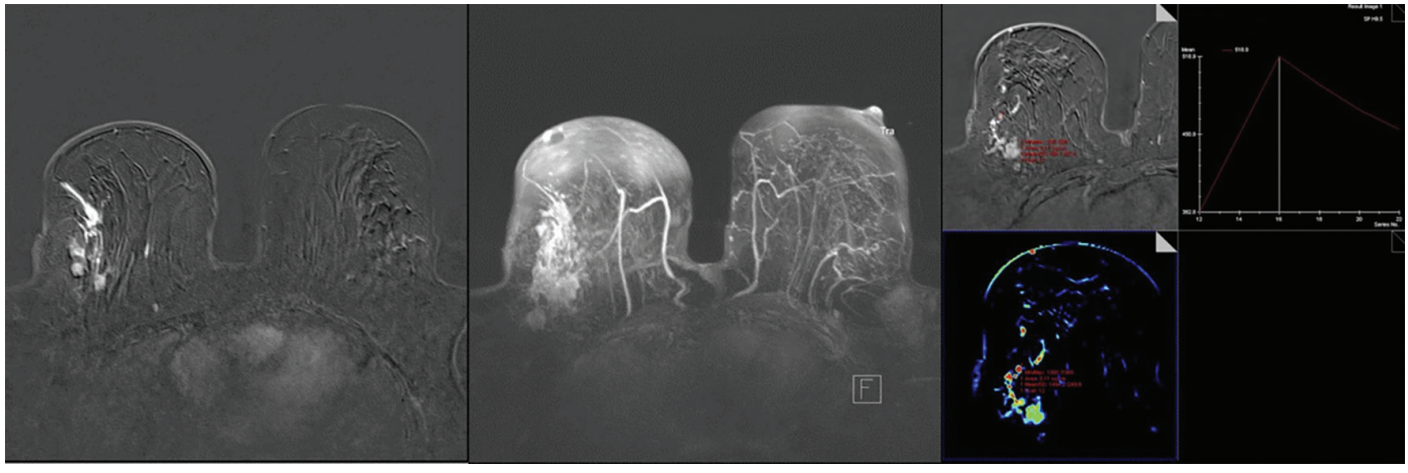

Figure 1. Left: Asymmetric regional enhancement in the right breast on subtraction images, middle: Maximal intensity projection image, right: Type 3 contrast enhancement pattern in mean curve analysis

The patient underwent breast biopsy, and the pathological diagnosis was lobular carcinoma. The breast biopsy was reported as C-erb-B2-positive invasive lobular carcinoma. A patient with bone and lymph node metastases underwent mastectomy after neoadjuvant chemotherapy. Chemotherapy treatment is currently ongoing. Joint complaints regressed after chemotherapy treatment.

DISCUSSION

PA is an important entity and a good imitator in rheumatology practice. The pathogenesis of PA is a direct effect of toxins produced by tumor cells, which trigger inflammation in the tissues where PA manifests. In addition, tumoral expression of antigens shared by the cells targeted by the autoimmune disease or to the release of intracellular antigens from apoptotic tumor cells can cross-react with synovial antigens to trigger PA (4).

In breast cancer, which has a significant rate among patients with PA, we presented 3 cases that developed an RA-like clinic 3 months before the cancer diagnosis. Two of these cases were invasive ductal cancer and one was invasive lobular cancer. In addition, metastases were present in two cases. In the largest PA series we have reported so far in the literature, the most common solid tumor after lung cancer was breast cancer. The pathological diagnosis of only 2 of them was known, and both were adenocarcinomas.

Among the 20 solid tumors reported by Morel et al. (5), only one case was breast cancer. The pathological diagnosis of this case was adenocarcinoma. The joints involved in this case were the small joints of the hand and wrist. In the series of 3 cases performed by Pines et al. (6), one female case aged 60 years had breast cancer, and the pathological diagnosis was adenocarcinoma. The patient had symmetrical polyarticular involvement and RF was positive. In the solid tumor series of 13 cases performed by Padhan et al. (7), 1 case was breast cancer and she presented with the complaint of polyarthritis. The patient's RF and anti-CCP autoantibodies were negative. The case was accompanied by palmar fasciitis. The mean time for patients to be diagnosed with breast cancer was 6 months. There was no palmar fasciitis in our patients. Especially in female patients over 50 years of age, patients with negative autoantibodies should be followed closely. It should be examined in terms of common malignancies (breast cancer) specific to that age range. In another study, in the case series of 39 solid tumor-associated PA cases by Kisacik et al. (3), 8 patients had breast cancer and 2 patients had a pathological diagnosis of adenocarcinoma. Solid tumor-associated arthritis usually has an acute onset and presents as an asymmetrical and oligoarticular joint pattern. In our breast cancer-associated arthritis cases, there was an acute onset, oligoarticular, and asymmetrical involvement pattern. The demographic characteristics of the cases reported in the literature who developed PA due to breast cancer are shown in Table 1.

In a study, when compared with cases with early RA, malignancy-related arthritis cases present with more asymmetric, oligoarticular, and large joint involvement, and it seems useful to be careful in this respect (3). In the series of 21 cases performed by Wen et al. (8), 1 female patient was diagnosed with RA, and she was diagnosed with breast cancer at the end of 12 months. In the cases we have presented, the pathological type of breast cancer has been described in detail. In the cases we presented, it was determined that they had breast cancer within 3 months. In cases where early RA is considered and steroid and non-steroidal anti-inflammatory treatment is started and no response is obtained, it may seem appropriate to conduct a malignancy screening considering that age range. In addition, in female patients diagnosed with seronegative arthritis, breast, and other organ examinations should not be ignored in the clinical examination and should be performed carefully. The clinician should be careful in this regard.

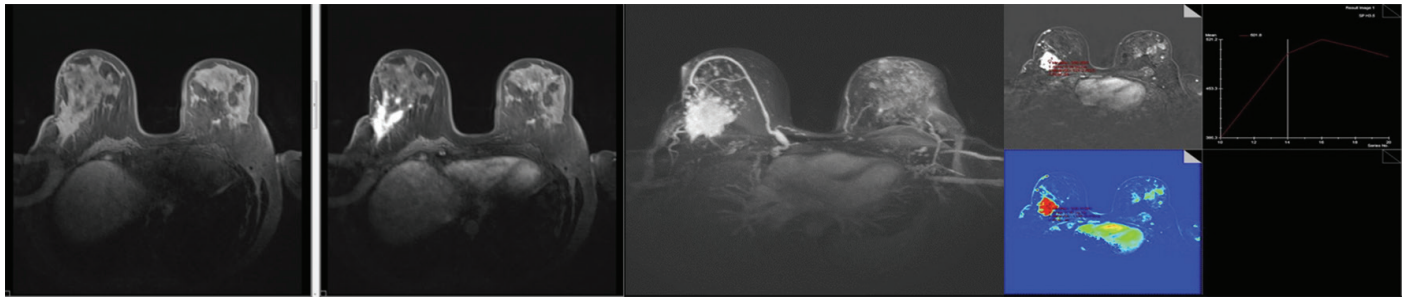

Figure 2. Left: Comparison of pre-contrast and early arterial phase T1 fat-suppressed images, middle: MIP image, right: Type 3 contrast enhancement pattern in mean curve analysis

MIP: Maximal intensity projection

Table 1. Demographic characteristics of the cases in the literature

Author(s) referance	Patients number	Age (years)	Joint pattern	Serological markers (RF, anti-CCP)	Pathological diagnosis
Morel et al. (5)	1	ND	Symmetric polyarthritis Wrists, hands	RF; negative CCP; ND	Galactophoric Adenocarcinoma
Pines et al. (6)	1	60	Symmetric polyarthritis	RF; positive CCP; ND	Adenocarcinoma
Padhan et al. (7)	1	66	Polyarthritis (MCJ, wrists, PIJ)	RF and CCP; negative	ND
Kisacik et al. (3)	8	43-66	Asymmetrical, oligoarticular	ND	2 patients adenocarcinoma 6 unknown
This study	3	58, 56, 44	Asymmetrical, oligoarticular	RF and CCP; negative	Ductal carcinoma Lobular carcinoma

RF: Rheumatoid factor, Anti-CCP: Anti-cyclic citrullinated peptide, ND: Not determined, MCJ: Metacarpophalangeal joint, PIJ: Proximal interphalangeal joint

PA can be caused by both solid and hematological malignancies. In our series, 60% of solid tumors, 40% of hematological malignancies, and 43.5% of solid tumors consisted of lung cancer (3). In another study, 76% of cases were solid tumors and 24% were hematological malignancies (5). Lung cancer cases constituted 50% of solid tumors (5). Lymphoma and leukemia among hematological malignancies are prominent diagnoses.

In cases of PA, malignancy is usually diagnosed after arthritis. In our previous series, the mean time between symptoms and malignancy was 5 months (3). In another series, this rate was found to be 4.4 months (5). In the cases presented here, the diagnosis of malignancy was made within an average of 3.3 months.

CONCLUSION

PA must be considered in cases of early arthritis. It is important that breast cancer has an important place in paraneoplastic cases, that patients should be questioned in their anamnesis, especially in seronegative cases, and that imaging methods should be used in cases of clinical suspicion. Breast cancer is the most common PA after lung cancer. Because the treatment response and clinical course of the pathological subgroups are different, it can provide more information in the subsequent follow-ups of patients who develop arthritis. Consequently, studies with larger case series related to pathological subgroup classification are needed in breast cancer-associated PA series.

Ethics

Informed Consent: Informed consent forms were obtained from the patients.

Authorship Contributions

Surgical and Medical Practices: F.A., N.Y.S., E.K., Concept: F.A., N.Y.S., E.K., Design: F.A., N.Y.S., E.K., Data Collection or Processing: F.A., N.Y.S., E.K., Analysis or Interpretation: F.A., N.Y.S., E.K., Literature Search: F.A., N.Y.S., E.K., Writing: F.A., N.Y.S., E.K.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

REFERENCES

1. Manger B, Schett G. Paraneoplastic syndromes in rheumatology. Nat Rev Rheumatol 2014;10:662-70.
2. Geng G, Yu X, Jiang J, Yu X. Aetiology and pathogenesis of paraneoplastic autoimmune disorders. Autoimmun Rev 2020;19:102422.
3. Kisacik B, Onat AM, Kasifoglu T, et al. Diagnostic dilemma of paraneoplastic arthritis: case series. Int J Rheum Dis 2014;17:640-5.
4. Schultz H, Krenn V, Tony HP. Oligoarthritis mediated by tumor-specific T lymphocytes in renal-cell carcinoma. N Engl J Med 1999;341:290-1.
5. Morel J, Deschamps V, Toussirot E, et al. Characteristics and survival of 26 patients with paraneoplastic arthritis. Ann Rheum Dis 2008;67:244-7.
6. Pines A, Kaplinsky N, Olchovsky D, et al. Rheumatoid arthritis-like syndrome: a presenting symptom of malignancy. Report of 3 cases and review of the literature. Eur J Rheumatol Inflamm 1984;7:51-5.
7. Padhan P, Thakur B, Singh P, et al. Rheumatic manifestations as initial presentation of malignancy: a case series from a tertiary care center in India. Eur J Rheumatol 2018;6:71-5.
8. Wen J, Ouyang H, Yang R, et al. Malignancy dominated with rheumatic manifestations: a retrospective single-center analysis. Sci Rep 2018;8:1786.