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Should Mammography Be a Prerequisite Prior to Initiation of Biological Agents in Patients With Psoriasis?

Funda Tamer[1], Ayla Gulekon[1]

1 Gazi University School of Medicine Department of Dermatology, Ankara, Turkey

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Corresponding author: Funda Tamer, Assoc. Prof. MD, Gazi University School of Medicine Department of Dermatology, Ankara, Turkey. E-mail: fundatmr@yahoo.com

ABSTRACT

Introduction: Psoriasis patients may be susceptible to malignancy due to chronic inflammation. Moreover, biological agents which are used in the treatment of psoriasis might increase the risk of malignancy due to their immunosuppressive effect.

Objectives: We evaluated the mammography results of female patients with psoriasis aged over 40 years before the initiation of biological agent treatment. We aimed to determine whether breast cancer screening with mammography should be a prerequisite before the initiation of biological agent treatment for psoriasis.

Methods: Between April 2019 and March 2021, medical records of female psoriasis patients aged over 40 years were reviewed retrospectively.

Results: This study included 42 female psoriasis patients (mean age: 53.52 ± 7.09). BI-RADS score was 2 in 18 (42.9%) patients, 1 in 13 (31%) patients, 3 in 9 (21.4%) patients and 4A in 1 (2.4%) patient. Isodense masses were detected in 10 (23.8%) patients, while 6 (14.3%) patients had intramammary lymph nodes. Mammography revealed microcalcifications in 6 (14.3%) patients, macrocalcifications in 1 (2.4%) patient and a hamartoma in 1 (2.4%) patient. Isodense masses, calcifications and intramammary lymph nodes were associated with long disease duration (> 10 years). Intramammary lymph nodes were more common in patients treated with biological agents previously compared to biologic-naive patients.

Conclusions: We suggest that female patients over 40 years, especially those who had a long disease duration, family history of breast cancer and previous history of treatment with biological agents should undergo mammography before the initiation of biological agents for the treatment of psoriasis.

Introduction

Psoriasis is a chronic inflammatory skin disorder accompanied by various comorbidities such as psoriatic arthiritis, metabolic syndrome and cardiovascular disease [1]. Since chronic inflammation has been implicated in the etiopathogenesis of both psoriasis and malignancy, it has been suggested that psoriasis might be associated with increased risk of malignancy. Development of cancer was reported 1.18 times more common in patients with psoriasis compared to individuals without psoriasis [2]. Furthermore, mortality rates were elevated in accordance with the severity of psoriasis. Malignancies such as squamous cell carcinoma, lymphoma, colorectal, pancreatic, kidney, liver, esophageal and laryngeal cancer have been related to psoriasis [2]. High prevalence of breast cancer has also been reported in patients with psoriasis [3]. However, relationship between psoriasis and the risk for the development of malignancy remains controversial [4].

On the other hand, increased use of biological agents in the treatment of psoriasis leads to concerns about whether biological agents increase the risk of malignancy or not [5]. It has been suggested that tumor necrosis factor-α (TNF-α) inhibitors, anti-interleukin (IL)12/IL-23 and anti-IL-17A antibodies might increase the risk of malignancies due to their immunosuppressive effects [6]. For instance, use of TNF-α inhibitors such as etanercept, adalimumab and infliximab longer than 12 months has been implicated in increased risk for malignancy [5]. Development of breast cancer was reported in a patient following systemic psoriasis treatment with conventional therapy, adalimumab and ustekinumab [6]. It has been suggested that breast cancer was one of the most commonly detected malignancy in patients who received ustekinumab [7]. Biological agent treatment is not recommended in patients who had an active malignancy within the last five years [8].

Evaluation of patients with psoriasis before and throughout the biological agent treatment according to their medical history of cancer and risk for the development of cancer is crucial [9]. Therefore, patients with psoriasis receiving biological agents should be encouraged to participate in national cancer screening programmes [9,10]. However, it has been reported that patients with psoriasis who were treated with biological agents did not undergo recommended tests for breast cancer screening adequately despite increased risk for malignancy [11].

Objectives

Within this study, we evaluated the mammography results of female patients with psoriasis aged over 40 years before the initiation of biological agent treatment in order to detect premalignant and malignant breast lesions. We aimed to reveal whether breast cancer screening with mammography should be a prerequisite prior to biological agent treatment for psoriasis or not.

Methods

Between April 2019 and March 2021, medical records of the female psoriasis patients aged over 40 years who underwent mammography before the initiation of biological agent treatment were reviewed retrospectively. Gazi University Ethics Committee approval was obtained for this study (approval number: 2021-412). Patients who had an increased risk for the development of breast cancer such as previous breast cancer, radiation exposure to the chest, high hereditary risk for breast cancer, patients with ovarian and endometrial malignancies and immunocompromised patients were excluded from the study. Mammography was routinely performed in female psoriasis patients over the age of 40 years before treatment with biological agents for screening premalignant or malignant lesions of the breast. Breast imaging-reporting and data system (BI-RADS) [12], breast density categories, masses, lymph nodes, calcifications and localization of the lesions were evaluated.

Statistical analysis was performed using SPSS version 20.0. Data were represented as mean ± standard deviation (SD) or median for quantitative variables, counts and percentage for categorical variables. Differences between two groups were evaluated by chi-square test. $P < 0.05$ was considered as statistically significant.

Results

This study included 42 female patients with a mean age of 53.52 ± 7.09 (range: 41-65 years). Thity-two (76.2%) patients had psoriasis vulgaris, 5 (11.9%) patients had palmoplantar psoriasis and 5 (11.9%) patients had generalized pustular psoriasis (Table 1). The mean disease duration was 17.07 ± 10.99 years (range: 1-47). Twenty-eight (66.7%) patients did not complain of joint pain, whereas 14 (33.3%) patients had psoriatic arthritis. Past medical history of 16 (38.1%) patients was unremarkable. Ten (23.8%) patients had hypertension, 7 (16.7%) patients had both hypertension and type 2 diabetes, 5 (11.9%) patients had type 2 diabetes, 2 (4.8%) had hypothyroidism, 1 (2.4%) had coronary artery disease and 1 (2.4%) had granulomatous mastitis. Only 1 (2.4%) patient had a family history of breast cancer.

Forty-one (97.6%) patients were treated with conventional systemic treatments such as methotrexate, cyclosporine and acitretin, 7 (16.6%) patients were treated with phototherapy and 19 (45.2%) patients were treated with biological agents, previously. Twenty-three (54.8%) patients

Table 1. Characteristics and mammography results of female psoriasis patients who underwent mammography before the initiation of biological agent treatment

Patients with psoriasis (n = 42)				
Mean age (years, ± SD)	53.52 ± 7.09	(range: 41-65)		
Mean disease duration (years, ± SD)	17.07±10.99	(range:1-47)		
Psoriatic arthritis	Patients with arthritis 14 (33.3)	Patients without joint pain 28 (66.7)		
Comorbidities, n (%)	Patients with comorbidities 26 (61.9)	Patients without comorbidities 16 (38.1)		
Psoriasis type, n (%)	PV 32 (76.2)	PPP 5 (11.9)	GPP 5 (11.9)	
Previous treatment, n (%)	Conventional treatment 41 (97.6)	Phototherapy 7 (16.6)	Biological treatment 19 (45.2)	
Breast density type, n (%)	A 4 (9.5)	B 24 (57.1)	C 13 (31)	D 1 (2.4)
BI-RADS score, n (%)	1 13 (31)	2 18 (42.9)	3 9 (21.4)	4A 1 (2.4)
Isodense mass, n (%)	Patients with IM 10 (23.8)	Patients without IM 32 (76.2)		
Localization of IM, n (%)	Left breast 5 (11.9)	Right breast 2 (4.8)	Bilateral 3 (7.1%)	
Intramammary lymph node	Patients with ILN 6 (14.3)	Patients without ILN 36 (85.7)		
Localization of ILN, n (%)	Left breast 4 (9.5)	Right breast 1 (2.4)	Bilateral 1 (2.4)	
Other lesions, n (%)	Microcalcifications 6 (14.3)	Macrocalcifications 1 (2.4)	Both micro and macrocalcifications 1 (2.4)	Hamartoma 1 (2.4)

BI-RADS = Breast imaging-reporting and data system; GPP = Generalized pustular psoriasis; ILN = Intramammary lymph node; IM = Isodense mass; PPP = Palmoplantar psoriasis; PV = Psoriasis vulgaris; SD = standard deviation.

were biologic- naïve. Among the patients who were treated with biological agents previously, 13 (31%) patients received anti-TNF-α agents such as infliximab, adalimumab, etanercept and certolizumab pegol, 5 (11.9%) patients received both anti-TNF-α agents and ustekinumab, and 1 (2.4%) patient received ustekinumab.

Mammographic breast density was type B in 24 (57.1%) patients, type C in 13 (31%) patients, type A in 4 (9.5%) patients and type D in 1 (2.4%) patient. BI-RADS score was 2 in 18 (42.9%) patients, 1 in 13 (31%) patients, 3 in 9 (21.4%) patients and BI-RADS score was 4A in 1 (2.4%) patient. No statistically significant association was observed between BI-RADS score and disease duration or previous biological agent treatment (P = 0.51 and P = 0.65, respectively). The patient with BI-RADS 4A had microcalcifications with loose clusters in some areas, and mild pleomorphism in the upper outer quadrant of the left breast which was revealed to be nodular adenosis with columnar cell change.

Isodense masses of the breast were observed in 10 (23.8%) patients whereas mammography of 32 (76.2%) patients did not reveal a breast mass. Isodense masses were localized on the left breast in 5 (11.9%) patients and on the right breast in 2 (4.8%) patients. Moreover, in 3 (7.1%) patients, isodense masses were localized on the breasts bilaterally. Seven (16.7%) patients had 1 isodense mass, 3 (7.1%) patients had multiple isodense masses. Largest size of the isodense breast masses ranged between 5 to 14 mm. Furthermore, mammography revealed microcalcifications in 6 (14.3%) patients, macrocalcifications in 1 (2.4%) patient, both microcalcifications and macrocalcifications in 1 (2.4%) patient and a hamartoma in 1 (2.4%) patient.

Intramammary lymph nodes were observed in 6 (14.3%) patients, whereas mamography did not reveal an intramammary lymph node in 36 (85.7%) patients. Four (9.5%) patients had 1 intramammary lymph node, 1 (2.4%) patient had 2 and 1 (2.4%) patient had multiple intramammary lymph nodes, respectively. Intramammary lymph nodes were localized on the left breast in 4 (9.5%) patients and on the right breast in 1 (2.4%) patient. Intramammary lymph nodes were detected bilaterally in 1 (2.4%) patient. Moreover, in 1 (2.4%) patient mammography recommended further evaluation of an intramammary lymph node on the right breast, which was revealed to be reactive lymph node without an atypical cell.

The disease duration was less than 10 years in 4 (9.5%) patients with an isodense mass of the breast and more than 10 years in 6 (14.3%) patients with an isodense mass (P = 0.47). The disease duration was less than 10 years in 1 (2.4%) patient with calcifications of the breast and more than 10 years in 7 (16.7%) patients with calcifications (P = 0.21). The disease duration was less than 10 years in 1 (2.4%) patient with an intramammary lymph node and more than 10 years in 5 (11.9%) patients with intramammary lymph nodes (P = 0.41).

Five (11.9%) patients with an isodense mass of the breast were treated with biological agents, previously and 5 (11.9%) patients with an isodense mass were biologic-naïve (P = 0.72). Three (7.1%) patients with calcifications were treated with biological agents previously, however, 5 (11.9%) patients with calcifications were biologic- naïve (P = 0.62). Five (11.9%) patients with an intramammary lymph node were treated with biological agents previously and 1 (2.4%) patient with an intramammary lymph node was biologic- naïve (P = 0.04).

In addition, a 58-year-old female patient with a 30-year history of psoriasis vulgaris and psoriatic arthritis who had already been diagnosed with breast cancer was determined. Family history of the patient was remarkable for both psoriasis and breast cancer. The patient was treated with methotrexate, cyclosporine, acitretin, PUVA and adalimumab, previously. After 10 months of adalimumab treatment, the patient was diagnosed with grade 1 invasive ductal carcinoma, therefore adalimumab treatment was stopped.

Conclusions

Breast cancer is the most frequently detected malignancy and the second most frequent reason of malignancy related mortality in women globally. Breast cancer is an insidious disease and it is usually detected by routine screening procedures [13]. However, recommendations of major guidelines for breast cancer screening in the United States differ about the initiation age of breast cancer screening with mammography, screening intervals and when to discontinue mammography [14-17].

According to the American Cancer Society, individuals without medical history of breast cancer, BRCA1/BRCA2 gene mutation and former radiation treatment to the chest at the age of 10 to 30 years are at average risk for breast cancer. The American Cancer Society recommends to start breast cancer screening with mammography for women with average breast cancer risk at 45 years of age [14]. However, women aged 40 to 44 years may also undergo mammography if they request it. The American Cancer Society recommends to repeat mammography between the ages of 45 to 54 years annually and over the age of 55 years biennially. However, women aged 55 years and over may undergo mammography annually if they request. Breast cancer screening should also proceed in healthy individuals with life expectancy longer than 10 years [14]. Nevertheless, the American College of Obstetricians and Gynecologists recommends to start mammography at the age of 40 years, however, screening may be initiated between the ages of 40 to 49 years based on shared decision of the physician and the patient. Individuals should repeat mammography every year or biennially. Mammography is not required in women older than 75 years, however, it may also be stopped in accordance with the agreement of both the physician and the patient [15]. However, US Preventive Services Task Force recommends biennial mammography screening between the ages of 50 to 74 years [16,17]. Moreover, National Comprehensive Cancer Network recommends to start mammography at the age of 40 years and to repeat it every year [15].

Breast cancer has been associated with psoriasis [18]. It has been suggested that the risk of cancer might increase in patients with psoriasis due to chronic inflammation [19]. Elevated incidence of psoriasis has also been reported among patients with breast cancer [20]. In addition, there are concerns that biological agents may be associated with cancer development based on their effect on immune system [21]. Since biological treatment has been associated with malignancy, it is mandatory to exclude malignancies before the initiation of biological agents and to monitor patients for cancer development during treatment [22].

Within this study, mammography results of patients with psoriasis over the age of 40 years were evaluated before the initiation of biological agent treatment. Most of the patients (42.9%) had BI-RADS score 2, which indicated benign findings [12]. However, BI-RADS score 3, which indicated probably benign lesions requiring close follow-up was detected in 21.4% of the patients [12]. Furthermore, 1 patient had BI-RADS score 4A, which indicated 2% to 10% of risk of malignancy [12]. Isodense masses were detected in 23.8%, microcalcifications or macrocalcifications in 19.1% and intramammary lymph nodes in 14.3% patients. Isodense masses, calcifications and intramammary lymph nodes were more common in patients with history of psoriasis longer than 10 years. However, no statistically significant difference was observed between disease duration and the frequency of isodense masses, calcifications or intramammary lymph nodes (P = 0.47, P = 0.21, P = 0.41, respectively). On the other hand, intramammary lymph nodes were more common in patients who were previously treated with biological agents compared to biologic- naïve patients (P = 0.04). In addition, a patient with family history of both psoriasis and breast cancer who had already been diagnosed with breast cancer while receiving adalimumab was detected. Therefore, we suggest that female patients over 40 years, especially those who had a long disease duration, family history of breast cancer and previous history of treatment with biological agents, should undergo mammography screening before the initiation of biological agents for the treatment of psoriasis. The limitations of this study were small sample size and lack of a control group.

British Association of Dermatologists recommends the evaluation of psoriasis patients before the treatment with biological agents according to existing cancer or future malignancy risk and thus it directs patients to attend the national

cancer screening programmes [9]. Concerning with cancer and biological agents, Joint American Academy of Dermatology-National Psoriasis Foundation (AAD-NPF) guideline recommends patients to attend current and age-appropriate cancer screening [10,23]. European S3-Guideline suggests to perform clinical examination during the treatment of psoriasis with adalimumab, etanercept, infliximab and secukinumab [24,25]. Moreover, Japanese guidance for use of biologics for psoriasis recommends to collect medical history of malignancy from patients with psoriasis before the initiation of biological agent treatment [26].

Guidelines for the treatment of psoriasis with biological agents recommend to assess patients with medical history and physical examination to exclude malignancy [9,10,24-26]. However, British Association of Dermatologists guidelines for biologic therapy for psoriasis and Joint AAD-NPF point out the importance of the attendance of psoriasis patients to the national cancer screening programmes [9,10]. In the light of this information, there is no consensus on breast cancer screening guidelines regarding the necessity of clinical breast examination, initiation or cessation age of mammography and screening intervals [14-17]. Interestingly, the American Cancer Society does not recommend clinical breast examination. However, American College of Obstetricians and Gynecologists and National Comprehensive Cancer Network recommend clinical breast examination every 1 to 3 years in women aged 25-39 years and every year in women aged over 40 years [14,15]. Moreover, the American Cancer Society and American College of Obstetricians and Gynecologists stated that initiation or cessation age and screening intervals of mammography might be determined based on the preference of patients who had an average risk for breast cancer [14,15].

Since breast cancer is the most common malignancy in women, mammography should be considered as a prerequisite prior to initiation of biological agents in female patients with psoriasis. Discrepancies between breast cancer screening guidelines may lead psoriasis patients to non-adherence with cancer screening recommendations. Therefore, patients with psoriasis who undergo treatment with biological agents should be informed in detail about mamography screening intervals, which should also be included within psoriasis treatment guidelines.

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