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RISK FACTORS FOR DEVELOPING UPPER LIMB CELLULITIS AFTER BREAST CANCER TREATMENT

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ABSTRACT

Cellulitis is one of the most important troubling complications of breast cancer treatment. Therefore, elucidating the risk factors for cellulitis in patients that have undergone breast cancer treatment is crucial. This is a retrospective medical record study among 523 patients who had received breast cancer treatment and were referred to the Lymphedema Clinic. Data on age, height, weight, BMI (body mass index), education level, arm dominance, history of previous surgery, axillary lymph node dissection, radiotherapy, and chemotherapy were noted. The time between operation and onset of lymphedema, duration of lymphedema, history of cellulitis, and number of cellulitis attacks were recorded. Circumference measurements were taken at four points on the upper limb. Univariate analysis showed that longer duration of lymphedema, larger circumference of the unaffected arm and larger circumference of the arm with lymphedema were associated with higher risk of cellulitis (p=0.008, p=0.007, p< 0.001, respectively). The incidence of cellulitis was higher in patients with lymphedema than patients who had no lymphedema (p< 0.001). Moreover, the frequency of cellulitis was higher in patients with lower education level (p=0.015). It was deter-mined that patients with cellulitis needed more compression garments (p< 0.001) and multi-layered bandage therapy (p< 0.001) than those without. Regression analysis revealed that presence of lymphedema (p=0.036), duration of lymphedema (p=0.048), radiotherapy (p=0.01) and educational level (0.019) are significantly associated with developing upper extremity cellulitis. It is important to consider these risk factors for the prevention and management of cellulitis in patients who undergo treatment for breast cancer. Early detection and treatment of lymphedema also remains essential for these patients.

Keywords: breast cancer, cellulitis, lymphedema, risk factors

Breast cancer is the most common cancer among women (1). Modern treatment of breast cancer is multimodal with surgical resection, radiotherapy, chemotherapy, targeted therapies, and/or endocrine therapy as possibilities (2). Early diagnosis and improvements in breast cancer care have significantly increased the survival rate with the 5-year survival rate in women with stage 1 breast cancer at 86% (3).

As a result of the increased survival time after breast cancer treatment, management of post-treatment complications has gained importance. Lymphedema, the accumulation of protein-rich fluid in the interstitial space, is one of the most dreaded and troubling morbi-

dities of breast cancer treatment (4). Treatment related risk factors for lymphedema include axillary lymph node dissection, regional lymph node radiation, lack of breast reconstruction, and chemotherapy (5). Breast cancer related lymphedema alters functional abilities and may affect a patient's psychosocial adjustment (6).

In patients with lymphedema, bacteria may colonize the interstitial spaces and thrive in the protein-rich fluid of lymphedematous area. When combined with skin changes and lymphedema-associated immune compromise, infection is highly likely (7). Cellulitis is the most common infectious complication of lymphedema (8). Cellulitis is an acute inflammation of the skin and subcutaneous tissue (9). It usually presents as an acute, poorly demarcated area of erythema with the classic signs of inflammation: dolor (pain), calor (heat), rubor (erythema), and tumor (swelling) (10). The severity of the disease ranges from localized erythema to rapidly spreading erythema and fulminant sepsis seen with necrotizing fasciitis. Cellulitis most often affects the lower extremities but can present on any area of the body. Breast cancer patients are at risk for cellulitis after surgery and radiotherapy (11).

Cellulitis imposes severe restriction on activities of daily living and leads to poor quality of life in patients (12,13). Additionally, cellulitis damages the lymphatic system which may lead to increased lymphedema. Recurrence of episodes is frequent and hence resulting in long term antibiotic use (14). Therefore, it's at utmost importance to uncover risk factors for cellulitis in patients that have had breast cancer treatment. In our study, the factors leading to development of cellulitis in patients who underwent breast cancer surgery were investigated.

MATERIALS AND METHODS

This is a retrospective medical record study of 523 patients who referred to the Lymphedema Clinic of the Dokuz Eylul University Medical Faculty, Department of Physical Medicine and Rehabilitation after breast cancer treatment from 2010 to 2019. This study was conducted in accordance with the principles of Declaration of Helsinki and was approved by Institutional Ethics Committee and all patients provided a signed informed consent. Except for exclusion of those patients with primary lymphedema, all were included.

Data on age, height, weight, BMI (body mass index), education level, arm dominance, history of previous surgery, axillary lymph node dissection, radiotherapy, and chemotherapy were obtained. Time between operation and onset of lymphedema, duration of lymphedema, history of cellulitis, and number of cellulitis attacks were recorded. Circumference measurements were taken at four points on the upper limb: the metacarpal joint, wrist, forearm (10 cm below the lateral epicondyle), and brachium (10 cm above the lateral epicondyle). Arm circumference is defined as sum of these four measurements.

Statistical analysis was performed using SPSS version 22.0 statistical software (IBM, Armonk, NY). Descriptive data were presented as mean, standard deviation, median, frequency, and percentage. Normality assumption for the quantitative data was tested with a Shapiro-Wilk test. Univariate analyses were performed using an Independent Samples t-test for continuous variables. Chi square test was used to analyze 2x2 contingency tables. Factors emerging as significant in the univariate analysis or otherwise considered to be relevant were included in the multivariate analysis. Adjusted odds ratios (AOR) with 95% confidential interval (CI) of the final model were presented. P value of 0.05 was considered significant.

RESULTS

Demographical characteristics of the 523 patients included in the study are presented in *Table 1. Table 2* provides the clinical characteristics of the patients. Eighty-one (15.5%) of the patients had a history of cellulitis and only 30 (6%) of the patients experienced cellulitis after complete decongestive therapy.

Table 3 summarizes results of univariate analysis. Longer duration of lymphedema,

TABLE 1
Demographical Characteristics of Study Patients

Characteristic	Mean/Ratio ± Standard Deviation
Age (year)	57.72±11.79
Weight (kg)	75.57±13.80
Height (meter)	160.56±6.22
BMI (kg/m^2)	29.33±5.51
Sex	Female 519 (99%) Male 4 (1%)
Level of education	Primary School 183 (35%) Secondary School 42 (8%) High school 91 (17%) University 109 (21%)

BMI: Body Mass İndex

TABLE 2
Clinical Characteristics of Study Patients

Characteristics	Number (percentage %) (n=523)
Dominant extremity	Right 510 (97) Left 13 (3)
History of radiotherapy	Yes 474 (91) No 49 (9)
History of chemotherapy	Yes 484 (92.5) No 39 (7.5)
Compression garment	Yes 238 (45.5) No 285 (55.5)
Multi-layer bandaging	Yes 181 (35) No 342 (65)
Limb affected by lymphedema	Right arm 217 (41.5) Left arm 205 (39) Bilateral 8 (1.5) Lower and Upper Extremity (1) No lymphedema 92 (18)

larger circumference of the unaffected arm, and larger circumference of the arm with lymphedema were associated with higher risk of cellulitis (p=0.008, p=0.007, p< 0.001 respectively).

It was determined that the incidence of cellulitis was higher in patients with lymphedema than patients who had no lymphedema (p< 0.001). Moreover, the frequency of cellulitis was higher in patients with lower education level (p=0.015) (data not shown). There was no significant difference of age, BMI, height, weight, or time after surgery between the patients with or without cellulitis. Furthermore, univariate analysis revealed that circumference difference between the two arms, and history of radiotherapy or chemotherapy were found to have no effect on the risk of developing cellulitis. Univariate analysis also showed that educational level was the only significant factor that increased the number of cellulitis attacks (p=0.02) (data not shown).

Table 4 presents the results of multivariate regression analysis of risk factors for

TABLE 3
Univariate Analysis of Risk Factors for Upper Limb Cellulitis (All Values Are Mean)

	No Cellulitis n=442	Cellulitis n=81	Significance (p value)*
Age (year)	57.4±11.7	58.9±12.1	0.293
BMI (kg/m^2)	29.1±5.6	30.4±4.6	0.087
Circumference of unaffected arm	92.0±8.1	96.0±23.9	**0.007**
Circumference of affected arm	99.0±12.0	104.9±12.1	**< 0.001**
Circumference difference between two extremities	7.0±8.8	9.0±26.6	0.512
Presence of lympedema	Yes 352 No 90	Yes 79 No 2	**< 0.001**
Duration of lymphedema (years)	3.41	5.00	**0.008**
Time after surgery (years)	2.84	3.55	0.256
Radiotherapy	Yes 403 No 39	Yes 71 No 10	0.317
Chemotherapy	Yes 408 No 34	Yes 76 No 5	0.632
Axillary Lymph Node Dissection	Yes 430 No 12	Yes 81 No 0	0.134
Compression Garment Need	182	54	**< 0.001**
Multi-layered Bandage Therapy Needed	138	43	**< 0.001**

*Values in Bold are significant

TABLE 4
Regression Analysis of Risk Factors for Cellulitis of the Arm

Risk Factors	Significance (p value)*	Odds Ratio
Level of education	**0.019**	0.272 (0.092 to 0.805)
Duration of Lymphedema	**0.048**	1.06 (1.001 to 1.123)
Lymphedema	**0.036**	9.59 (1.153 to 79.767)
Radiotherapy	**0.010**	4.05 (1.389 to 11.804)
Circumference of Normal Arm	0.092	1.06 (0.997 to 1.037)
Circumference of Arm with Lymphedema	0.900	0.998 (0.973 to 1.024)

*Values in Bold are significant

cellulitis of the arm. The regression analysis revealed that presence of lymphedema, duration of lymphedema, radiotherapy, and educational level are significantly associated with developing upper extremity cellulitis following breast cancer treatment.

DISCUSSION

This is, to our knowledge, the first study of risk factors for developing cellulitis of the upper limb in patients who have undergone breast cancer treatment. Level of education, presence of lymphedema, duration of lymphedema, and radiotherapy were found to be significant risk factors for cellulitis by multivariate regression analysis.

Cellulitis has been linked to a number of risk factors. According to a study examining patients with cellulitis in the lower extremities, lymphedema was found to be the strongest risk factor (odds ratio 71.2, 95% confidence interval 5.6 to 908) (15). It is widely understood and accepted that the relationship bet-

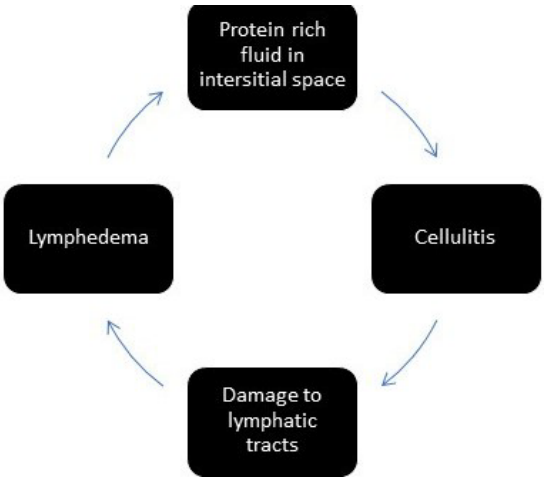

Fig. 1. *Relationship between lymphedema and cellulitis demonstrating a vicious cycle.*

ween cellulitis and lymphedema is a vicious cycle (16). The protein-rich lymphatic fluid serves as an excellent medium for bacteria to grow. Moreover, each episode of cellulitis further damages the lymphatic system, leading to a degree of secondary lymphedema, which in turn constitutes an increased risk for cellulitis (*Fig. 1*). Therefore, successful management of lymphedema and its complications is essential. Our findings emphasize the importance of early detection and treatment of lymphedema to prevent the occurrence of upper limb cellulitis.

Although there is paucity of studies investigating upper limb cellulitis, several studies that assess risk factors for lower limb cellulitis have been produced. A case-control study revealed that local factors such as disruption of the cutaneous barrier (leg ulcer, wound, fissured toe-web intertrigo, pressure ulcer, or leg dermatosis) and venous insufficiency are independent risk factors for lower limb cellulitis (15). A systematic review summarizing the risk factors, complications, and predictors of complications of lower limb cellulitis in Africa also reported that factors such as cutaneous barrier disruption, leg edema, history of skin disruption, presence of toe-web intertrigo, lymphedema, cosmetic depigmentation practice, and traumatic wounds were significantly associated with cellulitis. On the other hand, obesity was the only identified general risk factor for lower limb cellulitis (17). Another case control study suggested that being obese is an independent risk factor (18). Obesity causes immune system dysregulation which predisposes obese individuals to developing cellulitis (19). Obesity is also associated with other comorbid conditions, such as diabetes mellitus and hypertension, which may otherwise influence the risk for lower limb cellulitis. There was no statistically significant relationship between obesity or other general factors with cellulitis in our study.

A systematic review investigating risk factors for cellulitis showed that local risk factors appear to be more significant than general risk factors in the pathogenesis of cellulitis. General factors such as diabetes, smoking, and alcohol consumption were not found to be associated with cellulitis. In line with the above-mentioned studies, obesity was the only reported general risk factor of cellulitis (20).

Regression analysis showed that radiotherapy is another significant risk factor for developing upper limb cellulitis. The lymphatic circulation is influenced by radiotherapy, which enhances obstruction and progressive destruction of lymphatic communications, resulting in lymphedema (21). This lymphatic stasis appeared to be important in the development of cellulitis in our patients. Previous studies suggested that radiotherapy may also be responsible for delayed breast cellulitis (22). Rescigno et al (23) hypothesized that radiotherapy leads to delated breast cellulitis by radiotherapy-induced desquamation effect and squamous metaplasia of the duct epithelium.

Our findings also indicated that patients with higher level of education have significantly decreased risk of developing cellulitis. There are no prior studies investigating the effect of education on cellulitis, but previous studies regarding other infectious diseases suggest that the level of education could be a key determinant of information, attitudes, and behaviors related to the infections themselves (24). In this regard, level of education is an essential factor for both the acquisition of knowledge and the implementation of preventive

measures.

In our study, univariate analysis revealed that larger circumference of the unaffected arm was found to be associated with higher risk of cellulitis. Considering that obese people are more likely than people of normal weight to develop infections of various types, this can be related with obesity (25). Furthermore, larger circumference of affected arm is determined as another significant risk factor according to univariate analysis. It is believed that the patients' larger arm circumferences are linked to increased amount of lymphedema, which may have resulted in an increased risk of developing cellulitis. Nonetheless, according to the results of the multivariate regression analysis, neither the circumference of the unaffected arm nor the affected arm appeared to have a significant effect.

Along with identifying risk factors for upper extremity cellulitis, our investigation secondarily revealed several other significant facts concerning treatment for lymphedema. It was determined that patients with cellulitis needed more compression garments ($p< 0.001$) and multi-layered bandage therapy ($p< 0.001$) than those without (*Table 3*). This is likely due to the fact that cellulitis exacerbates lymphedema, necessitating the use of compression garments and therapy, but further investigations are needed.

Our study has some limitations. First, this study is limited by its retrospective nature. In addition, our study is university hospital-based, therefore the patients included in it may not be representative of all breast cancer patients. Furthermore, patients who did not attend the follow-up visits and had cellulitis may not have been detected. Cellulitis diagnosis was also based on clinical examination. This might lead to an under or overestimation of the condition. Finally, although the circumference measurements taken at 4 points appears to be adequate for our analysis, perhaps volume measurements of the whole limb may be more accurate to account for swelling outside of these four landmarks.

There are some case reports of patients who developed upper extremity cellulitis after undergoing breast cancer treatment (26). However, to the best of our knowledge, this is the first study to highlight the risk factors for upper limb cellulitis.

In conclusion, it is important to consider these risk factors for the prevention and management of cellulitis patients who undergo breast cancer treatment. Early detection and treatment of the lymphedema is also essential in these patients.

CONFLICT OF INTEREST AND DISCLOSURE

The authors declare no competing financial interests exist.

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