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RISK FACTORS FOR CELLULITIS IN PATIENTS WITH LYMPHEDEMA: A CASE-CONTROLLED STUDY

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ABSTRACT

Risk factors for cellulitis in lymphedema (LE) have never been evaluated in controlled studies. The objective of this study was to assess the risk factors for cellulitis in patients with LE using a case-controlled study method. Medical records of patients from November 2009 to September 2011 who met the following criteria were retrieved and analyzed: (a) clinical diagnosis of LE of the limb, (b) aged 18 or above, (c) no food allergy history and (d) no medical diagnosis of cancer metastasis. Overall, there were 179 cases of LE with cellulitis. Each case was matched by age (± 5 years) and gender with a patient with LE and without cellulitis for controls. Logistic regression with backward selection procedure was used to identify independent risk factors. The area under the receiver operating characteristics (ROC) curve of the final model was calculated. Independent risk factors for cellulitis in patients with LE were percentage difference in circumference of the limb (adjusted odds ratio (AOR)=1.07, 95% confidence interval (CI)=1.04-1.10), primary LE diagnosis (AOR=3.36, 95% CI=1.37-8.22), food-induced complication experiences (FIE: AOR=6.82, 95% CI=2.82-16.51) and systolic blood pressure (AOR=1.02, 95% CI=1.01-1.04). The area under the curve for the model was 0.80 (95% CI=0.75-0.85, p<0.001). No association was observed with hypertension, diabetes mellitus, body mass index and the duration of LE. This first case-controlled study highlights the important roles of dietary factors, percentage difference in circumference of the limb, and systolic blood pressure for developing cellulitis. The results suggest that controlling the percentage difference in circumference of the limb and systolic blood pressure together with restriction of fatty food and meat consumption may result in a decreased incidence of cellulitis among patients with LE.

Keywords: risk factors, cellulitis, case-control, lymphedema

One of the key functions of the lymph vascular system is to return liquid and solutes to the blood stream. The failure of lymph transport leads to a stagnation of proteins and fluid in the affected limb or tissue resulting in lymphedema (LE) and disability (1,2). Cellulitis is an acute infection of the dermal and subcutaneous tissue which can be life threatening (3,4). It is a common complication found in patients with LE due to inflammation and accumulation of fibroblasts, adipocytes and keratinocytes that can transform the initial soft swollen tissue into a hard fibrotic tissue (5,6).

The prevalence of cellulitis among patients with LE in Asia has been reported at 40-50% (7,8). Studies suggest that disruption

of cutaneous barrier, wounds, lymphedema, venous insufficiency, leg edema, and overweight were common risk factors of recurrent cellulitis in the general population (9-13). Despite the common occurrence of cellulitis in patients with LE, little is known about risk factors in this specific group of patients. The most extensive research has been conducted in breast cancer patients undergoing treatment (14-16), with no investigations looking at patients with LE. A recent study reported that breast-cancer related lymphedema had significantly higher medical costs and was twice as likely to have cellulitis (15). It is therefore pertinent to investigate risk factors for cellulitis in patients with LE.

PATIENTS AND METHODS

Study Design

Medical records of patients with lymphedema who visited the Thailand Lymphedema Day Care Center (TLDCC), Faculty of Tropical Medicine, Mahidol University from November 2009 to September 2011 were retrieved and reviewed. Inclusion criteria were (a) clinical diagnosis of LE of the limb, (b) aged 18 or above, (c) no food allergy history, and (d) no medical diagnosis of metastasis of cancer. The study protocol was approved by the Ethical Review Committee for Research Involving Human Research Subjects, Health Sciences Group, Chulalongkorn University (code: 132.1/53). Patient informed consent was not required by the local ethics committee. Patient data privacy was ensured through a number coding system replacing patients' name.

Case and Control

Cellulitis was identified by history of hospital admission or antibiotic prescription or three clinical symptoms including increased swelling or tightness, erythema of lymphedematous tissue, and localized or systemic heat. During the study period, there were 1,456 patients diagnosed with LE, 426 of whom met all inclusion criteria. Subsequently, 179 patients with cellulitis history were identified as cases. An equal number of controls who were diagnosed with LE without cellulitis history were matched by gender and age (± 5 years). Cases and controls were defined at the point of the first TLDCC visit.

Data Collection

Data of each patient at the first visit were extracted and recorded in a case record form (CRF). Collected parameters were (a) patients' demographics: age, sex, body mass index (BMI), and history of skin allergy reported by patients (b) vital signs: systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate (HR), (c) concurrent diagnosis: hypertension and diabetes mellitus, (d) LE characteristics: diagnosis (primary or secondary LE), affected organ (upper or lower extremity), percentage difference in circumference of the limb, duration of LE and food induced complication experiences (FIE).

Thirteen covariates including overweight (BMI >25 kg/m^2), LE diagnosis, affected organ, bilateral LE, percentage difference in circumference of the limb (>20), duration of LE (>5 years), hypertension, diabetes mellitus, history of skin allergy, food induced complication experience (FIE), SBP (>130 mmHg), DBP (>85 mmHg) and HR (>70 beats per minute), were analyzed. The definition of FIE has been previously described elsewhere (8). Briefly, FIE history was identified only if patients were able to report undesired symptoms induced by food and type of causative food as well as its onset within 48 hours during the first consultation. In this study, FIE must occur only in the lymphedematous tissue.

Statistical Analysis

Statistical analysis was undertaken using statistical package software (SPSS version

TABLE 1
Characteristics of the Study Population

	Total (n=358)	Lymphedema Case (n=179)	Lymphedema Control (n=179)	p-value
Age (yrs; means ± SD)†	55.7±12.7	55.6±12.8	55.7±12.5	0.613
Male sex (n,%)	54 (15.1)	27 (15.1)	27 (15.1)	1.000
Body Mass Index (BMI, kg/m^2; means ± SD)†	28.2±7.5	29.1±8.5	27.1±6.5	0.005‡
Duration of LE (yrs; means ± SD)	5.6±7.1	7.2±7.9	4.1±5.7	<0.001‡
Percentage difference in circumference of the limb (n=124 pairs; means ± SD)	19.5±13.8	24.6±13.9	15.4±11.7	<0.001‡

†Paired t-test analysis for Case vs Control; ‡ $p < 0.05$ indicated statistically significant

16.0). Univariate and multivariate analyses were performed. Univariate analysis was performed to identify potential risk factors of the primary outcome. McNemar's χ^2 test was used to analyze 2x2 contingency tables. A p value of less than 0.25 was used to identify potential predictors for the multivariate model (17). Multivariate logistic regression with backward selection procedure was used to assess covariates that independently contributed to the risk of cellulitis in patients with LE. Adjusted odds ratios (AOR) with 95% confidential interval (CI) of the final model were presented. A p value of less than 0.05 was considered statistically significant. To describe overall accuracy of the model, the area under the receiver operating characteristics (ROC) curve was reported.

RESULTS

The mean (±SD) of age and BMI of the study population (n=358) were 55.7±12.7 years old and 28.2±7.5 kg/m^2, respectively. Males accounted for 15.1% (n=54). The BMI, duration of LE, and percentage difference in circumference of the limb were significantly higher in the cases than the controls. *Table 1* shows a summary of patients' characteristics.

Univariate analysis indicated overweight, primary LE diagnosis, LE of the lower limb, percentage difference in circumference > 20, duration of LE > 5 years, FIE, SBP > 130 mmHg and DBP > 85 mmHg were potential risk factors for cellulitis in LE. Suggested odds ratio and 95% CI are displayed in *Table 2*.

Table 3 presents the results of multivariate analysis. The following four parameters were identified as predictive factors for cellulitis in patients with LE; percentage difference in circumference of the limb (AOR 1.07, 95% CI 1.04-1.10), primary LE diagnosis (AOR=3.36, 95% CI=1.37-8.22), FIE (AOR=6.82, 95% CI= 2.82-16.51) and SBP (AOR=1.02, 95% CI=1.01-1.04). The area under the receiver operator characteristics curve (AUC) for final model was 0.80 (95% CI 0.75-0.85; p<0.001) demonstrating an excellent discrimination ability (17).

DISCUSSION

To our knowledge, this is the first case-controlled study exploring risk factors for cellulitis in patients with LE. In our study, hypertension, diabetes mellitus, body mass index, and duration of LE were not

TABLE 2
Univariable Analysis of the Potential Risk Factors (N=179 pairs)

	Lymphedema (LE) Case N (%)	Control N (%)	Odds ratio (95% CI)	p-value
Overweight (BMI >25 kg/m^2)	124 (69.2)	103 (57.5)	1.74 (1.10-2.80)	0.017‡
Primary Lymphedema Diagnosis	64 (35.7)	44 (24.6)	2.43 (1.27-4.90)	0.006‡
Lower extremity LE	123 (68.7)	95 (53.1)	2.56 (1.45-4.68)	<0.001‡
Bilateral LE	43 (24.0)	42 (23.5)	1.08 (0.46-2.60)	1.000
Percentage difference in circumference of the limb>20 (n=124 pairs)	76 (61.3)	32 (17.9)	5.0 (2.59-10.59)	<0.001‡
Duration of LE >5 years	71 (39.7)	34 (19.0)	2.61 (1.59-4.42)	<0.001‡
Hypertension	47 (26.3)	54 (30.2)	0.81 (0.48-1.35)	0.463
Diabetes Mellitus	22 (12.3)	28 (15.6)	0.73 (0.36-1.45)	0.417
History of skin allergy	21 (11.7)	31 (17.3)	0.58 (0.28-1.17)	0.144
Food induced complication experiences (FIE)	54 (30.2)	11 (6.1)	7.14 (3.22-18.67)	<0.001‡
Systolic blood pressure >130 mmHg	81 (45.2)	50 (27.9)	2.07 (1.31-3.34)	0.002‡
Diastolic blood pressure >85 mmHg	72 (40.2)	39 (21.8)	2.27 (1.41-3.75)	<0.001‡
Heart rate >70 bpm	123 (68.7)	130 (72.6)	0.80 (0.47-1.35)	0.449

‡ $p < 0.05$ indicated statistically significant

TABLE 3
Independent Predictors of Cellulitis in LE Using Logistic Regression

Variable	Adjusted OR	95% CI	p-value
Percentage difference in circumference of the limb	1.07	1.04-1.10	<0.001
Primary Lymphedema Diagnosis	3.36	1.37-8.22	0.008
Food induced complication experiences (FIE)	6.82	2.82-16.51	<0.001
Systolic blood pressure	1.02	1.01-1.04	0.004

associated with cellulitis. We demonstrated that four covariates: percentage difference in circumference of the limb, primary LE diagnosis, FIE, and systolic BP, were independent risk factors for cellulitis in this specific group of patients.

The risk factor with highest AOR was the FIE. Our previous studies also found that individual dietary habits had an association with various patterns of cutaneous manifestation including cellulitis in patients with lymphedema (8,18,19). In addition, our previous study demonstrated that the level of high sensitivity C-reactive protein (hsCRP) and high consumption of fat and meat were statistically significantly associated with episodes of cellulitis (8). Some other studies also reported benefit of dietary control toward LE treatment showing an improvement of diameter of the affected limb using restricted long-chain triglycerides, low-fat, and weight-reduction diets (20,21).

Primary LE diagnosis was another important risk factor for cellulitis. Patients with primary LE showed greater risk for cellulitis than those with secondary LE.

This finding was consistent with previous studies (22,23) which indicated an association between subcutaneous tissue inflammation and primary LE. Damstra et al performed lymphoscintigraphy in 40 patients and found that patients presenting with the first episode of erysipelas often have signs of pre-existing lymphatic impairment (22). Edema, leg edema, and overweight/obesity are common independent predictive factors found for cellulitis among the general population (9,10,12,24). Our study using univariate analysis suggested overweight and LE of the lower limb were potential risk factors for cellulitis. However, multivariate analysis failed to confirm these results. This may be due to the fact that leg edema, overweight/obesity, and primary LE were highly correlated. We believe that pre-existing lymphatic impairment is probably a true primary factor.

In this study, we did not observe any association between cellulitis, hypertension, or diabetes mellitus. Some previous studies have reported that diabetes mellitus was associated with cellulitis (13,25,26). A possible explanation is that in the general population cellulitis is more common and more severe in diabetic than non-diabetic patients because of delayed wound healing especially in the lower limbs resulting in a higher chance of skin and soft tissue infection. In LE, however, this might not be true as shown in more recent studies (8,27,28) and in a chronic LE, delayed wound healing is already a common condition for patients regardless of concurrent diabetes mellitus. Concerning hypertension, no association with cellulitis has been reported and only an association with LE has been suspected (29,30). We did not find any association between hypertension and cellulitis in this study. However, multivariate analysis suggested SBP as a significantly independent risk factor for cellulitis in patients with LE. A recent study by Machnik et al demonstrated that a high-salt diet as one cause of hypertension leads to interstitial hypertonic Na^+ accumulation in skin resulting in increased density and hyperplasia of the lymph capillary network (31). Alternatively, high-salt diet caused hypertension might up-regulate tonicity-responsive enhancer-binding protein and vascular endothelial growth factor signaling to compensate for elevated blood pressure by promoting lymphangiogenesis (32). Lymphangiogenesis was reported to be related to the inflammatory process, which is consistent with the anti-inflammatory role of transforming growth factor ß. Recent results revealed that TGF-ß signaling acts as a lymphangiogenesis inhibitor in the inflammatory setting (33,34). This information also supports our results on percentage difference in circumference of the limb, the last independent risk factor from our model. A damaged lymphatic network might result in greater accumulation of interstitial fluid as evidenced by higher percentage difference in circumference of the limb.

One major concern in the long term treatment of patients with LE is the prevention of subcutaneous tissue inflammation and its recurrence because of aggravation and exacerbation of the LE condition and associated physical disabilities (35,36). Only antibiotic prophylaxis is currently reported to be an effective prevention of its recurrence (37,38). Nevertheless, our study has confirmed that awareness in dietary habits by limiting fatty food and high meat consumption may result in decreased incidence of cellulitis among patients with LE. Controlling the percentage difference in circumference of the limb and systolic blood pressure could also help to reduce occurrence of cellulitis in this group of patients. Our case-controlled retrospective data suggest that dietary guidelines and home-based compression garment and bandaging should be implemented especially in the group of patients with primary LE to reduce the incidence of cellulitis. Whether these strategies alone are sufficient to prevent cellulitis episodes in patients with LE or if antibiotic prophylaxis is also required needs to be further investigated in prospective trials.

The presence of potential biases in recruitment of cases in our study needs to be considered when evaluating the results. Our center is highly specialized in LE treatment and therefore most patients who come to our center therefore are medically complicated and with frequent cases of cellulitis. Additionally, potential biases in the assessment of risk and information need to be considered. We attempted to minimize these biases by limiting our study to a single physician and trained staff using the same methods for each measurement.

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