Massive Localized Lymphedema: A Case-Control Study

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BACKGROUND: Massive localized lymphedema (MLL) is an area of skin and subcutaneous overgrowth associated with obesity. The purpose of this study was to determine whether MLL results from obesity-induced lymphedema (OIL) and to characterize the prevalence and risk factors for the condition.

STUDY DESIGN: Patients evaluated in our Lymphedema Program between 2009 and 2016 were reviewed for obese individuals (BMI $\geq$30 kg/m^2) who had lower-extremity lymphatic function evaluated by lymphoscintigraphy. Candidate variables included age, sex, BMI, duration of lymphedema, infection history, and lymphoscintigraphy findings. A possible association between candidate variables and presence of MLL was determined using multivariable logistic regression. Optimal cutoff for BMI in predicting MLL was identified by receiver operating characteristic curve analysis.

RESULTS: Eighty-two patients were included in the study population. In patients with MLL (n = 17), all had OIL and none had primary or secondary lymphedema (median BMI 66 kg/m^2; interquartile range 62 to 78). Massive localized lymphedema involved the thigh (n = 16; bilateral = 10, unilateral = 6), genitalia (n = 3), and suprapubic area (n = 2). Control patients without MLL (n = 65) had primary (46%), secondary (37%), or obesity-induced (17%) lymphatic dysfunction (median BMI 36 kg/m^2; interquartile range 32 to 45). Logistic regression indicated a significant relationship between BMI and MLL condition; patients with a BMI >56 kg/m^2 had a 213-times greater odds of MLL developing vs patients with BMI $\leq$56 kg/m^2 ($p < 0.0001$). Age, sex, duration of obesity, and infection history were not associated with development of MLL (all $p > 0.2$).

CONCLUSIONS: Massive localized lymphedema is a consequence of OIL and affects approximately 60% of obese patients with lower-extremity dysfunction; a BMI >56 kg/m^2 significantly increases the risk. Obese individuals should be referred to a bariatric weight-loss center before their BMI reaches a threshold for OIL and MLL to develop. (J Am Coll Surg 2017;224:212−216.

Massive localized lymphedema (MLL) is a region of soft-tissue overgrowth that occurs in obese patients.[1,2] The thighs are most commonly affected and the enlarged areas exhibit features of chronic lymphedema (eg thickened skin, lymphorrhea). Tissue hypertrophy can limit ambulation, cause infection, and make it difficult to fit into clothing. The mechanism for development of MLL is thought to be due to localized obstruction of lymphatic drainage by excessive skin and subcutaneous tissue.[2] We have shown that massive obesity can cause lower-extremity lymphatic dysfunction, termed *obesity-induced lymphedema* (OIL).[3,4] The purpose of this study was to test our hypothesis that MLL occurs secondary to OIL, and to determine the prevalence and risk factors for the condition.

METHODS

Obese patients (BMI $\geq$ 30 kg/m^2) referred to our Lymphedema Program with lymphedema between 2009 and

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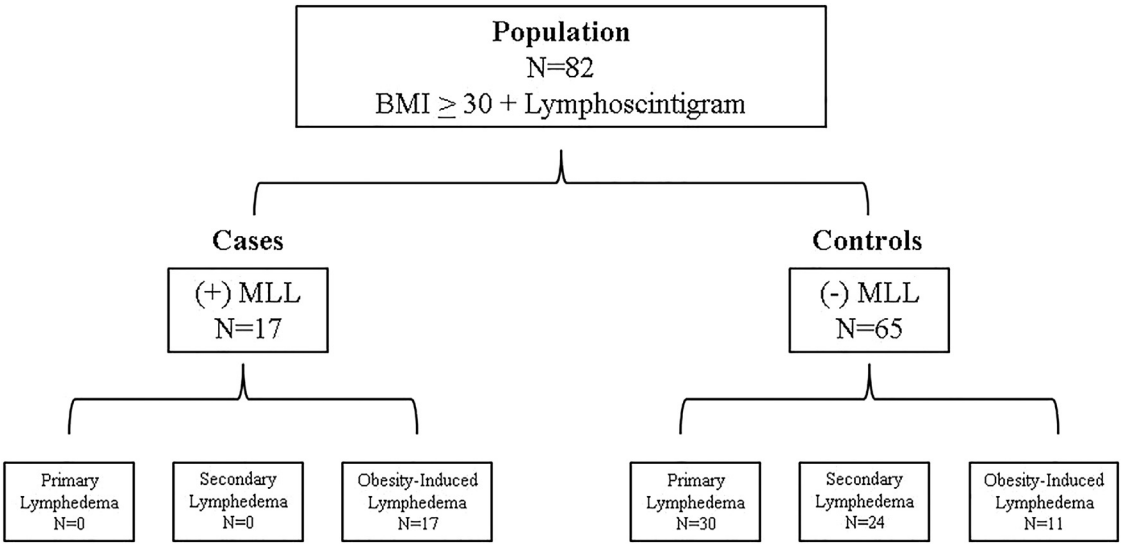

Figure 1. Case-control study design. MLL, massive localized lymphedema.

2016 were studied. All individuals underwent lymphoscintigraphy to assess their lower-extremity lymphatic function. A case-control study was performed to evaluate patients with and without MLL. Candidate variables included age, sex, BMI, type of lymphedema, duration of disease, and infection history.

Patients and controls were compared using Student's *t*-test for age, duration of obesity, and BMI; Fisher's exact test was used for the presence of MLL. Logistic regression was applied to assess the relationship between BMI and MLL among the cases with the likelihood ratio test to determine the significance of BMI as a predictor for MLL.[5] Multivariable logistic modeling was used to test whether candidate variables influenced development of MLL.[6] Receiver operating characteristic curve analysis with the Youden J-index was used to identify the optimal BMI cutoff value for predicting MLL. Logistic regression with the Wald test then was used based on the BMI cutoff for estimating the odds of MLL and 95% CI.[7] Two-tailed values of $p < 0.05$ were considered significant. Statistical analysis was performed using the IBM SPSS software, version 23.0 (IBM Corp).

RESULTS

Eighty-two patients met inclusion criteria (Fig. 1). Patients with MLL (n = 17) and controls (n = 65) both exhibited lymphatic dysfunction; however, patients with MLL had a significantly higher BMI (median BMI 66 kg/m^2; interquartile range 62 to 78) compared with controls without MLL (median BMI 36 kg/m^2; interquartile range 32 to 45; $p < 0.0001$) (Table 1). All patients with MLL had OIL compared with 17% of patients in the control group (Fig. 2). Massive localized lymphedema involved the thigh (n = 16; bilateral = 10, unilateral = 6), genitalia (n = 3), and suprapubic (n = 2) areas. The relationship between MLL and BMI was strongly correlated (likelihood ratio test = 40.96; $p < 0.0001$): the probability of MLL developing was 4% with BMI 40 kg/m^2, 15% with BMI 50 kg/m^2, 40% with BMI 60 kg/m^2, 75% with BMI 70 kg/m^2, and 92% with BMI 80 kg/m^2 (Fig. 3).

Obesity-induced lymphedema patients with a BMI >56 kg/m^2 had 213 times greater odds of MLL developing vs patients with a BMI ≤56 kg/m^2 (95% CI, 17.7−2566; $p < 0.0001$). The BMI cutoff of 56 kg/m^2 demonstrated a sensitivity of 94% (16 of 17 patients

Table 1. Demographic Characteristics of Patients with Massive Localized Lymphedema and Controls

Variable	Patients with massive localized lymphedema (n = 17)	Controls (n = 65)	p Value
Age, y, median (IQR)	61 (48−67)	55 (34−65)	0.217
Female sex, n (%)	9 (53)	45 (69)	0.255
Duration of symptoms, y, median (IQR)	11 (4−20)	6 (3−17)	0.297
BMI, kg/m^2, median (IQR)	66 (62−78)	36 (32−45)	<0.0001*
BMI cutoff >56 kg/m^2, n (%)	16 (94)	5 (8)	<0.0001*

BMI cutoff was determined by receiver operating characteristic analysis, yielding a sensitivity of 94% and a specificity of 92%.
*Statistically significant.
IQR, interquartile range.