The diagnostic unreliability of classic physical signs of lymphedema

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ABSTRACT

Objective: In most communities, the diagnosis of lymphedema in the lower extremity currently rests on clinical signs. Lymphoscintigraphy, which is objective, is performed infrequently to confirm the clinical suspicion. Given absence of a curative option for lymphedema, it is essential to obtain an accurate diagnosis before committing the patient to lifelong conservative therapy. The aim of this study was to evaluate the diagnostic accuracy of clinical signs in comparison to lymphoscintigraphy, the current objective standard.

Methods: Retrospective review of contemporaneously collected data of 636 consecutive limbs with swelling (318 left, 318 right) that underwent initial evaluation during a 12-month period between 2016 and 2017 was performed. All limbs were assessed for classic clinical signs of lymphedema including dorsal hump of the foot, square toes, Kaposi-Stemmer sign, and nonpitting edema. Lymphoscintigraphy was routinely performed for objective evaluation. The 436 patients who underwent the study were scored positive for lymphedema on the basis of transit time delay for the radioisotope in minutes, presence of dermal backflow, presence of collateral channels, intensity of uptake in the main channel and lymph nodes, number of nodes in the groin, and presence of popliteal nodes. Analysis was carried out to determine sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of the clinical signs in determining whether a patient had lymphedema. In addition, regression analysis was carried out to evaluate the predictive value of different clinical signs in determining lymphedema. Patients with positive clinical signs but with normal findings on lymphoscintigraphy who did not have a medical cause for swelling underwent workup to determine a possible venous cause.

Results: Of 636 limbs with swelling, 436 (69%) underwent lymphoscintigraphy, the findings of which were normal in 178 (41%) and abnormal in 258 (59%). Of the 636 swollen limbs, 96 (15%) had clinical signs of lymphedema; 95% had dorsal hump, 37% had square toes, 32% had presence of Kaposi-Stemmer sign, and 12% had nonpitting edema. Of these 96, lymphoscintigraphy was performed on 66 (69%); 45 of 66 (68%) patients with clinical signs were positive for lymphedema; the remaining 32% were normal. Conversely, among 258 swollen limbs with abnormal findings on lymphoscintigraphy, only 45 (17%) had one or more of the clinical signs. Sensitivity and specificity of clinical signs in predicting lymphoscintigraphy-confirmed lymphedema were 17% and 88%, respectively. Overall accuracy was 47%. Of the clinical signs, only the Kaposi-Stemmer sign was a significant predictor of lymphedema (odds ratio, 7.9; $P = .02$). In patients with positive clinical signs but normal findings on lymphoscintigraphy, venous obstruction was the most common cause of swelling.

Conclusions: Clinical signs of lymphedema appear to be unreliable in making a correct diagnosis of lymphedema in one-third of patients. Conversely, in lymphoscintigraphy-confirmed lymphedema, only 17% had positive clinical signs. Of the clinical signs, only Kaposi-Stemmer sign has some predictability in determining lymphoscintigraphy-confirmed lymphedema. Venous obstruction is the most common cause of clinical signs in patients without lymphedema. Routine use of lymphoscintigraphy is recommended in patients to make an objective diagnosis of lymphedema. (J Vasc Surg: Venous and Lym Dis 2019;7:890-7.)

Keywords: Lymphedema; Phlebolymphedema; Lymphoscintigram; Secondary lymphedema

Solutes, proteins, and water continuously pass on from the capillaries into the interstitial space to form interstitial fluid. This fluid is then collected by first-division lymphatic plexuses called collectors that unite to form afferent lymphatic trunks.[1,2] These afferent trunks are able to pump the fluid, now termed lymph, into nodal tissue by virtue of the smooth muscles present in their wall.[1,2] Within the lymph nodes, absorption is carried out primarily of water, to the extent that the concentration of protein in the efferent lymphatic channels is almost twice as much as in the afferent lymphatics.[3] Total afferent lymph fluid production is 4 to 8 L/d.[4,5] It takes about 9 to 18 hours for the plasma volume to circulate through the interstitial compartments and lymphatic

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systems.[6] This rapid circulation results in prompt development of lymphedema after obstruction of the lymphatic system. The diagnosis of lymphedema is often made clinically without any radiologic or nuclear medicine adjuncts. Clinical signs classically used to make a diagnosis of lymphedema include dorsal hump of the foot, square toes, Kaposi-Stemmer sign, and nonpitting edema (Figs 1 and 2).[7] The accuracy of such clinical signs compared with the current standard, lymphoscintigraphy, has not been determined. In addition, lymphedema can be due to secondary causes, including chronic venous insufficiency. Data suggest that such lymphedema is more common than primary lymphedema in the lower extremity in Western societies.[8,9] Venous edema can also mimic lymphedema. These aspects highlight the importance of an accurate diagnosis of lymphedema and exploration of alternative causes when necessary. This study evaluated the diagnostic reliability of "classic" clinical signs by comparing them with lymphoscintigraphy through retrospective review of contemporaneously collected data.

ARTICLE HIGHLIGHTS

- **Type of Research:** Single-center retrospective analysis of prospectively collected data
- **Key Findings:** Data of 436 consecutive limbs with swelling that underwent lymphoscintigraphy revealed that clinical signs of lymphedema are unreliable in making the correct diagnosis in one-third of the patients. Venous obstruction was the most common cause of swelling in patients without lymphedema.
- **Take Home Message:** Routine lymphoscintigraphy is recommended for diagnosis of lymphedema.

METHODS

Review of contemporaneously entered electronic medical record data of 636 consecutive lower limbs with swelling during a 12-month period (2016-2017) was performed. The presence or absence of classic clinical signs recorded for all patients during the study period was examined. The signs were recorded by nurse practitioners or physicians well versed in making such identification. These signs included dorsal hump of the foot, square toes, Kaposi-Stemmer sign, and nonpitting edema (Fig 1). Lymphoscintigraphy was performed in all limbs except in those patients who refused, had allergy to the isotope binder, or could not obtain insurance approval for the study. A total of 436 patients underwent the study. Evaluation of lymphoscintigraphy results reported by a radiologist blinded to the clinical status of the patient was performed. Patients with positive clinical signs but with normal findings on lymphoscintigraphy who did not have a systemic disorder as a cause of limb swelling underwent venous workup to determine a possible venous cause.

Patients' consent for the study and approval from the Institutional Review Board of the hospital were obtained.

Lymphoscintigraphy. Lymphoscintigraphy was routinely performed for objective evaluation using the technique described previously.[8,10] It involved injecting ~600 μCi of technetium Tc 99m-labeled sulfur colloid (filtered) intradermally by a 27-gauge needle or tuberculin syringe between the first and second toes and asking the patient to ambulate for 15 minutes. If this was not possible, the feet were massaged for the same duration. A gamma camera with a large field of view, the

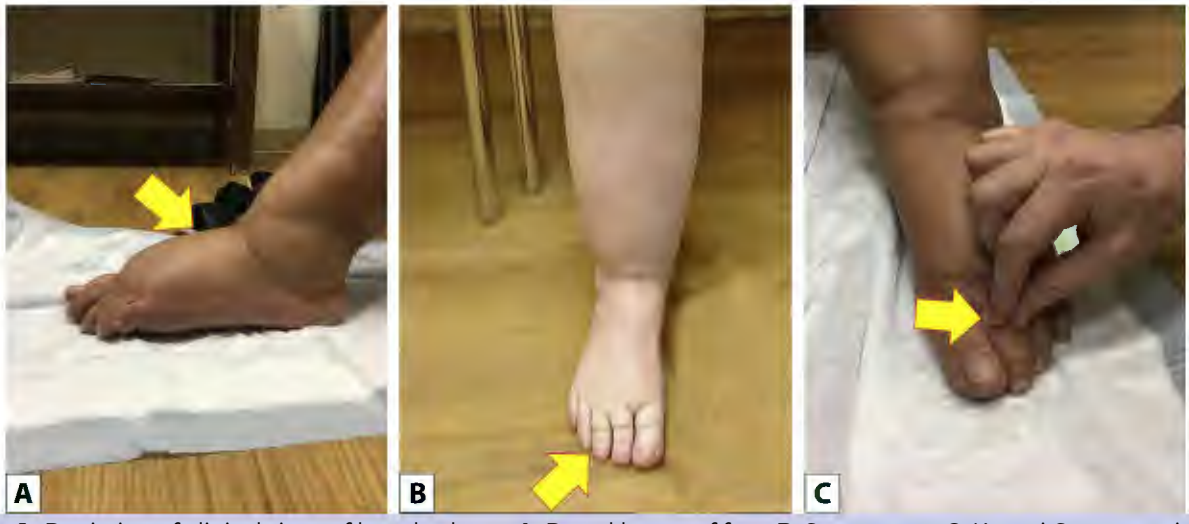

Fig 1. Depiction of clinical signs of lymphedema. **A,** Dorsal hump of foot. **B,** Square toes. **C,** Kaposi-Stemmer sign.

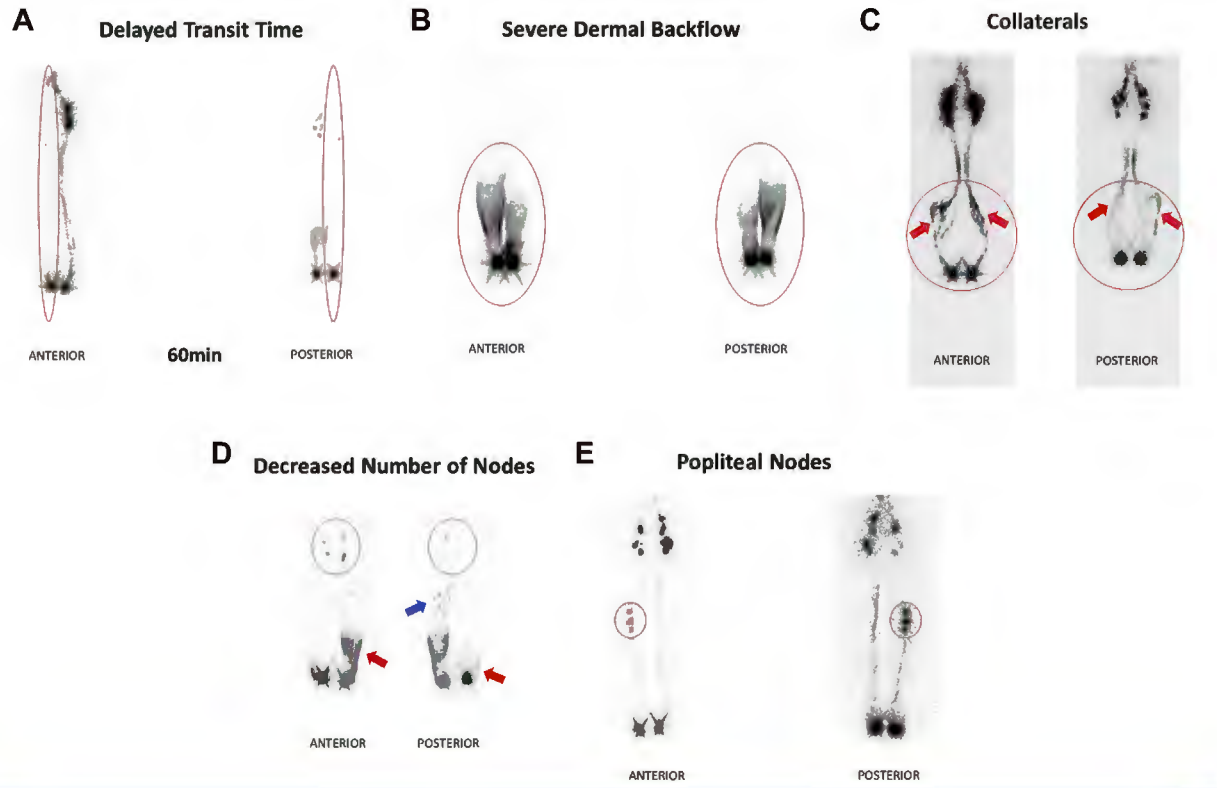

Fig 2. Lymphoscintigraphy findings diagnostic of lymphedema. **A,** Delayed transit time. Lymphoscintigraphy revealing delayed transit on the right side. Even at 60 minutes, there is no filling of the lymphatic channels and nodes on the right. **B,** Dermal backflow. Lymphoscintigraphy depicting severe dermal backflow on both sides. **C,** Presence of collaterals. Lymphoscintigraphy revealing presence of bilateral collateral channels of lymphatic drainage below the knee (*red arrows within circles*). **D,** Decreased number of lymph nodes visualized. Lymphoscintigraphy demonstrating bilaterally reduced number of inguinal lymph nodes with uptake (*circles*) and dermal backflow more severe on the left (*red arrow*). Popliteal nodes can also be seen on the left side (*blue arrow*). **E,** Visualization of popliteal lymph nodes. Lymphoscintigraphy demonstrating popliteal nodes on the right side (*in circle*).

collimator setting on low energy, high resolution and a parallel hole, with 20% energy window centered at 140 keV was used to obtain imaging. With the patient in a supine position, anterior and posterior scans were obtained from the waist to the toes at 20 minutes using a scan speed of 8 cm/s. If the pelvis or legs were too large for the imaging field of view, static views were obtained. If there was delay in uptake of the radiotracer, repeated images were obtained at 40 and 60 minutes. The images were saved on dual-intensity whole body display with and without the masking of injection sites.

Interpretation of lymphoscintigram. The lymphoscintigram was scored by a radiologist blinded to the patient's clinical picture. A combination of visual interpretation and semiquantitative analysis was used to evaluate the lymphoscintigram. This represents an adaptation of the Mayo Clinic transport index originally derived from the scoring system reported by Kleinhans et al.[11-13] The parameters used to qualify a lymphoscintigram as being positive for lymphedema were the transit time delay in minutes, the presence of dermal backflow, the presence of collateral channels, the intensity of radioisotope uptake in the main channel and lymph nodes, the number of nodes in the groin, and the presence of popliteal nodes (Fig 2). The transit time was graded as being normal if the time required for the radioisotope to show up in the groin nodes was <20 minutes. If it was >20 minutes, the scan was graded mild lymphedema for a delay of 20 to 40 minutes, moderate lymphedema for a delay between 40 and 60 minutes, and severe lymphedema for a delay >60 minutes. This represented the semiquantitative aspect of the grading system. The rest of the parameters were qualitatively scored in a binary fashion as being present or not. Five or more nodes was used as the cutoff for the number of nodes parameter. Presence of one or more positive parameters constitutes a diagnosis of lymphedema based on lymphoscintigraphy. A time delay >60 minutes and presence of dermal backflow were considered indicators for severe lymphedema.

Statistical analysis. All statistical analysis was performed using SPSS statistics version 24 software (IBM Corp, Armonk, NY). Analysis was carried out to determine

Table I. A 2×2 contingency table for diagnostic testing analysis

	Lymphoscintigraphy		Total
Clinical signs	+	−	
+	45	21	66
−	213	157	370
Total	258	178	436

Table II. Results of diagnostic testing of clinical signs of lymphedema vs lymphoscintigraphy

Variable	%
Sensitivity	17
Specificity	88
Positive predictive value	68
Negative predictive value	43
Accuracy	47

sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of the clinical signs in determining whether a patient had lymphedema. In addition, multivariable logistic regression was used to evaluate the ability of four variables—dorsal hump of the foot, square toes, Kaposi-Stemmer sign, and nonpitting edema—to predict a positive lymphoscintigram. Correlation of lymphoscintigraphy findings (positive or negative) between individual lower limbs in the same patient was also evaluated using Spearman correlation. P value $< .05$ was considered significant.

RESULTS

Of 636 limbs with swelling, 436 (69%) underwent lymphoscintigraphy, the findings of which were normal in 178 (41%) and abnormal in 258 (59%). No complications were noted from the test. Of the 636 swollen limbs, 96 (15%) had clinical signs of lymphedema (95% dorsal hump, 37% square toes, 12% nonpitting edema, and 32% Kaposi-Stemmer sign). Of these 96 limbs, lymphoscintigraphy was performed on 66 (69%); 45 of 66 (68%) were positive for lymphedema and the remainder were normal. Conversely, among 258 swollen limbs with abnormal lymphoscintigraphy findings, only 45 (17%) had at least one clinical sign. Correlation of lymphoscintigraphy findings (positive or negative) between individual lower limbs in the same patient was found to be low (Spearman correlation, 0.3; $P < .01$).

Diagnostic testing analysis. Sensitivity of clinical signs in predicting lymphedema was 17%, specificity was 88%, positive predictive value was 68%, and negative predictive value was 43%. Overall accuracy was 47% (Tables I and II).

Predictability of classic clinical signs for lymphedema. Multivariable logistic regression analysis revealed that of dorsal hump of the foot, square toes, Kaposi-Stemmer sign, and nonpitting edema, only Kaposi-Stemmer sign was a statistically significant independent predictor of a positive lymphoscintigraphy result with an odds ratio of 7.9 ($P = .02$; Table III).

Classic clinical signs of lymphedema due to alternative cause. Of the 66 limbs (32%) with classic clinical signs of lymphedema, 21 had normal findings on lymphoscintigraphy. The most common cause of such mimicking was deep venous obstruction (76% [16/21]). The alternative causes are listed in Table IV.

DISCUSSION

Clinical signs of lymphedema. Swelling is one of the defining features of lymphedema. Although it is pitting in the early stages, the edema becomes nonpitting as the condition progresses. Other features noted in lymphedema are the slow reduction of swelling with elevation and the lack of response to diuretics.[7] Skin changes noted and generally accepted as classic include dorsal hump of the foot, Kaposi-Stemmer sign, square toes, and nonpitting edema.[7] Whereas dorsal hump of the foot arises from swelling, the Kaposi-Stemmer sign—the inability to pinch the skin at the base of the second toe—arises because of the thickening of the skin.[14] This sign has been reported to be a highly specific but not very sensitive sign.[7] Square toes result from the combination of swelling, skin thickening, and compressive effect of the adjacent toes and have been considered diagnostic of lymphedema.[15] Other signs include horny, scaly skin due to hyperkeratosis and warty appearance of the skin. Nonpitting edema is believed to arise from marked tissue fibrosis and thickening.[15] Papillomatosis and elephantiasis arise because of the progressive dilation of the dermal lymphatics and worsening fibrosis.[15]

Diagnostic testing for lymphedema. Nuclear medical, radiologic, and near-infrared fluorescence studies exist to make a diagnosis of lymphedema. Whereas lymphoscintigraphy and lymphangiography fall in the nuclear medicine category, magnetic resonance and computed tomography lymphangiography and duplex ultrasound fall within the purview of radiologic imaging. Near-infrared fluorescence represents a newer modality to define lymphatic function and anatomy using fluorescent contrast agents.[16] Lymphoscintigraphy has been in use for more than three decades, with multiple studies reporting sensitivity and specificity often exceeding 90%.[9,11,12,17] The study is minimally invasive and has few drawbacks.[9,12,18] The role of this study beyond making a diagnosis and assisting with surgical planning has also been reported, although it cannot be used to confirm patency of lymphatic bypasses.[11,13,19] Quantitative evaluation of the nuclear isotope uptake has been found to be

Table III. Results of multivariable logistic regression: Odds of positive lymphoscintigraphy result with each clinical sign of lymphedema

Variable	Odds ratio	CI		*P*
		Upper limit	Lower limit	
Dorsal hump	1.21	0.58	2.52	.61
Square toes	0.64	0.18	2.35	.62
Kaposi-Stemmer sign	7.88	1.34	46.26	.02
Nonpitting edema	0.99	0.23	4.32	.99

CI, Confidence interval.

unreliable, and so either visual interpretation or a semiquantitative evaluation of the findings or a combination of the two (as used in this study) is usually used.[7,9,13] Whereas historically lymphangiography had an important role to play in the diagnosis of lymphedema, multiple limitations including the risk of embolization, infection, and lymphatic damage have restricted the role of this study. Currently, its use is limited to diagnosis of thoracic, abdominal, and pelvic lymphatic disease, including fistulas.[11] With regard to the use of magnetic resonance, computed tomography, and infrared technology, further study is required to define diagnostic parameters and to enable more widespread use. In such a setting, the best diagnostic modality currently available to confirm the diagnosis of lymphedema is lymphoscintigraphy.

Poor predictive value of classic clinical signs. The role of the classic clinical signs of lymphedema in diagnosis of lymphedema has previously not been explored. Many practices use the presence of such signs to make a clinical diagnosis of lymphedema and subsequently to prescribe treatment. Our study highlights the shortcomings of such an approach. Of patients who presented with positive clinical signs, more than one-third did not have lymphoscintigraphy-confirmed lymphedema. In addition, only 17% of patients with lymphoscintigraphy-confirmed lymphedema have the classic clinical signs, underscoring the importance of diagnostic testing to confirm the diagnosis of lymphedema. Sensitivity of the clinical signs for diagnosis of lymphedema was low at 17%. Specificity was better at 88%. The shortcomings of the use of clinical signs in making a diagnosis of lymphedema are probably best highlighted by the positive and negative predictive values of 68% and 43%, respectively. Overall, the accuracy of 47% underscores the difficulty in depending on a clinical diagnosis of lymphedema. Multivariable regression analysis carried out in terms of the ability of the classic clinical signs to predict a positive lymphoscintigram revealed that only the Kaposi-Stemmer sign was a statistically significant independent predictor of a positive scan with an odds ratio of 7.9 ($P = .02$; Table III). Patients with this sign are almost eight times as likely to have a positive lymphoscintigraphy result than if they did not have the sign. This is in line with what has been previously reported in the literature.[7] These results highlight the importance of using objective testing to confirm diagnosis of lymphedema.

Secondary venous lymphedema (phlebolymphedema). Up to 30% of patients with chronic venous insufficiency as outlined previously have concomitant lymphedema.[8,11,20,21] Such lymphedema might be the most common form of secondary lymphedema in Western populations, given the relative absence of infectious disease like filariasis in these societies. In our study, the incidence of phlebolymphedema was 30% (64/213). The importance of defining such coexisting disease cannot be underscored enough, given the possibility of benefit in such patients by correction of the venous disease—obstruction and reflux.[8,10] However, up to 27% of such patients might not have symptom relief even after the correction of venous obstruction.[10] A realistic discussion with the patient regarding outcomes is essential before the correction of venous obstruction. With the correction of obstructive venous disease in patients with phlebolymphedema, up to 25% may have normalization of the lymphoscintigram (Fig 3).[8] The algorithm used in our practice is depicted in Fig 4. The mechanism of secondary lymphedema in patients with venous disease is not clearly understood. The possibility of an overload effect that contributes to an abnormality on scanning that resolves when the venous disease is corrected is appealing. With time, permanent damage to the lymphatics results, leading to irreversibility.[10,13] Damage to the precollector system secondary to inflammation at the microvascular level has also been put forth as a mechanism.[22-24]

Table IV. Alternative causes of leg swelling in patients with clinical signs of lymphedema but with normal findings on lymphoscintigraphy

Alternative causes of leg swelling	No.(%)
Venous	16 (76)
Renal	2 (10)
Endocrine	1 (4)
More than one cause	2 (10)
Total	21 (100)

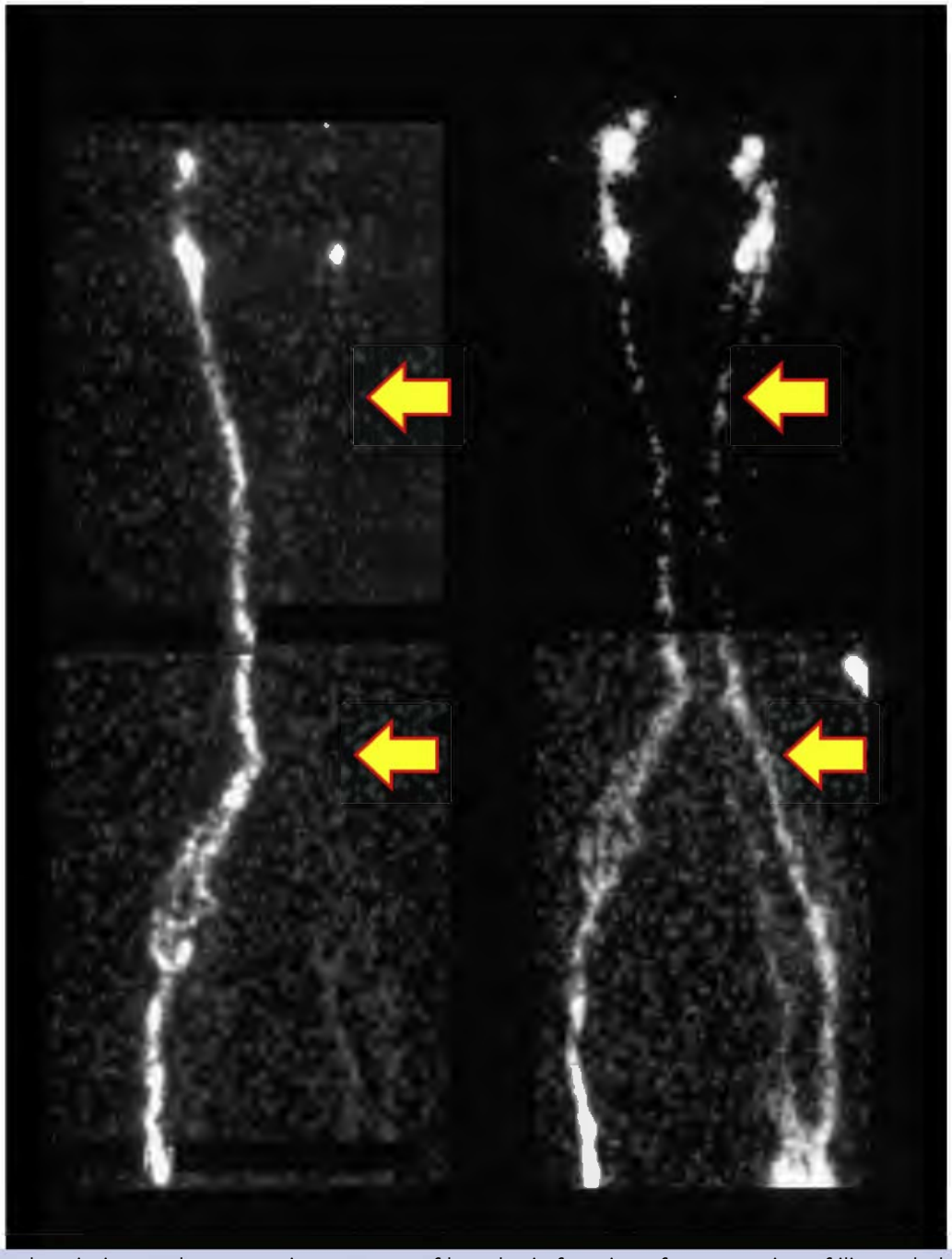

Fig 3. Lymphoscintigram demonstrating recovery of lymphatic function after correction of iliocaval obstruction. Uptake in the lymphatic channels and lymph nodes not seen on the *left* is now seen on the *right*.

Classic clinical signs of lymphedema can be generated by alternative causes. Whereas secondary lymphedema can coexist with venous disease, it is also possible, in our experience, for other forms of edema to mimic lymphedema. Such patients can present with the classic clinical signs of lymphedema but have a normal lymphoscintigram (Fig 5). In our study, the incidence of such mimicking was approximately 32%, with a venous cause being the most common. This highlights the importance of careful venous testing in such patients to identify correctable culprit disease.

This study has the shortcomings that come with being a retrospective review of contemporaneously obtained data. Lymphoscintigraphy could be performed in only 69% of patients with clinical signs and in a similar percentage of patients with swelling. In addition, the sensitivity and specificity of lymphoscintigraphy are in the 90% to 100% range, raising the small possibility of false-negative

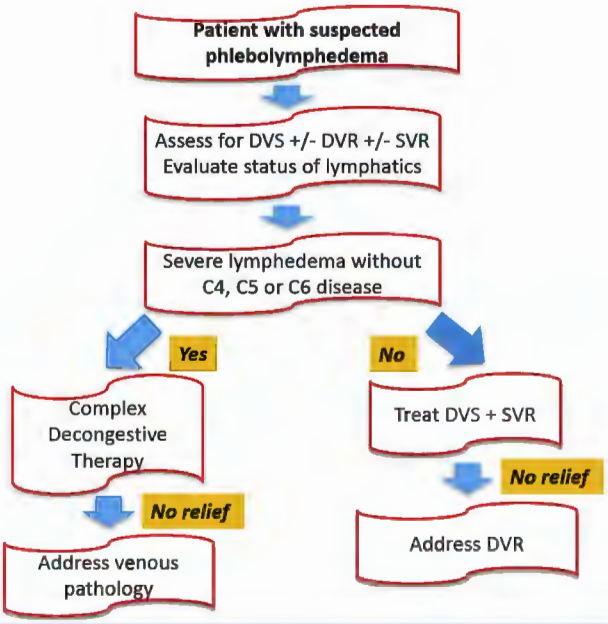

Fig 4. Algorithm for management of a patient presenting with phlebolymphedema. *DVR,* Deep venous reflux; *DVS,* deep venous stenosis; *SVR,* superficial venous reflux.

scans.[11,12,17] Whereas these drawbacks can affect the results, they represent common problems encountered in clinical research. This study's findings that almost one-third of patients with clinical signs of lymphedema do not have lymphoscintigraphy-confirmed lymphedema and that only 17% of patients with lymphoscintigraphy-confirmed lymphedema have the classic clinical signs will, it is hoped, encourage further research in the process, shedding more light on this important topic. Another aspect to be considered is that although lymphoscintigraphy is minimally invasive, there are still concerns for infection, local reactions, allergy to the isotope, and pain associated with the procedure. However, given the importance of establishing an accurate diagnosis of lymphedema, we think that such diagnostic testing is necessary before counseling treatment of lymphedema. It is possible that in the future, such invasive testing will be replaced by noninvasive techniques for diagnosis of lymphedema.

CONCLUSIONS

Clinical signs of lymphedema appear to be unreliable in making a correct diagnosis of lymphedema in one-third of patients. Conversely, in lymphoscintigraphy-confirmed lymphedema, only 17% had positive clinical signs. Of the clinical signs, only Kaposi-Stemmer sign has some predictability in determining lymphoscintigraphy-confirmed lymphedema. Venous obstruction is the most common cause of clinical signs in patients without lymphedema. Routine use of lymphoscintigraphy is recommended in patients to make an objective diagnosis of lymphedema.

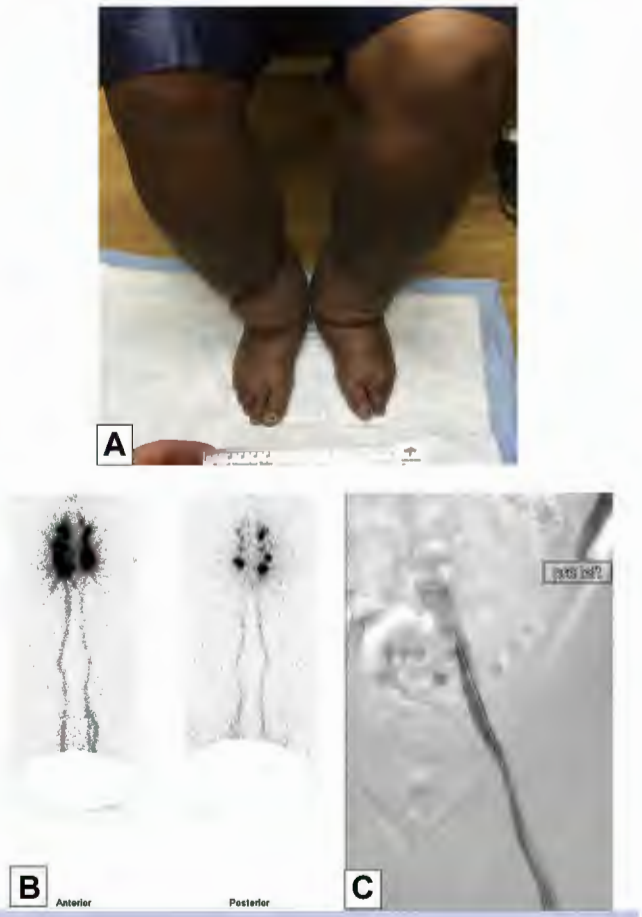

Fig 5. Unreliability of clinical signs of lymphedema. **A,** Mimicry of clinical signs of lymphedema with venous disease. **B,** Normal lymphoscintigram. **C,** Femoroiliocaval obstruction noted on venogram.

AUTHOR CONTRIBUTIONS

Conception and design: AJ, SR
Analysis and interpretation: AJ, SR, CM, NP
Data collection: AJ, CM, NP
Writing the article: AJ, SR, CM, NP
Critical revision of the article: AJ, SR
Final approval of the article: AJ, SR, CM, NP
Statistical analysis: AJ, NP
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Overall responsibility: AJ

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