Original Article

Skin and Subcutaneous Tissue Ultrasonography Features in Breast Cancer-Related Lymphedema

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Objective: To investigate skin, subepidermal low echogenic band (SELEB), and subcutaneous tissue (SCT) thickness as well as the degree of increase in subcutaneous echogenicity (SEG) and subcutaneous echo-free space (SEFS) in arms with lymphedema (LE).

Materials and Methods: The skin and SCT of both arms of 30 patients with unilateral stage II breast cancer-related LE were scanned at five points (medial/lateral upper arm/forearm and dorsum of the hand). SEG and SEFS grades were determined according to severity (range: 0–2).

Results: All measured parameters, except the SEFS in the medial upper arm, were significantly higher on the LE side than on the normal (N) side. The parameters differed most remarkably in the medial forearm (MFA; skin: LE 1.7 ± 0.8 mm vs. N 0.8 ± 0.2 mm; SELEB: LE 1.0 ± 0.6 mm vs. N 0.3 ± 0.1 mm; SCT: LE 8.7 ± 3.4 mm vs. N 3.8 ± 2.0 mm; SEG: LE 0.9 ± 0.5 vs. N 0.1 ± 0.3; and SEFS: LE 0.5 ± 0.7 vs. N 0).

Conclusion: The differences in the thickness of the skin, SELEB, and SCT and the SEG and SEFS grades between the LE and N arms seemed most evident in the MFA.

Keywords: ultrasonography, arm, lymphedema

Introduction

We have previously reported that skin and subcutaneous tissue (SCT) ultrasonography helps to diagnose, determine the severity of, and evaluate the treatment effects in leg lymphedema (LE).1–3) Although some authors have reported skin and SCT thicknesses determined using ultrasonography in patients with breast cancer-related LE (BCRL),4–8) the number of available studies that have conducted qualitative assessments is limited.9,10) Therefore, we aimed to study the skin and SCT ultrasonography findings of patients with BCRL.

Patients and Methods

This retrospective study was approved by the Institutional Review Board of Yamaguchi University Hospital (Ube, Yamaguchi, Japan), and the need for individual patient consent was waived. In this study, we reviewed the skin and SCT ultrasonography findings of 30 women with unilateral BCRL who visited our clinic between June 2015 and May 2016. The patients’ characteristics are summarized in Table 1. Only patients with stage II LE defined by the International Society of Lymphology11) were included in this study because no patients with stage III LE visited during the study period and because stage I LE was difficult to differentiate from arm edema of other causes. The patients who had known systemic edemagenic conditions (e.g., cardiac/hepatic/renal failure, terminal cancer, on chemotherapy), and/or with cancer recurrence were excluded. At the time of the visit, each patient underwent a skin and SCT scan using an ultrasound system (LOGIQ S6; GE Healthcare, Little Chalfont, Buckinghamshire, UK) with a 7- to 12-MHz linear transducer. All the images were acquired between 11:00 a.m. and 03:00 p.m. by a single examiner (K.N.). The points of scanning were as follows:

- Medial upper arm (MUA): from the medial side of the upper arm to the biceps brachii muscle;
- Lateral upper arm (LUA): from the lateral side of the upper arm to the biceps brachii muscle;
- Medial forearm (MFA): from the medial side of the forearm to the brachioradial muscle;
- Lateral forearm (LFA): from the lateral side of the forearm to the brachioradial muscle; and
- Dorsum of the hand (DH): on the first dorsal interosseous muscle of the hand.

The probe was placed longitudinally on the arm. The size and gain were adjusted as necessary to optimize image.
quality and boundary definition. In particular, when subcutaneous echogenicity (SEG) was evaluated, the B-mode gain was adjusted so that the subepidermal low echogenic band (SELEB) clearly appeared black, or otherwise normal subcutaneous fat in parts of the body other than the arms appeared black. The thickness of each structure was defined as follows (Fig. 1):

- Skin: the distance between the posterior echogenic border of the epidermal entrance echo and the posterior echogenic border of the dermis (because an epidermal entrance echo does not reflect the true thickness of the epidermis);
- SELEB: the distance between the anterior and posterior echogenic borders of SELEB; and
- SCT: the distance between the posterior echogenic border of the dermis and the anterior echogenic border of the deep muscular fascia.

Since the borders of these structures were irregular and were not always located parallel to the epidermal surface, the distances were measured at three points (right, middle, and left) of each acquired image and averaged (Fig. 1). The ratio of increase in the thickness of each structure in the LE arm compared to that in the contralateral normal arm was calculated as shown below:

\[
\text{Increase ratio} = \frac{\text{thickness in the LE side} - \text{thickness in the normal side}}{\text{thickness in the normal side}}.
\]

When the border of the papillary dermis and SCT (dermo-hypodermal junction [DHJ]) was severely blurred, the skin and SCT thickness could not be measured. The SEG and subcutaneous echo-free space (SEFS) were graded as we previously reported.\(^3,12\)

**SEG grade**

Grade 0: No or little increase in echogenicity in the subcutaneous layer. Horizontal or obliquely oriented echogenic lines caused by connective tissue bundles are clearly observed.

Grade 1: Diffuse and monotonous increases in echogenicity in the subcutaneous layer. Echogenic lines are unclear but identifiable.

Grade 2: Diffuse increases in echogenicity. Echogenic lines are not identifiable.

**SEFS grade**

Grade 0: No SEFS.

Grade 1: Horizontally oriented (<45 degrees to the skin) SEFS only.

Grade 2: Presence of vertically oriented (≥45 degrees to the skin) SEFS bridging the horizontally oriented SEFSs.

Ultrasonography images were analyzed by a single interpreter (K.S.).

**Statistical analysis**

The results are expressed as mean ± standard deviation or count, unless otherwise indicated. In order to test the differences in the thickness of structures between the normal and LE arms, the Mann–Whitney U test was used. In order to test the differences in SEG and SEFS grades, the Chi-square test was used. Statistical analyses were performed using JMP 11.0 (SAS Institute, Cary, NC, USA). A p value <0.05 was considered significant.

**Results**

Representative skin and SCT ultrasonography images are shown in Fig. 2. The measurements and grading are summarized in Table 2. In all scan points, the skin, SELEB, and SCT thicknesses increased in the LE arms than in the normal arms. Measurement of skin and SCT thickness could not be performed because of blurring of the DHJ in only 8 (MUA, 2; MFA, 2; LFA, 3; and DH, 1) out of the 150 images (5%). The SEG and SEFS grades increased in all scan points except the SEFS in the MUA. SEFS was not observed in 15 LE arms (50%), while an increase in SEG was confirmed in all LE arms. An increase in SEG/SEFS grades according to gravity, that is, higher SEG/SEFS grades in the forearm than in the upper arm, could not be confirmed.

**Discussion**

In the current study, we reported the measurements of skin, SELEB, and SCT thicknesses and SEG/SEFS grades in patients with stage II BCRL.

The measured distance of the skin was similar to that in previous reports, which used a 20-MHz transducer.\(^5\) Compared to our SCT measurements, Mellor et al. reported thicker SCTs both in the affected and unaffected arms, but this might be related to racial differences between the study populations. Increased SEFS can be seen in various types
Fig. 1 (A) The points of scanning and (B) definition of echogenic borders. a: The posterior echogenic border of the epidermal entrance echo, that is, the anterior echogenic border of the SELEB; b: the posterior echogenic border of the SELEB; c: the posterior echogenic border of the papillary dermis, that is, the anterior echogenic border of the SCT; and d: the posterior echogenic border of the SCT, that is, the anterior echogenic border of the deep muscular fascia. (C) Representative ultrasonography images. Ultrasonography images of the medial forearms of a patient with right unilateral arm lymphedema are shown. The rectangles indicate the scan points. On the side with the lymphedema, the skin, SELEB, and SCT are thicker. Note that a large part of the border between the skin and SCT is blurred. SELEB: subepidermal low echogenic band; SEG: subcutaneous echogenicity (grade); SEFS: subcutaneous echo-free space (grade); SCT: subcutaneous tissue.

Fig. 2 (A) Difference ratio, (B) Difference in SEG and SEFS grades. *p <.05 between the arm with lymphedema and the normal arm. SELEB: subepidermal low echogenic band; SCT: subcutaneous tissue; MUA: medial upper arm; LUA: lateral upper arm; MFA: medial forearm; LFA: lateral forearm; DH: dorsum of the hand; SEG: subcutaneous echogenicity (grade); SEFS: subcutaneous echo-free space (grade)
Table 2  Measured variables

<table>
<thead>
<tr>
<th></th>
<th>Skin (mm)</th>
<th>SELEB (mm)</th>
<th>SCT (mm)</th>
<th>SEG</th>
<th>SEFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>MUA LE</td>
<td>1.3 ± 0.5§</td>
<td>0.7 ± 0.4§</td>
<td>8.2 ± 4.2§</td>
<td>0.9 ± 0.4§</td>
<td>0.2 ± 0.5</td>
</tr>
<tr>
<td>N</td>
<td>0.8 ± 0.2</td>
<td>0.3 ± 0.1</td>
<td>5.3 ± 2.8</td>
<td>0.3 ± 0.4</td>
<td>0</td>
</tr>
<tr>
<td>LUA LE</td>
<td>1.7 ± 0.5§</td>
<td>0.9 ± 0.4§</td>
<td>11.5 ± 3.6§</td>
<td>0.8 ± 0.4§</td>
<td>0.3 ± 0.5§</td>
</tr>
<tr>
<td>N</td>
<td>1.1 ± 0.3</td>
<td>0.4 ± 0.2</td>
<td>8.7 ± 4.5</td>
<td>0.1 ± 0.3</td>
<td>0</td>
</tr>
<tr>
<td>MFA LE</td>
<td>1.7 ± 0.8§</td>
<td>1.0 ± 0.6§</td>
<td>8.7 ± 3.4§</td>
<td>0.9 ± 0.5§</td>
<td>0.5 ± 0.7§</td>
</tr>
<tr>
<td>N</td>
<td>0.8 ± 0.2</td>
<td>0.3 ± 0.1</td>
<td>3.8 ± 2.0</td>
<td>0.1 ± 0.3</td>
<td>0</td>
</tr>
<tr>
<td>LFA LE</td>
<td>1.4 ± 0.5§</td>
<td>0.7 ± 0.3§</td>
<td>5.5 ± 2.2§</td>
<td>0.7 ± 0.5§</td>
<td>0.2 ± 0.5§</td>
</tr>
<tr>
<td>N</td>
<td>0.9 ± 0.3</td>
<td>0.4 ± 0.2</td>
<td>3.3 ± 2.0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>DH LE</td>
<td>1.3 ± 0.4§</td>
<td>0.7 ± 0.3§</td>
<td>4.6 ± 3.6§</td>
<td>0.8 ± 0.5§</td>
<td>0.4 ± 0.6§</td>
</tr>
<tr>
<td>N</td>
<td>0.8 ± 0.2</td>
<td>0.4 ± 0.1</td>
<td>1.9 ± 0.9</td>
<td>0.4 ± 0.5</td>
<td>0</td>
</tr>
</tbody>
</table>

§p < .05 vs. N. SELEB: subepidermal low echogenic band; SCT: subcutaneous tissue; SEG: subcutaneous echogenicity; SEFS: subcutaneous echo-free space; MUA: medial upper arm; LUA: lateral upper arm; MFA: medial forearm; LFA: lateral forearm; DH: dorsum of the hand; LE: lymphedema; N: normal

of edema,¹³ and it is affected by age and time of day.¹⁴ Nevertheless, SELEB in the LE side seemed apparently thicker than that in the normal side. The currently employed 12-MHz linear transducer was apparently insufficient to delineate skin and SCT structures clearly; therefore, the measurements obtained using this technique, particularly those of the skin and SELEB, were nothing more than reference values. Even when a higher-resolution machine is used, the distances measured using ultrasonography have inherent problems, for example, whether the beam entered perpendicularly to the structures, or whether the scan point is identical among the patients. Nevertheless, the difference was obvious, and therefore, the measured values seemed accurate enough to support the intuitive assessment of the difference between the LE and normal arms on ultrasonography images. Blurring of the DHJ is caused by severe fibrosis of this area, which is obscure even in histological specimens.¹⁶ This blurring, however, was found only in 5% of the images analyzed in the current study, which was much less than the percentage of blurring seen in stage II leg LE (range: 24%–47%).¹¹

Increased SEG is considered a result of increased cell density and collagen content in the tissue,¹⁷,¹⁸ which indicates the presence of nonspecific local inflammation. Since lymph stasis causes chronic inflammation due to uncontrolled responses of macrophages and CD4+ cells,¹⁹,²⁰ it may be reasonable to presume that SEG increases in the extremity with LE without exception. In contrast, SEFS, which represents the accumulation of fluid in the space of the superficial fasciae, was found in only half of the LE arms. This result implies that the true nature of LE is not that of an edema but that of a chronic inflammation.

Increase in skin, SELEB, and SCT thicknesses as well as SEG/SEFS grades were most evident in the MFA, through which runs the ulnar lymphatic bundle.¹⁶ We speculated that lymph in the MFA was less drained than that in the MUA; lymph from both the structures are supposed to drain into the axillary lymph nodes in the normal condition. One possible explanation is that the MFA has less communication with the lymph pathway that drained to the deltoideopectoral and/or supraclavicular lymph nodes. Another possible explanation is that MFA is relatively in dependent position than MUA, and therefore fluid and cells were accumulated due to gravity. This seemed different from the draining pattern in legs with LE, in which an increase in the above parameters was evident along the entire course of the superficial leg lymphatic trunk.¹,²

Limitations

The current definitions of SEG and SEFS grades are based on empirical facts; therefore, future studies should verify these using pathological data. Additionally, interobserver and intraobserver differences in assigning SEG and SEFS grades have not yet been tested; this also needs to be validated in future studies.

Conclusion

We reported the skin, SELEB, and SCT thicknesses as well as SEG and SEFS grades in arms with LE and normal arms of patients with BCRL. The increase in these parameters was most evident in the MFA of the arm with LE.

Acknowledgment

None.

Disclosure Statement

There are no conflicts of interest to declare.

Author Contributions

Study conception: KS
Data collection: KS, KN, TH, MS, YT, and TM
References