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MR IMAGING, PROTON MR SPECTROSCOPY, ULTRASONOGRAPHIC, HISTOLOGIC FINDINGS IN PATIENTS WITH CHRONIC LYMPHEDEMA

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ABSTRACT

Lymphedema is a progressive disease with multiple alterations occurring in the dermis. We undertook this study using high-frequency ultrasonography (US), magnetic resonance imaging, proton MR spectroscopy and histology to examine structural changes occurring in the subcutaneous tissue and precisely describe the nature of intralobular changes in chronic lymphedema. Four cutaneous and subcutaneous tissue biopsies from patients with chronic lymphedema during lymphonodal transplantation were studied. We performed US with a 13.5 MHz transducer, TSE T1 and TSE T2 magnetic resonance images with and without fat-suppression, MR Chemical Shift Imaging Spectroscopy and histological evaluation on these biopsies. We found that normal subcutaneous septa are seen as hyperechogenic lines in US and hyposignal lines in MRI and that hyperechogenic subcutis in US can be due to interlobular and intralobular water accumulation and/or to interlobular and intralobular fibrosis. Our study also confirms the usefulness of MR spectroscopy to assess water or fat content of soft tissue. Thus, multiple imaging modalities may be necessary to precisely delineate the nature of tissue alterations in chronic lymphedema.

Keywords: lymphedema, magnetic resonance imaging, ultrasonography, magnetic resonance spectroscopy, histology, adipose tissue, fibrosis

Lymphedema is a progressive condition with abnormal accumulation of macromolecules and water as a result of insufficient lymphatic drainage which can lead to chronic inflammation and definitive fibrosis. In the majority of cases, the diagnosis of lymphedema can be determined by history and physical examination. However, a clinical assessment solely based on the physical examination cannot consistently and reliably evaluate the presence of edema or fibrosis. Association with other diseases such as phlebedema (phlebolymphedema), lipedema (lipolymphedema), or both (lipophlebolymphedema) can occur. Imaging techniques such as interstitial (indirect) lymphangiography with non-ionic contrast agents, lymphoscintigraphy, computed tomography (CT), magnetic resonance imaging (MRI) or ultrasound (US) are useful to confirm the diagnosis of lymphedema or to demonstrate lymphedema components in patients with lipedema or phlebedema (1). Changes reported in lymphedema include an increase of the dermis thickness, hyperechogenicity or

stone-paved picture of the subcutis, and fluid retention located in the dermis, interlobular space, and superficial fascia (2,3). US or MRI easily demonstrate these findings (4,5) but there is a variety of explanations about the nature of changes including: fibrosis (1,6-8), adipogenesis (4,9), intracellular fluid accumulation (7), and dilated lymphatic vessels (5). The purpose of this study was to investigate the imaging findings in chronic lymphedema using US, conventional MRI, proton MR spectroscopy, and histology.

MATERIALS AND METHODS

Four cutaneous and subcutaneous biopsies during lymphonodal transplantation in patients (3 women; 1 man, aged 22 to 70 years; mean 46 years) with clinical manifestations of unilateral limb chronic secondary lymphedema were examined. The width of the specimen varied from 27 to 50 mm and always contained a dermo-epidermal component. In one subject, the biopsy was obtained only from the normal side. Our local ethics committee approved the study, and informed consent was obtained from all subjects. Ultrasonography was performed using a 13.5 Mhz linear transducer. MRI was performed with a whole-body 1.5 T scanner (symphony; Siemens Medical Systems, Erlangen, Germany). MR images were acquired with a 7 cm circular surface coil specially designed for skin or finger imaging. T1 and T2 with and without fat saturation transaxial and coronal magnetic resonance images with respectively 3mm and 2.5mm slice thickness were obtained on each specimen (T1-weighted images: TR=330ms, TE=22ms, pixel size=0.2mm x 0.2mm; T2 weighted images: TR=2000ms, TE=99ms, pixel size=0.4mm x 0.4mm). STIR (Short Time Inversion Recovery) coronal images were obtained with TR =4900 ms, TE=65 ms, pixel size=0.9mm x 0.8mm and slice thickness 4mm. In order to determine water and fat distribution in biopsies, a chemical shift imaging (CSI) proton spectroscopy was applied with TR= 1500ms, TE=30ms, and a voxel size=5x6x6mm. Surface areas under water and fat peaks were determined with a curve-fitting software, and relative amount of water in the subcutaneous tissue was calculated by dividing the area under the water-specific peak by the area of the fat-specific peak (W/F ratio) avoiding the relative intensity variation of individual components of the ratio, e.g., due to coil position. Following MRI, tissue biopsies were formaldehyde fixed and paraffin embedded. Multiple sections were obtained in the same coronal axis of MRI and US imaging slices and stained with Masson Trichrome for collagen visualization.

RESULTS

Ultrasound Imaging

The subcutaneous tissue of the normal biopsy demonstrated a homogeneous hypoechogenicity with thin hyperechogenic bands *(Fig. 1)*. There was good topographical correlation of theses hyperechogenic bands, hyposignal thin hypodermic septa in MRI and interlobular connective tissue in histology *(Fig. 2)*. In all pathological biopsies, there was an increase of the echogenicity of the subcutaneous tissue. In one case, the hyperechogenicity was maximal with disappearance of the dermo-hypodermal junction *(Fig. 3)*.

Magnetic Resonance Imaging and Spectroscopy

The normal aspect of the subcutis displayed a preserved fatty signal (hypersignal on T1 weighted images; highly hyposignal on fat-suppressed sequences) with thin trabecular septa hyposignal on all sequences. Hyperechogenic areas previously seen in US were hyposignal on all sequences or hyposignal on T1 weighted images and hypersignal on T2 weighted and fat-suppressed images *(Fig. 4a,b)*. Spectroscopy suggested that a hyposignal area on all sequences contained little water and a

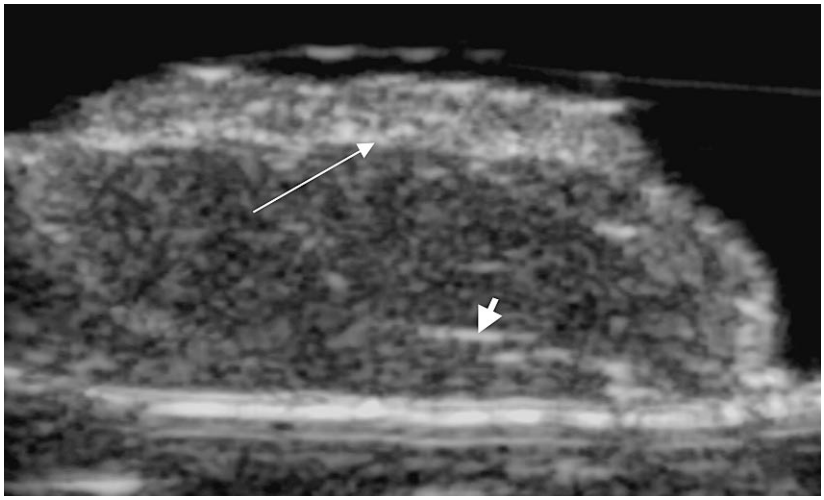

Fig. 1. US of biopsy from a normal arm displays hypodermal tissue that is hypoechogenic with thin hyperechogenic septa (short white arrow) and a well defined dermo-hypodermic junction (long white arrow).

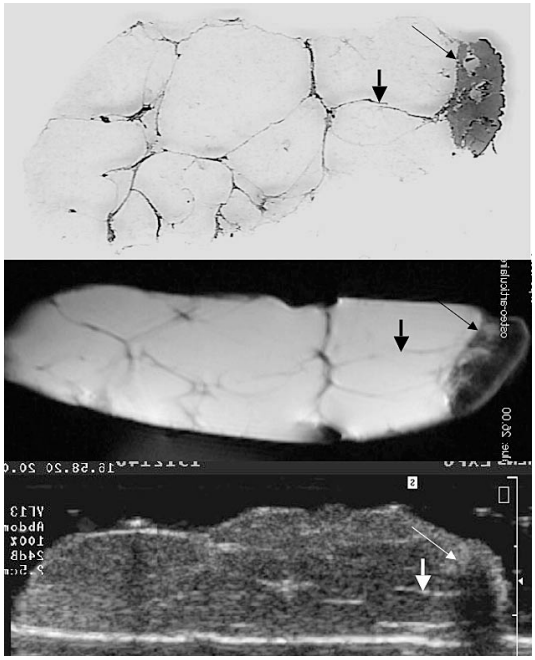

Fig. 2. Correlation between histology (top), T1 weighted MR image (center) and US (bottom). Interlobular septa are hyposignal in T1 (short black arrow) and hyperechogenic in US (short white arrow). In the US image, only septa perpendicular to the ultrasound beam are visualized. The dermo-hypodermic junction is identified by a long thin arrow in all three panels.

hypersignal area on T2 weighted images contained high peak of water *(Fig. 4c)*.

Tissue Histology

The subcutaneous tissue of the normal biopsy presented thin interlobular septas and thin delineations of adipocytes *(Fig. 5a)*. There was good topographical correlation of hyperechogenic bands in US, hyposignal thin hypodermic septa in MRI and interlobular conjunctive tissue in histology *(Fig. 2)*. Areas of hyposignal on all sequences were hightly invaded by fibrosis *(Fig. 5b)*. Histology also demonstrated the presence of interlobular and intralobular components of fibrosis *(Figs. 5c,d)*.

DISCUSSION

Our study confirms the usefulness of MR spectroscopy to evaluate water accumulation in the dermis due to lymphedematous changes. These findings confirm previous work on dermal water assessment in swelling by Gniadecka (2,3) and in a recent study with lymphedema patients by Tassenoy (9). In chronic lymphedema, the fibrotic component

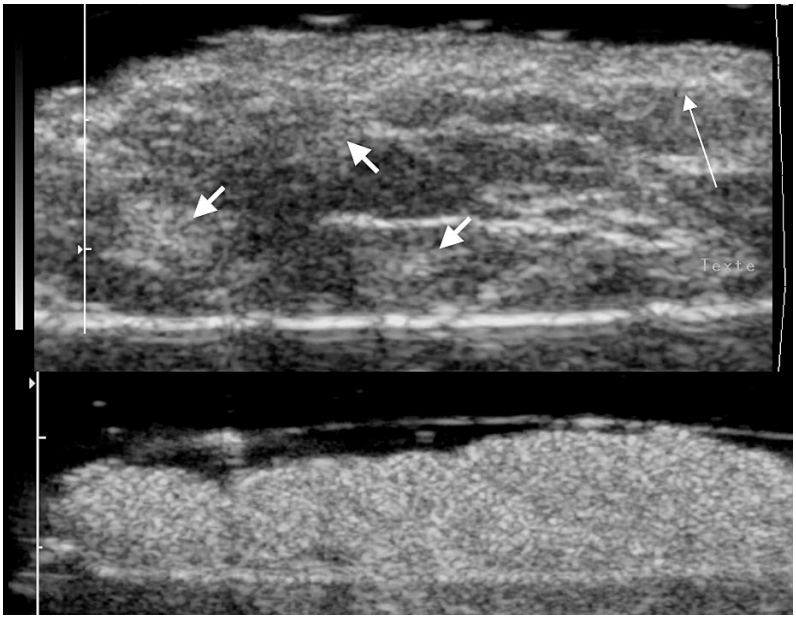

Fig. 3. US of pathological biopsies demonstrate (top) the presence of areas of ill-defined hyperechogenicity in the hypodermis (short white arrow) and well-defined dermo-hypodermic junction (long white arrow). Another pathological biopsy (bottom) displays diffuse intense hyperechogenicity.

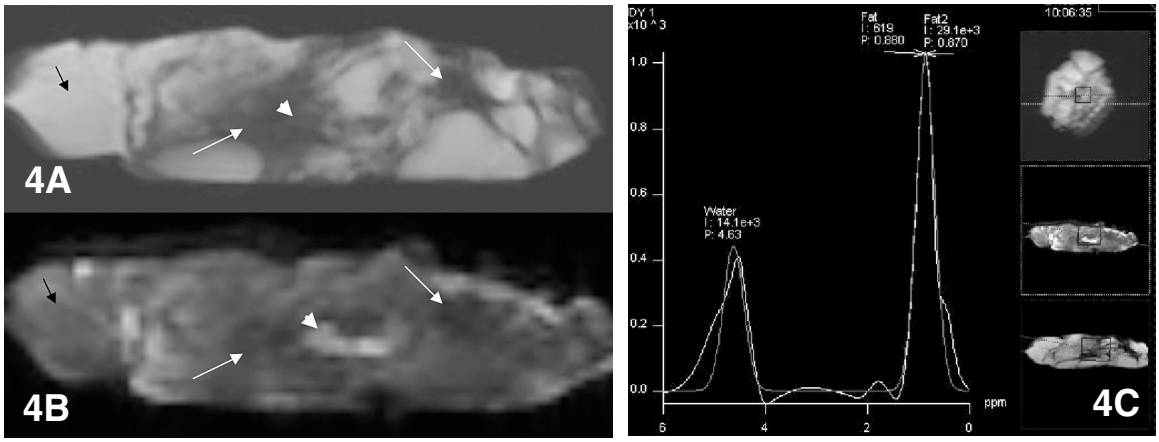

Fig. 4A,B) MR imaging of the biopsy with diffuse intense US hyperechogenicity (bottom Fig. 3). A: T1 weighted image - B: TSE T2 fat-suppressed image. Hyposignal areas seen in both sequences (thin white arrows) suggests fibrosis. Hyposignal area in T1 weighted images and hypersignal in TSE T2 fat-suppressed image (short white arrows in both) indicate water accumulation. Hypersignal area in T1 weighted images and hyposignal areas in TSE T2 fat-suppressed image (thin black arrows in both) suggest preserved area of hypodermal fat. C: CSI Spectroscopy of the area delineated by the short white arrows in A and B demonstrates a water peak confirming water in that specific area.

of the trabecular subcutaneous structures characterized by hyposignal in both T1 and T2 weighted MR sequences has been observed by several authors (1,6-8) but the precise location to intra or interlobular was imprecise. In a high-resolution MRI study of Idy-Peretti

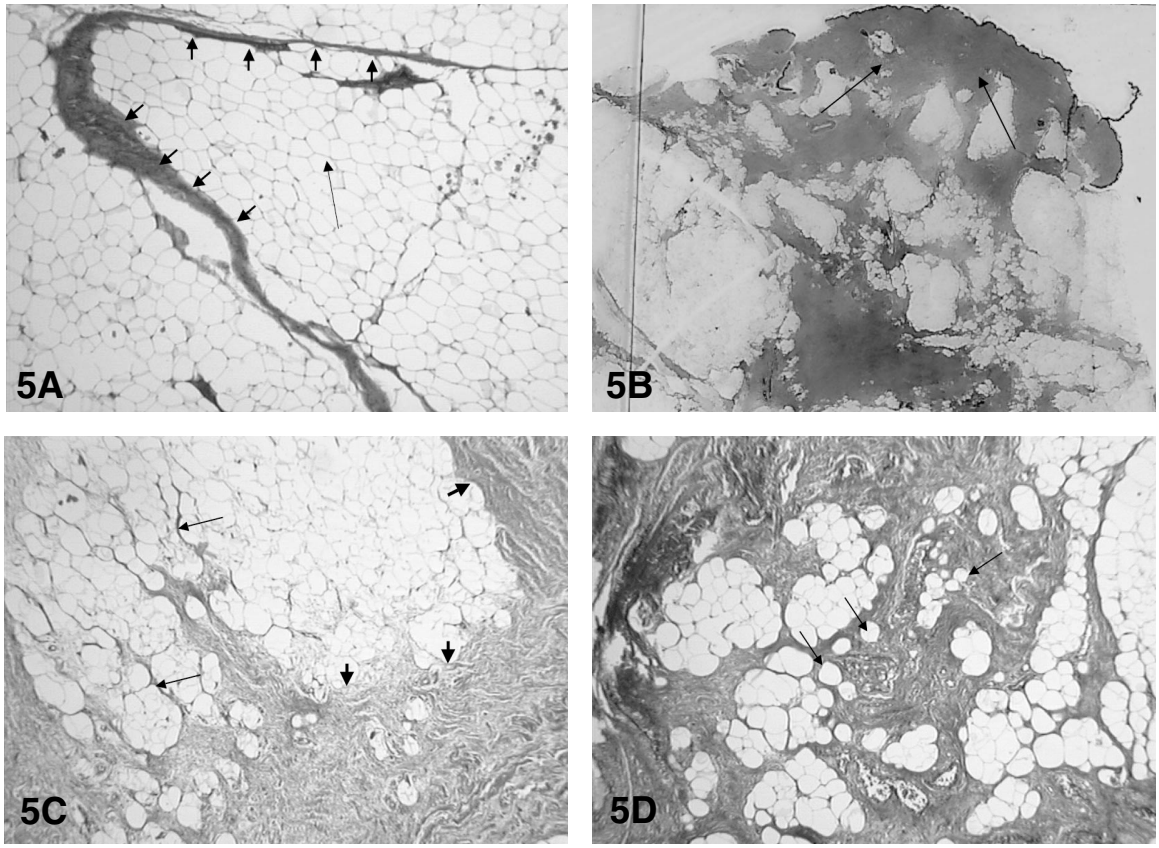

Fig. 5. A) Histological section from the normal hypodermal tissue biopsy stained with Masson trichrome demonstrates a thin interlobular septa (short black arrow) and thin delineation of adipocyte (long black arrow). (B) Histology of the same biopsy sample from bottom of Fig. 3 and Fig. 4 demonstrates extensive fibrosis seen by multiple dark areas of collagen with disappearance of the dermohypodermal junction (long black arrow). (C) Another biopsy demonstrates the presence of interlobular and intralobular components of fibrosis with widening of interlobular septa (short black arrow) and intralobular collagen accumulation (thin black arrow). (D) High intralobular fibrosis with isolated adipocytes (thin black arrows).

et al (4), the mean thickness of the fat lobule was significantly larger in the lymphedematous limb compared with that in normal legs. The MRI signal of these larger lobules was similar in pathologic and normal limbs suggesting a mechanism of fattening of the connective tissue in the chronic lymphedematous limb. The histologic and spectroscopic study by Tassenoy suggests that the hyperechogenicity of the subcutis is correlated with increase of the fat-to-water ratio measured by MRI supporting this mechanism of fattening. Our study confirms that there are intralobular changes in chronic lymphedema, but that the hyperechogenicity of the lobule can be due either to intralobular fibrosis (in our study) or to fatty accumulation (Tassenoy). This hyperechogenicity of the fat lobule only means an increase of interfaces between tissues of different acoustic impedance but it doesn't demonstrate the real nature, be it fibrotic or hydric, of the modification. Some authors (5,10) suggest that diffuse hypoechogenicity or hyperechogenicity of subcutaneous tissues or of subfascial compartments reflects water accumulation or diffuse fibrosclerosis,

but it should be kept in mind that ultrasonography can only demonstrate the architectural changes of a tissue and not its chemical changes (5). Moreover, hyperechogenicity of the subcutaneous fat is described in pathologic conditions other than lymphedema such as phlebedema, acute post traumatic edema, and lipoma. These are sometimes hyperechogenic by US and hyperechogenicity of the subfascial compartment is found in "non fibrotic" conditions such as amyotrophy for example (11,12). Preserved fatty signal (hypersignal on T1, hyposignal on fat-suppressed sequence) or hyposignal on all sequences suggesting fibrosis in MRI can help differentiate fat accumulation from fibrosis.

CONCLUSION

Our study confirms that there are intralobular changes in chronic lymphedema. However, hyperechogenic lobules can be due to various conditions, and it is necessary to correlate different imaging techniques to assess the real nature of the modifications in lymphedema. MR spectroscopy and histologic correlation can help to increase our understanding of tissue changes in lymphedema.

REFERENCES

1. Astrom, KG, S Abdsaleh, GC Brenning, et al: MR imaging of primary, secondary, and mixed forms of lymphedema. Acta Radiol. 42 (2001), 409-616.
2. Gniadecka, M, B Quistorff: Assessment of dermal water by high-frequency ultrasound: comparative studies with nuclear magnetic resonance. Br. J. Dermatol. 135 (1996), 218-224.
3. Gniadecka, M: Localization of dermal edema in lipodermatosclerosis, lymphedema, and cardiac insufficiency. J. Am. Acad. Dermatol. 35 (1996), 37-41.
4. Idy-Peretti, I, J Bittoun, F Alliot, et al: Lymphedematous skin and subcutis: In vivo high resolution magnetic resonance imaging evaluation. J. Invest. Dermatol. 110 (1998), 782-787.
5. Matter, D, E Grosshans, J Muller, et al: Apport de l'échographie à l'imagerie des vaisseaux lymphatiques par rapport aux autres méthodes. J. Radiol. 83 (2002), 599-609.
6. Haaverstad, R, G Nilsen, P Rinck, et al: The use of MRI in the diagnosis of chronic lymphedema of the lower extremity. Int. Angio. 13 (1994), 115-118.
7. Dimakakos, PB, Th Stephanopoulos, P Antoniades, et al: MRI and Ultrasonographic findings in the investigation of lymphedema and lipedema. Int. Surg. 82 (1997), 411-416.
8. Duewell, S, KD Hagspiel, J Zuber, et al: Swollen lower extremity: Role of MR imaging. Radiology 184 (1992), 227-231.
9. Tassenoy, A, K Vermeiren, P van der Veen, et al: Demonstration of tissue alterations by ultrasonography, magnetic resonance imaging and spectroscopy, and histology in breast cancer patients without lymphedema after axillary node dissection. Lymphology 39 (2006), 118-126.
10. Doldi, SB, E Lattuada, MA Zappa, et al: Ultrasonography of extremity lymphedema. Lymphology 25 (1992), 129-133.
11. Inampudi, P, JA Jacobson, DP Fessell, et al: Soft-tissue lipomas: Accuracy of sonography in diagnosis with pathologic correlation. Radiology 233 (2004), 763-767.
12. Strobel, K, J Hodler, DC Meyer, et al: Fatty atrophy of supraspinatus and infraspinatus muscles: Accuracy of US. Radiology 237 (2005), 584-589.

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