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DISSEMINATED LYMPHANGIOMATOSIS WITH SKELETAL INVOLVEMENT: DETECTION WITH MAGNETIC RESONANCE LYMPHANGIOGRAPHY

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ABSTRACT

Disseminated lymphangiomatosis is an uncommon disorder characterized by diffuse or multifocal proliferation of complex, irregular lymphatic channels involving soft tissue, viscera, retroperitoneum, eyes and the skeletal system.

Currently, magnetic resonance imaging, computed tomography, ultrasonography, and conventional radiography are the favored radiologic imaging modalities in assessing the extent of pathologic changes in patients suffering from disseminated lymphangiomatosis. Historically, imaging evaluation was performed with conventional lymphography.

We report on the first patient suffering from disseminated lymphangiomatosis with skeletal involvement, whose lymphatic vasculature of the lower limbs and pelvic region was evaluated with magnetic resonance lymphangiography.

Keywords: disseminated lymphangiomatosis, skeletal lymphangiomas, magnetic resonance lymphangiography

Disseminated lymphangiomatosis is an uncommon multisystem disease, characterized by diffuse proliferation of lymphatic vessels, which occurs primarily in children and adolescents under 20 years of age (1-3). The cause of this disease is unknown but the association of primary lymphatic dysgenesis with a lymphoproliferative process has been assumed. The prognosis is poor especially if visceral organ involvement is present, which can lead to chylothorax, chylopericardium and hepatosplenomegaly (1-6). Treatment choices for its sequelae are limited and only palliative. When lymphangiomatosis affects the skeletal system, visceral and soft tissue involvement are usually already present. The pelvic bones, vertebrae, shoulder girdle, ribs, and femora have been the most frequent locations of bone involvement (2,4-10).

Currently, magnetic resonance imaging (MRI), computed tomography (CT), ultrasonography and conventional radiography are the favored radiologic imaging modalities in assessing the extent of pathologic changes in patients suffering from disseminated lymphangiomatosis (5,8,11-14).

Magnetic resonance lymphangiography (MRL) with intracutaneous injection of an extracellular, paramagnetic contrast agent is an innovative diagnostic imaging method for the delineation of pathologically modified lymphatic pathways (15,16). The technique has proved to be safe and technically feasible in patients suffering from primary and secondary lymphedema (15,16). To our knowledge, this is the first report of a patient suffering from disseminated lymphangiomatosis with skeletal involvement, whose lymphatic vasculature was evaluated by MRL.

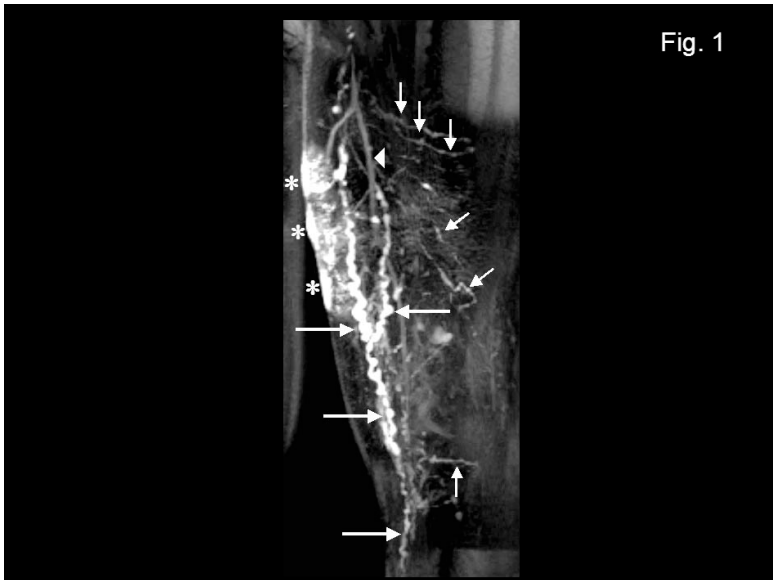

Fig. 1: Angled 3D spoiled gradient-echo MRL Maximum Intensity Projection (MIP)-image of the left thigh, obtained 45 minutes after gadoteridol injection, reveals several enlarged, tortuous lymphatic vessels up to a diameter of 5 mm (arrows) with retrograde flow of the contrast material from the injection sites (asterisks) indicating valve insufficiency. Furthermore, several collateral lymphatic vessels (small arrows) indicating delayed lymphatic flow with neovascularization are demonstrated. Note the concomitant enhanced vein, that shows a lower signal intensity (arrowhead).

CASE REPORT

A 27-year-old woman with disseminated lymphangiomatosis and centrally accentuated lymphedema was referred by the Foeldi Clinic for Lymphology for MRL. The indication for performing MRL was the evaluation of the lymphatic vasculature. The study had been approved by the local ethics committee, and the patient had given informed consent before the examination.

MRL was performed with a 1.5 T system (Avanto; Siemens Medical Systems, Erlangen, Germany). Three stations were imaged: first, the lower leg and foot region; second, the upper leg and the knee region; and third, the pelvic region and the proximal upper leg. A phased array body coil was used to image the pelvic region, and a dedicated peripheral surface coil was used to image the upper and lower leg. The extent of lymphedema was evaluated using a heavily T2-weighted 3D-TSE sequence (TR/TE: 2000/694; flip angle: 180°; matrix: 256 x 256; bandwidth: 247 Hz/pixel; 6/8 rectangular field of view 480 mm; slices: 96; voxel size: 2.0 x 1.9 x 1.7 mm; acquisition time: 4 min 48 sec). For MRL a 3D spoiled gradient-echo sequence (Volumetric Interpolated Breathold Examination, VIBE) was used: (TR/TE: 3.58/1.47; flip angle: 35°; matrix: 448x448; bandwidth: 490 Hz/pixel; 6/8 rectangular field of view with a maximum dimension of 500 mm; slices: 128; voxel size: 1.2 x 1.1 x 1.2 mm; acquisition time: 1 min 40 sec). The three stations were imaged without contrast material and subsequently repeated 5, 15, 25, 35, 45, and 55 minutes after intracutaneous application of gadoteridol (Prohance®, Bracco-Byk Gulden, Konstanz, Germany). To highlight the contrast media containing structures, image subtraction was performed and 3D maximum-intensity-projection (MIP) reconstructions calculated. A total contrast material dose of 20 ml and

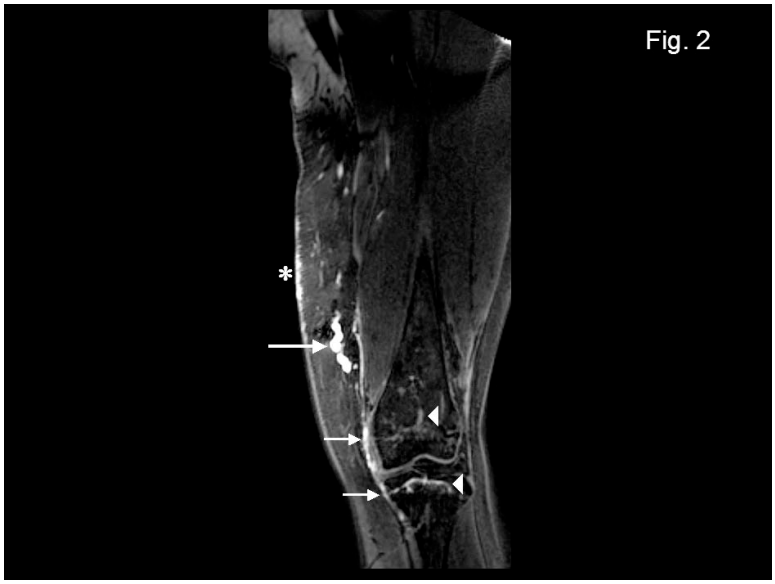

Fig. 2: Coronal 3D spoiled gradient-echo MRL source image, obtained 45 minutes after gadoteridol injection, reveals one enlarged, tortuous lymphatic vessel of 5 mm (large arrow). At the level of the left knee a direct connection was demonstrated between para- (small arrows) and intraosseous (arrowheads) lymphatic vessels in the left femur and tibia.

2 ml of mepivacainhydrochloride 1% were subdivided into 14 portions. Four portions were injected intracutaneously into the dorsal aspect of each foot in the region of the four interdigital webs; one portion was injected medial to both first proximal phalanges. Two portions were injected intracutaneously at the medial aspect of both thighs.

Clinical and sonographic examination revealed a centrally accentuated lymphedema with subcutaneous lymphangiomatous changes in the pelvic region and the medial aspect of the left thigh. Lymphedema of the lower extremities was predominantly left-sided with brownish discoloration of the skin in the medial aspect of the left thigh related to the lymphangiomatous changes. Additionally, several cutaneous lymph cysts were observed in that region, associated with recurrent infections with erysipelas. Furthermore, the patient suffered from severe vaginal and anal lymphorrhea.

MRL detected concomitant venous enhancement in the lower and upper leg 5 minutes after contrast material application. The lymphatic vessels of the right lower and upper leg were unremarkable with the best delineation at 35 and 45 minutes, respectively. MRL images of the left lower leg revealed delayed lymphatic flow with several dilated lymphatic vessels up to 3 mm. At the level of the left upper leg several enlarged, tortuous lymphatic vessels up to a diameter of 5 mm were detected, with the best demarcation at 45 minutes (*Fig. 1*). Furthermore, a direct extension of lymphatic vessels into the bone marrow could be observed in a few locations (*Fig. 2*).

Enhancement of the inguinal lymph nodes was observed after 25 minutes on the right side and after 35 minutes on the left side. The predominantly left-sided lymphedema demonstrated an epifascial distribution with a high signal intensity on T2-weighted images. An area of dermal back-flow was not detected.

The T2-weighted images demonstrated additionally the extensive dimension of the lymphangiomatous changes in the left femur and pelvic region with extension into the retroperitoneum (*Figs. 3,4*).

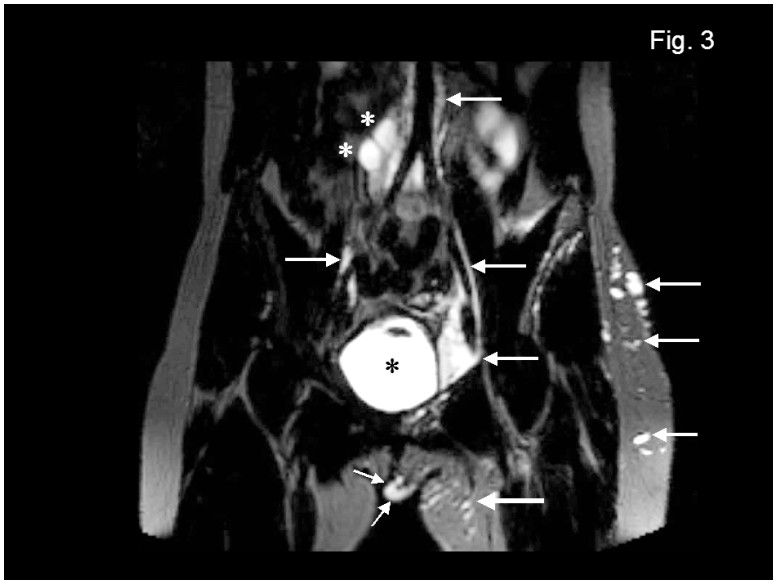

Fig. 3: Coronal heavily T2-weighted 3D-TSE source image depicts multiple lymphangiomatous changes in the left subcutaneous tissue and pelvic region extending to the retroperitoneal space (arrows). At the level of the aortic bifurcation two cystic lymphangiomas are revealed on the right side (asterisks). Corresponding to the clinically observed vaginal lymphorrhea, lymphangiomatous changes are demonstrated in the left groin (large arrow) with extension into the genital region and thickened, fluid-filled labia on the left side (small arrows).

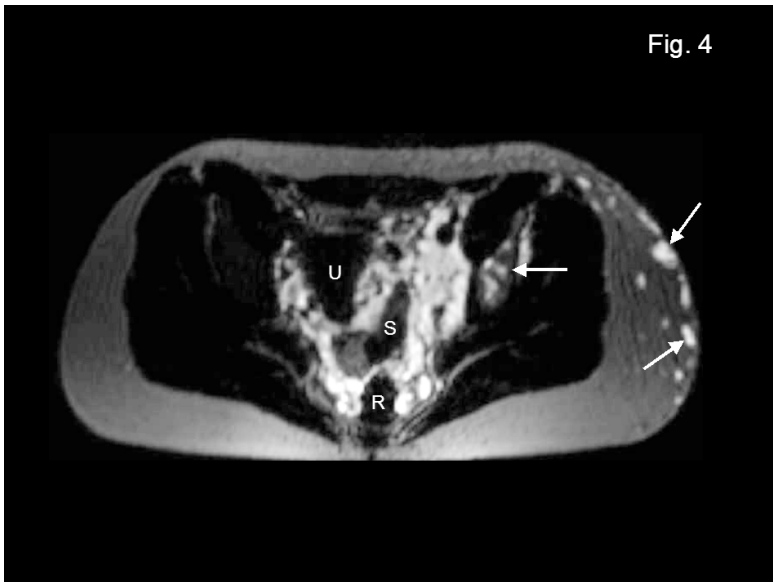

Fig. 4: Axial heavily T2-weighted 3D-TSE source image depicts multiple lymphangiomatous changes with a high signal intensity in the pelvic region surrounding the uterus (u), sigmoid colon (s) and rectum (r), applying to the clinically observed anal lymphorrhea. Furthermore, lymphangiomatous changes are observed in the subcutaneous tissue and os ileum on the left side (arrows).

For lymphedema treatment, a conservative approach was chosen during the patient's stay at the Foeldi Clinic for Lymphology. Complex decongestive therapy enabled the removal of approximately 2,300 ml edema volume in the left leg. The volume difference between the two legs was reduced to 400 ml compared to 1,800 ml at the beginning of therapy. At discharge, it was recommended to continue manual lymphedema treatment and to wear compression stockings. Furthermore, the patient was educated on the basics of skin hygiene to minimize skin infections.

DISCUSSION

Landing and Farber differentiated histologically three types of lymphangiomas (17): 1) Capillary or simple lymphangiomatosis, which is composed of capillary, thin-walled lymphatic channels; 2) Cavernous lymphangiomatosis, consisting of dilated lymphatic channels, frequently with fibrous adventitial coats; and 3) Cystic lymphangiomatosis, known as cystic hygroma, which seems to be the most common manifestation and occurs often in the neck or axilla in children.

Capillary lymphangiomas are most frequently present in the skin but have also been reported in bone. Cavernous lymphangiomas are seen in bone, soft tissue, and the viscera, and may appear unilocularly or in different regions. As seen in the reported patient, all three types can be present simultaneously in patients with lymphangiomatosis.

Up to 65% of lymphangiomas present during infancy or childhood (12). Although the onset of symptoms may appear very early in infancy, they are often not diagnosed correctly, and a definite diagnosis is often delayed. Although the lymphangiomas grow very slowly, they can expand and infiltrate the surrounding tissues (1-6). The symptoms of the patients correspond to their sites of involvement.

Bony lesions, which have been reported in up to 70% of patients with lymphangiomatosis, normally present with local pain or pathological fractures (2,4-10, 18-20). In contrast to the visceral involvement, bony lesions tend to remain stable, show no progression or even regress. The differentiation between lymphangiomatosis and "disappearing bone disease" (Gorham disease) is important. The latter usually presents with progressive lysis of contiguous affected bones.

Presently, to confirm skeletal involvement, a biopsy is taken, which can demonstrate a lymph-filled multilocular cavity with an endothelial lining (2). However, if the lymph-filled areas are replaced by fibrous tissue, a histological diagnosis is very difficult. Furthermore, histologic differentiation between lymphangioma and hemangioma may be very difficult due to the similarity of endothelial-lined cystic lesions.

There is no curative treatment for generalized lymphangiomatosis (1-6). Although surgery is recommended for localized lymphangiomatous changes, excision of generalized lymphangiomatosis is normally impossible due to the infiltrative growth of the disease. For visceral involvement, palliative procedures often include draining pericardial effusions or pleurodesis for recurrent pleural effusions. Treatment with interferon-alfa or radiation therapy has also been reported to be effective (1-6). Skeletal lymphangiomatous lesions, however, often receive no treatment because the lesions tend to remain stable.

Because the exact delineation of the lymphangiomatous extension gives important prognostic information, radiologic examinations are relevant for planning the patient's treatment. Radiographic images of the disease may demonstrate solitary or multiple osteolytic lesions (2,4-10). The lesions are normally well-defined, but thinning and bulging of the cortex are frequently seen, and lesions may demonstrate destruction of the cortex. CT scanning provides exact delineation of the osteolytic but usually not the prolifera-

tive changes in the intraosseous vessels. Furthermore, CT allows biopsy guidance.

MRI represents the best technique to assess the complete extent and infiltrative components of diffuse lymphangiomatosis (5,11-13). Furthermore, MRI is capable of exactly describing the anatomic relationship and possible involvement of vital structures such as the spinal canal. Additionally, MRI demonstrates the detail of the tubular structures of cavernous lymphangiomas better than CT. Lymphatic vessels have mostly a low signal on T1-weighted sequences and a high or isointense signal intensity on T2-weighted images. However, probably due to the high protein or fat content, lymphatics may also demonstrate a high signal on T1-weighted sequences. Furthermore, MRI is useful for long-term follow-up and in the differentiation of early, active stages from later stages where fibrous tissue replacement has taken place.

Conventional lymphangiograms have been performed in several patients with lymphangiomatosis (4,7,9,10,21). Irregular pooling of contrast media has been seen quickly in the soft tissues and it has been demonstrated that the occurrence of contrast media in the skeletal system appears at 24 hours or even later. Characteristic lymphographic findings in the soft tissue are delayed drainage with lymphatic obstruction and consequent formation of dilated, collateral lymphatic vessels. Furthermore, a paucity of normal lymph nodes in the affected regions has been reported (4,7,9,10,21).

Little is known about the pathologic changes in the lymphatic system of the skeleton. In lymphangiomatosis, several reports have demonstrated the mechanism of contrast filling by lymphography in the osteolytic bone areas (4,7,9,10,21). It seems that insufficiency of the lymphatic valves within the dysplastic subcutaneous and osseous lymphatic vessels leads to a lymphatic back-flow into the bones similar to the dermal back-flow phenomenon. Due to the concept of two injection sites at the medial aspect of the left thigh, MRL could exactly verify this mechanism in the reported patient. Retrograde flow of the contrast material from the injection sites into the left femur and tibia was observed in enlarged lymphatic vessels, indicating valvular insufficiency.

Osteolysis in the skeletal system probably results from pressure atrophy of ectatic endothelial-lined channels (21). The continuously increased dilatation of the intraosseous lymphatic cavities could thereby explain the slow progression of the osteolytic changes. Consequently lymphangiomatosis involvement of the skeletal system therefore probably originates in congenital malformations of the lymphatic system similar to primary lymphedema. It is important, therefore, to note that patients described in earlier reports and our patient had lymphedema in addition to the skeletal lesions (9,21), and MRL was able to visualize the direct connection between the dysplastic subcutaneous lymphatics and the cystic bone cavities, thereby vividly demonstrating the impairment of the lymphatic circulation.

In contrast to conventional lymphography observations, enhancement of intraosseous lymphatics could be seen by 15 minutes after contrast material injection by MRL in our patient. The diagnosis of skeletal involvement can thereby be confirmed with MRL if contrast material is demonstrated within the bones.

Lytic lymphangiomatous bone lesions may simulate a skeletal tumor or metastasis. If, however, MRL is performed, it is possible to make the diagnosis of skeletal involvement in a patient with lymphangiomatosis even before an eventual biopsy is performed.

In conclusion, MRL is of great value in patients suffering from lymphangiomatous disease as it can reveal key and functional changes in the lymphatic vessels with high resolution. Furthermore, the diagnosis of skeletal involvement can be made by MRL possibly without the need for biopsy.

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