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MAGNETIC RESONANCE LYMPHOGRAPHY DEMONSTRATES SPONTANEOUS LYMPHATIC DISRUPTION AND REGENERATION IN OBSTRUCTIVE LYMPHEDEMA

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ABSTRACT

The present study was aimed at observing both the damage and change process undergone in lymphatic collectors in obstructive extremity lymphedema. Forty-five patients with obstructive extremity lymphedema who had been examined with magnetic resonance lymphangiography (MRL) were enrolled in the study. Among this group, 36 were diagnosed with secondary lymphedema of the lower extremity and 9 exhibited upper extremity lymphedema after mastectomy. Morphological damage as a result of obstruction of collecting lymph vessels was recorded and analyzed. Obvious damage to the lymph vessels was found in all of the 36 lower extremity lymphedema cases with different lengths of history, including vessel disruption in 21 and lymphatic regeneration in 15. Lymphatic damage occurred in the anterior tibial area of the lower leg in almost every case. In 9 cases with upper extremity lymphedema, collecting lymphatic disruption and lymph tracer leakage was seen in multiple patterns. Imaging displayed that ruptured lymph collectors healed spontaneously or regenerated into a segment of the lymphatic network. The present study provided real-time images of collecting lymphatic vessels in obstructive lymphedema. These were seen to have undergone disruption, displayed lymphorrhoea, and/or lymphatic regeneration. In addition, the images suggest that the anterior tibial lymphatic is the weak point of the lymphatic pathway in the lower limb.

Keywords: MR lymphangiography, magnetic resonance imaging, obstructive limb lymphedema, lymphatic disruption, lymphatic regeneration, lymphangiogenesis, lymphorrhoea, lymph vessel, lymph flow, lymph leakage, lymphatic network, lymph collector

Lymphedema is a condition characterized by swelling in one or more extremities resulting from impaired flow of the lymphatic system. The lymphatic system returns interstitial fluid through the thoracic duct to the bloodstream, where it recirculates back to the tissues. Lymphedema affects approximately 140 million people worldwide (1) and may be inherited (primary) or caused by injury to the lymphatic vessels (secondary). Secondary lymphedema is frequently seen after lymph node dissection, surgery and/or radiation therapy, and tumor metastasis to lymph nodes. It can also be caused by a compromised lymphatic system resulting most frequently from lymphatic fillariasis, but also from cellulitis and lymphadenitis. Lymphatic obstruction is the principal cause of secondary lymphedema.

Obstruction of the lymphatic pathway may cause a series of pathophysiological changes in disturbed vessels, including decreased number, diameter, thickness of the wall, and luminal narrowing or obliteration (2-4). Most previous studies on the lymphatics in lymphedematous limbs have primarily focused on histological studies of lymphatic vessels under the microscope. The processes occurring in the main lymphatic trunks during the evolution of obstructive lymphedema in the limbs are still poorly understood, largely as a result of a lack of objective image methods to examine the pathology of lymphatic trunks particularly over time. Therefore, some of the treatments commonly used (e.g., microsurgical procedure), may not have a clear depiction of the lymphatic system before treatment. High-resolution MR lymphangiography (MRL) has been shown to be useful in the diagnosis of peripheral lymphatic system disorders (5-7). Intracutaneously injected paramagnetic contrast material was found to be easily absorbed by initial lymph vessels, and this procedure permits dynamic and real time observation of contrast enhancement in lymphatic vessels and drainage nodes. It is particularly useful in studying the structural changes of peripheral lymphatic channels and lymph nodes. Recently, a study on obstructive extremity lymphedema in the senior author's clinic using MRL showed characteristic changes of lymphatic collectors, including rupture, lymphorrhoea, and regeneration in affected upper and lower limbs. This current study presents clinical and imaging data from 45 patients that may help in understanding the pathophysiological changes in lymphatic collectors and the appropriate management of obstructive lymphedema.

MATERIAL AND METHODS

The present study included 45 patients (20 men, 25 women with a mean age of 49.2 years, range 11-78 years) diagnosed with secondary lymphedema. Thirty-six exhibited lower extremity lymphedema (24 after lymph node dissection, surgery and/or radiation therapy, 7 after lymph node metastasis, 3 after injury, 2 after lymphadenitis), which was bilateral in 3. The remaining 9 patients exhibited upper extremity lymphedema after mastectomy. The mean duration of lymphedema before the MRL examination was 2 years and 4 months (range 1 month to 12 years). Of the 45 patients with 48 affected limbs, 43 were diagnosed with stage II extremity lymphedema, with most of them exhibiting pitting edema, and 5 were diagnosed with stage III lymphedema (ISL classification). No patients in this study had experienced trauma to the lymphedematous limbs, and none of them had received treatment for lymphedema before the MRL examination.

MRL was performed as described previously (5,6) using a 3.0T MR unit (Philips Medical System, Best, The Netherlands). First, 3D heavily T2-weighted MR imaging was performed. After injection of paramagnetic contrast agent gadobenate dimeglumine (Gd-BOPTA) into the digital web spaces (4 points for each limb, 0.7-0.8ml/each point; MultiHance®; Bracco, Milan, Italy), 3D fast spoiled gradient-recalled echo T1-weighted images were acquired using a fat saturation technique at consecutive time points for dynamic observation. Six consecutive acquisitions were performed in the leg, with each acquisition taking 3 min. Five consecutive acquisitions were performed in the inguinal region and thigh, with each taking 3 min. Maximum intensity projection (MIP) reconstruction imaging was performed to map lymphatic vessels.

The Wilcoxon test was used in the statistical analysis. P values of 0.05 were considered as significant.

RESULTS

After intracutaneous injection, contrast material was rapidly absorbed by the primary lymphatic vessels and transported in the

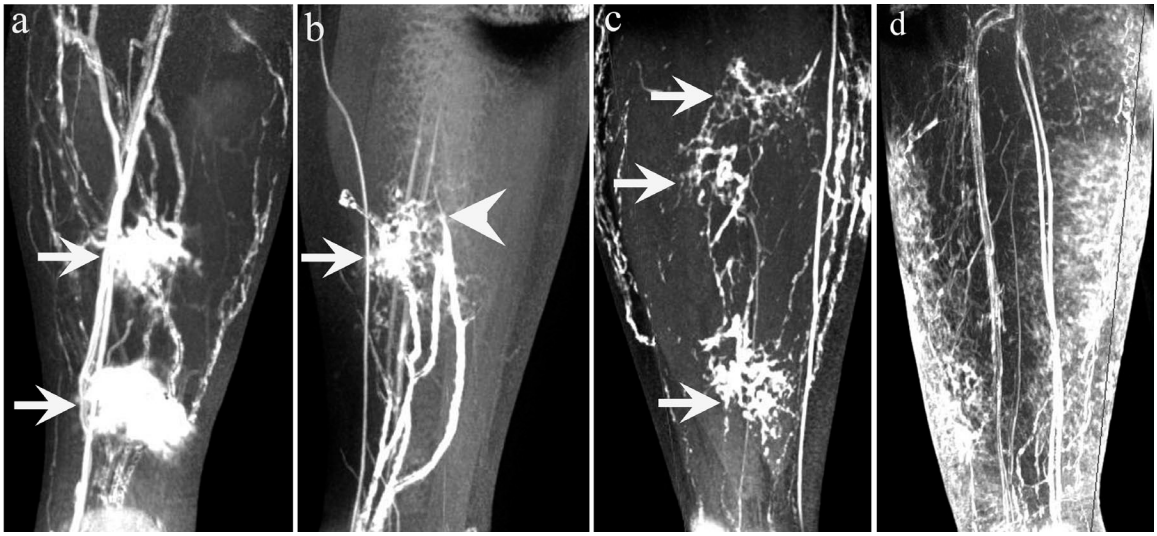

Fig. 1. Anterior tibial lymphatic damage on MR lymphangiogram. a. Lymphatic rupture and lymphorrhea (arrows) in a left lower leg lymphedema. b. Disruption of the collecting lymph vessels with lymph leakage (arrow) in a left lower leg. Only lymph collectors distal to the rupture point were enhanced (arrowhead). c. Segments of regenerated lymphatic network (arrows) displayed in a lymphedematous right leg. d. "Dermal backflow" characterized by massive diffusion of high signal intensity in the skin of an affected right leg.

lymph. Enhancement of lymphatic vessels was seen during dynamic MRL, and drainage patterns of lymphatic vessels were clearly observed. In the healthy limb, superficial collectors are typically straight and have the same caliber along their entire length (8). The superficial lymphatic system of the lower extremity drains the skin and subcutis in places where the skin lies directly over bone (anterior surface of the tibia) and periosteum (8). No enhanced lymph vessels were visualized in most of the contralateral healthy limbs. In some non-edematous limbs, weaker enhanced lymphatic channels were observed. Lymphatic collectors in the lymphedematous extremity were tortuous and significantly dilated with a diameter range of 0.7-10mm in lower limbs and 0.5-5mm in the upper limb.

In 36 patients with 39 lymphedematous lower limbs, obvious damage of collecting lymphatic vessels on MR lymphangiogram was seen in 36 limbs including vessel disruption, lymph leakage, and regeneration of small lymphatics between the broken vessels. In all limbs, damage to vessels occurred in the anterior tibial area of the lower leg and involved the anterior tibial lymph vessel. Among the damaged vessels, one or two anterior tibial lymphatic channels were found to be ruptured with leakage of contrast-enhanced lymph into the surrounding region (*Fig. 1a*) in 21 cases. Totally nonfunctional collecting lymph vessels in the lower leg without inflow of lymph in the proximal segment were seen in one patient (*Fig. 1b*). In 15 limbs, a segment of enhanced lymphatic network was seen bridging the trunks of collecting vessels without lymph leakage in the tibial area (*Fig. 1c*). In a few patients "dermal backflow" caused by lymph filling in the skin of affected limbs was seen. Although both collecting vessel disruption and "dermal backflow" involved extravasation of contrast-enhanced lymph into the tissue on the MRL images, there were significant differences between the two. In "dermal backflow," contrast material had extravasated to the dermis and was seen as massive diffusion of high signal intensity in the skin of the lower limb (*Fig. 1d*). In lymphatic disruption, a

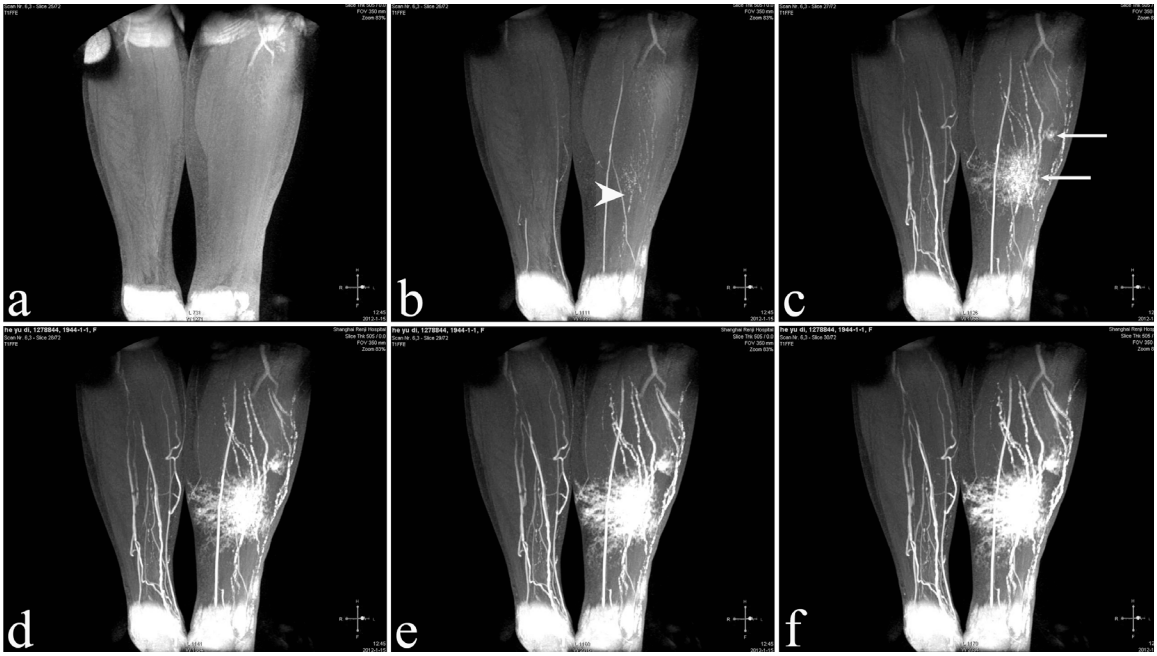

Fig. 2. Dynamic imaging MR lymphangiogram shows lymphatic disruption and lymph leakage in the left lower leg. a. No lymph vessels were visualized on initial inspection. b. Lightly enhanced collecting vessels (arrow head) were observed in the distal part of the lower leg at 8 min. c-f. Anterior tibial lymphatic disruptions and lymph leakage (arrows) were displayed and extravasation of contrast and the enhancement of lymph vessels became evident over time (last image was at 18 min.).

single break in a vessel was usually seen in the middle of its course along the lower leg and the leaking contrast material radiated from the break in the significantly dilated collector with extent increasing with time on dynamic MRL images (*Fig. 2*). In a woman with bilateral lymphedema, lymphorrhoea was observed on images of her lower legs 6 months after surgical treatment of endometrial carcinoma. Lymphorrhoea had completely disappeared in both legs and a mass of proliferated new vessels appeared 1 year later (*Fig. 3a-c*). These results suggest that the anterior tibial lymph vessel is the weak point of the lymph pathway in the lower extremities, and the imaging features of the vessels, such as disruption, lymphorrhoea, and regeneration, reflect the evolution of both lymphatic damage and repair in obstructive lymphedema.

In upper extremities, collecting lymphatic disruption and lymph leakage were also observed (*Fig. 4a*). However, the damage to lymphatic vessels appeared random. One or many leaks and a regenerated lymphatic network were seen in either the radial and/or the ulnar side of the forearm (*Fig. 4b*). Images of lymphatic damage were different from "dermal backflow" on MRL imaging and were characterized by massive high signal intensity in the distal region of the arm (*Fig. 4c*).

At the time of MRL, the median (range) duration of lymphedema in patients with lymphatic rupture and lymph leakage seen on MRL imaging was 6 (1-60) months (29 cases), and in patients with obvious lymphatic regeneration 24 (6-300) months (16 cases). The difference was significant (P=0.0023).

In most cases, stagnant lymph and tissue fluid had accumulated above the deep fascia

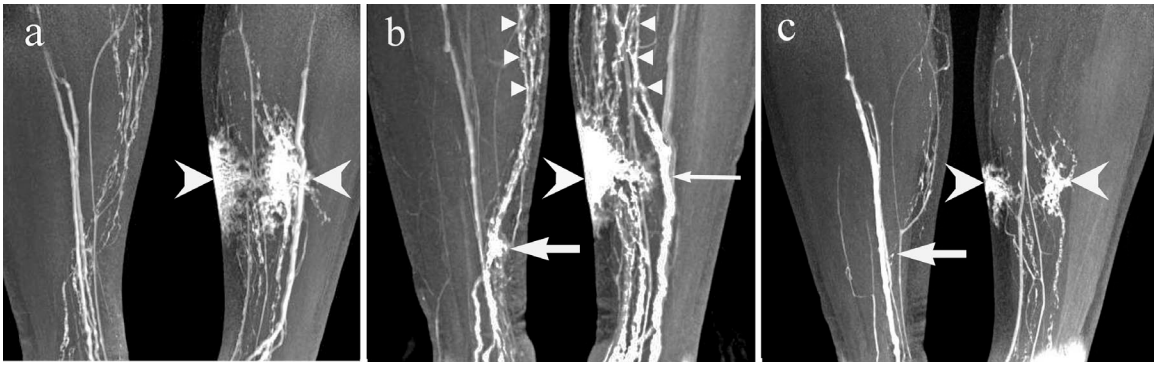

Fig. 3. MR lymphangiogram shows the evolution of lymphatic damage in a patient with bilateral lymphedema. a. Anterior tibial lymph collector disruption and lymph leakage (arrowheads) displayed in the left lower leg six months after the first appearance of lymphedema. b. One point of lymph leakage was significantly reduced (small arrow) leaving another (arrowhead) in the left leg one month after compression therapy while a new lymphatic disruption was seen in the right lower leg (large arrow). c. Lymphorrhea completely disappeared in the right leg (arrow) and a collection of regenerated new vessels appeared between the former ruptured lymphatic collectors in the left leg one year later (arrowheads).

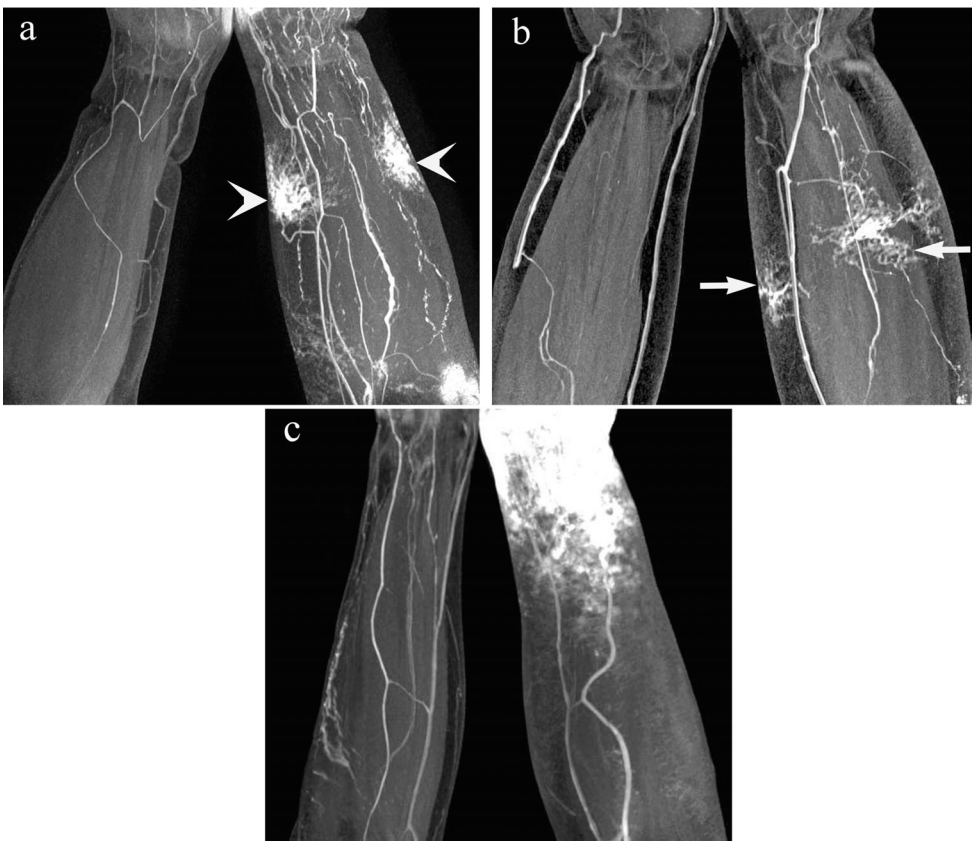

Fig. 4. MRL imaging shows lymphatic damage in the lymphedematous upper extremity after mastectomy. a. Lymph collector disruption and lymphorrhea (arrowheads) in the forearm. b. Lymphatic network regeneration (arrows) in the forearm. c. The "dermal backflow" was seen as massive high signal intensity in the distal region of the arm.

TABLE 1
Demographic Data in Obstructive Lymphedema Patients with Collecting Lymphatic Damage

	Upper Extremity	Lower Extremity
Patients (cases)	9	36
Etiology		
Mastectomy/Lymph node dissection	9	
Surgery/radiation therapy		22
Lymph node metastasis		7
Injury		3
Lymphadenitis		2
Affected limb		
Unilateral	9	31
Bilateral		3
Episodes of erysipelas	1	17
Clinical features		
Stage II	9	32 /39 limbs
Stage III		5/39 limbs
MRL findings		
Lymphatic disruption & lymphorrhea	8	21
Lymphatic regeneration (newly generated network)	1	15
Dermal backflow	1	3

and no fibrosis was seen in the subcutaneous layer of the affected limbs on cross-sectional MR imaging. This suggests that most of these patients presented with lymphedema in a relatively early stage. Among the 45 investigated patients, 18 experienced one or more episodes of erysipelas; but there appeared to be no association between the inflammation and the observed lymphatic damage.

The clinical features and MRL findings of lymphatic damage in the study group of 45 patients are summarized in *Table 1.*

DISCUSSION

Lymphostasis due to obliteration of lymphatic pathways inevitably affects the structure and function of the vessels. The lymphatic pathology in turn has a profound impact on the development and prognosis of the disease. The present study used MRL to demonstrate distinctive pathological changes in the collecting lymph vessels including disruption, lymphorrhoea, and regeneration in obstructive lymphedema. The observed lymphatic damage may be characteristic of progressive changes in collecting lymphatic vessels during the course of obstructive lymphedema. Lymphatic collectors underwent spontaneous rupture, and lymph leakage followed lymph stagnation in the vessel and increased luminal pressure when the upstream pathway was blocked.

Under normal conditions, lymph flow is not continuous and the rhythm of contractions of lymph vessels is approximately three per min (9). In obstructive lymphedema, collecting lymph vessels are significantly dilated and their wall is stretched leading to an increase in the force and frequency of the contractions (10). Both spontaneous contractions of the lymphatics and voluntary contractions of the calf muscles generate pressure that propels the lymph. Lymph pressure may increase to 200mmHg, which is ten times higher than normal (9). When the lymphatics are constantly distended with lymph, these high efficiencies, plus significantly increased luminal pressure, may lead to tearing of the thin lymphatic wall and lymph leakage.

In contrast to the upper limb where lymphatic rupture and lymphorrhoea occurred sporadically in the forearm, damage to the collecting lymph vessels in the lower limb commonly occurred in the pretibial area of the middle third of the lower leg, reflecting that the anterior tibial lymph vessel in the lower leg is the weak point of the lymphatic pathway in lower limbs. The most likely reasons is that anterior tibial lymph vessels

are the main lymphatic trunks in the lower limb that go straight up to the inguinal nodes with few collateral branches connecting with adjacent vessels, relieving the intraluminal pressure, and alleviating lymph stagnation. Second, the anterior tibial lymph vessels are located in the distal part of the extremity where the edema occurs first and is more serious in the course of the lymphedema. Third, the pretibial region of the lower leg is tightly enclosed by intermuscular septae and muscle membranes, and the skin directly covers the bone and periosteum, so that the space is almost non-distendable. In addition, the superficial lymphatic trunks running along this region have little protective soft tissue padding (11). Therefore, the dilated lymphatic vasculature, with a stretched wall, may easily be damaged by the high pressure inside and outside the lumen (10).

The observed phenomena of lymph vessel breakage and repair are presumably dynamic and recurring events occurring in the obstructed collector during progression of the disease, i.e. lymph vessel breakage is followed by spontaneous repair and regeneration of the lymphatic network. Generally, lymphangiogenesis is an effective and rapid process (12-14). The repair of damaged vessels in obstructive lymphedema might not include end-to-end reconnection, so the gaps between the ruptured vessels were bridged by a network of small vessels. As a result, the repaired vessels extended the lymphatic channels of the affected limb. It is noteworthy that not all of the broken lymphatic collectors in the extremity were repaired. In a previous study, we found lymphatics that ended at the distal third of the lower leg apparently without proximal channels in a considerable number of patients (15).The failure of regeneration of the broken vessels might lead to the obliteration of the proximal part of the vessels and worsening of the lymphedema.

As lymphatic vessels are fragile and may rupture spontaneously in obstructive lymphedema, early diagnosis and localizing lymphatic damage is important to allow proper management of lymphatic injury as well as to prevent obliteration of the lymphatic collectors. For example, microsurgical procedures (such as lymphatic-venous shunting) might be unsuitable for an extremity lymphedema with lymphatic breakage and lymph leakage. Furthermore, the effect of manual lymph drainage/compression on the damaged lymph vessels is unclear, and whether local delivery of lymphatic growth factor would benefit the lymphatic healing and regeneration is unproven. Equally important is determining how to avoid lymphatic vessel damage, as well as how to protect lymphatic vessels in the weak region in obstructive lymphedema.

In conclusion, the observed damage to lymphatic collectors in this study may be common and unique pathological characteristics in obstructive lymphedema and further, the damaged lymph collectors were found to be capable of repair and regeneration. In addition, the anterior tibial lymph vessels in the pretibial region were weak points identified as the lymph pathway in lower limbs. These phenomena may be helpful in elucidating the pathophysiology of obstructive lymphedema and may lead to both improved prevention and management strategies.

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