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Review of Dancing Parasites in Lymphatic Filariasis

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ABSTRACT

Lymphatic filariasis is an infection transmitted by blood-sucking mosquitoes with filarial nematodes of the species *Wuchereria bancrofti, Brugia malayi und B. timori*. It is prevalent in tropical countries throughout the world, with more than 60 million people infected and more than 1 billion living in areas with the risk of transmission. Worm larvae with a length of less than 1 mm are transmitted by mosquitoes, develop in human lymphatic tissue to adult worms with a length of 7–10 cm, live in the human body for up to 10 years and produce millions of microfilariae, which can be transmitted further by mosquitoes. The adult worms can be easily observed by ultrasonography because of their size and fast movements (the so-called "filarial dance sign"), which can be differentiated from other movements (e. g., blood in venous vessels) by their characteristic movement profile in pulsed-wave Doppler mode. Therapeutic options include (combinations of) ivermectin, albendazole, diethylcarbamazine and doxycycline. The latter depletes endosymbiotic Wolbachia bacteria from the worms and thus sterilizes and later kills the adult worms (macrofilaricidal or adulticidal effect).

Introduction

Parasitic diseases are rarely encountered in Europe and the clinical and imaging features are generally not well known. In the era of worldwide migration and refugees, knowledge of such diseases has gained importance as illustrated by multiple recently published reports of hydatid diseases [1–5], schistosomiasis [6, 7], fasciolosis [8], ascariasis [9], liver flukes [10], toxocariasis and other rare intestinal diseases [11, 12]. This article describes the clinical and imaging features along with current treatment strategies for filariasis.

Across the world, nematodes (roundworms) cause a wide variety of parasitic infections of the subcutaneous and lymphatic tissue of almost all organs with significant economic and psychosocial damage. Three species, *Wuchereria bancrofti* (90 % of lymphatic filariasis infections, humans are the only hosts), *Brugia malayi* (up to 10 % of lymphatic filariasis infections, humans, domestic and wild animals are hosts), and *B. timori*, cause lymphatic filariasis (LF) affecting approx. 60 million patients worldwide [13]. Lymphangitis, lymphedema and the formation of fibrosis, sclerosis and scars are

the pathophysiologically important sequelae. Loiasis and onchocerciasis are rarely associated with lymphedema.

LFI caused by *W. bancrofti* is common in the tropical regions of India and Southeast Asia, Pacific islands, Latin America and Caribbean area as well as in sub-Saharan Africa. *B. malayi* occurs mainly in China, India, Malaysia, Indonesia, the Philippines and the Pacific islands. *B. timori* occurs only on the Timor Island of Indonesia and some neighboring islands.

Nematodes are transmitted by mosquitoes. The mosquito vectors for filariasis vary geographically including the genus Culex, Anopheles, Aedes, Mansonia, and Coquillettidia. Humans are the so-called definitive host where the sexual stages develop. The adult worms do not replicate in humans. Therefore travelers have a short exposure to infective larvae and the disease ceases generally after a certain period. Transmission most often happens in childhood [14, 15]. The disease is almost not detected in travelers and very rarely in expatriates.

The larvae develop into mature adult worms, which mate and produce sheathed microfilariae with mainly nocturnal periodicity. In addition, a mosquito ingests the microfilariae again during a blood meal; these develop into larvae, which can infect another human when the mosquito takes a subsequent blood meal, completing the life cycle.

The prevalence increases with age. Travelers usually have insufficient exposure to filariasis to develop sufficiently high worm burdens. More often a local hypersensitivity including eosinophilic infiltrate with lymphangitis and lymphadenopathy, urticaria, and peripheral eosinophilia is observed.

Humans are infected during a blood meal. The mosquito-transmitted larvae develop into mature adult worms in about 9 months. The adult parasites can be observed in lymphatic vessels. Larvae appear in the blood stream after a prepatent period of about 12 months. They often show periodic activity in the blood stream. In areas with mosquitos that are active at night, the larvae appear in the blood in astonishingly precise nocturnal periods. In areas with mosquitos that are active during the day, the larvae can be detected in the blood during the day, e. g., *Brugia malayi*. The adult worms survive for approximately five years. The size of the filariae is species-dependent from 10 – 100 mm in length and 0.07 × 0.1 mm in width. In ultrasound images the echoes appear bigger than the real worm. Measurements resulted in echoes of up to 2.5 mm.

Filarial disease is influenced by the extent and duration of exposure to infective mosquito bites, i. e., the quantity of accumulating adult worm antigen in the lymphatics. The adult worms in the lymphatics induce an inflammatory response [16] but also mechanical damage [17]. As rickettsia-like organisms, Wolbachia are endosymbiotic to adult worms [18] and may be responsible for the inflammatory changes [19–24]. Treatment with antibiotics such as doxycycline or rifampicin kills Wolbachia and as a result the adult worms become sterile and can no longer reproduce. As such, treated patients are no longer infectious.

Symptoms and Clinical Manifestations

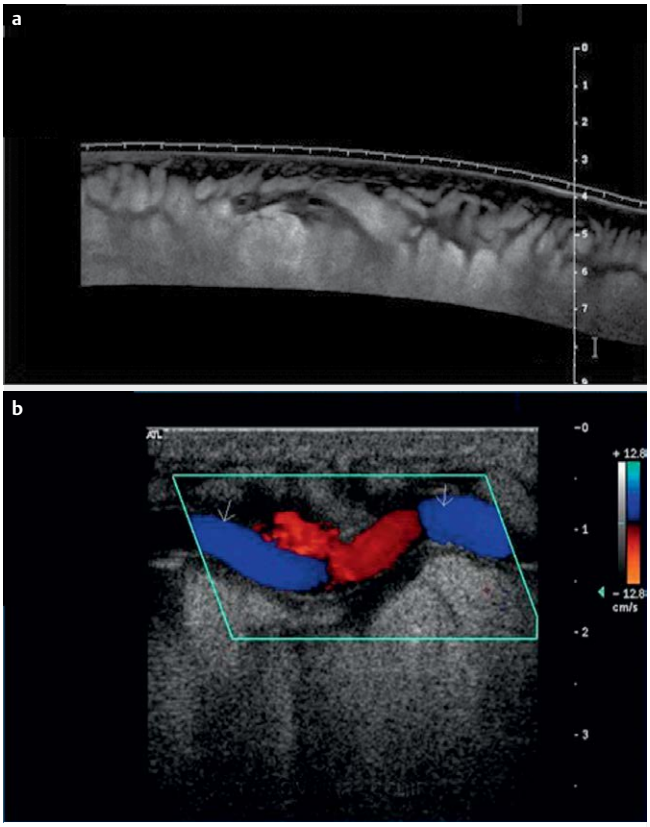
Only one third of infected patients develop overt symptoms [25]. Symptoms range from asymptomatic to severely disabling. The severity of symptoms and the course of the disease are determined by the extent and duration of the exposure to infective mosquito bites, the quantity of accumulating adult worm antigen in the lymphatics, the host immune response, and the number of secondary bacterial and fungal infections.

Acute disease

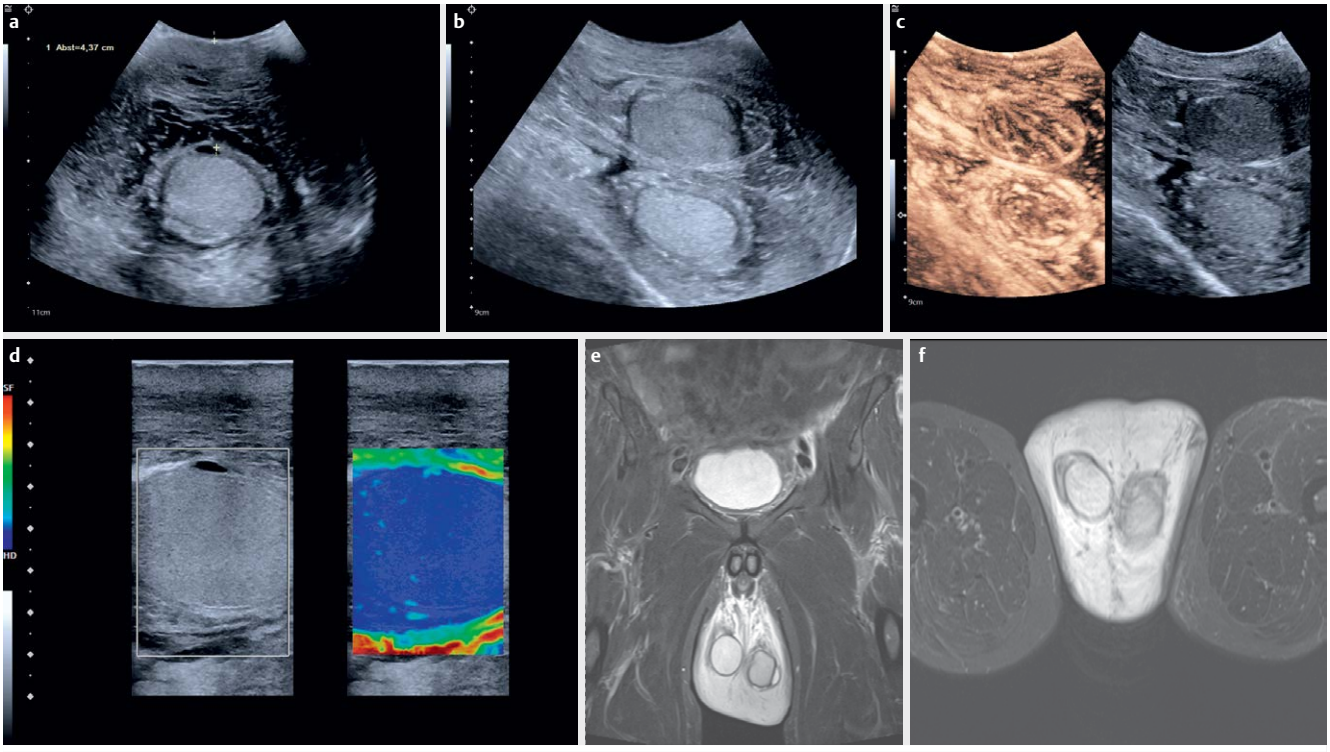
Acute disease is caused by spontaneous or drug-induced death of adult filariae, with filarial fever, chills, acute lymphadenopathy (with retrograde lymphangitis, mainly the inguinal lymph nodes), myalgia and tropical pulmonary eosinophilia with microfilariae trapped in the lungs characterized by nocturnal wheezing [26]. In general, the recurrent acute inflammation occurs once, twice or five times a year and resolves after few days to one week depending on severity [27–29].

Chronic disease

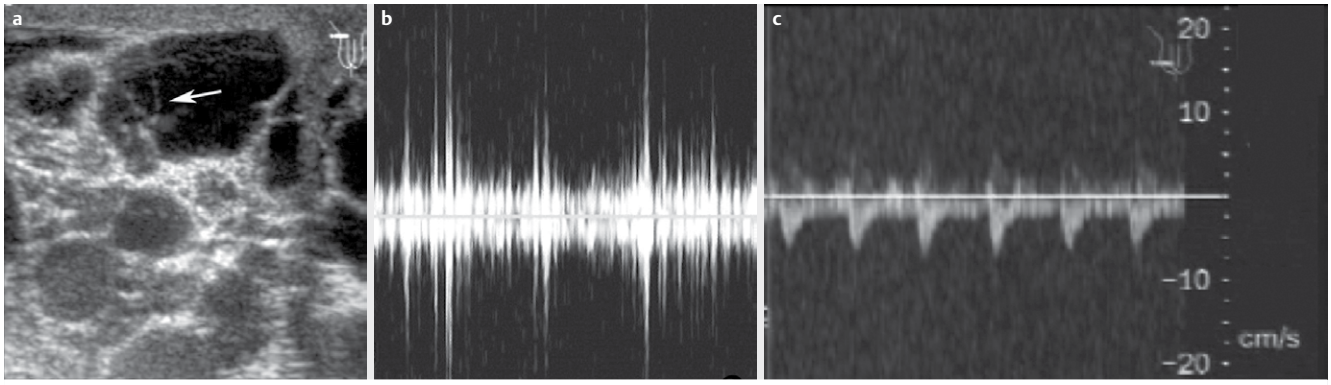
Local symptoms (pitting lymphedema, hydrocele) are the prominent signs of chronic infection within the skin and the surrounding tissues, especially the lower extremities [30]. The mechanism might be partially explained by bacterial superinfection (e. g., interdigital microtrauma), and once the lymphatic vessels are damaged, lymphedema may progress even in the absence of filarial infection [31]. In Brugian filariasis ulcerating abscess formation may occur along the involved lymphatics including the genitalia. Many organs can be involved, including the scrotum (scrotal lymphangiectasia, hydrocele up to 30 cm, epididymitis and rarely orchitis),



▶ **Fig. 1** Leg filariasis, B-mode imaging of leg filariasis **a**, color Doppler imaging of leg filariasis **b** in a patient with subcutaneous thickening.



▶ **Fig. 2** 60-year-old patient from Guatemala, Latin America with recurrent scrotal swelling with thickness of the pure scrotum without testis of >40 mm **a** and **b**, the swelling is indicated between markers) on both sides **b**. A hydrocele was operated on a few years ago. Treatment with mebendazole has been reported during that time. The "filarial dance sign" could be seen on real-time ultrasound below the testis. The testes showed increased stiffness using elastography **c** and little contrast enhancement on contrast-enhanced ultrasound **d**, indicating chronic orchitis. MRI images (T2, koronar) are also shown **e**, **f**.



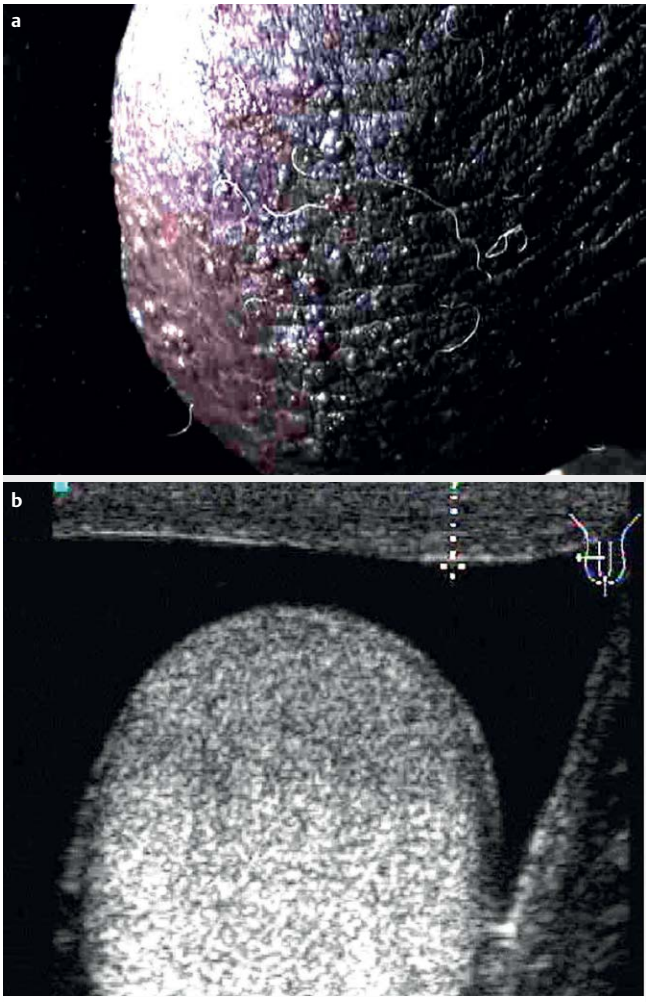
▶ **Fig. 3** Ultrasound of enlarged lymph vessels in the scrotal area; in the left part of the biggest vessel, a moving worm can be detected **a**. On pulse wave Doppler, the movements appear as irregular amplitudes **b** and can be differentiated from pulsating vessels **c**.

urogenital and renal manifestations [32–34] with chyluria (intestinal lymph may be intermittently discharged into the renal pelvis [35], ovary and inner genital [36], eyes and heart. The hydrocele is a fluid collection between the parietal and visceral layers of the tunica vaginalis, surrounding the testis and spermatic cord. Progressive non-pitting lymphedema with limb swelling is related to chronic inflammation of the lymphatic vessels resulting in hyperpigmentation and hyperkeratosis and sometimes elephantiasis of the lower limbs. The breast can be involved in females.

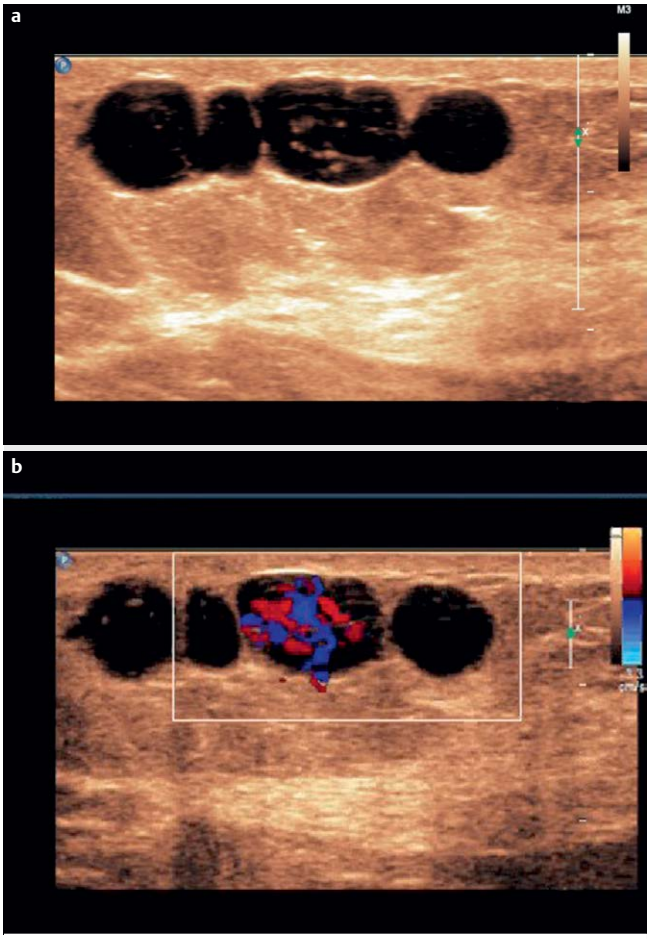
Diagnosis

Confirming serological diagnosis

Blood eosinophilia is typical, sometimes exceeding 3/nL [26] and serves as screening in patients with typical symptoms. Diagnosis of LF can be best achieved by detecting circulating filarial antigen (CFA) of *W. bancrofti*-DNA in the blood [37–43], detecting circulating microfilariae or by detecting adult worms in the lymphatics [44]. Examination of blood smears is a less sensitive but acceptable



▶ **Fig. 4** Lymph scrotum with thickened skin **a**. Thickness can be measured by ultrasound **b**.



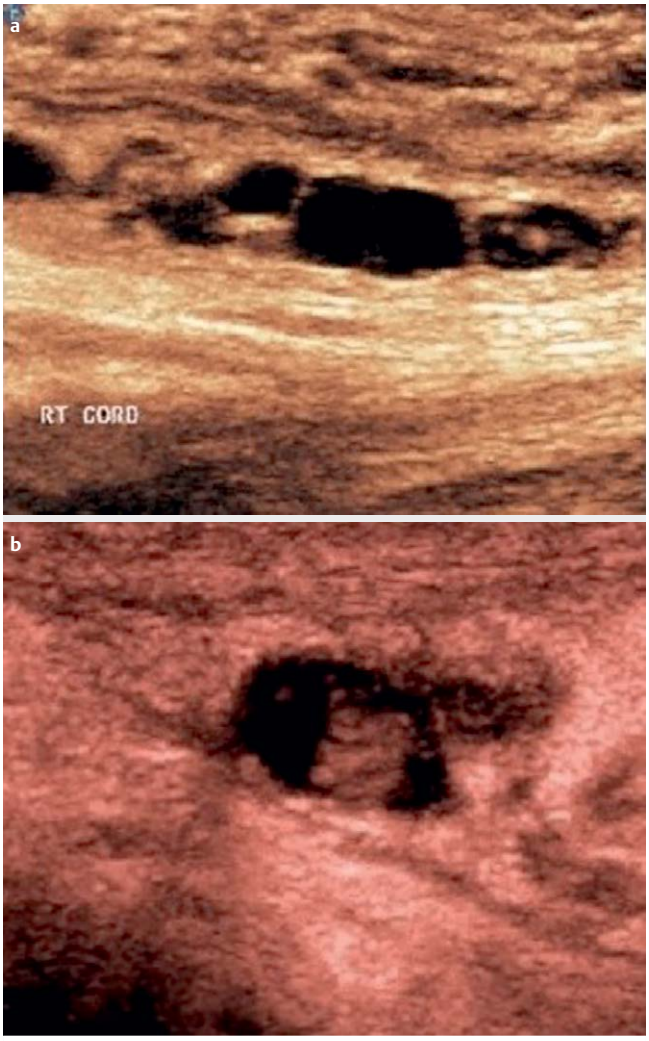
▶ **Fig. 5** Breast filariasis. B-mode imaging **a** and color Doppler imaging of breast filariasis **b**. Irregular amplitudes of color signals could be used to make a differential diagnosis.

alternative in settings where antigen testing is not available. Blood tests have better sensitivity than biopsy and histological evaluation [45, 46]. CFA is diagnostic in *W. bancrofti* only but false-positive *W. bancrofti* antigen testing may occur in patients with severe circulating Loa loa microfilariae [47, 48]. Negative blood results have been observed in treated "burned out" infections [46, 49, 50]. Definitive diagnosis of filariasis requires blood smear examination for microfilariae or the presence of circulating filarial antigen. Serological testing may be helpful in appropriate clinical settings. Unless they use the single recombinant antigen Wb 123 (which is not commercially available) [51], antifilarial serologic antibody tests do not differentiate between the various types of filarial infections and often show a cross-reaction with antigens from other diseases caused by helminths [52]. They do not allow differentiation between acute and chronic infection [53]. Species-specific polymerase chain reaction techniques have been used but they are not commercially available [54, 55]. Examination of concentrated [56] blood smears using Giemsa or Wright stains (taken during the nocturnal activity period) for microfilariae is a second-line diagnostic tool if circulating antigen testing is not available or Brugian filariasis is suspected [57, 58]. Morphologic characteristics on blood smear allow differentiation of the LF species. *W. bancrofti* and both Brugia species have an acellular staining sheath visible on light microscopy. *W. bancrofti* has no nuclei in its tail whereas *B. malayi* has terminal and subterminal nuclei in its tail.

Imaging diagnosis

Imaging in general and ultrasound specifically may demonstrate the parasites' respective complications [59–63]. Damaging conventional X-ray contrast lymphangiography has been replaced by scintigraphy [33].

X-ray lymphangiograms made in patients with filarial lymphedema show a typical pattern of varicosities which clearly differentiate this condition from lymphostatic verrucosis, the prevalent form of non-filarial lymphedema [64]. Also, lymphography was useful in the treatment of chyluria [65]. Contrast lymphangiography, while widely used to visualize the morphology of the lymphatic vessels [66], carries the potential risk of lymphatic damage. The unpredictable consequences of such studies have hampered the early evaluation of the lymphatics of asymptomatic individuals [67]. To overcome these difficulties, lymphoscintigraphy using radiolabeled albumin or dextran has been developed [68]. This technique can be performed and repeated safely so that serial studies of individuals



▶ **Fig. 6** Cord filariasis, grayscale imaging of cord filariasis **a**, detailed view of small adult worms **b**.

are possible. Preliminary studies with this technique have demonstrated the presence of lymphatic abnormalities in asymptomatic microfilaremics with no evidence of edema. Lymphoscintigraphy allows clear and precise analysis of lymphatic system function in patients at risk. This technique could be used for the examination of infected but asymptomatic individuals to determine whether they have morphological or functional lymphatic abnormalities and how these alterations could be changed, especially by chemotherapy. It could also provide a new epidemiological tool for detailed studies of morbidity due to endemic filariasis.

Ultrasound allows the detection of moving adult worms in lymphatic vessels ("filarial dance sign") and also monitoring of the effectiveness of treatment [69–77] (▶ **Video 1**). Pulsating blood vessels can be differentiated from irregular moving worms containing lymphatics by Doppler ultrasound [78–81] (▶ **Video 2**). The "filarial dance sign" has been observed in many organs including the limbs [71, 80] ▶ **Fig. 1**, scrotum [69, 70, 72–74, 82–84] ▶ **Fig. 2** and ▶ **Fig. 3**, breast and axillary lymphatics [75, 78, 85, 86] ▶ **Fig. 4** and ▶ **Fig. 5** or cord ▶ **Fig. 6**. The role of different ultrasound techniques in evaluating lymphatic disease has been extensively described [87–95]. The role of contrast-enhanced ultrasound [88, 96–102] and elastography [99–101, 103–106] in the evaluation of filariasis has not yet been described. Both methods might be helpful in identifying fibrosis and scars. Contrast-enhanced ultrasound can also be used to evaluate the lymphatic tissue directly [107, 108].

Almost no helpful and specific experience has been published about CT [109–111] and MRI [112–115] findings in filariasis also due to the small size of the parasites.

Differential Diagnosis

The differential diagnosis of LF with retrograde lymphedema includes primary lymphedema, progressive cellulitis, neoplastic diseases (e. g., cancer) and a variety of inflammatory diseases (e. g., antegrade bacterial lymphangitis, tuberculosis), as well as loiasis, onchocerciasis, podoconiosis (abnormal inflammatory reaction to mineral particles in altitudes higher than mosquito transmission zones for filariasis (above 1 500 m)) [116]. Loiasis and onchocerciasis are rarely associated with lymphedema.

The filarial nematode *L. loa* causes loiasis. The diagnosis is established by identifying the migrating adult worm in the subcutaneous tissue swelling (calabar) of the distal limbs and during the subconjunctival migration of the worm around the orbita or by detecting microfilariae in a blood smear [47, 117, 118]. False-positive antigen tests for *W. bancrofti* in the setting of *L. loa* microfilaremia may complicate the diagnosis of occult *W. bancrofti* in coinfected patients.

The filarial nematode *Onchocerca volvulus* causes onchocerciasis. The clinical manifestations include skin and eye involvement and systemic manifestations. The so-called "hanging groin" is a result of skin atrophy of the groin and anterior thigh. Chains of (scary) lymph nodes result in folds of loose skin.

Treatment

Early treatment is recommended also in asymptomatic patients to prevent lymphatic disease. In patients with advanced disease with scars and fibrotic tissue, treatment success is less obvious. The treatment of local and systemic secondary bacterial infections is mandatory and includes regular antibiotics and prophylactic antibiotics in some cases and the use of antibacterial creams on damaged skin and small erosions. Careful attention to hygiene including regular nail cleaning, wearing of shoes, washing of affected areas daily, etc. is important. The affected limb(s) should be regularly exercised and if necessary lymph flow should be enhanced by complex decongestive therapy (CDT). Elevation of the affected limb during the night is recommended after the exclusion of arterial occlusive disease.

The standard treatment of choice in monoinfection of *Wucheria bancrofti*, *Brugia malayi*, and *Brugia timori* is diethylcarbamazine (DEC, 6–10 mg/kg for up to 2 (3) weeks) [1, 119–121]. The dosage and mechanism of action depend on the species [122–124]. DEC is not recommended in pregnancy.

Patients with proven or suspected coinfection of LF and onchocerciasis without ocular involvement should undergo treatment of onchocerciasis first. LF pre-treatment in the form of ivermectin 150 µg/kg in a single dose should be given to reduce the microfilarial load [124–129]. Ivermectin can be followed by the above-

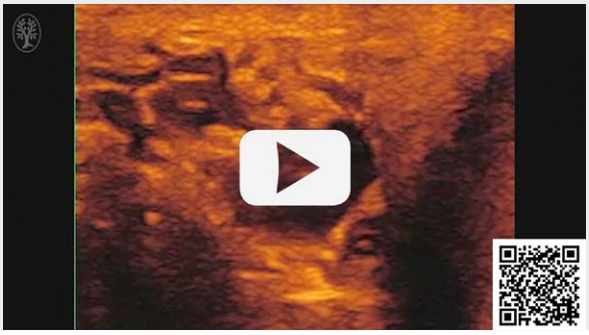
mentioned standard treatment for LF, DEC after one month or later [130, 131]. Doxycycline (200 mg orally once daily for four to six weeks) followed by ivermectin (150 µg/kg orally single dose) can be used as an alternative to the standard treatment [132]. It is macrofilaricidal, i. e. it kills the adult worms and constitutes a curative therapy.

Albendazole shows at least partial macrofilaricidal activity against adult worms and has been effective and safe in patients with concomitant loiasis or onchocerciasis [133, 134]. Complex lymphatic decongestive physiotherapy should accompany drug treatment.

Surgical drainage of hydroceles may give immediate relief but recurrence may occur [19].

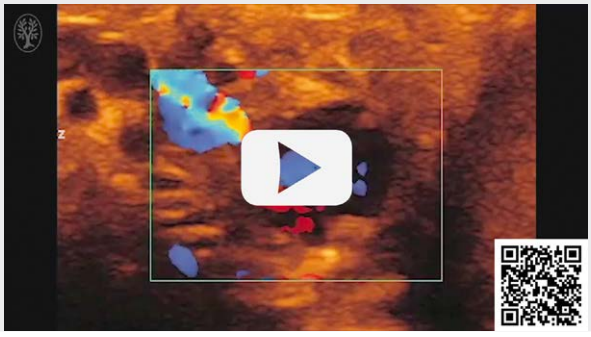
The reproductive lifespan of adult parasites has been estimated to be 4–6 years, explaining the effectiveness of mass treatment programs (Global Program for the Elimination of LF) [121, 135–138]. Such programs have suppressed transmission to < 1 percent. *W. bancrofti* has no animal hosts and might be the best target for elimination. Other filariases, e. g., Brugian, have a domestic and wild animal reservoir and elimination does not seem feasible. Triple-drug single dose treatment with ivermectin, diethylcarbamazine, and albendazole has been successful in endemic areas [139, 140].

VIDEO 1



▶ **Video. 1**

VIDEO 2



▶ **Video. 2**

Conflict of Interest

Authors declare that they have no conflict of interest.

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