

Review of Dancing Parasites in Lymphatic Filariasis




Authors

Christoph F. Dietrich¹, Nitin Chaubal², Achim Hoerauf³, Kerstin Kling⁴, Markus Schindler Piontek⁵, Ludwig Steffgen⁶, Sabine Mand³, Yi Dong⁷

Affiliations

- 1 Caritas-Krankenhaus, Medizinische Klinik 2, Bad Mergentheim, Germany
- 2 Thane Ultrasound Centre, Thane Ultrasound Centre, Thane, India
- 3 Institut für Med. Mikrobiologie, Immunologie und Parasitologie (IMMIP), Universität Bonn, Bonn, Germany
- 4 Department of Infectious Disease Epidemiology, Robert Koch-Institute, Berlin, Germany
- 5 Caritas Krankenhaus Bad Mergentheim, Academic Teaching Hospital of the University of Würzburg, Medical Clinic 2, Bad Mergentheim, Germany
- 6 Trainings-Zentrum Ultraschall-Diagnostik LS GmbH, Ultrasound, Mainleus, Germany
- 7 Zhongshan Hospital, Ultrasound, Shanghai, China

Key words

parasite, guideline, elastography, contrast-enhanced ultrasound

received 28.11.2018

revised 04.04.2019

accepted 01.05.2019

Bibliography

DOI <https://doi.org/10.1055/a-0918-3678>

Ultrasound Int Open 2019; 5: E65–E74

© Georg Thieme Verlag KG Stuttgart · New York

ISSN 2199-7152

Correspondence

Dr. Christoph F. Dietrich, MD

Caritas-Krankenhaus,

Medizinische Klinik 2,

Uhlandstraße 7,

97980 Bad Mergentheim,

Germany

Tel : +49/7931/58 2201, Fax: +49/7931/58 2290

Christoph.Dietrich@ckbm.de

ABSTRACT

Lymphatic filariasis is an infection transmitted by blood-sucking mosquitoes with filarial nematodes of the species *Wuchereria bancrofti*, *Brugia malayi* and *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 aduicidal 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], toxocarosis 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

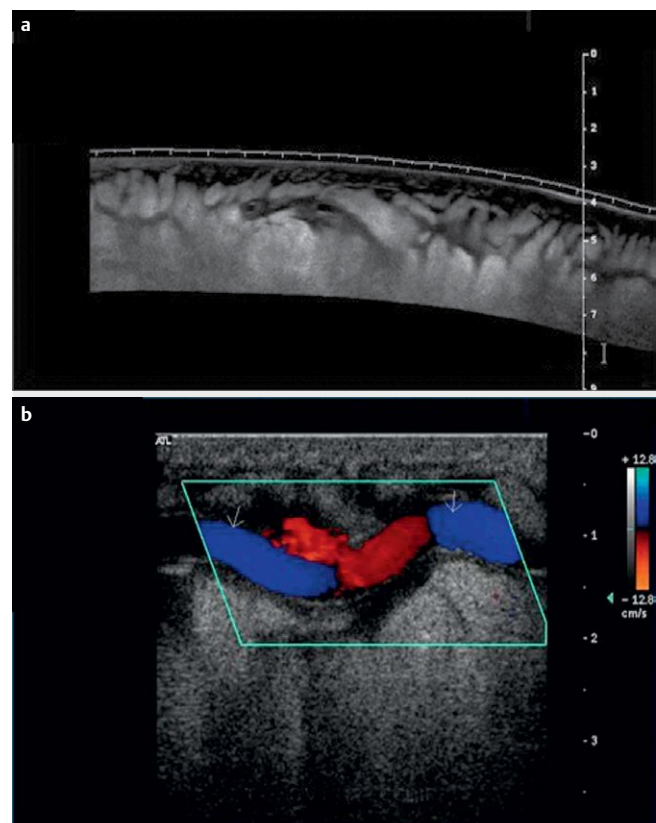
by the extent and duration of the exposure to infective mosquito bites, the quantity of accumulating adult worm antigen in the lymphatics, the host immune response, and the number of secondary bacterial and fungal infections.

Acute disease

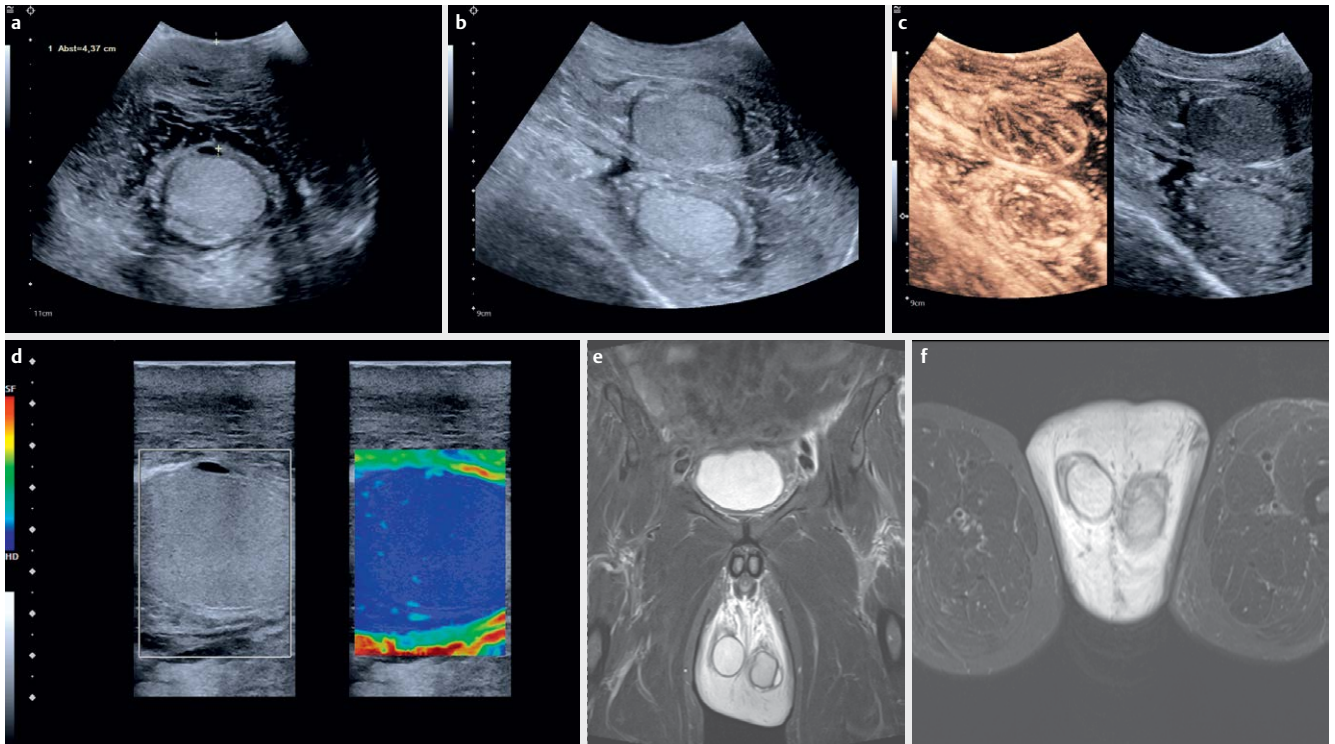
Acute disease is caused by spontaneous or drug-induced death of adult filariae, with filarial fever, chills, acute lymphadenopathy (with retrograde lymphangitis, mainly the inguinal lymph nodes), myalgia and tropical pulmonary eosinophilia with microfilariae trapped in the lungs characterized by nocturnal 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

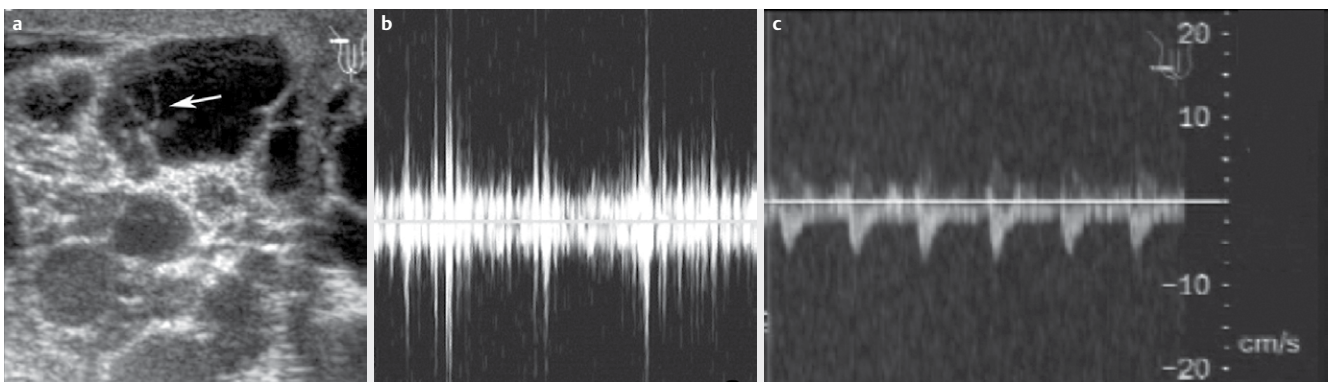
Local symptoms (pitting lymphedema, hydrocele) are the prominent signs of chronic infection within the skin and the surrounding tissues, especially the lower extremities [30]. The mechanism might be partially explained by bacterial superinfection (e. g., interdigital microtrauma), and once the lymphatic 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**.



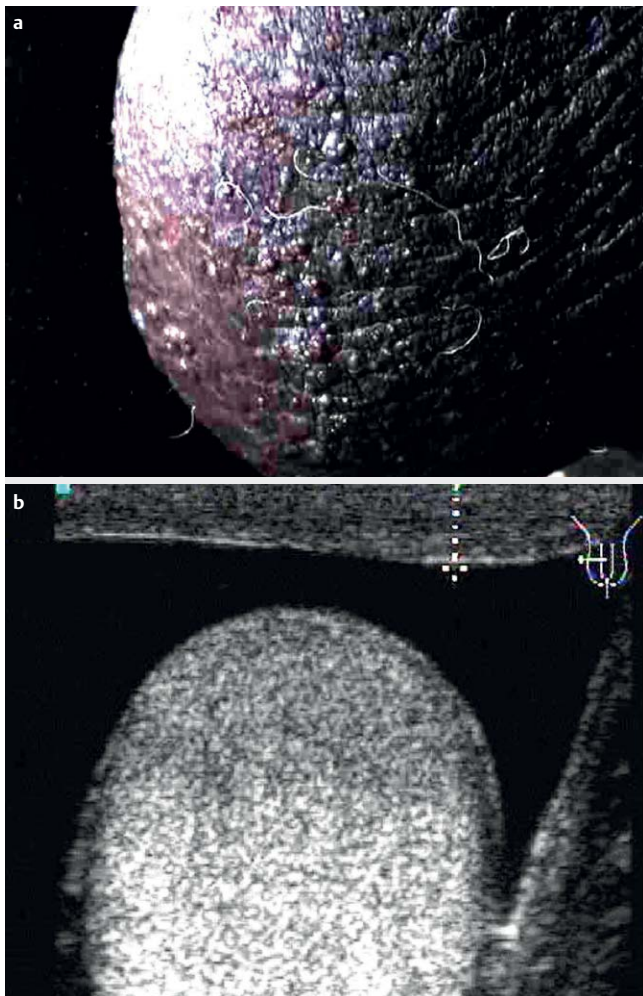
► **Fig. 3** Ultrasound of enlarged lymph vessels in the scrotal area; in the left part of the biggest vessel, a moving worm can be detected **a**. On pulse wave Doppler, the movements appear as irregular amplitudes **b** and can be differentiated from pulsating vessels **c**.

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

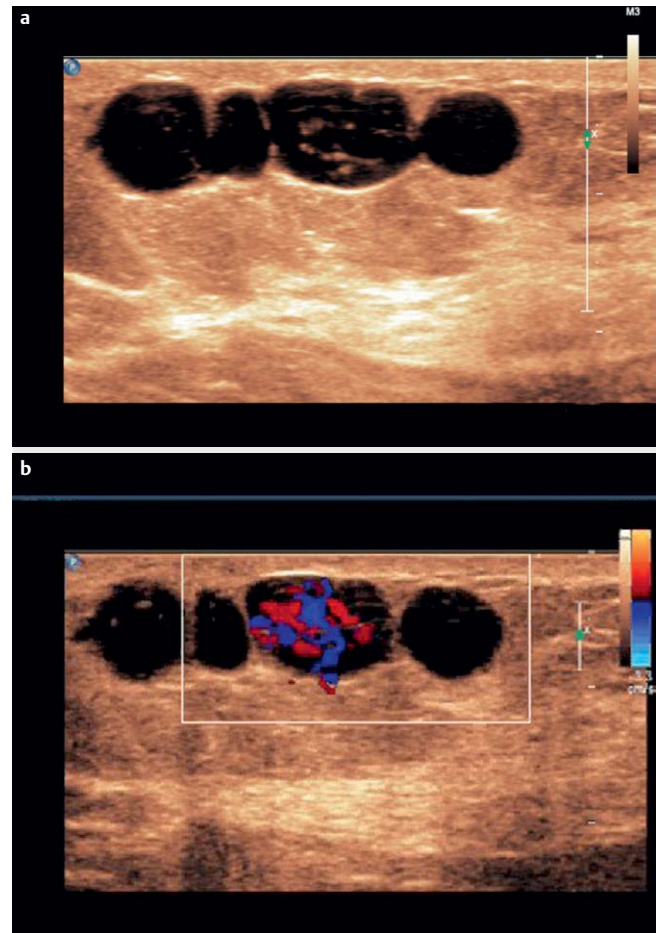
Confirming serological diagnosis

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**.

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



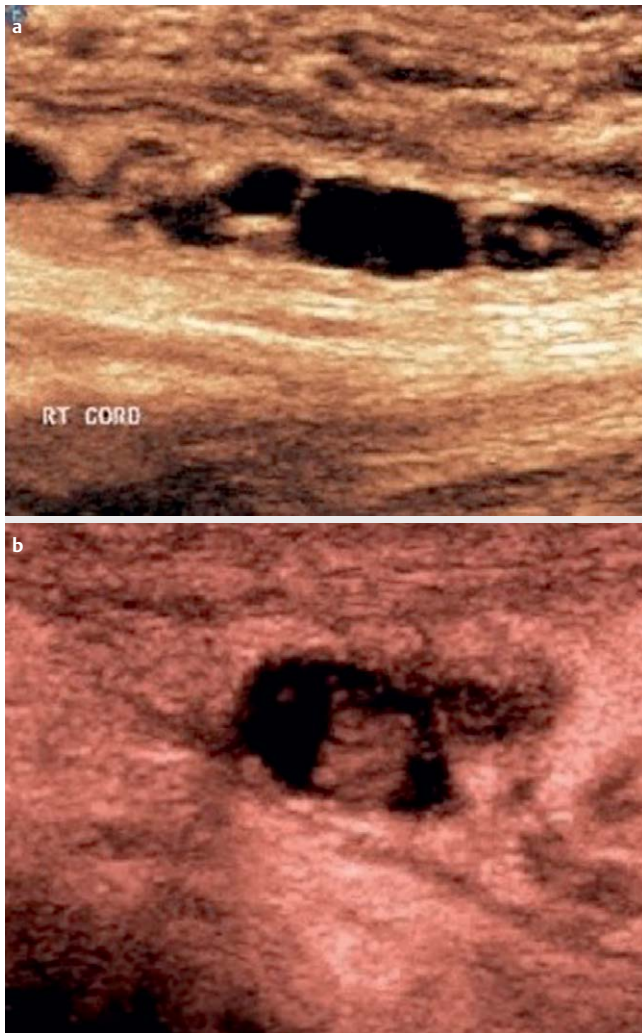
► **Fig. 5** Breast filariasis. B-mode imaging **a** and color Doppler imaging of breast filariasis **b**. Irregular amplitudes of color signals could be used to make a differential diagnosis.

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 coinfecting 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].

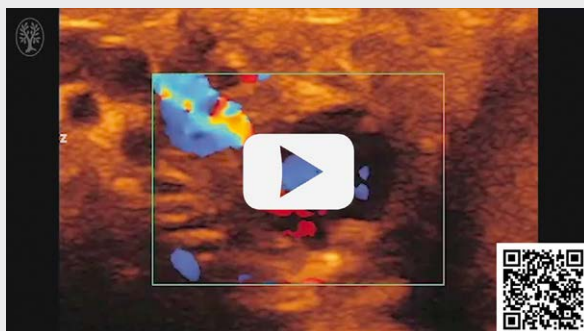
The reproductive lifespan of adult parasites has been estimated to be 4–6 years, explaining the effectiveness of mass treatment programs (Global Program for the Elimination of LF) [121, 135–138]. Such programs have suppressed transmission to < 1 percent. *W. bancrofti* has no animal hosts and might be 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.

References

- [1] Dietrich CF, Lorentzen T, Appelbaum L, Buscarini E, Cantisani V, Correas JM, Cui XW et al. EFSUMB Guidelines on Interventional Ultrasound (INVUS), Part III - Abdominal Treatment Procedures (Long Version). *Ultraschall Med* 2016; 37: E1–E32.
- [2] Dietrich CF, Lorentzen T, Appelbaum L, Buscarini E, Cantisani V, Correas JM, Cui XW et al. EFSUMB Guidelines on Interventional Ultrasound (INVUS), Part III - Abdominal Treatment Procedures (Short Version). *Ultraschall Med* 2016; 37: 27–45
- [3] Dietrich CF, Mueller G, Beyer-Enke S. Cysts in the cyst pattern. *Z Gastroenterol.* 2009; 47: 1203–1207
- [4] Rhomberg F. [Therapy of filariasis]. *Dtsch Med Wochenschr* 1969; 94: 1457
- [5] Brunetti E, Tamarozzi F, Macpherson C, Filice C, Piontek MS, Kabaalioglu A, Dong Y et al. Ultrasound and cystic echinococcosis. *Ultrasound Int Open* 2018; 4: E70–E78
- [6] Richter J, Azoulay D, Dong Y, Holtfreter MC, Akpata R, Calderaro J, El-Scheich T et al. Ultrasonography of gallbladder abnormalities due to schistosomiasis. *Parasitol Res* 2016; 115: 2917–2924
- [7] Richter J, Botelho MC, Holtfreter MC, Akpata R, El Scheich T, Neumayr A, Brunetti E et al. Ultrasound assessment of schistosomiasis. *Z Gastroenterol* 2016; 54: 653–660
- [8] Dietrich CF, Kabaalioglu A, Brunetti E, Richter J. Fasciolosis. *Z Gastroenterol* 2015; 53: 285–290
- [9] Dietrich CF, Sharma M, Chaubal N, Dong Y, Cui XW, Schindler-Piontek M, Richter J et al. Ascariasis imaging: Pictorial essay. *Z Gastroenterol* 2017; 55: 479–489
- [10] Christmann M, Henrich R, Mayer G, Ell C. [Infection with fasciola hepatica causing elevated liver-enzyme results and eosinophilia – serologic and endoscopic diagnosis and therapy]. *Z Gastroenterol* 2002; 40: 801–806
- [11] Dietrich CF, Lembcke B, Jenssen C, Hocke M, Ignee A, Hollerweger A. Intestinal ultrasound in rare gastrointestinal diseases, update, part 1. *Ultraschall Med* 2014; 35: 400–421
- [12] Dietrich CF, Lembcke B, Jenssen C, Hocke M, Ignee A, Hollerweger A. Intestinal ultrasound in rare gastrointestinal diseases, Update, Part 2. *Ultraschall Med* 2015; 36: 428–456
- [13] Ramaiah KD, Ottesen EA. Progress and impact of 13 years of the global programme to eliminate lymphatic filariasis on reducing the burden of filarial disease. *PLoS Negl Trop Dis* 2014; 8: e3319
- [14] Witt C, Ottesen EA. Lymphatic filariasis: An infection of childhood. *Trop Med Int Health* 2001; 6: 582–606
- [15] Malhotra I, Mungai PL, Wamachi AN, Tisch D, Kioko JM, Ouma JH, Muchiri E et al. Prenatal T cell immunity to *Wuchereria bancrofti* and its effect on filarial immunity and infection susceptibility during childhood. *J Infect Dis* 2006; 193: 1005–1013
- [16] Ottesen EA. The Wellcome Trust Lecture. Infection and disease in lymphatic filariasis: An immunological perspective. *Parasitology* 1992; 104: Suppl S71–S79
- [17] Bennuru S, Nutman TB. Lymphatics in human lymphatic filariasis: In vitro models of parasite-induced lymphatic remodeling. *Lymphat Res Biol* 2009; 7: 215–219
- [18] Grobusch MP, Kombila M, Autenrieth I, Mehlhorn H, Kreamsner PG. No evidence of *Wolbachia* endosymbiosis with *Loa loa* and *Mansonella perstans*. *Parasitol Res* 2003; 90: 405–408

- [19] Taylor MJ, Hoerauf A. Wolbachia bacteria of filarial nematodes. *Parasitol Today* 1999; 15: 437–442
- [20] Punkosdy GA, Addiss DG, Lammie PJ. Characterization of antibody responses to Wolbachia surface protein in humans with lymphatic filariasis. *Infect Immun* 2003; 71: 5104–5114
- [21] Taylor MJ. Wolbachia in the inflammatory pathogenesis of human filariasis. *Ann NY Acad Sci* 2003; 990: 444–449
- [22] Taylor MJ, Cross HF, Ford L, Makunde WH, Prasad GB, Bilo K. Wolbachia bacteria in filarial immunity and disease. *Parasite Immunol* 2001; 23: 401–409
- [23] Taylor MJ. A new insight into the pathogenesis of filarial disease. *Curr Mol Med* 2002; 2: 299–302
- [24] Lammie PJ, Cuenco KT, Punkosdy GA. The pathogenesis of filarial lymphedema: Is it the worm or is it the host? *Ann NY Acad Sci* 2002; 979: 131–142. discussion 188–196
- [25] Nutman TB, Kazura J. Lymphatic Filariasis. In Guerrant R, Walker DH, Weller PF. (eds). *Tropical Infectious Diseases: Principles, Pathogens and Practice*. 3rd ed. Philadelphia: Saunders Elsevier; 2011
- [26] Ottesen EA, Weller PF. Eosinophilia following treatment of patients with schistosomiasis mansoni and Bancroft's filariasis. *J Infect Dis* 1979; 139: 343–347
- [27] Pani SP, Srividya A. Clinical manifestations of bancroftian filariasis with special reference to lymphoedema grading. *Indian J Med Res* 1995; 102: 114–118
- [28] Pani SP, Yuvaraj J, Vanamail P, Dhanda V, Michael E, Grenfell BT, Bundy DA. Episodic adenolymphangitis and lymphoedema in patients with bancroftian filariasis. *Trans R Soc Trop Med Hyg* 1995; 89: 72–74
- [29] Dreyer G, Medeiros Z, Netto MJ, Leal NC, de Castro LG, Piessens WF. Acute attacks in the extremities of persons living in an area endemic for bancroftian filariasis: Differentiation of two syndromes. *Trans R Soc Trop Med Hyg* 1999; 93: 413–417
- [30] McPherson T, Persaud S, Singh S, Fay MP, Addiss D, Nutman TB, Hay R. Interdigital lesions and frequency of acute dermatolymphangioadenitis in lymphoedema in a filariasis-endemic area. *Br J Dermatol* 2006; 154: 933–941
- [31] Mand S, Debrah AY, Klarmann U, Batsa L, Marfo-Debrekyei Y, Kwarteng A, Specht S et al. Doxycycline improves filarial lymphedema independent of active filarial infection: A randomized controlled trial. *Clin Infect Dis* 2012; 55: 621–630
- [32] Supali T, Wibowo H, Ruckert P, Fischer K, Ismid IS, Purnomo Djuardi Y et al. High prevalence of *Brugia timori* infection in the highland of Alor Island, Indonesia. *Am J Trop Med Hyg* 2002; 66: 560–565
- [33] Freedman DO, de Almeida Filho PJ, Besh S, Maia e Silva MC, Braga C, Maciel A. Lymphoscintigraphic analysis of lymphatic abnormalities in symptomatic and asymptomatic human filariasis. *J Infect Dis* 1994; 170: 927–933
- [34] Dreyer G, Ottesen EA, Galdino E, Andrade L, Rocha A, Medeiros Z, Moura I et al. Renal abnormalities in microfilaremic patients with Bancroftian filariasis. *Am J Trop Med Hyg* 1992; 46: 745–751
- [35] Franco-Paredes C, Hidron A, Steinberg J. A woman from British Guyana with recurrent back pain and fever. Chyluria associated with infection due to *Wuchereria bancrofti*. *Clin Infect Dis* 2006; 42: 1340–1291
- [36] Sethi S, Misra K, Singh UR, Kumar D. Lymphatic filariasis of the ovary and mesosalpinx. *J Obstet Gynaecol Res* 2001; 27: 285–292
- [37] Chandrasena TG, Premaratna R, Abeyewickrema W, de Silva NR. Evaluation of the ICT whole-blood antigen card test to detect infection due to *Wuchereria bancrofti* in Sri Lanka. *Trans R Soc Trop Med Hyg* 2002; 96: 60–63
- [38] Chanteau S, Moulia-Pelat JP, Glaziou P, Nguyen NL, Luquiaud P, Plichart C, Martin PM et al. Og4C3 circulating antigen: A marker of infection and adult worm burden in *Wuchereria bancrofti* filariasis. *J Infect Dis* 1994; 170: 247–250
- [39] Chesnais CB, Missamou F, Pion SD, Bopda J, Louya F, Majewski AC, Weil GJ et al. Semi-quantitative scoring of an immunochromatographic test for circulating filarial antigen. *Am J Trop Med Hyg* 2013; 89: 916–918
- [40] Rocha A, Addiss D, Ribeiro ME, Noroes J, Baliza M, Medeiros Z, Dreyer G. Evaluation of the Og4C3 ELISA in *Wuchereria bancrofti* infection: Infected persons with undetectable or ultra-low microfilarial densities. *Trop Med Int Health* 1996; 1: 859–864
- [41] Turner P, Copeman B, Gerisi D, Speare R. A comparison of the Og4C3 antigen capture ELISA, the Knott test, an IgG4 assay and clinical signs, in the diagnosis of Bancroftian filariasis. *Trop Med Parasitol* 1993; 44: 45–48
- [42] Weil GJ, Curtis KC, Fakoli L, Fischer K, Gankpala L, Lammie PJ, Majewski AC et al. Laboratory and field evaluation of a new rapid test for detecting *Wuchereria bancrofti* antigen in human blood. *Am J Trop Med Hyg* 2013; 89: 11–15
- [43] Weil GJ, Ramzy RM. Diagnostic tools for filariasis elimination programs. *Trends Parasitol* 2007; 23: 78–82
- [44] Kumar B, Karki S, Yadava SK. Role of fine needle aspiration cytology in diagnosis of filarial infestation. *Diagn Cytopathol* 2011; 39: 8–12
- [45] Weil GJ, Jain DC, Santhanam S, Malhotra A, Kumar H, Sethumadhavan KV, Liftis F et al. A monoclonal antibody-based enzyme immunoassay for detecting parasite antigenemia in bancroftian filariasis. *J Infect Dis* 1987; 156: 350–355
- [46] Nicolas L, Plichart C, Nguyen LN, Moulia-Pelat JP. Reduction of *Wuchereria bancrofti* adult worm circulating antigen after annual treatments of diethylcarbamazine combined with ivermectin in French Polynesia. *J Infect Dis* 1997; 175: 489–492
- [47] Bakajika DK, Nigo MM, Lotsima JP, Masikini GA, Fischer K, Lloyd MM, Weil GJ et al. Filarial antigenemia and Loa loa night blood microfilaremia in an area without bancroftian filariasis in the Democratic Republic of Congo. *Am J Trop Med Hyg* 2014; 91: 1142–1148
- [48] Pion SD, Montavon C, Chesnais CB, Kamgno J, Wanji S, Klion AD, Nutman TB et al. Positivity of antigen tests used for diagnosis of lymphatic filariasis in individuals without *wuchereria bancrofti* infection but with high loa loa microfilaremia. *Am J Trop Med Hyg* 2016; 95: 1417–1423
- [49] McCarthy JS, Guinea A, Weil GJ, Ottesen EA. Clearance of circulating filarial antigen as a measure of the macrofilaricidal activity of diethylcarbamazine in *Wuchereria bancrofti* infection. *J Infect Dis* 1995; 172: 521–526
- [50] Weil GJ, Lammie PJ, Richards FO Jr., Eberhard ML. Changes in circulating parasite antigen levels after treatment of bancroftian filariasis with diethylcarbamazine and ivermectin. *J Infect Dis* 1991; 164: 814–816
- [51] Steel C, Golden A, Kubofcik J, LaRue N, de Los Santos T, Domingo GJ, Nutman TB. Rapid *Wuchereria bancrofti*-specific antigen Wb123-based IgG4 immunoassays as tools for surveillance following mass drug administration programs on lymphatic filariasis. *Clin Vaccine Immunol* 2013; 20: 1155–1161
- [52] Lammie PJ, Weil G, Noordin R, Kaliraj P, Steel C, Goodman D, Lakshmikanthan VB et al. Recombinant antigen-based antibody assays for the diagnosis and surveillance of lymphatic filariasis – A multicenter trial. *Filaria J* 2004; 3: 9
- [53] Kubofcik J, Fink DL, Nutman TB. Identification of Wb123 as an early and specific marker of *Wuchereria bancrofti* infection. *PLoS Negl Trop Dis* 2012; 6: e1930
- [54] Lucena WA, Dhalia R, Abath FG, Nicolas L, Regis LN, Furtado AF. Diagnosis of *Wuchereria bancrofti* infection by the polymerase chain reaction using urine and day blood samples from amicrofilaraemic patients. *Trans R Soc Trop Med Hyg* 1998; 92: 290–293

- [55] Ramzy RM, Farid HA, Kamal IH, Ibrahim GH, Morsy ZS, Faris R, Weil GJ et al. A polymerase chain reaction-based assay for detection of *Wuchereria bancrofti* in human blood and *Culex pipiens*. *Trans R Soc Trop Med Hyg* 1997; 91: 156–160
- [56] Dissanayake S, Rocha A, Noroes J, Medeiros Z, Dreyer G, Piessens WF. Evaluation of PCR-based methods for the diagnosis of infection in bancroftian filariasis. *Trans R Soc Trop Med Hyg* 2000; 94: 526–530
- [57] Weller PF, Ottesen EA, Heck L, Tere T, Neva FA. Endemic filariasis on a Pacific island. I. Clinical, epidemiologic, and parasitologic aspects. *Am J Trop Med Hyg* 1982; 31: 942–952
- [58] Mak JW, Cheong WH, Yen PK, Lim PK, Chan WC. Studies on the epidemiology of subperiodic *Brugia malayi* in Malaysia: Problems in its control. *Acta Trop* 1982; 39: 237–245
- [59] Dreyer G, Figueredo-Silva J, Carvalho K, Amaral F, Ottesen EA. Lymphatic filariasis in children: Adenopathy and its evolution in two young girls. *Am J Trop Med Hyg* 2001; 65: 204–207
- [60] Estran C, Marty P, Blanc V, Faure O, Leccia MT, Pelloux H, Diebolt E et al. [Human dirofilariasis: 3 cases in the south of France]. *Presse Med* 2007; 36: 799–803
- [61] Aguiar-Santos AM, Leal-Cruz M, Netto MJ, Carrera A, Lima G, Rocha A. Lymph scrotum: An unusual urological presentation of lymphatic filariasis. A case series study. *Rev Inst Med Trop Sao Paulo* 2009; 51: 179–183
- [62] Rocha A, Braga C, Belem M, Carrera A, Aguiar-Santos A, Oliveira P, Texeira MJ et al. Comparison of tests for the detection of circulating filarial antigen (Og4C3-ELISA and AD12-ICT) and ultrasound in diagnosis of lymphatic filariasis in individuals with microfilariæ. *Mem Inst Oswaldo Cruz* 2009; 104: 621–625
- [63] Ilyasov B, Kartashev V, Bastrikov N, Madjugina L, Gonzalez-Miguel J, Morchon R, Simon F. Thirty cases of human subcutaneous dirofilariasis reported in Rostov-on-Don (Southwestern Russian Federation). *Enferm Infecc Microbiol Clin* 2015; 33: 233–237
- [64] Cohen LB, Nelson G, Wood AM, Manson-Bahr PE, Bowen R. Lymphangiography in filarial lymphoedema and elephantiasis. *Am J Trop Med Hyg* 1961; 10: 843–848
- [65] Gandhi GM. Role of lymphography in management of filarial chyluria. *Lymphology* 1976; 9: 11–18
- [66] Dustmann HO. [Diagnosis, differential diagnosis and therapy of lymphedema]. *Z Orthop Ihre Grenzgeb* 1982; 120: 76–82
- [67] Lymphatic filariasis: Siagnosis and pathogenesis. WHO expert committee on filariasis. *Bull World Health Organ* 1993; 71: 135–141
- [68] Shelley S, Manokaran G, Indirani M, Gokhale S, Anirudhan N. Lymphoscintigraphy as a diagnostic tool in patients with lymphedema of filarial origin—an Indian study. *Lymphology* 2006; 39: 69–75
- [69] Amaral F, Dreyer G, Figueredo-Silva J, Noroes J, Cavalcanti A, Samico SC, Santos A et al. Live adult worms detected by ultrasonography in human Bancroftian filariasis. *Am J Trop Med Hyg* 1994; 50: 753–757
- [70] Noroes J, Addiss D, Amaral F, Coutinho A, Medeiros Z, Dreyer G. Occurrence of living adult *Wuchereria bancrofti* in the scrotal area of men with microfilaræmia. *Trans R Soc Trop Med Hyg* 1996; 90: 55–56
- [71] Dreyer G, Noroes J, Addiss D, Santos A, Medeiros Z, Figueredo-Silva J. Bancroftian filariasis in a paediatric population: An ultrasonographic study. *Trans R Soc Trop Med Hyg* 1999; 93: 633–636
- [72] Simonsen PE, Bernhard P, Jaoko WG, Meyrowitsch DW, Malecela-Lazaro MN, Magnussen P, Michael E. Filaria dance sign and subclinical hydrocoele in two east African communities with bancroftian filariasis. *Trans R Soc Trop Med Hyg* 2002; 96: 649–653
- [73] Chaubal NG, Pradhan GM, Chaubal JN, Ramani SK. Dance of live adult filarial worms is a reliable sign of scrotal filarial infection. *J Ultrasound Med* 2003; 22: 765–769. quiz 770–762
- [74] Shetty GS, Solanki RS, Prabhu SM, Jawa A. Filarial dance—sonographic sign of filarial infection. *Pediatr Radiol* 2012; 42: 486–487
- [75] Bayramoglu Z, Yilmaz R, Gocmez A, Salmaslioglu A, Acunas G. Filarial dance in the axillary lymph node. *Breast J* 2017; 23: 474–475
- [76] Dreyer G, Noroes J, Amaral F, Nen A, Medeiros Z, Coutinho A, Addiss D. Direct assessment of the adulticidal efficacy of a single dose of ivermectin in bancroftian filariasis. *Trans R Soc Trop Med Hyg* 1995; 89: 441–443
- [77] Noroes J, Dreyer G, Santos A, Mendes VG, Medeiros Z, Addiss D. Assessment of the efficacy of diethylcarbamazine on adult *Wuchereria bancrofti* in vivo. *Trans R Soc Trop Med Hyg* 1997; 91: 78–81
- [78] Mand S, Debrah A, Batsa L, Adjei O, Hoerauf A. Reliable and frequent detection of adult *Wuchereria bancrofti* in Ghanaian women by ultrasonography. *Trop Med Int Health* 2004; 9: 1111–1114
- [79] Shenoy RK, Suma TK, Kumaraswami V, Padma S, Rahmah N, Abhilash G, Ramesh C. Doppler ultrasonography reveals adult-worm nests in the lymph vessels of children with brugian filariasis. *Ann Trop Med Parasitol* 2007; 101: 173–180
- [80] Shenoy RK, Suma TK, Kumaraswami V, Rahmah N, Dhananjayan G, Padma S, Abhilash G et al. Preliminary findings from a cross-sectional study on lymphatic filariasis in children, in an area of India endemic for *Brugia malayi* infection. *Ann Trop Med Parasitol* 2007; 101: 205–213
- [81] Mand S, Marfo-Debrekyei Y, Dittrich M, Fischer K, Adjei O, Hoerauf A. Animated documentation of the filaria dance sign (FDS) in bancroftian filariasis. *Filaria J* 2003; 2: 3
- [82] Shenoy RK, John A, Hameed S, Suma TK, Kumaraswami V. Apparent failure of ultrasonography to detect adult worms of *Brugia malayi*. *Ann Trop Med Parasitol* 2000; 94: 77–82
- [83] Reddy GS, Das LK, Pani SP. The preferential site of adult *Wuchereria bancrofti*: An ultrasound study of male asymptomatic microfilaria carriers in Pondicherry, India. *Natl Med J India* 2004; 17: 195–196
- [84] Mand S, Debrah AY, Klarmann U, Mante S, Kwarteng A, Batsa L, Marfo-Debrekyei Y et al. The role of ultrasonography in the differentiation of the various types of filaricæ due to bancroftian filariasis. *Acta Trop* 2011; 120: Suppl 1 S23–S32
- [85] Dreyer G, Brandao AC, Amaral F, Medeiros Z, Addiss D. Detection by ultrasound of living adult *Wuchereria bancrofti* in the female breast. *Mem Inst Oswaldo Cruz* 1996; 91: 95–96
- [86] Patil JA, Patil AD, Ramani SK. Filarial “dance” in breast mass. *AJR Am J Roentgenol* 2003; 181: 1157–1158
- [87] Hocke M, Ignee A, Dietrich C. Role of contrast-enhanced endoscopic ultrasound in lymph nodes. *Endosc Ultrasound* 2017; 6: 4–11
- [88] Chiorean L, Cui XW, Klein SA, Budjan J, Sparchez Z, Radzina M, Jenssen C et al. Clinical value of imaging for lymph nodes evaluation with particular emphasis on ultrasonography. *Z Gastroenterol* 2016; 54: 774–790
- [89] Dietrich CF. Contrast-enhanced endobronchial ultrasound: Potential value of a new method. *Endosc Ultrasound* 2017; 6: 43–48
- [90] Ignee A, Atkinson NS, Schuessler G, Dietrich CF. Ultrasound contrast agents. *Endosc Ultrasound* 2016; 5: 355–362
- [91] Jenssen C, Annema JT, Clementsen P. Ultrasound techniques in the evaluation of the mediastinum, part 2: Mediastinal lymph node anatomy and diagnostic reach of ultrasound techniques, clinical work up of neoplastic and inflammatory mediastinal lymphadenopathy using ultrasound techniques and how to learn mediastinal endosonography. *J Thorac Dis* 2016; 7: E439
- [92] Dietrich CF, Jenssen C, Herth FJ. Endobronchial ultrasound elastography. *Endosc Ultrasound* 2016; 5: 233–238
- [93] Dietrich CF, Annema JT, Clementsen P, Cui XW, Borst MM, Jenssen C. Ultrasound techniques in the evaluation of the mediastinum, part 1: Endoscopic ultrasound (EUS), endobronchial ultrasound (EBUS) and transcutaneous mediastinal ultrasound (TMUS), introduction into ultrasound techniques. *J Thorac Dis* 2015; 7: E311–E325

- [94] Schreiber-Dietrich D, Pohl M, Cui XW, Braden B, Dietrich CF, Chiorean L. Perihepatic lymphadenopathy in children with chronic viral hepatitis. *J Ultrason* 2015; 15: 137–150
- [95] Cui XW, Hocke M, Jenssen C, Ignee A, Klein S, Schreiber-Dietrich D, Dietrich CF. Conventional ultrasound for lymph node evaluation, update 2013. *Z Gastroenterol* 2014; 52: 212–221
- [96] Dietrich CF, Averkiou M, Nielsen MB, Barr RG, Burns PN, Calliada F, Cantisani V et al. How to perform Contrast-Enhanced Ultrasound (CEUS). *Ultrasound Int Open* 2018; 4: E2–E15
- [97] Sidhu PS, Cantisani V, Deganello A, Dietrich CF, Duran C, Franke D, Harkanyi Z et al. Role of Contrast-Enhanced Ultrasound (CEUS) in Paediatric Practice: An EFSUMB Position Statement. *Ultraschall Med* 2017; 38: 33–43
- [98] Trimboli P, Dietrich CF, David E, Mastroeni G, Ventura Spagnolo O, Sidhu PS, Letizia C et al. Ultrasound and ultrasound-related techniques in endocrine diseases. *Minerva Endocrinol* 2018; 43: 333–340
- [99] Dietrich CF, Rudd L, Saftiou A, Gilja OH. The EFSUMB website, a great source for ultrasound information and education. *Med Ultrason* 2017; 19: 102–110
- [100] Dong Y, D'Onofrio M, Hocke M, Jenssen C, Potthoff A, Atkinson N, Ignee A et al. Autoimmune pancreatitis: Imaging features. *Endosc Ultrasound* 2018; 7: 196–203
- [101] Dong Y, Jurgensen C, Puri R, D'Onofrio M, Hocke M, Wang WP, Atkinson N et al. Ultrasound imaging features of isolated pancreatic tuberculosis. *Endosc Ultrasound* 2017; 7: 119–127
- [102] Dietrich CF, Greis C. [How to perform contrast enhanced ultrasound]. *Dtsch Med Wochenschr* 2016; 141: 1019–1024
- [103] Barr RG, Cosgrove D, Brock M, Cantisani V, Correas JM, Postema AW, Salomon G et al. WFUMB guidelines and recommendations on the clinical use of ultrasound elastography: Part 5. Prostate. *Ultrasound Med Biol* 2017; 43: 27–48
- [104] Cosgrove D, Barr R, Bojunga J, Cantisani V, Chammas MC, Dighe M, Vinayak S et al. WFUMB guidelines and recommendations on the clinical use of ultrasound elastography: Part 4. Thyroid. *Ultrasound Med Biol* 2017; 43: 4–26
- [105] Hocke M, Braden B, Jenssen C, Dietrich CF. Present status and perspectives of endosonography 2017 in gastroenterology. *Korean J Intern Med* 2018; 33: 36–63
- [106] Berzigotti A, Ferraioli G, Bota S, Gilja OH, Dietrich CF. Novel ultrasound-based methods to assess liver disease: The game has just begun. *Dig Liver Dis* 2018; 50: 107–112
- [107] Dietrich CF, Ponnudurai R, Bachmann Nielsen M. [Is there a need for new imaging methods for lymph node evaluation?]. *Ultraschall Med* 2012; 33: 411–414
- [108] Cui XW, Ignee A, Bachmann Nielsen M, Schreiber-Dietrich D, Demolo C, Pirri C, Jedrejczyk M et al. Contrast enhanced ultrasound of sentinel lymph nodes. *Journal of Ultrasonography* 2013; 13: 73–81
- [109] Jung J, Chang J, Oh S, Yoon J, Choi M. Computed tomography angiography for evaluation of pulmonary embolism in an experimental model and heartworm infested dogs. *Vet Radiol Ultrasound* 2010; 51: 288–293
- [110] Takahashi A, Yamada K, Kishimoto M, Shimizu J, Maeda R. Computed tomography (CT) observation of pulmonary emboli caused by long-term administration of ivermectin in dogs experimentally infected with heartworms. *Vet Parasitol* 2008; 155: 242–248
- [111] Oshiro Y, Murayama S, Sunagawa U, Nakamoto A, Owan I, Kuba M, Uehara T et al. Pulmonary dirofilariasis: Computed tomography findings and correlation with pathologic features. *J Comput Assist Tomogr* 2004; 28: 796–800
- [112] Martin TN, Weir RA, Dargie HJ. Contrast-enhanced magnetic resonance imaging of endomyocardial fibrosis secondary to Bancroftian filariasis. *Heart* 2008; 94: 1116
- [113] Shukla-Dave A, Degaonkar M, Roy R, Murthy PK, Murthy PS, Raghunathan P, Chatterjee RK. Metabolite mapping of human filarial parasite, *Brugia malayi* with nuclear magnetic resonance. *Magn Reson Imaging* 1999; 17: 1503–1509
- [114] Blacksins MF, Lin SS, Trofa AF. Filariasis of the ankle: Magnetic resonance imaging. *Foot Ankle Int* 1999; 20: 738–740
- [115] Shukla-Dave A, Fatma N, Roy R, Srivastava S, Chatterjee RK, Govindaraju V, Viswanathan AK et al. 1H magnetic resonance imaging and 31P magnetic resonance spectroscopy in experimental filariasis. *Magn Reson Imaging* 1997; 15: 1193–1198
- [116] Tekola Ayele F, Adeyemo A, Finan C, Hailu E, Sinnott P, Burlinson ND, Aseffa A et al. HLA class II locus and susceptibility to podoconiosis. *N Engl J Med* 2012; 366: 1200–1208
- [117] Wanji S, Amvongo-Adjia N, Koudou B, Njouendou AJ, Chounna Ndongmo PW, Kengne-Ouafou JA, Datchoua-Poutcheu FR et al. Cross-reactivity of filarial ICT Cards in areas of contrasting endemicity of loa loa and mansonella perstans in cameroon: Implications for Shrinking of the lymphatic filariasis map in the central african region. *PLoS Negl Trop Dis* 2015; 9: e0004184
- [118] Wanji S, Amvongo-Adjia N, Njouendou AJ, Kengne-Ouafou JA, Ndongmo WP, Fombad FF, Koudou B et al. Further evidence of the cross-reactivity of the Binax NOW(R) Filariasis ICT cards to non-Wuchereria bancrofti filariae: Experimental studies with Loa loa and Onchocerca ochengi. *Parasit Vectors* 2016; 9: 267
- [119] Hoerauf A. Filariasis: New drugs and new opportunities for lymphatic filariasis and onchocerciasis. *Curr Opin Infect Dis* 2008; 21: 673–681
- [120] Moore TA, Reynolds JC, Kenney RT, Johnston W, Nutman TB. Diethylcarbamazine-induced reversal of early lymphatic dysfunction in a patient with bancroftian filariasis: Assessment with use of lymphoscintigraphy. *Clin Infect Dis* 1996; 23: 1007–1011
- [121] Tisch DJ, Michael E, Kazura JW. Mass chemotherapy options to control lymphatic filariasis: A systematic review. *Lancet Infect Dis* 2005; 5: 514–523
- [122] Frayha GJ, Smyth JD, Gobert JG, Savel J. The mechanisms of action of antiprotozoal and anthelmintic drugs in man. *Gen Pharmacol* 1997; 28: 273–299
- [123] Maizels RM, Bundy DA, Selkirk ME, Smith DF, Anderson RM. Immunological modulation and evasion by helminth parasites in human populations. *Nature* 1993; 365: 797–805
- [124] Klion AD, Ottesen EA, Nutman TB. Effectiveness of diethylcarbamazine in treating loiasis acquired by expatriate visitors to endemic regions: Long-term follow-up. *J Infect Dis* 1994; 169: 604–610
- [125] Addiss DG, Beach MJ, Streit TG, Lutwick S, LeConte FH, Lafontant JG, Hightower AW et al. Randomised placebo-controlled comparison of ivermectin and albendazole alone and in combination for Wuchereria bancrofti microfilaraemia in Haitian children. *Lancet* 1997; 350: 480–484
- [126] Cao WC, Van der Ploeg CP, Plaisier AP, van der Sluijs IJ, Habbema JD. Ivermectin for the chemotherapy of bancroftian filariasis: A meta-analysis of the effect of single treatment. *Trop Med Int Health* 1997; 2: 393–403
- [127] Chodakewitz J. Ivermectin and Lymphatic Filariasis: A clinical update. *Parasitol Today* 1995; 11: 233
- [128] Gardon J, Gardon-Wendel N, Demanga N, Kamgno J, Chippaux JP, Boussinesq M. Serious reactions after mass treatment of onchocerciasis with ivermectin in an area endemic for Loa loa infection. *Lancet* 1997; 350: 18–22
- [129] Ottesen EA, Vijayasekaran V, Kumaraswami V, Perumal Pillai SV, Sadanandam A, Frederick S, Prabhakar R et al. A controlled trial of ivermectin and diethylcarbamazine in lymphatic filariasis. *N Engl J Med* 1990; 322: 1113–1117

- [130] Greene BM, Taylor HR, Cupp EW, Murphy RP, White AT, Aziz MA, Schulz-Key H et al. Comparison of ivermectin and diethylcarbamazine in the treatment of onchocerciasis. *N Engl J Med* 1985; 313: 133–138
- [131] Lariviere M, Vingtain P, Aziz M, Beauvais B, Weimann D, Derouin F, Ginoux J et al. Double-blind study of ivermectin and diethylcarbamazine in African onchocerciasis patients with ocular involvement. *Lancet* 1985; 2: 174–177
- [132] Taylor MJ, Hoerauf A, Bockarie M. Lymphatic filariasis and onchocerciasis. *Lancet* 2010; 376: 1175–1185
- [133] Dreyer G, Addiss D, Williamson J, Noroes J. Efficacy of co-administered diethylcarbamazine and albendazole against adult *Wuchereria bancrofti*. *Trans R Soc Trop Med Hyg* 2006; 100: 1118–1125
- [134] Gayen P, Nayak A, Saini P, Mukherjee N, Maitra S, Sarkar P, Sinha Babu SP. A double-blind controlled field trial of doxycycline and albendazole in combination for the treatment of bancroftian filariasis in India. *Acta Trop* 2013; 125: 150–156
- [135] Hopkins DR. Disease eradication. *N Engl J Med* 2013; 368: 54–63
- [136] Kroidl I, Saathof E, Maganga L, Clowes P, Maboko L, Hoerauf A, Makunde WH et al. Prevalence of Lymphatic filariasis and treatment effectiveness of albendazole/ivermectin in individuals with HIV co-infection in Southwest-Tanzania. *PLoS Negl Trop Dis* 2016; 10: e0004618
- [137] Ottesen EA. Major progress toward eliminating lymphatic filariasis. *N Engl J Med* 2002; 347: 1885–1886
- [138] Thomas G, Richards FO Jr., Eigege A, Dakum NK, Azzuwut MP, Sarki J, Gontor I et al. A pilot program of mass surgery weeks for treatment of hydrocele due to lymphatic filariasis in central Nigeria. *Am J Trop Med Hyg* 2009; 80: 447–451
- [139] 489 Global programme to eliminate lymphatic filariasis: Progress report. 2014. *Wkly Epidemiol Rec.* 2015; 90: 489–504
- [140] Thomsen EK, Sanuku N, Baea M, Satofan S, Maki E, Lombore B, Schmidt MS et al. Efficacy, Safety, and pharmacokinetics of coadministered diethylcarbamazine, albendazole, and ivermectin for treatment of bancroftian filariasis. *Clin Infect Dis* 2016; 62: 334–341