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Primary Lymphedema: Update on Genetic Basis and Management

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Significance: Primary lymphedema is a chronic condition without a cure. The lower extremities are more commonly affected than the arms or genitalia. The disease can be syndromic. Morbidity includes decreased self-esteem, infections, and reduced function of the area.
Recent Advances: Several mutations can cause lymphedema, and new variants continue to be elucidated. A critical determinant that predicts the natural history and morbidity of lymphedema is the patient's body mass index (BMI). Individuals who maintain an active lifestyle with a normal BMI generally have less severe disease compared to subjects who are obese. Because other causes of lower extremity enlargement can be confused with lymphedema, definitive diagnosis requires lymphoscintigraphy.
Critical Issues: Most patients with primary lymphedema are satisfactorily managed with compression regimens, exercise, and maintenance of a normal body weight. Suction-assisted lipectomy is our preferred operative intervention for symptomatic patients who have failed conservative therapy. Suction-assisted lipectomy effectively removes excess subcutaneous fibro-adipose tissue and can improve underlying lymphatic function.
Future Directions: Many patients with primary lymphedema do not have an identifiable mutation and thus novel variants will be identified. The mechanisms by which mutations cause lymphedema continue to be studied. In the future, drug therapy for the disease may be developed.

Keywords: extremity, genetic, lymphedema, management, morbidity, mutation

SCOPE OF REVIEW AND SIGNIFICANCE

Primary lymphedema is a rare condition that is poorly understood. Few physicians focus on this disease, which is associated with several myths. Novel causative mutations continue to be elucidated. The purpose of this review is to provide the current understanding of the genetic etiopathogenesis, diagnosis, and treatment of primary lymphedema. This review presents the most current understanding of primary lymphedema since the senior author's previous reviews on this topic.[1] The information in this article will facilitate both research and clinical care in the field.

TRANSLATIONAL RELEVANCE

Most patients with primary lymphedema do not have an identifiable mutation and thus the genetic etiology of their disease is unknown. Discovery of additional variants will further our understanding of lymphedema pathogenesis. Once a causative mutation is known, basic and translational researchers then can

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study how the mutation affects lymphatic function. Deciphering the mechanisms by which mutations cause lymphedema will lead to improved treatments for patients. Drugs for lymphedema do not exist; translation of basic research may result in medications that will protect against developing lymphedema, prevent its progression, or cause it to regress.

CLINICAL RELEVANCE

Primary lymphedema is an uncommon condition and few physicians focus on the disease. Identification of causative mutations enhances diagnosis and management. Recent data show that a major variable that predicts morbidity is the patient's body mass index (BMI). Obese individuals are more likely to suffer infections, have larger extremities, and experience disability. Current evidence illustrates that suction-assisted lipectomy effectively reduces limb volume in patients who have excess subcutaneous adipose tissue. Suction-assisted lipectomy also can improve the subject's underlying lymphatic function.

BACKGROUND

Lymphedema is divided into primary and secondary disease.[2] Primary lymphedema results from an error in lymphatic development. Secondary lymphedema is caused by injury to a normally developed lymphatic system. Primary lymphedema is rare, affecting $\sim$1/100,000 children.[3] The term "lymphedema" often is used generically to describe an overgrown limb, regardless of the underlying etiology.[4,5] Primary lymphedema traditionally has been described according to the age of the patient when the swelling develops: "congenital," "praecox," or "tarda."[2] This classification system, however, is not standardized and developmental terminology should be used: onset in infancy, childhood, adolescence, or adulthood.[6,7]

The lymphatics in primary lymphedema are either hypoplastic/aplastic (89%) or hyperplastic (11%).[8] The maldeveloped structures do not have the capacity to return interstitial fluid to the venous circulation, which causes lymphedema. Compensatory lymphaticovenous connections can occur to help return lymph fluid proximally and may be associated with less severe disease.[9] Over time, the diseased area enlarges because the interstitial lymphatic fluid causes adipose deposition; fat in an extremity can increase by 73%.[9,10] Individuals who maintain a normal BMI have less progression than obese patients.[11] Lymphedema worsens through four stages: Stage 0 (no edema, but abnormal lymph transport), Stage 1 (edema that improves with limb elevation), Stage 2 (pitting edema not resolved with elevation), and Stage 3 (fibroadipose deposition).[12] Patients with unilateral lower extremity lymphedema have a 9–25% risk of developing the condition in their contralateral limb.[6,8]

GENETIC ETIOPATHOGENESIS

The majority of patients with primary lymphedema have sporadic disease with an unknown mutation. Genetic causes are found in only 36% of patients with familial disease and 8% of patients without a family history.[13] More than 20 genes are known to cause primary lymphedema: *ADAMTS3*, *BRAF*, *CCBE1*, *EPHB4*, *FAT4*, *FLT4/VEGFR3*, *FOXC2*, *GATA2*, *GJA1*, *GJC2*, *HGF*, *IKBKG*, *KIF11*, *MAP2K1*, *MAP2K2*, monosomy X, *PIEZO1*, *PIK3CA*, *PTPN11*, *PTPN14*, *RASA*, *RASA1*, *RIT1*, *SOS1*, *SOX18*, *TSC1*, *TSC2*, and *VEGFC* (Table 1; Fig. 1).[14,15]

Genotype–phenotype associations in primary lymphedema can occur. Milroy disease presents at birth and is caused by mutations in *VEGFR3*.[13] Lymphedema-distichiasis syndrome results from inactivating mutations in *FOXC2* and is associated with an extra row of eyelashes, eyelid ptosis, and/or yellow nails.[16] Hennekam lymphangiectasia-lymphedema syndrome is an autosomal recessive disease with general lymphatic dysplasia, developmental delay, flat faces, hypertelorism, and a broad nasal bridge caused by mutations in *CCBE1*, *FAT4* and *ADAMTS3*.[17–19] Microcephaly-chorioretinopathy-lymphedema syndrome results from variants in *KIF11*; patients have central nervous system, lymphatic, and ocular abnormalities.[20] Meige disease is associated with missense mutations in *GJC2* and refers to familial lymphedema that manifests during adolescence.[21,22] Hypotrichosis-lymphedema-telangiectasia (*SOX18* mutation) causes sparse hair and telangiectasias. Patients with Turner (XO) syndrome have a 57% risk of lymphedema.[23] Noonan syndrome (*PTPN11*/*SOS1*) may manifest with generalized lymphedema, intestinal lymphangiectasis, and/or fetal hydrops; patients have a 3% risk of lymphedema.[24] Noonan syndrome also has been associated with mutations in *BRAF*, *KRAS*, *MAP2K1*, *MAP2K2*, and *RIT1*.[15] Patients with tuberous sclerosis (*TSC1* and *TSC2*) have a 4% risk of lymphedema.[25]

Autosomal dominant lymphatic-related fetal hydrops (*EPHB4*) is a generalized lymphatic dysplasia causing fetal hydrops.[26] Primary lymphedema associated with choanal atresia results from

Table 1. *Mutations associated with primary lymphedema*

Condition	*Gene*	*Effect of Mutation*	*Inheritance*
Capillary malformation	*PIK3CA*	Activating missense causing constitutively active PI3K-AKT signaling	Somatic
Choanal atresia/lymphedema syndrome	*PTPN14*	Loss of function frameshift nonsense in the protein tyrosine phosphatase that inhibits VEGFR3	Autosomal recessive
Cholestasis-lymphedema syndrome (Aagenaes syndrome)	*CCBE1*	Loss of function causing decreased activation of the VEGF-C ligand	Autosomal recessive
CLOVES syndrome	*PIK3CA*	Activating missense resulting in constitutively active PI3K-AKT signaling	Somatic
CM-AVM/lymphedema	*EPHB4*	Inactivating heterozygous missense in the tyrosine kinase domain of EPHB4	Autosomal dominant
	RASA1	Loss of function in the RAS GTPase-activating protein upregulating RAS/MAPK signaling	
Ectodermal dysplasia, anhidrotic, immunodeficiency, osteoporosis, and lymphedema	*IKBKG*	Hypomorphic decreasing IKBKG activation of NF-κB	X linked
Fetal hydrops	*EPHB4*	Inactivating heterozygous missense in the tyrosine kinase domain of EPHB4	Autosomal dominant
Hennekam syndrome type 1	*CCBE1*	Homozygous or compound heterozygous in the calcium-binding EGF domain inhibiting activation of the VEGFC ligand	Autosomal recessive
Hennekam syndrome type 2	*FAT4*	Loss of function homozygous or compound heterozygous	Autosomal recessive
Hennekam syndrome type 3	*ADAMTS3*	Loss of function bi-allelic missense in the prodomain and the peptidase domain of ADAMTS inhibit activation of the VEGFC ligand	Autosomal recessive
Hereditary lymphedema type 3/ generalized lymphatic dysplasia of Fotiou	*PIEZO1*	Activating or inactivating homozygous or compound heterozygous missense, nonsense, and splice site in the mechanosensitive ion channel PIEZO1	Autosomal recessive
Hypotrichosis-lymphedema-telangiectasia	*SOX18*	Loss of function homozygous missense or heterozygous nonsense affecting the alpha-helix of the DNA-binding domain of the transcription factor SOX18	Autosomal recessive
Klippel–Trenaunay syndrome	*PIK3CA*	Activating missense results in constitutively active PI3K-AKT signaling	Somatic
Lymphedema-distichiasis syndrome	*FOXC2*	Loss of function heterozygous in the transcription factor FOXC2	Autosomal dominant
Lymphedema-lymphangiectasia	*HGF*	Possible loss of function results in decreased activation of the c-MET receptor tyrosine kinase	Autosomal dominant
Meige disease	*GJC2*	Heterozygous missense affecting gap junction protein connexin 47	Autosomal dominant
Microcephaly-chorioretinopathy-lymphedema	*KIF11*	Loss of function variable types result in dysfunctional EG5, a kinesin-type motor protein, and activation of PI3K-AKT signaling	Autosomal dominant
Milroy-like disease	*VEGFC*	Loss of function frameshift results in truncated inactive VEGFR-3 ligand	Autosomal dominant
Noonan syndrome	*BRAF* *MAP2K1* *MAP2K2* *PTPN11* *RIT1* *SOS1*	Variable types result in RAS-MAPK pathway dysregulation	Autosomal dominant
Oculodentodigital dysplasia/ lymphedema syndrome	*GJA1*	Missense affects gap junction protein connexin 43	Autosomal dominant
Parkes-Weber syndrome	*EPHB4*	Inactivating heterozygous missense in the tyrosine kinase domain of EPHB4	Autosomal dominant
	RASA1	Loss of function in the RAS GTPase-activating protein upregulating RAS/MAPK signaling	
Primary congenital lymphedema (Milroy disease)	*VEGFR-3*	Inactivating missense in the tyrosine kinase domain of VEGFR-3 resulting in decreased downstream signal transduction	Autosomal dominant
Primary lymphedema with myelodysplasia (Emberger syndrome)	*GATA2*	Loss of function heterozygous truncating in the transcription factor GATA2	Autosomal dominant
Tuberous sclerosis	*TSC1* *TSC2*	Loss of function resulting in constitutive activation of mTOR	Autosomal dominant
Turner syndrome	*Monosomy X*	Chromosomal aneuploidy	X linked

a frameshift mutation in *PTPN14*.[27] Lymphedema-cholestasis syndrome (*CCBE1*) is characterized by neonatal intrahepatic cholestasis and lymphedema.[28] Mutations in *IKBKG* are associated with the X-linked syndrome anhidrotic ectodermal dysplasia with immunodeficiency, osteoporosis, and lymphedema.[14] Hereditary lymphedema type 3/ general lymphatic dysplasia of Fotiou (*PIEZO1*) is characterized by lymphedema of all four limbs, genitalia, and face and fetal hydrops.[29]

Mutations in *HGF* can cause lymphedema and visceral lymphangiectasia.[30] Oculodentodigital syndrome (abnormalities of the face, eyes, dentition, and digits, including hypotelorism, hypoplastic alae nasi, microphthalmia, microcornea, microdontia, and syndactyly) is associated with lymphedema and caused by a mutation in *GJA1*.[31] Variants in *GATA2* result in lymphedema and acute myeloid leukemia (Emberger syndrome).[32] Primary lymphedema also can occur in combina-

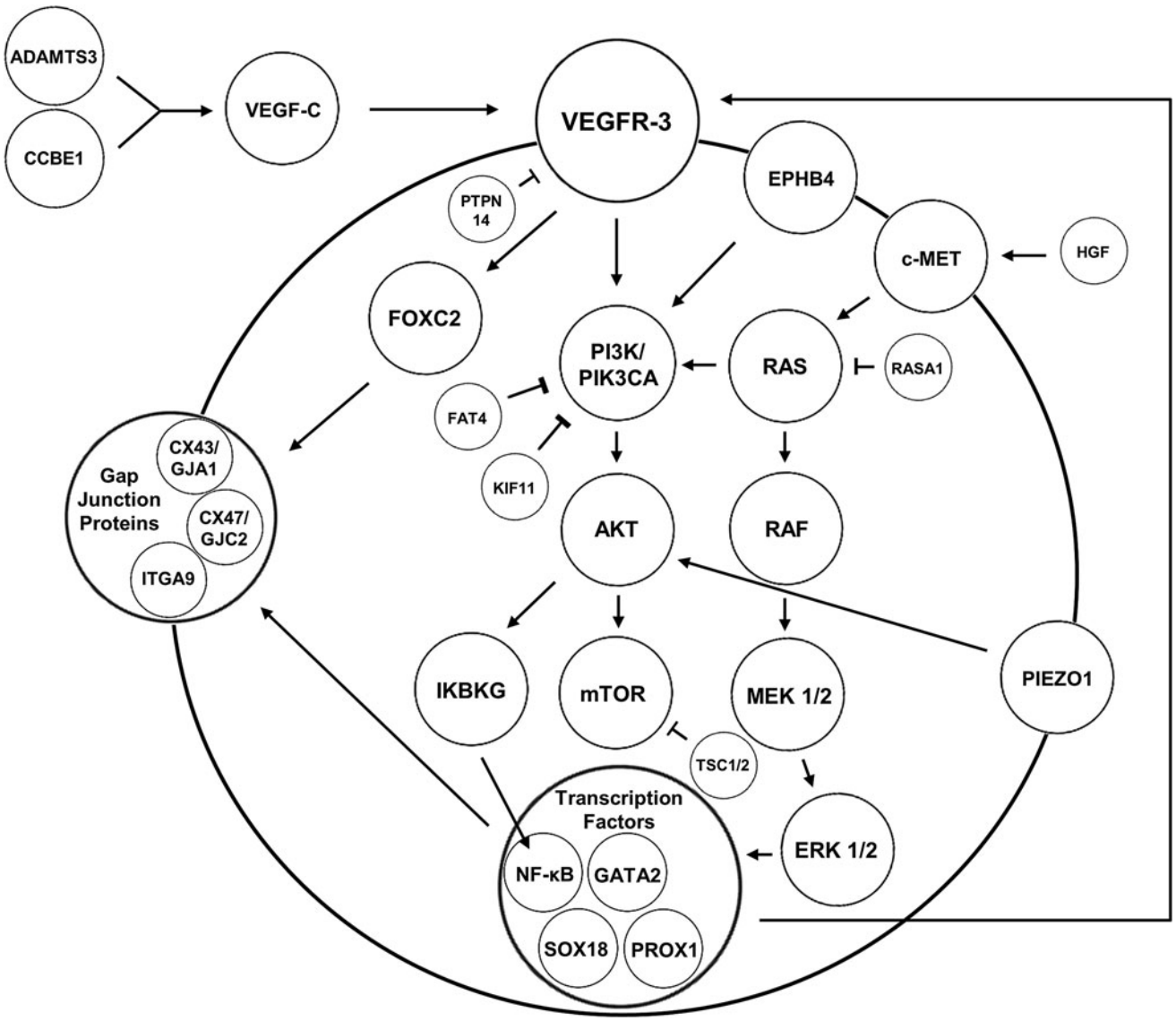

Figure 1. Signaling pathways and mutations associated with primary lymphedema.

tion with other vascular anomalies and overgrowth conditions: (i) capillary malformation (*PIK3CA* mutation),[33,34] (ii) Klippel–Trenaunay syndrome (*PIK3CA* mutation), (iii) CLOVES syndrome (*PIK3CA* mutation), and (iv) Parkes-Weber syndrome (*RASA* and *EPHB4* mutations).

MANAGEMENT

Clinical Features

In the pediatric population, onset occurs in infancy (49%), childhood (10%), or adolescence (41%) (Fig. 2).[6] Males are more likely to present in infancy (68%), while females commonly develop the disease during adolescence (55%).[6] The lower extremities are affected in 92% of patients; 50% have unilateral lymphedema and 50% have bilateral disease.[6] Bilateral lower extremity lymphedema is more common in patients presenting in infancy (63%), compared to adolescence (30%).[6] Eighteen percent have genital lymphedema, which is usually associated with lower extremity lymphedema (4% have isolated genital involvement). Adult-onset primary lymphedema (>21 years) occurs in 10% of patients, typically affects one lower extremity, is not associated with systemic lymphatic anomalies, and familial transmission is rare.[35] Ten percent of patients have upper extremity lymphedema; 50% have other lymphatic anomalies, including lower extremity lymphedema, and familial transmission is rare.[36]

The most common problem caused by lymphedema is psychosocial morbidity because the involved area does not look normal. A lymphedematous extremity has an increased risk of cellulitis

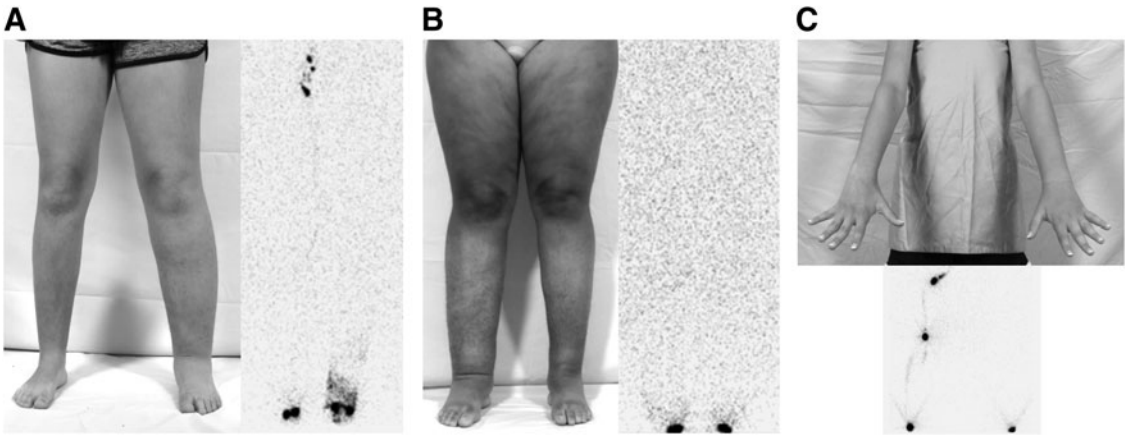

Figure 2. Phenotypes of primary lymphedema. **(A)** Eleven-year-old female with left lower extremity disease. Her lymphoscintigram showed absence of tracer uptake into the left inguinal nodes as well as dermal backflow. **(B)** Eighteen-year-old female with lymphedema affecting both legs. Her lymphoscintigram illustrated no inguinal node tracer uptake bilaterally. **(C)** Thirteen-year-old female with left arm lymphedema and absence of tracer uptake into her left axillary nodes.

compared to the nonaffected limb.[37] Fifteen percent of patients will develop cutaneous problems such as bleeding from vesicles, fungal toenail lesions, hyperkeratosis, lymphorrhea, and verrucous changes.[6] Lymphangiosarcoma has been described in patients with primary lymphedema and prognosis is poor.[38]

Diagnosis

Ninety percent of patients with primary lymphedema can be diagnosed by history and physical examination. Patients are queried about a family history of extremity edema and infections in the limb. Individuals are asked about potential variables that might be associated with lymphedema (e.g., Turner syndrome and Noonan syndrome). Lymphedema almost always affects the distal extremity and the Stemmer sign is 92% sensitive and 57% specific for the disease.[39] If the examiner is unable to pinch the skin on the dorsum of the hand or foot (positive Stemmer sign), then it is likely the patient has lymphedema.

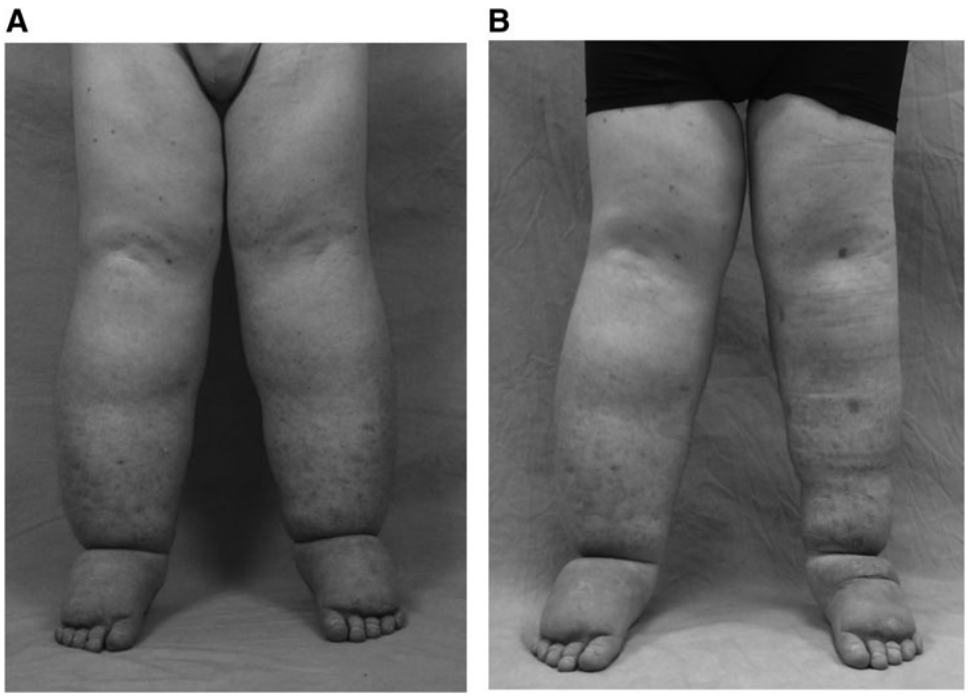

Figure 3. Operative management of primary lymphedema. **(A)** Adolescent male with bilateral lower extremity lymphedema. **(B)** Improved volume of his left leg following suction-assisted lipectomy.

Clinically, the severity of lymphedema can be categorized as mild (<20% increase in extremity volume), moderate (20–40% increase in extremity volume), or severe (>40% increase in extremity volume).[12] Lymphoscintigraphy is the definitive test to diagnose lymphedema and is 100% specific and 96% sensitive for the condition.[40] A radiolabeled colloid is injected into the dorsum of the hand or foot and is only taken up by lymphatic vessels. Delayed transit time to the regional lymph nodes, dermal back-flow, and collateral lymphatic channels represent abnormal lymphatic function.[41]

TAKE-HOME MESSAGES

- Although many mutations and syndromes are associated with primary lymphedema, the majority of patients do not have an identifiable disease-causing variant.
- Most patients who maintain an active lifestyle and normal BMI have minimal progression of their disease.
- Children are encouraged to engage in all sports and wear compression stockings as much as possible.
- Operative intervention is indicated in a minority of patients and we favor suction-assisted lipectomy. As the pathophysiology of primary lymphedema continues to be elucidated, improved therapies will be developed.

Treatment

The most important variable that determines the morbidity of lymphedema is the patient's BMI. Obese subjects with lymphedema have an increased risk of infection and larger extremities.[11] Patients are counseled to exercise and maintain a normal body weight. Individuals with >3 episodes of cellulitis each year are given chronic suppressive antibiotic therapy. The mainstay of treatment for lymphedema is compression stockings. In the pediatric population, we often recommend commercially available socks instead of medical-grade garments to increase compliance. Pneumatic compression delivers intermittent pressure through a power source and inflatable sleeve. In children, we only prescribe pneumatic compression for adolescents or younger children with severe disease. Massage and bandaging regimens are difficult in the pediatric population and we prefer stockings and pneumatic compression.

Operative intervention is rarely indicated for patients with primary lymphedema. Individuals are considered for a surgical procedure if they have significant morbidity, despite conservative interventions. The role of lymphatic-venous anastomosis (LVA) or lymph node transfer is less clear in patients with primary lymphedema compared to secondary disease because they have hypoplastic/aplastic lymphatics. Patients with primary lymphedema also have an increased risk of developing donor site lymphedema from the harvest of lymph nodes because of their underlying genetic abnormality. Suction-assisted lipectomy (liposuction) is our first-line operative intervention for extremity lymphedema because of its efficacy, consistent results, and low morbidity (Fig. 3).[42] Liposuction increases cutaneous blood flow, reduces the risk of cellulitis, and improves quality of life.[9] The procedure also can provide physiological benefit by improving lymph flow.[43] Skin and subcutaneous adipose excision are required for severe lymphedema with significant skin excess and for genital lymphedema.

Challenges and Future Interventions

Although most patients who maintain a normal BMI and active lifestyle do not have significant worsening of their disease, primary lymphedema remains an incurable and progressive condition. The disease commonly is confused with other conditions and one-fourth of patients diagnosed with "lymphedema" have another disease.[4] The differential diagnosis of primary lymphedema includes other vascular anomalies and overgrowth syndromes, venous stasis, systemic conditions (cardiac, hepatic, renal, and autoimmune), orthopedic and rheumatologic disorders, lipedema, and obesity. It is important to accurately diagnose the patient with lymphedema, typically using lymphoscintigraphy, because the prognosis and treatment of the condition is different than other diseases in its differential diagnosis.

The most common microsurgical procedures used to treat secondary lymphedema are LVA and vascularized lymph node transfer (VLNT). These techniques attempt to improve lymph flow and are best indicated in early lymphedema before significant fibroadipose tissue has developed. Microsurgical procedures for primary lymphedema, however, are less clear because patients have hypoplastic or absent lymphatic vessels.[8] Individuals also are at increased risk of donor site lymphedema from VLNT because they have an underlying mutation affecting their lymphatics and are at risk for developing lymphedema at other anatomical sites. As new causative mutations are identified and our understanding of these variants improves, targeted therapy may prove to prevent the onset of lymphedema. For example, drugs may block abnormal signaling pathways or stimulate lymphangiogenesis. Topical, injectable, or systemic pharmacotherapy

also may be able to prevent the worsening of lymphedema by preventing fibroadipose deposition.

AUTHORS' CONTRIBUTIONS

Both authors made substantial contributions to the work, drafted and revised the work, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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Abbreviations and Acronyms

BMI = body mass index
LVA = lymphatic venous anastomosis
VLNT = vascularized lymph node transfer