Epidemiology and Morbidity of Lymphedema

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Key Points

- Lymphedema is common, affecting approximately 140–250 million persons worldwide and 1/1,000 Americans.
- 99 % of patients with lymphedema develop the condition following axillary/inguinal radiation and/or lymphadenectomy or from a parasitic infection.
- Patients with lymphedema may have minimal morbidity from the disease.
- The most common problem from lymphedema is that it can lower a patient's self-esteem because the disease causes a deformity of their limb or genitalia.
- Other complications of lymphedema include: infection, decreased ability to use the affected area, and rarely malignant degeneration.

Introduction

Lymphedema is a common condition, although the exact prevalence is unknown. The disease is a major burden to the health care system because it is chronic and incurable. Although lymphedema can cause major morbidity, many patients have minimal problems if they are compliant with conservative treatments. In some individuals, however, the condition can be significantly progressive and life-threatening. In general, patients with primary (idiopathic) lymphedema have less morbidity compared to individuals with secondary disease from injury to a normally functioning lymphatic system [1]. Patients born with an anomalous system may compensate better for lymphatic dysfunction compared to individuals who had a normal lymphatic system that was disrupted by trauma.

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Epidemiology

Overview

Lymphedema is a common condition, and may affect as many as 140–250 million persons worldwide [2]. Two population studies have estimated the prevalence of lymphedema to be between 1.33 and 1.44 per 1,000 persons in two European countries [3, 4]. The true rate of lymphedema is unknown, but is likely underestimated because patients with latent or mild disease may not seek treatment. Approximately 99 % of individuals with lymphedema have secondary disease; primary lymphedema is rare (Table 4.1). In developed countries the most common cause of lymphedema is lymphadenectomy and/or radiation for cancer treatment. In third-world nations lymphedema most frequently arises because of a parasitic infection. At least 90 % of patients with lymphedema worldwide have lower extremity

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Table 4.1 Epidemiology of lymphedema (listed from most common to least common)

Primary (prevalence 1/1,00,000 persons)	Secondary (prevalence 1/1,000 persons)
Infant-onset	Filariasis
Adolescent-onset	Axillary/inguinal lymphadenectomy
Childhood-onset	Axillary/inguinal radiation
Adult-onset	Obesity

disease because of (in order): filariasis, inguinal radiation/lymphadenectomy, obesity, or primary lymphedema. Nine percent of patients with lymphedema have upper extremity disease; most are women who have been treated for breast cancer. Isolated genital lymphedema is the third most common site of disease (~1 %) and usually results from inguinal radiation/lymphadenectomy, obesity, or primary lymphedema. Genital lymphedema typically is associated with lower extremity disease.

Primary Lymphedema

Primary lymphedema is rare, affecting approximately 1/100,000 children [5]. In the pediatric population onset occurs in infancy (49.2 %), childhood (9.5 %), or adolescence (41.3 %) [1]. Primary lymphedema develops during adulthood in 19 % of patients [6]. Males are more likely to present in infancy (68 %), while females most commonly develop the disease during adolescence (55 %) [1]. The lower extremities are affected in 91.7 % of patients; 50 % have unilateral lymphedema and 50 % have bilateral disease [1]. Bilateral lower extremity lymphedema is more common in patients presenting in infancy (63 %), compared to adolescence (30 %) [1]. Eighteen percent of children with primary lymphedema have genital disease, which is usually associated with lower extremity lymphedema. Four percent of patients with primary lymphedema have isolated genital involvement. Sixteen percent of children with idiopathic lymphedema have upper extremity disease [1]. Rarely, a child can have lymphedema affecting the legs, genitalia, and/or arms.

Secondary Lymphedema

Cancer-Related Treatment

Injury to the lymphatic system is responsible for approximately 99 % of adult cases and 3 % of pediatric disease [1]. The overall risk of lymphedema following treatment for malignancy is 15 %; the two variables that most importantly predict if a patient develops the condition is if he/she underwent lymphadenectomy or radiation [7]. The overall risk of lymphedema after treatment for the following cancers (including patients who did and did not have lymphadenectomy or radiation) has been estimated to be: head/neck (4 %), genitourinary (10 %), melanoma 16 % (arm 5 %, leg 28 %), gynecologic (20 %), sarcoma (30 %) [7].

Upper extremity lymphedema from breast cancer treatment is the most common etiology of the disease in the USA. One-third of women who have axillary lymphadenopathy and radiation develop the condition [8]. Edema typically begins 12 months following the injury to lymph vessels [9]. Three-fourths of patients develop swelling within 3 years after the injury and the risk of lymphedema is 1 % each year thereafter [10]. Advanced disease, the extent of resection, and number of lymph nodes removed increases the risk of lymphedema [11]. Modified radical mastectomy has a greater chance of causing lymphedema compared to partial mastectomy; removal of more than 15 axillary lymph nodes increases the rate of lymphedema tenfold, compared to excising less than 5 nodes [12]. Sentinel lymph node biopsy reduces the rate of lymphedema (0.5 %) compared to axillary lymph node dissection [13]. Radiation is a major risk factor for breast cancer-related lymphedema; when the axilla is included in the radiation field the risk of lymphedema doubles, compared to radiation of the breast and supraclavicular nodes only [14]. In patients who have undergone lymphadenectomy and/or radiation, the most significant variable

that will increase their risk of lymphedema is obesity [15].

Pelvic or abdominal malignancy is the most frequent reason for lower extremity lymphedema. The rate of lymphedema following lymphadenectomy and/or radiation for the following malignancies has been estimated to be: prostate (13 %), uterine (18 %), melanoma (25 %), vulvar (28 %), sarcoma (25 %). penile (30 %), cervical (42 %) [4]. Lower-extremity and genital lymphedema rates decrease when inguinal sentinel lymph node biopsy is performed (1.9 %) instead of lymphadenectomy [16].

Filariasis

A parasitic infection is the most common etiology of lymphedema in the world; 90 % of cases are cause by *W. bancrofti* [2]. Eighty-three countries are endemic to the disease; 70 % of cases are in Bangladesh, India, Indonesia, and Nigeria [2]. Other affected areas include Africa (central), Brazil, Burma, China (southern), Dominican Republic, Guiana, Guyana, Haiti, Malaysia, Nile delta, Pacific Islands, Pakistan, Sri Lanka, Surinam, and Thailand [2]. It is estimated that although 120 million people are infected with a lymphedema-causing parasite, 40 million persons exhibit lymphedema clinically [2]. Patients at risk for filariasis live in tropical/subtropical environments because these habitats are humid which is necessary for the parasites to survive [2]. Most individuals with filariasis live in rural locations that have poor sanitation [2]. The most common location for lymphedema caused by filariasis is the lower extremity and/or genitalia, but the upper extremity and breast can be affected as well.

Obesity

Obesity affects one-third of the US population, and 6 % have a body mass index (BMI) >40 [17]. The proportion of the population that is obese is increasing at a rate of 2–4 % every 10 years [17]. Patients with a BMI > 50 are at risk for developing obesity-induced lower extremity lymphedema, and individuals with a BMI > 60 are very likely to have the disease. Although the percent of the US population with a BMI > 60 is unknown, using a conservative estimate of 0.5 % then the number of Americans (population 315 million) with obesity-induced lymphedema would be 1.575 million.

Morbidity

Some patients with lymphedema do not have problems, while others can have significant complications (Table 4.2). Generally, individuals who are compliant with intervention have less disability than patients who are noncompliant (Fig. 4.1). Individuals with an active lifestyle have fewer problems than patients who are sedentary. Exercise likely improves proximal lymphatic flow by muscle contraction and helps the individual maintain a normal BMI. Obese individuals have more complications from lymphedema compared to normal-weighted persons because obesity adversely affects lymphatic function [15, 18]. Morbidity from lymphedema is described below from the most common problem, to the least frequent complication.

Progression

Almost all patients with lymphedema have progression of their disease. Over time the high-protein interstitial fluid causes subcutaneous adipose deposition [19]. Consequently, the circumference of the limb or genitalia gradually enlarges. Fat in an extremity can increase by 73 % [19]. As the lymphedematous area becomes larger, the patient's ability to use the area decreases.

Table 4.2 Morbidity from lymphedema (listed from most common to least common)

Progression of disease
Lowered self-esteem
Infection
Fitting clothing
Difficulty using the extremity
Skin changes
Massive localized lymphedema
Discomfort
Malignant transformation

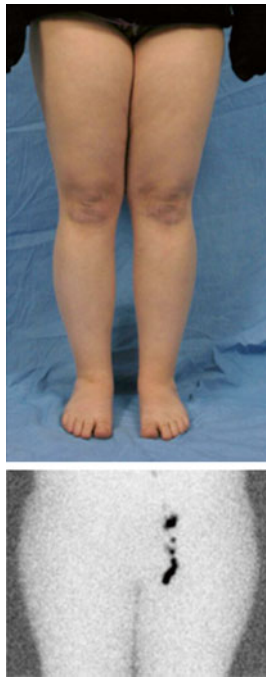

Fig. 4.1 Asymptomatic lymphedema. 19-year-old female with recent swelling of the right lower extremity. Lymphoscintigram shows absent transit of tracer to the right inguinal nodes 2 h following injection. The patient does not have any complaints and the appearance of her legs is similar

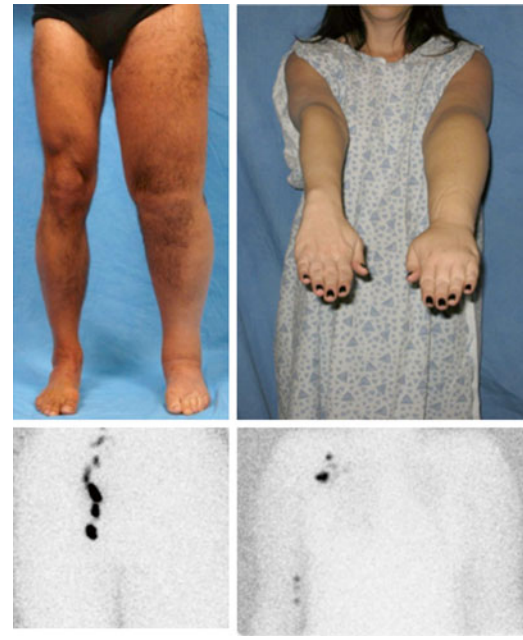

Fig. 4.2 Psychosocial morbidity caused by lymphedema. (*Left*) 50-year-old male with adult-onset left-lower extremity lymphedema. (*Right*) 40-year-old female with left upper extremity lymphedema following breast cancer treatment. Both patients had lowered self-esteem because they were unhappy with the appearance of their diseased limb

Psychosocial

Lymphedema negatively impacts a patient's social well-being, body image, and sexuality [20]. The most common problem expressed by patients with lymphedema is that they are unhappy with the appearance of their limb or genitalia. Patients have lowered self-esteem because the involved area does not look normal (Fig. 4.2). The more severe the disease, the greater the loss of self-esteem and negative impact on quality of life. Unilateral limb involvement can be more distressing than bilateral disease because the asymmetry is more noticeable. Individuals may not feel comfortable wearing clothing that exposes their diseased limb. Patients may avoid changing clothes in front of their peers or refrain from swimming. Lymphedema can impede the establishment of new relationships and genital disease can negatively impact an individual's sexual activity.

Patients with secondary lymphedema from cancer treatment often state that although they are cured of their malignancy, lymphedema is a daily reminder of their cancer. Children with primary disease often feel that they are "different" than their peers; the emotional aspect of their condition worsens during adolescence. Many patients believe that wearing a compression garment is a worse deformity than the appearance of their lymphedematous extremity. The most common reason for individuals to seek surgical intervention is to improve the appearance of the area affected by lymphedema. Patients with psychosocial distress can be helped with counseling. Conservative compression strategies, as well as excision of excess subcutaneous fat using liposuction, can improve a patient's asymmetry as well as their self-esteem.

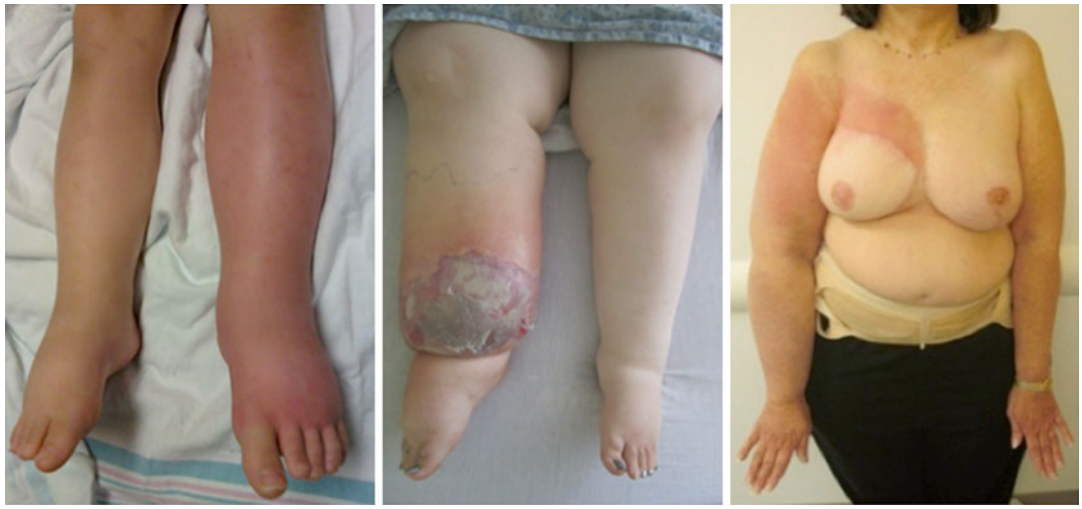

Fig. 4.3 Lymphedematous areas are at increased risk for infection. (*Left*) 4-year-old male with primary lymphedema developed left leg cellulitis requiring hospital admission. (*Center*) 18-year-old female with primary lymphedema had right lower extremity infection necessitating intravenous antibiotics; note skin epidermolysis and blistering. (*Right*) 64-year-old female with cellulitis complicating secondary lymphedema of the right arm following breast cancer treatment

Infection

The most frequent "functional" problem caused by lymphedema is infection. A lymphedematous extremity has a significantly increased risk of cellulitis compared to the non-affected limb (Fig. 4.3). Lymph stagnation increases the risk of infection after minor trauma because of: (1) impaired immunosurveillance (lymphatics function as an immunologic defense), (2) decreased oxygen delivery to the skin, and (3) a proteinaceous environment favorable for bacterial growth. In one community study of both primary and secondary lymphedema, 29 % of patients had an infection over the previous 12 months, and one-fourth required hospitalization for intravenous antibiotics [3]. In another study of patients with primary lymphedema, 19 % have a history of cellulitis, 13 % have been hospitalized, and 7 % have >3 attacks each year [1].

Infections in a lymphedematous area typically do not spontaneously occur, but result from a break in the skin. The most common etiology is incidental trauma; the patient is unaware of a cut or scrape. Less frequently, the source of an infection can be a problem with a finger/toe nail. Rarely, a systemic infection can secondarily infect a lymphedematous extremity.

Cutaneous infection in patients with lymphedema can spread more quickly compared to individuals without the disease. A superficial cellulitis may develop rapidly into sepsis. Patients are counseled to seek medical attention quickly if they suspect an infection in a lymphedematous area. Often, individuals will carry oral antibiotics with them and administer the medication during the onset of the infection. Patients who have ≥3 episodes of cellulitis/year are placed on chronic suppressive antibiotic therapy following infectious disease consultation. The most frequent organism responsible for cellulitis is *Streptococcus* (*S. Pyogenes*), and patients are usually treated with penicillin or cephalexin.

Fitting Clothing

A common complaint from patients with lymphedema is that they have difficulty fitting clothing (Fig. 4.4). Symptoms are exacerbated when the individual has unilateral disease because of the asymmetry between the limbs.

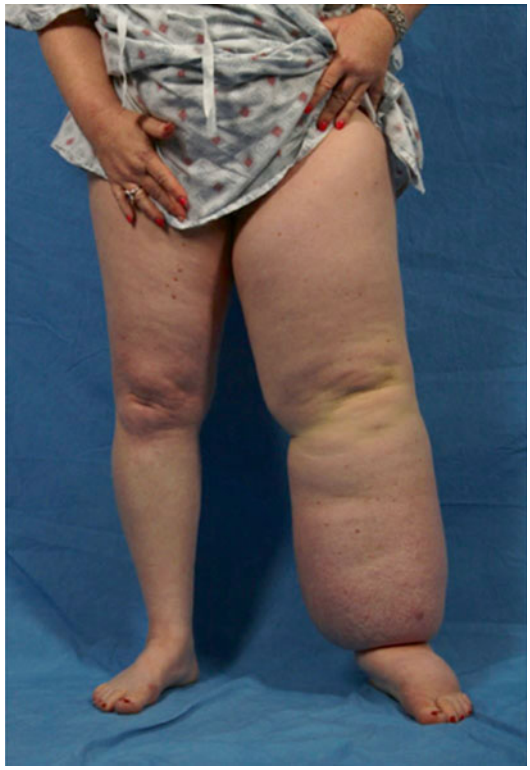

Fig. 4.4 Patients with lymphedema can have difficulty fitting clothing. 55-year-old female with secondary lower extremity lymphedema has problems wearing pants because her left leg is significantly larger than her unaffected extremity

The most problematic location is the feet: (1) individuals may have to wear two different sized shoes and/or (2) patients have problems with pressure from the shoe and need to wear sandals or other open footwear. Individuals with significant lower extremity lymphedema have difficulty fitting jeans or slacks and often need to wear oversized sweat pants. Patients with severe upper extremity lymphedema may not be able to wear tight-fitting long sleeve shirts and instead use short sleeves and/or oversized shirts. Individuals with upper extremity disease may need to have the size of their rings and wrist jewelry increased.

Orthopedic

Lymphedema is confined to the skin and subcutaneous tissue and does not directly involve muscles, bones, or joints. The disease, however, can secondarily affect the musculoskeletal system because of circumferential overgrowth of the skin and subcutaneous tissue. Because lymphedema does not affect bone, children are not at risk for vertical limb overgrowth and do not need to be monitored for a leg-length discrepancy.

Patients with lymphedema can have reduced ability to use an extremity (particularly an arm) because of weakness and/or heaviness. The ability to use the limb for daily activities can be further impeded by operative or radiation fibrosis which may affect joint mobility. In early disease controlled compression therapy using custom compression garments can improve the use of the limb for activities of daily living.

As the lymphedematous extremity enlarges, the ability to use the limb for routine activities decreases. Muscle mass increases in an extremity with lymphedema because the added subcutaneous adipose tissue acts as a "weight" that builds muscle strength [19]. For example, secondary upper extremity lymphedema increases the amount of subcutaneous adipose (73 %), muscle (47 %), and bone (7 %) [19]. Hypertrophied muscles enable the patient to use the lymphedematous limb with minimal morbidity initially. However, added muscle mass cannot compensate for severely affected limbs and patients can have decreased function. For example, individuals with significant upper extremity disease may have difficulty lifting their arm over their head which can impede getting dressed (Fig. 4.5). Patients with severe lower extremity disease can have problems ambulating because of the weight of the extremity (Fig. 4.6). As the size of a limb increases, patients can have discomfort from stress on their joints.

Musculoskeletal manifestations of lymphedema typically occur with severe disease following fibroadipose deposition. Consequently, conservative interventions (e.g., compression garments, pneumatic compression, massage) are unlikely to significantly alleviate symptoms. Morbidity can be improved with an excisional operative procedure to reduce the amount of subcutaneous tissue which facilitates the use of the extremity. I prefer suction-assisted lipectomy because it can significantly improve extremity volume, has predictable and long-lasting results,

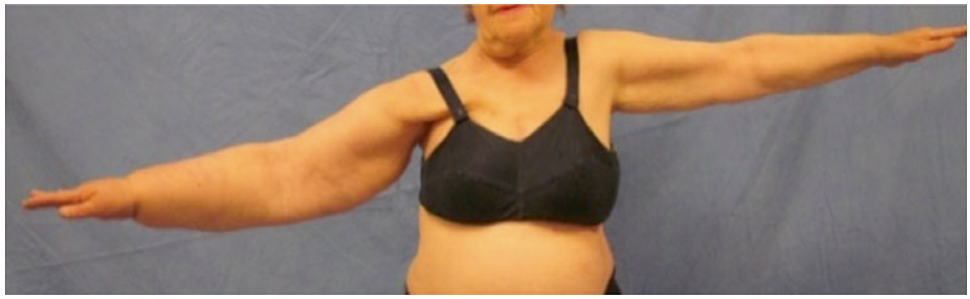

Fig. 4.5 Upper extremity lymphedema can negatively affect arm function. 86-year-old female with secondary upper extremity lymphedema following breast cancer treatment. Note her inability to fully raise her right arm

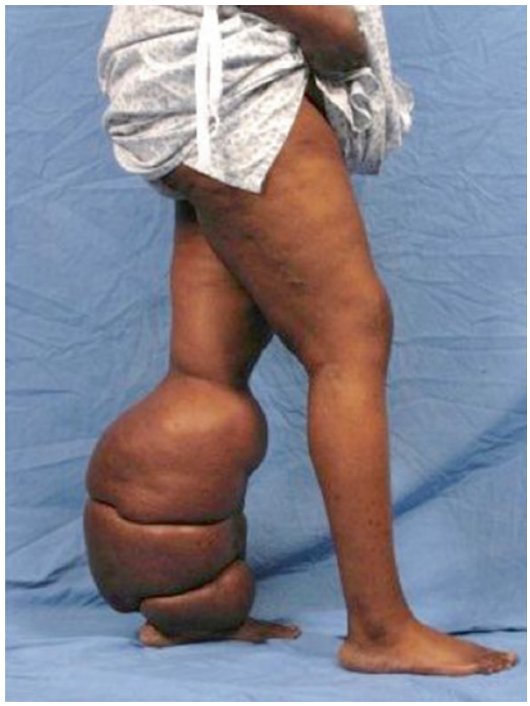

Fig. 4.6 Lower extremity lymphedema can limit ambulation. 40-year-old female with adolescent-onset primary lymphedema. She has difficulty ambulating because of the weight of her left extremity

and is safe. Other options to reduce the excess tissue of the extremity is staged skin/subcutaneous excision or the Charles procedure.

Skin Changes

Patients with lymphedema generally have normal appearing skin. However, individuals with lymphedema can develop cutaneous lymphatic vesicles that may cause: (1) a "cosmetic" deformity, (2) bleeding, (3) or leakage of fluid (lymphorrhea) (Fig. 4.7). The skin also may become hyperkeratotic (Fig. 4.8) [1]. Ulceration rarely affects patients with lymphedema because their arterial and venous circulations are intact. Vesicles and hyperkeratosis most frequently involves the distal lower extremity, particularly the feet and toes. The penis and scrotum also can exhibit lymphatic vesicles. A lymphedematous upper extremity is less frequently complicated by cutaneous pathology.

The appearance of lymphatic vesicles and hyperkeratosis can lower a patient's self-esteem. Lymphatic vesicles also are a portal of entry for bacteria and can significantly increase the risk of infection. Typically, patients who have repeated episodes of cellulitis also have numerous lymphatic vesicles involving their skin. When vesicles bleed or leak lymph fluid the patient's clothing becomes saturated which causes distress. In addition, leaking vesicles are typically malodorous which further creates psychosocial morbidity.

Vesicles can be treated with sclerotherapy, carbon dioxide laser, or resection. Excision usually is not performed because the area of vesicles is large and the distal extremity is an unfavorable location for the removal of skin. Injecting vesicles with a scleroscent causes scarring which effectively reduces leakage; I prefer sodium tetradecyl sulfate. Carbon dioxide laser also causes fibrosis of the vesicles and gives favorable results. Localized vesicles can be treated with sclerotherapy in the office, but large areas are best managed with carbon dioxide laser under general anesthesia.

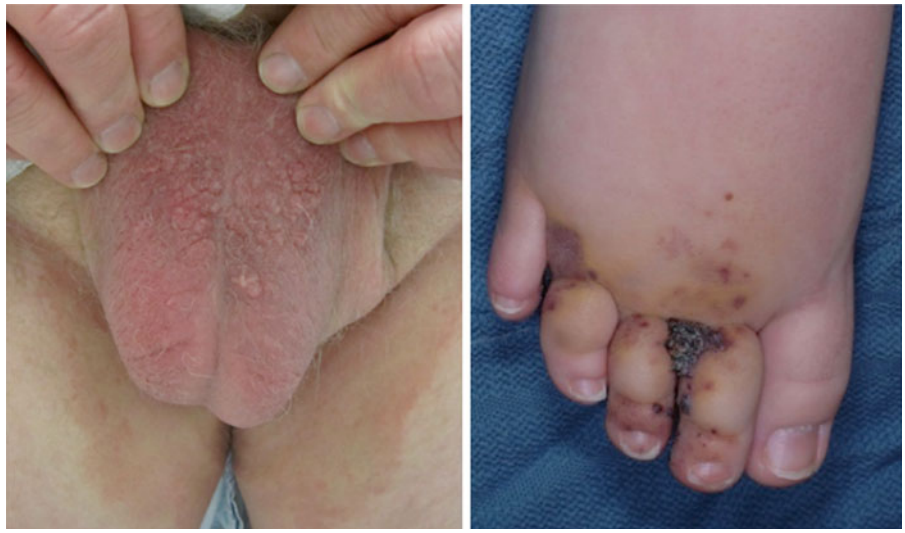

Fig. 4.7 Vesicles can develop in lymphedematous areas. (*Left*) 51-year-old with secondary lower extremity and genital lymphedema has scrotal vesicles leaking lymph fluid (lymphorrhea). (*Right*) 11-year-old male with primary lower extremity lymphedema has vesicles of his feet causing bleeding and multiple infections

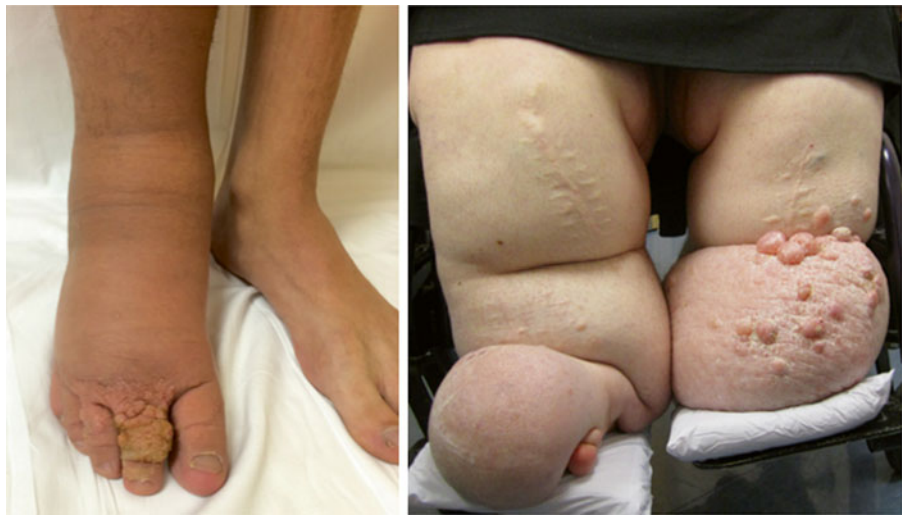

Fig. 4.8 Lymphedema can cause hyperkeratosis. (*Left*) 21-year-old male with primary lymphedema has had progressive overgrowth of his second toe that has impeded his ability to wear shoes, caused pain, and leaked fluid. (*Right*) 40-year-old female with a history of myelomeningocele and primary lymphedema has hyperkeratotic lesions on her left lower extremity

Massive Localized Lymphedema

Obesity can result in a large, localized area of overgrowth termed "massive localized lymphedema" (MLL) (Fig. 4.9) [21]. The condition is uncommon and affects extremely obese patients. The average age of individuals is 47 years and males and females are affected equally [22]. Mean patient body mass index is 61 [22]. MLL involves the thigh (49 %), lower abdomen (18 %), penis/scrotum (12 %), suprapubic area (7 %), vulva (4 %), distal leg (7 %), and arm (3 %) [22]. The average size and weight of MLL is 37.4 cm and 9.3 kg, respectively. Although MLL of the

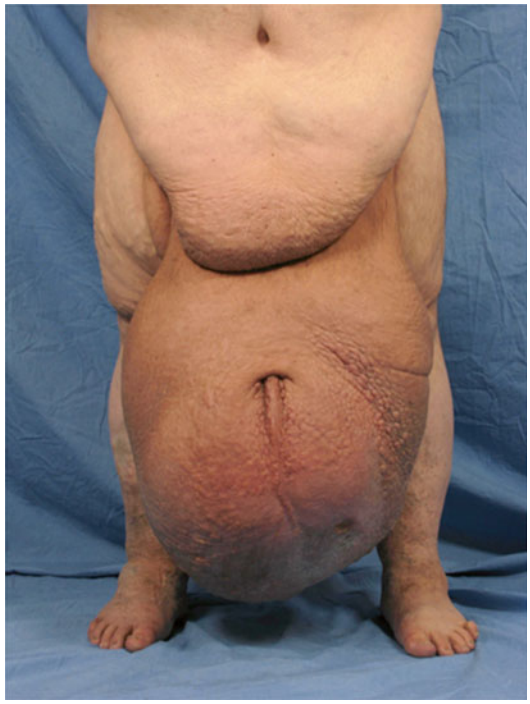

Fig. 4.9 Massive localized lymphedema. 48-year-old with obesity-induced lymphedema who developed massive localized lymphedema of his scrotum

extremities is typically unilateral, both lower extremities usually have underlying lymphatic dysfunction of the entire limb. Patients with MLL can have difficulty ambulating and fitting clothing. When the lesion involves the perineal area individuals may have problems sitting. Similar to other locations with lymphedema, angiosarcoma can develop in MLL [22].

MLL can be improved with weight loss, and patients are referred to a bariatric surgery center. Following massive weight loss, if the localized area remains symptomatic it can be removed. If an area of MLL is resected prior to weight loss the operative morbidity and recurrence rate are significantly higher than removing the area once the patient has lowered his/her body mass index.

Pain

Lymphedema generally is a painless; significant discomfort is not consistent with the disease. If a patient complains of significant pain, then he/she likely does not have lymphedema. However, as the circumferential overgrowth of the extremity worsens and the limb becomes heavier, underlying musculoskeletal discomfort can occur primarily because of stress on joints. The limb can feel heavy for the patient and cause fatigue, weakness, and or paresthesias [23].

Malignant Transformation

Chronic lymphedema can predispose an individual to lymphangiosarcoma in the affected extremity, although the risk is very low (~0.07–0.45 %) [24]. Stewart–Treves "syndrome" is not a syndrome and classically refers to a lymphangiosarcoma arising in a lymphedematous upper extremity following treatment for breast cancer (Fig. 4.10) [24]. The condition is better described as *Stewart–Treves Tumor*. The malignancy also can develop in chronic lower extremity lymphedema resulting from inguinal radiation and/or lymphadenectomy. Lymphangiosarcoma has been described in patients with primary lymphedema (in both the upper and lower extremity) as well as in areas of massive localized lymphedema [22, 24]. Prognosis is poor because of pulmonary metastasis and local recurrence. Mean survival is <2 years following diagnosis. If metastases are not present on imaging, early amputation may allow long-term survival. Chemotherapy and radiation have minimal efficacy [24].

Genitourinary

Generally, the primary morbidity of penile/scrotal lymphedema is psychosocial because patients do not like the appearance of their genitalia (Fig. 4.11). "Functional" problems with genital lymphedema are uncommon. Penile/scrotal lymphedema does not affect sexual function or sterility. Rarely, dysuria or phimosis can occur. Patients with severe penile/scrotal lymphedema may have difficulty fitting clothing, leaking lymphatic vesicles, and/or infections. Conservative management for symptomatic patients is to apply compression using tight fitting exercise shorts. Vesicles may be treated using sclerotherapy or

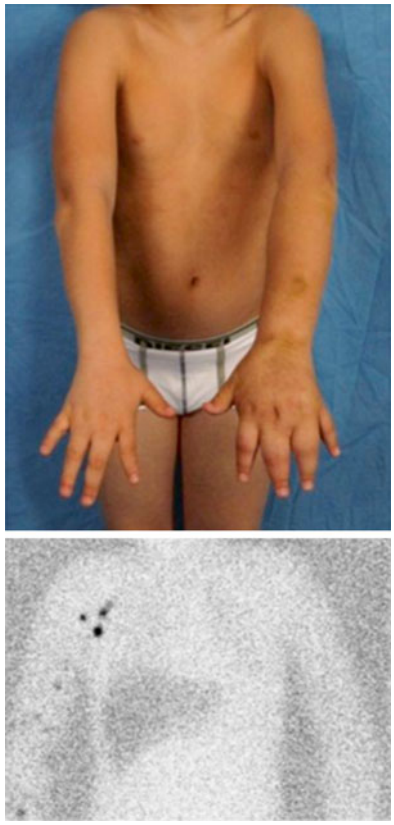

Fig. 4.10 Lymphangiosarcoma in a lymphedematous extremity. 12-year-old male with infant-onset primary lymphedema developed pain and hardening of this hand/forearm over the previous 3 months. Lymphoscintigraphy illustrated absence of tracer uptake in his left axilla. Biopsy showed lymphangiosarcoma

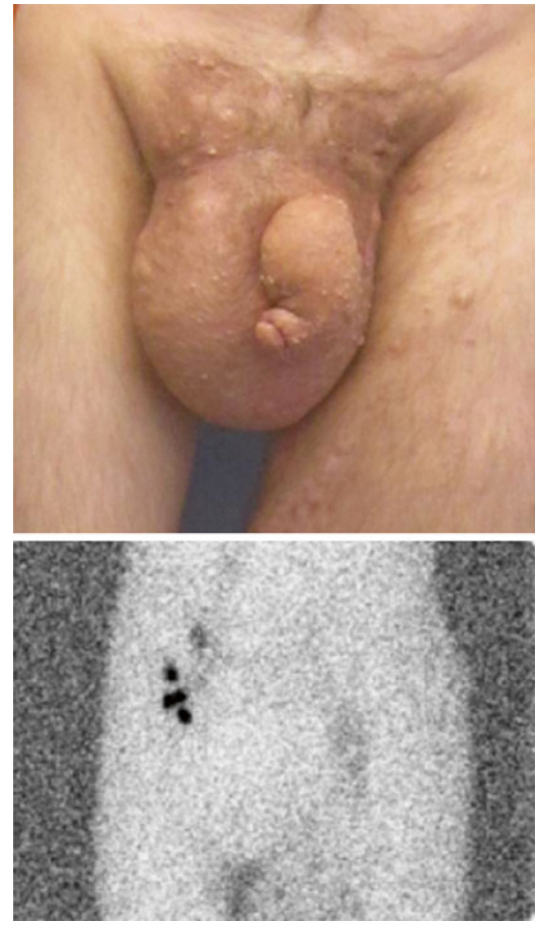

Fig. 4.11 Morbidity of genital lymphedema. 24-year-old with adolescent-onset primary lymphedema who was unhappy with the appearance of his genitalia; he also complained of leaking lymphatic vesicles. Lymphoscintigram shows absence of tracer in his left inguinal nodes 3.5 h following injection

carbon dioxide laser. The appearance of the genitalia and morbidity can be improved by resecting skin and subcutaneous tissue.

Congestive Heart Failure

The patient in our experience with the most severe manifestation of lymphedema developed congestive heart failure from his disease (Fig. 4.12). He had primary lymphedema of his right lower extremity that steadily worsened over the course of his life that caused him to be non-ambulatory. He developed high-output congestive heart failure because of the amount of blood flow that was being shunted to his massive extremity. Following staged subcutaneous excision of 45 lb of skin and subcutaneous tissue, his congestive heart failure resolved.

Conclusions

Lymphedema is a common condition. Most patients develop the disease following lymphadenectomy/radiation or from a parasitic condition. Patients may also develop idiopathic lymphedema from the anomalous development of the lymphatic system. Although many individuals

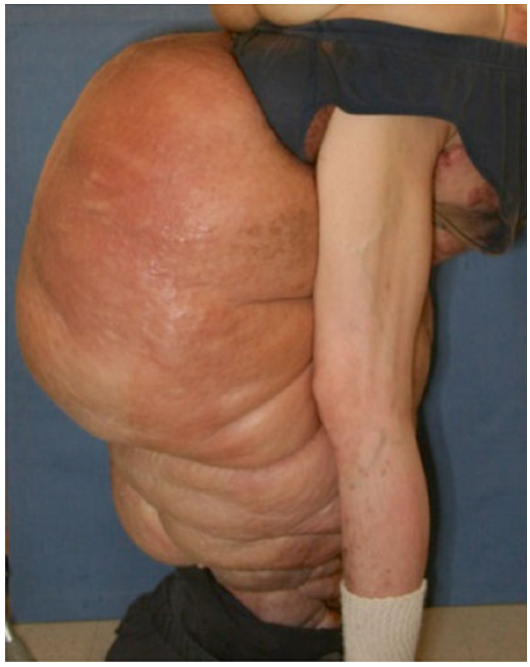

Fig. 4.12 32-year-old male with massive lower extremity lymphedema causing congestive heart failure because of excessive blood flow to the limb

with lymphedema have minimal morbidity, the disease can cause significant problems, e.g., psychosocial distress, infection, difficulty using the diseased area, malignant degeneration.

References

1. Schook CC, Mulliken JB, Fishman SJ, Grant F, Zurakowski D, Greene AK. Primary lymphedema: clinical features and management in 138 pediatric patients. Plast Reconstr Surg. 2011;127:2419–31.
2. Mendoza N, Li A, Gill A, Tyring S. Filariasis: diagnosis and treatment. Dermatol Ther. 2009;22:475–90.
3. Moffatt CJ. Lymphoedema: an underestimated health problem. QJM. 2003;96:731–8.
4. Rockson SG. Estimating the population burden of lymphedema. Ann N Y Acad Sci. 2008;1131:147–54.
5. Smeltzer DM, Stickler GB, Schirger A. Primary lymphedemas in children and adolescents: a follow-up study and review. Pediatrics. 1985;76:206–18.
6. Wolfe J, Kinmonth JB. The prognosis of primary lymphedema of the lower limbs. Arch Surg. 1981;116:1157–60.
7. Cormier JN, Askew RL, Mungovan KS, Xing Y, Ross MI, Armer JM. Lymphedema beyond breast cancer: a systematic review and meta-analysis of cancer related secondary lymphedema. Cancer. 2010;116:5138–49.
8. Gärtner R, Mejdahl MK, Andersen KG, Ewertz M, Kroman N. Development in self-reported arm-lymphedema in Danish women treated for early-stage breast cancer in 2005 and 2006 - a nationwide follow-up study. Breast. 2014;23:445. doi:10.1016/j.breast.2014.03.001. pii: S0960-9776(14)00042-3.
9. Johansson K, Branje E. Arm lymphoedema in a cohort of breast cancer survivors 10 years after diagnosis. Acta Oncol. 2010;49:166–73.
10. Petrek JA, Senie RT, Peters M, Rosen PP. Lymphedema in a cohort of breast carcinoma survivors 20 years after diagnosis. Cancer. 2001;92:1368–77.
11. Dayangac M, Makay O, Yeniay L, Aynaci M, Kapkac M, Yilmaz R. Precipitating factors for lymphedema following surgical treatment of breast cancer: implications for patients undergoing axillary lymph node dissection. Breast J. 2009;15:210–1.
12. Yen TW, Fan X, Sparapani R, Laud PW, Walker AP, Nattinger AB. A contemporary, population-based study of lymphedema risk factors in older women with breast cancer. Ann Surg Oncol. 2009;16:979–88.
13. McLaughlin SA, Wright MJ, Morris KT, Giron GL, Sampson MR, Brockway JP, Hurley KE, Riedel ER, Van Zee KJ. Prevalence of lymphedema in women with breast cancer 5 years after sentinel lymph node biopsy or axillary dissection: patient perceptions and precautionary behaviors. J Clin Oncol. 2008;26:5220–6.
14. Hayes SB. Does axillary boost increase lymphedema compared with supraclavicular radiation alone after breast conservation? Int J Radiat Oncol Biol Phys. 2008;72:1449–55.
15. Helyer LK, Varnic M, Le LW, Leong W, McCready D. Obesity is a risk factor for developing postoperative lymphedema in breast cancer patients. Breast J. 2010;16:48–54.
16. Van der Zee AG, Oonk MH, De Hullu JA, Ansink AC, Vergote I, Verheijen RH, Maggioni A, Gaarenstroom KN, Baldwin PJ, Van Dorst EB, Van der Velden J, Hermans RH, van der Putten H, Drouin P, Schneider A, Sluiter WJ. Sentinel node dissection is safe in the treatment of early-stage vulvar cancer. J Clin Oncol. 2008;26:884–9.
17. Flegal KM, Carroll MD, Ogden CL, Curtin LR. Prevalence and trends in obesity among US adults, 1999–2008. JAMA. 2010;303:235–41.
18. Greene AK, Grant FD, Slavin SA. Lower extremity lymphedema and elevated body mass in obese patients. N Engl J Med. 2012;366:2136–7.
19. Brorson H, Ohlin K, Olsson G, Karlsson MK. Breast cancer-related chronic arm lymphedema is associated with excess adipose and muscle tissue. Lymphat Res Biol. 2009;7:3–10.
20. Fu MR, Ridner SH, Hu SH, Stewart BR, Cormier JN, Armer JM. Psychosocial impact of lymphedema: a

systematic review of literature from 2004–2011. Psychooncology. 2013;22:1466–84.
21. Farshid G, Weiss SW. Massive localized lymphedema in the morbidly obese: a histologically distinct reactive lesion simulating liposarcoma. Am J Surg Pathol. 1998;10:1277–83.
22. Chopra K, Tadisina KK, Brewer M, Holton LH, Banda AK, Singh DP. Massive localized lymphedema revisited: a quickly rising complication of the obesity epidemic. Ann Plast Surg. 2015;74:126–32.
23. Brorson H, Ohlin K, Olsson G, Langstrom G, Wiklund I, Svensson H. Quality of life following liposuction and conservative treatment of arm lymphedema. Lymphology. 2006;39:8–25.
24. Sharma A, Schwartz RA. Stewart-Treves syndrome: pathogenesis and management. J Am Acad Dermatol. 2012;67:1342–8.