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Sumner A. Slavin
Håkan Brorson
Editors

Lymphedema

Presentation, Diagnosis, and Treatment

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This book is dedicated to patients with lymphedema—we hope that it improves their quality of life and translates into improved therapies.

Preface

Although lymphedema affects millions of people around the world, the pathophysiology of the disease is poorly understood and the condition remains incurable. Lymphedema is associated with many myths; patients often are misdiagnosed and receive incorrect treatment. Individuals with lymphedema typically are medical nomads being transferred from physician to physician until they find someone who understands their disease. The goal of this book is to improve the lives of patients with lymphedema by providing an evidence-based resource for health-care providers.

The editors of the book direct Lymphedema Programs and share many principles related to the management of lymphedema. Experts from around the world were recruited to author chapters on his/her expertise. The book was designed to be clinically oriented, rather than focused on history or research; references were limited to no more than 30 for each chapter. The book was written to be an easy-to-read resource that highlights principles by including an abstract, conclusion, and list of key points. The text also can be used for more in-depth study of a subject, teaching, or research. Hopefully, the book will stimulate readers to improve their understanding of lymphedema and to develop better treatments.

Boston, MA, USA — Arin K. Greene
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Acknowledgments

The Editors

We thank all of the contributing authors who have shared their expertise to improve the care of patients with lymphedema. We also thank Springer Publishing, and particularly Elektra McDermott, who have done an outstanding job editing and helping us put the book together.

Arin Greene

My interest in lymphedema began when I was exposed to children with primary disease in the Vascular Anomalies Center at Boston Children's Hospital. I was troubled by the significant morbidity that lymphedema could cause, the lack of understanding regarding its pathogenesis, and the often less-than-satisfactory treatments. My passion for the condition was further stimulated by Sumner Slavin who exposed me to patients with secondary lymphedema in the Lymphedema Program at the Beth Israel Deaconess Medical Center.

I would like to thank Sumner Slavin and Håkan Brorson who have been my biggest influences in the field of lymphedema. I am also grateful to Steven Fishman and John Mulliken who not only first exposed me to primary lymphedema but also have encouraged my interest in lymphedema and recommended that patients with primary lymphedema be managed in our dedicated Lymphedema Program rather than the Vascular Anomalies Center. I would like to acknowledge John Meara who has encouraged my interest in lymphedema and given me tremendous professional support. Dr. Meara also supported moving the Lymphedema Program from the Beth Israel Deaconess Medical Center to the Department of Plastic and Oral Surgery at Boston Children's Hospital. Since relocating the center to our department several years ago, we have been able to manage both children and adults with the disease. In addition, we have learned from our high volume of patients, which has translated into innovation and improved care.

Our multidisciplinary management of patients with lymphedema would not be possible without the work of Jennifer Jagielski and Susan Rajotte who attend our Lymphedema Clinics and provide static and pneumatic compression, respectively. I am grateful for our other team members, Elizabeth Hunter, Ashley D'Eon, and Reid Maclellan, who provide outstanding patient care and administration. I would like to thank our close colleagues in the

Nuclear Medicine Department, Frederick Grant and Stephan Voss, who perform lymphoscintigraphy on our patients and collaborate with us through research as well.

Finally, I want to acknowledge my family. I am not sure I would be a plastic surgeon today without my grandparents, Albert and Ruth, who had a profound influence on my life. Most importantly, I want to thank my wife, Sarah, and three boys, Albert, Mac, and Henry, who encourage and support the passion I have for my "job."

Contents

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List of Editors

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Part I

Overview of Lymphedema

The Lymphatic System

1

Reid A. Maclellan

Key Points

- The lymphatic system travels parallel to the cardiovascular system.
- In the extremities there are both superficial and deep lymphatics.
- The thoracic duct is the main lymphatic collecting vessel; it obtains lymph fluid from the entire body except the upper right quadrant.

Introduction

The lymphatic system parallels the cardiovascular system. It consists of lymphatic vessels and secondary lymphoid organs. It returns lymph fluid to the circulation via a one-way system [1]. Lymphatic vessels were first described as "white blood" by Hippocrates who coined the term "chyle" from the Greek *chylos,* meaning juice [1, 2]. Gaspar Aselli first illustrated the lymphatic system in 1622. As he was studying the abdomen of a well-fed dog, he noted a large number of mesentery cords that were very white and extremely thin. A white milk-like substance discharged from the vessels as he dissected them. *De lactius sive lacteis venis* was the first color-printed medical publication [1, 3]. An additional 300 years passed before it was discovered that the lymph system is responsible for returning protein molecules from tissues back to the central circulation. It also was determined that blocking lymphatic vessels led to lymphedema [4].

The lymphatic system is an open, linear structure. In the extremities it consists of an epifascial and a subfascial arrangement. It begins by collecting lymph fluid in tissue, delivers the fluid to filtering nodes through many small afferent vessels, exits the nodes via large efferent channels, and ends at the lymph–vein connection of the thoracic duct [5]. The lymphatics are absent in the brain, spinal cord, retina, bone, and cartilage [1].

Lymphatic Anatomy

Vasculature

Lymphatic capillaries are designed to obtain drained lymph fluid. They only have a single layer of overlapping lymphatic endothelial cells that are attached by filament bundles. In comparison to blood capillaries, they are not lined by a basement membrane or smooth-muscle like pericytes. This allows them to be highly permeable to interstitial fluid and macromolecules [6, 7]. Lymphatic capillaries normally are collapsed because they do not have the type of hemodynamic pressure that blood capillaries have that forces them to stay open [1, 8, 9]. An increase in interstitial pressure leads

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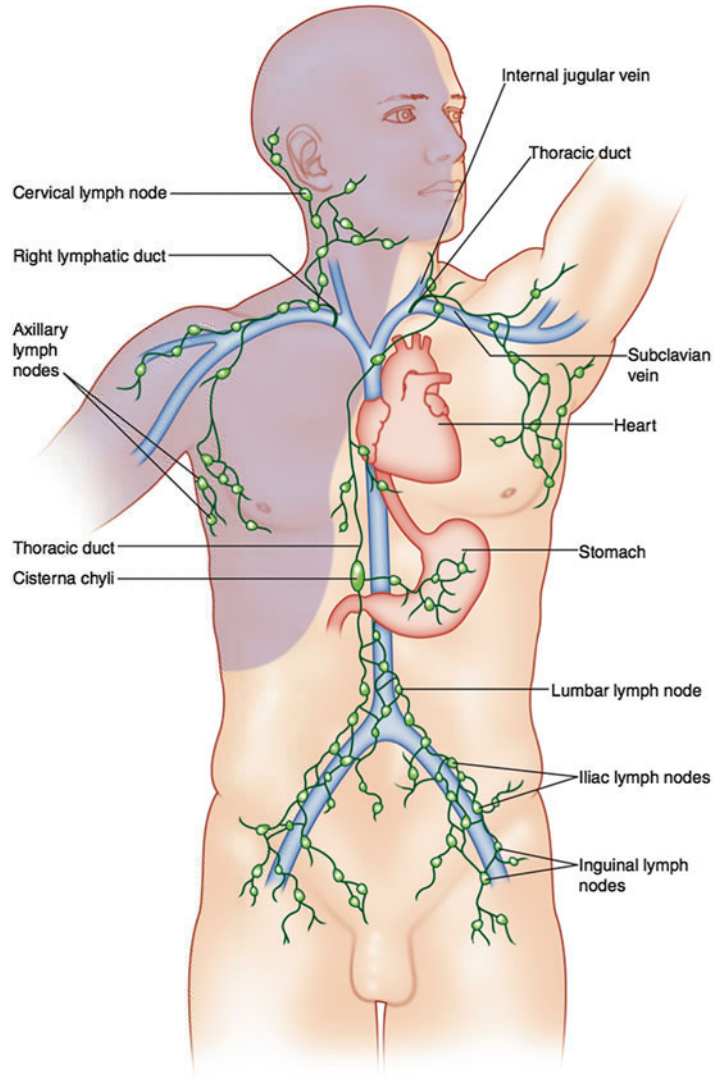

Fig. 1.1 Schematic of the lymphatic collection system. The right lymphatic duct obtains lymph fluid from the *shaded area*, while the thoracic duct accumulates lymph from the *non-shaded region*

to the anchoring filaments pulling the lymphatic endothelial cells apart and opening the capillaries. Lymph fluid then drains into the lymphatic capillaries [7, 10]. These capillaries are connected to precollecting lymphatic vessels, which eventually merge into secondary lymphatic collecting vessels.

Unlike lymphatic capillaries, lymphatic collecting vessels are constructed to return drained fluid into the circulation. They have lymphatic endothelial cells that are surrounded by a continuous basement membrane and pericytes. These endothelial cells tightly line up side by side [1, 11]. The collecting vessels possess valves that inhibit retrograde lymph flow. Muscle contraction propels lymph fluid through the collecting vessels [1].

Thoracic Duct

The thoracic duct is the main lymphatic collecting vessel of the body. It obtains lymph fluid from the entire body except the right head and neck, right hemithorax, and right upper extremity (Fig. 1.1).

It measures approximately 45 cm in length and 5 mm in width [12]. The thoracic duct is divided into three parts: abdominal, thoracic, and cervical. The duct originates with the abdominal portion at the cisterna chyli and ascends upward to form the thoracic portion as it traverses the aortic hiatus of the diaphragm into the posterior mediastinum [13]. The duct continues posteriorly along the esophagus until it reaches the fifth thoracic vertebra where it ascends on the left of the esophagus. The cervical segment of the duct begins when it descends across the subclavian artery at the seventh cervical vertebra [13]. The cervical thoracic duct is the widest of the three parts and has the greatest amount of variability between patients. There also are move valves in the "cervical" region than any other portion of the duct [14].

Several researchers have studied the termination of the thoracic duct. One anatomist reviewed over 500 patients and cadavers and determined 36 % of ducts end in the internal jugular vein, 34 % terminated in the junction of the internal jugular and subclavian veins, 21 % had multiple closures, and 17 % concluded in the subclavian vein [15]. Another group found the most common location of cessation was the venous angle (38 %) followed by the external jugular vein (28 %) and internal jugular vein (27 %) [16]. They noted 7 % of patients had a complex configuration. These individuals had a higher likelihood of metastasis in the cervical region [16]. Surgeons should take extra caution when dissecting in the vicinity of the thoracic duct because of its highly variable anatomy.

Right Lymphatic Duct

The right lymphatic duct drains the upper right body including the right head and neck, right upper extremity, right diaphragm, right lung, lower left lung, most of the heart, and part of the right lobe of the liver [13]. It is formed by the joining together of the right jugular, right subclavian, and right bronchomediastinal lymphatic trunks and measures 2 cm in length, respectively. The right bronchomediastinal trunk is the vestigial portion of the embryologic right thoracic duct [13]. The right lymphatic duct mainly terminates in the junction of the right subclavian and right internal jugular veins; however, it has numerous variations like the thoracic duct [13].

Cisterna Chyli

The cisterna chyli is a 2–5 cm elongated sac located retroperitoneally approximately at the second lumbar vertebra. It is the beginning of the thoracic duct. It drains lymph from the right and left lumbar trunks, the intestinal trunk, and the lowest intercostal vessels. These vessels either form a single sac or multiple sacculations. The union of the individual vessels may occur in the thoracic region instead of the abdomen [14]. The lumbar trunks obtain lymph from the pelvis, kidneys, adrenal glands, and area of the abdominal wall below the umbilicus. The intestinal trunk drains lymph from the celiac and superior mesenteric arteries [13].

Lymphatics of the Extremity

In the extremities there is an epifascial and a subfascial lymphatic system. The epidermal valveless lymphatics drain toward the subdermal valved lymphatics which then flow to collecting vessels above the fascia. The subdermal lymphatics are responsible for draining the integument and normally follow along with the veins. The epifascial and subfascial lymphatics communicate via perforators. The deep lymphatics flow below the deep fascia and course parallel with the main vascular structures [5]. In both the superficial and deep lymphatic system several small afferent lymphatic vessels lead lymph fluid to lymph node sinuses. The fluid exits the lymph node hilum via large efferent channels on its return to the cardiovascular system [5, 17]. The epifascial lymph nodes interconnect into four central draining chains: the paired axillary and inguinal lymph node systems [5].

The superficial lymphatic system of the upper extremity is divided into an ulnar bundle and a

radial bundle. The ulnar bundle drains the medial arm and follows the basilic vein to the axillary lymph nodes [5]. Part of the ulnar bundle branches at the hiatus basilicus and connects with the deep lymphatic system of the upper extremity via perforators. The radial bundle obtains lymph from the lateral arm and accompanies the cephalic vein until it joins the axillary lymph nodes at the lower margin of the pectoralis major muscle [5]. Lymph will then drain from the axillary lymph nodes to either the supraclavicular and/or infraclavicular lymph node and then to either the thoracic duct (left upper extremity) or the right lymphatic duct (right upper extremity) [5].

The epifascial system of the lower extremity collects lymph from the skin and subcutaneous layers and is divided into two bundles: ventromedial and dorsolateral bundles [5]. The dorsolateral bundle parallels the lesser saphenous vein, passes through the popliteal nodes, continues as the subfascial lymphatics of the thigh, and ends either in the deep inguinal or anterior iliac nodes. The ventromedial bundle runs with the greater saphenous vein but has greater variability in how it terminates [5]. The subfascial system accompanies the anterior and posterior tibial vasculature until they join with the dorsolateral bundle at the popliteal nodes. These collector vessels drain the muscles and fascia of the lower extremity [5].

Lymphatic Function

The lymphatic vasculature recycles interstitial fluids from veins back to the circulatory system, contributes to the immune response, and participates in the digestive tract [1, 5, 18]. Fifty to 100 % of plasma exits into the interstitium daily and provides nourishment to surrounding tissues [19, 20]. Ninety percent is recycled via venous capillaries; however, the remaining fluid has a molecular weight that is too large to pass through these vessels [5, 19, 20]. The differences in hydrostatic pressure and colloidal pressure in surrounding tissues and the lymphatic vasculature force the high molecular weight plasma through collecting lymphatics [5]. The lymph is then transported back to the cardiovascular system. The lymphatics also function in the immune system both by activating inflammatory responses in lymphatic endothelial cells and trafficking lymphocytes and antigen-presenting cells to lymph nodes [1, 21]. The lymphatics final purpose is to assist in the digestive tract. Lacteals are specialized lymphatic vessels located in the intestines. They carry fats and lipids in the form of chylomicrons [1, 22].

Conclusion

The lymphatic system runs one-way. The extremities have an epifascial and a subfascial system for collecting lymph. Lymph fluid drains from capillaries to afferent collecting vessels to lymph nodes to efferent lymphatic vessels to either the thoracic duct or the right lymphatic duct and back to the cardiovascular system.

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Pathophysiology of Lymphedema

2

Geoffrey E. Hespe, Matthew D. Nitti, and Babak J. Mehrara

Key Points

- Lymphedema is a pathophysiologic process resulting from injury, infection, obstruction, or congenital defects in the lymphatic system.
- Primary lymphedemas occur as a result of genetic or developmental abnormalities in the lymphatic system; secondary lymphedemas are caused by secondary insults to the lymphatic system
- The histological hallmarks of lymphedema are lymphatic fluid stasis, chronic inflammation, fibroadipose tissue deposition, and hyperkeratosis.
- Risk factors for development of lymphedema include genetic abnormalities, obesity, radiation, and infection.
- Cellular mechanisms of lymphedema are unknown; however, recent studies have demonstrated a critical role for CD4+ cells in the regulation of fibrosis in animal models and correlative clinical studies.

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Introduction

The lymphatic system is an essential component of the circulatory system whose main roles are maintaining fluid homeostasis, acting as a conduit for migration and transport of immune cells, regulation of inflammatory responses, and enabling dietary absorption of fat. Networks of lymphatic vessels begin as blind-ended lymphatic capillaries and transport interstitial fluid unidirectionally back to the heart. Disruption of lymphatic vasculature secondary to chronic parasitic infections, during the course of cancer treatment, after trauma, or as a consequence of genetic mutations results in stasis of protein rich interstitial fluid and chronic inflammation. These pathologic changes, over time, lead to lymphedema; a progressive disease characterized by adipose deposition and tissue fibrosis. It is well established that patients with lymphedema have significant impairments in quality of life, recurrent infections, and in some cases deadly secondary tumors.

Broadly speaking, lymphedema can be categorized as either primary or secondary. Primary lymphedema, as the name implies, is caused by abnormal development of the lymphatic system or pathological changes intrinsic to the lymphatic vasculature. These developmental abnormalities may be related to genetic defects that either directly or indirectly regulate lymphatic differentiation and function. In contrast, secondary lymphedemas occur as a consequence of postnatal iatrogenic, infectious, or traumatic insults to the

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lymphatic system. Although both primary and secondary lymphedemas share similar pathologic features including chronic swelling, inflammation, adipose deposition, and fibrosis, there important pathologic distinctions remain between patient responses, disease course, and response to treatments. In addition, although recent studies have improved our understanding of the pathology of lymphedema in general, the mechanisms that regulate these disease specific responses remain unknown and are an important area of research.

Classification of Lymphedema

Primary Lymphedema

Primary lymphedemas can be classified either by the timing of presentation, mode of inheritance (genetic linked or sporadic), or region of pathology (e.g., systemic or visceral). Traditionally, the timing of presentation has been used most commonly to categorize patients as having congenital lymphedema (i.e., present at birth), developing lymphedema around the time of puberty (lymphedema praecox), or presenting in adults older than 35 years (lymphedema tarda). The vast majority of patients present with either congenital lymphedema or lymphedema praecox; lymphedema tarda is diagnosed in less than 10 % of patients [1].

Classification of lymphedema based on timing of presentation is not particularly useful since there is no reference to the pathological causes. More recently, Connell et al. published a classification system and diagnostic algorithm that subcategorizes congenital lymphedemas as syndromic, systemic/visceral, disturbed growth, congenital onset, and late onset [2]. This classification system is helpful because it takes a more functional approach to lymphatic development and will likely aid in identifying genetic mutations due to its more inclusive nature.

Primary lymphedemas, in general, affect females twice as often as males and tend to more frequently involve the lower extremities. It is estimated that nearly 30 % of patients with primary lymphedema have an identifiable genetic mutation (often in the signaling pathway for vascular endothelial growth factor-C (VEGF-C)). The most studied example of this scenario is **Milroy's disease**, a form of congenital primary lymphedema that is caused by a heterozygous inactivating mutation of FLT4, the gene that encodes for the receptor for VEGF-C (Vascular Endothelial Growth Factor Receptor-3 (VEGFR-3). Milroy's disease is a familial, sex-linked condition and accounts for approximately 2 % of all lymphedemas. These patients most commonly have bilateral lower extremity lymphedema that is, in some cases, accompanied by hydroceles. Another common genetic cause of lymphedema is an autosomal dominant condition known as *lymphedema–distichiasis syndrome.* These patients have an autosomal dominant mutation in the FOXC2 gene, resulting in a combination of lower extremity lymphedema and an extra row of eyelashes.

Sporadic (i.e., not familial) cases are the most common causes of primary lymphedema accounting for ~60 % of all patients with lymphedema. The most common form of sporadic primary lymphedema is **Meige's disease**. Patients with this disorder present with symptoms usually around the time of puberty with a female to male ratio of 4:1. These facts have led some authors to suggest that female sex hormones may play a role in the development of lymphedema.

Secondary Lymphedema

Secondary lymphedema is the most common cause of lymphedema and develops secondary to either direct or indirect injury to the lymphatic system. The most common form of secondary lymphedema worldwide is filariasis, a condition in which parasitic roundworms *Wuchereria bancrofti* occupy the lymphatic vasculature, thereby blocking the flow of lymph from the extremity. Although the true incidence of filariasis remains unknown, estimates ranging between 140 and 200 million are commonly cited among patients residing primarily in third world countries [3]. In contrast, this form of lymphedema is very rare in developed countries.

In developed countries secondary lymphedema occurs most commonly as a complication of cancer treatment with breast cancer being the most common cause. It is estimated that nearly one in three patients who undergo axillary lymph node dissection for staging or treatment of breast cancer go on to develop lymphedema. Lymphedema, however, is not limited to breast cancer survivors, as a recent study demonstrated that nearly one in six patients who undergo treatment for other solid tumors such as melanoma, sarcoma, and gynecological malignancies also go on to develop lymphedema [4]. Even relatively minor disruption of the lymphatic system with sentinel lymph node biopsy, a procedure in which only a few lymph nodes are sampled for cancer staging, can result in lymphedema in 5–7 % of patients [5]. Lymphedema can also develop in patients who do not have lymph node biopsy but rather wide skin excisions (for example during the course of treatment for sarcoma or melanoma) particularly when these procedures are combined with radiation therapy suggesting that extensive injury of either the deep (i.e., lymph nodes) or superficial (i.e., dermal) lymphatic system can result in lymphedema development.

Importantly, the development of lymphedema after lymphatic injury usually occurs in a delayed fashion. Thus, although virtually all patients experience minor swelling immediately following surgery, in the vast majority of cases the swelling resolves within the first 4–6 weeks. However, a subset of patients develop recurrent swelling at a later point, typically 6–12 months postoperatively (77 % within the first 3 years) that does not resolve. In these cases, the diagnosis of lymphedema can be made when other causes of swelling (e.g., recurrent disease, deep venous thrombosis, systemic fluid overload,) are ruled out. This diagnosis is often confirmed with physiologic studies such as lymphoscintigraphy or indocyanine green near infrared angiography demonstrating diminished lymphatic transport capacity, dermal back flow, and dysfunctional lymphatic vessels. Lymphedema may even develop after very prolonged periods of time in at-risk patients with the longest reported case occurring 30 years after the initial surgery. In these cases, often an inciting event such as an infection or additional injury precedes the development of progressive limb swelling and lymphedema.

Recent studies have suggested that progression of lymphedema may be retarded during its early stages through the use of conservative measures such as compression garments or manual lymphatic massage therapy. Although there is some debate regarding the efficacy or timing of these treatments in preventing lymphedema development, the fact that measures aiming to decrease interstitial fluid stasis can alter disease progression/development is interesting and suggests that lymph stasis (rather than lymphatic injury alone) is necessary for development of lymphedema. However, once lymphedema develops it is usually progressive and chronic in nature although there is wide variability in the rate at which pathologic changes occur. Thus, in some cases lymphedema has a smoldering course with relatively mild changes in limb volume or tissue changes over very long periods of time (often years), while in other cases there is rapid progression of disease with disabling swelling and physiologic changes.

Risk Factors for Lymphedema

A large number of epidemiologic studies have analyzed genetic and comorbid factors that increase the risk of developing lymphedema. A clear understanding of these risk factors is important in preoperative surgical consultation and can be used as a means of tailoring surgical procedures to individual patients in an effort to decrease the risk of lymphedema development.

Genetics

The discovery of lymphatic markers and mechanisms that regulate lymphangiogenesis has led to an attempt by numerous researchers to test the hypothesis that mutations in the coding or non-coding regions of these genes increase the risk of developing primary or secondary lymphedema.

The majority of these studies have been performed in patients with primary lymphedema; however, recent studies have also targeted genetic risk factors for secondary lymphedema. The study of genetic risk factors for development of secondary lymphedema is interesting and based at least partially on the observation that some patients with breast cancer-related lymphedema exhibit abnormalities in lymphatic transport even in their unaffected normal extremity.

An interesting report by Mendola and colleagues from the lymphedema research group analyzed genetic mutations in 78 patients with familial (i.e., inherited) and 149 patients with sporadic primary lymphedemas. The investigators found that mutations in seven genes encoding molecules regulating VEGFR3 and its downstream pathways were responsible for 36 % of inheritable forms of primary lymphedema. In contrast, only 8 % of patients with sporadic primary lymphedema exhibited these mutations [6]. These findings are important and demonstrate that complex pathways regulate development of hereditary lymphedema. More importantly, these studies highlight the need for additional study since the majority of hereditary and sporadic primary lymphedema patients did not exhibit known genetic mutations.

Recent studies provide support for the theory that genetic mutations may also increase the risk of secondary lymphedema after surgery. For example, Feingold et al. sequenced the coding and flanking noncoding regions of the hepatocyte growth factor (HGF) and its high affinity receptor MET in 59 women with breast cancer-related upper extremity lymphedema, and 159 unrelated matched controls. This analysis was based on previous studies demonstrating that this signaling pathway is an important regulator of lymphangiogenesis in a number of physiologic settings [7]. Interestingly, the authors identified an increased rate of mutations in HGF/MET pathways in patients with lymphedema suggesting that impairments in lymphatic regeneration after injury due to dysfunctional HGF/MET signaling contributes to an increased risk of developing lymphedema. In a follow-up case–control study (80 patients with breast cancer-related lymphedema compared with 108 breast cancer controls), Feingold and colleagues found mutations in CJC2 (encoding connexin 47), a gap junction protein that is thought to regulate dermal lymphatic transfer, in four patients with lymphedema but not in any of the controls. Similar mutations have been observed in cohorts of patients with primary lymphedema [8]. Interestingly, in contrast to their previous report the authors identified only one patient with a MET mutation, suggesting that larger samples of patients are needed for these studies.

Newman and colleagues used a nested case–control approach to study genetic changes in 22 patients who developed breast cancer-related lymphedema within 18 months of surgery (case) as compared to 98 patients who did not develop lymphedema. The authors reported that single nucleotide polymorphisms (SNPs) within VEGFR2, VEGFR3, and RORC were associated with development of lymphedema [9]. SNPs are variations in DNA sequence that occur normally in the general population. These variations can occur in both coding and noncoding regions of the DNA and although gene function may be normal under physiologic conditions, some SNPs may lead to gene function changes that increase the risk of pathology. Future studies in this arena should focus on identifying the functional gene changes that occur in patients with SNPs that increase the risk of lymphedema after breast surgery.

Obesity

The increased risk of developing lymphedema in obese patients is well described in previous epidemiologic studies. In a seminal study in 1957, Treves followed over 1,000 patients after treatment for breast cancer and found that obese patients were at significantly increased risk of developing lymphedema [10]. This observation has been confirmed in numerous subsequent studies. For example, Werner et al. reviewed 282 patients with upper extremity lymphedema after treatment for breast cancer and showed that patients with a higher body mass index (BMI) also had a higher incidence of lymphedema. Another prospective study examined the risk of

developing lymphedema in the upper extremity in 137 patients with breast cancer and showed that patients with a BMI >30 had a threefold greater risk than patients with a BMI < 25 [11]. The best supporting evidence is a randomized controlled trial in which patients with upper arm lymphedema underwent 12 weeks of dieting and nutritional counseling as compared with patients who did not. The results showed that patients who lost weight had significant reductions in arm volumes and upper arm lymphedema when compared to the control patients who did not diet [12]. These results suggest that lymphatic impairment in obesity is reversible. More importantly, these studies show that obesity and lymphedema are intricately linked. This is not surprising since a defining feature of chronic lymphedema is progressive adipose tissue deposition. This observation has led some authors to conclude that lymphedema may be a form of "regional" obesity in which tissues are more prone for depositing fat in the setting of caloric excess. This hypothesis is supported by the fact that lymphatic fluid has been shown to increase adipocyte proliferation and differentiation and by other studies demonstrating that even mild lymphatic injury activates expression of genes necessary for adipocyte activation.

Obesity, independent of surgery, has been shown to decrease lymphatic function. For example, previous studies have shown that obese patients have decreased clearance of macromolecules from the skin and subcutaneous tissues as compared with lean individuals [13, 14]. In addition, Greene and colleagues have shown that morbidly obese patients (BMI > 59) develop primary lower extremity lymphedema (i.e., without antecedent trauma or injury) characterized by decreased lymphatic transport and dermal back flow on lymphoscintigraphy [13]. Interestingly, the upper extremity seems to be less susceptible to obesity-induced lymphedema as the obese patients in Greene's series who developed upper extremity lymphedema tended to be significantly more obese (BMI > 65) than those who had just lower extremity lymphedema.

In order to study the molecular mechanisms that regulate obesity induced lymphatic function, Weitman et al. and Blum and colleagues have used a mouse model of diet induced obesity and have found that increasing obesity results in impaired transport of interstitial fluid, decreased migration of immune cells, decreased pumping capacity of collecting lymphatics, and abnormal lymph node architecture [15, 16]. Further investigation with this model showed that obese mice have heightened inflammatory responses following lymphatic injury and that these promoted increased adipose deposition and fibrosis.

Radiation

Radiation therapy is frequently used as an adjunct to the treatment of a variety of cancers. Although these treatments are highly effective in some settings, they also are known to cause significant tissue damage and fibrosis. Not surprisingly, numerous studies have shown that radiation therapy delivered to lymph node basins is a significant contributor to the development of lymphedema particularly when radiation follows surgical injury. Thus, radiation in isolation is rarely associated with development of lymphedema; however, the combination of surgery and radiation significantly increases risks. For example, Hinrich et al. analyzed 105 patients who received postmastectomy radiotherapy and found that total dose, posterior axillary boost, and overlapping techniques were significantly associated with development of lymphedema [17]. Other studies have suggested that radiation increases the risk of lymphedema by as much as tenfold.

Although the precise mechanisms by which radiation increases the risk of lymphedema remain unknown, preclinical studies suggest that radiation-induced fibrosis is a major contributor. For example, using a mouse tail model of radiation injury, Avraham and colleagues demonstrated that lymphatic endothelial cells are sensitive to radiation and that this injury can induce apoptosis and subclinical lymphatic dysfunction [18]. These findings were corroborated by a clinical study demonstrating that radiation treatment decreases the density of small vessel lymphatics [19]. Interestingly, however, in the mouse studies protection of lymphatic endothelial cells from

apoptotic death did not decrease lymphatic dysfunction even though the lymphatic architecture was largely preserved. In contrast, inhibition of radiation induced fibrosis markedly improved lymphatic function suggesting that changes in the extracellular matrix independently regulate lymphatic function. Therefore, clinical strategies that decrease fibrosis after radiation treatment may be a novel means of decreasing the risk of lymphedema in cancer survivors.

Infection

Patients who undergo lymph node dissection are at increased risk for infections. Unfortunately, infections often precede the development of lymphedema and may cause progressive damage to the lymphatic system. This concept is supported by numerous studies examining the association between cellulitis and development of lymphedema after treatment for gynecological or breast malignancies. For example, Gould et al. assessed complications associated with inguinal lymphadenectomy in vulvar cancer and found that patients who developed early cellulitis were at a significantly increased risk for the development of subsequent lymphedema [20]. Another cross sectional study evaluating 807 patients with lymphedema secondary to breast cancer treatment found that a past history of cellulitis was a significant factor associated with increased upper extremity volume [21]. This finding led the authors to conclude that avoidance of cellulitis through meticulous skin care is an effective means of preventing development or progression of lymphedema.

Lymphedema Staging

Clinical Staging

Whether it is primary or secondary lymphedema, the timeline by which symptoms present themselves is highly variable and difficult to predict. Likewise, staging systems for lymphedema are numerous and inconsistent. Many traditional classifications rely on clinical findings and physical exam to diagnose lymphedema. The most commonly used staging system is The International Society of Lymphology staging system that divides lymphedema into four stages. Briefly, a patient is classified as having **Stage 0**, or *latent*, lymphedema when their lymphatic vasculature has been damaged but they have no clinically measurable swelling or edema. These patients may present with subjective symptoms of heaviness, discomfort, or early fatigue in the affected extremity with activity. **Stage I** lymphedema, or *spontaneously reversible lymphedema*, occurs when measureable swelling starts to occur and is manifested by pitting edema. Patients with stage I lymphedema primarily have accumulation of interstitial fluid in the limb, and as a result, may have an excellent response to conservative treatments such as compression or complete decongestive therapy. **Stage II** lymphedema, or *spontaneously irreversible lymphedema*, is described as non-pitting swelling of the limb. At this point, adipose deposition and fibrosis prevent conservative therapies from being highly effective (hence the lack of pitting) and, as a result, patients have relatively modest improvements secondary to compression. The most advanced stage of lymphedema, **Stage III** lymphedema, is also known as lymphostatic elephantiasis, which is characterized by significant non-pitting swelling, fibroadipose deposition, hyperkeratosis, and acanthosis. These patients, in general, do not respond to conservative measures and typically have progression of disease.

Campisi et al. have proposed another alternative, albeit less commonly used staging system for lymphedema; stage I is defined as initial or irregular edema, stage II is persistent lymphedema, stage III is persistent lymphedema with lymphangitis, stage IV is fibrolymphedema ("column" limb), and stage V is elephantiasis [22].

Other studies have classified lymphedema based on circumference measurements or changes in excess volume relative to the contralateral normal limb (or preoperative) measures [23]. A change in circumference of less than 2 cm is considered to be mild lymphedema, a change in 2–4 cm is considered to be moderate