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Chapter 5

Lymphedema

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Overview

Lymphedema is a chronic and progressive disease that is physically deforming, functionally debilitating, and psychologically distressing to those affected. Characterized by the abnormal accumulation of protein-rich interstitial fluid, lymphedema generally affects the ex-

tremities with swelling, inflammation, and irreversible tissue changes. Lymphedema has significant deleterious effects on patient physical function, psychosocial well-being, and health-related quality of life (HRQOL).

Currently, there is no cure for lymphedema. Management options include symptomatic management and procedures for mitigating disease progression. Worldwide, approximately 200 million people are affected by lymphedema, and of those, about 5 million are Americans. The incidence in the United States ranges from around 50,000 to 200,000 individuals each year. The vast majority of lymphedema cases can be classified as secondary lymphedema and are a result of cancer treatment.

As survival from breast cancer improves, yearly burden and disability from Breast Cancer-Related Lymphedema (BCRL) have increased. It is predicted that incidence of lymphedema will only increase moving forward, as radiation therapy and obesity continue to increase, and patients with breast cancer are now living longer due to effective chemotherapeutic regimens and early detection of disease.

The Lymphatic System

The lymphatic system functions to clear the interstitial space of proteins and lipids, transporting them to the vasculature based on a differential pressure gradient. The lymphatics include both superficial and deep systems, both which contain semilunar valves, as well as intracellular gaps that allow for movement of the proteins and fats. Lymphatic cell architecture is characterized by endothelial cells that are not continuously adherent, and the presence of microfilaments to effectively tether lymphatic capillary endothelial cells to scaffolding in the interstitium. In the setting of increased tissue turgor, like in edematous states, microfilaments become tense, pulling endothelial cells apart, thus widening intracellular openings and permitting leakage of fluid back into the interstitium.

Physiologic lymphatic flow occurs due to three main reasons: 1) a pressure gradient that promotes lymphatic fluid movement to areas of lower pressure that is maintained, in part, by opening and closing of valves, 2) contraction of endothelial smooth muscle contraction, and 3) sub-adjacent skeletal muscle contraction. All three components compose the lymphangion, the basic functional unit of the lymphatic system.

As lymphatic fluid collects in the interstitium, it creates a pressure gradient that forces lymphatic fluid into lymphatic capillaries and pre-collectors in the skin and subcutaneous tissue. The pre-collectors then drain deeper into larger collecting vessels in the deeper subcutaneous tissue. Once in these larger collecting vessels, or lymphangions, lymph is propelled forward by the pressure gradient, endothelial smooth muscle contraction, and sub-adjacent skeletal muscle contraction all with the help of the semilunar valves. Eventually, lymph is re-

turned to the circulatory system at the level of the subclavian vein.

Pathophysiology of Lymphedema

The underlying pathophysiologic mechanisms of lymphedema continue to be a topic for research; however, there are two basic conditions that produce lymphedema: 1) lymphatic drainage dysfunction due to a malformed or disrupted lymphatic system which leads to insufficient absorption of ultrafiltrate to be transported back to the circulatory system, and 2) the abnormal accumulation of protein-rich interstitial fluid and subsequently increased tissue oncotic pressure which leads to swelling, inflammation, and irreversible tissue changes.

Lymphatic dysfunction often begins with lymphatic vessel ectasia and valvular dysfunction. Cyclical reflux of lymphatic fluid into the interstitial space initiates a chronic inflammatory process that results in extracellular matrix remodeling and fibrosis, adipose differentiation, and progressive fibrosis and sclerosis that all leads to eventual obliteration of the lymphatic vessel lumen. As the cyclical impairment continues, the channels become more diseased, with an ever increasing amount of fibrosed and sclerosed lumens. In turn, this leads to the accumulation of fluid and macromolecules in the interstitum, causing an increase in oncotic pressure. Other cellular processes also take place concomitantly, which include collection of immune cells, cytokines, and microorganisms, all of which lead to chronic inflammation, infection, progression of fibrosis and fatty hypertrophy of the extremity.

Disease progression starts proximally and progresses distally. In the early stages of lymphedema, pitting edema is present due to the aforementioned high tissue oncotic pressure. However, as the disease progresses, non-pitting edema becomes more present.

Symptoms and Functional Impairment of Lymphedema

Patients frequently experience many subjective symptoms with many objective findings. Common complains include a heaviness or stiffness in the affected area, swelling, pain, neuropathic pain, recurrent cellulitis. Functionally, patients may experience difficulties with ADLs and may be unable to find conventional clothing that fits due to profound lymphedema. It is estimated that BCRL cost patients nearly 15,000 USD annually [1] with an even greater cost burden on the healthcare system at large, estimated to cost the US healthcare system nearly 1 billion dollars annually [2].

Risk factors for lymphedema include a BMI greater than 25 kg/m^2, axillary or pelvic lymph node dissection, radiation exposure, and genetic predispositions. Of these risk factors, obesity is best recognized, with weight reduction identified as an evidence-based method to improve symptoms. Further, there is an increasing amount of evidence that suggests that resistance exercise among other forms of exercise may provide a clinical benefit for patients with

lymphedema [3,4].

Categories of Lymphedema

Lymphedema may be broadly categorized into primary and secondary causes.

Primary lymphedema refers to developmental disorders with congenital abnormalities in lymphatic structure or function [Brouillard]. Primary lymphedema may present at any age and is notoriously difficult to diagnose due to significant heterogeneity of symptoms, and a relatively low prevalence. Historically, infantile forms of primary lymphedema were referred to as Milroy's Disease; in adolescence, it was referred to as Meige's Disease or lymphedema praecox; and in adulthood, it was termed lymphedema tarda. However, with increasing access to genetic sequencing, new classification systems that utilize clinical and genetic findings are emerging [5]. Primary lymphedema may be further subclassified into hypoplastic or hyperplastic forms which may be localized or systemic. Further, a number of congenital syndromes may have lymphatic abnormalities, such as Turner Syndrome, Prader-Willi, and Noonan Syndrome.

Secondary lymphedema refers to the destruction or obstruction of lymphatic ducts from a non-congenital cause. Iatrogenic causes include surgery to the inguinal or axillary regions or radiation therapy. However, trauma or infection are also common causes. In Low-Income Countries (LICs), *Wucheria bancrofti* is the most common cause of secondary lymphedema [6]. In Middle-Income Countries (MICs) and High-Income Countries (HICs), tissue trauma from surgery is the most common cause of secondary lymphedema [7]. The vast majority of cases in the United States are secondary lymphedema, which occur when lymphatic architecture is destroyed or obstructed due to surgery, radiation therapy, trauma, or infection. In particular, BCRL is the most common cause of secondary lymphedema in the United States.

Lymphedema and Cancer

Breast Cancer-Related Lymphedema (BCRL) has an overall risk of approximately 17%. Data have shown that the risk with sentinel lymph node biopsy alone is about 5 to 17% and increases substantially as more extensive surgical intervention is performed. With axillary lymph node dissection, the risk increases to 20 to 40%, and when combined with radiation therapy, is 49%. Classically, BCRL will present 8 to 12 months after surgery. Of those who will go on to develop BCRL will by 3 years. After this period, the annual risk of developing BCRL is 1 percent. However, the rate of disease progression has significant variation. The risk factors for developing lymphedema increase with Axillary Lymph Node Dissection (ALND), increasing number of lymph nodes removed, mastectomy, radiation therapy, and obesity [8].

The overall risk of developing lymphedema secondary to cancers other than breast can-

cer is 15.5% and varies significantly based on the type of malignancy. Melanoma has a 16% risk with increasing risk of developing lymphedema when involving the lower extremity. A 20% risk was found in gynecologic cancers, and 10% in genitourinary cancers. Head and neck cancers had a low risk of lymphedema, at 4%. Sarcomas were associated with the highest risk in the cohort at 30%. Notably, there was increased risk of developing lymphedema following pelvic dissection (22%) or undergoing radiation therapy (31%) [9].

Lymphedema Staging Systems

International Society of Lymphology (ISL) Staging

The most commonly used clinical staging system for lymphedema was created by the International Society of Lymphology (ISL). The ISL staging system is based primarily around clinical symptoms and limb appearance. The scale is from 0 to 3, with 0 representing a nearly normal limb, and 3 representing severe lymphedema [10].

ISL Stage 0 specifically refers to latent or subclinical lymphedema. On physical exam, there is no edema that can be appreciated, but lymph transport may be impaired. Stage 0 may last for months to years before edema becomes evident. ISL Stage 1 is characterized by the early accumulation of proteinaceous fluid, and edema that resolves with compression or limb elevation. On exam, there is clinically-evident distal swelling and pitting edema in this stage. ISL Stage 2 is characterized by fibrofatty deposition and fibrosis. In contrast with Stage 1, Stage 2 is characterized by non-pitting edema that will not resolve with limb elevation as the sole therapy. Further, Stemmer Sign may be present in ISL Stage 2. This finding refers to the inability to easily pinch finger or toe skin due to swelling. Lastly, ISL Stage 3 represents severe disease. It is characterized by lymphostatic elephantiasis with non-pitting edema. Other late findings may include acanthosis, fat deposits, a peau d'orange appearance, and hyperkeratosis [10].

Indocyanine Green (ICG) Staging

ICG staging is another method used to qualify lymphedema severity. This method requires the injection of indocyanine green dye to evaluate lymphatic channels using near infrared imaging. ICG staging is generally either with the Arm Dermal Backflow scale (ADB) [11] or the MD Anderson classification (MDA) [12]. While there remains a lack of consensus regarding the superior scale [Jørgensen], both are a helpful clinical tool to stratify patients by disease severity. Both scales are rated from 0 to 5 with 0 representing normal linear lymphatic flow, without reflux or backflow.

On the ADB scale, severity is characterized by the pattern of dermal backflow. Normal flow of lymph follows a unidirectional linear pattern. Abnormal patterns include splash with

minor dermal backflow, to stardust with moderate dermal backflow, and eventually diffuse when there is profound dermal backflow. Specifically, ADB stage 1 is comprised of a splash pattern around the axilla, stage 2 refers to the presence of a proximal stardust pattern between the olecranon and the axilla, stage 3 involves the extension of the stardust pattern distal to the olecranon, stage 4 shows stardust patterning that involves the hand, and stage 5 is characterized by a diffuse pattern in addition to a background stardust pattern that affects the entire limb [11].

Comparatively, the MD Anderson Classification more generally describes the pattern of lymphatic flow with less of an emphasis on distal spread. In MDA stage 1, there remain patent lymphatic channels with minimal dermal backflow, stage 2 involves a decrease in the number of patent lymphatics with segmental dermal backflow, stage 3 demonstrates a significant decline in patent lymphatic channels with minimal patent lymphatics and significant dermal reflux, stage 4 is defined by dermal backflow that involves the hand, and stage 5 is characterized by ICG that does not progress proximally to the site of injection [12].

Evaluation of the Lymphatic System

Lymphoscintigraphy

Lymphoscintigraphy is a nuclear medicine study that incorporates the use of technetium-99 to identify lymphatic drainage and lymph nodes. Most commonly, this modality is utilized to identify sentinel lymph nodes in breast cancer or melanoma.

In this method, a radioactive isotope (technectium-99m sulfur colloid) is injected at the distal extremity. A ‘gamma camera’ captures an image that reflects the amount of radiotracer absorbed. Areas with increased absorption appear dark, while areas without absorption are light. Lymph node basins have profoundly increased absorption and appear dark and lobular on images. Areas of obstruction or pooling are referred to as ‘dermal reflux’ or ‘dermal backflow,’ and have a diffuse pattern on imaging.

There are significant disadvantages to lymphoscintigraphy as the primary modality for evaluating lymphedema. Compared to other imaging modalities, the resolution is poor which provides limited anatomic information for preoperative planning. Further, the images are static and do not give a true functional assessment of the lymphatic channels and provide limited evaluation of the soft tissue.

ICG Lymphography

ICG lymphography is another means for lymphatic evaluation, what is referred to as lymphatic mapping. By employing indocyanine green, which is a water-soluble compound that binds to proteins and emits fluorescence in a near infrared spectrum (750-810 nm). By us-

ing a near infrared camera, one can visualize the fluorescence real-time of dynamic lymphatic flow. This method of lymphatic mapping is frequently used intraoperatively to determine if the patient is a candidate to perform lymphovenous bypass.

This method involves the injection of ICG dye into the digital webspaces and volar wrist and observing the functional lymphatics with the Hamatatsu near-infrared camera. Functional lymphatics are marked using a sterile marking pen, and candidate sites for anastomosis are identified.

While Magnetic Resonance Lymphangiography (MRL) is superior to ICG lymphography for mapping, particularly as it evaluates both the deep and superficial systems as well as venous outflow, not all patients are candidates can tolerate MRL nor is it available at every center, so ICG lymphography remains a widely used and excellent tool for mapping.

Magnetic Resonance Lymphangiography (MRL)

MRL is the best imaging modality for evaluating lymphatic function, as it provides both anatomic and dynamic information in a high-resolution format. Anatomically, lymphatic channels are able to be readily visualized, and it is possible to differentiate patent channels from diseased channels. Functionally, the gadolinium can be visualized as it flows through channels and venous outflow tracts. Further, lymphatics can be easily distinguished from veins which aids in preoperative planning. Technological advancements permit image enhancement with 3D reconstruction, limb volume calculations, and facilitate the calculation of lymphatic flow velocity within the channels.

In this study, soft tissue changes are projected on the images with fluid showing high-intensity epifascial enhancement. MRL has shown to be invaluable with determining the presence, location, and severity of lymphedema, as well as the number, size, and depth of the channels and their distance to the nearest venules for lymphovenous bypass.

Regarding disadvantages, as with MRI, MRL is a time-consuming study that is expensive. The gadolinium that is injected is non-specific for lymphatics like that of technecium-99 with lymphoscintigraphy. Access to MRL technology and cost are the largest barriers to widespread adoption and utilization of this technology. Despite these disadvantages, the resolution and results from MRL are nothing short of incredible.

Treatment

Medical Management

Primary therapy of lymphedema first begins with exhausting excellent medical management. This includes use of elastic bandages, compressive sleeves or gloves, and complete

decongestive therapy (CDT). CDT is usually separated into 2 phases. The first phase includes meeting with an occupational therapist 5 times per week for 6 consecutive weeks for manual lymphatic drainage, compression, exercises, and skin care. There is some evidence to show improved patient outcomes with CDT as opposed to standard compression therapy. Phase 2 of CDT involves life-long self-directed maintenance. Studies have been performed that show some evidence to suggest improved outcomes of CDT vs compression and elevation; however, these studies had relatively small sample sizes from single therapist/single institutions.

One randomized trial of 95 patients with upper extremity lymphedema after breast cancer treatment compared the clinical outcomes of standard compression and CDT as well as quality of life. They observed that there was a statistically significant difference in absolute volume loss between groups (140mL with standard compression, 250mL with CDT, $p = 0.03$), as well as a non-significant increase in the percent reduction of upper extremity volume at 6 weeks (23% with standard compression, 29% with CDT, $p = 0.34$). However, they did not identify a difference in quality of life between groups [13].

Other medical management modalities include use of diuretics, which can also help treat concomitant congestive heart failure exacerbations or venous stasis wounds. Coumarin stimulates extracellular albumin phagocytosis by macrophages. Steroids and NSAIDs have also show some symptomatic relief in patient with significant inflammation and pain. Stenting for venous insufficiency has been performed, but namely on significant lower extremity lymphedema.

Surgical Treatment

The surgical management of lymphedema can be divided into two major categories: ablative procedures and physiologic procedures. Ablative procedures aim to excise diseased tissue to improve patient functional status, decrease overall limb volume, and facilitate patient hygiene in severe disease. Comparatively, physiologic procedures aim to restore lymphatic flow to improve drainage and prevent disease progression. Ablative procedures include the Charles Procedure, staged subcutaneous debulking, and liposuction. Physiologic procedures include Lymphovenous Anastomoses (LVAs) and Vascularized Lymph Node Transfers (VLNTs).

Ablative Procedures

Ablative procedures are generally reserved for patients with severe progressive disease after significant fibro-fatty changes are present. We'll start by discussing the Charles Procedure. The name of this procedure is actually a longstanding misnomer, seeing as Sir Rich Henry Havelock Charles is known for describing the treatment for scrotal lymphedema in 1901, having treated 140 patients with this condition. He had never treated a patient with leg

edema, but in 1950, Sir Archibald McIndoe, an eminent British Plastic Surgeon wrote an article in which he mistakenly claimed that Sir Charles had treated a patient with lower extremity lymphedema with excision of subcutaneous tissue and skin grafts in 1912. Since then, the error has been propagated throughout the years. Either way, this morbid procedure involves resection of tissue down to fascia and reconstruction with skin grafts. As you can imagine, any remaining residual lymphatic function that patient had is destroyed.

Stage subcutaneous debulking is another ablative procedure that helps control the volume of the limb and is performed through a series over wedge excisions to decrease bulk.

Of the ablative procedures, liposuction is the most common to still be performed today, but with the understanding that the patients must commit themselves to life-long compression, as recurrence is nearly immediate when compression garments are removed. One study published in 2007 reported a 106% mean edema volume reduction at 10 years, but with the caveat of the patient always wearing compression stockings.

Physiologic Procedures

Lymphovenous Bypass

Of the physiologic procedures, lymphovenous bypass, also known as lymphovenous anastomoses (LVAs) were first described in 1977, but it became popularized in the 2000s with the introduction of ICG lymphangiography. What you achieve by performing an LVA is a redirection of subdermal lymphatic flow into the low pressure subdermal venous system. As you might imagine, these vessels are small ranging in size from 0.3 to 0.8 mm in diameter and constitute supermicrosurgery. Special instruments that are very delicate are required, as well as a microscope that has very high magnification potential.

LVAs can be used to treat early stage lymphedema where a number of functional lymphatic channels are present. Planning for LVAs can be achieved with identification of functional lymphatic channels in the extremity using ICG lymphography or the higher-powered MRL imaging study. If both modalities are available, mapping in clinic can help to determine if a patient is a candidate for LVAs and MRL can help to determine the ideal target sites.

When performing LVAs, intraoperative mapping is first performed. Once functional lymphatics have been mapped and marked, a small amount of lymphazurin blue is injected subcutaneously just distal to the site of the planned incision. Under the microscope, a small incision is then made with careful dissection under the microscope to identify lymphazurin blue-stained lymphatics and adjacent venules in the dermal and subdermal planes. Once these vessels are dissected freely, they are ligated an end-to-end or an end-to-side anastomosis is conducted using super microsurgical instruments and 11-0 nylon suture. Frequently, a 4-0

prolene stent is placed between the lymphatic channel and the venule during the anastomosis to ensure luminal patency and prevent back-walling. Prior to tying the last suture of the anastomosis, the prolene stent is removed. Anastomosis patency is then confirmed with a strip test as well as seeing lymphazurin blue dye traverse the anastomosis from the lymphatic channel into the low pressure venule.

Evidence to support the efficacy of performing LVAs has been published dating back to the early 2000s. In one study, 12 patients underwent CDT and 12 patients underwent LVAs for the treatment of upper limb lymphedema. In the LVA patient cohort, there was a 47% reduction in excess volume of the extremity when compared to 12% in the CDT cohort [14].

Another larger study in 2016 observed the clinical outcomes of 84 patients that underwent LVAs for lower limb lymphedema. They found that 48% of patients had improvement in extremity circumference and 62% of patients reported at a subjective improvement in symptoms. Notably, the authors identified a statistically-significant decrease in the frequency of cellulitis events from 0.89 to 0.13 cases per year ($p = 0.00084$) [15].

LVA is an effective tool in the treatment of both upper extremity and lower extremity lymphedema [16-18]. In 2013, one study compared both upper and lower extremity lymphedema clinical outcomes following LVA. Of the upper extremity cases, there was a 32% volume differential from pre-op at 12 months, a 96% subjective symptomatic improvement, and an overall 74% quantitative improvement up through 12 months. The lower extremity group had substantially fewer patients but did identify subjective symptom improvement in 57 percent of patients. They also stratified the data by MDA ICG staging and found that stages 1 and 2 had significantly better improvement than stages 3 and 4 [12].

LVAs are excellent physiologic treatment options for early stage and/or mild lymphedema in patients that still have functioning nodal basins. To proceed with LVAs, ICG lymphography or MRL must show intact lymphatic function and minimal fibrofatty changes. Based on the published data, LVAs are more effective in managing upper extremity lymphedema than lower extremity lymphedema. Before ICG and MRL, lymphovenous anastomoses were limited to random incisions and explorations to identify potential sites for anastomosis. Unsurprisingly, patient selection was challenging as well as identifying functional lymphatic channels. With the use of ICG and MRL, better planning and patient selection is possible which leads to a higher number of successful bypasses and better clinical outcomes.

Vascularized Lymph Node Transfer (VLNT)

The next of the physiologic procedures is vascularized lymph node transfer. This was first described in 1979 and, at a fundamental level, refers to orthotopically placed lymph nodes. This procedure is indicated in patients with total occlusion or a complete lack of uptake in

nodal basins on lymphoscintigraphy or the patient has ISL stage 2 or greater lymphedema and has exhausted at least 12 months of conservative therapy with compression and/or decongestive therapy.

There are two proposed theories of how vascularized lymph node transfers treat lymphedema, including functioning as a lymphatic pump and stimulating the induction of lymphangiogenesis.

The lymphatic pump theory hypothesizes that arterial pulsations in the flap generate hydrostatic force that continues through the tissue and forces fluid from the interstitium into the flap, essentially functioning as a physiologic LVA. The lymph that is drawn into the flap then drains toward areas of low pressure into the transferred nodes.

The other theory of induction of lymphangiogenesis is based on the idea lymph nodes produce VEGF, which induces lymphangiogenesis *in situ*. This lymphangiogenesis creates channels between the interstitium and the transferred nodes draw fluid from the extremity to be absorbed into the nodes and subsequently drained into low pressure venous system.

There are various donor sites for vascularized lymph node transfers, each with their own risk of donor site lymphedema. The groin is the most popular donor site, and travels along the SCIA axis. In this approach, central and medial nodes below the groin crease should be avoided. Thoracic nodes are anterior to the latissimus and lateral to the breast. They run along branches of the lateral thoracic vessels. The submental nodes are beneath the mandible and are fed by the submental artery which is a branch of the facial artery. Care must be taken to avoid damaging the marginal mandibular nerve. The supraclavicular donor site is located between the posterior triangle of the neck between the omohyoid muscle and the anterior scalene muscle. Notably, while this donor site has a low risk of donor site lymphedema, there is a risk of thoracic duct injury. Mesenteric nodes and omental transfers are intraperitoneal donor sites that can also be used as convenient vascularized transfers.

In 2012, a large review article of 1500 patients over a 20-year period with documented stage 1, 2, or 3 lymphedema who underwent VLNT. They found that 98% of patients who underwent vascularized lymph node transfer demonstrated at least some degree of improvement. When stratified by stage, of the patients who were either stage 1 or stage 2, 40% went on to complete normalization with no additional therapy needed. Of those that were stage 3, 95% were reported to have some degree of improvement; however, still most still required compression therapy [19].

There remains a significant amount of variation across VLNT protocols, including diagnosis, treatment, and the clinical outcomes measured. A systematic review that included 6 studies and a total of 156 patients noted that there was substantial variation in volume reduction,

ranging from 10 to 67 percent, after VLNT, but that there were improvements in patient quality of life following the procedure [20]. A more recent prospective study of 89 patients undergoing VLNT saw statistically significant improvement in qualitative lymphedema-specific disease burden assessments, average reduction in limb volume, improvements in bioimpedance score. Notably, there was a 93 percent reduction in cellulitis cases, and 34% of patients were able to discontinue compression entirely [21]. Other smaller studies have similarly reported reductions in extremity circumference as well as improvements in lymphedema-specific quality-of-life outcomes.

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