CHAPTER 26

LYMPHEDEMA

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I. DEFINITION

A. Chronic, progressive swelling in tissues due to insufficient drainage of interstitial fluid

II. EPIDEMIOLOGY

A. Over 300 million cases worldwide
B. By etiology: 90% secondary lymphedema (lymphatic filariasis is the most common cause worldwide), 10% primary lymphedema
C. Primary lymphedema is relatively rare – incidence 1.2:100,000 for persons age < 20 years (Schook et al, 2011)
D. By location: 90% lower extremity, 10% upper extremity, < 1% genitalia
E. Becoming a major public health issue in developed countries due to increased cancer survivorship

III. ETIOLOGY

A. Loss of lymphatic outflow can be due to primary lymphedema (inherent channel dysfunction) or secondary lymphedema (acquired insult causing physical interruption or dysfunction)
B. Primary lymphedema (can also be part of syndrome or vascular malformation)
   1. Lymphedema Congenita: resents age < 1-2 years, often bilateral limb involvement
      a. Milroy Disease: hereditary form presenting at birth with family history of lymphedema congenita
         i. Genetic mutation in vascular endothelial growth factor receptor-3 (VEGFR
      b. Lymphedema Praecox: often unilateral limb involvement
      c. Most common form of primary lymphedema
      d. Meige disease: adolescent onset, usually with family history
      e. Lymphedema Tarda: presents later in adult life, usually 3rd or 4th decade
C. Secondary lymphedema
   1. Infection
      a. #1 cause in developing countries
      b. Lymphatic Filariasis: blood borne nematode infection that directly obstructs lymphatic channels
i. Common organisms: *Wucheria bancrofti, Brugia malayi, Brugia timori*

2. Lymph node dissection (sentinel lymph node biopsy, nodal basin dissection)
   a. #1 cause in developed countries
   b. Cancer related lymphedema is one of the most distressing complications of sentinel lymph node biopsy or complete nodal basin dissection

3. Tumor excision
4. Trauma
5. Obesity
6. Vascular anomaly

IV. PATHOPHYSIOLOGY

A. Chronic disease of lymphatic system characterized by fluid accumulation and deposition of fibroadipose tissue

B. Evolution of chronic lymphedema generally involves
   1. Mechanical disruption of channel flow preventing outflow of interstitial fluid
   2. Accumulation of protein rich fluid leading to pitting edema and limb heaviness
   3. Chronic fluid stasis activates inflammatory pathways
   4. Long-standing inflammation promote deposition of fibroadipose tissue leading to non-pitting edema
   5. Skin trophic changes result from chronic dermal inflammation

V. DIFFERENTIAL DIAGNOSIS: LIMB ENLARGEMENT

A. Lipidema
B. Lipodystrophy
C. Hemihypertrophy
D. Edema
   1. Cardiac insufficiency
   2. Renal insufficiency
   3. Hepatic insufficiency
   4. Venous insufficiency
   5. Nutritional insufficiency
E. Deep vein thrombosis
F. Thyroid disease with pre-tibial myxedema

VI. CLINICAL PRESENTATION

A. Subjective
   1. Pain
   2. Swelling
   3. Heaviness of involved limb
   4. Inability to find properly fitting clothing
5. Decreased use of involved limb
6. Aesthetic concerns
B. Objective
   a. Doughy swelling of the extremity
   b. **Stemmer sign:** inability to grasp skin on dorsum of second digit of foot
   c. Edema – pitting vs. non-pitting
   d. Skin trophic changes: hyperkeratosis, acanthosis, skin ulcerations, plaques
   e. Recurrent soft tissue infections – cellulitis, erysipelas, lymphangitis
C. Source of multiple, hospital admissions; potentially prolonged duration
D. **Can be life threatening!!!**

VII. **CLASSIFICATION**

<table>
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<tr>
<th>Stage 0 (or Ia)</th>
<th>Latent or subclinical condition where swelling is not evident despite impaired lymph transport. It may exist months or years before overt edema occurs (Stages I–III)</th>
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<tr>
<td>Stage I</td>
<td>Early accumulation of fluid relatively high in protein content that improves with limb elevation. Pitting may occur.</td>
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<td>Stage II</td>
<td>Limb elevation alone rarely reduces tissue swelling and pitting is manifest.</td>
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<td>Stage II (late)</td>
<td>Loss of pitting edema due to fibrosis and deposition of lymphadiposal tissue.</td>
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<td>Stage III</td>
<td>Lymphostatic elephantiasis. Gross limb enlargement with absent pitting. Trophic skin changes develop, such as acanthosis, fat deposits, and warty overgrowths.</td>
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Table 1. International Society of Lymphology (ISL) Classification

A. Newer classifications consider limb circumference or estimated limb volume
B. Limb circumference should be measured at defined points (reduces variability between evaluators)
VIII. INVESTIGATIONS

A. Lymphatic Filariasis (if patient is from or recently travelled to endemic region)
B. Nocturnal blood smear: microscopic identification of microfilariae with Giemsa or hematoxylin & eosin (H&E) stain. Blood collection should be done at night to coincide with peaks levels of microfilariae.
C. Serum antifilarial IgG4 Assay: serologic study that detects elevated levels of antifilarial IgG4 in blood of patients with active filarial infection.
D. Standardized limb circumference measurements: measure circumference in office at set intervals (e.g. 4 cm) from tip of 2nd toe (lower extremity) or long finger (upper extremity). Allows for calculation of estimated limb volume.
E. Direct lymphangiography: visualize lymphatic channels using oil-based iodine contrast agent directly injected into lymphatics (rarely done today).
F. Lymphocintigram: nuclear medicine technique to visualize lymphatic channels using injection of filtered colloid of Technetium-99m (Tc$^{99m}$) subdermally into limb. Tc$^{99m}$ selectively taken up by lymphatics to allow visualization.
G. Laser angiography with indocyanine green (ICG): similar technique to lymphocintigram but uses ICG injection that can be performed in office or operating room settings. It is commonly used intraoperative to plan the location of the lymphaticovenular anastomosis (Figure 2).
H. MR-Lymphangiogram: high resolution imaging of lymphatic system. Injection of ferumoxytol can help distinguish lymphatics from veins
I. Lymphedema Index (L-Dex): office-based device measures differences in fluid accumulation between limbs.
J. Other possible investigations
   1. Ultrasound: if clinical concerns of DVT
   2. Fungal culture: if concerns of superimposed fungal infection
Figure 2. Imaging used to identify lymphatic channels. Magnetic resonance lymphangiogram showing (A) veins with a smoother appearance and (B) lymphatic channels with beadlike characteristics. Laser angiography with subdermal injection of indocyanine green (ICG) can also be used to observe lymphatic channels (C) that preferentially take up ICG in the interstitium. Arrows demonstrate shadow from an overlying vein that has not taken up ICG in this study. From Kung, T, et al. Current concepts in the surgical management of lymphedema. Plast Reconstr Surg 2017;139(4):1003e-1013e.

IX. MANAGEMENT

A. Non-operative Management
1. Medical management for lymphatic filariasis, if infection present
   a. Diethylcarbamazine (DEC) - #1 choice in North America
   b. Ivermectin – kills only microfilariae but not adult worm
   c. Albendazole
   d. Doxycycline
2. Limb elevation
3. Compression garment
4. Decongestive therapy
   a. Massage/manual drainage
   b. Intermittent pneumatic compression
5. Complete decongestive therapy: combination of lymphatic massage and compression
6. Weight loss
7. Skin and foot care
   a. Low pH, water-based lotion to prevent fungal infection
   b. Topical +/- systemic antifungal agents
8. Experimental
a. Low level laser therapy
b. VEGF-C therapy – not indicated in cancer pts as can promote tumor growth
c. Stem cell therapy with bone marrow or adipose-derived mesenchymal stem cells
d. *Note: Recent evidence suggests that even with aggressive nonsurgical therapy and a fully compliant patient, lymphedema disease progression can still occur resulting in morbidity.

B. Operative Management
1. Excisional Procedures: remove chronic lymphadiposal tissue
2. Liposuction – useful for reducing fat accumulation
3. Serial Excision – useful for skin/fat accumulation and removal of festoons
4. Charles Procedure – radical excision of lymphedematous tissue, limb resurfaced with split thickness skin graft
5. Physiological Procedures: restore lymphatic outflow
   a. Axillary vein decompression
   b. Lymphaticovenular anastomosis (LVA) – anastomose lymphatic channel to venule for improved outflow
   c. Vascularized lymph node transfer (VLNT) – selective transfer of lymph nodes on a vascular pedicle from non-lymphedematous region
      i. Potential lymph node donor sites: omentum, groin, axilla, supraclavicular, submental
      ii. Reverse lymphatic mapping an option to prevent unintentional harvest of sentinel lymph nodes, reducing the risk of lymphedema in donor site
d. Vascularized lymphatic channel transfer (VLCT) – transfer of vascularized lymph channels, replaces segmental gap in lymphatics

Figure 3. Schematic (left) and intraoperative view through a microscope showing anastomosis of a lymphatic channel to a small vein (venule).
X. COMPLICATIONS

A. Limited mobility and functional disability
B. Lymphorrhea
C. Recurrent infections – result in multiple hospital admissions, can be life threatening
D. Slow- or non-healing wounds
E. Chronic cutaneous changes
F. Psychosocial morbidity
G. Venous insufficiency
H. DVT
I. Malignancy
J. **Stewart-Treves Syndrome**: cutaneous angiosarcoma that develops in the setting of chronic lymphedema. Best treated by wide local excision or amputation.

REFERENCES