



A Review Article of Lymphedema in Gynecologic Malignancies: A Practical Approach

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Abstract

Lymphedema is an unusual and specific type of peripheral edema resulting from obstruction or disruption of lymphatic system. The present review was conducted on PubMed, UpToDate, and ClinicalKey databases before 2016. The keywords included lymphedema or leg edema AND advanced malignancy. The primary review revealed 104 full text publications, of which 24 relevant articles were selected and another 17 relevant articles from the reference list of the selected articles were added, as well. Practical points in diagnosis and treatment of lymphedema in gynecologic malignancies are presented in the below subtitles: -basic descriptions, classifications, and epidemiology; -clinical presentation and diagnostic tests; -differential diagnosis; -non-surgical management; -surgical management.

Keywords: Lymphedema, Neoplasm, Radiotherapy, Lymph Node Excision, Iran

1. Context

Edema is described as increased extracellular volume. Anasarca is generalized and severe fluid retention. Different causes of edema are renal disease, drug induced disorder, hepatic cirrhosis, pregnancy and premenstrual tension, pulmonary edema, venous thrombosis, malnutrition, hypoalbuminemia, allergic reactions, and idiopathic edema (1, 2).

An unusual and specific type of peripheral edema resulting from obstruction or disruption of lymphatic system is called lymphedema.

The most common cause of lymphedema is radical lymphadenectomy for malignancy due to removal or lymphatic injury resulting in lymph retention out of lymphatic system. Lymphedema occurs after surgery or radiation therapy (2-4). This review focuses on practical points in diagnosis and treatment of lymphedema in gynecologic malignancies.

2. Methods

A comprehensive research was conducted in PubMed, UpToDate, and ClinicalKey databases using keywords "lym-

phedema or leg edema" and "advanced malignancy" to find English and full text available articles before 2016.

2.1. Data Synthesis

In overview of articles, 24 out of 104 articles were selected including 13 out of 33 from UpToDate, 6 out of 32 from PubMed, and 5 out of 40 from ClinicalKey. The final review was conducted on the 24 selected articles and 17 extra articles found from the reference list of the selected articles (totally 41 articles).

2.2. Basic Descriptions, Classifications, and Epidemiology

2.2.1. Basic Descriptions

Lymphatic system harbors the following characteristics.

- 1- One-way passage to drain protein, antigens, and activated immune cells to lymph nodes and venous system.
- 2- Passive movement is conducted by muscle contractions and artery pulsations.
- 3- Internal valves in lymphatic system prevent backward movement.
- 4- Primary lymphatic vessels are thin, blind ending, low-pressure system specialized to permit passive entrance of cells and materials into this system, enlarging gradually diameter of the channels.

5- Lymphatic channels contain colorless fluid and white blood cells and activated immune cells.

6- Playing an immune role against infection by translation of antigens and activated immune cells to lymph nodes (3-6).

Abnormal uptake of lymph due to obstruction or disruption of lymphatic system is called lymphedema. Lymphedema is under-diagnosed, chronic, disabling, and uncompromising to manage disorder. Lymphedema is classified into primary (congenital) and secondary types. Secondary lymphedema is mostly due to endemic infections such as filariasis and podoconiosis (the second cause of chronic disability in the world). In non-endemic areas such as western world, secondary lymphedema is caused by malignancy or surgical and radiation modalities for cancer treatment (4, 6, 7).

2.3. Epidemiology

Prevalence of lymphedema depends on age, sex, and its cause. For instance in the endemic areas of Africa and Asia for filarial infection, the most common cause of lymphedema is filariasis. In the developed countries, most of lymphedema cases are due to cancer and its treatment (6-11).

2.4. Classification

Clinical classification of severity of lymphedema is described in several systems.

Clinical stage of lymphedema according to international society of lymphology (ISL) is based on softness of the extremity, response to elevation, and level of disability and edema (4, 6, 7, 12).

Stage 0-subclinical or latent phase:

Most patients are asymptomatic or report mild discomfort in the extremity. Normal appearing leg reveals abnormal lymph transit in imaging. This condition might preexist months or years before clinical lymphedema.

Stage 1-reversible mild edema:

Retention of protein rich fluid results in pitting edema without fibrosis.

Edema is resolved by leg elevation in a time interval about 24 hours. In this stage, maximum difference of limb size is less than 3 cm, called mild lymphedema according to the American Physical Therapy Association (APTA).

Stage 2-irreversible moderate edema:

Fibrosis exists resulting in non-pitting edema. Leg elevation is not effective to resolve edema.

In this stage, difference of limb size is 3-5 cm called moderate lymphedema according to APTA.

Stage 3-elephantiasis:

Edema is non-pitting with trophic changes in the skin including fat deposits, acanthosis, and warty overgrowth.

In this stage, difference of limb size is more than 5 cm called severe lymphedema according to APTA (4, 6, 7, 12).

Clinical grading according to the national cancer institute common terminology criteria for adverse events (CTCAE) is described based on physical examination and functional shortage as follows:

Grade 1-skin mild thickening and discoloration

Grade 2-prominent discoloration and leathery skin with papillary formation. Daily activities are limited.

Grade 3-daily self-care activities and routine life are disturbed (6, 12, 13).

2.5. Clinical Presentation and Diagnostic Tests

2.5.1. Clinical Presentation

In patients with leg edema, history might reveal risk factors of lymphedema. These factors include onset, involved areas, and other symptoms, promotion of clinical symptoms, history of cancer treatment (lymphadenectomy), and radiotherapy, traveling to lymphedema endemic areas, and family history regarding hereditary causes. Some drugs cause edema such as non-steroidal anti-inflammatory agents. Clinical symptoms of lymphedema gradually appear. Lymphedema following lymphadenectomy or radiation slowly progresses in one or both extremities distal to treated area. Sometimes before clinical lymphedema, patients suffer mild pain and heaviness in the affected extremity followed by discomfort and significant edema. Edematous stage of lymphedema might be regional, and merely involve the proximal or distal (digital) extremity. In more advanced patients, pitting edema converts to non-pitting edema. In the case of pitting edema, finger pressure can move interstitial water. In advanced stages of lymphedema, limited activity of the affected limb due to its weight exists and routine daily work is disturbed. Fibrosis results in thick hardened and pigmented (pink to red) skin. Orange like appearance of the skin due to fat deposit with pitting view and small warts happen. Vesicles with sometimes leaking fluid (clear lymph, white chyle or blood) are mostly seen in genitalia (5-7).

2.5.2. Physical Signs

Circumferential measurement of extremity: circumference measurement of the involved and non-involved limb is a simple and available method. Studies revealed correlation of volume with this measurement. The best approach might be the measurement in 4 points of lower extremity including: the first place at the metatarsal - phalangeal joint (if edema exists in this point), the second place is 2 cm above the medial malleolus, the third site is 10 cm above the superior border of the patella, and the

last (fourth) place is 10 cm below the inferior border of the patella. Difference of the size is a basic parameter in determination of lymph edema severity (classification of mild, moderate, and severe based on APTA). Difference of at least 2-3 cm in comparison with other extremity is clinically significant (stage 1 and mild class). This measurement besides pitting state, non-pitting state, and fibrosis is useful for diagnosis, staging, classification, and follow-up of the treatment.

2.5.3. Volume Measurement of Extremity

Volume measurement is estimated in three methods as follows:

1- Water displacement: placing the involved limb into a water tank and measuring the replacing water is the basis for this method. If the difference in the volume of water displacement between the affected and control limbs is equal or more than 200 mL, lymphedema is diagnosed. This method commonly is used in studies. Simple, small, and homemade forms of the instrument are available and appropriate for home and outpatient clinical measurements.

2- Optoelectronic volumetry: this method is based on infrared optoelectronic measurement. Infrared ray could scan and estimate volume of the extremity.

3- Volume measurement by truncated cone formula: in this method, the measurement is done in distance points of 4 cm and transformed into volume via truncated cone formula.

A clinical index of lymphedema is called Kaposi-stemmer sign that is non-folding in grasping of the skin in the dorsum base of the second toe of the foot. The other sign in advanced lymphedema is Milroy's disease: severe edema of lower extremity resulting in buffalo hump in dorsal side of foot-leg and upward turning of toenails. In the pitting state of lymphedema, pressure at least for 5 seconds on the limb can result in a small hole in finger touch place. This sign in advanced lymphedema disappears (5-7, 14, 15). Lymphedematous limb is predisposed to infection, cellulitis, dermatitis, eczema, ulceration, and fungal infection. An interesting point of chronic lymphedema is predisposition to malignant vascular or lymphatic tumors.

2.6. Differential Diagnosis

There are conditions associated with limb edema in differential diagnosis of lymphedema as follows:

1- Chronic venous insufficiency: This condition shares many similarities with lymphedema. Both present with pitting edema, without skin changes (early stage of lymphedema), absence of varicose veins, and reduction of

symptoms and edema by leg elevation. Venous insufficiency is bilateral rather than unilateral in lymphedema. Doppler sonography clarifies venous valvular insufficiency. Lymphoscintigraphy is necessary in individual cases to definite diagnose.

2- Deep vein thrombosis (DVT): Triad of acute edema, pain, and erythema in one extremity is typical of DVT. Doppler sonography helps in differential diagnosis in suspicious clinical states.

3- Post phlebitis (post-thrombotic) syndrome: Chronic pain, venous dilation, edema, color change, and ulcers all following an episode of DVT can occur. This condition might lead to lipodermatosclerosis and chronic edema of extremity. History of DVT is the main guide in diagnosis.

4- Lipedema: Lipedema is a rare x-linked dominant hereditary adipose disease, exclusively in women, and often in overweight women. Bilateral adipose deposit in the lower extremity leads to enlarged limbs. Bilateral pattern of lipedema and lack of affected below mallei and familial history differentiate this condition from lymphedema.

5- Armchair legs: Armchair legs are due to persistent sitting position with hanging legs in immobile people. Lymphatic drainage is reduced resulting in bilateral functional lymphedema.

6- Post-operative edema: Every operation with disruption of lymphatic drainage might result in post-operative edema. This kind of edema is transient. Venous thrombosis is suspected in post-operative severe edema.

7- Tumor: New onset edema after cancer surgery, months or years later, might be due to primary tumor recurrence or second primary tumor such as lymphangiosarcoma.

8- Myxedema: Myxedema is due to retention of glycosaminoglycans and water in the skin resulting in non-pitting edema.

9- Limb hypertrophy: Difference in the size of extremities is detected in some hereditary syndromes such as Klippel-Trenaunay syndrome and Proteus syndrome.

10- Medical causes: In every lower limb edematous patient, medical causes should be evaluated such as kidney disease, protein insufficiency, nephropathy, heart failure, pulmonary hypertension, and other medical problems.

11- Podoconiosis: It is a condition of prolonged retention of silica via barefoot walking leading to non-filarial elephantiasis (5, 7, 16-20).

At first to rule out renal disease, hypoalbuminemia, heart disease, coagulation defects, infection, liver failure, allergy, and making sure of other causes of limb edema are considered. Primary common tests include urinalysis, serum albumin, liver function tests, and other related laboratory tests (4, 5).

2.7. Diagnostic Tests and Imaging

2.7.1. Lymphoscintigraphy

Radionuclide lymphoscintigraphy is considered the standard and reliable diagnostic method to differentiate venous edema from lymphatic edema although it is not commonly used. In venous edema, clearance is rapid and in lymphedema, clearance is asymmetric, delayed or absent.

Clearance speed is the qualitative approach which might miss mild (grade 1) cases of lymphedema. In the quantitative approach, accumulation of radiotracer in lymph nodes is detected, with sensitivity of 100% shown in some studies. That is, the best method to rule out lymphedema as the cause of extremity edema might be negative quantitative lymphoscintigraphy. Although lymphoscintigraphy is the method of choice to diagnose lymphedema, in common practice it is not routine in the case of typical clinical feature (4-7).

2.7.2. Lymphography

Contrast lymphography shows anatomy of the lymphatic system. After injection of contrast media, plain radiography, CT, and MRI are used to image lymphatic system (6, 18).

Computed tomography (CT) and magnetic resonance imaging (MRI): Both CT and MRI are commonly available although they are not strong in differential diagnosis of lymphedema from other causes of extremity edema. The role of these imaging modalities is mostly played in detection of other causes of lymphedema (including obstruction, malignancy, and tumor recurrence) and severity of lymphedema. MRI transcends to CT due to more accuracy in identifying dilated lymph channels and ability to detect water and soft tissue pathologies. In MRI and CT, "honey comb" pattern of subcutaneous tissue is described for lymphedema, which is not appeared in other causes of edema (4-6).

2.7.3. Sonography

2.7.3.1. Venous Doppler Sonography

Sonography is able to detect lymph flow by Doppler waves. On the other hand, venous Doppler sonography is recommended in all new onset limb edema. Venous Doppler sonography might clarify deep vein thrombosis, which is considered in differential diagnosis of lymphedema and it is more probable in the case of lymphedema, as well. The diagnosis of other etiologies of limb edema such as venous insufficiency, lymphatic obstruction, and filariasis is made by this method (14, 15, 19-21).

2.7.4. Other Assays

Perometry: Infrared light beams are used to detect passage of electrical current through tissues in the diagnosis of lymphedema (4).

Biopsy: lymph nodes sampling should not be done in prolonged lymphedema due to possibly worsening the condition. In three situations, biopsy is necessary including probable malignancy in lymph nodes, skin malignancy, and warty lesions (6).

2.8. Non-Surgical Management

Lymphedema as a chronic lifelong disease is managed by symptom. Natural history of lymphedema is progression to later stages resulting in disability (12, 22).

Lymphedema as a morbid condition disturbs patients in the following ways:

- 1- Disorganized daily activity
- 2- Cosmetic view
- 3- Emotional concepts due to lifelong and chronic character of lymphedema

Management of lymphedema is the best in multimodality and multidisciplinary teams. The main goals of any management modality are as follows:

- 1- Reduction of edema
- 2- Prevention of progression
- 3- Prevention of infection
- 4- Improvement of cosmetics
- 5- Improvement of daily activities (4-6, 12, 22).

2.9. Limb Elevation

Elevation is a simple adjuvant modality by unknown mechanism that probably via reduction of hydrostatic pressure facilitates lymph drainage. Elevation is not a definite and effective measure for long time treatment. On the other hand, it is preferred for rest hours when the patient is not in upright position. In the case of limb elevation during day hours, routine activities and exercise as a more effective recommendation might be reduced (4, 5, 23, 24).

2.10. Exercise and Diet

Low calorie diet and weight loss improve lymphedema management especially in obese patients. Reduction of body fat content by exercise besides weight reduction help more in lymphedema management due to swelling tendency in fat tissues (4, 6). Exercise alone is regarded as an effective treatment. There is no contraindication or limitation in exercise except in case of co-existent cardiopulmonary disease. Probable mechanisms of exercise in lymphedema improvement are as follows:

- 1- Reducing intra thoracic pressure during inspiration and more respiratory effort and facilitating lymph flow and lymph clearance

2- Weight reduction improves compression pump efficacy and lowers body fat content that all result in lymphedema improvement.

Compression garment should be used during exercise (4-6, 12, 25-27).

3. Compression

There is a spectrum of compressive methods. Multiple layer stretch compression bandages are commonly used in the first step, followed by elastic stockings for maintenance. Elastic stocking is more expensive that needs to replace every 4 - 6 months. Daytime use of elastic stocking might be followed by nighttime bandage. Another option is intermittent pneumatic compression that might be used 4-8 hours a day. Nursing home care and cost of device are added together resulting in the higher cost of the method. Lymph edema therapist should supervise sequence of compressive methods and proper balance of pressure in distal and proximal parts of the affected limb (5, 12, 28-33).

3.1. Manual Lymph Drainage and Physiotherapy

Manual massage by trained person might mobilize lymph in distal to proximal direction and facilitate filling and contraction of lymph channels. This treatment phase (the first phase) is accompanied by compression garment (daytime) and bandage (night time) to improve symptoms in the maintenance phase (the second phase) (5, 12).

3.2. Skin care (Avoid of Infection/Injury)

Lymphedema patients are at risk of infection and recurrent infection particularly cellulitis and lymphangitis. Bacterial colonization in the edematous limb's skin leads to increased infection risk. Sometimes prophylactic antibiotics and keratolytic ointments such as salicylic acid can be prescribed. Lymphedema is the predisposing factor to cellulitis. Cellulitis itself results in the progression of lymphedema (5, 12, 14).

3.3. Drug Therapy

Drug therapy is not effective in lymphedema management. Effect of coumarin has been mentioned controversial in different studies. Diuretics are not helpful in long-term use (5, 12).

3.4. Surgical Management

Selection of operative methods in a subgroup of patients is characterized as follows:

- 1- Non-responsive to conservative therapies
- 2- Local lesions or malformations
- 3- Recurrence of limb cellulitis
- 4- Lymph leakage into body compartments
- 5- Functional disability
- 6- Severe cosmetic disorder
- 7- Severe pain (non-responsive to medical therapy)
- 8- Disturbed quality of life due to psychological points

Before surgical intervention, confirmation of the etiology is mandatory. Chronic conditions such as heart failure, venous disorders, and protein deficit should be ruled out. Preoperative evaluation of degree (severity) and stage of lymphedema besides Doppler sonography are helpful. Venous Doppler sonography can detect venous thrombosis (5, 6, 34).

There are two main types of surgery including reduction and reconstruction procedures.

Reduction (debulking) surgery: These procedures such as liposuction (in early stages), Charles and Homan's (in severe lymphedema) remove excessive tissue. In early stages (before fibrosis), liposuction removes adipose tissue as the solid part of edema. In the fibrotic stages, Charles and Homan's reductions (in severe lymphedema) remove excessive tissue. In early stages (before fibrosis), liposuction removes adipose tissue as the solid part of edema. In the fibrotic stages, surgical Charles and Homan's reductions are suggested, including removal of large sections of fibro sclerotic tissue, adipose tissue, and skin.

Reconstructive (physiological) surgery: These procedures induce lymph-vein shunt or autologous vessel transplantation. The aim of reconstruction procedures is creation of new conduits to facilitate lymph flow. Lymph is guided to lymphatic or venous circulation. Lymphatic-lymphatic bypass, lympho-venous, lymphaticovenular procedures, and vascularized lymph node auto transplantation are examples of reconstruction operations (5, 6, 11, 34-37).

3.5. Prevention of Progression and Recurrence of Lymphedema (Patient Education)

There are many advices and methods to prevent clinical progression of lymphedema and its recurrence after treatment, as follows:

- 1- Patient should be aware of size change by limb circumference measurement in regular intervals. Patient should report any color and sensation change.
- 2- Prolonged standing, sitting or crossing the legs in working time or daily activities should be avoided.

Increased hydrostatic pressure interferes with lymph drainage.

3- Weight gain and obesity should be avoided.

4- Tight shoes and stockings should be avoided. Closed shoes instead of sandals protect feet.

5- Lymphedema predisposes patients to skin infections. Patients should be aware of self-protection including:

- Using moisturizing creams to prevent dry skin

- Avoid of skin breaks, cuts, and burns during routine daily activities. Shaving just by electric machines and use of sunscreen creams in sun exposure are recommended

- Paying attention to small breaks in the skin by topical antibiotic solutions and informing medical care unit

6- Sauna, hot tubs, and steam baths might result in the progression of lymphedema and they are better to be avoided.

7- Intravenous lines, venography, acupuncture and any injection in the affected limb should be avoided.

8- In the case of long air travel (more than 4.5 hours), compression garment, exercise, and massage prevent worsening of lymphedema (3, 4, 5, 12).

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