Pathophysiology of Edema

As described in chapter 1, there is always fluid within the interstitial space, the space between tissue cells. The amount of fluid depends on 2 factors: the amount introduced into the interstitial space, and the amount removed from it. Fluid enters the space from arterioles and venules; some returns to the venules, and the remainder is taken up by the lymphatics. In the normal physiologic state, entrance and exit are approximately equal, so that tissues retain their usual morphologic appearance and function (1,2).

Edema (swelling) develops when the volume of interstitial fluid increases, either from increased inflow or decreased outflow, or both (3).

Lymphatic Causes of Edema

Primary Lymphedema

Primary lymphedema results when the lymphatics do not or cannot propel the lymph in adequate amounts, and the fluid sequesters within the interstitial or lymphatic spaces. It develops from an alteration or deficiency within the lymphatic collecting or transport systems. Primary lymphedema often occurs in the lower extremities, and affects women more than men (4–6). Many lymphatic malformations are described in chapter 4; a few are briefly reviewed below:

- Milroy disease (hereditary lymphedema type I) is a familial congenital disease and appears at or soon after birth (7,8) (Figure 2-1).
- Meige disease (hereditary lymphedema type II) develops later, e.g. at puberty, often after a minor injury, and causes foot and ankle swelling. Girls are affected more often than boys (9,10).
- Lymphedema praecox, another term for the 2 syndromes described above, has an early onset up to age 35 years (10,11).
- Lymphedema tardum is similar to praecox, but has an onset after age 35 years (10,11).
- Lymphangiomas are congenital, benign, often cystic malformations of the lymphatics and may be associated with other vascular malformations (4,12).

Secondary Lymphedema

Secondary lymphedema is swelling that follows some other incident or event, such as infection or injury (12,13).

Infection

- Filariasis, the most common cause of secondary lymphedema in the world, affects patients who have lived in or traveled in areas endemic with the disease; the worm’s larvae migrate to the lymphatics, causing obstruction and damage (13,14) (Figure 2-2).
- Recurrent cellulitis, e.g. erysipelas, is acute and unilateral in the affected limb, often entering skin from a fungal skin infection (15,16).
- Lymphogranuloma venereum, a sexually transmitted disease, caused by chlamydia, often with enlarged inguinal lymph nodes.
- Scrofula, old term for tuberculous lymph nodes of the neck.
2. Differential Diagnosis of Lymphedema

**FIGURE 2-1.** (A) An example of Milroy disease, the right leg of this 2-year-old baby has been swollen since birth. (B) This woman had mild swelling of the legs noted at age 10 years. The swelling was progressive until her lymphedema was finally diagnosed and treated at age 36. Dermal backflow is more prominent in the right leg, but is present in both (see Figure 2.8). The feet show the typical changes of lymphedema—swelling of the toes and feet, with deep flexion creases. (Photos courtesy Emily Iker.)

**FIGURE 2-2.** Filariasis, as seen in this man’s legs, is endemic in Haiti and many other countries. (Photo courtesy CL Morgan.)

**Cancer Treatment and Other Types of Trauma**

- Any treatments, whether surgical or irradiation, can interrupt the normal flow of lymph, that results in the accumulation of lymph, i.e., lymphedema.
- Lymphadenectomy, or surgical excision of the inguinal, iliac, or auxiliary lymph nodes, the most common non-infectious cause worldwide, especially following breast cancer treatment, of chronic unilateral swelling (17).
- Nonsurgical trauma, e.g. radiation therapy to lymph node groups, may cause chronic unilateral swelling.
- Surgery of the prostate, uterus, or cervix may cause bilateral swelling.
- Recurrent and metastatic malignancy.
- Reconstructive arterial surgery, e.g. saphenous vein harvest for coronary artery bypass.

**Inflammation**

- Any of a group of non-infectious diseases causing edema, pain, or erythema.
- Systemic lupus erythematosus
- Rheumatoid arthritis, which may have combined muscle pump failure due to fixation and stiffening of the joints.
- Psoriatic arthritis
- Chronic dermatitis
- Retroperitoneal fibrosis
- Panniculitis
- Systemic diseases, e.g. Grave’s disease, myxedema
- Podoconiosis, elephantiasis caused by silica crystal absorption into the foot with lymphatic damage (Figure 2-3)
FIGURE 2-3. (A) Although the swelling in this patient’s hands is mild, it nevertheless represents myxedema. (B) Her feet begin to show typical changes of lymphedema, with deepening of the flexion creases and swelling of the toes. (Photos courtesy CL Morgan.)

FIGURE 2-4. (A) This 46-year-old woman had surgery and radiation for uterine cancer. Lymphedema in her left leg is confirmed by the lymphoscintigram, which shows marked dermal backflow. (B) In another patient, the right greater saphenous vein was harvested for a coronary artery bypass; lymphatic damage caused later lymphedema. Here the left leg shows the changes of chronic venous insufficiency with hyperpigmentation, slight edema, and hyperkeratosis. (Photos courtesy Emily Iker.)
• Factitious, self-inflicted trauma, e.g. constricting a limb with a rubber band to induce swelling (18).
• External injury to the body, e.g. an auto accident (Figure 2-4)

Other Causes of Edema

Chronic Venous Insufficiency

As explained in chapter 1, properly functioning venous and lymphatic systems help maintain a balance between interstitial and lymphatic fluid. A change in one system affects the other (12,19–22).

With venous disease in the legs, there is usually chronic damage to the veins and their valves. The result of valve failure is continuing reflux (backward flow of blood), increasing pressure on normal veins and damage to the surrounding tissues and lymphatic structures—chronic venous insufficiency (4,20,22). (See chapter 7 for more information.)

Hypoalbuminemia

Reduced blood concentration of proteins, especially albumin, reduces osmotic (oncotic) pressure and the reabsorption of interstitial fluid into the venous capillaries. Swelling is usually chronic, often bilateral (12,17).

• Excessive loss of albumin, glomerulonephritis, nephrotic syndrome, extensive burns.
• Malabsorption syndromes, inadequate absorption of protein, steatorrhea syndromes, protein calorie malnutrition, starvation, e.g. Kwashiorkor.
• Inadequate synthesis of albumin, cirrhosis, liver failure.

Drug-induced Edema

Several medications can cause or contribute to edema, complicating diagnosis (12,17,18). They include:

• hormones, estrogens, testosterone, corticosteroids, progesterone, and androgens
• antihypertensives, guanethidine, β-adrenergic blockers, calcium channel blockers, clonidine, hydralazine, methyldopa, minoxidil, reserpine, and labetalol
• nonsteroidal anti-inflammatory drugs, (NSAIDs)
• antidepressants, e.g. trazodone
• hypoglycemics, e.g. pioglitazone and rosiglitazone
• cytokines: GM-CSF, G-CSF, IL-4, IL-2, Interferon-a
• chemotherapeutics, e.g. cyclophosphamide, cyclosporine, mitramycin, and cytokine arabinoside
• antiviral, e.g. acyclovir

Differential Diagnosis of Edema

The differential diagnosis of edema requires a thorough historical review, physical examination, evaluation of treatment response, and occasionally special laboratory investigations. The examination report should include a diagram of the limb or affected area and standard measurements, e.g. limb circumference. Staging using these criteria is discussed in chapter 3.

Duration and Distribution

If the duration of the swelling is short, perhaps hours or days, and it is unilateral and painful, an acute process is suggested: deep vein thrombosis, cellulitis, abscess, ruptured Baker cyst, trauma, muscle compartment syndrome, ruptured gastrocnemius muscle, or reflex sympathetic dystrophy (12,18).

If the onset is gradual and progressive, over a period of weeks or months, and it is unilateral and painless, a chronic process is suggested: chronic venous insufficiency, post-thrombotic syndrome, lymphedema, (primary or secondary type), external venous compression, arteriovenous fistula, Klippel-Trenaunay syndrome, and soft-tissue or vascular tumors (12,17).

If the onset is gradual and progressive and swelling is bilateral, possible causes include: congestive heart failure, glomerulonephritis, the nephrotic syndrome, hypoproteinemia, drug reactions, cirrhosis of the liver, pretibial myxedema, constrictive pericarditis, lower limb dependency syndrome, lipedema, bilateral chronic venous insufficiency, bilateral lymphedema, or a malignancy in the pelvis, abdomen, or the retroperitoneal space. Advanced prostate carcinoma can cause lymphatic obstruction and bilateral leg edema, as can ovarian carcinoma or other pelvic tumors (12,17,18).
Dermatologic Changes

Skin changes are common with many types of swelling (22,23). They include:

- venous hypertensive pigmentation due to hemosiderin deposition, eczema, atrophie blanche (white atrophy), lipodermatosclerosis, or ulceration (Figure 2-5)
- taut skin, the inability to pinch a fold of skin at the base of the second toe (Kaposi-Stemmer sign), or prominent skin creases in the feet
- hyperkeratosis or papillomatosis (a warty skin texture)
- cellulitis, especially when recurrent (Figure 2-6)

Diagnostic Laboratory Tests for Systemic Disease

- The cardiopulmonary system is evaluated with chest x-rays, electrocardiograms, and echocardiograms.
- Kidney and liver functions are assessed with standard blood testing, which should include the blood albumin concentration.
- Thyroid function is also tested with standard blood tests, e.g. T3, T4.

Testing for Venous Disease

- different non-invasive and invasive tests are used to evaluate the veins for blood clots and function
- D-dimer, blood testing for deep vein thrombosis
- ultrasonographic imaging, to assess the deep, perforator, and superficial venous systems of the legs for evidence of old deep vein thrombosis and for the degree of valvular incompetence and reflux (Figure 2-7)
- contrast venography, to check for the presence of pelvic or abdominal thrombus
- computed tomography (CT) to check for pelvic pathology, especially malignancies and retroperitoneal fibrosis
- assessment of the ankle-brachial pressure index (ABPI), which is useful in determining arterial insufficiency in the legs of older patients and diabetics; compression therapy may worsen peripheral arterial disease.

Testing for Lymphedema

Lymphangioscintigraphy is the best laboratory test for lymphedema. A radioisotope-labeled colloid is injected into the web space between the...
2. Differential Diagnosis of Lymphedema

**Figure 2-6.** This man suffered a right deep vein thrombosis 12 years before this photograph was taken. There is marked hyperpigmentation, eczematoid changes in the calf with white atrophy, and small ulcerations on the ankle. Little edema had developed. (Photo courtesy LL Tretbar.)

**Figure 2-7.** Duplex ultrasonography is noninvasive, safe, and reproducible; it is relatively inexpensive and exhibits a high degree of accuracy. (Photo courtesy LL Tretbar.)
first and second toes. Using a gamma camera, the colloid movement is measured as it travels toward the proximal lymph nodes (24–26) (Figure 2-8). Slow progress of the radioisotope, compared with the normal lower limb, suggests hypoplasia of the peripheral lymphatics, as in primary lymphedema. If the radioisotope escapes from the main lymph channels, especially into the skin, it is called dermal backflow. This finding suggests lymph reflux, often seen in secondary lymphedema with proximal lymph obstruction.

Lymphangiography is another option that is rarely used today. This test uses radio-opaque lipiodol injected directly into a peripheral lymph vessel; x-rays monitor its proximal progress. This test is used for planning surgical lymphovenous anastomoses and for research purposes (27,28).

Both computed tomography (CT) and magnetic resonance imaging (MRI) show a typical subcutaneous honeycomb pattern in lymphedema, but not in other edemas. Of the 2, MRI is the superior test, as it also detects excess fluid (Figure 2-9).

**Lipedema**

In determining lipedema, an MRI will show that the soft-tissue swelling consists only of fat. The peripheral lymphatics are normal; there is no honeycomb appearance, and subcutaneous edema is absent. However, late lymphatic changes may develop (27) (Figure 2-10).
FIGURE 2-10. (A) Lipedema is characterized by a swelling of the hips and legs, but usually with none in the feet. In this case, a lymphoscintigram was normal. The fatty changes developed over a number of years; the feet are beginning to show lymphedematous changes, e.g. deep flexion creases and swelling of the dorsum and toes. (Photo courtesy Emily Iker.) (B) This woman’s legs were normal until she had a car accident that traumatized them. The lipedema developed only in her legs; the torso and feet were spared. An ulcer that formed after a recent infection is seen on her left leg. (Photo courtesy CL Morgan.) (C) Diagnosis is difficult in this case: the feet are reasonably normal, but there are changes in the lower calves that suggest venous insufficiency. Extreme obesity is apparent as well, with a panniculus hanging below the patient’s clothing. This patient deserves a complete evaluation that should include lymphangioscintigraphy. (Photo courtesy LL Tretbar.)
Summary

Information obtained from clinical and laboratory testing can help determine the probable cause of edema. Clinical evaluation with a thorough medical history is usually sufficient, as laboratory testing (e.g. lymphangioscintigraphy, MRI) is not always available. As accurate diagnosis is important, so that an appropriate treatment program can be planned and expectations of the treatment can be reviewed with the patient.

References

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