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Lymphedema for Health Care Professionals

What are the unique features of the edema in lymphedema?

Most other forms of edema other than lymphedema represent the accumulation of water in the tissues. In general, there is a driving force, that is to say, a pressure gradient that will not allow the fluids to return from the tissues to the circulatory lumen. This would be true in heart failure, liver disease, and venous disease, among many other conditions. In lymphedema, it is the unique proteinaceous content of the interstitial fluid that is the driving force for edema accumulation. Protein has obligatory lymph transport from the interstitium and, when lymph transport is impaired, the increased oncotic pressure predicated edema formation. This accumulation of protein-enriched interstitial fluid seems to orchestrate many of the unique clinical features of lymphedema: in addition to pitting edema, we see a change in the architecture of the skin itself. There is an increase in cell mass and an increased deposition of fat in adipocytes that are present in the dermis and the subdermis. There is an increased deposition of collagen, which yields a nonelastic component to the skin and changes the function of the skin. There is an impairment in immune traffic, which leads to an increased propensity to inflammation and infection. In addition, inflammation is a major driving force to the propagation and worsening of disease with time.

How can clinicians reliably differentiate among the types of edema?

Fortunately, a well-trained clinician can usually recognize lymphedema at the bedside: inelasticity of the skin (*ie*, the increased content of collagen) becomes very evident as a thickening of the skin markings. In the feet, for example, indentation of the skin at the base of the toes is typical. The digits square off. In fact, involvement of the foot is typical in lymphedema, but distinctly uncommon in other forms, where the edema typically does not extend beyond the ankle. Stemmer's sign (inability to tent the skin at the base of the digits) is considered pathognomic of lymphedema.

What are the medical complications of lymphedema?

At a subjective level, lymphedema patients struggle with issues related both to body image and to function. Subjectively, they also frequently

experience pain and discomfort. Objectively, lymphedema is important because of the ever-present threat of infection. Soft tissue infections are common. They are often recurrent and typically don't have an identifiable antecedent. Once an organism penetrates the cutis, it can create protracted infection that is difficult to eradicate. In lymphedema, it may take weeks or months to cure soft tissue infection.

In addition to infection, lymphedema patients experience adipose deposition, fibrosis, loss of joint function and even deleterious effects upon the blood vasculature.

What investigations are useful for the diagnosis and monitoring of patients with lymphedema?

At the simplest level, it is prudent to screen the patient for concomitant venous obstruction that may otherwise be occult. The one *caveat* is that all of the diagnostic measures that are typically employed to screen for acute DVT are not very effective for the diagnosis of chronic obstructive disease (either unresolved thrombosis or fibrosis in the vein). So we typically don't recommend Doppler ultrasonography as a screening modality, but, rather, some direct imaging of the venous anatomy. At Stanford, we rely upon contrast CT imaging of venous anatomy.

Radionuclide lymphoscintigraphy can be used for functional imaging of the lymphatics. Unfortunately, this nuclear imaging modality is not available in all centers.

Among the more 'cutting edge' technologies, bioimpedance measurements can be used to serially monitor patients for subtle manifestations of extracellular fluid accumulation that can presage the development of lymphedema in high-risk patient subgroups.

What are the mainstays of therapy for patients with lymphedema?

Treatment measures for lymphedema are effective but, of course, not curative. We use physical techniques to stimulate lymphatic contractility and to improve lymphatic drainage. These methods are called, collectively,

decongestive physiotherapy, or complex decongestive physiotherapy (CDPT). The components of CDPT include manual lymphatic massage or drainage (MLD), multilayer bandaging, exercise, and skin care.

MLD is a very light massage technique that stimulates lymphatic contractility by improving the entry of protein and fluid into the lymphatic capillaries in the skin. The therapist will use a very light stretching technique on the skin to open the capillaries but not sufficient to increase skin blood flow.

The multilayer bandaging, applied by a trained physiotherapist, creates a boundary compartment in which the lymph system is maximally stimulated during muscular use.

Exercise is synergistic with all of the other modalities. Skin care is very important to limit the adverse effects of the lymphedema that will in turn encourage the ingress of bacteria that may lead to soft tissue infection.

In the chronic setting, once the limb is at its nadir volume, the patient's limb is measured for a compression garment, typically beginning with a class 2 (30 to 40 mm HG). The garment creates a gradient of pressure from distal-to-proximal. The intent of the garment is not to render the limb smaller, but to prevent it's growing in size with time.

What about diuretic therapy?

A common health care provider error is to assume that this form of edema mandates diuretic therapy. However, in pure obstructive lymphedema, diuretics may transiently decompress the limb but, ultimately, will not ameliorate the condition and may have undesirable after-effects. In lymphedema, the driving force for edema accumulation is retained interstitial protein and other macromolecules. No matter how much one contracts the extracellular space through Na^+ and water clearance, the protein will remain and re-stimulate edema formation. In addition, concentrating the interstitial macromolecular concentration may be undesirable.

On the other hand, if the patient has concomitant venous edema, the venous component will respond favorably to a diuretic approach.

In lymphedema diagnosis and management, what are the options for patient referral?

First of all, it is important to identify local treatment resources. Identify those individuals in the community who have been well trained in lymphedema therapeutic techniques and have sufficient expertise and experience to treat the patients well. Once you establish the diagnosis, you need to guide the therapist in applying the components of CDPT to the patient's care, to initiate antibiotic therapy when it's necessary for soft tissue infection and to ensure that there is appropriate follow-up and that the initial responses to treatment are upheld.

For difficult diagnostic and management issues, the resources of the Stanford Center for Lymphatic and Venous Disorders are available where geographically appropriate.

Are there risks or benefits to exercise therapy in patients with lymphedema?

There are major benefits provided that the patient completes the initial acute treatment phase with CDPT. Once limb volume is minimized, daily treatment with the compression garment is necessary and, at minimum, use of the garment during exercise is necessary. It has been shown that with appropriate compression, exercise actually has a salutary effect. On the other hand, in the absence of compression, exercise might sufficiently stimulate blood flow to the limbs to trigger lymphedema in someone at risk or to exacerbate pre-existing edema. Therefore, heavier exertion, typically the use of weights, which is not contra-indicated in lymphedema patients, must be done with an appropriately sized garment. And the patient's exercise has to be staged to an appropriate maximal level.

Are there new therapies on the horizon?

Yes. Here at Stanford, we devote a significant research effort to finding better therapeutics for lymphedema, and there is interest at other centers as well. There have been major recent advances in comprehension of the factors in human biology that promote lymphatic development and

lymphatic repair. Growth factor therapy is a distinct future possibility. We are also working actively on other molecular therapies. Many of the molecular driving forces that promote and sustain lymphedema are yielding to investigation. In the future, it is very likely that specific drug classes will be able to be prescribed to abrogate the abnormal tissue responses in lymphedema and to restore the tissues to their pre-morbid state. In this regard, we have had initial successes in animal models of lymphedema.