Chapter 16
Differential Diagnosis – General Considerations

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Introduction

To gain an accurate differential diagnosis of a limb in a presenting patient, a parallel medical and lymphedema assessment should be made. There are strong benefits when the assessment/diagnosis of lymphedema is able to be established early because, currently, noninvasive bio-impedance-spectroscopy (BIS) can detect lymphedema in its "subclinical" form (International Society of Lymphology "stage 0"), enabling earlier targeted treatment and better outcomes.

Bio-impedance spectroscopy can also be used in the differential diagnosis of lymphedemas from myxedemas and lipedemas, but it has not yet shown to be able to separate primary from secondary lymphedemas, or lymphedemas from conditions exhibiting fluid changes, such as phlebedema or phlebolymphedema. Details of BIS will be presented later in this book.

This guiding chapter is intended to generate confidence in treatment selection and direction derived from an early, accurate, and differential diagnosis. It is based around a scenario of a patient who presents with a swollen limb (either in whole or in part) subsequent to surgery and radiotherapy as part of treatment for cancer, and on the frequently mistaken assumption that the swelling is lymphedema.

There are many etiologies for a swollen limb, and exploring these is crucial, not only from the point of view of an accurate diagnosis, but also because these etiologies often require differing targeting, treatment sequencing, and treatments. From the patient's perspective, knowing that the swelling is not lymphedema, and is not likely to lead to it, can provide significant relief from the fear of this manifestation as a potential sign of the return of the cancer and from the fear that the swelling may persist for life.

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For those without lymphedema, but for whom the risk is present, the onset of clinically overt lymphedema is likely to be preventable through this recognition, with a targeted treatment response to the early signs, through education and through some relatively simple management options. It is in this early detection and screening that the general practitioner and specialist have an important role to play.

For those who present with a swollen limb, the first task is to determine the reason for the swelling, and to determine whether it is associated with a failure of the lymphatic system or is due to some other underlying problem. Once the lymphatic factors are determined, the next step is to explore if there are likely to be underlying primary malformations or secondary change and then to target treatment and management, all of which is dealt with in detail in later chapters.

Differential Diagnosis: Other Reasons for a Swollen Limb

The first part of the assessment should be a medical one, with the aim of excluding other causes of swelling before the nature of the lymphedema is explored.[1]

When a patient presents with a swollen arm, then it is likely to be lymphedema unless there are issues of axillary venous stenosis or vascular entrapment in scar tissue, both of which are straightforward to determine. However, there can be many reasons for a patient's presentation with a swollen leg. Ideally, these should be identified and an attempt made to treat or manage them prior to dealing with the lymphatic problems, particularly when they may be having an impact on the load upon a compromised lymphatic system.[2]

Edema can reflect generalized (but sometimes regional) accumulation of vascular pericapillary fluids associated with increased intracapillary pressure within the lower extremities, due to a dysfunctional lymphatic system caused by chronic venous insufficiency. Edema is associated with acute DVT, post-thrombotic syndrome, arthritis, Baker's cyst for unilateral swellings, and congestive heart failure, chronic venous insufficiency (CVI), stasis edema, renal or hepatic dysfunction, hypoproteinemia, hypothyroidism, medication-induced edemas and lipedemas for bilateral swellings.

Phlebedema, the excessive accumulation of fluids due to lymphatic overload that is a consequence of the additional load imposed by a failing vascular system when the lymphatic system is still healthy and capable of working optimally.[3] Examples are early-stage chronic venous insufficiency, often associated with problems of vascular fragility, inflammation of the blood vessel walls, and venous thrombosis. The term phlebo-lymphedema, perhaps represents a semantic nuance, but there may be a need to understand the pathogenesis, i.e., which came first, lymphatic (lympho-phlebedema) or vascular dysfunction (phlebo-lymphedema)?

On most occasions, the lymphatic system is structurally and functionally normal and can manage a large additional load of fluids, such as that which occurs when there is a compromised venous system; however, continuing excessive loads above

the maximum transport capacity can lead to its failure.[4] If, in addition, the lymphatic system has a structural impairment of the type that occurs when the lymphatic system is malformed, the transport capacity can be significantly reduced.

If the assessment shows an underlying issue with the lymphatic system, one of the aims should be to work in concert with a lymphatic disease specialist to determine what might be done to improve lymphatic function.

Guidelines for the differential diagnosis are not yet well-defined or agreed upon. Most of our diagnostic outcome terminology, and the situations in which the term "lympho-phlebedema" might be used are based upon the status of the lymphatic system and whether or not it is able to function within its limits.[4,5]

Myxedema is associated with a dysfunctional thyroid (usually hypothyroidism), which, if uncorrected, can lead to the accumulation of mucinoid materials (proteoglycans) in the tissues. Testing of thyroid function will help confirm if it is this that contributes to the limb swelling.

Lipedema is the excessive accumulation of fatty subcutaneous tissues due to a metabolic disorder. It is easily distinguished from lymphedema by the fact that lipedema usually affects both legs with sparing of the feet, the skin on the affected limbs bruises easily, and often there is pain with externally applied pressure. In regions affected by abnormal fat deposition, there is no tendency to pit and the skin is soft and elastic. Even with apparent lipedemas there are various forms and a true lipedema must be differentiated from lipo-hypertrophy. The latter is normally distinguished by a slender trunk and symmetrical fat deposits in the hips and legs. Most concur that lipo-hypertrophy does not present in its latter stages with excessive fluid accumulation, as occurs with the later stages of lipedema – which is correctly called lipo-lymphedema. Their differential diagnosis will be dealt with in the next chapter.

Differentiating the Lymphedemas

Any recommendations concerning the screening and diagnosis of lymphedema, should take note of the recommendations of the International Lymphoedema Framework (ILF)[1] and the International Society of Lymphology (ISL),[2] as well as many regional groups (European Lymphology Society, Italian, German, and Dutch societies).[6]

As a starting point, the ISL consensus recommends using a three-stage classification system, with a growing movement toward a four-stage system that encompasses the latent or sub-clinical stage.[2] These stages refer only to the physical condition of the extremities and it is acknowledged that a more detailed and inclusive classification must be created based on our growing comprehension of the underlying pathophysiologies. Within each stage there is currently an "inadequate but functional severity assessment" based on simple volume differences, but these changes can be varying degrees of fluid, fat, and fibrous accumulation as the lymphedema progresses. Within the ISL severity assessment, "minimal" is described as

less than a 20% increase (over normal limb or baseline – allowing for limb dominance), "moderate" when it is 20–40%, and "severe" when it is more than 40%.[2] Of course, it is never advisable to concentrate exclusively on the physical elements of disease: there is a range of instruments to assess disability, quality of life, etc., but, in realistic terms, these aspects will not have an impact on the accuracy of differential diagnosis and are considered in subsequent chapters.

One aspect of accurate diagnosis is lymphoscintigraphy. A lymphoscintigram can give an indication of the functional status of the lymphatic system, where and which drainage pathways are hypo- or dysfunctional, where there are areas of dermal backflow or reflux. Lymphoscintigraphic processes and techniques have yet to be well standardized, but the outcomes (both qualitative and quantitative) can provide strong evidence for a dysfunctional lymphatic system.[7] This and other diagnostic tools will be considered in subsequent chapters.

Filarial Lymphedema

Lymphedema often only manifests during the latter stage of this disease, a fact that is often overlooked. The clinical manifestation and presentation depends on the type and feeding preferences of the mosquito carrying the filarial parasite. The major diagnostic confirmation is achieved through sero-conversion and through examination of a peripheral blood sample taken in the late evening or early morning. A thoroughly conducted medical history will help to determine if the patient has lived in areas where the parasite is endemic.

Malignant Lymphedema

Usually associated with a rapid onset and a location that is more proximal/central than the more commonly encountered forms of iatrogenic lymphedema, this variant occurs through reduction of lymph transport as a consequence of external obstruction of nodes or collectors, or through invasion and proliferation of neoplastic tissues. In addition to the differential diagnostic points already considered, there can be significant pain, as well as abnormalities of the skin, which can often be shiny and sometimes cyanotic as well.

Factitious Lymphedema

This may occur in patients who seek attention for an illness initiation or exacerbation. A good differential diagnosis is best gained through a detailed medical/surgical history.

Primary Lymphedema

In all tests, primary lymphedemas resemble the secondary form. This differential diagnosis is generally best established through a review of the patient's family, medical, and surgical history. Approximately 3–10% of lymphedemas are primary in nature and caused by some heritable malformation (generally hypoplasia, but sometimes hyperplasia) of the lymphatic system, which can become apparent at birth (Nonne–Milroy), puberty (Meige or praecox) or in later life (tarda). Some patients may be surprised at the onset of the lymphedema after an apparently minor surgical intervention, but an exploration of family history may expose genetic predisposition.

When a Patient Might First Present

A person who has a damaged lymphatic system has a lifetime risk of developing lymphedema, although the risk level may vary with time. It is the responsibility of both patient and physician to keep the risk as low as possible by recognizing and managing all of the factors that can increase the lymphatic load.

Risk Factors to Consider at Presentation

Some risk factors, such as body mass, skin integrity, activity levels (inactivity seeming to be the worst), constrictive clothing (particularly underwear that has elastic across the line of the groin) and bras (those that are under-wired and have narrow straps) are under a patient's control.

Some factors, such as patient age, the extent of axillary or groin clearance, the area of radiotherapy, whether the surgery/radiotherapy was on the dominant arm, seroma duration, the number of drains, and wound infection, are beyond the patient's control.

Signs to Look for at Presentation

Even if there is no obvious swelling, it is worth testing whether the distal part of the limb shows signs of pitting or considering the use of one of the more objective instruments to detect subtle fluid differences through bio-impedance spectroscopy.[8] These are dealt with in other chapters of this book.

It is important to be aware that lymphedema progresses in a different fashion than hydrostatic edema. There is no epi-fascial fatty tissue deposition in edema, but this is characteristic of lymphedema as it progresses (ISL stage II and III).

There may also be signs of tissue changes associated with the accumulation of fibrotic tissue (ISL stage III). These changes can often be detected through conducting a "pinch and roll test," by holding the affected tissues between the thumb and forefinger and gently rolling the tissues between them (generally referred to as a Stemmer sign when used at the base of the digits of the hand or foot). While not always useful in early lymphedema, the Stemmer sign is common in the middle and late stages. The Stemmer sign is useful to distinguish lipedema and other forms of tissue swelling from lymphedema, although the Stemmer sign is best used in combination with other diagnostics. A positive Stemmer sign reflects the inability to pick up a fold of skin at the base of the big toe or fingers; more objective correlates can be detected through tissue tonometry, ultrasound or some other measure of epifascial tissue change.[9]

To determine if the limb is swollen, a circumference measurement can be performed at fixed points in the fore/upper arms or calf and thigh. Unfortunately, this is only useful if the problem is a unilateral one, where a comparison can be made with the contra-lateral (normal) limb and the progression assessed against this baseline. If the problem is bilateral, then, at best, the measurements can be used as a baseline, acknowledging that this baseline may not be the beginning of the lymphedema. There are international best practice guidelines for this.[1,9]

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