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Imaging the lymphatic system

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ABSTRACT

Visualization of the lymphatic system is clinically necessary during diagnosis or treatment of many conditions and diseases; it is used for identifying and monitoring lymphedema, for detecting metastatic lesions during cancer staging and for locating lymphatic structures so they can be spared during surgical procedures. Imaging lymphatic anatomy and function also plays an important role in experimental studies of lymphatic development and function, where spatial resolution and accessibility are better. Here, we review technologies for visualizing and imaging the lymphatic system for clinical applications. We then describe the use of lymphatic imaging in experimental systems as well as some of the emerging technologies for improving these methodologies.

Introduction

The lymphatic system is responsible for maintaining proper tissue–fluid balance, organizing the immune system and absorbing lipids in the gut. It consists of the lymphatic vessels and lymph nodes through which lymph and immune cells traffic to establish and maintain immune responses. Therefore, disruption of lymphatic function results in lymphedema—fluid accumulation in a tissue due to deficient lymphatic function—and local immuno-compromise, both of which lead to significant morbidity. The lymphatic system is also involved in cancer progression, as entry of metastatic cancer cells into the lymphatic system can result in lymph node metastases. Thus, the lymphatic system is central to a variety of pathological processes and many techniques have evolved to allow visualization of its anatomy and function (Rockson, 2003; Sevick-Muraca et al., 2014).

The lymphatic system consists of small lymphatic capillaries—termed initial lymphatics—that absorb interstitial fluid and cells to create lymph. These initial lymphatics bring lymph to the collecting lymphatic vessels, which are critical for transporting lymph over long distances through lymph nodes and eventually to the blood (Schmid-Schönbein, 1990). As opposed to the blood system, lymph flow is not always present, and is not driven by a central pump. This brings the possibilities of pathologies unique to the lymphatic system that generally manifest as problems with fluid homeostasis and the resulting edema. It also requires a different set of tools for diagnosis and analysis compared with the cardiovascular system.

In general, lymphatic vessels are difficult to visualize because they contain few cells, carrying mainly clear lymph fluid. This makes them difficult to locate and cannulate for angiographic techniques. Therefore, most visualization techniques rely on the natural ability of lymphatic vessels to absorb tracers injected into the tissue space. The tracer is then transported and concentrated into the proximal network, allowing detection by a variety of imaging modalities.

Imaging the lymphatic system in the clinic for assessment of function and diagnosis

Lymphography

Traditional lymphography and lymphangiography are natural extensions of angiography, a common method used to visualize the cardiovascular system by direct injection of a contrast agent into a vessel. One main difference is that intravascular contrast can be injected at any point in the cardiovascular system in order to highlight the entire blood vasculature. However, lymphatic contrast needs to be introduced in the periphery and will only highlight the lymphatic vessels draining that position. To identify a lymphatic vessel for cannulation, a contrast agent—such as Direct Blue or Patent Blue—is injected into the dermis where it is absorbed by initial lymphatics and fills the lymphatic vessels that drain the injection site. This allows identification of lymphatic channels that can then be cannulated and injected with an opaque contrast agent for radiographic imaging (Fig. 1A). Originally developed

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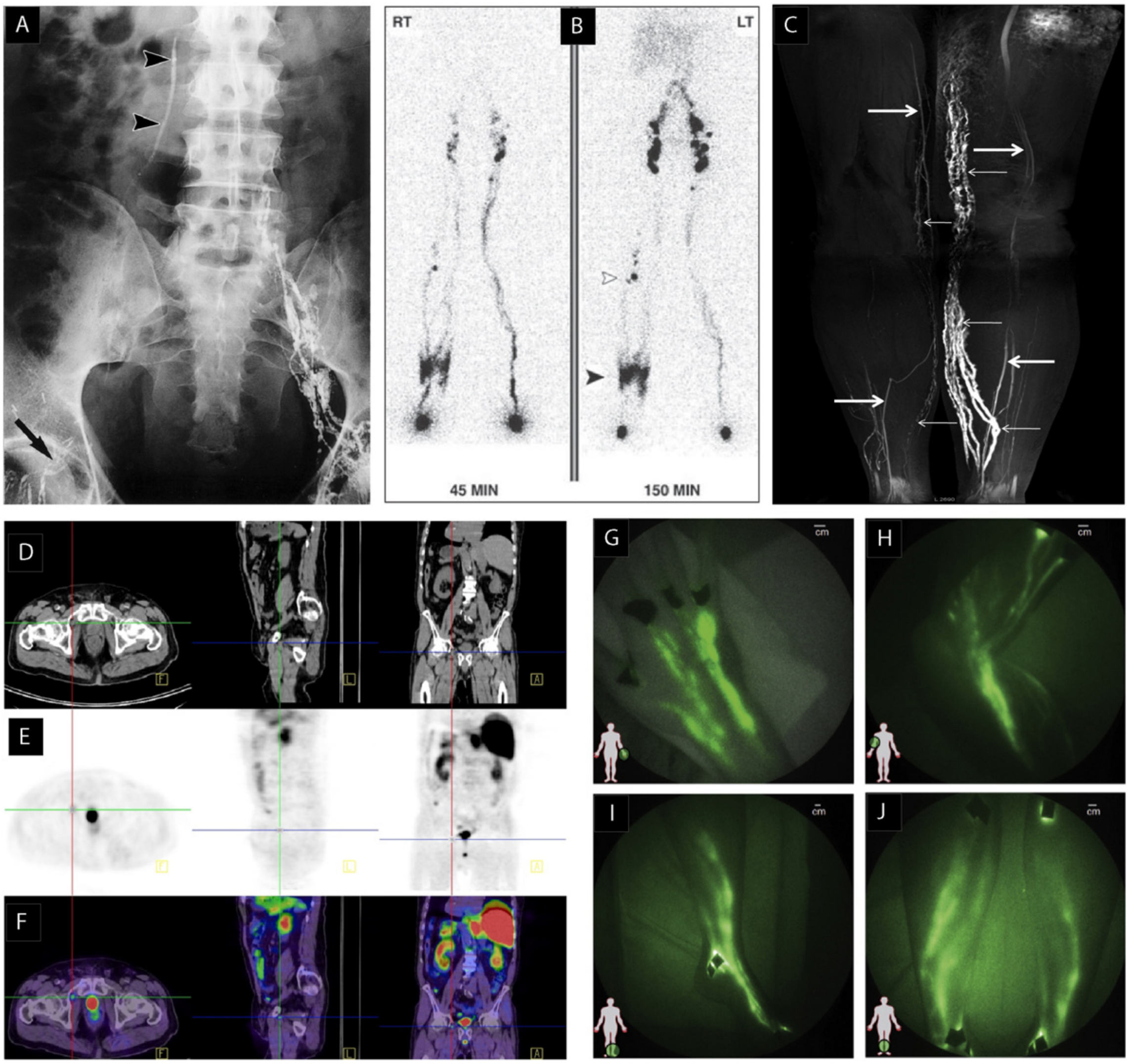

Fig. 1. Imaging lymphatic vessels and lymph nodes in the clinic. (A) Lymphogram of a patient with lymphovenous shunt after surgery for right-sided inguinocrural hernia showing lack of lymph flow in the inguinocrural region (arrowheads) (Guermazi et al., 2003, reproduced with permission). (B) Lymphoscintigraphy of bilateral limb swelling. Lymph rerouting through the skin of right lower limb (solid arrowhead) and the deep lymphatics is apparent. Several popliteal nodes (open arrowhead) are visible. The left limb appears normal in this lymphoscintigraph (Burnand et al., 2011, reproduced with permission). (C) Coronal 3D MR lymphography image of the lower extremities obtained after subcutaneous injection of contrast material. Abnormal, dilated lymphatic vessels extend from the left calf to the inner thigh (small arrows). Some lymphatic vessels in the contralateral normal limb appear discontinuous (small arrows). Veins appear as linear structures with lower intensity (large arrows) (Lu et al., 2012). (D–F) PET-CT after radical prostatectomy. CT images are in (D), PET images 60 min after the administration of ^{18}F-choline are in (E) and merged PET-CT images are in (F). The high intensity spot in the PET scan is a small right inguinal lymph node with likely metastasis (F: transverse plane; L: saggital plane; A: coronal plane) (Fortuin et al., 2013). (G–J) Near infrared imaging of healthy lymphatics in normal subjects. Lymphatic vessels in (G) hand, (H) arm, (I) foot, ankle, and leg, and (J) lower legs. Black spots are covered injection sites (Rasmussen et al., 2009, reproduced with permission).

by Kinmonth (1952) as a guide during surgical procedures, lymphangiography has been modified and adapted for other diagnostic and experimental applications. The technique, which requires multiple injections into the tissue and microcannulation of vessels, is invasive and time consuming (Clement and Luciani, 2004; Halsell et al., 1965; Weissleder and Thrall, 1989) and has generally been supplanted by newer methods, described below.

Lymphoscintigraphy

Lymphoscintigraphy is a commonly-used imaging method in the clinic (Mihara et al., 2012; O'Mahony et al., 2004; Sevick-Muraca et al., 2014; Weissleder and Thrall, 1989; Wen et al., 2014) that relies on a radioactive tracer such as ^{99m}-technetium (^{99m}-Tc) being injected in the tissue (Kim et al., 2004b; Mieog et al., 2011; Ogasawara et al., 2008; Shih et al., 2001). As it drains through the lymphatic system, it can be imaged using a scintillation camera that integrates the signal over time to produce a 2D image of the lymphatic network (Fig. 1B). By repeated imaging of a lymph node over time, lymphatic drainage can be assessed by the increase in signal intensity over time. However, the poor resolution of this technique does not allow clear identification of vessel or lymph node location.

3D imaging is also possible with scintigraphy. Single-photon emission computed tomography (SPECT) uses triangulated information from multiple detectors to reconstruct 3D images of radioactive tracers (Barrett et al., 2006; Mar et al., 2007; O'Mahony et al., 2006). It is advantageous to add conventional x-ray CT to this method, to perform SPECT/CT, which localizes the lymphatic tracer at relatively low resolution (1–2 cm), but in relation to the high-resolution anatomy provided by the CT scan (Basu and Alavi, 2009; Tseng et al., 2014; Vermeeren et al., 2009). This method has proven useful in analysis of lymphatic drainage and sentinel lymph node identification in cases of head and neck melanoma (Mar et al., 2007), and diagnosis of primary intestinal lymphangiectasia (Wen et al., 2014), breast cancer (Basu and Alavi,