lymphatics

Commentary

The Rise of Lymphatic Intervention: A Rapid Evolution

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For centuries, the lymphatic system was a known unknown. The small size of lymphatic vessels and the anatomic complexity of the lymphatic system limited its study to dissection and animal vivisection, which allowed gradual knowledge to be gained [1]. In the 1950s, two lymphatic imaging techniques emerged: lymphoscintigraphy and pedal lymphangiography [2,3]. Although lymphoscintigraphy was low in spatial resolution, the initial description of lymphoscintigraphy paved the way for understanding lymphatic flow patterns and provided a technically less challenging modality to image lymphatic flow patterns and is still used for sentinel lymph node identification. In contradistinction, pedal lymphangiography provided high spatial resolution imaging but was a technically challenging and time-intensive modality, which involved a pedal cutdown to visualize a dorsal foot lymphatic and accessing it before initiating a slow infusion of ethiodized oil contrast. Kinmoth noted that "lymph vessels, or at least normal ones, are much smaller than the arteries or veins... they contain colorless lymph, which makes them difficult to see, and under normal circumstances, they may be empty or nearly so, existing as potential spaces" [4]. Both modalities became widely available and were used in the ensuing decades; however, the popularity and practice of pedal lymphangiography waned in the 1990s as ultrasonography, computed tomography, and magnetic resonance imaging techniques supplanted its uses for cancer staging, the evaluation of infectious/inflammatory disease, and identifying primary lymphatic diseases.

In the 1990s, technical progress was made across a range of surgical specialties. Cancer patients could undergo more aggressive oncologic resections in a less invasive manner but then suffer from a post-operative lymphatic injury based on the surgical approach and intent of resection. For instance, patients undergoing esophagectomy for esophageal cancer suffered from post-operative chylothorax and, although surgically cured, then succumbed to a respiratory compromise, nutritional deficiency, and infections. An Interventional Radiologist at the University of Pennsylvania, Constantine Cope, pioneered the field of lymphatic intervention over a series of successive publications. Using pedal lymphangiography, Cope opacified retroperitoneal lymphatics to use as a percutaneous target to access the central lymphatic vessels and subsequently embolize the thoracic duct. Through his publications and prospective trials on thoracic duct embolization (TDE), Cope fundamentally changed the management of chylothorax and launched the field of lymphatic intervention [5–7].

In the ensuing decade, the adoption of TDE and innovation in lymphatic intervention was slow because few medical centers had the equipment, technical expertise, or resources available to perform pedal lymphangiography or TDE, nor was there widespread demand. In 2009, Itkin reported on over 100 patients who underwent TDE for traumatic chylothorax, further stoking interest in lymphangiography and lymphatic intervention [8]. In 2011 and 2012, intranodal lymphangiography (IL) was described in children and then adults, creating a paradigmatic shift in how lymphangiography was performed [9,10]. Intranodal lymphangiography is technically easier to perform than pedal lymphangiography, is more convenient for the operator and patient, does not require special needles or pumps, is considerably faster, does not require interdigital webspace dye injection or involve a cutdown, has fewer complications, and has become the standard approach for lymphangiography. Moreover, the ease of IL increased interest in lymphatic intervention, and its more widespread adoption allowed TDE to be routinely performed with higher technical and clinical success in less experienced operators [11–14]. More importantly, IL expanded the applicability of lymphangiography beyond TDE and allowed for innovation in non-fluoroscopic lymphatic imaging techniques.

Using intranodal delivery into the lymphatic system, non-contrast magnetic resonance lymphangiography (MRL), which could already image slow-flowing, stagnant, and dilated lymphatic structures, could be used for new applications. Adding a lymphatic contrast agent provides flow-related information and higher sensitivity imaging. Dynamic contrast-enhanced magnetic resonance lymphangiography (DCE-MRL) has high spatial and temporal resolution with improved lymphatic leak detection and helps in the procedural planning for complex lymphatic intervention [15,16]. More recently, the intranodal delivery of water-soluble contrast has been combined with dynamic computed tomography (CT) imaging to produce similar information to DCE-MRL without the technical difficulties or limitations of magnetic resonance imaging (MRI) and allow for faster exams and even wider dissemination [17].

The development of IL, intranodal glue embolization, hepatic lymphangiography, and mesenteric lymphangiography has further allowed for a deeper understanding of lymphatic anatomy, pathophysiology, and interventional capability. In combination with fluoroscopy and advanced imaging techniques, the successful interventional embolization of an increasing diversity of lymphatic conditions in a larger variety of patients has been described, including pediatric chylothorax, chylous ascites, lymphocele, lymphorrhea, protein-losing enteropathy, and plastic bronchitis [18–24]. These treatments involve novel approaches and utilize techniques that include retrograde transvenous lymphangiography, trans-cervical lymphangiography, and balloon occlusion retrograde abdominal lymphangiography, among others, to embolize abnormal or leaking lymphatic vessels with a high safety and low complication profile [25–29]. In a subset of these patients, thoracic duct stent-graft placement was initially described, which further evolved the approach beyond lymphatic embolization to lymphatic intervention with preservation of the central conducting lymphatics [20].

The preservation of the central conducting lymphatics during intervention has centered around lymphoplasty, lymphatic stent/stent-graft placement, recanalization, and a micro-surgical lymphovenous bypass. Case reports have demonstrated the ability to reconstruct damaged lymphatics with stent grafts as well as relieve chylothorax and chylous ascites with lymphatic recanalization through lymphoplasty [30,31]. In case series, terminal thoracic duct lymphoplasty, stenting, and micro-surgical lymphovenous bypass have relieved neck swelling, abdominal pain, ascites, pancreatitis, variceal hemorrhage, and chyluria [32–39].

A recent pilot study evaluated the role of thoracic duct stenting for the resolution of recalcitrant ascites in patients who were maximally medically managed, were not candidates for porto-systemic shunts, and were not liver transplant candidates [33]. Given that lymphatics play an integral role in fluid balance and the liver is one of the dominant sources of lymph production, it follows that liver disease necessarily affects lymphatics and fluid homeostasis. Portal hypertension and cirrhosis result in an increase in intrahepatic sinusoidal flow, altering the fluid dynamics and physiology in the space of Disse. Consequently, a much larger volume of lymph is produced, which increases flow in the lymphatic system and dilates the central conducting lymphatics. Although thoracic duct stenting was technically successful and decreased the pressure gradient in the thoracic duct in this pilot study, less than half of the cohort had improvement in their ascites. Continuing to understand how the progression of liver disease changes the lymphatic vessels allows intervention for patients and potentially prevents ascites, variceal bleeding, and hepatic encephalopathy. Further gains in the understanding of the interplay between hepatic, mesenteric, and peripheral lymphatics with the thoracic duct and the central venous circulation allow for the relief of a variety of other volume or flow-based disorders.

The lymphatic system permeates the human anatomy and is necessarily integral in the physiology of fluid balance, nutritional absorption, immune function, endocrine secretions, and the spread of malignancy. Understanding the interplay of lymphatics will continue to further the understanding of pathophysiology and offer additional avenues for the diagnosis and targeted therapeutics of many more disorders.

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