Near-Infrared Fluorescence Lymphatic Imaging of a Toddler With Congenital Lymphedema

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Primary lymphedema in the pediatric population remains poorly diagnosed and misunderstood due to a lack of information on the causation and underlying anatomy of the lymphatic system. Consequently, therapeutic protocols for pediatric patients remain sparse and with little evidence to support them. In an effort to better understand the causation of primary pediatric lymphedema and to better inform clinical care, we report the use of near-infrared fluorescence lymphatic imaging on the extremities of an alert, 21-month-old boy who presented with unilateral right arm and hand lymphedema at birth. The imaging results indicated an intact, apparently normal lymphatic anatomy with no obvious malformation, but with decreased lymphatic contractile function of the affected upper extremity relative to the contralateral and lower extremities. We hypothesized that the lack of contraction of the lymphatic vessels rather than an anatomic malformation was the source of the unilateral extremity swelling, and that compression and manual lymphatic drainage could be effective treatments.

Pediatric lymphedema is thought to be caused by developmental malformations of the lymphatic vessels, leading to chronic swelling that, if untreated, results in interstitial protein accumulation, tissue fibrosis and disfigurement, and reduced immune response.[1] Pediatric lymphedema is reported to occur in 1 in 6000 children[2] and can differ from adult lymphedema in that it is typically of primary, nontraumatic origin and may not progress to pitting edema.[3] In addition, there are no guidelines or evidence for its effective, physical treatment.[4] Management of pediatric lymphedema is typically based on adult treatments, which include manual lymphatic drainage (MLD), bandaging, and compression, all of which lack evidence for effective use in the pediatric population. Given the long-term disability in the affected child and the financial impact of this chronic, progressive condition, better treatment algorithms are critical to the management of pediatric lymphedema.

The main impediment to understanding and treating lymphedema is the lack of an imaging modality that is safe, inexpensive, and effective in the pediatric population to visualize lymphatic function in real-time. Near-infrared fluorescence lymphatic imaging (NIRFLI) has previously been used to provide high resolution, real-time images of adults with primary and secondary lymphedema.[5–8] The technology obviates the need for radiation and sedation. Previous studies in other pediatric patients with lymphatic anomalies, such as pleural effusion and ascites, have demonstrated NIRFLI's usefulness and safety profile.[9–11] We present a case of primary upper extremity lymphedema

abstract

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Dr Greives designed the study with Dr Sevick-Muraca, recruited the subject, provided clinical oversight, and critically reviewed and revised the manuscript; Dr Aldrich assisted with clinical data acquisition and analysis, and revised the manuscript; Dr Sevick-Muraca designed the study with Dr Greives, drafted the manuscript draft and critically reviewed the final manuscript, and approved the final manuscript as submitted; Dr Rasmussen designed the data collection instruments, acquired and analyzed the data, and drafted the initial manuscript; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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in a pediatric patient who underwent NIRFLI to determine the cause of the lymphedema.

CASE REPORT

A 21-month-old boy with primary lymphedema in the right hand and arm presented at the Vascular Anomalies Clinic at The University of Texas Health Science Center at Houston. The patient was an identical twin, born at 31 and 5/7 weeks after a pregnancy complicated with twin–twin transfusion, with the subject being the donor twin. Cardiac workup demonstrated mild asymptomatic ventricular hypertrophy with bradycardia, although no interventions were recommended. The patient was also diagnosed with glaucoma and had undergone bilateral corneal transplants. The subject's identical twin had none of these medical conditions. Parents were disease-free with an unremarkable medical history. At presentation, the subject was 30 inches tall and 26.8 pounds with a 32% volume increase of the right arm over the left. Ultrasound imaging performed on the right arm was negative for deep vein thrombosis. No previous therapeutic interventions for the lymphedema had been initiated.

Based on a Food and Drug Administration– (investigational new drug application number 102 827) and institutional review board–approved protocol, NIRFLI was offered to the patient's family to elucidate the cause of his lymphedema. After obtaining informed consent from the parents, an intradermal injection, containing 12.5 μg of indocyanine green (ICG) in 0.05 mL saline, was administered in the dorsum of each foot and hand for lymphatic uptake, for a total dose of 50 μg. The injection sites were covered with round bandages and black vinyl tape to prevent oversaturating the imaging device. Briefly, NIRFLI uses military-grade, night vision technology to acquire fluorescent images after illuminating the tissue surfaces with diffuse light that penetrates into tissues and excites the ICG.[12] Image acquisition rates of about 88 images per minute enabled visualization of ICG transit through functional lymphatics. Throughout the procedure, the subject was fully conscious and held on his mother's lap. No procedural sedation was used or needed for the injections or the image acquisition phase. The subject tolerated the injections and imaging well and eventually napped on his mother's lap during the imaging session. Images were displayed in near real-time and allowed for evaluation of abnormal lymphatic anatomy, including tortuous vessels, dermal backflow, and/or extravascular fluorescence, features that were common to lymphedema patients in previous studies.[5–8,13–15] Sequences of images were also assessed for contractile function, and, when observed, the rate of contractile propulsion events was calculated by dividing the number of observed pulsatile events by the time elapsed in the given sequences of images.

Lymphatic vessels with active contractile propulsion were observed immediately at the start of imaging with fluorescence pathways visible from the foot and hand injection sites to the draining lymphatic basins. As shown in Fig 1 (see Supplemental Video 1), the leg lymphatics were linear and well defined, as seen in healthy adults. The arm lymphatics were also linear and well defined (see Fig 2 for left arm [see Supplemental Video 2] and Fig 3 for right arm (see Supplemental Video 3]). There was a small area of possible dermal backflow in the lateral right wrist (Fig 3D), however, we could not definitively determine whether it represented dermal backflow or was possibly "contamination" on the surface of the skin, because small

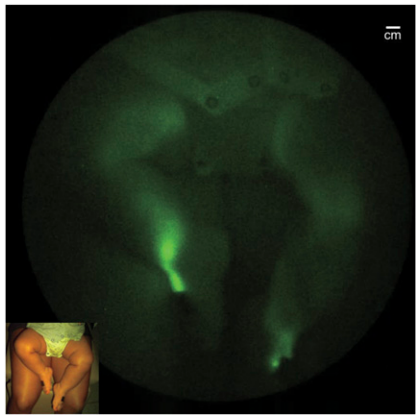

FIGURE 1
Fluorescent image of the lymphatics in the lower limbs of subject (see Supplemental Video 1).

splashes of ICG were observed near the injection site, as well as on the gloves of the physician injecting the ICG.

The rate of contractile lymph propulsion in both legs averaged ~3.8 propulsion events per minute (48 events observed) with no manual lymphatic stimulation, but vigorous kicking activity by the child. In the left arm, the observed propulsion rates increased from ~1.8 propulsion events per minute (5 events observed) to 3.4 propulsion events per minute (24 events observed) when the injection site was lightly massaged. Due to reduced lymphatic pumping in the right arm, the observed propulsion rate was <0.4 propulsion events per minute (1 event observed) before the start of massage. Nonetheless, we found contractile propulsion rates to be ~3.0 propulsion events per minute (41 events observed) with intermittent massage of the right hand and arm. In addition, we observed the recruitment of lymphatic vessels with active propulsion in the right arm in response to the massage.

Based on this information of normal anatomy but dysfunctional propulsion in the lymphatics of the patient's right arm, the patient and parents were referred to physical

therapy for treatment and training in MLD and compression therapy.

DISCUSSION

This study is the first near real-time anatomic evaluation of the lymphatics in a pediatric patient with primary lymphedema. For this patient with normal lymphatics but dysfunctional contractions, MLD and compression may be indicated. The patient's normal lymphatic anatomy is presented in contrast to other patients who have previously been imaged showing abnormal lymphatic anatomy or obstruction to flow, which may be better treated by surgical intervention. The use of NIRFLI to direct clinical therapeutics is a clear advance in the treatment of pediatric lymphedema.

As with any new diagnostic, concerns for patient comfort and safely are paramount. No procedural sedation was needed for image acquisition and the small injections were performed with a cold spray to the hands and feet to reduce pain at the injection site. The subject was generally free to move his hands and feet, although on occasion a hand or foot was gently restrained to obtain images at different arm or leg orientations or to gently massage his limbs. Although subject movement typically is not an issue for lymphatic anatomic imaging with NIRFLI, the lack of a stable field of view created difficulty when we sought to quantitate the lymphatic contractile function, as previously described in adults.[5–7] In future studies, the movement of young children may be minimized by imaging immediately after a meal, when the child is prone to napping, or while the child is distracted by audiovisual media. ICG itself has previously been shown to be safe in pediatric patients with a total dose of up to 2 mg/kg.[16]

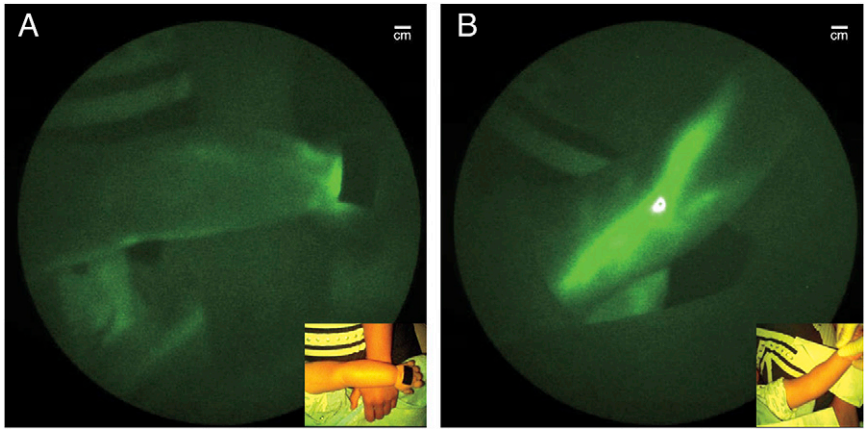

FIGURE 2
Fluorescent images of the A, lateral and B, medial left arm (see Supplemental Video 2) with what appears to be a cubital lymph node.

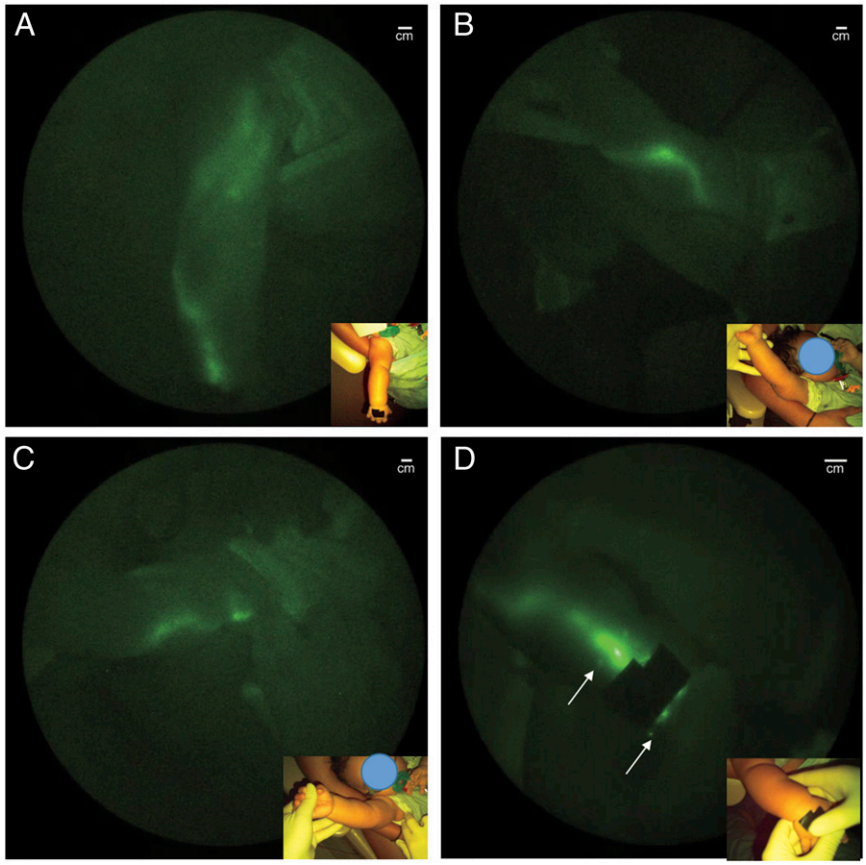

FIGURE 3
Fluorescent images of lymphatics in the A, lateral and B, medial right arm (see Supplemental Video 3), as well as the C, right axilla. D, Possible dermal backflow or contamination near right wrist.

The difference in the propulsion rates in the symptomatic and asymptomatic arms was expected. Rasmussen et al[6] previously reported similar reductions in the symptomatic arms of adults with unilateral lymphedema, as compared with the asymptomatic arms and to healthy adults in whom no statistical differences were noted between the

left and right arms. In addition, the improvement in the propulsion rates owing to the massage of the injection sites in this subject is similar to the improvement in lymphatic function in subjects who received MLD as reported by Tan et al.[7] However, the lack of obvious abnormal lymphatic anatomy was surprising because lymphatic dysplasia has previously been reported in congenital lymphedema.[17,18] In our previous imaging experience with >300 adolescents and adults, each subject with lymphedema had some degree of lymphatic anatomic abnormality, typically dermal backflow or, in rare cases, no visible lymphatics. Even in subjects with early symptoms of nonsyndromic primary lymphedema or with asymptomatic trauma-associated, acquired lymphedema, anatomic abnormalities were always present. Whether the development of lymphatic anatomic abnormalities is characteristic of more advanced stages of lymphedema that may occur later in this child remains to be investigated. However, NIRFLI shows normal lymphatic anatomy in this case of nonsyndromic, pediatric lymphedema. This finding differs from the work of Shibasaki et al[10] who reported the appearance of dermal backflow 3 to 6 hours after ICG injection in critically ill infants with congenital pleural effusion and ascites. Likewise, we have visualized abnormal lymphatic anatomies in children with chylothorax after heart surgery and intradermal ICG injection.[9] In this current case of nonsyndromic pediatric lymphedema, the lack of lymph-pumping function could be responsible for the unilateral swelling, and it is possible that stimulating the lymphatic pump through MLD techniques could reverse the swelling before any lymphatic deterioration occurs as a result of interstitial fluid build-up and adverse tissue remodeling. Others have recently discovered a lymphatic connection to glaucoma,[19] which could indicate future anomalous lymphatic development that would not be observed at the time of our imaging session.

In recent years, there have been limited reports of successful reductions of limb volume in adults with lymphedema after lymphovenous anastomosis to shunt lymph from the lymphatics directly into patent veins to bypass "blockages" within the lymphatic system.[20,21] If the cause of pediatric lymphedema is malformation of the lymphatic vasculature, then surgical strategies that seek to reestablish lymphatic transport could impact children with lymphedema. However, accurate real-time images of both the anatomy and function of these lymphatic vessels is a prerequisite to therapeutic protocol development.

Finally, it is noteworthy that, before presenting to our Vascular Anomalies Clinic and consistent with a recent report on the lack of guidelines for management of pediatric lymphedema,[4] the subject's parents were instructed not to begin lymphedema treatments of MLD and bandaging until the child grew older. Although the scope of our conclusions based on this single case study may be limited in the broader pediatric population, the imaging results presented in this report provide evidence that treatments to stimulate the lymphatic pump could be useful at young ages, whereas surgical strategies to correct lymphatic blockage would not. Additional studies are needed to (1) determine whether the observed phenotype is typical in the young pediatric population or, more probably, if a spectrum of phenotypes are observed; (2) whether those phenotypes may be linked to genetic abnormalities as was shown to be the case in an adult with primary lymphedema[22]; and (3) whether individualized management schemes for pediatric lymphedema may be devised using NIRFLI for point-of-care diagnostics and to guide effective interventions and follow outcomes.

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ABBREVIATIONS

ICG: indocyanine green
MLD: manual lymphatic drainage
NIRFLI: near-infrared fluorescence lymphatic imaging

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