Advances in Lymphatic Imaging and Lymphedema Treatment

10/12/22
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Stanford Cancer Imaging Training Fellow
Body MR Fellow
Disclosures

• Off label – this presentation will discuss off label use of:
  • Gadolinium contrast agents
  • Ferumoxytol
Overview

• Background on Lymphatic Disease and Lymphatic Imaging
• Drug Trial
• MR Lymphangiography
  • DARC-MRL
    • Technique
    • Staging
  • Subcutaneous Thickness Fraction
  • ION-MRL
• Teaser: Novel Treatment for Lymphedema
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• Teaser: Novel Treatment for Lymphedema
• “It is simple. Any doctor could have done it . . . You cannot help that which you have not sought to understand.”

- The Healer
The Lymphatic System

• The Lymphatic Continuum:
  • Lymphedema
  • Chylothorax
  • Chylous ascites
  • Cancer metastasis
  • Dementia
  • Autoimmune Disease
  • Lymphatic Vascular Malformations
  • Obesity Metabolic Syndrome
  • Lipidema
  • Generalized Lymphatic Anomalies
  • Organ Transplantation
  • CAD & CHF


Lymphedema

“IT’s a very rare disease—it doesn’t have a cure. It doesn’t even have a spokesperson.”
Lymphedema
Success!

• Lymphatic diseases and lymphedema added as eligible categories for research under the Department of Defense’s Peer-Reviewed Medical Research Program ($400 million-dollar annual budget)
Lymphedema

Neligan PC, Masia J, Piller NB. Lymphedema: Complete Medical and Surgical Management. NEW YORK: Thieme; 2015.
Lymphedema

**Lymphedema Staging**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Clinical Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Latent or subclinical condition in which swelling is not yet evident despite impaired lymph transport with subtle changes in tissue fluid or changes in subjective symptoms. It may exist months or years before overt edema occurs.</td>
</tr>
<tr>
<td>I</td>
<td>Early accumulation of fluid relatively high in protein content, which subsides with limb elevation. Pitting may occur.</td>
</tr>
<tr>
<td>II</td>
<td>Limb elevation alone rarely reduces tissue swelling, and pitting is common.</td>
</tr>
<tr>
<td>III</td>
<td>Lymphostatic elephantiasis in which pitting can be absent and trophic skin changes, such as acanthosis, fat deposits, and warty overgrowths, develop.</td>
</tr>
</tbody>
</table>

*Other classifications/authors use arabic numerals for these stages: 0, 1, 2, 3.
Clinical Need: Better quantification of lymphatic function
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Pilot studies demonstrate the potential benefits of antiinflammatory therapy in human lymphedema

Stanley G. Rockson,1 Wen Tian,1 Xinguo Jiang,1 Tatiana Kuznetsova,1 Francois Haddad,1 Jamie Zampell,1 Babak Mehrara,4 Joshua P. Sampson,1 Leslie Roche,1 Jinah Kim,1 and Mark R. Nicolls1

1Department of Medicine, Stanford University School of Medicine, Stanford, California, USA. 2Department of Medicine, VA Palo Alto Health Care System/Stanford University, Palo Alto, California, USA. 3Research Unit Hypertension and Cardiovascular Epidemiology, KU Leuven Department of Cardiovacular Sciences, University of Leuven, Belgium. 4Department of Surgery, Memorial Sloan Kettering Cancer Center, New York City, New York, USA. 5Department of Pathology, Stanford University School of Medicine, Stanford, California, USA.

*Ketoprofen issued BLACK BOX WARNING for increased risk of heart attack and stroke
Eicosanoid Inflammatory Pathway

Arachidonic Acid

FLAP

5-LO

COX1/2

PGs

LTA4

LTA4H

BLT1

LTB4

CysLTs

Montelukast

Ly293111 & shLtb4r1

Agents interfering with LTB4 signaling

Bestatin

Zileuton

Ketoprofen

Ibuprofen
Leukotriene B<sub>4</sub> antagonism ameliorates experimental lymphedema
Acebilustat is an orally bioavailable, small molecule inhibitor of the enzyme leukotriene A4 hydrolase (LTA4H)
Dermal Thickness

Normal

Lymphedema
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Challenges to Imaging the Lymphatic system

• Size of lymphatics:
  • Thoracic duct 2-5 mm in diameter\(^1\)
  • Often need contrast agent

• Unidirectional System:
  • Must get contrast "upstream" of the lymphatics to be visualized

• Specific Contrast requirements:
  • 10-50 nm (Bergqvist 1987)
  • Gad ~1nm leaks out of lymphatics

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MR Lymphangiography (MRL) Techniques

• Non-contrast MRL

• Intranodal MRL
  • Pediatric Central Lymphatics
  • Typically, with General Anesthesia

• Contrast Enhanced Peripheral MRL:
  • Gad-MRL
    • Venous contamination
  • DARC MRL (Maki et. Al. 2016)
    • IV Ferumoxytol suppresses venous signal
MR Lymphangiography (MRL) Techniques

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Intranodal MRL

- 4 yo M with Single ventricle physiology status post fontan complicated by protein losing interopathy
Intranodal MRL

Ax T1 UTE

IR Lymphangiogram with Lipiodol
- In remission with stable albumin levels and symptoms
- Can consider glue embolization if effect diminishes.
MR Lymphangiography (MRL) Techniques

- Non-contrast MRL
- Intranodal MRL
  - Pediatric Central Lymphatics
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- Contrast Enhanced Peripheral MRL:
  - Gad-MRL
    - Venous contamination
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    - IV Ferumoxytol suppresses venous signal

IV Ferumoxytol + GAD-MRL = DARC-MRL
<table>
<thead>
<tr>
<th>Suspected Upper Extremity Lymphedema</th>
<th>Non-contrast T2w FSE</th>
<th>Dermal Run Sign</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>- honeycombing</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- hyperintense signal of overlying thickened skin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- fluid signal within the subcutaneous tissue</td>
</tr>
<tr>
<td>ISL Stage</td>
<td>Dermal Backflow on Lymphoscintigraph by L-Dex</td>
<td>64</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Lower Extremity Lymphedema</th>
<th>Post-contrast T1w 3D SPGR</th>
<th>Inguinal node contrast ratio (SI post-contrast SI pre-contrast) at 5 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISL Stage</td>
<td></td>
<td>121</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Lower Extremity Lymphedema</th>
<th>T1 GRE</th>
<th>Fluid accumulation grade</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>0 = no fluid</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 = honeycombing/reticular pattern of fluid within the subcutaneous fat</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 = continuous visible stripe of fluid between the fat and investing muscle fascia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fat Accumulation Grade</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0 = no excess fat</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 = fat accumulation less than twice the width of the widest fat stripe on the unaffected side</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 = fat accumulation greater than twice the width of the widest fat stripe on the unaffected side</td>
</tr>
<tr>
<td>ISL Stage</td>
<td></td>
<td>66</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Lower Extremity Lymphedema</th>
<th>Post-contrast 3D Dixon</th>
<th>MRI Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1: no DBF, and lymph vessels are visible above the knee joint. Normal, nondilated lymphatic vessels can be seen above the knee joint and are slightly visible in the groin.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2: no DBF, and lymph vessels above the knee joint are not visible. Normal, nondilated lymphatic vessels can be seen below the knee joint.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3: DBF appears below the knee joint, and lymph vessels are seen above the knee joint.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4: both DBF and lymph vessels are seen below the knee joint.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5: DBF and lymph vessels are seen above the knee joint.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6: DBF is seen above the knee joint, lymph vessels are observed below the knee joint.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7: DBF appears only in the foot, and lymph vessels are not visualized proximal to the foot.</td>
</tr>
<tr>
<td>ISL Stage</td>
<td></td>
<td>113</td>
</tr>
</tbody>
</table>
Staging Lymphedema with DARC-MRL: Methods

- IRB approved retrospective study involving 20 patients with clinically diagnosed lymphedema
- ISL Clinical Stage: chart review
- Image Analysis:
  - Each lower limb divided into 6 regions: foot, lower leg, upper leg, lower thigh, upper thigh, and groin
  - Calculated for each limb:
    - Dermal Backflow Score: Sum of regions with dermal backflow
    - Edema Score: Sum of regions with edema
    - MRL Stage: Identical to Soga 2021
### DARC-MRL Staging Example

- ISL stage 3 lymphedema
- Edema Score: 3
- DBF Score: 3
- MRL Stage: 3

*Characterizing the foot can be problematic because of injection and coil coverage.*

<table>
<thead>
<tr>
<th>Edema</th>
<th>DBF</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

**Images:**
- Cor T2w FS
- Cor T1w FS postcon
Pearson's rho of 0.85 (p<0.01)  
Pearson's rho of 0.62 (p<0.01)  
Pearson's rho of 0.95 (p<0.01)
MRL Staging Conclusion

- The MRL stage, Dermal Backflow Score, and Edema Score statistically correlate with clinical lymphedema stage

- Interesting Observations:
  - Every patient with an MRL stage > 3 had an ISL Stage > 1
  - Every patient with an ISL stage of 3 had a T2 score > 4

- Next Steps: Work towards MRL interpretation algorithm and quantitative analysis
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The Subcutaneous Thickness Fraction: Methods

- Retrospective analysis of 20 patients (15 male, 5 female)
- Clinically diagnosed with lymphedema (14 unilateral, 6 bilateral)
  - In patients with unilateral lymphedema, the contralateral leg was given an ISL stage 0
- Underwent Clinical MR Lymphangiography

<table>
<thead>
<tr>
<th>Sequence</th>
<th>Parameters</th>
<th>Acquisition Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1-weighted 3D SPGR</td>
<td>DIXON fat separation, TE 1.1/2.2 ms, TR 5-15, Flip Angle 15°, matrix 320 x 320, slice thickness 1.6 mm, FOV 40-42 cm acquired on a 3T magnet, GE Signa Architect</td>
<td>~5 min</td>
</tr>
</tbody>
</table>

- International Society of Lymphology Clinical Stage was obtained from the clinical record
Mid-Thigh Measurements

• Thigh subcutaneous thickness fraction = subcutaneous thickness/(subcutaneous + muscle thickness)

• Measured at the distal aspect of the adductor longus; anterior 1/3 line of vastus lateralis
Mid-Calf Measurements

• Calf subcutaneous thickness fraction = subcutaneous thickness/(subcutaneous + muscle thickness)

• Measured at the distal margin of the gastrocnemius muscle belly along the line perpendicular and posterior to the interosseous septum.
• Strong positive correlation with a Pearson's rho of 0.59
• A statistically significant difference was observed between ISL lymphedema stage 1 and stage 2
A strong positive correlation was observed for both measures with a Pearson's rho of 0.60 for thickness fraction and Pearson's rho of 0.60 for the area fraction.

For the thickness fraction a statistically significant difference was observed between ISL stage 1 and 2.
<table>
<thead>
<tr>
<th>Assessed measure</th>
<th>Correlation with ISL</th>
<th>Pearson’s rho</th>
<th>P-value</th>
<th>Significant (after multiple comparison correction)</th>
</tr>
</thead>
<tbody>
<tr>
<td>thigh subcutaneous tissue thickness</td>
<td>moderate positive</td>
<td>0.27</td>
<td>0.09468776</td>
<td>no</td>
</tr>
<tr>
<td>thigh muscle tissue thickness</td>
<td>moderate negative</td>
<td>-0.29</td>
<td>0.07180457</td>
<td>no</td>
</tr>
<tr>
<td>thigh subcutaneous thickness fraction</td>
<td>moderate positive</td>
<td>0.38</td>
<td>0.01939431</td>
<td>no</td>
</tr>
<tr>
<td>thigh subcutaneous area fraction</td>
<td>moderate positive</td>
<td>0.33</td>
<td>0.04005312</td>
<td>no</td>
</tr>
<tr>
<td>leg subcutaneous tissue thickness</td>
<td>strong positive</td>
<td>0.59</td>
<td>7.29E-05</td>
<td>yes</td>
</tr>
<tr>
<td>leg muscle tissue thickness</td>
<td>low negative</td>
<td>-0.11</td>
<td>0.51131505</td>
<td>no</td>
</tr>
<tr>
<td>leg subcutaneous thickness fraction</td>
<td>strong positive</td>
<td>0.60</td>
<td>4.11E-05</td>
<td>yes</td>
</tr>
<tr>
<td>leg subcutaneous area fraction</td>
<td>strong positive</td>
<td>0.61</td>
<td>2.529E-05</td>
<td>yes</td>
</tr>
</tbody>
</table>
Conclusion

• **Leg** subcutaneous thickness, subcutaneous thickness fraction, and subcutaneous area fraction of lower limb strongly correlate with ISL lymphedema stage.

• **Thigh** subcutaneous thickness, subcutaneous thickness fraction, and subcutaneous area fraction of the thigh only *moderately* correlated with ISL stage. This correlates with disease progression.

• The leg subcutaneous thickness fraction is a quick assessment that can be easily reported.
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  - Typically, with General Anesthesia
- Gad-MRL
  - Intracutaneous Gad
  - Venous contamination
- DARC MRL (Maki et al 2016)
  - Intracutaneous Gad + IV ferumoxytol
- ION-MRL
  - Intracutaneous ferumoxytol
  - Ideal particle size 17-31 nm
  - Comparable transit time to gad
  - Risk of anaphylaxis (10x Gad)
  - Skin Discoloration
Normal Pig Gad-MRL and ION-MRL

- Lack of visualized contrast migration
- Groin and pelvic lymph nodes
- Retroperitoneal lymphatic contrast migration
- Normal inguinal lymphatic channel
- Mean 103 Hz

Images show different contrast agents and sequences:
- SPGR postcon gad
- UTE postcon ferumoxytol (TE 0.1 ms)
- R2* precon
- R2* postcon ferumoxytol
- UTE precon
- UTE postcon ferumoxytol
ION-MRL Case 1

- 58 yo M with metastatic gastric cancer status post gastrectomy with chylous ascites
- ION-MRL selected 2/2 renal failure
- ION-MRL demonstrated thoracic duct continuity and no evidence of extravasation
ION-MRL Case 2: 64 yo m with prostate cancer and left lower extremity edema.
ION-MRL Case 3

- 19-year-old male with protein-losing enteropathy with diffuse edema including the left lower extremity and bilateral hands.
ION-MRL Case 4

- 22-year-old male with left lower extremity edema s/p left iliac stent placement for presumed May-Thurner syndrome now with evaluation for vascularized lymph node transfer.
ION-MRL Summary

• Contrast remains in the lymphatic system without venous contamination
• Better visualization of the proximal lymphatic system
• No ultrasound guidance or general anesthesia
• Increased risk of adverse reaction
• Skin discoloration for weeks to months
• Dermal backflow is less conspicuous compared to DARC-MRL.
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Stellate ganglion block (SGB)

- **Blocking nerve signals** from the **stellate ganglion** with **local anesthetic** can help to:
  - Reduce **limb volume** in LE

Conclusions

• The lymphatic system is poorly understood and implicated in a variety of disease processes
• More funding is becoming available for lymphatic research
• New and emerging therapies are on the horizon
• Clinical need for advanced lymphatic imaging and function quantification
• MRL is a powerful tool but much work remains
Thanks

• T32 CA009695
• Stanford Biodesign Funding

Biodesign Team with Paul Yock, MD and Lyn Denend

Andreas Loening MD, PhD
Stan Rockson, MD
Shreyas Vasanawala MD, PhD
Dung Nguyen, MD