Introduction

- MRI - Essential part of current medical practice
- Gadolinium-based contrast agent improves results of MRI
- Five gadolinium-based contrast agents approved in the U.S. for MRI
  - Magnevist, MultiHance, Omniscan, OptiMARK, and ProHance
  - None FDA-approved for MRA
  - Gadodiamide (Omniscan®) and Gadopentetate (Magnevist®) linked to NSF
- Safe in patients with normal kidney function
- Decreased renal function: nephrogenic systemic fibrosis (NSF)

Gadolinium Link to NSF/NFD

- Gadolinium available as contrast agent since 1988
- Previously presumed to be safe for use in patients with decreased renal function when compared to iodinated contrast agents
- Gadolinium almost entirely excreted by the kidneys with half-life of 70 - 90 minutes
  - CrCl 31 - 60 mL/min: 5.6 hours
  - CrCl 15 - 30 mL/min: 9.2 hours
  - ESRD: 34.2 hours
- Highly dialyzable with removal of 78%, 96% and 99% with one, two or three standard dialysis sessions

Clinical Features of NSF

- Onset: Up to 2 - 3 months
- Initial reactions
  - Pain
  - Pruritus
  - Swelling
  - Erythema
  - Usually starts in the legs
- Late onset reactions
  - Thickened skin and subcutaneous tissues – ‘woody’ texture and brawny plaques
  - Fibrosis of internal organs (e.g., muscle, diaphragm, heart, liver, lungs)

Clinical Findings

- Areas of thick, hardened skin, commonly associated with brawny hyperpigmentation, and preferentially localized to extremities
- Extensive thickening of skin, often associated with brawny hyperpigmentation, and in some cases, distinct papules and subcutaneous nodules
Matched case-control study
- Suspected cases met either clinical or biopsy criteria, but not both
- Case-control study included confirmed cases from hospital
- Three controls per case-patient selected randomly from group of patients who were treated in same hospital A dialysis clinic or treatment center on same day that case was diagnosed

Characteristics of NFD Case-Patients and Matched Controls* From Hospital A

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Case-patients</th>
<th>Controls</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (y)</td>
<td>60</td>
<td>58</td>
<td>.04</td>
</tr>
<tr>
<td>Sex (%)</td>
<td></td>
<td>47</td>
<td>54</td>
</tr>
<tr>
<td>Male</td>
<td>53</td>
<td>61</td>
<td>.40</td>
</tr>
<tr>
<td>Median no. months since first diagnosis</td>
<td>20</td>
<td>24</td>
<td>.20</td>
</tr>
<tr>
<td>Primary type of dialysis in receiving 6 months (%)</td>
<td></td>
<td>.64</td>
<td></td>
</tr>
<tr>
<td>Hemodialysis</td>
<td>58</td>
<td>60</td>
<td>.80</td>
</tr>
<tr>
<td>Peritoneal dialysis</td>
<td>32</td>
<td>25</td>
<td>.10</td>
</tr>
<tr>
<td>No dialysis</td>
<td>11</td>
<td>16</td>
<td>.50</td>
</tr>
<tr>
<td>Comorbidities (%)</td>
<td></td>
<td>.47</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>37</td>
<td>37</td>
<td>.62</td>
</tr>
<tr>
<td>History of deep venous thrombosis</td>
<td>37</td>
<td>32</td>
<td>.02</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>52</td>
<td>50</td>
<td>.21</td>
</tr>
<tr>
<td>History of atherosclerosis</td>
<td>21</td>
<td>21</td>
<td>.13</td>
</tr>
<tr>
<td>Presumed diagnosis of NSF</td>
<td>76</td>
<td>31</td>
<td>.001</td>
</tr>
<tr>
<td>Median no. of equivalent days during remission/year</td>
<td>21</td>
<td>17</td>
<td>.40</td>
</tr>
</tbody>
</table>

* Case-patients: n = 19; controls: n = 57 (N = 76)

Odds ratios (Ors) for Selected Characteristics Among NFD Case-patients and Matched Controls* from Hospital A

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. of case-patients</th>
<th>No. of controls</th>
<th>Median Or (Lower 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Condylar</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of deep venous thrombosis</td>
<td>19</td>
<td>30</td>
<td>3.05 (1.04-8.79)</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>18</td>
<td>37</td>
<td>3.33 (1.25-8.79)</td>
</tr>
<tr>
<td>History of atherosclerosis</td>
<td>17</td>
<td>37</td>
<td>3.76 (1.64-8.63)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>16</td>
<td>37</td>
<td>3.13 (1.10-8.71)</td>
</tr>
<tr>
<td>Exposure to gadolinium-containing contrast agent</td>
<td>15</td>
<td>37</td>
<td>2.58 (1.04-6.32)</td>
</tr>
<tr>
<td>Prevalent pain in the extremities</td>
<td>15</td>
<td>36</td>
<td>1.26 (1.03-1.56)</td>
</tr>
<tr>
<td>Any vascular procedure</td>
<td>14</td>
<td>37</td>
<td>1.26 (1.03-1.56)</td>
</tr>
<tr>
<td>Depressed mood</td>
<td>13</td>
<td>37</td>
<td>1.26 (1.03-1.56)</td>
</tr>
</tbody>
</table>

Pathophysiology Model

Renal Insufficiency/ESRD
Gadolinium Exposure and Tissue Deposition
Activation of Tissue Dendritic Cells
Release of Local TGFb
Recruitment of Circulating Fibroblasts
Release of Collagen
Tissue Fibrosis

Who Is At Risk?

Higher risk
- Patients with CKD 4 and 5 (GFR < 30 mL/min)
- Patients on dialysis
- Patients with reduced renal function who have had or are awaiting liver transplantation

Lower risk
- Patients with CKD 3 (GFR 30 – 59 mL/min)
- Children under 1 year, due to immature renal function
Use of Gadolinium Contrast Media

- Risk of inducing NSF must always be weighed against risk of denying patients gadolinium enhanced scans which are important for patient management
- In patients with impaired renal function, liver transplant patients and neonates, benefits and risks of gadolinium enhancement should be considered very carefully due to increased risk for NSF
- In patients with CKD 4 and 5 (< 30 mL/min)
  - Always use least possible amount of contrast agent to achieve adequate diagnostic examination
  - Never use more than 0.3 mmol/kg of any Gd-CM
  - Never use gadolinium as contrast agent for radiography, computed tomography, or angiography as method of avoiding nephropathy associated with iodinated contrast media

Recommendations and Considerations for Health Care Professionals

- Screen all patients for renal dysfunction by obtaining history and/or laboratory tests
- For patients receiving hemodialysis, consider prompt HD following GBCA administration
  - At least 9 hours of hemodialysis (3 sessions) required to remove a Gd-CM
  - Unknown if HD prevents NSF

Treatment Options for NSF

- Only consistently effective treatment: renal recovery or transplant
- Other therapies
  - Physical Therapy
  - Extracorporeal photophoresis
  - Oral steroids (prednisone 1 mg/kg PO daily)
  - Topical Dovonex (under occlusion)
  - Plasmapheresis
  - Cytoxan
  - Thalidomide
  - Ultraviolet Therapy
  - High dose IVIG

Conclusion

Gadolinium-based contrast agents increase risk for nephrogenic systemic fibrosis (NSF) in patients with:
- Acute or chronic severe renal insufficiency (glomerular filtration rate < 30 mL/min/1.73m2)
- Acute renal insufficiency of any severity due to hepato-renal syndrome or in perioperative liver transplantation period