Nephrogenic Systemic Fibrosis: A New Threat in the Use of Gadolinium-Based Contrast Media

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Abstract

Nephrogenic systemic fibrosis (NSF) which used to be named nephrogenic fibrosing dermopathy is a new disease appears after 1997. It is characterized by scleroderma-like skin fibrosis and may systemically involve other organs, including heart, lung, liver, and striated muscle. The disease might be triggered by the exposure to Gadolinium (Gd)-based magnetic resonance image contrast agents, and develops exclusively in patients with various stage of renal failure. Gadodiamide (Omniscan®) is among them, most frequently reported in the cases of NSF. The gold standard of diagnosis is deep skin biopsy which showed CD 34/ procollagen dual positive in spindle cells, and absence of inflammation. There are several differential diagnoses to be made, such as cellulitis, drug reaction, scleroderma, scleromyxedema, and systemic sclerosis. To date, the disease mechanism is still unclear and there is no proven treatment for NSF. Therefore prevention of NSF should be emphasized. Food and Drug Administration recommends avoidance of Gd-containing contrast agents in patients with acute and chronic renal failure (glomerular filtration rate < 30 ml/min/1.73m²), unless the diagnostic information is essential and cannot be replaced by other image studies. The dose of Gd should not exceed the recommendation and there must be sufficient time for Gd elimination before readministration. Prompt hemodialysis (HD) should be considered in patients receiving dialysis after Gd exposure as Gd can be effectively eliminated via HD. [J Intern Med Taiwan 2009; 20: 226-231]

Key Words: Gadolinium, Nephrogenic systemic fibrosis, Renal failure

Introduction

Nephrogenic systemic fibrosis (NSF) is a scleroderma-like fibrotic disorder of the skin and other systemic organs in the setting of renal failure. It is a new disease first recognized in 1997 and described in the literature in 2000 in Lancet by Cowper et al. as nephrogenic fibrosing dermopathy (NFD)¹. The entity is later named NSF as it has systemic involvement of other organs². Since its recognition, there have been more than 200 cases reported worldwide. The disease is exclusively seen in patients with various degree of renal failure and most of whom have been exposed to gadolinium-containing contrast media³. Gadolinium (Gd)-based
Table 1. Characteristics of FDA-approved gadolinium-based contrast agents

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Trademark</th>
<th>Osmolality</th>
<th>Charge</th>
<th>Chelate content (mg/ml)</th>
<th>Stability Constant+</th>
<th>Route of elimination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gadobenate-dimeglumine</td>
<td>MultiHance</td>
<td>1970</td>
<td>Ionic</td>
<td>0.00</td>
<td>10¹¹⁴</td>
<td>Biliary/renal</td>
</tr>
<tr>
<td>Gadodiamide</td>
<td>Omniscan</td>
<td>650</td>
<td>Nonionic</td>
<td>12.00</td>
<td>10¹³²</td>
<td>Renal</td>
</tr>
<tr>
<td>Gadopentate-dimeglumine</td>
<td>Magnevist</td>
<td>1960</td>
<td>Ionic</td>
<td>0.40</td>
<td>10⁹⁶²</td>
<td>Renal</td>
</tr>
<tr>
<td>Gadoteridol</td>
<td>ProHance</td>
<td>630</td>
<td>Nonionic</td>
<td>0.23</td>
<td>10⁹⁵²</td>
<td>Renal</td>
</tr>
<tr>
<td>Gadoversetamide</td>
<td>Optimark</td>
<td>1110</td>
<td>Nonionic</td>
<td>28.40</td>
<td>10⁹²⁹</td>
<td>Renal</td>
</tr>
</tbody>
</table>

NOTE: Data are modified from Gröbner et al. and Parazella et al.
+The number of stability constant is proportional to the stability of the contrast agent.

MRI contrast media was first used in late 1980s, quite parallel with the first recognized case of NSF in 1997. It is widely used and has been thought to be safe before this new disease emerged. Gröbner first proposed that Gd-based MRI contrast media might trigger NSF from his observation of the five hemodialysis patients who developed NSF after exposure to Gd-containing MRI contrast agents in 2006. Epidemiologically, the risk of NSF is no difference between sex and ethnic group, and the age range of incidence is 8 to 87 year-old. Doe et al. reported a NSF incidence of 4.3 cases per 1000 patient-years and 2.4% risk for each Gd exposure. Yerram et al. suggested dosage-related toxicity or requirement of another cofactor in addition to Gd to trigger NSF. To date, the pathogenesis of this disease is still not clearly identified, but what is certain is that NSF is associated with significant mortality (5~67%) and morbidity. Here, we present a comprehensive review of the disease manifestations, diagnosis, treatment and prevention.

Gadolinium and NSF

There are five FDA-approved Gd-containing contrast agents for use during MRI in the market (Table 1). Gd-based contrast agents are almost exclusively excreted renally. Its half-life is 1.3 hour in healthy volunteers, while it is markedly prolonged up to 30-120 hours in chronic renal failure (2.6 hours in hemodialysis and 52.7 hours in peritoneal dialysis patients). Free Gd³⁺ ion is extremely toxic and is used in vivo in the form of chelate-binding to eliminate its toxicity. Delayed excretion of Gd-based contrast agents in renal failure patients enhanced the chance of transmetallization with endogenous ions and thus release of free Gd³⁺ which eventually deposit in the dermis. Macrophage would then phagocytose Gd³⁺ and produce local profibrotic cytokines as well as signals that attracting circulating fibrocyte (CF) to the tissue. Both the cytokines and CF would induce a fibrosing process mimicking the normal scar formation.

Among the five contrast media, Gadodiamide is less stable thus needs excess chelate to overcome transmetallization. This could probably explain why Gadodiamide (Omniscan) is most frequently reported in the cases of NSF, though Gadopentate (Magnevist) and Gadoversetamide (Optimark) have been reported too. Whether transmetallization plays a role in the development of NSF in patients with renal failure remains unproven. Gd-containing contrast medium alone is not sufficient to cause NSF as not all the renal failure patients who have been exposed to it developed NSF. Besides, NSF can develop in patients who have no documented use of the agent too. The cofactor, if any, is not yet been certain to date.
Clinical Manifestations

NSF is characterized by initial swelling of the distal extremities with subsequent painful indurations and thickening of the skin in the following weeks (Table 2). From the observation of 13 cases of NSF by Marckmann et al., the delay from exposure to the first sign of NSF could range from 2 to 75 days (median 25 days)14. The involved areas have the 'woody' texture and 'peau d'orange' appearance. The extremities are most often affected with the face always spared. There can be distinct nodules too. The disease may lead to skin stiffness and physical disability. Some will have deep bone pain over hips and ribs. Systemic involvements of heart, lung, liver, and striated muscles have been reported in some of the cases2,3. Occasionally soft tissue calcifications can be seen in the radiographs16.

Diagnosis and differential diagnosis of NSF

The diagnosis of NSF (Table 3) is easily missed if the physician is unaware of the disease. The gold standard of the diagnosis is deep skin biopsy along with the clinical histories and presentations. NSF has the unique histopathology as thickened dermis with bundles of collagen and surrounding clefts, mucin deposition, and a proliferation of the fibroblasts and elastic fibers. Most distinctly, there is absence of inflammation1. The immunohistochemical stain may showed CD34/ procollagen dual positive profiles in the spindle cells17.

Early stage of NSF may mimic cellulitis, panniculitis and drug reaction. A list of differential diagnoses should includes scleroderma, scleredema, scleromyxedema, systemic sclerosis/ morphea, eosinophilic-myalgia syndrome, eosinophilic fasciitis, chemical induced fibrosis, amyloidosis, carcinoid syndrome, calciphylaxis, porphyria cutanea tarda17,18 (Table 4).

Pathogenesis of NSF

The pathogenesis of NSF is unclear and some authors speculate that circulating fibrocyte that is postitive for CD34 and procollagen may play a role in the fibrosing process17,19. From the literatures, most of the patients of NSF have some proinflammatory condition, such as vascular thromboembolic events, constructive vascular procedures, or transplantation which precipitates to tissue injury7,20,21. Circulating fibrocyte which
involved in wound healing is thus recruited from the bone marrow and deposits in the dermis where they release cytokines and inducing tissue fibrosis. Recently, Gd was found in the biopsy specimens in patients of NSF using electron-dispersion spectroscopy and this further supports their association.\textsuperscript{22,23}

**Treatment and Prevention**

The treatments of NSF includes oral steroids, topical dovonex, extracorporeal photopheresis, plasmapheresis, cytoxan, thalidomide, UV therapy (PUVA), physical therapy (swimming, deep massage), pentoxifylline, high dose IVIG, and renal transplantation.\textsuperscript{124-29} Since the pathogenesis is not fully understood yet, therapeutic measures with proven efficacy are deficient to date. Complete spontaneous remission with ongoing kidney disease has not yet been reported. Some had improvement or remission after recovered renal function. Khurana et al. reported that only less than 5% has rapid and fulminant disease course causing death as the results of restriction of ventilation, accidental fall, and clotting complications.\textsuperscript{9} However there were other authors observed a mortality rate of 28–67%.\textsuperscript{5,7,8}

As there is no effective treatment at the presence, prevention of NSF becomes mandatory. Food and Drug Administration (FDA) issued a warning in June 2006 on the use of Gd-containing contrast agents in patients with chronic renal failure (GFR < 30 ml/min/1.73m\(^2\)) and acute kidney injury (Table 5). It advises on avoidance of Gd-containing contrast agent in this group of patient unless the examination is unable to be replaced by non-contrast MRI or other image studies such as conventional iodinated contrast-enhanced CT. Prompt dialysis after exposure in patients with hemodialysis may be helpful as the average excretory rates of Gd are 78%, 96% and 99% respectively in the first to the third hemodialysis sessions.\textsuperscript{30,31} The use of Gd-containing contrast medium should not exceed the recommended dose and it should be sufficient time to allow the elimination of the agent before readministration of the agent.\textsuperscript{32}

**Conclusions**

NSF is a scleroderma-like skin disease with systemic involvement that might be triggered by the exposure to Gd-containing MRI contrast agents. Patients with either acute or chronic renal failure are especially at risk of the disease. MRI is a common examination for various conditions. Careful evaluation of the renal function should be done in each patient before performing contrasted MRI/MRA. Alternative imaging method should be considered in renal insufficient patients concerning the increasing risk for NSF. Prompt hemodialysis is recommended in patients receiving dialysis after the drug exposure. As there is no effective treatment available, emphasis on the prevention is mandatory.

**Table 5. Prevention of nephrogenic systemic fibrosis**

<table>
<thead>
<tr>
<th>High risk groups</th>
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<tbody>
<tr>
<td>Acute or chronic kidney disease (GFR &lt; 30 ml/min/1.73m(^2))</td>
<td></td>
</tr>
<tr>
<td>Hepatorenal syndrome</td>
<td></td>
</tr>
<tr>
<td>Renal insufficiency in perioperative liver transplantation period</td>
<td></td>
</tr>
<tr>
<td>FDA recommendation on GBCA use</td>
<td></td>
</tr>
<tr>
<td>Screen all patients for renal dysfunction.</td>
<td></td>
</tr>
<tr>
<td>Avoid GBCA in high risk group</td>
<td></td>
</tr>
<tr>
<td>Do not exceed the dose recommended in GBCA product label.</td>
<td></td>
</tr>
<tr>
<td>Allow sufficient time for elimination for GBCA before readadministration.</td>
<td></td>
</tr>
<tr>
<td>Consider prompt hemodialysis post GBCA exposure in patient receiving dialysis.</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: GFR, glomerular filtration rate; FDA, Food and Drug Administration; GBCA, Gadolinium-based contrast agents.

**References**


腎因性全身性纖維化症
使用含钆之核磁共振顯影劑的新危機

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摘 要

腎因性全身性纖維化症（Nephrogenic systemic fibrosis, NSF），即之前的腎因性皮膚纖維化症（Nephrogenic fibrosis dermopathy）為一種全新的病症。其自1997年首次被發現後才陸續被報導。此病之表現主要為類硬皮症般的皮膚纖維化，且可能合併心、肺、肝、橫紋肌等全身器官的病變。NSF幾乎只發生在於腎臟功能衰竭的病人，並可能和使用含钆 (Gadolinium) 的核磁共振顯影劑有關，NSF的個案中以使用 Gadodiamide (Omniscan®) 之後發病最常被報導。此病的標準診斷方式是深層皮膚切片，病理組織學上會顯現 CD 34/procollagen 雙陽性的纖細胞，較獨特的是它沒有發炎現象。在鑑別診斷方面，需要與蜂窩性組織炎、藥物反應，硬皮症，厚皮性黏液水腫及全身性硬化症等疾病等作區分。由於NSF的致病機轉至今不明，加上沒有經證實有效的治療方式，故此病的預防甚為重要。美國食品及藥物管理局 (FDA) 建議腎衰竭的病人，無論是急性或慢性，凡腎絲球濾過率小於 30 ml/min/1.73m² 者要避免使用含钆之核磁共振顯影劑，除非此檢查極其重要且無法被取代。同時使用含钆顯影劑時，其最大劑量不可超出藥廠建議劑量，並且兩次檢查之間要有充裕的時間讓含钆顯影劑排出體外。在透析病人使用含钆顯影劑後，建議盡快安排血液透析以利钆的排出。