Nephrogenic Systemic Fibrosis

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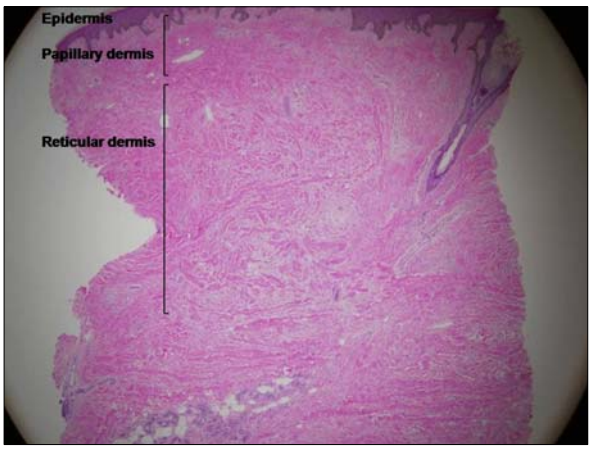
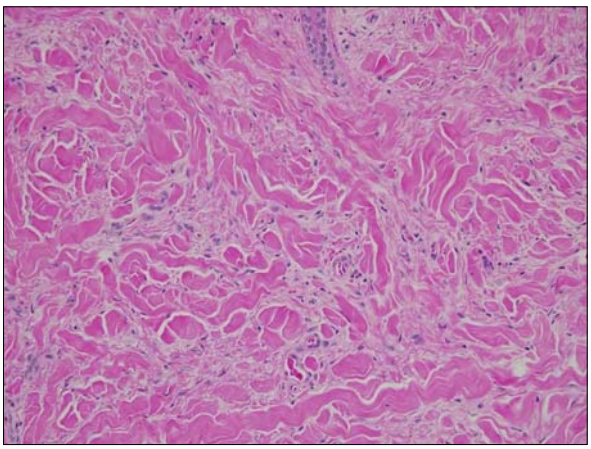
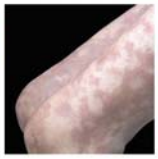
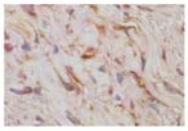




Definition

Nephrogenic systemic fibrosis (NSF)
recently identified fibrosing disorder
seen only in patients with kidney failure

1) Thickening / hardening of the skin overlying extremities and trunk
2) Marked expansion / fibrosis of the dermis a/w CD34(+) fibrocytes

History

First cases (1997~2000)
- severe skin induration in HD patients, KT failure patients
- Scleromyxedema (?)

Subsequent cases

	Past	Present
Patients	HD	PD, KT (allograft dysfunction), CKD (IV, V), AKI (F, dialysis)
Lesion	skin	Muscle, fascia Lung, heart
Terminology	Dialysis-associated systemic sclerosis Nephrogenic fibrosing dermatopathy	Nephrogenic systemic fibrosis

Health report timeline – June 2006.


U.S. Food and Drug Administration
CENTER FOR DRUG EVALUATION AND RESEARCH

Public Health Advisory
Gadolinium-containing Contrast Agents for Magnetic Resonance Imaging (MRI):
Omniscan, OptiMARK, Magnevist, ProHance, and MultiHance

None of these drugs are FDA approved for MRA.
The dose of gadolinium-containing contrast agent given to patients undergoing an MRA test is often higher (up to three times) than the approved dose for MRI.

Scientists first identified NSF/NFD in 1997 and the cause of NSF/NFD is unknown.
Worldwide, there are approximately 200 reports of NSF/NFD.

The patients developed NSF/SFD within 3 months (range 2 weeks to 3 months) after receiving the gadolinium-containing contrast agent.

Health report timeline – December 2006.


U.S. Food and Drug Administration
CENTER FOR DRUG EVALUATION AND RESEARCH

Public Health Advisory
Update on Magnetic Resonance Imaging (MRI) Contrast Agents
Containing Gadolinium and Nephrogenic Fibrosing Dermopathy

NSF/NFD began from 2 days to 18 months after exposure to the contrast agent.

- Patients with moderate to end-stage kidney disease may get NSF/NFD.

- Patients who believe they may have NSF/NFD should contact their doctor.

- When a patient with moderate to end-stage kidney disease needs an imaging study, select imaging methods other than MRI or MRA with a gadolinium-based contrast agent


GE Healthcare

Epidemiology

No predilection to NSF
by gender, age, race,
etiology of kidney disease, duration of renal failure

PD > HD
attack rate after exposure to gadolinium
4.6 cases/100 PD patients vs. 0.61 cases/100 HD patients

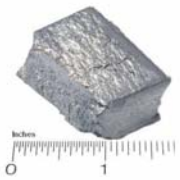
Gd removal rate : 73-78% - 93-96% - 99% in 1st, 2nd, 3rd hemodialysis session

Time of dialysis initiation to diagnosis of NSF
2 months ~ 15 years of series of 12 cases

Clustering of Cases, reported in US, Europe, Asia
underdiagnosed by clinicians who are unfamiliar with the condition

Etiology – Gadolinium

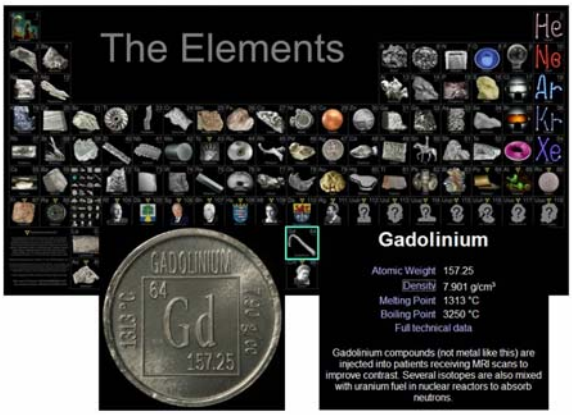
Gadolinium (Gd)



- Atomic No 64, rare earth (Lanthanide)
- Free Gd^{3+}, poorly soluble, highly toxic
- Tissue deposition (residence 4-11 months)

- administered as a chelate (bound to large organic molecule)
- non-tissue-specific, nonionic, hyperosmolal (650 mOsm/kg)
- excreted unchanged almost exclusively by the kidney

- half-life 1.3 hrs in healthy volunteers
  10 hrs in pts with eGFR 20-40 mL/min
  34 hrs in pts with eGFR < 20 mL/min (ESRD)
  1.9-2.6 hrs after HD



Etiology – Gadolinium

Free gadolinium (Gd^{3+})

- precipitate with anions (esp. ESRD) → tissue deposition
- bound to large molecule (chelate) → prevent dissociation

- disrupt Ca^{2+} passage in nerve and muscle cells
- interfere with intracellular enz. & cell memb. through transmetallation
  → replace endogenous metals (Zn, Cu)
- precipitate with phosphate as a cofactor in NSF development

Etiology – Gadolinium

FDA approved Ga-chelates

Brand name	Generic name	Empirical formula	Molecular weight (mOsm/kgH_2O)	NSF reported (cases)
Omniscan	gadodiamide	$C_{16}H_{28}GdN_5O_8 \cdot xH_2O$	789	283
Magnevist	gadopentetate	$C_{28}H_{54}GdN_5O_{20}$	1960	125
OptiMARK	gadoversetamide	$C_{26}H_{54}N_9O_{10}Gd$	1110	20
MultiHance	gadobenate	$C_{22}H_{29}GdN_2O_{11} \cdot 2C_7H_{17}NO_5$	1970	10
ProHANCE	gadoteridol	$C_{17}H_{29}N_4O_7Gd$	630	9

IV injection → vascular space → diffusion into extravascular tissue

Risk after Gd exposure in ESRD pts.
- 2.5~5.0%
- dose-dependent (double dose > single dose, OR 22.3)

Pathogenesis

- not well understood
- Tissue injury reaction – myofibroblasts in tissue – fibrogenic cytokines
  → cascade of events similar to wound healing

1. Activation of TGF-β-1 pathway
   - marked increase in TGF-β-1 mRNA in skin / fascia
     in association with large number of $CD68^+$/factor $XIIIa^+$ dendritic cells
   - Vicious cycle of TGF-β-1 and dendritic cells

2. Increased circulating fibrocytes
   - Direct stimulation of BM to produce CD34(+) circulating fibrocytes
   - Recruited circulating fibrocytes, rather than resident dendritic cells

Clinical manifestations

- Skin involvement in **ALL** patients & Systemic involvement in **SOME**.
- Latent period 2-4 weeks (2 days – 18 months)

- Chronic and unremitting course
  : 28% no improvement, 20% modest improvement, 28% died
  : More severe, rapid progression of skin lesion → poor prognosis & death

- Fulminant course (5%)
  : with flexion contracture & LOM
  : maybe due to repeated administrations of gadolinium

- Improvement or Remission
  : with recovery of renal function (clearance) – slow or stop progression
  : Less than 40%, complete remission following cessation of dialysis

Clinical manifestations

1. Skin involvement
   - Symmetrical, bilateral, fibrotic indurated papules, plaques, subcutaneous nodules
   - First ankles, lower legs, feet, hands
     → proximally thighs, forearms
   - edema
     → skin thickening, hardening
     → cobblestone, woody, peau d'orange app.
   - pruritus, sharp pain, burning sensation, LOM (flexibility loss)
   - Rarely in trunk, buttocks, head-sparing, No livedo reticularis

Clinical manifestations

2. Systemic involvement
   - Muscle induration
     : normal or slightly reduced strength
   - Joint contractures & LOM
     : without evidence of synovitis, arthritis
   - Fibrosis in lungs, diaphragm, myocardium, pericardium, pleura, dura mater
   - Yellow asymptomatic scleral plaques

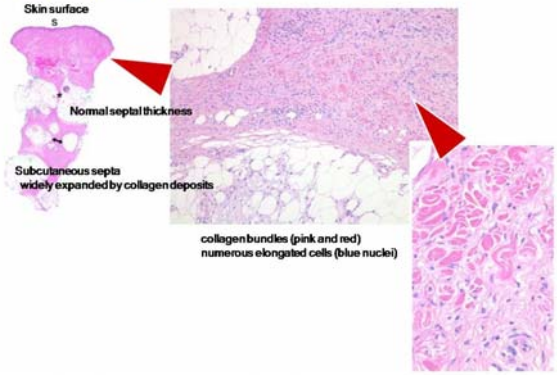
Diagnosis

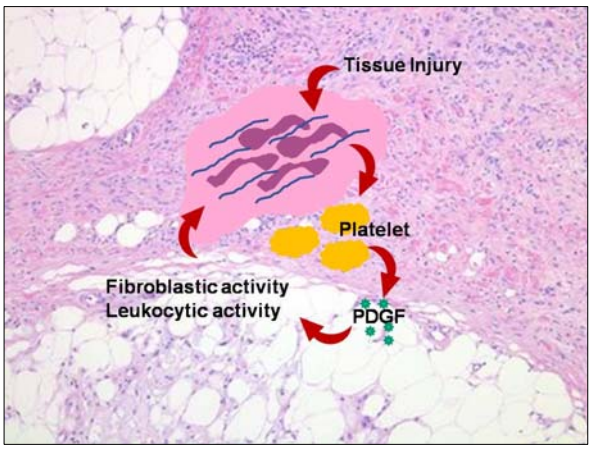
Clinical Hx
- Recent MR imaging procedure using Gadolinium
- Advanced chronic kidney disease

Histopathologic examination
- Deep incisional or punch biopsy
- Repeat biopsy

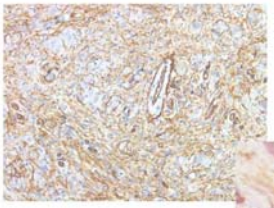
Laboratory tests
- Non-specific for NSF
- consistent with chronic inflammation

Pathologic findings

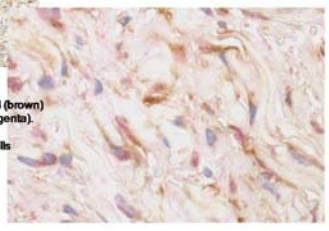




Pathologic findings



Dense network of CD34(+) dendritic processes (brown) among thickened collagen bundles (magenta)



Abundant elongated cells that express the cell surface antigen CD34 (brown) and produce the protein procollagen I (magenta).

This combination of findings identifies the cells as circulating fibrocytes.

Differential Diagnosis

Vs. Systemic sclerosis (scleroderma)
- Raynaud's phenomenon (-)
- ANA (-), Anticentromere or antiDNA topoisomerase I (Scl-70) Ab (-)

Vs. Scleromyxedema
- head-sparing
- monoclonal gammopathy – IgG lambda paraprotein (-)

Vs. Eosinophilic fasciitis
- frequent involvement in hands / feet
- eosinophilia (-), eosinophilic infiltration (-)

Systemic sclerosis

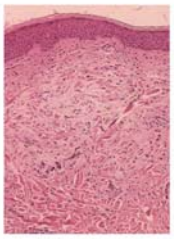
Raynaud's phenomenon

Multiple telangiectasia

Microstomy

Thick collagen bundles in the dermis.
Inflammation is absent. (H&E)

Scleromyxedema

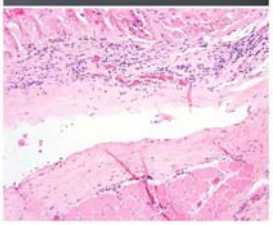


Fibroblast proliferation in the corium
with swollen, pushed aside collagen fibers and atrophic skin adnexa.
Minimal inflammatory infiltrates. (H+E, x 150).
Alcian blue staining showing mucin deposits throughout the corium (x 150).

Eosinophilic fasciitis

Symmetric, thick, sclerotic skin with a subtle yellow-orange hue, was present on the forearms, the upper arms, and thighs.

A groove sign was visible between the triceps and biceps of the medial upper arm.



1) foci of sclerosis at the dermosubcutaneous junction
2) thick subcutaneous septa and fascia
3) Perivascular and interstitial infiltrate of
lymphocytes, histiocytes, plasma cells, eosinophils
→ fibrosis, hyalinization of collagen
→ extends into the fascia and skeletal muscle.

Epidermis shows no pathologic changes

Treatment

No proven therapy
- improving renal function or the disease process
- intensive physical therapy to prevent or reverse joint contracture

Kidney transplantation to recover renal clearance, unproven efficacy

Extracorporeal photopheresis (ECP, photochemotherapy)
- extracorporeal exposure of peripheral blood mononuclear cells to photoactivated 8-methoxypsolaren (8~16 cycles at 2~4 week intervals)
→ induction of monocyte-derived TNF-α
→ suppress collagen synthesis, enhance collagenase production

UltravioletA (UV-A1) phototherapy – inhibit progollagen synthesis in skin

Plasmapheresis (1~3, five-day courses)

Photodynamic therapy, pentoxifylline, imatinib, Na thiosulfate, high dose IVIG

Topical, intralesional, oral glucocorticoid, cyclophosphamide

Prevention

FDA recommendations – avoidance of gadolinium

- Gadolinium-containing contrast agents, especially at high doses, should be used only if clearly necessary. Gadolinium should be avoided in patients with a diagnosis or clinical suspicion of NSF.
- Although there are no data that support the following approach, it may be prudent to institute prompt hemodialysis after the imaging study is completed if gadolinium is given

FDA definition

- Advanced kidney failure – requirement for dialysis or eGFR < 15 mL/min
- Risk group - acute or chronic severe renal insufficiency (eGFR < 30 mL/min)
  - acute renal insufficiency due to hepatorenal syndrome
  - perioperative liver transplantation period

Prevention

CKD stage IV-V (advanced kidney failure, eGFR < 30 mL/min)

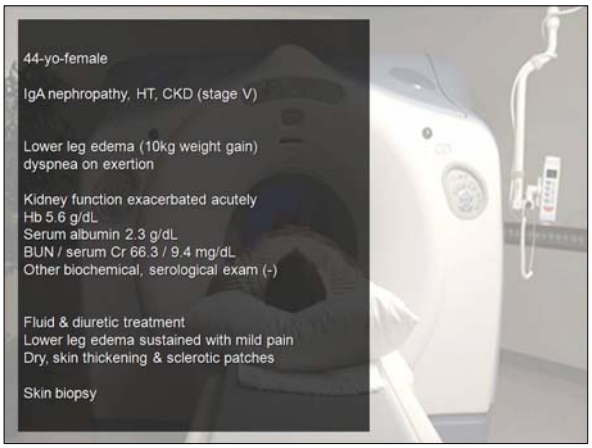
- almost all cases of NSF reported
- 2.5~5% incidence after gadolinium imaging study
- eGFR from SCr ONLY in patients with stable value – GFR overestimation
- Prefer the risk of radiocontrast nephropathy with iodinated contrast media

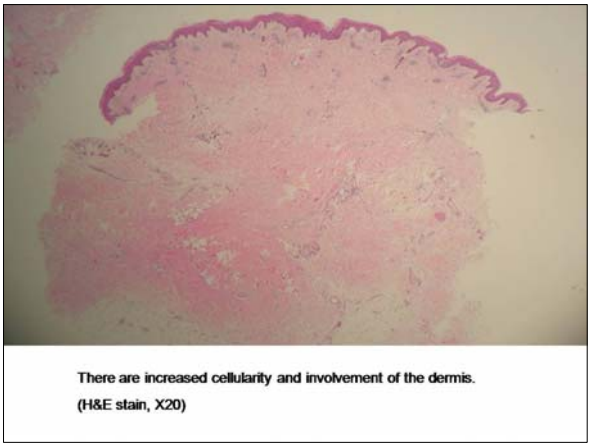
CKD stage III (eGFR 30~60 mL/min)

- 2 cases reported after repeated gadolinium exposure in the setting of AKI
- Prefer the risk of radiocontrast nephropathy, rarely a/c irreversible injury

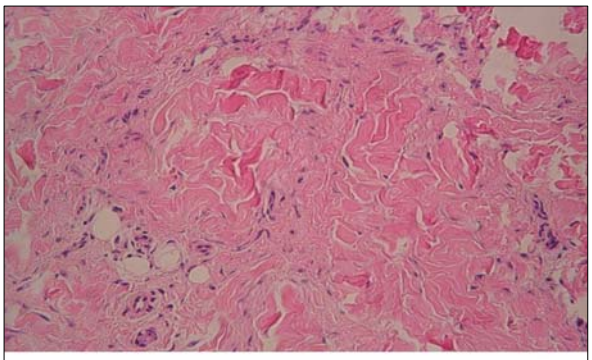
If gadolinium must be given…

1. Informed consent of benefits, risks, and alternatives
2. Other gadolinium preparations with low-incidence, low dose (<1/2 standard dose)
3. Hemodialysis immediately after gadolinium exposure
   1) Maintenance HD pts – imaging study just before next dialysis session, or additional dialysis session just after imaging study
   2) Maintenance PD pts – HD after exposure via temporary HD catheter, or more frequent PD cycles for >48hr after exposure with no periods of dry abdomen
   3) Pre-dialysis Pts
      - eGFR < 30 mL/min – vascular access (+) – HD ASAP
      - eGFR < 15 mL/min – vascular access (-) – HD initiation
      - eGFR 15-30 mL/min – vascular access (-) – HD (?), (catheter risk)
      - eGFR 30-60 mL/min – observation

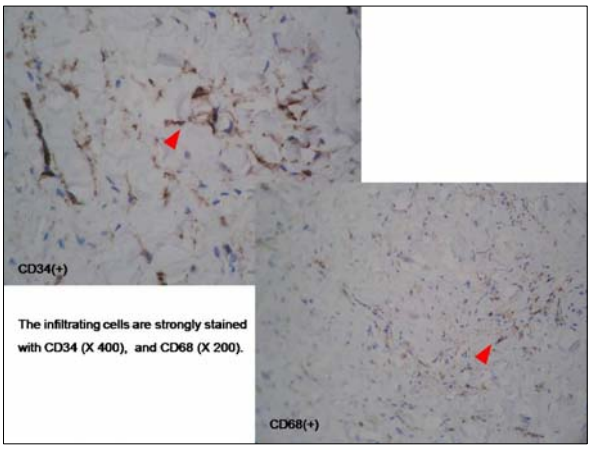




There are increased cellularity and involvement of the dermis.
(H&E stain, X20)



There are many atypical collagen fibers and increased mucin in deep dermis.
(H&E stain, X200)



The infiltrating cells are strongly stained with CD34 (X 400), and CD68 (X 200).

65-yo male

DM, HT, CKD (stage V)

dizziness, decreased mentality
cerebrovascular accident suspected

Non-specific interval changes in diagnostic work-up

MRI & MRA - MCA infarction
Conservative management and physiotherapy

Three weeks later,
Arm and leg erythema, edema exacerbated
Limitation of motion on elbow and both ankles

Skin biopsy

CKD (stage V)

MRI & MRA (gadolinium enhance)

Three weeks later
Erythema, edema
LOM

Skin biopsy

44-yo-female

IgA nephropathy, HT, CKD (stage V)

Lower leg edema (10kg weight gain)
dyspnea on exertion

Kidney function exacerbated acutely
Hb 5.6 g/dL
Serum albumin 2.3 g/dL
BUN / serum Cr 66.3 / 9.4 mg/dL
Other biochemical, serological exam (-)

Fluid & diuretic treatment
Lower leg edema sustained with mild pain
Dry, skin thickening & sclerotic patches

Skin biopsy

CKD (stage V)

No history of exposure to gadolinium

Non-specific latent peroid

Skin edema
Skin thickening

Skin biopsy

Nobody knows, BUT everybody knows…

Diagnosis of NSF
- History of recent MR imaging (Gadolinium) in advanced CKD patients
- Histopathologic examination – skin biopsy

Prevention of NSF
- Risk estimation

- CKD IV-V : absolute avoidance of gadolinium
- CKD III : relative avoidance of gadolinium

- If gadolinium must be given...
  Use other gadolinium preparations with low-incidence, low dose
  Hemodialysis immediately after gadolinium exposure