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GADOLINIUM LITIGATION

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NEPHROGENIC SYSTEMIC FIBROSIS

A Man-made Disease

- First described in 1997 in patients with end stage renal disease.
- Characterized by skin changes that mainly affect the limbs and trunk.
- Can progress to cause flexion contracture of joints.
- Old terminology: Nephrogenic Fibrosing Dermopathy (NFD).

Nephrogenic Systemic Fibrosis

- The fibrotic changes may also affect other organs such as muscles, heart, liver and lungs.
- Can lead to serious physical disability or even death.
- No consistently effective treatment.
- Disease too new for physicians to know how to treat it or to give a prognosis.

People with NSF have no idea what the future holds, because doctors do not know enough to tell them what to expect.

FIRST PUBLISHED REPORT

Scleromyxoedema-like cutaneous disease in renal dialysis patients.

Cowper et al. The Lancet 16 September 2000

Nephrogenic Fibrosing Dermopathy/Nephrogenic Systemic Fibrosis: Report of a New Case with Literature Review

Daram SR. Amer J Kidn Dis. (Oct. 2005) 46;4:754-759

RESEARCH LETTERS

We thank Karen Brown, Meira Bruce, Colan McCann, David Pemberton, Diane Ritchie, and the Scottish Blood Transfusion Service. The project is funded by the Department of Health.

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- 5 Goldman W, Huzar N, Smith G, Foster J, Hope J. PrP genotypes and agent effects in scrapie: change in clinic interaction with different isolates of agent in sheep, a natural host of scrapie. *J Gen Virol* 1994; 75: 989-95.

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Scleromyxoedema-like cutaneous diseases in renal-dialysis patients

Shawn E Cowper, Howard S Robin, Steven M Steinberg, Lyndon D Sai, Samardeep Gupta, Philip E LeBoit

15 renal dialysis patients have been identified with a skin condition characterized by thickening and hardening of the skin of the extremities and an increase in dermal fibroblast-like cells associated with collagen remodelling and mucin deposition. The disease closely resembles scleromyxoedema, yet has significant enough clinical and histopathological differences to warrant its designation as a new clinicopathological entity.

Since March, 1997, we have identified 15 renal-dialysis patients in California, Michigan, Ohio, and Mississippi,



Figure 1: A 31-year-old woman with a haemodialysis-associated cutaneous fibrosing disorder.



FDA: SERIOUS AND SOMETIMES FATAL NEPHROGENIC SYSTEMIC FIBROSIS/NEPHROGENIC FIBROSING DERMOPATHY

- As of December 21, 2006, the FDA had received reports of 90 patients in the U.S. with kidney disease who developed NSF/NFD after they had an MRI or MRA with a gadolinium-based contrast solution.
- A skin biopsy is necessary to make a definitive diagnosis.

FDA December 2006:

- Onset began from 2 days to 18 months
- Worldwide, about 215 patients with NSF/NFD have been reported.
- Of these reports, the medical histories of 75 of these patients were reviewed in detail, and all of the patients had received a gadolinium-based contrast agent for an MRI or MRA.

Under reporting

- Early reports of adverse events to FDA usually represent between 1% and 10% of the real number of adverse events.
- Therefore the real number of cases in the U.S. as of December 2006 is probably between 900 and 9,000.

Epidemiology

- Affects both sexes equally
- Age range reported from 8 to 87 years
- Occurs worldwide in all races

WHERE DOES GADOLINIUM COME FROM?

- Gadolinium occurs naturally and in the earth's surface.
- It is a metal, a basic chemical element.
- Gadolinium does not occur naturally in the human body.
- The only way it gets into the body is injection of a contrast solution containing it.
- Manufacturers of contrast solutions cannot blame people for contributing to causing NSF.

Gadolinium is detectable within the tissue of patients with nephrogenic systemic fibrosis.

High WA, Cowper SE et al. J Am Acad Dermatol 2007;56:21-6

Science of Gadolinium Contrast Solutions

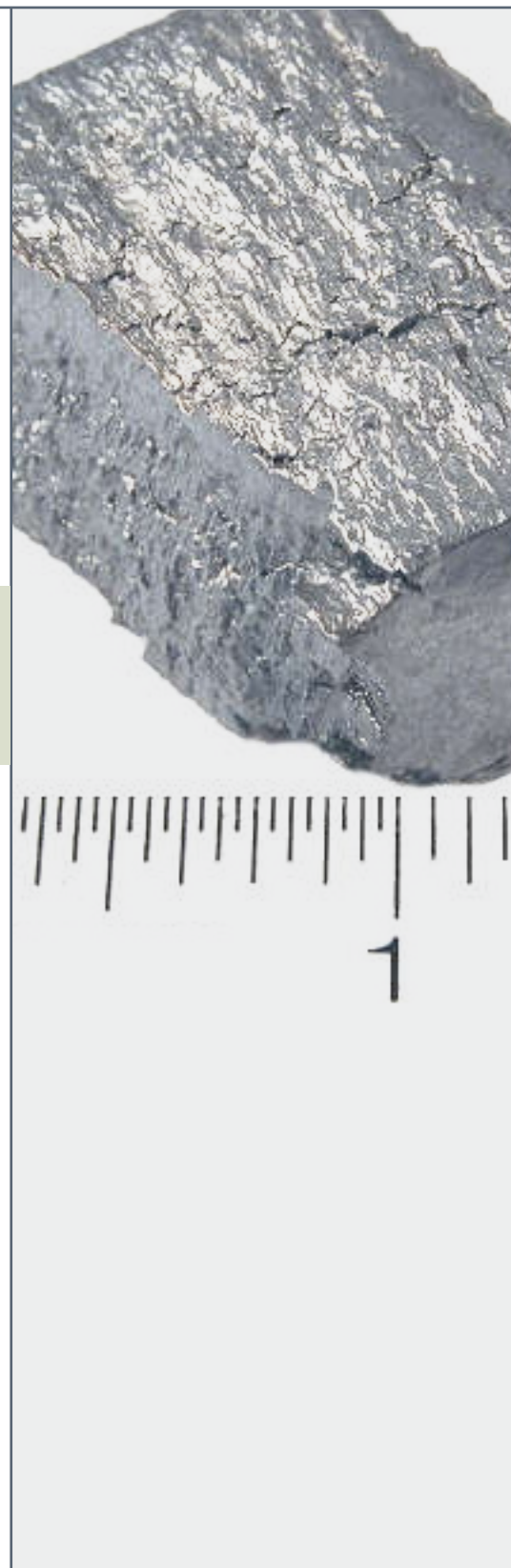
The Number of enhanced MRI's per year.

- 25-30% of MRI's are enhanced with contrast solution.
- About 23 million enhanced MRI's worldwide in 2005.
- About 10 million enhanced MRI's in U.S. in 2005.

GADOLINIUM IN THE BODY

- Gadolinium is not absorbed, breathed, eaten, or drunk.
- There is no background rate.
- Free gadolinium (Gd^{3+}) is a highly poisonous heavy metal, and this has been known for many years.

Shao-Pow et al. MR Contrast Agents - Physical and Pharmacologic Basics. J MAG RES IMAGING 25:884-899 (2007)



Because gadolinium is poisonous, it has to be coated to keep it from coming in contact with human tissue when use as MRI contrast material.

This coating process is called chelation.

The gadolinium is said to be “chelated” when chemicals are attached to it to insulate it from contact while in the body.

GADOLINIUM CONTRAST SOLUTIONS

- Eliminated from the body by kidneys.
- Person with normal kidney function should eliminate it in 2-4 hours.
- It can take 30 hours or more for a person with kidney impairment.

Gadolinium Contrast Agents

The contrast solution is not safe if the chelate coating is lost, and this is what happens over time if kidneys are not functioning properly.

PUBLISHED IN A RADIOLOGY JOURNAL IN 1994:

“It seems reasonable, however, to suggest caution in the use of any of these agents in patients with seriously impaired renal function in which circumstances the material is retained for a prolonged period.”

Dawson P, Gadolinium Chelate MR Contrast Agents (Editorial) Clin Radiol (1994) 49:439-442.



APRIL 2007 REPORT FROM A RETAINED EXPERT CON- CLUDES:

Free gadolinium is highly toxic.

- Animal studies done before product put on market show:
 - spleen degeneration,
 - necrosis of the liver, and
 - variety of blood disorders.
- The power of free gadolinium in the body to cause injury is well-known as shown in fundamental biological studies.
- The result of this type of injury, classically, is inflammation and fibrosis.

TRANSMETALATION

Transmetalation is the word used to describe the process where chelate atoms break their chemical bond with gadolinium and attach to other metal atoms in blood, such as iron. It is crucially important for the chelates to be strongly attached to gadolinium to avoid its toxic effects. The effects of transmetalation increase with time, so the longer the contrast solution remains in the body, the more transmetalization occurs, and eventually the gadolinium is free to invade body tissue.

GADOLINIUM

Case Selection and Rejection Criteria

- Severity of disease is not necessarily shown in photos, so don't judge the case from pictures.
- You won't really understand what those affected by NSF live with until you shake hands with one of them.

How is the diagnosis made?

Definitive diagnosis of NFD/NSF is made by full-thickness skin biopsy at the involved site.

Weiss et al., Nature Clinical Practice Nephrology (2007) 3, 111-115

Punch biopsy tools

These come in a variety of sizes. Family practice physicians use them routinely, but some do not go deeper than 5 mm and refer to dermatologist for deeper penetration.

Histopathologic Features

Specimen shows markedly increase cellularity with spindle-shaped fibrocytes and mucin with thickened collagen bundles that infiltrate deeply, extending into and widening the septa of the subcutaneous fat.



WHAT CASES TO TAKE?

- If NSF/NFD is confirmed by biopsy, take the case.
- If NSF/NFD is not confirmed by biopsy, do not take the case, until and unless it is confirmed.
- Traditional approach of getting medical records and having an expert review them will not work.
- Clients need to be told up front that there is no provable case without positive biopsy.
- Consider finding a physician who will do punch biopsies.

MANUFACTURERS OF GADOLINIUM CONTRAST SOLUTIONS

Five gadolinium contrast solutions are approved for sale in the US:

1. Omniscan (GE)
2. Magnevist (Bayer)
3. OptiMARK (Mallinckrodt/Tyco)
4. MultiHance (Bracco)
5. ProHance (Bracco)

FDA May 23, 2007

Reports of NSF following administration of gadolinium solutions show the risk of NSF by brand of solution used is:

1. Omniscan by GE (highest risk)
2. Magnevist by Bayer (second highest risk)*
3. OptiMARK by Tyco (third highest risk)

There are no reported cases of NSF with ProHance or MultiHance alone (both by Bracco)

*Bayer rank above Tyco might be attributable to higher sales for Bayer's Magnevist than Tyco's OptiMARK, and actual risk for Bayer product might be significantly lower than Tyco or GE.