



## Nephrogenic Systemic Fibrosis

- Nephrogenic systemic fibrosis is a newly discovered disease that has been associated with the use of gadolinium-based MRI contrast agents in patients with severe renal disease, most commonly those on dialysis
- If the patient has risk factors for kidney disease (> 60 years, diabetes, systemic lupus erythematosus, history of renal disease, multiple myeloma), a BUN/creatinine must be performed within 1 month of examination
- Consultation with a radiologist is suggested before administering Gd contrast agents to a pediatric patient or a patient with a eGFR of <60 ml/min/m<sup>2</sup>
- It is advisable that no patient with an eGFR of <30 ml/min/m<sup>2</sup> (Stage 4 or 5 kidney disease) should receive Gd contrast agents unless the benefits are deemed to outweigh the risks

Nephrogenic systemic fibrosis (NSF) is a new disease, first observed in 1997 and described in 2000, which occurs in patients with moderate to severe kidney disease, most commonly those on dialysis. The association between NSF and gadolinium-based MRI contrast agents was first noted in 2006 among patients who were being treated in a dialysis center in Austria. By December 2006, over 210 cases of NSF had been reported to occur in patients who had received Gd contrast agents and the U.S. Food and Drug Administration (FDA) issued an advisory. Since then, many more cases have been identified. The prevalence of NSF in patients with stage 5 renal disease (Table 1) has been estimated to be 3-13%.

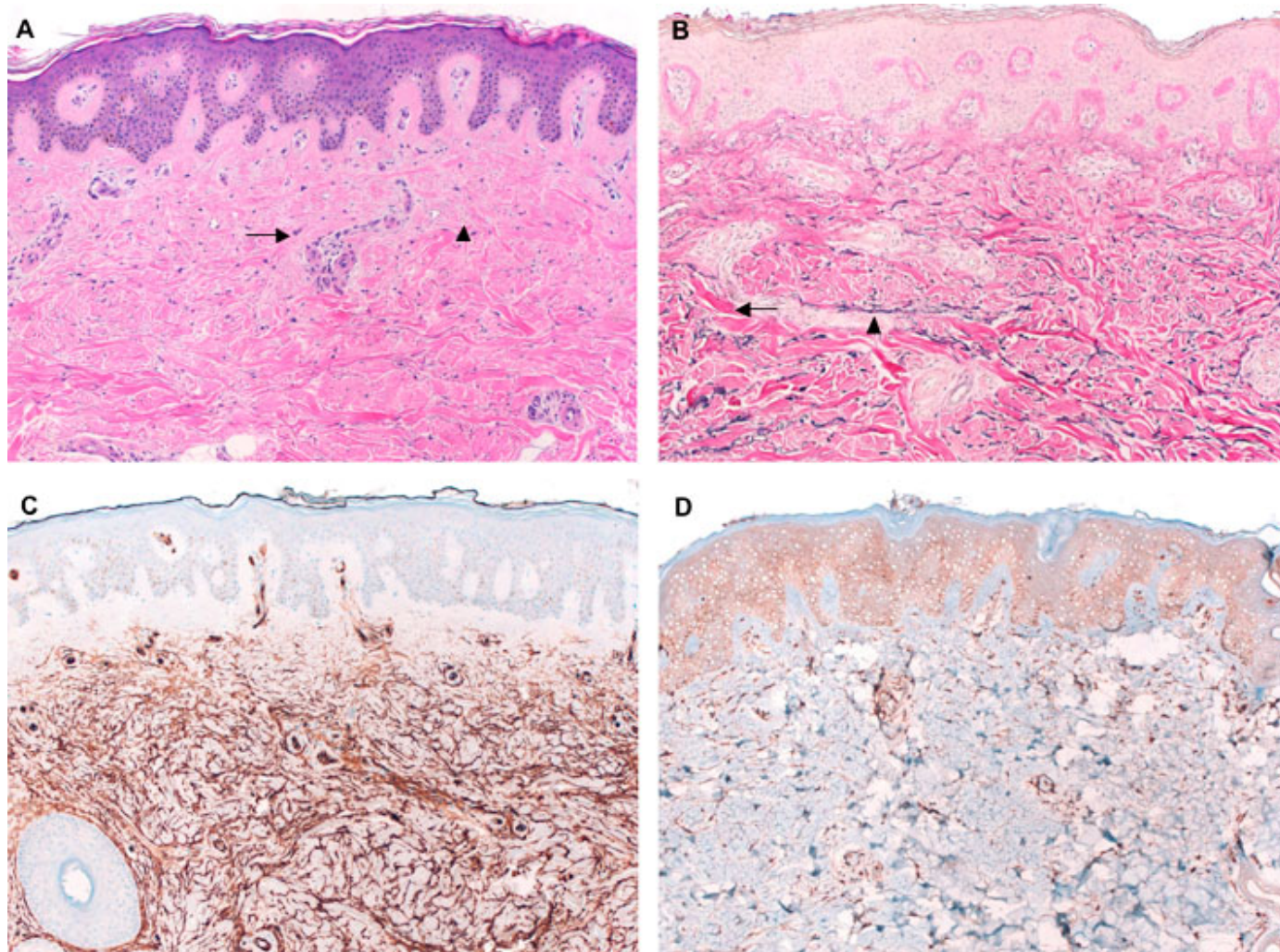
NSF is characterized by rapidly progressive skin hyperpigmentation, thickening, tethering to underlying fascia, and stiffening that can result in joint flexion contractures. It is painful, debilitating, and is associated with significantly increased mortality. Skin changes develop in the extremities, most commonly in the legs, and progress over a period of days to weeks (Figure 1). Skin changes rarely affect the torso and do not affect the face. NSF has been found in patients of all ages with renal failure. Skin biopsies show increased numbers of dermal fibroblasts, increased deposits of mucin, and abnormal distribution of collagen bundles (Figure 2). The condition was first called nephrogenic fibrosing dermopathy (NFD) but its name was changed to NSF when it was recognized that the disease affected more than the skin. It is now known that fibrotic changes can occur in both cardiac and skeletal muscle, the genitourinary tract, lungs, diaphragm, and dura mater. NSF may stabilize, but rarely remits and there is no consistently effective therapy.

It is not yet proven that gadolinium is the causative agent. Nevertheless, the relative risk of developing NSF in a patient with severe renal failure after Gd contrast agent administration has been estimated to be more



**Figures 1.** Characteristic skin changes seen in a patient with NSF showing hyperpigmentation, skin thickening, and joint flexion contractures. Photographs courtesy of Jonathan Kay, M.D.

than ten-fold. Most cases have been observed in patients with Stage 5 renal failure (estimated glomerular filtration rate, eGFR, of <15 ml/min/m<sup>2</sup>; Table 1) who were being treated by hemodialysis



**Figure 2.** Histologic sections of affected skin on the lateral thigh reveal a modest proliferation in fibroblast-like cells (arrow) and mucin (blue-grey deposits, arrowhead) without associated inflammation within the superficial and deep dermis (H&E, 100x, panel A). A ver Hoeff's elastin stained section highlights the elongated elastic fibers (arrowhead) in close apposition to brightly eosinophilic dermal collagen bundles (arrow) (panel B). Immunohistochemical staining for CD-34 reveals strong positive staining of spindle-shaped dermal fibroblasts (panel C) with increased numbers of Factor XIII positive cells throughout the dermis (panel D). *Images courtesy of Rosalynn M. Nazarian, M.D.*

or peritoneal dialysis. About 10% of cases have occurred in patients with Stage 4 chronic kidney disease (eGFR, 15-30 ml/min/m<sup>2</sup>). Other clinical conditions that have been suggested to be associated with NSF include dependent edema, a history of deep vein thrombosis, a history of recent surgery (especially vascular surgery), hypothyroidism, erythropoietin treatment, elevated serum ionized calcium or serum phosphate, acidosis, and active inflammatory disease. Skin changes may develop as early as within a month of exposure to Gd contrast agents to as long as 39 months after exposure, with symptoms appearing more rapidly in patients who have received higher doses of Gd contrast agents.

Although the mechanism of the development of NSF is not known, there is speculation that the slow disassociation of gadolinium from the chelate and its deposition in tissues, an effect that is likely to be much more significant in a patient with renal failure, may contribute to its onset. For example, in a patient with

an eGFR of 2-10 mL/min/m<sup>2</sup>, the half life of Gd contrast agent is about 34 hr, compared to 70-90 minutes in a patient with normal renal function in whom >98% is removed from the body within 12 hours. The rate of dissociation varies among the five Gd contrast agents approved for use in the USA. It has been suggested that the risk of developing NSF appears to be greatest with the use of gadodiamide (Gd-DTPA-BMA, Omniscan™), which may be more likely to release free gadolinium than some other agents but NSF cases have been identified among patients who have been exposed to other more stable Gd contrast agents. Thus, at this time caution must be exercised with the use of all Gd contrast agents.

### Precautions

Because the association of NSF and gadolinium is newly discovered and data are still emerging on the pathophysiology of the disease and the extent of the problem, guidelines are still evolving concerning the

use of Gd contrast agents. The current MGH guidelines are summarized in Figure 3. It is recommended that BUN/creatinine blood work be performed in all patients with risk factors for kidney disease (Figure 3) before the administration of Gd contrast agents. In the case of patients >60 years and patients of all ages with conditions listed in Table 2, the blood work should have been performed within 1 month before receiving Gd contrast agents. All pediatric patients should be approved for Gd contrast agent injection by a pediatric radiologist before the injection is administered. Multihance™ will be used in all pediatric patients. Patients aged 18-60 with no known risk factors for kidney disease are not required to have a BUN/creatinine test.

Stage		EGFR (ml/min/m <sup>2</sup> )
1	Kidney Damage with normal to high eGFR	≤90
2	Kidney damage with mild loss in eGFR	60-90
3	Moderate renal disease	30-60
4	Severe renal disease	15-30
5	Renal failure	<15 or dialysis

### Guidelines for Usage of MRI Gadolinium Contrast Agents

The Radiology Department is able to calculate the eGFR from the documented creatinine value of all patients. If a patient has an eGFR of >60 ml/min/m<sup>2</sup>, Gd contrast agent can be administered if it is indicated for the imaging study. If the eGFR is between 30-60 ml/min/m<sup>2</sup>, a single dose (20 ml) of Gd contrast agent within 24 hours can be used. A higher dose can be given if there is a medical necessity and the risks discussed with the patient. If the eGFR is <30 ml/min/m<sup>2</sup>, no Gd contrast agent should be used unless there is urgent medical necessity, in which case it can be administered after obtaining informed consent.

In patients who are on dialysis, a non-contrast MRI or alternate imaging modality should be considered. The decision to proceed with a contrast enhanced MRI can be made if the radiologist and referring physician decide that the benefit to the patient outweighs the potential risk. If Gd contrast agent is administered, hemodialysis immediately following the MRI examination should be considered. Peritoneal dialysis is not adequate to remove gadolinium from the body. If contrast-enhanced MRI is absolutely necessary in at-risk patients, the lowest effective dose of Gd contrast agent should be used. At MGH, gadobenate (Gd-BOPTA, Multihance™) will be used in at-risk patients.

### Further Information

The understanding of NSF and its management is still evolving and it is to be expected that the MGH imaging guidelines will be updated in the future.

For further questions on NSF, please contact [Hani H. Abujudeh, M.D.](#), Director of Patient Safety Committee, MGH Department of Radiology (617-726-8366) or [Jonathan Kay, M.D.](#), (617-726-7938), Rheumatology, Allergy, and Immunology Division, MGH Rheumatology Unit.

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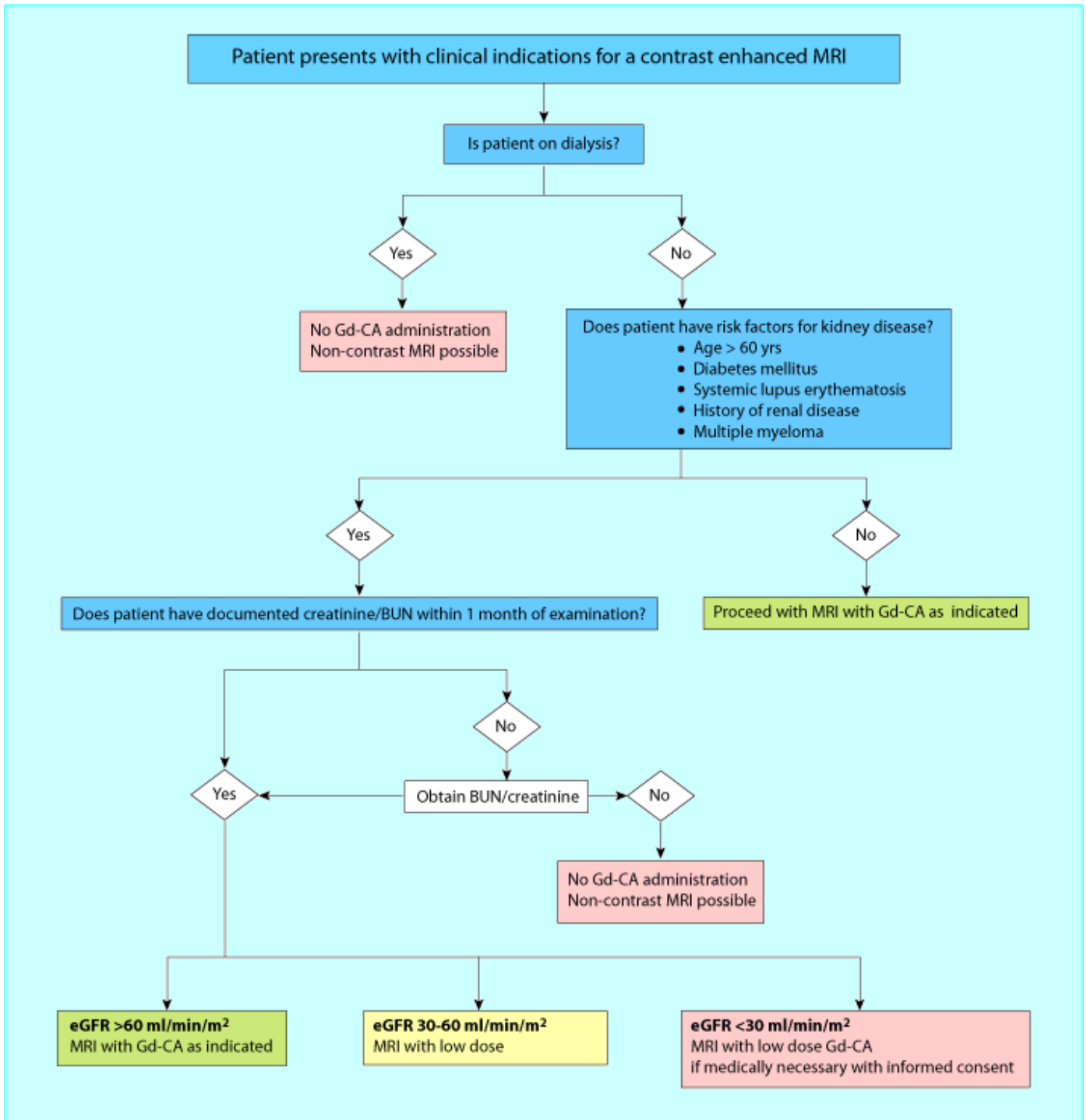


Figure 3. Guidelines for Usage of MRI Gadolinium Contrast Agents - Flow chart courtesy of Hani H. Abujudeh, M.D.

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