Factors relating to development of Nephrogenic Systemic Fibrosis following Gadolinium

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Objectives: Nephrogenic systemic fibrosis (NSF) is a recently described disorder, limited mainly to patients with advanced renal failure, in which patients develop skin thickening and fibrosis, sometimes extending throughout the connective tissues of the body. The FDA recently released an alert regarding the use of gadolinium-enhanced MRI in patients with advanced renal failure based on the association between NSF and high-dose gadodiamide administration in 25 European patients. The purpose of this study is to retrospectively investigate the relationship between NSF and gadolinium contrast administration at our institution.

Materials and Methods: Records from dermatopathology, nephrology, and MRI (January 1997 to present), were retrospectively reviewed to identify patients who developed NSF. The population of dialysis patients who underwent gadolinium (Gd) enhanced MRI but did not develop NSF were also studied. The correlation of NSF with Gd type, Gd dose and symptom onset, time between Gd administration and dialysis, bicarbonate and creatinine levels at the time of Gd administration, patient gender, and patient age were examined. Chi square analysis was used to determine the significance of differences in NSF incidence in different groups.

Results: Twenty-five patients were diagnosed with NSF by skin biopsy (Figure 1), including 14 female and 11 male patients, with a mean age of 50 (range = 13-82) years. All patients had either chronic (n = 22) or acute (n = 3) renal failure, and 17 were on dialysis before symptom onset. Two NSF patients were post liver transplant, and one was a month post pancreatic debridement. Eight NSF patients (33.3%) either had no prior Gd exposure (n = 5), remote Gd exposure > 11 months (n = 2), or limited data with no known exposure (n = 1).

A total of 274 patients with renal failure underwent Gd-enhanced MRI, of which 102 received single dose (<15mL) and 172 received double (30mL) or triple (45mL) dose (see Table 1). NSF was diagnosed in 17 patients after high dose ($\geq$ 30 mL) gadodiamide-enhanced MRI, and all patients had symptom onset within 4 months of contrast administration (mean = 53 days, range 15-102 days). Based on the 172 dialysis patients who underwent MR with high-dose gadodiamide (n = 131) or high dose Gd:DTPA (n = 41) but did not develop NSF, there was a 13% incidence of NSF with high-dose gadodiamide and 0% incidence following high-dose Gd:DTPA (p = 0.02). None of the 86 patients with renal failure receiving standard dose gadodiamide developed NSF, which was significantly different than the incidence of NSF in the high-dose cohort (p < 0.01).

Ten of the 17 NSF patients were on dialysis at the time of Gd injection, with a mean interval of 5.4 $\pm$ 2.9 days between Gd MRI and dialysis. In the 172 patients who received high dose Gd and did not develop NSF, the mean interval between Gd MRI and dialysis was a significantly shorter 1.4 $\pm$ 1.2 days (p = 0.006).

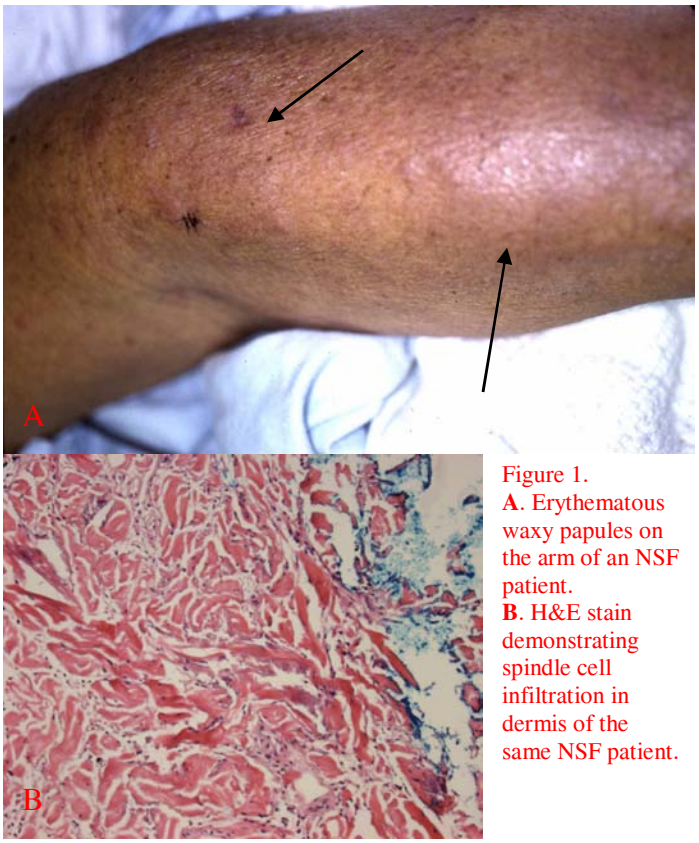

Figure 1.
A. Erythematous waxy papules on the arm of an NSF patient.
B. H&E stain demonstrating spindle cell infiltration in dermis of the same NSF patient.

Discussion: Our data demonstrated no cases of NSF associated with Gd:DTPA or single dose gadodiamide administration. There was a significantly increased incidence of NSF following high dose gadodiamide administration, however dialysis within 2 days of high dose contrast mitigated the risk of developing NSF.

Table 1. Incidence of NSF in patients receiving Gd contrast agents.

	High dose ($\geq$ 30 mL)			*Low dose ($\leq$ 15 mL)*		
	Total	NSF	%	Total	NSF	%
Gadodiamide	131	17	13	86	0	0
Gd:DTPA	41	0	0	16	0	0

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