Nephrogenic Systemic Fibrosis in Liver Disease: A Systematic Review

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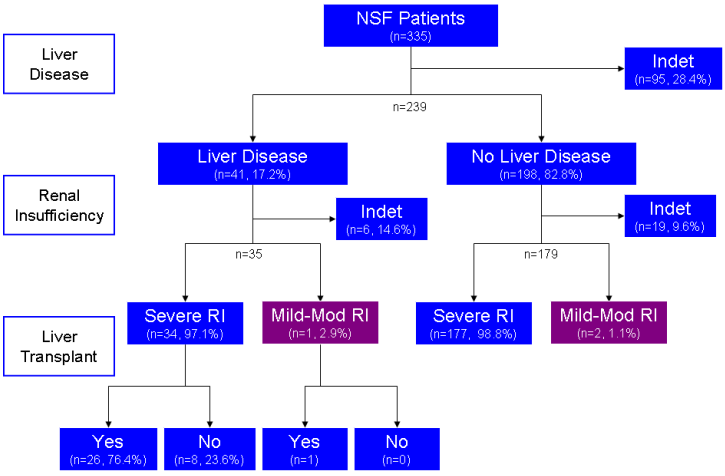
INTRODUCTION: Nephrogenic systemic fibrosis (NSF) is a disabling and potentially fatal disorder of widespread tissue fibrosis in patients with renal insufficiency.[1] It has also been described in patients with liver disease and concomitant renal insufficiency in the peri-operative liver transplantation period.[2] While its pathogenesis is unknown, recent published reports suggest a strong association of NSF with exposure to GBCAs.[3] Accordingly, in May 2007, the FDA issued a "black box warning", cautioning against the use of GBCAs in patients with "acute or chronic severe renal insufficiency (glomerular filtration rate [GFR] < 30 mL/min/1.73m^2), or acute renal insufficiency of *any severity* due to the hepato-renal syndrome or in the perioperative liver transplantation period."[4] This warning implies that liver disease confers a risk of NSF beyond that associated with renal insufficiency alone, and liver patients with only mild or moderate renal insufficiency (GFR ≥ 31 mL/min/1.73m^2) are also at risk for NSF. Introducing a new set of patients – those with liver disease – to closer scrutiny may have deleterious consequences since GBCA-enhanced MR imaging plays a centrol role in hepatocellular carcinoma screening in the pre-transplantion period and diagnosing post-operative transplantation complications. Our aim is to better characterize NSF risk in patients with liver disease, updating the findings of our systematic review of the literature accepted for oral presentation at the 2008 ISMRM meeting (Program #297).

METHODS: The English medical literature was reviewed in an attempt to identify all case reports, case series, and original research articles on NSF from September 2000, through August 2008. Articles were identified via PubMed searches of the terms "nephrogenic systemic fibrosis," "nephrogenic fibrosing dermopathy," and "dialysis-associated systemic fibrosis." Redundant cases were tallied only once; however, if the same patient was discussed in more than one article, novel information from the various articles was compiled to form a composite of that patient. The following data were collected for each unique patient: (A) demographics, (B) liver status (etiology of liver disease, presence of cirrhosis, history of hepatorenal syndrome, history of liver transplantation), (C) renal status (GFR, dialysis requirement, history of renal transplantation), and (D) GBCA exposure. In accordance with nephrology societies, severe renal insufficiency was defined as either a GFR < 30 mL/min/1.73m^2 or the necessity for dialysis. If there was insufficient information in the article to make a confident determination about a particular data category, then that item was marked "indeterminate". E-mail communication with corresponding authors was attempted whenever multiple cases were found from the same institution or city (to ensure that the cases were not redundant) or for clarification if we were unable to confidently determine the information within the various data categories. Two investigators independently evaluated each article. Discrepancies were arbitrated by a third review of the article and mutual agreement between the investigators.

RESULTS: A total of 303 articles from PubMed were reviewed, 112 of which detailed patient cases. From these, at least 335 unique patients were identified (mean age 49.6, range 8-87), though 99 additional patients (for a total of 434) may potentially be unique but, due to unclear reporting in the literature and inability to contact corresponding authors, are not included in the statistical analysis. Of the 335 unique NSF patients, liver disease was unable to be confidently assessed as being present or absent in 95 (28.4%) patients (Figure). Of the remaining 239 patients, liver disease was clearly present in 41 (17.2%) and absent in 198 (82.8%) patients. Renal insufficiency was not confidently assessed in 6 (14.6%) and 19 (9.6%) of the patients with and without liver disease, respectively. Of the remaining 35 liver disease patients, 34 (97.1%) had severe renal insufficiency, compared to 177 (98.8%) of the patients without liver disease. Therefore, the proportion of patients with severe renal insufficiency in both groups was similar (> 97.0%).

Among the 34 patients with liver disease and severe renal insufficiency, 26 (76.4%) proceeded to liver transplantation. The lone liver patient without severe renal insufficiency who developed NSF had a GFR of 69.6 mL/min/1.73m^2 prior to the first of four double-dose GBCA infusions (totaling 0.76 mmol/kg) over a 10 week period for abdominal MR angiographies in the setting of a failed liver transplant. His renal function subsequently worsened, with a nadir GFR of 34.6 mL/min/1.73m^2, and his post-operative course was further complicated by hepatic artery thrombosis, bile leak with peritonitis, and internal bleeding. Importantly, at no time was his GFR < 30 mL/min/1.73m^2.

As stated, there were 41 NSF patients with liver disease (mean age 52.7, range 32-77). Of the 27 patients who underwent liver transplantation, 15 (55.5%) developed NSF within 6 months (median 1.75 months, range 6-120 months). GBCA exposure was confirmed in 15 liver disease patients (36.6%), with 14 cases involving gadodiamide and the remaining one involving gadodiamide and gadobenate dimeglumine. GBCA exposure was not substantiated in the remaining 26 (63.4%) patients. The literature did not provide sufficient dosing information to be included in this analysis.



DISCUSSION: To our knowledge, this is the most exhaustive and systematic literature review of NSF conducted, including more patients and variables than in prior reviews and drawing from articles in radiology, pathology, nephrology, dermatology, and rheumatology journals. Severe renal insufficiency was present in similar proportions of NSF patients with and without liver disease. This suggests that liver disease does not confer increased risk for NSF development. Furthermore, data for GBCA exposure is lacking in liver patients – in our analysis, only 36.6% of liver disease patients with NSF were substantiated to have received GBCAs, intimating that in a certain proportion of liver disease patients, perhaps greater than 50%, a GBCA was never administered.

Patients with liver disease are at risk for NSF, but only to the extent that they are physiologically prone to severe renal insufficiency. While the FDA warning regarding the use of GBCAs in patients with severe renal insufficiency is well-substantiated, we believe the extension of the warning to liver patients with renal insufficiency of *any severity* may be premature. In the published literature, with one exception, every patient with liver disease who developed NSF also had severe renal insufficiency. The lone NSF patient with liver disease and without severe renal insufficiency was a severely ill patient with a large GBCA exposure and complicated post-operative course. Because renal insufficiency may develop rapidly and unpredictably in patients with liver disease, it may be prudent to measure GFR contemporaneously to the time of GBCA-exposure. However, if the GFR ≥ 31 mL/min/1.73m^2, the risk of NSF appears to be negligible.

CONCLUSION: With the limitations inherent to retrospective review, the published literature does not suggest that liver disease raises NSF risk beyond that of the underlying renal insufficiency.

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