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The NSF Conundrum

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Nephrogenic systemic fibrosis (NSF) is a rare, progressive, and sometimes fatal disorder found in patients with reduced kidney function. NSF is characterized by skin thickening, painful joint contractures, and fibrosis of multiple organs. There is an increasing recognition of NSF over the past decade and one of the first papers to describe NSF was a paper by Cowper et al in 2000.[1] In 2006, Marckmann et al and Grobner reported the association of NSF with gadolinium-based contrast agents (GBCAs).[2,3] In 2006 and 2007, the US Food and Drug Administration (FDA) released an advisory and asked magnetic resonance (MR) contrast manufacturers to include a box warning on risk of NSF. By 2011, the American College of Radiology (ACR) and Yale International NSF registry had tracked 500 and 360 cases of NSF, respectively. The reported incidence of NSF has been steadily decreasing over the last decade.[4]

The exact mechanism of NSF causation is still unknown, but the association between NSF and exposure to GBCAs is generally accepted. There are known differences in the likelihood of a patient developing NSF after exposure to different GBCA agents. Based on these differences, ACR categorized MR contrast agents into three groups in its latest manual on radiology-contrast agents in 2023 based on reported associations with NSF in vulnerable patients.[5] Group I consists of contrast agents with largest number of NSF cases, group II includes agents with few if any unconfounded cases, and group III includes agents for which data is limited. These recommendations are comprehensive and consider special situations such as patients already on dialysis and acute renal failure. In brief, group I contrast agents are contraindicated in severe renal dysfunction chronic kidney disease (CKD) 4 or 5 (estimated glomerular filtration rate [eGFR] <30 mL/min/1.73 m^2). A group II agent should be used in these patients if there is significant benefit from the use of MR contrast. Guidelines are less clear for those with CKD 3 (eGFR: 30–59 mL/min/1.73 m^2). For those with CKD 1 or 2 (eGFR: 60–119 mL/min/1.73 m^2), any MR contrast agent can be safely administered. GBCAs can be divided according to whether the ligand linked to gadolinium is linear or macrocyclic. In general, macrocyclic agents are more stable than linear agents (less dissociation of gadolinium from ligand).[6] In 2017, European Union imposed restrictions on the use of linear contrast agents and assessed the benefit–risk balance to be unfavorable.[7] However, a blanket restriction on the use of linear MR contrast agents has not been placed by the FDA in the United States.

Most of the published studies on this topic are from Western literature and only a few case reports have been published from India.[8,9] This may be due to several reasons. Until recently, widespread access to MRI and MRI contrast agents was limited especially in rural and semiurban areas. In India, there is no national registry or database for NSF that might affect reporting and estimates of magnitude. NSF usually begins a few days to months after the MRI contrast administration that may also add to confusion regarding cause and effect. The knowledge of this entity among internists, radiologists, and dermatologists is also variable that may also contribute to low numbers reported.

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In India, a lot of effort and thought go into assessing patients for the administration of MRI contrast. However, many practicing physicians and some radiologists do not possess significant awareness of issues related to MRI contrast, renal failure, and NSF. A GFR level of just 1 (or in some places serum creatinine of 0.1) less than the cutoff can trigger MRI contrast being contraindicated in some patients. The issue of acute renal failure or current dialysis is not often considered. Is the excessive fear of NSF truly warranted, especially when class II agents are available for use? Is it possible that the harm of not giving the MRI contrast agent outweighs the risk of developing NSF in many patients? MR contrast can certainly help in more accurate diagnosis in many patients. This is a critical issue that directly relates to patient care. None of the authors (who are primarily diagnostic radiologists with experience after postgraduation of 20 years or more) have observed a case of NSF in their patients. There is also no published study of NSF from India. We need to reflect on what this means for practicing radiologists in India. Should we convert completely to group II agents, lead a collaborative study of NSF in India with dermatologists, or improve awareness of newer concepts related to MR-contrast agents (differences between macrocyclic vs. linear contrast agents, renal function criteria as related to NSF, MR contrast deposition).[5,6,10]

The decision to administer contrast is crucial in improving diagnostic accuracy. To summarize, we feel a case-by-case benefit-to-risk assessment, discussion with referring physician and patient consent is warranted in all patients. This may lead to more patients being benefited by a contrast-enhanced study rather than decisions being bound by an excessive fear of NSF not based on evidence.

Conflict of Interest
None declared.

References

1 Cowper SE, Robin HS, Steinberg SM, Su LD, Gupta S, LeBoit PE. Scleromyxoedema-like cutaneous diseases in renal-dialysis patients. Lancet 2000;356(9234):1000–1001
2 Marckmann P, Skov L, Rossen K, et al. Nephrogenic systemic fibrosis: suspected causative role of gadodiamide used for contrast-enhanced magnetic resonance imaging. J Am Soc Nephrol 2006;17(09):2359–2362
3 Grobner T. Gadolinium–a specific trigger for the development of nephrogenic fibrosing dermopathy and nephrogenic systemic fibrosis? Nephrol Dial Transplant 2006;21(04):1104–1108
4 Mathur M, Jones JR, Weinreb JC. Gadolinium deposition and nephrogenic systemic fibrosis: a radiologist's primer. Radiographics 2020;40(01):153–162
5 American College of Radiology. Manual on contrast media. Reston, VA: American College of Radiology; 2023. Accessed February 29, 2024 at: https://www.acr.org/Clinical-Resources/Contrast-Manual
6 Weinreb JC, Rodby RA, Yee J, et al. Use of intravenous gadolinium-based contrast media in patients with kidney disease: consensus statements from the American College of Radiology and the National Kidney Foundation. Radiology 2021;298(01):28–35
7 (2017) EMA's final opinion confirms restrictions on use of linear gadolinium agents in body scans EMA/457616/2017. European Medicines Agency. Available at: https://www.ema.europa.eu/system/files/documents/referral/wc500230928_en.pdf
8 Reddy IS, Somani VK, Swarnalata G, Maitra S. Nephrogenic systemic fibrosis following hair-dye ingestion induced acute renal failure. Indian J Dermatol Venereol Leprol 2010;76(04):400–403
9 Waikhom R, Taraphder A. Nephrogenic systemic fibrosis: a brief review. Indian J Dermatol 2011;56(01):54–58
10 Starekova J, Pirasteh A, Reeder SB. Update on gadolinium based contrast agent safety, from the *AJR* special series on contrast media. Am J Roentgenol 2023 (e-pub ahead of print). Doi: 10.2214/AJR.23.30036

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