

## Use of GBCA in MRIs for High-Risk Patients

**To the Editor:** We read with interest the case report of nephrogenic systemic fibrosis (NSF) by Chuang, Kaneshiro, and Betancourt in the June 2018 issue of *Federal Practitioner*.<sup>1</sup> It was reported that a 61-year-old Hispanic male patient with a history of IV heroin abuse with end-stage renal disease (ESRD) secondary to membranous glomerulonephritis on hemodialysis and chronic hepatitis C infection received 15 mL gadoversetamide, a linear gadolinium-based contrast agent (GBCA) during magnetic resonance imaging (MRI) of the brain. Hemodialysis was performed 18 hours after the contrast administration.

Eight weeks after his initial presentation, the patient developed pyoderma gangrenosum on his right forearm, which was treated with high-dose steroids. He then developed thickening and induration of his bilateral forearm skin with peau d'orange appearance. NSF was confirmed by a skin biopsy. The patient developed contractures of his upper and lower extremities and was finally wheelchair bound.

This case is very concerning since no NSF cases in patients receiving GBCA have been published since 2009. Unfortunately, the authors give no information on the occurrence of this particular case. Thus, it is unclear whether this case was observed before or after the switch to macrocyclic agents in patients with reduced renal function. The reported patient with ESRD was on hemodialysis and received 15 mL gadoversetamide during MRI of the brain. In 2007 the ESUR (European Society of Urogenital Radiology) published guidelines indicating linear GBCA (gadodiamide, gadoversetamide, gadopentetate dimeglumine) as high-risk agents that may not be used in patients with  $eGFR < 30$  mL/min/1.73 m<sup>2</sup>.<sup>2,3</sup>

Consequently in 2007, the European Medicines Agency contraindicated these linear GBCA in patients with chronic kidney disease grades 4 and 5. Also in 2007 the US Food and Drug Administration (FDA) requested a revision of the prescribing information for all 5 GBCA approved in the US.<sup>4</sup> In response to accumulating more informative data, in 2010 the FDA again used this class labeling approach to

more explicitly describe differences in NSF risks among the agents.<sup>4</sup> FDA regulation and contraindication of the use of low-stability GBCA in patients with advanced renal impairment and robust local policies on the safe use of these agents have resulted in marked reduction in the prevalence of NSF in the US. This case report needs to clarify why a high-risk linear agent was administered to a patient with ESRD.

In 2006 Grobner and Marckmann and colleagues reported their observations of a previously unrecognized link between exposure to gadodiamide and the development of NSF.<sup>5,6</sup> It soon became clear that NSF is a delayed adverse contrast reaction that may cause severe disability and even death. Advanced renal disease and high-risk linear GBCA are the main factors in the pathogenesis of NSF. Additionally, the dose of the agent may play a role. NSF can occur from hours to years after exposure to GBCA. Not all patients with severe kidney disease exposed to high-risk agents developed NSF. Thus, additional factors were proposed to play a role in the pathogenesis of NSF. Among those factors were erythropoietin, metabolic acidosis, anion gap, iron, increased phosphate, zinc loss, proinflammatory conditions/inflammation and angiotensin-converting enzyme (ACE) inhibitors.<sup>7</sup> Although there is little proof with these assumptions, special care must be taken as shown by this reported patient with multiple inflammatory disorders.

**Gertraud Heinz, MD, MBA; Aart van der Molen, MD; and Giles Roditi, MD; on behalf of the ESUR Contrast Media Safety Committee**

**Author affiliations:** Gertraud Heinz is former President ESUR and Head of the Department of Radiology, Diagnostics and Intervention University Hospital St. Pölten Karl Landsteiner University of Health Sciences.

**Correspondence:** Gertraud Heinz (gertraud.heinz@stpoelten.lknoe.at)

**Disclosures:** The authors report no conflict of interest with regard to this article.

### References

1. Chuang K, Kaneshiro C, Betancourt J. Nephrogenic systemic fibrosis in a patient with multiple inflammatory disorders. *Fed Pract*. 2018;35(6):40-43.
2. Thomsen HS; European Society of Urogenital Radiology (ESUR). ESUR guideline: gadolinium based contrast media and nephrogenic systemic fibrosis. *Eur Radiol*. 2007;17(10):2692-2696.

3. Thomsen HS, Morcos SK, Almén T, et al; ESUR Contrast Medium Safety Committee. Nephrogenic systemic fibrosis and gadolinium-based contrast media: updated ESUR Contrast Media Safety Committee guidelines. *Eur Radiol*. 2013;23(2):307-318
4. Yang L, Krefting I, Gorovets A, et al. Nephrogenic systemic fibrosis and class labeling of gadolinium-based agents by the Food and Drug Administration. *Radiology*. 2012;265(1):248-253.
5. Grobner T. Gadolinium—a specific trigger for the development of nephrogenic fibrosing dermopathy and nephrogenic systemic fibrosis? *Nephrol Dial Transplant*. 2006;21(4):1104-1108.
6. 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(9):2359-2362.
7. Thomsen HS, Bennett CL. Six years after. *Acta Radiol*. 2012;53(8):827-829.

**To the Editor:** With great interest, I read the case report by Chuang, Kaneshiro, and Betancourt.<sup>1</sup> Patients with nephrogenic systemic fibrosis (NSF) are of special interest because the disease is still unclear as mentioned by the authors. Although new cases may occur,<sup>2</sup> this case raises some concerns that I would like to address.

First, it would be of great interest to know the date when the patient received the high-risk gadolinium-based contrast agent (GBCA) gadoversetamide. Unfortunately, the authors did not mention the date of the injection of the GBCA that probably caused NSF. Due to the obvious association between the applications of special GBCAs in 2006, the US Food and Drug Administration (FDA) warned physicians not to inject these contrast agents in patients with compromised kidney function.<sup>3</sup> Moreover, in 2007 the American College of Radiology (ACR) published guidelines for the safe use of GBCAs in patients with renal failure.<sup>4</sup> Also, the European Medicines Agency (EMA) demanded that companies provide warning in product inserts about the acquisition of NSF in patients with severe kidney injury.<sup>5</sup>

Second, the clinical illustration of the case is inadequate. In the manuscript, we read that the patient acquired NSF-characteristic lesions like peau d'orange skin lesions and contractures of his extremities, but unfortunately, Chuang, Kaneshiro, and Betancourt did not provide figures that show them. On the other hand, Figure 1 shows an uncharacteristic dermal induration around inflammatory and ulcerated skin lesion (pyoderma gangrenosum).<sup>1</sup> Such clinical signs are well known and occur

perilesional of different conditions independently of NSF.<sup>6-8</sup>

Third, the histological features described as presence of fibrotic tissue in the deep dermis in Figure 2, and dermal fibrosis with thick collagen deposition in Figure 3<sup>1</sup> do not confirm the existence of NSF.

Taken together, the case presented by Chuang, Kaneshiro, and Betancourt contains some unclear aspects; therefore, it is questionable whether the published case describes a patient with NSF or not. In the current presentation, the diagnosis NSF seems to be an overestimation.

NSF still is a poorly understood disorder. Therefore, exactly documented new cases could be of clinical value when providing interesting information. Even single cases could shed some light in the darkness of the pathological mechanisms of this entity. On the other hand, we should not mix the existing cohort of published NSF cases with other scleroderma-like diseases, because this will lead to a confusion. Moreover, such a practice could inhibit the discovery of the pathophysiology of NSF.

Ingrid Böhm, MD

**Author affiliations:** Ingrid Böhm is a Physician in the Department of Diagnostics, Interventional and Pediatric Radiology at the University Hospital of Bern, Inselspital, University of Bern in Bern, Switzerland.

**Correspondence:** Ingrid Böhm (ingrid.boehm@insel.ch)

**Disclosures:** The author reports no conflict of interest with regard to this article.

#### References

1. Chuang K, Kaneshiro C, Betancourt J. Nephrogenic systemic fibrosis in a patient with multiple inflammatory disorders. *Fed Pract*. 2018;35(6):40-43.
2. Larson KN, Gagnon AL, Darling MD, Patterson JW, Cropley TG. Nephrogenic systemic fibrosis manifesting a decade after exposure to gadolinium. *JAMA Dermatol*. 2015;151(10):1117-1120.
3. US Food and Drug Administration. A Public Health Advisory. Gadolinium-containing contrast agents for magnetic resonance imaging (MRI). <http://wayback.archive-it.org/7993/20170112033022/http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm053112.htm>. Published June 8, 2006. Accessed March 15, 2019.
4. Kanal E, Barkovich AJ, Bell C, et al; ACR Blue Ribbon Panel on MR Safety. ACR guidance document for safe MR practices: 2007. *AJR Am J Roentgenol*. 2007;188(6):1447-1474.
5. European Medicines Agency. Public statement: Vasovist and nephrogenic systemic fibrosis (NSF). <https://www.ema.europa.eu/en/news/public-statement-vasovist-nephrogenic-systemic-fibrosis-nsf>. Published February 7, 2007. Accessed March 15, 2019.
6. Luke JC. The etiology and modern treatment of varicose ulcer. *Can Med Assoc J*. 1940;43(3):217-221.
7. Paulsen E, Bygum A. Keratin gel as an adjuvant in the

treatment of recalcitrant pyoderma gangrenosum ulcers: a case report. *Acta Derm Venereol.* 2019;99(2):234-235.

8. Boehm I, Bauer R. Low-dose methotrexate controls a severe form of polyarteritis nodosa. *Arch Dermatol.* 2000; 136(2):167-169.

**Response:** We thank Drs. Heinz, van der Molen, and Roditi for their valuable response. The following is the opinion of the authors and is not representative of the views or policies of our institution. The patient in this case received a gadolinium-based contrast agent (GBCA) in 2015 and was diagnosed with nephrogenic systemic fibrosis (NSF) 8 weeks later. We agree with the correspondents that linear GBCAs should not be used in patients with eGFR < 30 mL/min/1.73 m<sup>2</sup>. To date, a few cases of patients who received GBCA and developed NSF since 2009 have unfortunately continued to be reported in the literature.<sup>1-3</sup> Our intention in publishing this case was to provide ongoing education to the medical community regarding this serious condition to ensure prevention of future cases.

We thank Dr. Böhm for her important inquiry. The patient received a histopathologic diagnosis of NSF. The report from the patient's left dorsal forearm skin punch biopsy was read by our pathologist as "fibrosis and inflammation consistent with nephrogenic systemic fibrosis," a diagnosis agreed upon

by our colleagues in the dermatology and rheumatology departments based on the rapidity of his symptom onset and progression. While we acknowledge that this patient had other inflammatory disorders of the skin that may have coexisted with the diagnosis, after weighing the preponderance of clinical evidence in support of the biopsy results, we believe that this represents a case of NSF, which is associated with high morbidity and mortality. Thankfully, the patient in this case engaged extensively in physical and occupational therapy and is still alive nearly 4 years later. We would like to thank all the letter writers for their correspondence.

**Author Affiliations:** Kelley Chuang and Casey Kaneshiro are Hospitalists and Jaime Betancourt is a Pulmonologist, all in the Department of Medicine at the VA Greater Los Angeles Healthcare System in California.

**Correspondence:** Kelley Chuang (kelleychuang@mednet.ucla.edu)

**Disclosures:** The authors report no conflict of interest with regard to this article.

#### References

1. Aggarwal A, Froehlich AA, Essah P, Brinster N, High WA, Downs RW. Complications of nephrogenic systemic fibrosis following repeated exposure to gadolinium in a man with hypothyroidism: a case report. *J Med Case Rep.* 2011;5:566.
2. Fuah KW, Lim CT. Erythema nodosum masking nephrogenic systemic fibrosis as initial skin manifestation. *BMC Nephrol.* 2017;18(1):249.
3. Koratala A, Bhatti V. Nephrogenic systemic fibrosis. *Clin Case Rep.* 2017;5(7):1184-1185.