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reports related to linear GBCAs. In the present study, we communicated our immediate findings following a large retrospective study of NSF patients at our Hospital, all receiving a gadolinium-based contrast agent during the period 1997–2009. Specifically, we address the finding of two NSF cases that suggest, gadobutrol to be a possible cause of NSF.

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More detailed information about renal function of Case 1 is shown in Table 1. In brief, although a small but steady reduction in MDRD GFR was shown following exposure to gadobutrol, GFR remained at stages 3 and 4 throughout the monitoring period. It has been debated that medication, in particular erythropoietin, could participate as a co-factor in the development of NSF [2]. Case 1 was prescribed with the following medication: pantoprazole, acetylsalicyl acid and ramipril; whereas Case 2 was prescribed with erythropoietin, pantoprazole, acetylsalicyl acid, Phos-Ex, simvastatin, actrapid, Insulatard, enalapril, Furix, Kaleorid and dipyridamole.

We agree with Prof. Morcos that prior exposure to GBCAs may lead to deposition of gadolinium in bone. But given the proximity of gadobutrol dosing and onset of NSF symptoms, we believe it is unlikely that mobilization of bone gadolinium resulting from gadodiamide administered 7 years previously contributed to this case. In fact, because it has been shown that gadolinium can be found in bone after the administration of both linear (Omniscan[®]) and macrocyclic (ProHance[®]) agents in normal individuals [3], it is not possible to conclude that the mobilization of retained gadolinium is an issue restricted to linear GBCAs. It should be noted that the species of the bone gadolinium [i.e. ‘free’ gadolinium (dechelated) or intact GBCA] was not determined in this study [3].

There are strong data linking the development of NSF with impaired renal function at the time of GBCA administration [4], GBCA dose [5] and the presence of inflammatory states [6]. It should be emphasized that, at the time of the gadodiamide exposure, Patient 2 had a normal kidney function.

Importantly, as the exact role of gadolinium is unknown in this disease, withdrawal of biopsies for measurement of gadolinium in the skin is not a prerequisite in the diagnosis of NSF.

As a comment to the ProHance study [7], which the authors are referring to, to our knowledge, the patients were not examined by an experienced dermatologist or rheumatologist with a profound knowledge of scleroderma or other fibrotic skin diseases. It is our opinion that NSF

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Reply

Firstly, we would like to thank the authors for their exquisite emphasis on our recent published experience [1]. We agree with Prof. Morcos that supplementary data and information would have been valuable in our understanding of nephrogenic systemic fibrosis (NSF), and as this study was performed retrospectively, there are limitations on forming definitive conclusions about the overall link between gadobutrol and NSF, as is also the case for many

Table 1. Biochemistry data for Case 1 before and after exposure to gadobutrol (19 June 2008)

Date	Creatinine ($\mu\text{mol/L}$)	MDRD GFR (mL/min)	Phosphate (0.76–1.23 mmol/L)	Calcium ion (1.18–1.32 mmol/L)	Parathyroid hormone (1.6–6.9 pmol/L)
14 May 08	190	34			
01 July 08	201	31			
07 August 08	181	35			
15 October 08	214	29	1.25	1.25	4.8
14 January 09	229	27			
19 March 09	214	29			
22 September 09	283	21	0.92	1.15	
29 December 09	264	23	0.80	1.14	

cannot be diagnosed in a single patient based entirely on the patient's medical records and conditions, as a firm examination including a skin biopsy must be undertaken. Robert F. Reilly reported that they might have missed milder presentations of NSF, or the clinicians may have missed full-blown cases of NSF [7].

In the FINEST study [8], which the authors are also mentioning in their comments, we find it interesting that, among the 308 patients included, none showed signs of cutaneous disorders within 4 months after MRI. These patients were all inspected by a physician, whereas no experienced dermatologist with hands-on experience was involved. Furthermore, they reported their retrospective inclusion period between July 2005 and July 2006, with a follow-up of 4 months. However, speculations could be drawn that NSF cases (if any) had not been established during these few months.

With regard to the Varani [9] *in vitro* study of human dermal fibroblasts in monolayer culture, it was reported that gadodiamide, gadopentetate, gadobenate and gadoteridol all caused persistent, increased fibroblast proliferation and increased production of the regulators of collagen turnover [matrix metalloproteinase-1 (MMP-1) and tissue inhibitor of matrix metalloproteinase-1 (TIMP-1)]. This suggests that all GBCAs may stimulate the same fibrotic processes in human tissue at high concentrations.

We recognize that today's list of NSF cases is highest for the linear-structured gadolinium-chelated agents, but based on our study, we strongly believe that gadobutrol could be involved in the development of NSF in a way similar to those reported involving other gadolinium-containing agents. Thus, we feel that macrocyclic agents may currently not be considered as a safe MRI agent for renal impaired patients.

Conflict of interest statement. None declared.

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Twinkling sign?

Recently, Andrulli *et al.* [1] published a study about twinkling artefacts. The authors suggest that one should not speak of 'twinkling artefacts' but rather of 'twinkling signs', as this phenomenon plays an important role in kidney stone diagnosis. Both twinkling artefacts [2] and urine jet have been identified for many years but little used for purposes of diagnosis. Unlike other countries, in Switzerland, these phenomena were introduced by Jürg Prim into the course catalogue of the learning objectives for abdominal sonography training as early as 2003.

In fact, the search for stones in the renal sinus and in the ureter is not easy. Previously, the sensitivity of ultrasonography to ureteral stones was low with only 19–37% reported [3]. Thanks to the twinkling artefact, kidney stone diagnosis has been greatly enhanced. In addition, many ureteral stones and also renal sinus stones have been discovered. Our prospective study [4] showed that, with the combined utilization of twinkling artefacts, modern equipment and indirect signs of a stone, sensitivity, comparable with CT, of 98.2% and specificity of 100% were achieved. More recent studies by Park *et al.* [5] achieved a sensitivity of 93 and 98.5%, respectively, and specificity of 95 and 100%, respectively. In the study by Park *et al.* [5], twinkling in 184 of 214 stones was detectable (86%).

Indirect signs of nephrolithiasis are important, and here, urine jet plays an important role. A normal value is two jets per ureter per minute. The measurements are carried out between 3 and 5 min. But the twinkling artefact arises not only from renal stones, it also exists in many other formations with hard echoes. For example, some of these formations include calcifying pancreatitis or colonic air. Because twinkling is not specific only to urethral stones, I think that we should continue to speak of twinkling artefacts, and not, despite its usefulness, of twinkling signs.

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