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Letters and Replies

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Comments on the case report reported by Elmholdt *et al.*

Sir,

We read with interest the recent report by Elmholdt *et al.* [1], documenting two cases of nephrogenic systemic fibrosis (NSF) following exposure to a large dose of the macrocyclic gadolinium (Gd) contrast-enhancing agent (GdCA), gadobutrol (Gadovist, Bayer-Schering, Germany). However, we have several reservations about this report including the following:

(i) In Case 1, in which the patient developed a mild form of NSF, the authors have not provided information either about the blood chemistry of the patient (serum creatinine, phosphate, calcium and parathyroid hormone) or about medications the patient was receiving at the time of administration of the GdCA. The serum creatinine cited had been measured a month before CA administration when estimated glomerular filtration rate (eGFR) was 34 mL/min. It is not clear from the report whether the renal function was stable during this month or whether there was a progressive decline.

(ii) Case 2 was 'confounded' as the patient received both gadodiamide (Omniscan) (10 mL) in 2001 when renal function was normal (eGFR >60 mL/min) and gadobutrol (15 mL) in 2008 when the patient was suffering from end-stage renal disease with eGFR 11 mL/min. The patient also had an elevated serum phosphate and parathyroid hormone at the time of the last MRI examination. The patient also developed severe peritonitis a week after the gadobutrol injection. Six months later, the patient developed NSF affecting mainly his hands. Again, no information was provided about medications the patient was receiving during this period.

(iii) The authors concluded that these two cases were caused by gadobutrol but did not explore the possible role of a number of co-factors that may promote fibrosis; these include inflammation, hyperphosphataemia and medications such as erythropoietin.

(iv) In Case 2, the patient received gadodiamide 7 years prior to the administration of gadobutrol. It is feasible that some Gd had been deposited in the bone after this gadodiamide injection [2]. The delayed development of NSF could have been due to mobilization of the Gd from the bone induced by the development of hyperparathyroidism in 2008.

(v) It would have been useful to examine the biopsy specimens for the presence of Gd to confirm that the observed NSF is due to Gd exposure.

(vi) The two patients received high doses of gadobutrol (17.5 mL in Case 1 and 15 mL in Case 2) which are equal to 35 and 30 mL, respectively, of a GdCA with a 0.5-mol/L concentration. The European Society of Uroradiology (ESUR) and regulatory authorities in Europe recommend the use of the lowest possible dose of the most stable GdCA in patients with advanced renal impairment in order to minimize the risk of NSF. This advice has not been adopted in the management of these reported cases. It may be noted that high-quality diagnostic MR angiography can now be achieved with 'half' of the traditional doses used in the past with modern MRI software and equipment.

It is well recognized that there are many pathways that may lead to fibrosis, the final outcome of chronic inflammatory insults of affected tissues. According to Wahba *et al.* [3], a mild form of NSF may develop in an absence of Gd exposure, caused by background pro-inflammatory and pro-fibrotic conditions. It was also recognized as far back as the early 1980s that lanthanides promote fibrillogenesis [4,5]. More recently, it has been shown experimentally that Gd can stimulate the proliferation of human fibroblasts and accumulation of collagen *in vivo* and *in vitro* [6,7]. This effect was evident with low-stability, non-ionic linear chelates but was absent *in vivo* with the stable macrocyclic agents [6] and required a massive dose of the non-ionic macrocyclic agent gadoteridol (ProHance, Bracco, Italy) *in vitro* to induce a stimulatory effect on fibroblasts [7].

The authors' conclusion that macrocyclic agents have similar potential to induce NSF as the linear chelates is misleading and is not supported by a very large body of available clinical and experimental data [8]. The suggestion that the low prevalence of NSF with the macrocyclic agents is due to a lower share of the market is also misleading. In France, where the ionic macrocyclic agent gadoterate (Dotarem, Guerbet, France) has been the most commonly used GdCA for the last 20 years, they have not observed a single case of NSF in spite of using this agent in patients with end-stage renal disease [9]. In the USA, a centre, which used only the macrocyclic agent gadoteridol (ProHance, Bracco, Italy) in dialysis patients with ESRD, also did not find any cases of NSF [10].

In summary, the two cases reported by the authors do not constitute conclusive evidence that there is a significant risk of NSF after exposure to macrocyclic GdCA.

Conflict of interest statement. S.K.M. received a research grant from Guerbet, France and lecture fees from Guerbet, France and Bracco, Italy, and is an expert witness in NSF litigations in the USA. P.D. had nothing to declare.

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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 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.

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

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

Date	Creatinine (μmol/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	