Nephrogenic systemic fibrosis: risk factors suggested from Japanese published cases

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ABSTRACT. The aim of this article is to review the published cases of nephrogenic systemic fibrosis (NSF) in Japan. The Japanese medical literature database and MedLine were searched using the keywords NSF and nephrogenic fibrosing dermopathy (January 2000 to March 2009). Reports in peer-reviewed journals and meeting abstracts were included, and cases with biopsy confirmation were selected. 14 biopsy-verified NSF cases were found. In seven of eight patients reported after the association between gadolinium-based contrast agent (GBCA) and NSF was proposed, GBCA administration was documented: five received only gadodiamide; two received both gadodiamide and gadopentetate dimeglumine. In four cases, the amounts of contrast agent were registered: two received only a single dose (0.1 mmol kg^{-1} body weight) whereas the other two received 7–15 ml (the body weight was not disclosed) for each MR examination. Five patients had multiple injections of GBCA before NSF developed. Except for one patient in whom renal assessment was not reported, none of the patients had an estimated glomerular filtration rate $>30 \text{ ml min}^{-1} 1.73 \text{ m}^{-2}$ and all received dialysis. 5 of the 8 patients (63%) in whom GBCA exposure was confirmed were treated with peritoneal dialysis. Skin lesion of the lower extremity was the first symptom in 12 patients (86%), whereas 2 patients had primarily symptoms from the upper extremity. In three cases, GBCA was administered even after onset of the NSF symptoms because of the physicians' lack of knowledge about the possible association between GBCA and NSF. NSF is found among Japanese end-stage renal failure patients even after examinations using a single dose.

Received 12 March 2009
Revised 18 June 2009
Accepted 22 June 2009

DOI: 10.1259/bjr/17689538

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Radiology

Nephrogenic systemic fibrosis (NSF) is a rare disease that occurs in patients with renal failure; it can be devastating and usually initially appears as skin thickening and hardening, and occasionally progresses to limb contractures, leading to severe disability and even death [1–9]. It can be very painful. The disease was first diagnosed in 1997 and a report first published in 2000 [10]. A confident diagnosis requires a combination of clinical history, physical examination and pathological assessment of the skin biopsy specimen [1–9]. The exact pathophysiology of NSF remains uncertain, but the possible association between gadolinium-based contrast agent (GBCA), which is widely used for MRI, and NSF was proposed in 2006 [7, 11]. The leading hypothesis for the aetiology of NSF due to GBCA is that free gadolinium may be released from the chelates and bound by phosphate, which prevents reassociation with the chelates; patients with end-stage renal failure are exposed to the agents longer than patients with normal renal function owing to their slower excretion.

A total of 190 biopsy-proven cases had been published in the peer-reviewed literature by 1 February 2008 [12]; 83% had received gadodiamide (Omniscan®, Daiichi

Sankyo, Tokyo, Japan). No one had reported development of NSF after exposure to the macrocyclic agents, *i.e.* gadoteridol or gadoterate meglumine alone. The NSF-associated warnings concerning GBCA use were first released in May 2006 in Europe [13], June 2006 in the USA [14] and March 2007 in Japan [15]. Most NSF cases have been reported in the USA and Europe. There are only a few Asian cases reported in the English literature [16–19], despite approximately 20% of GBCAs in the world being used in Japan (personal communication with employees of Daiichi Sankyo, Tokyo, Japan; Bayer Yakuhin, Osaka, Japan; Eisai, Tokyo, Japan). It has been suggested that there is no race difference in NSF occurrence [1, 12]. Therefore, we undertook a review of the Japanese literature.

Methods and materials

Japania Centra Revuo Medicina (the Japanese medical literature database) and MedLine were searched (January 2000 to March 2009) using the key words nephrogenic systemic fibrosis (NSF), nephrogenic fibrosing dermopathy (NFD) and their Japanese names, including case reports and meeting abstracts. From all the results of the MedLine search, only the reports from Japan were picked out. The data search was performed by one of the authors

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(YT) and all these reports were entirely reviewed. Overlaps were excluded. The Japanese vendors were also contacted. Whenever possible, the authors were contacted to obtain further information.

Results

A total of 17 Japanese cases were found. In 14 cases, the diagnosis of NSF was confirmed by histopathology (Table 1) [20–31]. 3 of 17 reported cases were not included in the further analyses: 1 case was reported to a GBCA vendor but not published as a case report or presented at a meeting as there was no information about pathological diagnosis; and in another 2 cases presented at a meeting, NSF was suspected clinically but the pathological examination did not diagnose NSF. To our knowledge, seven cases have been reported to GBCA vendors: three of them were excluded because of a lack of pathological information, and the other four cases overlapped with those found in the Japana Centra Revuo Medicina database.

Table 2 presents a summary of NSF cases. Out of the 14 patients 12 underwent dialysis (3–22 years), and five of eight patients (63%) with documented GBCA exposure were treated with peritoneal dialysis when GBCA was administered. One patient (Pt. no. 5) suffered from biopsy-proven hypertensive nephrosclerosis (estimated glomerular filtration rate (eGFR) $21.8 \text{ ml min}^{-1} 1.73 \text{ m}^{-2}$; chronic kidney disease (CKD) stage 4), but was not under dialysis. One patient (Pt. no. 3) suffered from chronic renal failure due to diabetic nephropathy, but the eGFR was not reported. Except for this patient, none of the patients had an eGFR $>30 \text{ ml min}^{-1} 1.73 \text{ m}^{-2}$, and all received dialysis. The interval between GBCA administration and dialysis was unknown in many cases.

Six of these 14 patients were reported before the association between GBCA and NSF had been suggested (Pt. nos 1–5, 7) [7, 11]. There was no mention of GBCA exposure in the original reports. Two of the six patients were reported again later. In one patient (Pt. no. 7) the use of GBCA before NSF onset was confirmed by the patient's records, but the type of GBCA could not be verified. In another patient (Pt. no. 5), the use of GBCA could not be confirmed despite an extensive search for the patient's medical record. In another patient (Pt. no. 6), the use of GBCA could not be confirmed (personal communication).

In seven of eight patients reported after the association between GBCA and NSF had been proposed, GBCA exposure was documented. All seven patients had gadodiamide before developing NSF. In five patients, GBCA was administered for MRI for various tumours, and in one patient (Pt. no. 7) for MR angiography (MRA). In the last patient (Pt. no. 10), the purpose of GBCA administration was not reported. In Japan, two linear chelates GBCA (gadodiamide and gadopentetate dimeglumine (Magnevist®, Bayer Yakuhin, Osaka, Japan)) and two macrocyclic chelates GBCA (gadoteridol and gadoterate meglumine) are available.

In four cases, the amounts of contrast agent were registered. Two received only a single dose (Pt. nos 8 and 12), whereas the other two (Pt. nos 11 and 13) had 7–15 ml of the agent (the body weight was not disclosed,

but likely to be less than double dose) per MR examination. Five patients were exposed to multiple injections of GBCA before NSF developed. 1 patient with hepatocellular carcinoma (Pt. no. 8) received GBCA 14 times over a period of 31 months, gadopentetate dimeglumine eight times and gadodiamide six times. NSF developed after the tenth administration of GBCA. In three cases, GBCA was administered even after onset of NSF symptoms because the physicians were unaware of the possible association between GBCA and NSF.

The interval between the last GBCA administration and the first symptoms of NSF varied from four days to one month. Skin lesions of the lower extremity were the first symptom in 12 patients (86%), whereas two patients had primarily symptoms of the upper extremity. Nine of 14 patients (64.3%) developed joint contractures.

Discussion

To date, more than 500 NSF cases have been reported worldwide to health authorities [2]. However, several of those cases have not been systematically validated. Furthermore, only a few of those cases were Japanese. Nevertheless, we were able to find 14 Japanese biopsy-verified cases. The incidence of NSF after administration of gadodiamide to patients with severe renal dysfunction has been estimated at 2–10% [4, 32–35], and even higher if the skin of exposed patients was examined or if the patients had more than one injection [34]. In Japan, approximately 1 500 000 enhanced MRI examinations, corresponding to approximately 1% of the Japanese population, are performed annually. Approximately 20% of GBCAs in the world are being used in Japan (data obtained from three vendors in Japan). There are about 275 000 patients treated with dialysis in Japan [36]. Therefore, there should be between 55 and 275 NSF cases per year in Japan if 1% of the population receives GBCA. However, the literature search did not reveal more than 14 biopsy-verified cases.

Primarily, GBCA seems to correlate with the occurrence and/or severity of NSF [1–9, 37]. In one report [4], 12 of 207 patients (5.8%) who underwent MR examinations with a double dose of gadodiamide developed NSF, but none of the 94 patients with a single dose developed NSF. In Japan, gadodiamide is not approved at doses higher than 0.1 mmol kg^{-1} body weight. Double-dose administration has been allowed for very limited indications (gadoteridol for diagnosis of brain metastasis, and gadopentetate dimeglumine for MRA from the abdomen through lower extremities). Enhanced MRA, in which double or triple doses of GBCA may be occasionally necessary to obtain good-quality images, has not been widely used in Japan, although off-label use cannot be excluded. In this literature review, five patients were exposed to multiple injections of GBCA before NSF developed, possibly resulting in a high cumulative dose of GBCA. However, two patients received only a single dose of gadodiamide. This finding documents that NSF may develop after a single normal dose of GBCA as well as after multiple injections. This is in accordance with the European and American findings [1–9].

Table 1. Nephrogenic systemic fibrosis (NSF) cases reported in Japan

Pt. no. [ref.]	Age/sex	GBCA use ^a	Dose of GBCA	Number of GBCA use before NSF onset	Interval between GBCA use and onset of NSF	Anatomical site of first onset	Joint contracture	Dialysis (years) or CKD stage	Other possible risk factors	GBCA use before NSF onset
1 [20]	51/F	NR	–	–	–	Legs	Yes	HD [17]		–
2 [21]	59/F	NR	–	–	–	Legs	NR	HD		–
3 [22]	49/M	NR	–	–	–	Legs	NR	NR		–
4 [22]	81/F	NR	–	–	–	Legs	NR	HD		–
5 [23]	29/F	No	–	–	–	Legs	NR	No dialysis CKD stage 4		–
6 [24]	61/F	No	–	–	–	Legs	Yes	HD [12]		–
7 [25]	57/M	Yes ^b	NR	NR	NR	Legs/arms	Yes	PD		Apr 2000
8 [26]	44/M	Omniscan	15 ml (0.12 mmol kg ⁻¹)	1 ^f	1 month	Left arm	Yes	HD [8]	Acute rejection of implanted kidney	Jul 2000
9 [27]	58/M	Omniscan	NR	4 ^f	NR	Right arm	Yes	HD [3] ^g		2003–2004
10 [28]	66/M	Omniscan and Magnevist ^c	NR	4	NR	Legs/arms	No	HD [20]		Dec 2001 to Apr 2003
11 [29]	52/F	Omniscan and Magnevist ^e	7–15 ml	10 ^f	1 month	Legs	Yes	PD [18]	Liver cirrhosis	May 2003 to Dec 2005
12 4 ^d	14/M	Omniscan	10 ml (0.11 mmol kg ⁻¹)	3	4 days	Legs/arms	Yes	PD		Sep 2006 to Jan 2007
13 [30]	24/M	Omniscan	10 ml	1	1 week	Legs/arms	Yes	PD [22]		Nov 2006
14 [31]	71/F	Omniscan	NR	2	NR	Legs	Yes	PD and HD [3]	Deep vein thrombosis	2007

CKD, ; GBCA, gadolinium-based contrast agent; HD, haemodialysis; PD, peritoneal dialysis; NR, not reported.

^aOmniscan (gadodiamide), Magnevist (gadopentetate dimeglumine).

^bTwo GBCA administration was confirmed, but the agent was not specified.

^cThis patients received gadodiamide three times and gadopentetate dimeglumine once.

^dPresented in a meeting, but no abstract available. One of the authors (YT) contacted to the radiologist who reported this case and got detailed information.

^eThis patient received gadopentetate dimeglumine eight times and gadodiamide six times, and NSF appeared after gadopentetate dimeglumine (15 ml) administration, which was the tenth administration of GBCA.

^fAdditional GBCA was administered even after NSF onset.

^gThis patient had undergone peritoneal dialysis before haemodialysis started.

Table 2. Summary of nephrogenic systemic fibrosis (NSF) cases in Japan

	Number of cases
NSF cases confirmed by histopathology in Japan	14
GBCA exposure before NSF onset (n=14)	
Omniscan	5
Omniscan and Magnevist	2
Not specified	1
No exposure	2
NR	4
Amount of GBCA per MR examination (n=8)	
Single	2
Likely to be less than double (7–15 ml)	2
NR	4
Time of GBCA injection (n=8)	
Single	2
Multiple	5
NR	1
Dialysis status or CKD stage (n=14)	
Peritoneal dialysis	4
Peritoneal and haemodialysis	1
Haemodialysis	7
CKD stage 4 without dialysis	1
NR	1
GBCA administration even after onset of NSF (n=8)	3
Skin lesion of the first symptoms (n=14)	
Legs	8
Arms and legs	4
Arms	2
Joint contracture (n=14)	
Present	9
Absent	1
NR	4

GBCA, gadolinium-based contrast agent; NR, not reported.

Second, we suspect a limited knowledge about NSF among Japanese physicians, *e.g.* nephrologists, radiologists, dermatologists, pathologists, might be the reason, although there is no definite data to support this. In particular, patients with non-severe disease may have been overlooked; nine of 10 Japanese patients with information about the severity were found to have severe disease (joint contracture). In 86% of patients primary symptoms appeared in the lower extremities. Non-disabling lesions on the lower extremities may be easily overlooked [1–9]. Since double doses or more are rarely used in Japan (and in none of the current cases), the likelihood of the disease seems to be lower but not absent and the percentage of non-severe disease may be higher [1–9, 33]. Some NSF patients may have escaped correct diagnosis of NSF, because of the physicians' lack of knowledge and also because of mild symptoms.

Suggested risk factors of NSF include the use of less stable GBCA, high cumulative doses of GBCA, peritoneal dialysis rather than haemodialysis, proinflammatory processes or events, the use of erythropoietin, high serum calcium or phosphate levels, etc. [1–9, 37–39]. Since the overwhelming majority of reported NSF cases have been associated with the less stable non-ionic linear GBCA (gadodiamide), the use of this agent is considered as a major risk factor. However, cases after exposure to gadopentetate dimeglumine have been also reported. Currently, the European Health Authorities [39] have contraindicated the use of those agents in patients with a

GFR below $30 \text{ ml min}^{-1} 1.73 \text{ m}^{-2}$ and advised that they are used only with caution in patients with a GFR between 30 and $60 \text{ ml min}^{-1} 1.73 \text{ m}^{-2}$. Both *in vivo* and *in vitro* the linear chelates (gadodiamide and gadopentetate dimeglumine) are less stable than the macrocyclic chelates (gadoteridol and gadoterate meglumine). Reilly [40] found no cases of NSF in 141 long-term haemodialysis patients with 198 gadoteridol exposures. Our Japanese results are in accordance with these results. Broome [12] did not find any cases of NSF after exposure to gadoteridol or gadoterate meglumine in the peer-reviewed literature. In Japan, the market share of gadopentetate dimeglumine is around 50%, followed by gadodiamide (30%) and gadoteridol (10%) (data obtained from three vendors in Japan). The high prevalence of NSF after exposure to gadodiamide in this study cannot be explained by market share. It has been suggested that gadodiamide has been preferred for patients with reduced renal function [2]. If this is true, the disproportionate association of gadodiamide with NSF could be explained. However, no data are currently available to support this hypothesis: it has not been documented in Europe [41] and our discussions with Japanese colleagues have not revealed this to be the case. However, stability differences as an important NSF risk factor are still too contentious to confirm, and further studies are necessary.

It is also noteworthy that five of eight patients (63%) with documented GBCA exposure underwent peritoneal dialysis when GBCA was administered. In Japan, only 3.4% of 275 000 patients receiving dialysis undergo peritoneal dialysis [36]. The high prevalence of NSF in patients treated with peritoneal dialysis suggested that peritoneal dialysis might be associated with increased risk of NSF. Dechelating and release of gadolinium ion is more likely to occur when GBCA remains inside the body for prolonged periods. In one report, the mean half-life of GBCA was prolonged from 1.3 h in healthy controls to 2.6 h in patients undergoing haemodialysis and 52.7 h in those undergoing continuous ambulatory peritoneal dialysis [42].

This review has several limitations: first, so-called reporting bias was essentially unavoidable. Only severe cases may be reported. However, the disproportionate association of gadodiamide with NSF can't be explained by either reporting bias or market share. Second, in two patients the use of GBCA could not be confirmed in their medical records. There have also been a few case reports in which exposure to GBCA could not be confirmed from patients' medical records [43]. Recently, Deng et al [44] reported seven NSF patients; although six patients had no known exposure history to GBCA, tissue gadolinium levels tested for three of these patients were significantly increased compared with normal tissue, supporting the association of GBCA and NSF. Without examining affected tissue for the presence of gadolinium, a history of exposure to GBCA cannot be excluded with certainty, since documentation of contrast media use is often inadequate [45]. In addition, relying on a patient's recollection of exposure of GBCA may be unreliable, since patients with chronic kidney disease usually undergo many investigations over the years, often in more than one centre, and it is difficult for such patients to be certain about the nature of the examinations.

In conclusion, NSF also occurs in Japan. It was seen after a single dose and multiple single doses of GBCA in patients with end-stage renal failure (with eGFR $<30 \text{ ml min}^{-1} 1.73 \text{ m}^{-2}$, or with dialysis). The high prevalence of NSF in patients treated with peritoneal dialysis suggested that peritoneal dialysis may be associated with increased risk of NSF. The lower number of reported NSF cases in Japan than in Europe and the USA may be because a dose higher than a single dose of 0.1 mmol kg^{-1} has not been approved, except for very limited indications.

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