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Is this really a true case of NSF following Gadovist exposure alone?

Wollanka et al. describe the development of nephrogenic systemic fibrosis (NSF) 16 months after exposure to high-dose administration of gadobutrol (Gadovist, Bayer Schering Pharma, Berlin, Germany) and 1 month after iodinated contrast media in a patient established on haemodialysis ‘for several years’. The authors suggest that the loss of residual ‘biosynthetic’ renal function following iodinated contrast media may have precipitated the development of NSF in a patient with previous gadobutrol exposure possibly via an FGF23-dependent process [1].

Whilst this patient has features consistent with NSF, the authors do not give the results of laboratory data such as serum electrophoresis, anti-nuclear antibody, anticientromere antibodies, anti-topoisomerase 1 antibodies, glycosylated haemoglobin or other laboratory analyses aimed at excluding an alternative diagnosis. It is now widely accepted that NSF should be diagnosed using a combination of clinical, histological and laboratory features [2]. All three are essential to avoid misdiagnosis and are not described for this case. Scleroderma, an important differential diagnosis, is not definitively ruled out from the pathological description given. The authors should state that this underlying disease has been excluded by their pathologist, who is not an author of the case report.

The authors also refer to residual renal function (RRF) without providing information on urine output or estimates of native creatinine clearance that are required to estimate RRF. RRF has important survival benefits for patients on renal replacement therapies including haemodialysis [3]. However, patients on haemodialysis, unlike peritoneal dialysis, often lose RRF soon after initiating haemodialysis. The authors do not give the date of commencing or details of renal replacement therapy, but the presence of RRF after ‘years’ on haemodialysis would be unusual. Additionally, creatinine, phosphate and haemoglobin values are given to imply a reduction in RRF following iodinated contrast. The influences on these parameters in haemodialysis patients is multifactorial and dependent on the quality of haemodialysis, time of sampling and general patient condition in addition to RRF and should not be used to imply RRF.

Wollanka et al. appear to describe the first reported case of NSF attributed to the sole administration of the macrocyclic gadolinium-based contrast agent (GBCA) gadobutrol. Whilst cases have been described in association with macrocyclic agents before, these have been rare and always confounded, i.e. a linear GBCA has also been administered prior to the development of NSF in the individual. It is now appreciated that linear GBCAs, especially non-ionic structures such as gadodiamide, convey the highest risk of developing NSF in individuals with severely impaired renal function. This is thought to be related to a combination of reduced renal clearance and relative structural instability which combined make the liberation of toxic, ‘free’ gadolinium more likely. This ‘transmetallation’ theory, with the release of free gadolinium that would then immediately complex with other anions such as phosphate, is believed to be central to the pathogenesis of NSF. The macrocyclic GBCAs such as gadobutrol, however, are orders of magnitude more stable than the linear agents as measured by their thermodynamic, kinetic and conditional stability constants and the potential for the release of ‘free’ gadolinium from macrocyclic GBCAs is thought to be virtually non-existent in vivo in comparison with linear GBCAs where the potential is extremely low but measurable [4–6]. The authors do not give a comprehensive list of imaging procedures prior to 2005 and, as such, prior exposure to additional GBCAs, in particular linear chelate GBCAs, could have been...
mis. whilst the authors also seem to subscribe to the transmetallation theory of causation, they do not provide a hypothesis on how a macrocyclic GBCA may dissociate to release a substantial amount of ‘free’ gadolinium.

The authors raise an interesting theory to explain the well-documented delay which can occur between the administration of GBCAs and the development of NSF, but they do not submit conclusive evidence that this case was indeed NSF or that their patient received only gadobutrol.

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**4. Morcos SK. Nephrogenic systemic fibrosis following the administration of extracellular gadolinium based contrast agents: is the stability of the contrast agent molecule an important factor in the pathogenesis of this condition? Br J Radiol 2007; 80: 73–76**


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**Reply**

The nephrogenic systemic fibrosis (NSF) diagnosis in our patient seems very likely considering the typical clinical and histological picture, and the fact that alternative diseases that might have caused similar symptoms were excluded by extensive diagnostic measures. In addition to the investigations described in the published case [1], also extensive laboratory analyses were performed, including protein electrophoresis, immune electrophoresis, anti-nuclear antibody (ANA) screening, extractable nuclear antigen (ENA) blot with the analysis of specific auto-antibody (anti-topoisomerase-1 antibodies, anti-centromer antibodies), anti-glutamic acid decarboxylase (GAD) antibody and anti-ampiphysin antibody. This led to the exclusion of systemic collagenosis, like systemic lupus erythematosus, scleroderma and mixed connective tissue disease as well as of Sjögren syndrome and stiff-man syndrome.

The diagnosis of NSF in a patient with terminal renal failure and gadolinium-based contrast media (Gd-CM) exposure was supported by nearly all major clinical criteria of NSF diagnosis as defined by Cowper et al. [2], in particular, induration of the skin of the lower and upper legs with patterned plaques and joint contractures. Also, the major histological criteria were identified, including increased cellularity with few inflammatory cells, presence of fine collagen and rope collagen surrounded by clefts, CD34+ spindle and epithelioid cells, and septal involvement. This, in addition to the exclusion of alternative disorders causing similar symptoms, makes the diagnosis of NSF in our patient very likely. The remaining question is whether the identified NSF could be related to other Gd-CM. However, according to our patient’s information and the radiologist’s report, no other contrast-enhanced magnetic resonance imaging (MRI) than the two MRIs with Gadovist had been performed. One of the reasons why the differential diagnosis was rather difficult in our patient, despite the typical clinical and histological signs, was the fact that no association between NSF and the exposure to macrocyclical Gd-CM was considered possible.

Based on the presented data, we believe to have published the first true NSF case in association with Gadovist exposure. Contrary to the information in the Letter to the Editor, this case is not the only unconfounded NSF case reported in association with macrocyclical Gd-CM. Suspected cases with a possible causality are known for each of the authorized macrocyclical Gd-CM, with most of them related to Gadovist (*BfArM’s ADR database). In association with macrocyclical Gd-CM in general, there are several reports of causally suspected NSF cases not confounded by linear Gd-CM in temporal relation to the NSF diagnosis, among them cases following single application of a normal dose and even two cases in patients who did not suffer from severe renal failure (in both these cases also Gadovist was used). No causally suspected NSF cases in patients without severe renal failure have been reported on any of the ionic linear products, not even on gadopentetate (Magnevist), the most commonly used Gd-CM. The relatively low number of NSF cases reported on macrocy-