

Case Report

Two cases of nephrogenic systemic fibrosis after exposure to the macrocyclic compound gadobutrol

Tina Rask Elmholdt^{1,2,3}, Bettina Jørgensen^{2,4}, Mette Ramsing⁵, Michael Pedersen^{1,2}
and Anne Braae Olesen^{2,3}

¹MR Research Centre, ²Institute of Clinical Medicine, ³Department of Dermatology, ⁴Department of Nephrology and ⁵Department of Pathology, Aarhus University Hospital, Aarhus, Denmark

Correspondence and offprint requests to: Michael Pedersen; E-mail: michael@mr.au.dk

Abstract

Nephrogenic systemic fibrosis (NSF) is a disease with progressive fibrosis. We describe two cases of NSF after exposure to a macrocyclic gadolinium-based contrast agent (GBCA) gadobutrol, which has been considered as a low-risk agent compared to linear GBCAs. The first case had chronic kidney disease (CKD) Stage 3 and was exposed to 17.5 ml of gadobutrol. The second case has been exposed twice to GBCA: 10 ml of gadodiamide (in 2001) and 15 ml of gadobutrol (in 2008). Before the second exposure, he had CKD Stage 5 and was in haemodialysis. Both patients have been diagnosed with NSF. Our cases suggest that cyclic GBCAs can also cause NSF.

Keywords: chronic kidney disease; contrast-enhanced MRI; gadobutrol; nephrogenic systemic fibrosis

Background

Nephrogenic systemic fibrosis (NSF) is a novel iatrogenic connective tissue disease [1]. Until now it has only been described in patients with acute or chronic kidney disease (CKD). A strong association between NSF and gadolinium-based contrast agents (GBCA) has been shown in many studies [2–4]. The condition is characterized by progressive fibrosis, thickening of the skin and restrained joint movements. NSF can be painful to the patient and may have involvement in other organs and tissues [5]. Currently, diagnosis of NSF cannot be made with a single marker, but is instead concluded from the clinical picture, medical history, a skin biopsy and blood samples, e.g. autoantibodies, in order to exclude other connective tissue diseases.

Case reports

Case 1

A 59-year-old man with chronic kidney failure since 2003 was referred to a GBCA magnetic resonance imaging

(MRI) in 2008. The indication was severe claudication. A dosage of 17.5 ml of gadobutrol (Gadovist®) was injected. The creatinine was 190 µM, corresponding to an estimated modification of diet in renal disease (MDRD) glomerular filtration rate (GFR) of 34 ml/min 1 month prior to MRI, categorizing him as CKD Stage 3. The patient has never been on dialysis.

Within a week after the exposure, the patient developed a universal rash and was examined by a dermatologist. A biopsy showed a moderate but manifest increased cellularity and an increased number of CD34-positive spindle cells (Figure 1A and B). Eosinophils, which would have been expected in a more classical drug-related rash, were not present. The CD34-positive spindle cells were arranged in a ‘tram-tracking’ pattern around elastic fibres, which have been considered characteristic for NSF [6]. Both fine and coarse collagen fibres were present. Histomorphology was found consistent with the skin changes found in NSF at an early stage.

Later, he developed pain of the muscles and joints and he was referred to a dermatological examination in 2009. The patient had symmetrical thickening and hardening of the skin on the lateral parts of the femur. Blood samples showed negative autoantibodies.

A punch biopsy from affected skin, performed 9 months after gadobutrol exposure, showed more unspecific histological changes. Epidermis was atrophic, the basal keratinocytes were slightly hyperpigmented and the dermal cellularity was decreased (Figure 1C and D). The number of CD34-positive fibrocytes was normal to slightly decreased.

Subcutaneous fibrosis and septation was present. Dermal vessels were slightly atrophic due to a diffuse and focally hyalinized fibrosis, and a sparse subepidermal mucinosis was found.

With reference to the clinical course and the histological findings, it was concluded that the observed changes likely represented a late stage of NSF similar to observations by Bangsgaard *et al.* [7]. Other conditions with dermal fibrosis, such as scleroderma, scleromyxedema, pretibial myxoedema and eosinophilic fasciitis, were excluded.

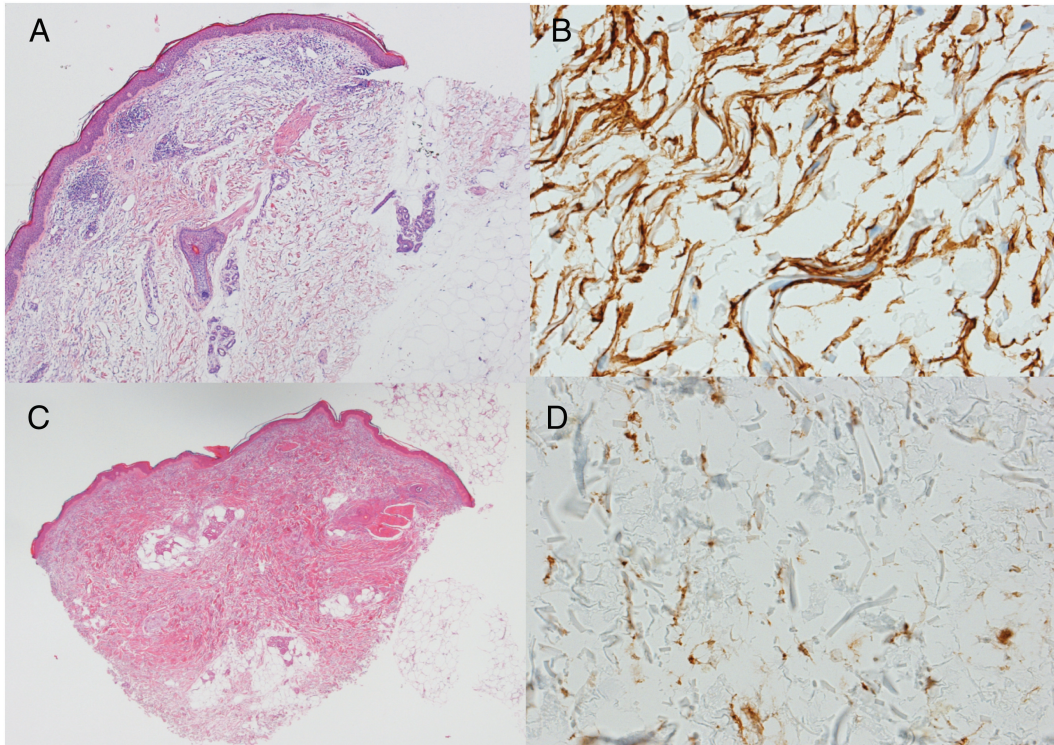


Fig. 1. (A+B) Acute stage (HE): increased cellularity with increased number of CD34-positive fibrocytes. (C+D) Late stage (HE): dermal and subcutaneous fibrosis.

Case 2

A 56-year-old man with insulin-dependent diabetes mellitus was referred to a GBCA MRI in 2001. He was exposed to 10 ml of gadodiamide (Omniscan®). Creatinine was 86 μM , corresponding to a MDRD GFR >60 ml/min. Peritoneal dialysis was initiated in 2007 and replaced by haemodialysis in 2008. A second MRI was performed in 2008 where 15 ml gadobutrol was administered. Approximately 4 months prior to this MRI, blood samples showed creatinine 498 μM corresponding to an estimated MDRD GFR of 11 ml/min (CKD Stage 5), phosphate concentration of 1.87 mM (normal range, 0.76–1.23 mM), ionized calcium of 1.02 mM (normal range, 1.18–1.32 mM), parathyroid hormone of 13.1 pM (normal range, 1.6–6.9 pM).

One week after gadobutrol exposure, the patient was hospitalized with severe peritonitis. Six months later, the patient suffered from pain and disability of the hands together with dysaesthesia of his leg. He was referred to a dermatological examination in 2009. The patient had symmetrically peau d'orange changes at the femur and tightening of the skin on his fingers and hands. He had disfiguration of the fingers and was unable to bend them. Blood samples showed negative autoantibodies.

A punch biopsy from affected skin was performed, showing a slightly atrophic epidermis, decreased cellularity and fibrotic and focally hyalinized dermis. The fibrosis expanded septally into the subcutis. The number of CD34-positive fibrocytes was not increased. We concluded that

the histomorphology was consistent with a late stage of NSF. Other conditions with dermal fibrosis, such as scleroderma, scleromyxedema, pretibial myxedema and eosinophilic fasciitis, were excluded.

Discussion

NSF is a debilitating and sometimes fatal condition. It has been associated with GBCAs in patients with severe renal impairment, as a prolonged circulation time of GBCAs occurs in the vascular system in such patients. Though the exact pathogenesis of NSF remains unknown, a prevailing theory is that gadolinium is released from its chelate by competitive binding with other metals in the body through a process known as transmetallation, and widespread fibrosis is thought to begin through concomitant interaction with circulating fibrocytes [3].

On the basis of the available evidence, the general opinion suggests that the risk of NSF in patients with advanced renal insufficiency is not the same for all GBCAs because distinct physiochemical properties affect their stabilities and thus the release of free gadolinium ions. GBCAs that consist of ionic cyclic chelate (Dotarem®, Prohance®, Gadovist®) are least likely to release toxic free gadolinium ions into the body, whereas GBCAs that consist of non-ionic linear chelate (Omniscan®, Optimark®, Magnevist®, Multihance®, Primovist®, Vasovist®) are most likely to release free gadolinium ions [8,9]. In this paper,

we report that gadobutrol (Gadovist®) can cause NSF in renally impaired patients.

In the first case, a man developed NSF after being exposed to gadobutrol. He had never been on dialysis and he was categorized as CKD Stage 3 (MDRD GFR = 34 ml/min) before exposure to GBCA. The symptoms appeared in the first week after GBCA exposure. A punch biopsy was performed and, in this acute phase, the number of CD34 cells were significantly elevated in the dermis. In a second biopsy withdrawn around 1 year after GBCA exposure, the increase of fibrosis was dominating in the histological description. In the second case, a man was exposed to both gadodiamide and gadobutrol within a period of 7 years. Exposure to gadobutrol in 2008 initiated symptoms and signs of NSF. He was categorized as CKD Stage 5 (MDRD GFR = 11 ml/min). Both cases were diagnosed with a late-phase NSF. Recently, the first case connecting gadobutrol alone to the development of NSF has been reported [10]. They hypothesized that the fibroblast growth factor 23 (FGF23) and the Klotho protein signalling pathway could serve as the missing links and increased serum phosphate level could be an indicator of FGF23 over-expression [10]. In case 2, we observed a slight elevation of the phosphate level prior to the second MRI.

In summary, we presented two NSF cases caused by a cyclic GBCA. These findings demonstrate the risk of NSF using all available GBCAs. The majority of NSF cases reported in the literature have so far been related to linearly structured GBCAs, which could be explained by their significantly higher market share over time and a presumably higher risk to dissociate into free gadolinium ions and chelates. Therefore, this study supports the view that both linear and cyclic gadolinium-containing agents may cause NSF in renally impaired patients.

Conflict of interest statement. None declared.

References

1. Cowper SE, Robin HS, Steinberg SM, Su LD, Gupta S, LeBoit PE. Scleromyxoedema-like cutaneous diseases in renal-dialysis patients. *Lancet* 2000; 356: 1000–1001
2. Grobner T, Prischl FC. Patient characteristics and risk factors for nephrogenic systemic fibrosis following gadolinium exposure. *Semin Dial* 2008; 21: 135–139
3. Abraham JL, Thakral C, Skov L, Rossen K, Marckmann P. Dermal inorganic gadolinium concentrations: evidence for *in vivo* transmetallation and long-term persistence in nephrogenic systemic fibrosis. *Br J Dermatol* 2008; 158: 273–280
4. 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: 2359–2362
5. Swaminathan S, High WA, Ranville J *et al.* Cardiac and vascular metal deposition with high mortality in nephrogenic systemic fibrosis. *Kidney Int* 2008; 73: 1413–1418
6. Cowper SE, Rabach M, Girardi M. Clinical and histological findings in nephrogenic systemic fibrosis. *Eur J Radiol* 2008; 66: 191–199
7. Bangsgaard N, Marckmann P, Rossen K, Skov L. Nephrogenic systemic fibrosis: late skin manifestations. *Arch Dermatol* 2009; 145: 183–187
8. Penfield JG, Reilly RF. Nephrogenic systemic fibrosis risk: is there a difference between gadolinium-based contrast agents? *Semin Dial* 2008; 21: 129–134
9. Idee JM, Port M, Robic C, Medina C, Sabatou M, Corot C. Role of thermodynamic and kinetic parameters in gadolinium chelate stability. *J Magn Reson Imaging* 2009; 30: 1249–1258
10. Wollanka H, Weidenmaier W, Giersig C. NSF after Gadovist exposure: a case report and hypothesis of NSF development. *Nephrol Dial Transplant* 2009; 24: 3882–3884

Received for publication: 2.2.10; Accepted in revised form: 22.2.10