NSF after Gadovist exposure: a case report and hypothesis of NSF development

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Abstract

So far no cases of nephrogenic systemic fibrosis (NSF) have been published on macrocyclical gadolinium-based contrast media (Gd-CM), assumed as low NSF risk CM due to their complex stability. In our haemodialysis-dependent patient, the first symptoms indicating NSF appeared about 16 months after the exposure to Gadovist, a macrocyclical Gd-CM, and 1 month after x-ray angiography with iodinated CM (Ultravist). This indicates that in addition to excretory renal failure and Gd-CM exposure, the loss of biosynthetic renal function could be essential for NSF development. A hypothesis of possible pathways involved in the development of NSF is presented.

Keywords: FGF23-Klotho axis; hypothesis of NSF development; macrocyclical gadolinium-based contrast media; NSF; case report

Background

Nephrogenic systemic fibrosis (NSF), recently described as an adverse drug reaction to gadolinium-based contrast media (Gd-CM), is a very rare disease occurring almost exclusively in patients with end-stage renal failure (ESRF). While the pathway of NSF development is still unknown, the potential to trigger NSF depends on the molecular structure and ionity of gadolinium chelates and is highest for linear non-ionic gadolinium preparations like gadodiamide (Omniscan). About 3% of patients with stage IV or V renal insufficiency exposed to Omniscan are affected by NSF; this rate seems to be 10–20 times lower for other Gd-CM [1–4]. The relatively low prevalence of NSF in patients at risk exposed to Gd-CM and the characteristic great variability in the time span between Gd-CM exposure and NSF manifestation, ranging from a few days to several years, strongly indicate that other factors determine the outbreak of this disease.

Case report

A 69-year-old male patient with ESRF, dependent on haemodialysis for several years, was referred to a neurological department because of painful muscle stiffness and weakness, and skin fibrosis of the legs reaching up to the waist (rock-hard skin with slight brown discoloration, leather-like skin), accompanied by progressive stiffness of the related joints. On the upper extremities, less pronounced fibrotic changes were identified. The skin fibrosis started to manifest itself in the summer 2006, about 1 year before admission to hospital for differential diagnosis (DD) and 16 months after the first exposure to Gadovist 30 ml (Bayer Schering Pharma, Berlin, Germany) for MRI angiography of the pelvic and leg region performed in April 2005. In the meantime (July 2005 and June 2006), two x-ray angiographies of the arm with arteriovenous fistula were performed using 30 ml of iodinated CM (Ultravist), and in June 2007, 1 month before hospital admission, another MRI enhanced by 10 ml of Gadovist took place.

Besides renal insufficiency with serum creatinine values in the range between 7.6 and (Hb 9.7), mg/dl accompanied by hyperphosphataemia (phosphate 6.1 mg/dl) and anaemia (Hb 9.7), the patient suffered also from generalized arteriosclerosis, atrial fibrillation and a thrombosis of the vena brachialis right (arteriovenous fistula arm) with chronic venous oedema, persisting despite the insertion of a stent, as well as muscle weakness and claudication-like symptoms, interpreted in terms of peripheral artery occlusive disease (PAOD). For DD, extensive investigations were carried out, including MRT of the upper leg muscles, neurophysiological examination (NLG/EMG), lumbal myelography and CT-scan after myelography, LWS x-ray, colour duplex sonography of the trunk and legs, tumour search with thorax CT and gastroscopy and finally histology of a tissue section from the upper lateral leg. The histological examination revealed inflammation-free skin, subcutis and muscular fascia, fibrotic changes of the dermis with CD34-expressing cells and collagen-rich tendon and muscle fascia (Figures 1 and 2). The Esinophilic fasciitis,
systemic collagenosis, systemic amyloidosis, Stiff–Mann syndrome and PAOD of the upper legs were clearly excluded. Therefore, only NSF or skin changes of paraneoplastic origin were considered responsible for the described symptoms. At present, 2 years since the clinical investigations, the paraneoplastic cause of the disease is also most likely to be excluded given the nearly unchanged general health condition of the patient, apart from progressive stiffness of the leg and trunk with current wheelchair dependence.

Discussion

The fact that NSF occurs only in a small number of gadolinium-exposed patients with ESRF, and that its symptoms frequently abate after a successful renal transplantation or renal function improvement but do not after gadolinium elimination via haemodialysis, indicates that deterioration of biosynthetic renal function, which is partly preserved despite excretory renal failure, may be causally involved in NSF manifestation and the course of the disease. The fibroblast growth factor 23 (FGF23) and the Klotho protein-signalling pathway could serve as the missing links [5–8]. This can be explained as follows: the circulating concentration of FGF23, recognized to be a novel phosphate-lowering factor (phosphatatonin), increases as renal function declines [5]. The Klotho protein, recently identified as an irreplaceable converter of the FGF1(IIIc) receptor into the FGF23-specific receptor, and fundamentally important for the interaction between FGF23 and the FGF23 receptor, is secreted in the kidney due to increased levels of FGF23 [6]. Consequently, in biosynthetic renal insufficiency, impaired expression of the Klotho protein and hence impaired generation of FGF23 receptors with consecutive FGF23 dysfunction and hyperphosphataemia must be suspected. This in turn, via a negative feedback, may lead to further overexpression of FGF23 and an uncontrolled increase of its serum concentration. It seems likely that an oversupply of FGF23, via an unspecific interaction with other FGF receptors, could activate the proliferation of circulating fibrocytes, which were identified in NSF patients. Circulating fibrocytes are CD34-expressing cells rich in collagen and known to assist in wound healing and tissue remodelling. These cells are recruited by chemokine signals to sites of tissue injury, in the present case gadolinium-injured skin [9]. The attenuation of basic FGF activity by Klotho as well as the competition between the two factors for the FGF1(IIIc) receptor suggest a potential for unspecific activity of FGF23 with FGF receptors. Also, the fact that both FGF23 and CF are of bone marrow origin opens up the possibility for interaction because increased local activity (FGF23 overexpression) could promote the synthesis of other factors, e.g. CF.

Knowing that strong variations of FGF23 levels on the one hand and reduced expression of Klotho in spite of high concentrations of FGF23 on the other hand were described in patients on haemodialysis [8], it seems very likely that the biosynthetic renal function is involved in this regulation. Also, the observation that in haemodialysis patients a high level of serum FGF23 is associated with increased mortality due to vascular calcification [7,8], whereas an intact FGF23-Klotho axis seems to protect against cardiovascular diseases [8], supports the hypothesis that patients with ESRF accompanied by biosynthetic renal impairment due to Klotho deficiency are likely to be affected by overexpression of FGF23. Based on this hypothesis, an increased serum phosphate level could be an indicator of FGF23 overexpression.

This hypothesis is further supported by the observation that in our patient the first signs of skin fibrosis appeared about 1 month after the second x-ray arteriovenous fistula angiography with iodinated CM, a known nephrotoxic agent, and that anaemia (Hb 9.7 mg/dl) and hyperphosphataemia (6.1 mg/dl) were noted in addition to serum creatinine in the range between 7.6 and 9.8 mg/dl at the investigation into DD.

Our hypothesis could explain the vast variation in the time span between Gd-CM exposure and NSF manifestation as well as the relatively low prevalence of NSF in
patients with ESRF exposed to Gd-CM, characteristic for this disease. The hypothesis may also open up ways to identify patients at risk.

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References

Might there be an association between polycystic kidney disease and noncompaction of the ventricular myocardium?

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Abstract
We report on a paediatric case of autosomal dominant polycystic kidney disease, where myocardial hypertrophy proved a consequence of noncompaction of the ventricular myocardium. Deletion of PKD1 and PKD2, the genes responsible for polycystic renal disease, has been linked also to disorganized myocardial arrangement in experimental animals. Two adults with polycystic kidney disease and myocardial hypertrophy in whom a careful diagnostic workup led to a diagnosis of non-compaction of the ventricular myocardium have been reported in the literature. Nephrologists must be aware of the possible association between the two diseases because early recognition of the disease may help in preventing the onset of complications.

Keywords: autosomal dominant polycystic kidney disease; child; noncompaction of the ventricular myocardium

Introduction
Autosomal dominant polycystic kidney disease (ADPKD) is the most common familial diseases of the kidneys. Anatomical manifestations are multiple cysts in the kidneys and liver, but also cardiovascular abnormalities [1] and increased left ventricular mass often in the absence of hypertension [2].

Noncompaction of the ventricular myocardium (NVM) is a rare congenital cardiomyopathy [3] resulting primarily from a premature stop of normal development of the endocardium and myocardium [4]. The disease can be sporadic or familial. Its hallmarks are deep intertrabecular recesses communicating with the ventricular cavity. Although the anatomic substrate may be evident at birth, clinical presentation can occur at any age, ranging from a complete lack of symptoms to disabling congestive heart failure, arrhythmias and systemic thromboembolism [5].

The association between polycystic renal disease and noncompaction of the ventricular myocardium has been