

Nephrogenic Fibrosing Dermopathy (NFD) in renal function compromised patients - Gadolinium deposition evidenced by energy filtering electron microscopy (EFTEM).

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Nephrogenic Fibrosing Dermopathy (NFD), now termed **Nephrogenic Systemic Fibrosis** (NSF), is a recently emerged acquired disorder of the skin and systemic tissues, first described in 2000 by Cowper [1]. It is observed exclusively in patients with renal insufficiency and a history of exposure to gadolinium (Gd) based MRI contrast agents [2, 3]. Gd, introduced in 1988 as a paramagnetic contrast agent, is widely used in MR imaging as a relatively safe complex with an inorganic linear or macrocyclic chelate. It is distributed equally in the extracellular compartment and is excreted almost exclusively by the kidney, its half-life increasing dramatically with kidney function deterioration (healthy humans half-life = 1.3 hours versus patients with End-Stage-Renal-Disease = about 120 h) [4]. The pathogenesis of the disorder is not understood, the role of circulating fibroblasts in the fibrosing tissue hypothetical, and the mechanism of the assumed trigger function of Gd elusive [5].

We studied ultrastructurally a skin lesion of a 76-y old man with clinical symptoms of a suspected NFD lasting for 5 months; the diagnosis was confirmed by histopathological methods (pronounced fibrosis of corium and subcutis, positive evidence of CD34 and CD68 cells, minimal focal inflammatory cell infiltrates).

The EM study of deparaffinized skin samples of this patient, utilizing electron spectroscopic imaging (ESI) and electron energy loss spectroscopic (EELS) microanalysis [6], revealed numerous small Gd deposits in a wide perivascular zone of the skin vessels [7]. Simultaneously tiny iron clusters were detected in some Gd-deposits as well as in the adjacent stromal tissue (**Fig.1**), search for calcium and magnesium presence in the available material was negative.

This finding supports the Gd transmetallation hypothesis and its possible direct toxic effect in different tissues and also supports its possible trigger function for the circulating fibroblasts [8]. We also provide ultrastructural evidence for the ability of lesional fibroblasts to differentiate into myofibroblastic cells [9]. In conclusion, the results support the pivotal role of gadolinium chelates in the development of nephrogenic systemic fibrosis.

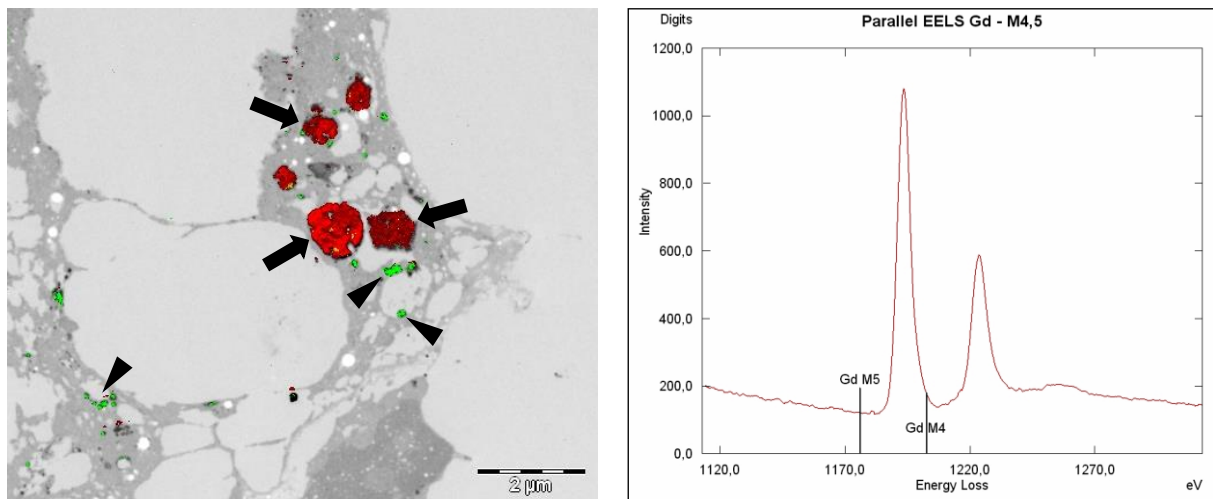


Figure 1: Nephrogenic Systemic Fibrosis.

Left: Gadolinium and iron mapping in the skin lesion (perivascular area) using ESI. The net Gd (red, arrows) and iron (green, arrowheads) signals were combined with the inverted HCl-image (High Contrast Image acquired at 250 eV energy loss in EFTEM-mode) of the non-stained section. Note the tiny iron colocalisation in the intracellular Gd deposits (diameter 100 to 1000 nm) in histiocytes and in the adjacent tissue. Bar 2μm.

Right: Parallel EELS-spectrum. Record of the measured (EFTEM spot mode) Gd signal (from the large red deposit shown in the left image) displaying the typical “white line” peaks of energy loss at 1,185 eV characteristic for the Gd element.

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