

Postmortem ICP-MS and MR analysis of gadolinium concentration and distribution in three confirmed NSF cases

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Introduction. Nephrogenic systemic fibrosis (NSF) is a debilitating fibrosing disorder that develops in patients with underlying kidney disease, following exposure to gadolinium (Gd)-containing magnetic resonance imaging (MRI) contrast agents. Although initially identified as a skin disease, prominent systemic involvement has become evident as more cases have appeared. Gd has been quantified in the skin of NSF subjects and recently Gd has been quantified in internal organs upon postmortem analysis [1,2]. We sought to better understand the organ distribution of Gd in NSF subjects and hypothesized that ex vivo MR imaging may inform on the distribution and speciation of Gd in various organs. If Gd is in a form that is accessible to tissue water, one expects shortened T1, T2, and T2*. If the Gd is highly concentrated and localized, e.g. precipitated, it may have little effect of T1, but the local field inhomogeneity should have a strong T2* effect.

Methods. Formalin fixed tissue from 3 confirmed NSF cases was obtained. Subjects had all received gadopentetate dimeglumine (GdDTPA) in cumulative doses ranging from 35 (Patient A, 2 doses over 14 mos.), 130 (B, 7 doses over 16 mos.), to 198 mL (C, 9 doses over 64 mos.). Gd was determined by ICP-MS and is reported as nmol Gd per gram wet weight of tissue. Tissue ca. 5 mm³ was suspended in an inert perfluorocarbon matrix and imaged at 9.4T. T1, T2, T2* maps were made at 100x100µm in-plane resolution using inversion-recovery spin echo (T1), multislice multiecho spin echo (T2), or multislice multiecho gradient echo (T2*) sequences.

Results and Discussion. Gd distribution varied among the three subjects, Fig 1. Gd was quantifiable in all tissue assayed. Extremely high Gd values were observed in the kidney cortex and the heart (left ventricle). 2/3 subjects had relatively low levels in the liver in contrast to what may have been expected based on animal studies [3]. Imaging revealed an apparently uniform Gd distribution in the heart samples, whereas regions of short relaxation times were heterogeneously distributed through the kidney. Fig 2 shows maps from heart and kidney containing similar Gd concentrations. The relatively long T1 in this heart section (600±36ms) coupled with very short and punctate T2* (7±10ms) distribution suggests the Gd is sequestered (e.g. precipitate and/or endosomal) with little access to tissue water.

Fig. 1 Gd content in various organs obtained post-mortem in subjects with confirmed NSF

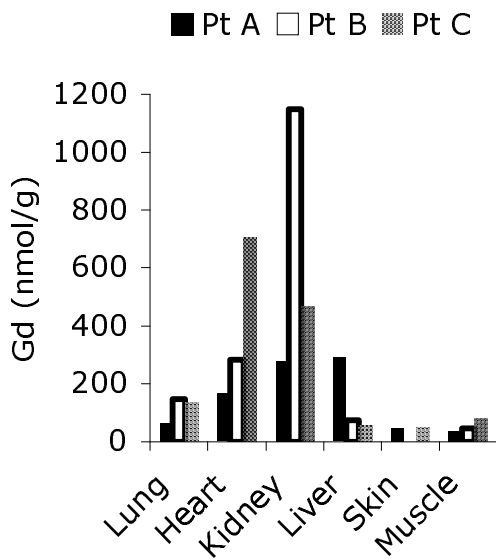
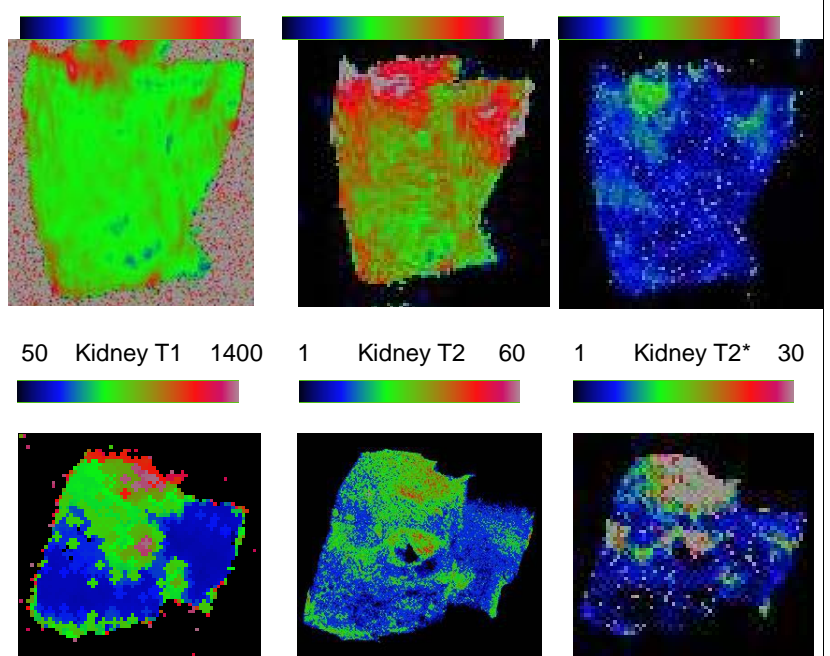


Fig. 2 T1, T2, and T2* maps (ms) of post-mortem heart and kidney containing approximately the same concentration of Gd



Conclusions. Gd levels observed in skin biopsies of NSF patients may represent the tip of the iceberg. Very high Gd concentrations are found in kidney and cardiac tissue of NSF patients in contrast to Gd distributions observed in rodent models. Ex vivo MR may inform on Gd distribution and speciation within tissue.

References: ¹Swaminathan et al. *Kidney Int.* 2008, 73:1413. ²Kay et al. *N. Engl. J. Med.* 2008, 358:827. ³Tweedle et al., *Invest. Radiol.* 1995, 30:372.