

Report MD-375

NSF is an emerging and severe pathology associated with the use of Gd-based contrast agents for MRI procedures in patients with renal diseases.

The disease manifestation consist in fibrosing processes in skin and internal organs, where a presence of gadolinium was found, mainly is complex precipitates together with iron and phosphorus, several month after the MRI procedure. The mechanisms are unknown and still under investigation.

Our experiments for MD325 were aimed to reproduce an animal model reassembling the features of NSF, by producing a condition of renal impairment and by administrating high doses of contrast agents.

The intent was particularly to verify if the use of synchrotron XRF microscopy could reveal early features of altered metabolism and disposition of contrast agents that could help the comprehension of the pathology.

Mice with 5/6 nephrectomy where administered with 3 doses (5 times that corresponding to the normal clinical dose) of 2 commercial contrast agents (Omniscan or Magnevist). 2 weeks after administration (to allow complete drug elimination) and 5 weeks after surgery, the animals were scarified and tissues collected. The animals do not manifest the features of NSF and their renal function was only slightly impaired. Samples were also collected from animals with sham surgery and treated with contrast agents.

At ID21 different histological samples of liver, skin, hair, tooth were analysed. The incident photon energy was set to 7.2KeV, and the beam was focussed onto the sample by means of a W zone plate, 100 nm in spatial resolution, on a spot 0.3 x 1.5 μm (HOR x VERT). The flux at the SDD photodiode was 9.45 10⁸ photons/s.

Only in one sample type (with nephrectomy and treatment with one of the two contrast agents) Gd was found.

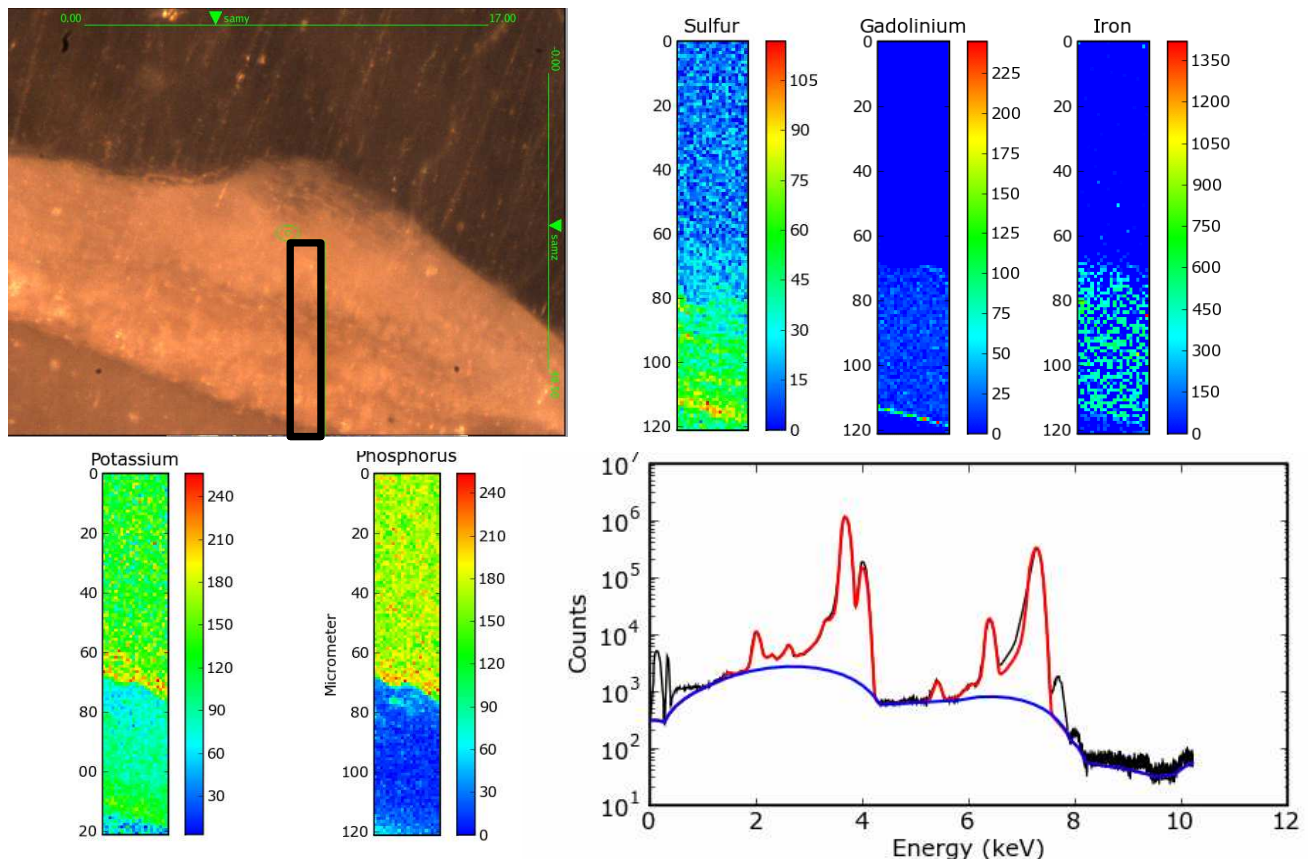


Fig. 1 Optical image of periodontal tissue, XRF maps and average spectrum.

The presence of Gd was found to be specific in this sample with good signal to noise ratio. In other tissues (teeth) of treated animals (normal renal function) the potential signal from gadolinium was not distinguishable from background.

The results seem to indicate that high (not clinical) doses of one of the two drugs (we prefer to not disclose the brand name before of confirming results) under mild renal impairment can result in an accumulation of drug and/or gadolinium in the periodontal tissue of mice. Results with the second drug in similar conditions must be better analyses and repeated due to possible defects in samples (periodontal tissue was greatly removed).

We are still analyzing our data and also performing conventional histological analyses.

Since the periodontal tissue of mice is a continuously regenerating district our result could suggest that contrast agents can have a tropism for organs (as also skin) with rapid renewal processes. This may have important implications in the understanding the NSF pathology.

Additional experiments are needed to confirm our results that are reporting something of absolutely new in the NSF research. Animals are currently under treatment to develop a more severe renal impairment and to be treated with the 2 contrast agents. Samples from different tissues will be collected, with particular attention to incisors and periodontal tissue.