Report MD-462

NSF was first recognized in 1997 in 15 dialyzed patients and described in 2000 (1). This rare and highly debilitating disorder is characterized by extensive thickening and hardening of the skin associated with skin-colored to erythematous papules that coalesce into erythematous to brawny plaques with an “peau d’orange” appearance. The distal extremities are the most common area of involvement, followed by the trunk. It is worth noting that the face and neck are virtually never involved (2).
NSF always occurs in patients with severe or end-stage chronic kidney disease (CKD) (eGFR < 30 ml/mn/1.73 m2), usually in those requiring a treatment by dialysis (3).
The disease manifestation consist in fibrosing processes and lesions are characterised by the presence of gadolinium, found mainly is complex precipitates together with iron and phosphorus, several months after the MRI procedure. The mechanisms are unknown and still under investigation.
Our experiments for MD-462, a continuation of the previous MD-375, were aimed to settle an animal model reassembling the features of NSF, by producing a condition of renal impairment and by administrating high doses of contrast agents. Our study required XRF analyses to detect minimal presence of Gd in the tissues potentially affected.
During the previous beamtime MD-375 (see report) we analyzed a number of mice with 5/6 nephrectomy that 3 weeks after surgery were administered with high doses of two contrast agents (Omiscan or Magnevist). The animals had been sacrificed 2 weeks after drug treatment and many organs had been analyzed for Gd presence. The measurements revealed that we were able to find Gd only in one sample from a nephretectomized animal that had received Omniscan. The positive tissue was the periodontal tissue of incisors.
During the recent Md-462 beam time we analyzed a new set of tissues animals treated during a more severe stage of nephropathy as indicated by plasmatic parameters (urea : 83,00 mg/dl, creatinin: 0,60 mg/dl). A similar condition was obtained 6 weeks after surgery and at this time we administered contrast agents. The animals had received 2 doses of contrast agents (Omiscan or Magnevist) for a total of at least 0.6 mg/kg (body weight) each animal.
After 4 weeks the animals however do not manifest the classical features of NSF. At this time the animals (with nephrectomy, sham operated, both treated and controls) were sacrificed and heats from 10 animals have been fixed in formalin, included in resin and different sections were obtained in order to select regions of periodontal tissue.
At ID21 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 0.2 x 0.9 µm (HOR x VERT).
We found Gd at sensitive level in many regions of histological samples corresponding to periodontal tissue, found in all the operated animals that received the contrast agents.

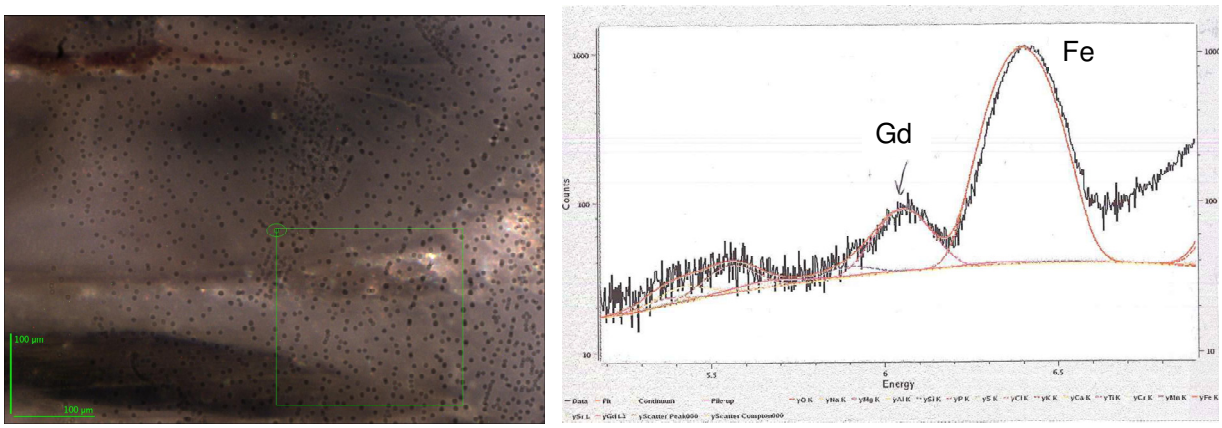

Fig. 1 Spectra (right) at long time of acquisition (Pymca screen) of a small region of the inset of the optical image (left) (tooth, boon and periodontal tissue).

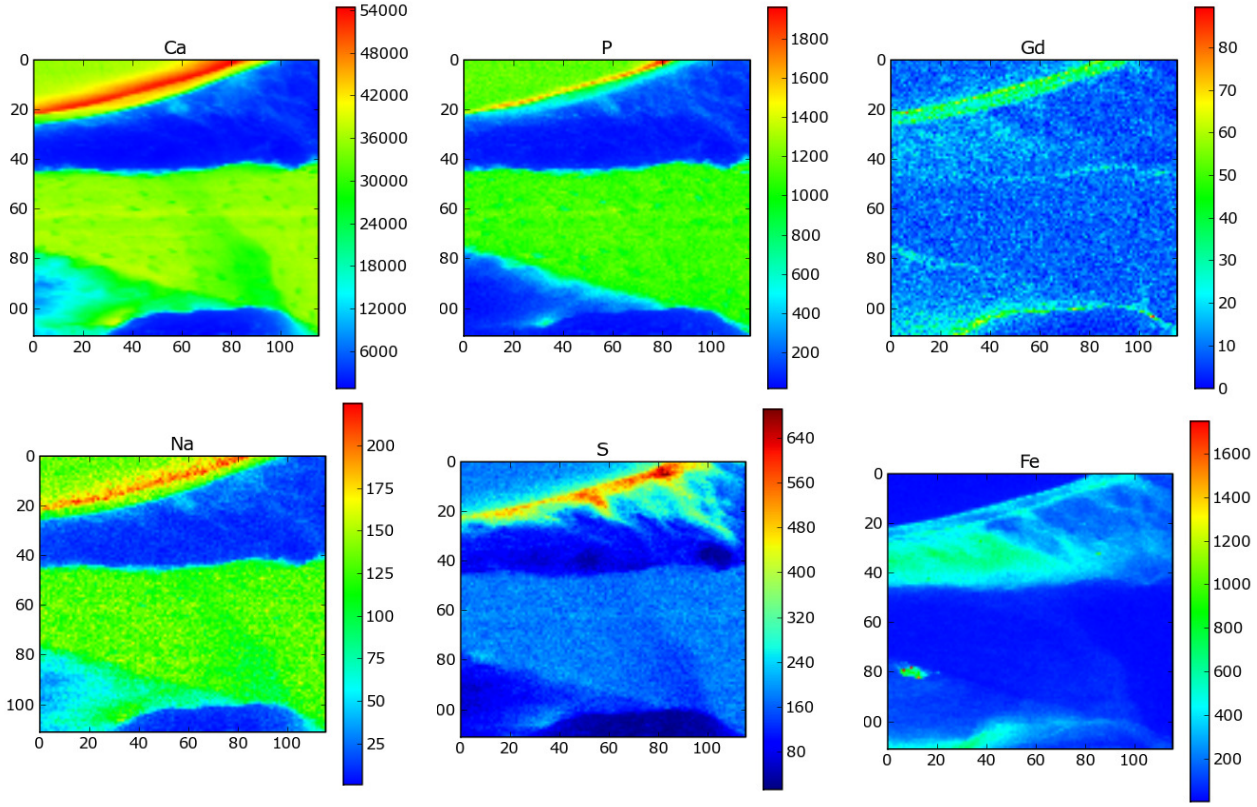

Fig.2 XRF analyses of the selected area in figure 1 (inset in optical image) and presence of Gd with a specific location in a region rich in Fe and S.

The presence of Gd was found to be specific with good signal to noise ratio. Results will be correlated with conventional histological analyses.
The results clearly confirm and expand previous results indicating that high doses of 2 linear contrast agents (Gd complexes) administered in mice under reduced renal function (previous experiments) and more under severe kidney impairment can result in an accumulation of drug and/or gadolinium in the periodontal tissue.
We did not find by XRF analyses any other organ or tissue involved by the phenomenon.
Since periodontal tissue of mice is a continuously regenerating district, our result could suggest that contrast agents have a tropism for organs (as also skin) with rapid renewal processes. This may have important implications in the understanding the NSF pathology and, by the way indicate that mouse periodontal tissue could represent a new cellular site for investigations.
We hope to divulgate the results very soon since they could advantage other researchers in unravelling to understand the molecular mechanisms that contribute to the development of NSF in some patients.
We also demonstrated the advantages of using XRF microscopy in the studies on NSF, specially in tissues where common surface elemental analyses (such as SEM-EDS) (4) could be insufficient to detect low levels of Gd as those relevant to study early stages of pathology.

1. Cowper SE, Kuo PH, Bucala R. Nephrogenic systemic fibrosis and gadolinium exposure: association and lessons for idiopathic fibrosing disorders. Arthritis Rheum 2007; 56: 3173-3175
2. 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
3. Galan A, Cowper SE, Bucala R. Nephrogenic systemic fibrosis (nephrogenic fibrosing dermopathy). Curr Opin Rheumatol 2006; 18: 614-617
4. Abraham JL, Thakral C. Tissue distribution and kinetics of gadolinium and nephrogenic systemic fibrosis. Eur J Radiol 2008; 66 : 200-207