# Multiorgan gadolinium (Gd) deposition and fibrosis in a patient with nephrogenic systemic fibrosis—an autopsy-based review

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## Abstract

**Background.** Nephrogenic systemic fibrosis (NSF) is a systemic disorder of patients with severe renal insufficiency who have received gadolinium (Gd)-based magnetic resonance contrast agents (GBCAs). The causative association with Gd exposure was strengthened by the demonstration of Gd in various tissues of NSF patients, predominantly at the bulk chemical level. The distribution of Gd at the histologic level of organs other than skin has not been reported previously.

**Methods.** We analysed tissues from an autopsy case with verified advanced NSF by light microscopy and scanning electron microscopy/energy-dispersive X-ray spectroscopy. Furthermore, we reviewed published literature to compare the histological and histochemical findings in NSF patients and chronic renal failure (CRF) patients without NSF.

**Results.** Insoluble Gd–phosphate deposits were detected in the skin, liver, lungs, intestinal wall (ileum), kidney, lymph node, skeletal muscle, dura mater and cerebellum of the NSF autopsy case, primarily in vascular walls. Some, but not all, Gd deposits were seen in fibrotic areas. Literature review highlighted that non-specific tissue fibrosis and calcification are frequent findings in tissues of patients with CRF with and without NSF.

**Conclusions.** Vascular and extracellular Gd deposits are found in multiple organs of NSF patients, associated with calcification, and often in fibrotic areas. Gd deposits are not seen in patients with CRF unexposed to GBCAs but rarely may be seen in GBCA-exposed patients without clinical signs of NSF. Apart from diagnostic findings in skin, fibrosis of muscle and dura may be more prominent in NSF patients. Our findings should stimulate further investigation of mechanisms of fibrosis and pathologic calcification.

**Keywords:** calcification; gadolinium; nephrogenic systemic fibrosis; renal failure; SEM/EDS

Initially recognized as a fibrosing dermopathy [1], nephrogenic systemic fibrosis (NSF) involves a multitude of organs involved and was first identified in 2003 [2]. Epi-demiologic studies implicated gadolinium (Gd) from magnetic resonance imaging (MRI) contrast agents as a trigger for the development of NSF [3, 4], and scanning electron microscopy (SEM) with energy-dispersive X-ray spectroscopy (EDS) demonstrated insoluble Gd deposition in lesional skin [5, 6]. The deposition of Gd in tissues, which played a major role in incriminating the metal, has so far been demonstrated predominantly in skin. However, autopsy studies have also documented the presence of Gd in skin, heart, blood vessels, lungs, lymph nodes, spleen, liver, kidney and dura of NSF patients. To date, the presence of Gd has mostly been shown by destructive method (inductively coupled plasma mass spectrometry) in organs other than skin [7, 8]. It is therefore unknown where and in what chemical form Gd may be deposited in non-skin organs and tissues. In the present study, we performed a search for Gd deposits *in situ* in various organs from the autopsy of a known case of advanced NSF (from Marckmann *et al.*'s Danish series of NSF cases [9], using SEM/EDS). In addition, we reviewed the presence of fibrosis in different tissues of chronic renal failure (CRF) patients with and without NSF in order to identify NSF-specific findings.

## Case report

The decedent was a 36-year-old woman who was on chronic hemodialysis (HD) since 1990 for renal failure attributed to chronic pyelonephritis. She received a renal transplant in 1990 (acutely rejected) and in 1992, followed by loss of graft function in 2003. The graft was removed in 2004. Since 2003, the patient developed multiple intra-abdominal abscesses with cutaneous fistulas. In December 2006, she had severe symptoms of NSF including contractures of the fingers, toes, ankles, knees and hips after repeated magnetic resonance scans with Gd enhancement (Omniscan®, total dose 65 mL or 32.5 mmol corresponding to 0.50 mmol/kg—the patient weighed 65 kg). The patient had severe secondary hyperparathyroidism when she received her NSF-eliciting Omniscan infusion: the plasma concentration of ionized calcium was in the normal range, 1.14 mmol/L (4.64 mg/dL); plasma phosphate was highly elevated, 3.48 mmol/L (10.5

mg/dL) and parathyroid hormone was also high, 627 pg/mL (65 pmol/L). Also, she was treated with relatively high intravenous doses of an erythropoietin (EPO)-analogue (epoetin-beta, Neorecormon, 20 000 IU weekly). In 2007, she was experimentally, but unsuccessfully, treated with sodium thiosulphate for her NSF symptoms [10]. She died in January 2008, 1 day after surgery for an intra-abdominal abscess.

A complete autopsy showed brawny induration and thickening of the skin of the arms and legs. There was moderate cardiomegaly and thickening of the bronchial tree. Occluding and chronically organized thrombi were present in the right superior caval and internal jugular veins. There were extensive adhesions in the abdomen, which made it difficult to identify some organs. The native kidneys were atrophic (length 7–8 cm), and scattered, slightly enlarged lymph nodes were present in the retroperitoneum. The meninges were thickened, adherent to the skull and appeared to be ossified in certain areas.

### Microscopic findings

The skin in the involved areas showed heavy bands of collagen in the dermis with an increase in fibroblasts and calcium deposits (Figure 1A and B). There were wide fibrous bands in the subcutaneous tissue with high cellularity and large areas of calcification. The heart (Figure 2) showed diffuse myocardial fibrosis with probable arterial medial calcification. There was osseous metaplasia in the right atrium with osteoclast-like giant cells in the epicardium. Sections of skeletal muscle (Figure 3A) showed vascular calcification and focal CD34-positive cellular fibrosis. Lungs showed acute and chronic venous stasis with mild to moderately increased fibrosis in the alveolar walls, interstitium and pleurae. The bronchi appeared normal with fibrosis in the adjacent vascular wall adventitia (Figure 4A). The native kidneys (Figure 5) were extensively atrophic and there was chronic venous stasis in the liver. Apart from focal calcifications and osseous metaplasia in the dura mater (Figure 6), the central nervous system (CNS) showed no other abnormality. Paraffin blocks were not available for further analysis for some organs.

### Gadolinium detection in tissues

Freshly cut surface of paraffin blocks (sent from Denmark) were examined directly in SEM, using the variable pressure system of the Aspex® (Delmont, PA) scanning electron microscope, as previously described [11]. Operating conditions were 20 keV accelerating voltage, 15- to 16-mm working distance, 0.15 torr pressure in the specimen chamber and beam current ~500 pA. Backscattered electron imaging revealed the relatively high atomic number inorganic materials in a low atomic number organic matrix (tissue). The EDS spectra collected from individual features of micrometer dimensions were compared with standard reference spectra of chemical elements, thus demonstrating the elemental composition of each feature. As we have previously reported in other NSF cases studied, all the detected Gd deposits were in the form of insoluble phosphates [12] with P, Ca and Na (and occasionally also K).

Gd deposits were detected in the skin, liver, lungs, intestinal wall (ileum), kidney, lymph node, skeletal muscle, dura mater and cerebellum (see Figures 1, 3–8). Gd deposits were not detected in the heart (see Discussion), thrombosed vessels, decalcified bone, pons, thalamus and corpus striatum. The predominant site of Gd deposits was in vessel walls, although they were also detected in the parenchyma of the various organs, in the fibrous areas as well as intracellularly. In the skin, they were found around the vessels, in the basement membrane of the sweat glands, in the subcutaneous collagenous septae and around large dermal and subcutaneous calcific deposits (Figure 1C–E). The skeletal muscle showed Gd deposits around blood vessels, in between muscle bundles and around fat compartments and was associated with Zn in certain areas (Figure 3B–D). The lungs showed Gd to be deposited in the alveolar septae, near the pleural surface and around large blood vessels (Figure 4). In the kidneys, it localized to the tubular basement membrane and blood vessels (Figure 5). The liver had an intracellular Gd deposit in a hepatocyte (Figure 8). The lymph node contained prominent deposits of Gd in a necrotic area. In the cerebellum, Gd was found in the perivascular glial cells (Figure 9).

In the tissues which showed huge calcific deposits such as skin and dura mater, Gd was detected in scattered deposits around the large deposit (Figure 6). However, no Gd could be detected within the largest calcified area.

## Discussion

Our NSF autopsy case confirms the multiorgan deposition of gadolinium in NSF and is the first demonstration that non-skin Gd deposits have the same chemical composition as skin deposits, with all detected Gd associated with P and Ca. This confirms that Gd is released from chelate and forms insoluble precipitates with hydroxyapatite-like composition. With Gd suspected to trigger the fibrosis seen in NSF [3], it is interesting that Gd is not detected in all fibrotic areas and is frequently detected in vessel walls where calcification in renal failure occurs. Administered intravenously, Gd would first encounter the vascular system and this could partially explain the location of the deposits seen. Also, some Gd deposits may not always be detectable with the analytical methodology used.

There is not yet consensus on the relative roles of chelated Gd, 'free' $Gd^{3+}$, insoluble deposits of Gd phosphates and chronic renal insufficiency itself in the induction of fibrosis in NSF. Edward et al. [13] have concluded that the chelated Gd is responsible for the fibrosis in NSF, but they also showed that the free $Gd^{3+}$ is potent in causing fibrosis at lower concentration than the chelated Gd. Li et al. [14] reported that Gd phosphate nano particles are biologically active and that the Gd released from these particles has cell-cycle promoting effects on fibroblasts in vitro. Also, serum from NSF patients increased cell hyaluronan and collagen synthesis by fibroblasts in vitro [15]. Interestingly, serum from dialysis patients without NSF also caused increased hyaluronan in this same model. However, the response to the serum of the dialysis patients was much lower in comparison to serum from NSF patients. Furthermore, two cytokines, osteopontin and MCP-1 have been reported
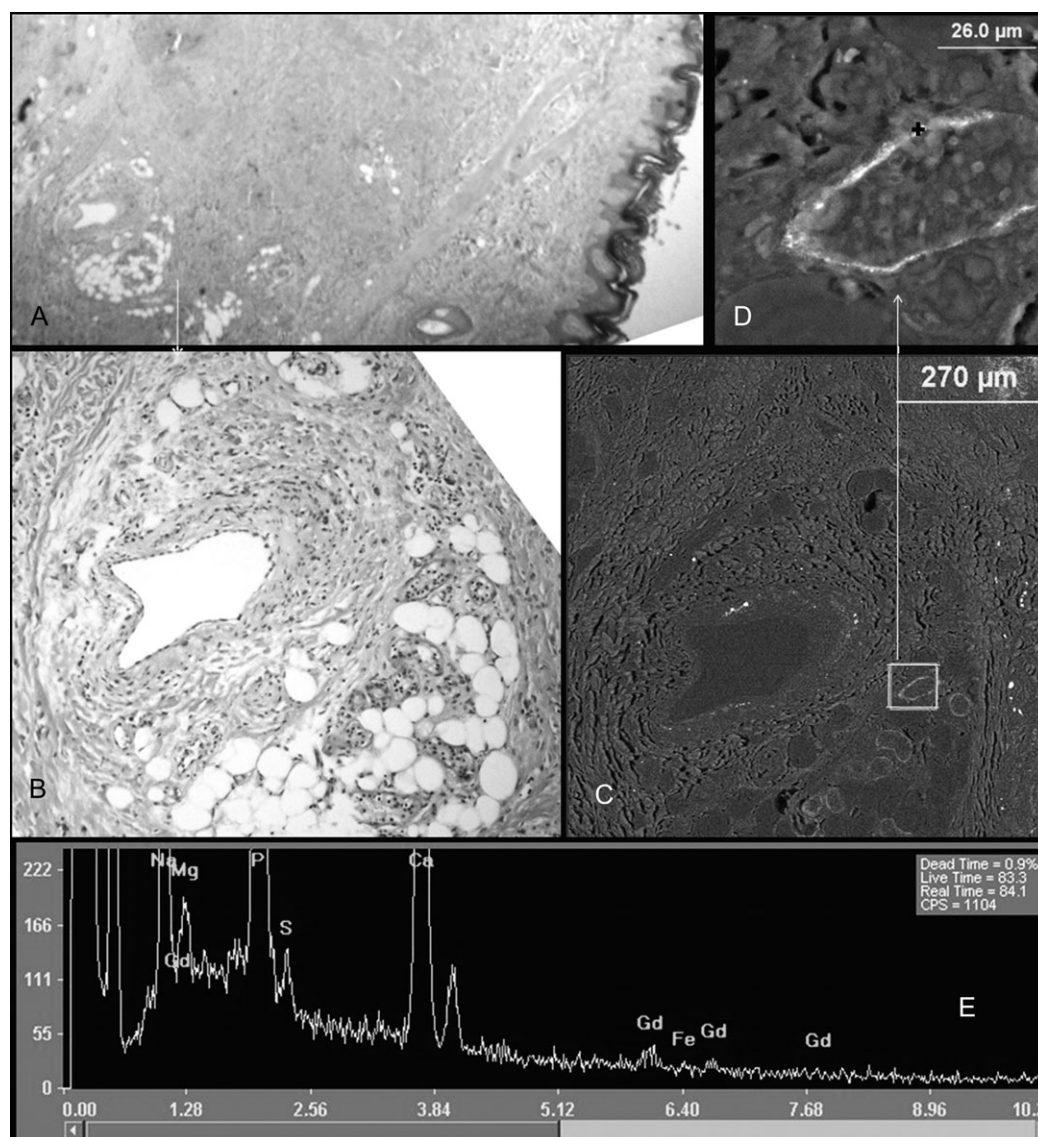
**Fig. 1.** Skin: (**A**) Low power view of affected skin with epidermis on the right. (**B**) High power view of blood vessel and sweat glands in the dermis. (**C**) SEM image of the same area as in (**B**) showing calcification along the vessel wall and around sweat glands. (**D**) Magnified view of the sweat gland. (**E**) EDS spectrum of analysis at spot indicated by '+' in D.

to be upregulated in nephritis and nephropathy [16]. Thus, it is quite possible that inflammatory and fibrotic effects can develop at sites remote from the Gd deposits in NSF, mediated by soluble growth factors and cytokines. The severe hyperphosphataemia, the hyperparathyroidism and the high EPO dose may all have contributed to an exaggerated fibrotic response to Omniscan in our patient [17].

Our inability to detect Gd in the large calcific deposits could be a limitation of our method as the very large amounts of calcium in these deposits may have led to a reduction in the relative percentage of Gd content to below our detection limits. This leads to an interesting question as to whether Gd can induce further massive calcium deposition in preexisting deposits. Increased stromal and vascular calcification has been noted in a subset of NSF patients [18]. A recent report [19] very relevant to this issue showed that Gd itself can increase

the formation of insoluble calcium phosphates and the profibrotic action of macrophages *in vitro*.

In this case, we could not detect Gd in the heart, which showed substantial fibrosis [although we have detected Gd deposits in other NSF autopsy myocardium (R. L. Davis, D. Xia , J.L. Abraham, unpublished results)]. There are several possible explanations: first, the Gd concentration in the heart might have been below the sensitivity of our method; second, the presence of formalin pigment in sections of the heart indicates acidic fixation, which may have dissolved Gd deposits. No Gd was detected in the bone marrow (which had been decalcified prior to paraffin embedding—decalcification of course solubilizes calcified tissue to enable microtome sectioning).

To our knowledge, this is the first time Gd deposition has been documented in the brain parenchyma in NSF. Preclinical safety studies performed on animals failed to reveal any
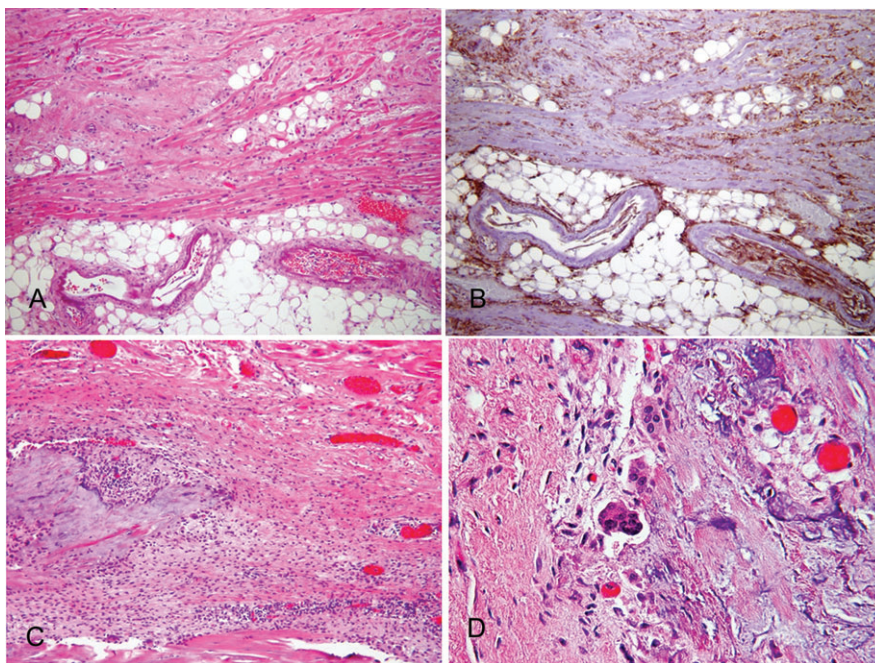
**Fig. 2.** Heart: (**A**) fibrosis in the heart atrio-ventricular nodal area. (**B**) CD34 stain. (**C**) Areas resembling metaplastic ossification. (**D**) Osteoclast-like giant cells.

neurological effect of chelated Gd when given intravenously. There is however proof of Gd toxicity in the brain when administered by the intraventricular route in rats [20] and also by intravenous route after blood brain barrier (BBB) disruption [21]. Lanthanum, similar to Gd a member of the lanthanoid rare earth metal family, has been shown to accumulate in the brain of rats with renal failure without artificial induction of BBB disruption [22]. Acute Gd encephalopathy has been reported in renal failure [23]—in this particular case, the patient developed acute renal failure and deteriorating mental status after administration of repeated and high dose of gadolinium-containing contrast agent. The subsequent non-contrast-enhanced MRI scans showed increasing cerebrospinal fluid (CSF) hyperintensity. The improvement in mental status coincided with the expected clearance of serum gadolinium and resolution of CSF hyperintensity. The authors hypothesized that the patient's deteriorating mental status was a result of gadolinium encephalopathy. The presence of Gd in the absence of any pathologic changes, such as gliosis, in the cerebellum in our case may indicate an early disease process or an incidental finding.

There remains the dilemma of determining which pathologic findings are specific for NSF as opposed to underlying chronic kidney disease. Increasing number of autopsies are expected to be performed on patients with NSF, and attributing a certain pathological finding to NSF requires careful consideration of its likelihood and frequency in renal failure patients without NSF. While most reports of systemic involvement in NSF highlight the extensive fibrosis of different organs, renal failure itself is associated with protean manifestations—some reflecting underlying disease other than renal failure itself. In the next section, we review the autopsy findings in CRF without NSF and compare them with those in NSF.

*Skin*

Cutaneous disorders are common in end-stage renal disease (ESRD), with 50–100% of the patients having at least one dermatological disorder. These manifestations (other than NSF) range from non-specific disorders like pruritus, xerosis, acquired ichthyosis and half-and-half nail to specific conditions like acquired perforating dermatoses, calciphylaxis and bullous dermatoses [24]. Pathological findings include ulcerations, epidermal hyperplasia, acanthosis, hyperpigmentation and transepidermal elimination canals with dermal amorphous material. Features of calcific uraemic arteriolopathy (calciphylaxis) include epidermal ulceration, dermal necrosis and mural calcification with intimal hyperplasia of small- and medium-sized blood vessels in dermis and subcutaneous tissue. There is acute and chronic calcifying septal panniculitis with delicate calcium deposition surrounding lipocytes or global calcification of septal capillaries in subcutaneous tissues. The incidence of calciphylaxis is reported to be 1% in patients with CRF and 4% of patients receiving haemodialysis [24]. Systemic findings have also been described in association with cutaneous necrosis and have been termed systemic calciphylaxis.

Skin is the primary organ affected by NSF. The histopathologic changes include deposition within the dermis and subcutis of dual-positive CD34/procollagen-1 spindle cells and collagen bands with intervening clefts and occasionally mucin. Microscopically, the findings related to calcification in NSF overlap with those seen in calciphylaxis [18]. Some authors describe the same Transforming Growth Factor- beta1 pathway as being responsible for both calcification and fibrosis [25], whereas others have tried to incriminate calcification to be intrinsic to the pathophysiology of NSF [18].
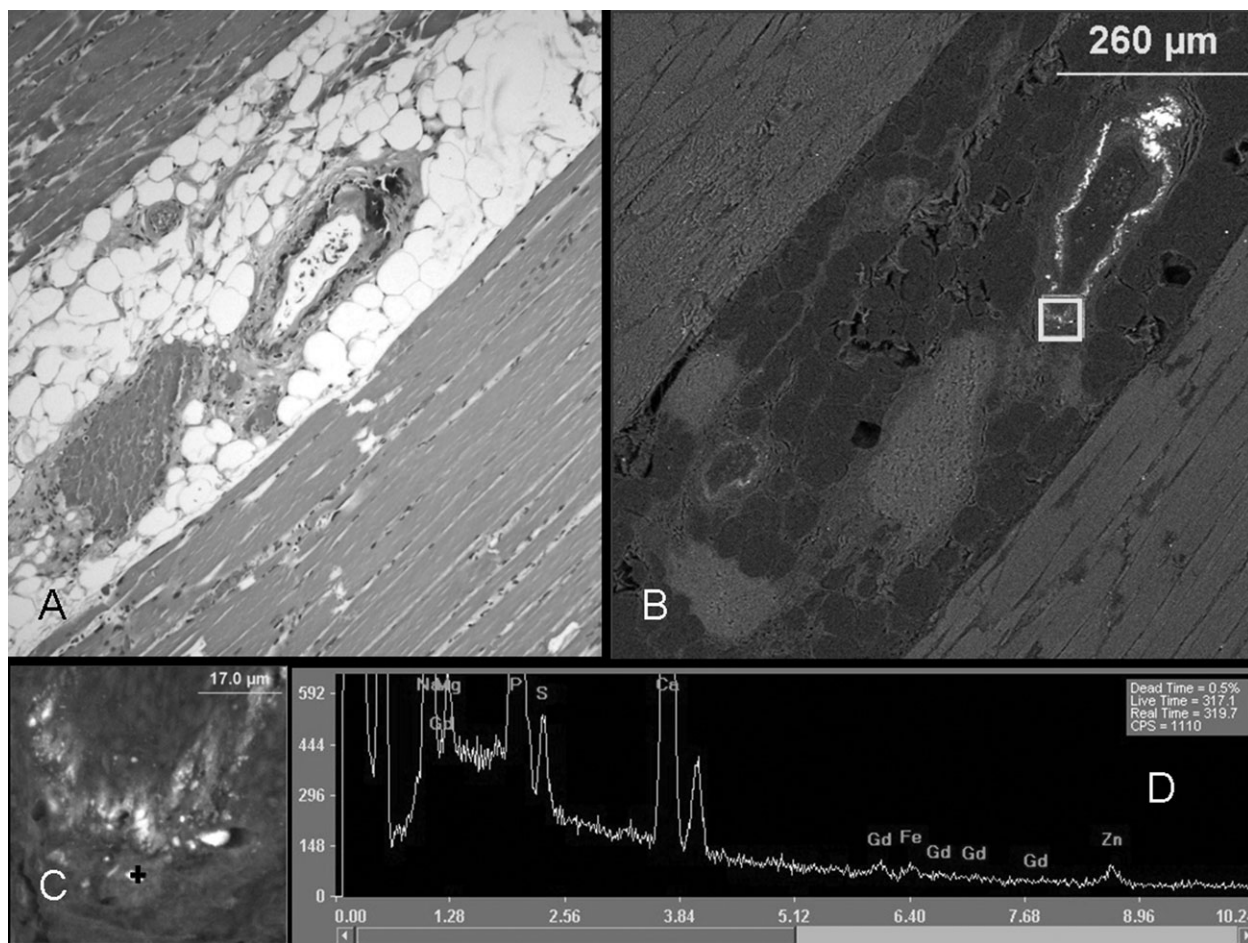
**Fig. 3.** Skeletal muscle: (**A**) Light micrograph of skeletal muscle with calcified vessel and intervening adipose tissue. (**B**) SEM image of the same area as in (**A**). (**C**) Magnified view of the boxed area as in (**B**). (**D**) EDS spectrum at '+' in (**C**), showing Gd with Ca, P, Na, Mg and Zn.

*Heart*

Cardiac involvement is a common finding in CRF. In a review of cardiac pathology in CRF [26], Hutchins describes coronary artery lesions, extensive calcification associated with hyperparathyroidism, myocardial hypertrophy, ischaemic heart disease, valvular changes and cardiomyopathy. He mentions that the relationship of cardiomyopathy to CRF is uncertain. Also (p. 93), "The uraemic patient with severe long-standing hypertension may develop intimal fibroelastosis of medium-sized muscular arteries". Calcification and oxalate crystal deposition in cardiac tissues (valves, myocardium and vasculature) may be extensive in CRF.

Nowack *et al.* [27] note that cardiovascular disease accounts for >50% of overall mortality and morbidity in patients with ESRD. This has reportedly become more apparent with prolonged survival on maintenance HD. Most patients die from sudden cardiac death of unknown cause. This may be related to the high prevalence of left ventricular (LV) dysfunction secondary to LV hypertrophy in dialysis patients.

Nowack *et al.* also noted that there was 'an ongoing dispute concerning the type of LV hypertrophy that prevails in uraemic patients'. Impaired diastolic LV function seems to be a common finding. They mention that uraemic cardiomyopathy may involve specific structural alterations, e.g. intermyocar-

diocytic fibrosis. In a discussion of interstitial myocardial fibrosis, they note that this could contribute to diastolic dysfunction. Experimentally, this is demonstrable in rats with short-term uraemic (21 days) [28]. This was measured morphometrically as a statistically significant increase in cytoplasm of interstitial cells (characterized as pericytes or fibroblasts), with a volume density of 0.035 in uraemic versus 0.006 in controls ($P < 0.001$). This apparently resulted from activation of interstitial cells.

Interstitial fibrosis was reported in the 1940s in hearts of patients who died from uraemic [29, 30]. Diffuse intermyocardiocytic fibrosis and deposition of collagen fibers was reported in autopsies of uraemic patients [31]. Mall *et al.* reported that uraemic was related to fibrosis independent of hypertension, diabetes, anaemia, heart weight and presence or absence and type of dialysis procedures. They noted that lesions were more severe in the right than left ventricle.

Mild to extensive interstitial calcium deposition in the heart with accompanying patchy to dense fibrosis had been noted in patients undergoing prolonged dialysis. This may also involve the cardiac conduction system and there may be an associated giant cell reaction [32].

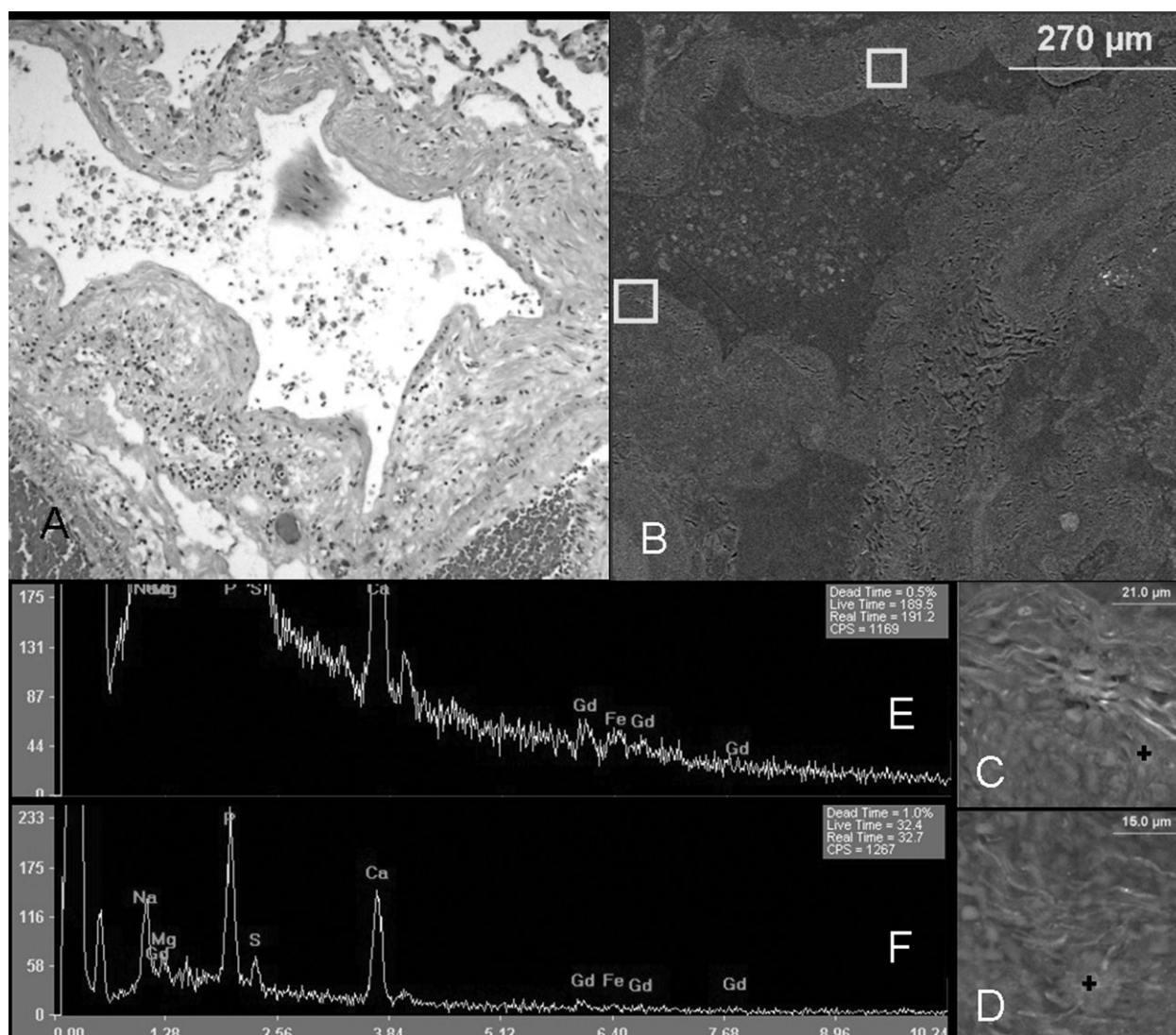Cardiovascular involvement in NSF has been reported to be the cause of death (or has contributed to mortality) in

**Fig. 4.** Lung: (**A**) Light micrograph of a pulmonary vessel. (**B**) SEM —positive BSE image of the same area as in (**A**). (**C**) and (**D**) Higher magnification of the two boxed areas in (**B**). (**E**) and (**F**) EDS spectra of the spots indicated by '+' in (**C**) and (**D**), respectively.

some NSF cases [7, 33]. The spectrum of cardiac findings in the autopsy reports of NSF varies—patchy to dense interstitial fibrosis, calcification and fibrosis of cardiac conduction system, thick fibrous plaques of mitral valve leaflets, dense fibrous tissue around the great vessels, multiple subendocardial fibrotic plaques and calcified vessel surrounded by fibrosis [2, 7, 8, 33–37].

Although fibrosis seems to be a common finding in both ESRD and NSF, the extent of fibrosis as dense fibrosis or in the form of fibrous plaques may be more supportive of a systemic involvement with NSF. This can be strengthened by the presence of CD34/procollagen + spindle cells in the fibrous areas. However, an absence of these cells does not necessarily rule out NSF as older lesions in the skin have been described to lose such positivity. Another finding that has been noted by a few authors is the fibrous thickening surrounding vessels or adventitial fibrosis. Although patients with ESRD are likely to have hypertension leading to such changes, this observation may merit further consideration.

## Lungs

The postmortem pulmonary findings in 46 HD patients have been retrospectively studied [38]. There was no control group. Only one subject had normal lungs. Twenty-six different diagnoses were made, with acute and chronic diseases being found in 44 and 37 patients, respectively. The most common acute disease was pulmonary oedema, which was found in 19 patients. Fluid overload, LV failure and probably hypoprotaeinemia and increased capillary permeability may have contributed. Pulmonary fibrosis and metastatic calcification were the most common of the chronic diseases. Eleven patients had pulmonary arteriosclerosis thought to reflect pulmonary hypertension.

In a study of pulmonary pathology of 20 patients with spinal cord injury and CRF by Fairshter *et al.* [39], the most common finding was bronchitis and pulmonary venous congestion. This was followed by interstitial and pleural fibrosis, pneumonia and pulmonary oedema.
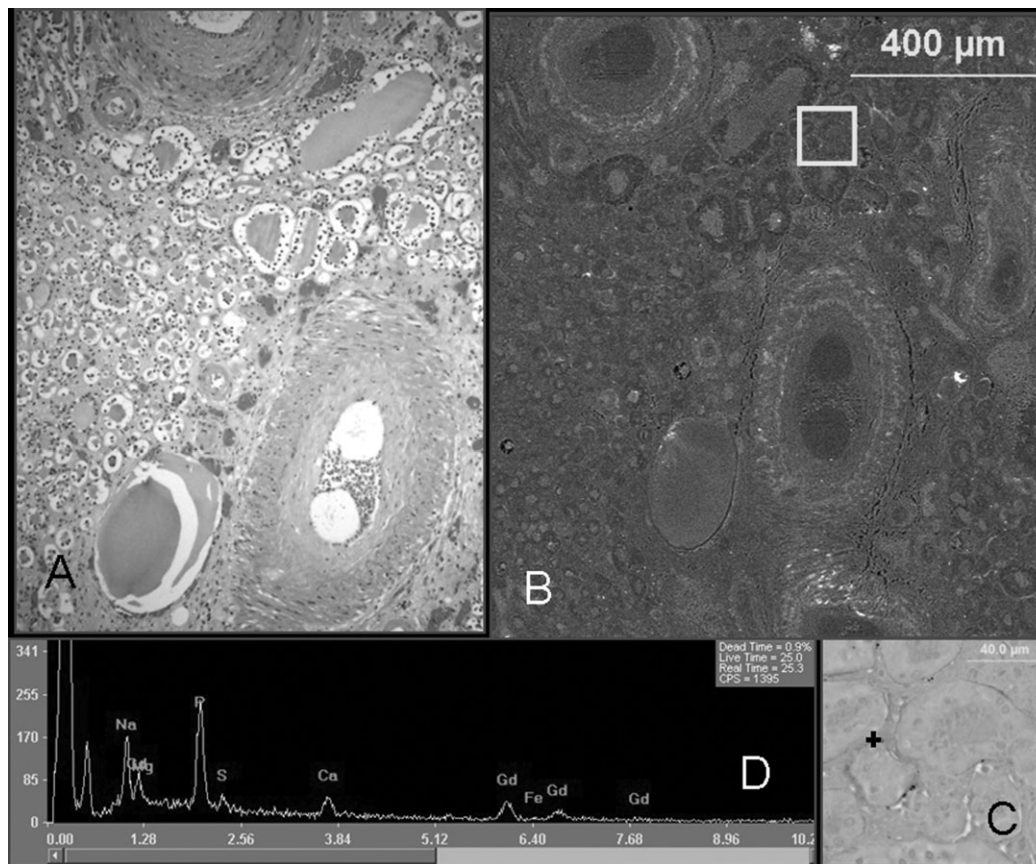
**Fig. 5.** Kidney: (**A**) Light micrograph of kidney showing atrophic changes and arteriosclerosis. (**B**) SEM —positive BSE image of same area as in (**A**). (**C**) Higher magnification SEM -negative BSE image of the boxed area in (**B**). (**D**) EDS spectrum of the spot indicated by '+' in (**C**).

Pulmonary pathology findings in the autopsy cases of NSF reported to date are diffuse moderate pleural and interlobular septal fibrosis with moderately severe transmural fibrosis of the bronchioles, thickened parietal and visceral pleura, mild and patchy interstitial fibrosis and 'interstitial fibrosis consistent with NSF' [8, 33, 36, 37]. Ongoing studies from our laboratory have shown that metastatic calcification appears to be the most common finding in the lungs of NSF autopsy patients [40]. This is not specific for NSF, of course, since it is commonly seen in ESRD or in any person dying with hypercalcaemia and hyperphosphatemia.

Adventitial and perivascular fibrosis of the small- and medium-sized arterioles of the lungs in a background of moderate interstitial fibrosis has been noted in a study of NSF patients by Jimenez *et al.* [41]. As they point out 'although less well recognized than the medial and intimal fibroproliferative lesions typically found in the pulmonary vasculature of patients with systemic sclerosis and pulmonary hypertension, adventitial fibrosis has also been described in these patients'. Such adventitial and perivascular fibrosis was also observed in small myocardial blood vessels in this study.

### Muscle

Patients with chronic renal insufficiency and uraemic myopathy show only mild and non-specific abnormalities on routine histologic sections [42]. Increased variation in fibre size, type 2 muscle fibre atrophy, and increased number of internalized nuclei may also be found in non-NSF uremic patients [42].

Muscle has been the most common organ involvement besides skin in NSF cases. Apart from muscle contiguous with the affected skin, muscles of diaphragm, skeletal muscle of the esophagus and deep muscles like the psoas have shown significant pathology, such as grossly fibrotic and indurated diaphragm and central tendon fibrosis [2, 8, 33, 34, 36, 37, 41]. Microscopically, the muscles show severe atrophy with infiltration of perimysium and endomysium with fibrous tissue [41, 43]. Greater collagen deposition was seen in the perimysial region than in the endomysial region in some cases [43].

### Dura

Limited calcification of certain parts of the dura like the falx cerebri and parasagittal dura has been seen with aging. More significant calcification has been reported in association with CRF and hyperparathyroidism, rarely with focal osseous metaplasia [44]. Of CRF patients on chronic hemodialysis reported by Barber [45], only 1 of 13 cases had autopsy-confirmed dural calcification. Ritchie and Davison [44] reported dural calcification as a complication of prolonged haemodialysis. Dural calcification may also occur in previous haemorrhage or infection, pseudoxanthoma elasticum and basal cell nevus syndrome [46].
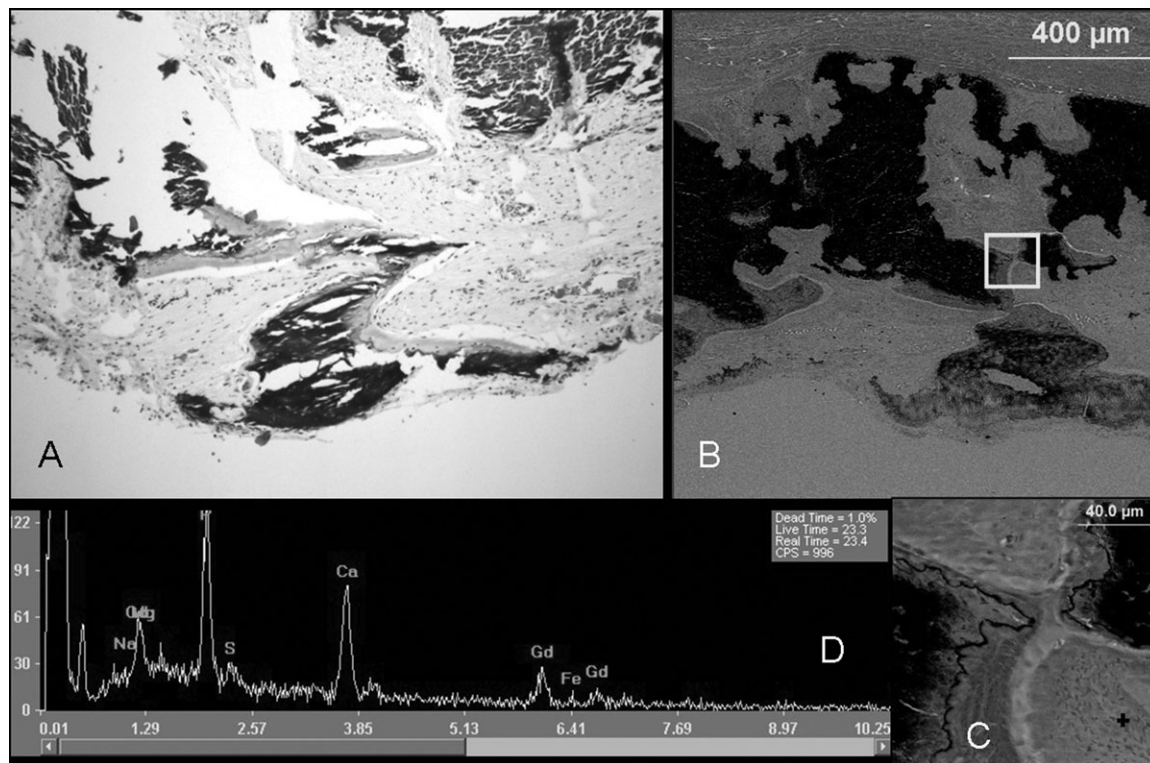
**Fig. 6.** Dura: (**A**) Light micrograph of areas with heavy calcification and osseous metaplasia. (**B**) SEM -negative BSE image of similar area; calcified tissue is dark. (**C**) Higher magnification of the boxed area as in (**B**). (**D**) EDS spectrum at the spot indicated by '+' in (C).
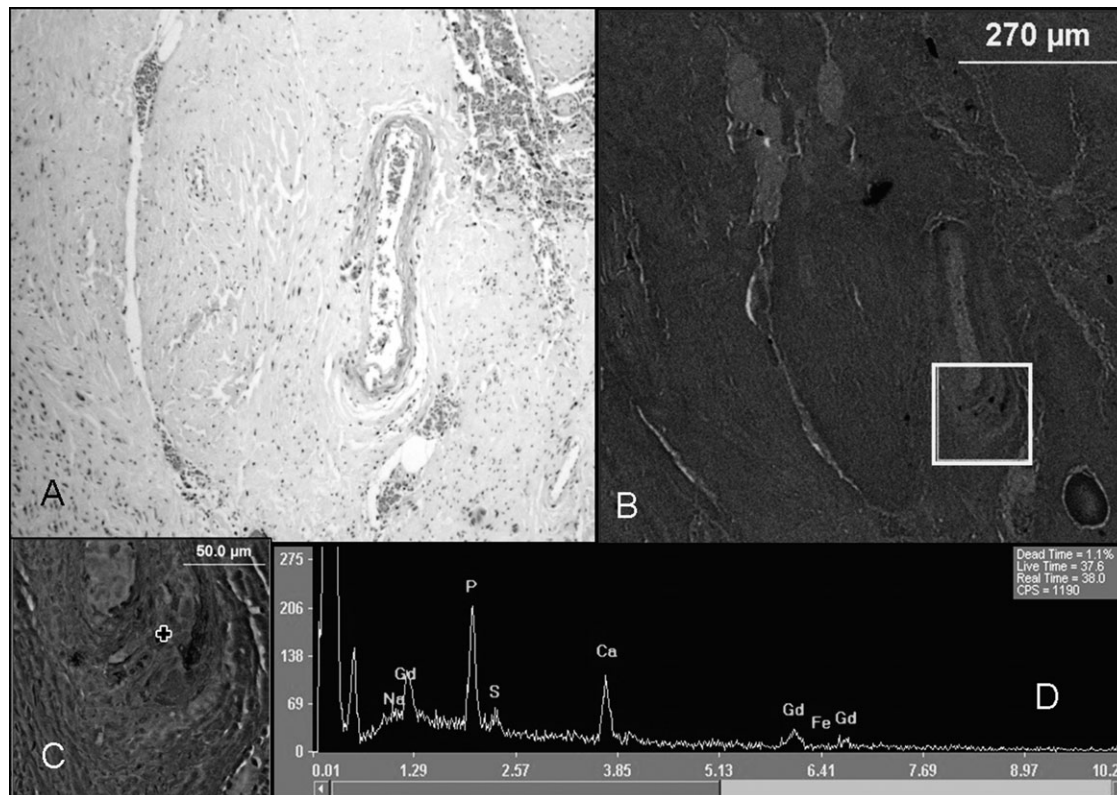


**Fig. 7.** Dura: (**A**) Light micrograph of dural vessel. (**B**) SEM image of same vessel. (negative BSE) (**C**) Magnified view of boxed area as in (**B**). (**D**) EDS spectrum at the spot indicated by '+' in (C).
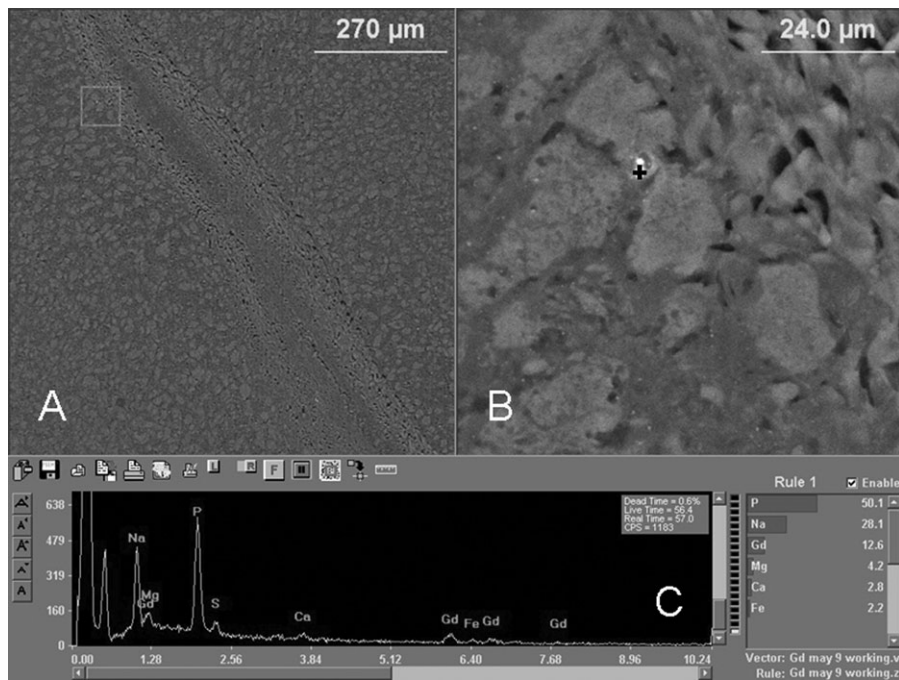
**Fig. 8.** Liver: (**A**) SEM image of liver. (**B**) Magnified view of the boxed area in (**A**). (**C**) EDS spectra of the bright intracellular deposit in (**B**).
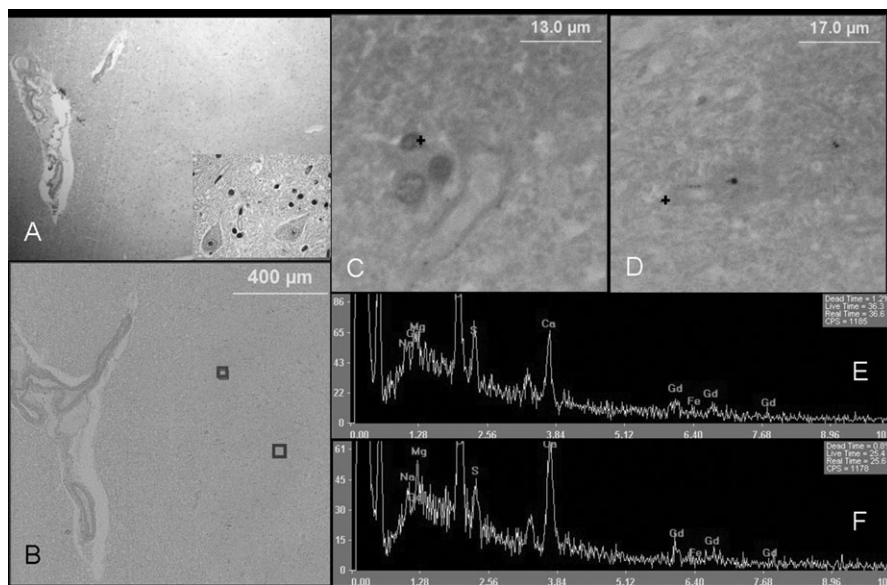


**Fig. 9.** Cerebellum: (**A**) Light micrograph of cerebellum. Inset showing high power view. (**B**) SEM image of the area in (**A**). (**C**) and (**D**) Magnified views of the boxed areas in (**B**). (**E**) and (**F**) EDS spectra of the spots indicated by '+' in (C) and (D), respectively. (all negative BSE images).

Dural fibrosis has been reported in a number of NSF autopsies, with or without accompanying dural calcification [8, 33, 35, 37]. A rare case has been reported where biopsy-proven dural involvement has preceded clinical skin involvement [47]. To our knowledge, such extensive fibrosis of the dura is not observed in CRF *per se*. However, extensive dural fibrosis may be seen in idiopathic hypertrophic pachymeningitis and locally surrounding previous infectious foci or tumour.

*Eye*

Ocular calcification may be seen in CRF and other metabolic conditions such as hyperparathyroidism, sarcoidosis and calciphylaxis. Also, in the elderly, Cogan's plaques are acellular calcium phosphate deposits in the sclera [48].

Findings in NSF include scleral redness or 'injection' and scleral plaques [49, 50]. While Cogan's plaques, or so-called, 'senile plaques' are often seen with aging [51],

their occurrence at a young age in patients with NSF is quite striking. These plaques and deposition of Gd associated with them and in other parts of the eye have been recently studied in our laboratory [52]. The cellular findings include CD34-positive cellular fibrosis appearing different from the Cogan's plaques.

### Central nervous system

Previous necropsy studies of patients dying of CRF in general show non-specific findings related to concomitant underlying disease. About 10% of uraemic patients have small intracerebral haemorrhages and necrotic foci in the granular layer of the cerebral cortex. About 2% of the patients also show focal glial proliferation [53].

The detection of Gd in the cerebellum prompted us to look for any reported CNS pathology in NSF. Our search was negative except for a single case of acute Gd encephalopathy in a non-NSF case [23].

### Other organs

Pathological changes in the endocrine organs at autopsy have been studied in a small series of patients with CRF [54]. Testicular atrophy is a prominent finding at autopsy in patients on dialysis and is present after transplantation. Thyromegaly was seen in over half and in a third of CRF patients on dialysis and with transplant, respectively [54]. Parathyroid hyperplasia was observed in almost all the CRF patients on dialysis but not often after transplant [54].

Possible involvement by NSF has been reported in the tunica albuginea of testis, rete testis, kidneys and thyroid [33].

## Conclusions

In summary, the demonstration of Gd phosphate-containing deposits in specific sites may help elucidate the pathogenesis of NSF. We do not believe at present that there are clear guidelines that allow discrimination between those systemic pathologic findings specific for NSF as opposed to CRF itself. It may be that the systemic pathologic findings in NSF represent an acceleration and increased severity of those seen in CRF in the absence of NSF. For example, isolated myocardial/pericardial fibrosis is not specific for NSF. It appears that most of the reported fibrosis in NSF develops where there is normally some dense fibro-connective tissue, including dermis, dura mater, diaphragm, sclera, perimysium of muscles and vascular adventitia. Careful history, analysis for Gd and definitive skin findings for NSF are important in making this differential diagnosis. The question remains open as to the relative causal contributions of NSF and CRF to systemic fibrosis observed in a patient with a clear clinical and dermatopathologic diagnosis of NSF.

The precipitation of calcium phosphates is a major finding common to both NSF and CRF. The preexisting calcium–phosphate imbalance in patients with CRF may be vital in the risk of developing NSF when Gd is administered as MRI contrast. Although at least one case–control

series reported increased phosphate and ionized Ca as risk factors for developing NSF [17], more studies to test this hypothesis are needed. It will be difficult to do further prospective studies in humans as, fortunately, with recognition of the relationship of NSF to Gd release from MRI contrast agents, the disease incidence has dropped to nearly zero [55]. Attempts to treat existing NSF and/or to prevent its progression are still important areas for research, and focus on the Gd incorporation into and solubility of calcium–phosphate deposits may be worthwhile. Potentially important insights into mechanisms of fibrosis and pathologic calcification will likely result from future NSF- and Gd-related investigations.

*Conflict of interest statement.* None declared.

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