Case Report

Nephrogenic fibrosing dermopathy: a novel, disabling disorder in patients with renal failure

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Introduction

Nephrogenic fibrosing dermopathy (NFD) is a rare, recently described cutaneous fibrosing disorder that primarily affects patients with a history of renal disease [1]. Since the first report in 2000 by Cowper et al., about 100 cases of NFD have been described worldwide, and clusters have been observed in dialysis units and medical centres in the US, the UK and Switzerland. The disorder is not limited to haemodialysis patients as was suggested by initial observations, but may also occur in patients receiving peritoneal dialysis and in patients suffering from renal insufficiency who never have been dialysed [1–4,7]. Patients typically develop acute, lumpy, plaque-like indurations involving the extremities, and occasionally the trunk and buttocks. The head is almost always spared. The diffuse skin thickening and hardening may be accompanied or preceded by isolated nodules and, rarely bullae. Pruritus and burning pain are common clinical complaints, and sometimes there is a palpable warmth. The lesions may be complicated by flexion contractures of the adjacent joints. The disease appears to have a chronic and unremitting course in most patients [1,2,7]. The aetiology and pathogenesis remain largely unknown. As a consequence, therapeutic measures with proven efficacy are non-existing to date. In the present paper we report two additional cases of NFD recently identified in our unit. Furthermore, an overview of the available literature data is presented. The main aim is to make the nephrology community aware about this disabling skin condition.

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Cases

Case 1

A 56-year-old Caucasian man presented at the hospital with a history of progressive thickening and hardening of the skin in all four limbs. The skin lesions occurred 3 weeks after a transplantation of a first cadaveric renal graft. The induction immunosuppressive regimen included corticosteroids, mycophenolate mofetil and tacrolimus. On the eighth postoperative day, the patient underwent a semi-urgent transplant nephrectomy because of primary non-functioning. Histopathologic examination of the nephrectomy specimen revealed diffuse cortex necrosis. The patient’s medication at the time of the first skin manifestations included enoxaparine, amiodarone, calcium carbonate, erythropoietin alfa, calcitriol, omeprazole and bisoprolol.

The patient had been in haemodialysis therapy for 5 years for end-stage renal failure secondary to adult polycystic kidney disease. His medical history included arterial hypertension and ischaemic heart disease.

Before the onset of skin lesions, the patient had noted an abnormal stiffness and oedema affecting his four limbs. Initially, the skin surface resembled the peel of an orange. Thereafter, nodules occurred progressively. Finally, the nodules coalesced into plaques of hardened and thickened skin with irregular edges, most prominent on the left lower arm, both hands (including the palms) and on the right leg and foot. About 2 months after the appearance of the first skin lesions the patient was referred to our hospital for further diagnosis. At that time, the disorder was still progressing at a slow but steady pace. The patient was further disabled to an important degree, mainly as a result of severe flexion contractures, which were most prominent in the left elbow-, wrist and finger-joints (Figure 1). Moreover, he complained of intractable burning pain at the sites of the lesions, for which opioid analgesics had to be prescribed. The lesions felt warm on palpation. There were no lesions on the face,
neck or trunk. The arteriovenous fistula in the affected left arm was occluded.

Routine laboratory analyses did not reveal important abnormalities. The C-reactive protein was slightly raised, sedimentation rate was normal. Thyroid function tests were unremarkable. Antinuclear antibody (ANA) and anti-neutrophil cytoplasmic autoantibody (ANCA) testing were negative. Serum and urine protein electrophoresis showed no monoclonal fraction. The patient tested negative for anti-phospholipid, hepatitis B and C, HIV and for anti-*Treponema pallidum* antibodies.

Ultrasound imaging of the arms showed diffuse infiltration of the s.c. tissues, at the sites of the clinical lesions. Magnetic resonance imaging of the left lower arm showed a very inhomogeneous pattern of the musculature, as seen in myositis, as well as abnormally inflamed subcutaneous adipose tissue. Bone scintigraphy (tracer: Tc99m-MDP) showed an irregular and increased tracer-capture in the soft tissues of the extremities, mainly the left arm and right lower leg, corresponding with the most severely affected limbs. Whole-body positron emission tomography performed 45 min after the i.v. injection of 10 mCi of 18F-fluorodeoxyglucose (FDG-PET) showed a clearly increased metabolic activity at the sites of clinical lesions.

A skin biopsy showed histopathological features currently associated with NFD [2]. There was an increased cellularity in the dermis and in the s.c. septa, which were both widened. This increased cellularity consisted especially of plump spindle shaped mononuclear cells admixed with few multinucleated cells. An Alcian blue stain revealed an increased deposition of acid mucins in the dermis. Immunohistochemically, numerous Factor XIIIa spindle shaped cells were found. In contrast, CD34-positive spindle shaped or dendritic cells were less prominent. The CD68 stain showed scattered macrophages between the spindle shaped and dendritic cells (Figure 2).

**Case 2**

A 57-year-old Caucasian liver transplant recipient presented with painful oedema of all limbs, followed by thickening and hardening of the skin, which had a grey-brown discolouration. He also noted a pruritic sensation of the skin and pain on palpation. The patient had been treated with haemodialysis for ~1 month when the skin lesions first appeared. The end-stage renal failure was secondary to acute idiopathic membranoproliferative glomerulonephritis with intracapillary and extracapillary proliferation. The glomerulonephritis was resistant to classical therapy with pulse corticosteroids and plasmapheresis. The immunosuppressive treatment was complicated with an invasive pulmonary mycosis with *Aspergillus fumigatus*. The latter was successfully treated with liposomal amphotericin B and subsequently echinocandins.

In the patient had undergone an orthotopic liver transplantation ~2 months before presentation because of hepatocellular carcinoma in a cirrhotic liver. The end-stage liver disease was secondary to hereditary haemochromatosis. His medical history was remarkable for insulin-dependent diabetes mellitus and several episodes of *Clostridium difficile* colitis post-transplantation.

His maintenance therapy included corticosteroids, mycophenolate mofetil, liposomal amphotericin B, acyclovir and co-trimoxazole.

Immunological screening was unremarkable. ANA and ANCA testing were negative. Serum and urine protein electrophoresis showed no monoclonal fraction. The patient tested negative for hepatitis B and C antibodies.

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**Fig. 1.** The forearms and hands of a patient with nephrogenic fibrosing dermopathy. The swelling of both hands, accompanied by palmar erythema and contractures of the fingers is obvious. The arteriovenous fistula is occluded (arrow).
Whole-body FDG-PET performed 2 months after the onset of the skin lesions showed increased metabolic activity in the limbs at the sites of the clinical lesions (Figure 3).

The following months, the oedema progressively resolved but a diffuse thickening and hardening of the skin persisted. The patient moreover developed flexion contractures of the ankle-, knee-, hip- and elbow joints. These contractures caused severe physical disability. At the time of discharge, 5 months after the start of the skin lesions, the patient was almost bed-ridden. Fortunately, the skin disorder tended to stabilize and improve spontaneously thereafter. The skin hardness improved and thanks to intensive physiotherapy, the mobility of most joints was restored. Nevertheless, the diffuse thickening persisted. Therefore, a skin biopsy was performed and showed the typical histopathologic features of NFD.

**Discussion**

NFD is a newly recognized cutaneous fibrosing disorder marked by the acute onset of induration mostly involving the upper and lower limbs of patients with acute or chronic renal failure. The first case was
observed in 1997, and as of May 2003, about 100 cases have been reported to the Centers for Disease Control and Prevention (CDC). This number probably represents an underestimation of the real incidence. Forty-three cases have been described in literature to date, mostly as case reports [2,4–9]. The clinical characteristics of these patients as well as remarkable laboratory values are summarized in Table 1. Patients of all ages may suffer from this skin disorder. A slight male preponderance is observed. All causes of renal failure are represented equally. Most of the patients are treated with haemodialysis at the time of presentation. Patients on peritoneal dialysis or patients with renal dysfunction free of any form of dialysis may be affected as well. The duration of kidney disease seems not to be important in the development of NFD. Some patients with NFD developed skin tightening in the earliest stages of kidney diseases, while others had prior kidney disease for several years. The range of clinical manifestations of NFD continues to expand. Patients with NFD typically describe swelling and tightening of the skin, usually limited to the extremities. The lesions are often preceded by painful anasarca. The condition may develop over a period of days to several weeks. In many cases, the skin thickening inhibits the flexion and extension of adjacent joints, resulting in contractures. Severely affected patients may be unable to walk, or fully extend the joints of their arms, hand, legs and feet. The skin changes may start as reddened or darkened patches, papules or plaques. In time, the skin may feel ‘woody’ and the surface may resemble the peel of an orange. Patients may experience a burning sensation, itching or even severe sharp pains in the involved areas. Both a symmetrical and asymmetrical distribution of the lesions have been described. The areas between ankles and thighs most commonly involved, followed by involvement of the lower arms. Hand and foot swelling with blister-like lesions has also been reported. Some patients have reported yellow papules or plaques on or near the eyes.

The aetiology and pathogenesis of NFD are unknown. The recent emergence and clustering of cases at medical centres and renal transplant centres suggest the possible involvement of an infectious agent or toxic contaminant, although none were identified to date [2,4,5,6]. At the time of presentation, several patients were treated with calcineurin inhibitors, which are known to increase the level of TGF-β [10,11]. In susceptible patients, this cytokine may mediate the florid fibroplastic proliferation that characterizes the disease. Reviewing the available laboratory data, a high prevalence of antiphospholipid antibodies (a marker of small-vessel vasculopathy) and the HLA-A2 allele was noted in patients. The relevance of these laboratory data with regard to the pathogenesis of NFD has to be elucidated by further research.

NFD resembles other fibrosing skin disorders including scleromyxoedema, scleroderma, eosinophilic fasciitis, eosinophilia-myalgia syndrome and Spanish toxic oil syndrome [3–7]. The specific distribution of

Table 1. Clinical characteristics of patients with NFD at the time of presentation

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<td>Age (year)</td>
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<td>56.0 ± 15.5</td>
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The specificity of NFD remains to be elucidated by further research.
cutaneous involvement, the occurrence in the setting of renal failure, and the unique histopathologic features (i.e. thickened collagen bundles with surrounding clefts, mucin deposition, and a proliferation of fibroblasts and elastic fibres) distinguish NFD from the other fibrotic disorders.

Our two patients completely fulfilled the diagnostic criteria of NFD. A previously unreported finding in our two cases was the clear visualization of the skin lesions by scintigraphic techniques. Both PET and bone scintigraphy showed increased tracer captation in the limbs at sites corresponding with the clinical skin lesions. Soft tissue accumulation of Tc99m-MDP used for bone scintigraphy is well known in areas of infection and necrosis. It reflects inflammation-induced loss of the cell membrane integrity, which results in an influx and fixation of the tracer intracellularly. Whole-body FDG-PET is now widely accepted for cancer staging and restaging. More recently this technique has also been proposed for the evaluation of inflammatory or infectious diseases. It is based upon the aspecificity of FDG as a tracer, which not only shows increased accumulation in cells after malignant transformation, but also in activated inflammatory cells, including monocytes and macrophage. The potential use of this technique in inflammatory disease, besides initial evaluation of disease extent and intensity, could be the evaluation and/or comparison of the efficacy of different therapeutics. In this case, quantitative PET should be used to correlate the change of FDG-metabolism in the lesion, indirectly reflecting inflammatory activity, in relation to the treatment.

As NFD is a rare, relatively recent diagnosis, the course of the disorder remains largely unknown. Some patients report a spontaneous gradual improvement in mobility and slight softening of the skin over time. Complete spontaneous healing in a patient with ongoing kidney disease has not yet been reported. Recent evidence indicates that the disorder does not predispose to the development of new systemic, immunologic or malignant diseases [7].

There is currently no effective treatment. Oral steroids have been tried empirically by several clinicians based on the hypothesis that growth factors such as TGF-β may be implicated in the pathogenesis. Other options include topical vitamin D analogues, plasmapheresis, photopheresis, cytotoxan, thalidomide and ultraviolet therapy [3]. Intense physiotherapy is advised in every patient to prevent or reverse limb disability related to contractures of the joints.

In an attempt to collect and organize information about patients with NFD from all over the world, the CDC constructed a NFD registry. The ultimate goal of this project is to identify factors that may be related to or causative of NFD. In addition, information about treatment successes and failures is collected in order to try to find effective therapies and design future medication/therapy trials. All physicians who have encountered patients with suspected or proven NFD are encouraged to contact the CDC [3].

Conflict of interest statement. None declared.

References


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