Case Report

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End-stage disease of native kidneys in a patient with biopsy-proven Arndt-Gottron scleromyxoedema and recurrence in the transplanted kidney

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Abstract

End-stage renal disease-stage 5 chronic kidney disease (CKD) of the native kidneys, related to biopsy-proven Arndt-Gottron scleromyxoedema, developed in a male patient. From 1998 until 2001, the patient was treated by haemodialysis. In June 2001, cadaveric kidney transplantation was performed. In January 2004, a kidney biopsy was performed because of deteriorating renal function revealing relapse of scleromyxoedema with typical concentric narrowing of the arterioles due to accumulation of mucopolysaccharides with severe glomerular ischaemia.

Arndt-Gottron scleromyxoedema is an as yet unsuspected cause of stage 5 CKD of the native kidneys. Moreover, the disease can relapse in the transplanted kidney, again leading to intractable transplant stage 5 CKD.

Keywords: Arndt-Gottron; scleromyxoedema; end-stage renal disease; chronic kidney disease; renal failure; ischemia; kidney transplantation; mucin deposition; skin fibrosis

Introduction

Scleromyxoedema is a rare disorder characterized by the proliferation of fibroblasts and deposition of mucin in the dermis [1]. The skin condition results in a distinctive generalized thickening and stiffening of the skin and small lichenoid papules and amorphous, Alcian blue-stainable deposits in the dermis. The disease occurs in both men and women between the third and seventh decades. Sclerodactyly, pruritus and microstomia are frequent cutaneous manifestations of this disease [1]. Mobility of the patient can be disturbed. The following criteria for diagnosing scleromyxoedema were proposed in 2001: (i) generalized papular and sclerodermoid eruptions; (ii) mucin deposition, fibroblast proliferation and fibrosis in the skin; (iii) monoclonal gammopathy and (iv) the absence of thyroid disease [2].

Extracutaneous manifestations are frequent. IgG-λ paraproteinaemia is seen in up to 83% of cases. Most frequently associated with this disease are musculoskeletal findings such as proximal myopathy and arthralgia, oesophageal dysmotility and dysphagia, as gastrointestinal findings, and central nervous system abnormalities. Ureteral strictures have been described [2].

Its pathophysiology and treatment are still unclear. The disease is rarely self-limited, and it is often resistant to therapy. A wide array of mostly immunomodulatory or immunosuppressive strategies have been used without consistent effect, including the use of topical and systemic corticosteroids, retinoids, psoralen ultraviolet A therapy (PUVA) and photopheresis, plasmapheresis and plasma exchange, interferon-α, melphalan, cyclosporine, cyclophosphamide and IV immunoglobulins [2–4].

A recent review considered renal involvement in scleromyxoedema incidental [1]. However, we describe here a patient with scleromyxoedema who had renal involvement—showing typical histological findings of scleromyxoedema on renal biopsy and developing stage 5 chronic kidney disease (CKD). After transplantation, he had a recurrence in his graft, with the same typical lesions and parallel deterioration of the function of his grafted kidney.

Case report

In 1995, this white male patient then 53 years old was diagnosed to have scleromyxoedema—Arndt–Gottron
syndrome—confirmed with a skin biopsy. Clinically, his condition involved the entire skin, including the face. Because of incapacitating mobility disturbances and muscular weakness, he needed special assistance in daily living. He presented with a monoclonal gammopathy of unknown significance (MGUS) and with the Grzybowski syndrome, with multiple eruptive keratoacanthomas, which were treated by cryotherapy. For his scleromyxoedema, the patient had received courses of PUVA, interferon-α and IV immunoglobulins, after which his skin disease became clinically stable. Interferon had to be stopped, however, because of intolerance and depression.

In 1997, he developed mild peripheral polyneuropathy together with two pulmonary lesions, which were found on a CT scan of the thorax and which remained unchanged throughout follow-up. The MGUS also remained unchanged. Renal failure developed over time and we performed a biopsy when the patient’s glomerular filtration rate (GFR) was 60 ml/min/1.73 m².

Fig. 1. Renal biopsy studies (A) native renal biopsy (Alcian Blue, AB × 25). Deposition of AB positive material in the wall of a medium sized artery (arrow); (B) native renal biopsy (electron microscopy, EM × 3000): ischaemic changes in the glomerulus; (C) BK virus nephritis in the transplanted kidney, 9 months after transplantation, without obvious vessel alterations compatible with scleromyxoedema; (D) renal transplant biopsy, 30 months after renal transplantation, presence of AB positive mucoid material (arrow) in the wall of the arterioles (AB × 25); (E) EM of transplant kidney (×3000): vascular changes characterized by increased cellular space between the smooth muscle cells (white arrows), due to the accumulation of whorls of basement membrane material. The clear spaces represent glucosamine aggregates; (F) transplant nephrectomy specimen. Severely altered explant revealing chronic nephropathy with thickened medium sized vessels, compatible with severe scleromyxoedema lesions.
demonstrating, with electron microscopy as well, renal involvement by scleromyxoedema (Figure 1A and B) as evidenced by Alcian blue-positive mucin deposition in the wall of the arterioles and ischaemic changes. Congo red and periodic acid-Schiff stains were negative. We also diagnosed sleep apnoea and arterial hypertension (WHO stage 1). A deficit in diffusion capacity on pulmonary function testing (DLCO 44%) was tentatively attributed to the accumulation of mucopolysaccharides. His thyroid function tests were always normal, and Raynaud’s phenomenon and autoantibodies were absent.

In December 1998, the patient went on haemodialysis for CKD stage 5. Basal cell epitheliomata of the skin of the face and arm were resected in February 2000 and November 2001. These basal cell skin lesions did not constitute reason for denying the patient enrolment on the waiting list for transplantation; and he had an uncomplicated cadaveric kidney transplantation in June 2001—with an HLA mismatch of 2/6 and a cold ischaemia time of 23 h 30 min. After a post-transplantation induction therapy with basiliximab, he was started on maintenance therapy with tacrolimus, mycophenolate mofetil and steroids. His serum creatinine when first discharged from the hospital was 1.5 mg/dL. Because of the CMV donor positivity, recipient negativity constellation, the patient received a 3-month course of 3 g of oral ganciclovir daily. His hypertension was successfully treated with the ACE inhibitor quinapril, 20 mg daily. His post-transplantation course was complicated in March 2002 when he developed BK virus (BKV) nephritis with a positive PCR in urine and plasma, and a positive graft biopsy (Figure 1C). That biopsy specimen was devoid of signs of scleromyxoedema—unlike what had been found in the native kidney. Immunosuppression was reduced, by tapering and stopping tacrolimus, after which his creatinine remained stable at a level of ~2.2 mg/dL. BKV plasma PCR became negative after 3 months, and remained negative thereafter. In 2003, spino-cellular epitheliomata developed on his right ear, back and eyelid—his skin having thereafter. In 2003, spino-cellular epitheliomata developed on his right ear, back and eyelid—his skin having

In 2003, spino-cellular epitheliomata developed on his right ear, back and eyelid—his skin having remained remarkably stable during the previous 2 years. We treated these new lesions with surgical resections and photodynamic therapy.

At the end of 2003, his creatinine started to rise towards 2.5 mg/dL, corresponding with a Cr-EDTA clearance of 35 ml/min/1.73 m². A kidney biopsy revealed nine ischaemic glomeruli with sclerotic basal membrane along with tubulo-interstitial involution and interstitial fibrosis. The arterioles demonstrated severe concentric narrowing of the lumen, with accumulation of mucopolysaccharides in the arteriolar wall staining with Alcian blue, a typical feature of Arndt–Gottron scleromyxoedema, showing lesions similar to those in the skin biopsies of patients with scleromyxoedema. Glomerular ischaemia, identified in biopsy, is typical for obliterating arteriolar disease, and is attributable to the accumulation of mucopolysaccharides in the wall of the arterioles.

There is only one other description of the association of scleromyxoedema and progressive renal failure [8]. Kantor et al. [8] in 1986 described a case of rapidly progressing renal failure in a patient with uncontrolled arterial hypertension and scleromyxoedema. In that case, the biopsy of the native kidney demonstrated concentric lamellar fibrosis of the small arteries and intimal proliferation and myxoid degeneration, and electron microscopy showed a diffusely thickened glomerular basement membrane with focal broadening of the epithelial foot processes, mesangial interposition and prominent subendothelial lucent zones. On post-mortem tissue, Alcian blue, indicating the presence of acid mucopolysaccharides, prominently stained the extracellular matrix of the intimal wall of renal vessels, with lesions ranging in diameter from 100 to 300 μm [8].

The pathogenesis of scleromyxoedema remains unknown, but a circulating factor causing pathology in multiple organs, including the GI system, the central nervous system, the pulmonary system and the musculoarticular system, seems a very likely factor. Various hypotheses have been elaborated. The most common hypothesis is that the underlying defect is a disorder of fibroblasts, causing mucin deposition. The pathology in the skin is caused by the accumulating fibroblasts that produce mucin: It is the same mucin that we find in renal vessels but without the associated fibroblasts, which may indicate that an excess of mucin is deposited in inappropriate places, such as the arteriolar wall, slowly causing ischaemia of various internal organs. The basis of a second hypothesis is the
observation that, in up to 80% of cases, patients have an MGUS IgG λ, but plasma cell dyscrasia or multiple myeloma is not consistently concomitant. The significance of this paraproteinemia is not clear, and the protein does not directly stimulate fibroblast proliferation—although sera from some patients in one study did stimulate fibroblast proliferation in vitro, but not in another [2]. Standing as arguments against this second hypothesis are the following observations: the disease and the cutaneous lesions can appear before the paraproteinemia does; the paraproteinemia persists after eventual clinical remission, and there is no correlation between the level of paraproteinemia and disease progression. Kulczyński et al. [2] even proposed an alternative hypothesis: that acidic mucin is the primary abnormality and that the paraproteinemia is a mono- or poly-clonal B-cell response to mucin deposition.

Scleromyxoedema must be clinically differentiated from other mucinous deposition diseases, such as localized scleroderma, sclerodermatous systemic sclerosis and prebiliary myxoedema. A negative thyroid evaluation, as in our patient, may help differentiate it from hypothyroidism, which also is a mucinous deposition disorder [6]. A history of Raynaud’s phenomenon is more indicative of systemic sclerosis/scleroderma. But that was absent in our patient, as were autoantibodies and other signs of CREST (calcinosis, Raynaud, oesophageal dysmotility, sclerodactyly and telangiectasia)—which are of course not essential for the diagnosis of systemic sclerosis, as in the unusual presentation of scleroderma sine scleroderma. Furthermore, in our patient, arterial blood pressure was perfectly controlled throughout his disease history, before as well as after transplantation—therefore, ruling out a hypertensive crisis. Monoclonal gammopathy, in contrast to scleromyxoedema, is not a typical feature associated with systemic sclerosis. On clinical grounds, scleromyxoedema can be discriminated from systemic sclerosis on the basis of the presence of an indurated erythematous skin with papules and longitudinal facial folds. In our patient, the skin biopsy and the clinical course were unequivocally indicative of scleromyxoedema.

A histological picture identical to the one described in his native kidneys, in combination with evolving and intractable renal failure, developed when our patient was ‘re-challenged’ with a new set of unaffected glomeruli at transplantation. In the presence of the underlying scleromyxoedema, these glomeruli became histologically ischaemic and physiologically inefficient over 30 months after transplantation. Immunosuppression according to standard post-transplantation protocols did not halt this deterioration—though various forms of immunosuppression can slow down scleromyxoedema progression in some patients, as happened in the native kidney in this patient (while being treated with interferon and IVIG).

Our patient developed an episode of BKV nephropathy, which resolved following reduction of immunosuppression. We even eliminated the potentially nephrotoxic calcineurin inhibitor tacrolimus from the therapeutic drug regimen. BKV activity, as monitored by plasma PCR remained negative, and subsequent renal histology did not demonstrate evolving BKV nephritis or BKV expression in renal tissue. Hence, it is unlikely that the further decline in kidney function in the grafted kidney was attributable to BKV infection or calcineurin inhibitor toxicity. Whether or not decreasing immunosuppression, to control BKV, triggered the recurrence of scleromyxoedema in the transplanted kidney remains unclear.

The lesions observed in the kidney biopsy specimens present the same morphological aspects as the typical skin lesions. The kidney biopsy of the native kidney of our patient and the biopsies done 30 months after transplantation and at transplant nephrectomy all have the typical common features of scleromyxoedema, mucin deposition and ischaemic glomeruli. In interesting contrast, the biopsy of the grafted kidney at 9 months post-transplantation showed no such typical lesions; but later there was progression of severity of lesions in the graft in parallel with the deterioration of kidney function. In view of the scarcity of reports associating scleromyxoedema and stage 5 CKD, and since the disease is mostly associated with severe hypertension, doubts may be raised about the causative role of scleromyxoedema in renal failure. The recurrence of renal failure in the transplanted kidney of our patient with well controlled blood pressure, together and in parallel with the development of the typical lesion of the disease in that kidney, however, is a strong argument in favour of a direct association between scleromyxoedema and renal failure.

A few cases of a scleromyxoedema-like disease, nephrogenic fibrosing dermopathy or nephrogenic systemic fibrosis (NFD-NSF), restricted mostly to the skin, have been described in patients with stage 4-5 CKD. The condition is characterized by scleromyxoedema-like, hyperpigmented, thickened sclerotic skin plaques, papules and subcutaneous nodules, which developed acutely while patients were already having renal replacement therapy. NFD is phenotypically similar to scleromyxoedema, but with some notable exceptions, including the sparing of the face and absence of systemic involvement and paraproteinemia. In NFD there is a more subtle increase in mucinous-like substance than in true scleromyxoedema, with arrays of collagen bundles surrounding fibroblast-like cells in the dermis [9–13]. It is possible that intermediate-sized hyaluronan, normally cleared by the healthy kidneys, accumulates in the skin and stimulates fibrous deposition [14]. In June 2006, the US Food and Drug Administration (FDA) issued a first warning on the use of gadolinium-based contrast agents for magnetic resonance imaging, since cases of NFD-NSF in relation to gadolinium had been described in patients with a GFR <30 ml/min/1.73m² [15]. Our patient developed his scleromyxoedema disease at CKD stage 2 (GFR 60–89 ml/min/1.73m²) and transplant CKD stage 2-Ⅲ without any gadolinium administration ever.
The evolution over time of our patient’s condition is different from NFD, since he had scleromyxoedema years before the discovery of renal failure and start of haemodialysis in 1998. His condition also was systemic, with diffuse involvement of the skin, including the face, the typical MGUS, the pulmonary lesions, the pulmonary diffusion deficit and the renal histological lesions. Other patients with scleromyxoedema develop involvement of other organ systems—with cardiac, gastrointestinal and neurological disease. In addition, in our patient renal function was largely corrected after transplantation, to be lost again when lesions of scleromyxoedema reappeared in the grafted kidney.

In conclusion, the present case strongly speaks for renal involvement in scleromyxoedema, in both native and transplanted kidneys. The re-challenge that occurred when the patient received a renal graft (which he eventually lost) is highly supportive of this hypothesis.

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References


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