Nephrogenic Systemic Fibrosis

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Abstract

Nephrogenic Systemic Fibrosis (NSF) is a potentially fatal dermatological condition found exclusively in patients with advanced renal failure. There is minimal literature regarding the epidemiology and outcomes of patients with NSF in Ireland. A retrospective chart review was performed for all patients with NSF in Ireland. Ireland’s experience with the disease was examined in light of international reports. There have been three cases of NSF in Ireland; an area which serves 1.3 million people, giving a point prevalence among Irish end-stage kidney disease patients of 0.002. There was a large variation in disease severity between the three patients. All three patients had significant exposure to gadolinium chelate. Caution with gadolinium administration must be exercised in patients with advanced renal failure.

Introduction

Nephrogenic systemic fibrosis (NSF) is a disorder of skin fibrosis which was first reported in 2000.1,2. Its previous name – nephrogenic fibrosing dermopathy – was changed when it was discovered that deeper structures including viscera can be involved. Although most reports are in dialysis-dependent adults (90%), it can also present in advanced chronic kidney disease and in patients with a failing renal allograft. Little is known about the prevalence and outcomes of NSF in Ireland.

Methods

All nephrology centres in the Republic of Ireland and Northern Ireland were contacted via an attending consultant. All contacted consultants were easily able to identify those with NSF in their patient cohort. Three patients with NSF were identified nationwide and a detailed chart review was performed for each of these patients. Radiology archives were accessed to quantify past gadolinium exposure. The Irish experience was examined in light of international reports.

Case 1

A sixty five year old woman was followed in Nephrology outpatient clinic for fifteen years with slowly progressive chronic kidney disease secondary to chronic pyelonephritis. An unexpected acute deterioration in renal function, with severe pulmonary oedema, necessitated emergency dialysis via a right internal jugular central venous catheter (CVC). Over the following months, several attempts at fistula formation were unsuccessful. Despite meticulous hygiene and catheter care, she developed recurrent severe catheter related sepsis necessitating numerous changes of the CVC. Over time, she developed stenosis in all of the central veins of her neck and thorax. This was confirmed by three separate Magnetic Resonance Venography (MRV) studies. Femoral venous access was similarly complicated by infections and stenosis, again confirmed by means of an MRV study. 20ml of gadopentetate dimeglumine was administered for each of the five scans, resulting in a cumulative dose of 50mmol of gadolinium chelate.

Due to failing vascular access and recurrent catheter-related sepsis, a switch to peritoneal dialysis was made. Weeks later, sclerotic skin plaques were noted over her distal upper and lower limbs. These lesions were associated with distal arthralgia and restriction of joint motion. Laboratory investigations including anti-nuclear antibody, complement levels and anti-scl-70 were normal. Skin biopsy was performed and confirmed the clinical suspicion of NSF in 2008 (Figure 1, Figure 2). Light therapy was poorly tolerated and topical preparations were used to little effect. The sclerotic plaques gradually extended to proximal sites and included uncomfortable involvement of the perineum. Peritoneal dialysis was complicated by recurrent peritonitis and was discontinued after eighteen months. Haemodialysis was resumed via trans-lumbar, and later trans-hepatic, venous access. Given the unusually high number of severe infections an immunodeficiency work-up was performed. It did not reveal any specific underlying immunodeficiency other than her known renal disease. As a result of joint and skin restriction, the patient is no longer independently mobile. She has chronic daily pain necessitating opioid analgesia with a markedly restricted functional status.

Case 2

A thirty eight year old woman developed end stage kidney disease at the age of seventeen due to primary focal segmental glomerulosclerosis (FSGS). She dialysed via a left forearm fistula for four weeks prior to a deceased donor renal transplant. Recurrence of her primary disease led to transplant failure after one year. She had two further relapses of FSGS (one due to polycystic kidney disease (PKD), the other due to polyoma virus infection. Prior to her second transplant she dialysed by means of peritoneal dialysis. This option was eventually exhausted due to recurrent peritonitis and haemodialysis resumed via a left upper limb graft. Over the years her dialysis access was complicated by infections and central venous stenosis. Huge effort was put into establishing graft access but several grafts were lost over time to infection and thrombosis necessitating CVC access. Over the years she had four MRV scans to assess her vasculature and plan for dialysis access, each using 20ml of gadopentetate dimeglumine. She also had gadolinium enhanced MRI brain in 2000 when she developed herpes encephalitis (10ml gadopentetate dimeglumine). The cumulative dose of gadolinium chelate was 45 mmol.

In 2006, four years after her last MRI scan, she presented to a dermatologist with progressive symmetrical hardness and tightness of the legs and hands which had progressed over four months (Figure 3). Examination revealed diffuse thickening and tightening of the skin of the hands and legs, sparing the chest and face. Antinuclear antibody, C3, C4 and anti-scl-70 were normal. A biopsy was taken from the right lower limb and confirmed the clinical suspicion of NSF. Numerous other co-morbidities have complicated this patient case including two separate bowel perforations, severe renal bone disease, parathyroidectomy, paroxysmal atrial fibrillation and dialysis related amyloidosis. However, in

Figure 1: High power light microscopy (x40 objective lens, haematoxylin & eosin stain) of deep dermis demonstrates abundant spindle fibroblasts and fibrosis (top) extending into subcutaneous fat (bottom)

Figure 2: Low power light microscopy (x2 objective lens, mason trichrome stain) shows increased dermal fibrosis with abundant spindled fibroblasts and fibrosis

Figure 3: Thickening of the skin with brawny pigmentation, hypopigmented areas, and ‘peau d’orange’ appearance

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terms of her NSF, this patient remains independently mobile and relatively unrestricted four years after initial diagnosis.

Case 3
A sixty four year old male was referred to the renal services following nephrectomy for renal cell carcinoma in a single functioning kidney. His background was significant for coronary artery bypass grafting and an abdominal aortic aneurysm repair. He commenced haemodialysis through a CVC. Over the coming months he had several unsuccessful attempts at arteriovenous fistula formation. His background was further complicated by a lumbar epidural abscess. Prolonged antibiotics led to eventual recovery as demonstrated on five serial MRI scans. 10ml of gadopentetate dimeglumine was administered with each MRI scan. The cumulative dose of gadolinium chelate was 35mmol.

Six months later, the patient noticed new skin changes peripherally. The skin on his limbs became tight and sclerotic with mild restriction of joint motion in the upper limbs. ANA, anti scl-70 and complement levels were normal. A clinical diagnosis of nephrogenic systemic fibrosis was made. Emollients were employed with significant improvement in discomfort. Although the clinical course of this man NSF was relatively benign, he died some years later, in 2010, from unrelated causes.

Discussion
Patients with NSF present with symmetrical skin induration which preferentially affects the limbs. Pain is often a prominent feature and eventually restriction of joint motion can be experienced. Systemic involvement has been described. Involvement of muscle, fascia, lung parenchyma, myocardium and pericardium has been reported. NSF tends to be chronic and, if visceral involvement is prominent, can hasten death. Treatment related improvement has been documented but this appears to be limited to those with renal recovery. A fulminant form of the disease has been described and appears related to multiple gadolinium exposure.

The diagnosis of NSF relies on the above clinical features in combination with specific histological features including fibroblast proliferation and thick collagen bundles. Immunochemical staining reveals abundant CD34+ dermal rarl. A reproducible clinico-pathological diagnostic scoring tool has been developed and publication is awaited.

Avoidance of gadolinium chelate in patients with a glomerular filtration rate of less than 30ml/min/1.73m2 is crucial in the prevention of NSF. Such caution is now routinely advised on product literature. Several different gadolinium preparations exist and have different NSF risk profiles. Gadodiamide is thought to be the most toxic and has largely been replaced by gadobenate dimeglumine and gadopentetate dimeglumine, although both of these have also been associated with the disease. It has been suggested that gadoteridol is the least toxic gadolinium preparation; this preparation is not widely used in Ireland. Evidence for various therapeutic approaches is limited given the small numbers of patients worldwide with documented disease. Physiotherapy with appropriate splinting is universally recommended. The main therapeutic goal is restoration of renal function, typically by means of renal transplant. However, renal transplant does not always lead to an improvement in condition, as previously reported by our group. The lack of universal access to MRI in Ireland is probably a major contributing factor to the relatively low prevalence here. However, appropriate caution should be exercised when imaging patients with advanced renal failure to avoid future cases.

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