Intestinal manifestations with a surface-treated AN69 membrane and ACEI during haemodialysis

Sir,

AN69-associated reactions in haemodialysed patients receiving angiotensin-converting enzyme inhibitors (ACEI) are well-documented [1]. The negatively charged AN69 membrane is thought to activate the bradykinin system. Moreover, ACEI reduces bradykinin inactivation. Surface-treated AN69 is considered to be safer in that regard. To our knowledge, only one case of anaphylactoid reaction induced by ACEI during haemodialysis with a surface-treated AN69 membrane has been reported [2]. We report here two patients who had a more subtle presentation with predominantly intestinal manifestations.

Case 1

A 54-year-old male with end-stage renal disease (ESRD) consequent to IgA nephropathy had been on chronic haemodialysis (4 h, three times per week) for 2 years. He was dialysed using a surface-treated AN69 membrane (Nephral ST®, 500, Gambro) for 4 months. His medication included metoprolol, furosemide, amiodarone, calcium carbonate, sevelamer, allopurinol, oxybutinin, epoetin-α, calcitonin, warfarin and naproxen. On 8 November 2004, ramipril 2.5 mg once daily was initiated for hypertension and cardiovascular protection. At the next dialysis, the patient presented moderate abdominal cramping and diarrhoea upon dialysis. These symptoms did not recur until 19 November. They were present on 22 and 24 November, when medical attention was first requested. At this time, the working diagnosis was viral gastroenteritis. However, by caution, the dialyser was changed for a cellulose triacetate membrane (Exeltra®, 210, Baxter). Abdominal gastrointestinal symptoms and diarrhoea completely disappeared with the new dialyser. The surface-treated AN69 membrane was then reintroduced on 1 December 2004. Less than 1 h after the beginning of haemodialysis, severe abdominal cramps and diarrhoea occurred again. The patient had diaphoresis but no breathing problems or angioedema. The blood pressure remained stable. The treatment was immediately stopped. Intravenous diphenhydramine 50 mg and hydrocortisone 100 mg were given. Symptoms resolved rapidly, and haemodialysis was started again with a cellulose triacetate membrane dialyser without any other adverse event. Ramipril was maintained.

Case 2

A 47-year-old man on chronic haemodialysis 4 h three times a week since October 2003 was known to have type 2 diabetes. He was dialysed using a surface-treated AN69 membrane since the first dialysis treatment. His medication included metoprolol, calcium carbonate, aspirin, alfacalcidol, gliclazide, furosemide, temazepam and enalapril 2.5 mg four times a week. Enalapril was prescribed from 2003 but compliance was variable. From August to December 2004, enalapril was taken less than once a week. After January 2005, he took enalapril 2.5 mg four times a week, more regularly. In September 2004, he presented two episodes of massive diarrhoea in the first hour of dialysis treatment, associated with a drop of his blood pressure. Starting early January, these symptoms occurred with almost every treatment, corresponding to his improved compliance to enalapril. On 25 February 2005, the dialyser was changed for a haemophan membrane (GFS®, 20, Gambro) for this problem. Since then, he has had no diarrhoea during the treatment and no initial fall in blood pressure has been observed. Enalapril was continued without any problem.

In vitro studies showed that increasing the membrane electronegativity enhances bradykinin generation [3]. The angiotensin-converting enzyme degrades bradykinin; consequently, ACEIs reduce this process and favour bradykinin build-up. AN69 membrane is one of the membranes with the highest electronegative surface. A surface-treated AN69 membrane with polyethylenimine(PEI) has recently been made available. The polycationic saline solution (PEI) reduces the surface electronegativity and therefore the bradykinin production [3]. Surface-treated AN69 membrane was reported safe in patients receiving ACEI [4]. However, an anaphylactoid reaction after a single dose of captopril during haemodialysis was previously reported [2]. Our patients presented more subtle symptoms. In case 1, the patient presented a more rapid and severe reaction upon rechallenge, suggesting a real AN69-associated reaction in presence of ACEI. Surface-treated AN69 membrane or ACEI not used concomitantly in this case was tolerated without any problem for many months. In the second case, ACEI and a surface-treated AN69 membrane used concomitantly seemed to have been well-tolerated at first, when compliance to enalapril was questionable. No other explanation was found for the abdominal symptoms in January than a reaction to the filter, since the symptoms suddenly ceased after the dialyser was changed. We felt that challenging this patient again with a surface-treated AN69 membrane would have been dangerous and unethical.

Even if surface-treated AN69 membrane was shown to be less electronegative, the coating of PEI may not cover perfectly all electronegative charges. Variability within dialysers or between fibres filaments is possible.
These uncovered charges can activate the Hageman factor and consequently contribute to bradykinin generation. We can imagine a spectrum of bradykinin synthesis in this context ranging from mild non-specific symptoms to anaphylactoid reactions. Our patients were probably in the middle of this spectrum. Moreover, bradykinin is thought to be a mediator of gut sensitivity [5]. Interindividual differences in susceptibility to hypersensitivity reaction in patients haemodialysed with an AN69 membrane, while on treatment with an ACEI can be partly explained by different degrees of enzyme activity. However, bradykinin generation was not measured in our cases, and we cannot prove their exact role in the symptoms presented by our two cases.

In conclusion, the safety of surface-treated AN69 membrane used concomitantly with ACEI should be more formally evaluated. This may help to recognize and describe the spectrum of hypersensitivity reactions in this context. We recommend changing the dialysate when facing a new or suspect intestinal manifestation in patients dialysed with a surface-treated AN69 membrane and receiving ACEI, if any doubt is present.

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Familial Mediterranean fever triggered by renal transplantation

Sir, Hereditary periodic fever syndromes are a group of non-autoimmune diseases characterized by episodic fever, and include familial Mediterranean fever (FMF), hyperimmunoglobulin-D syndrome, tumour necrosis factor receptor-1-associated periodic syndrome and Muckle–Wells syndrome [1,2]. Of these, FMF is the most common and best known [1]. FMF mainly affects patients of Mediterranean descent, namely Turks, Jews, Armenians and Arabs [3]. However, the disease has become more widespread because of migration [3]. The diagnosis of FMF is still based on clinical criteria established and confirmed by several studies [2]. A positive family history, recurrent fever episodes and a favourable response to colchicine are the mainstay of diagnosis [2]. Since the discovery of the FMF gene, almost 30 new mutations have been detected [2,3]. However, the molecular basis of the disease is still obscure [3]. One of the major complications of FMF is systemic amyloidosis, which can result in end-stage renal disease, necessitating organ replacement [4]. The association of FMF with certain forms of vasculitis mainly Henoch–Schoenlein purpura, polyarteritis nodosa and Behcet’s disease (BD) have been reported [2,5]. We describe here an unusual case of FMF that presented early after renal transplantation in a patient with end-stage lupus nephritis. To our knowledge, such a clinical scenario has not been previously reported.

A 35-year-old woman who had suffered from lupus nephritis for 6 years and end-stage renal disease for 1 year received a kidney transplantation. The post-transplantation immunosuppressive regimen included cyclosporin (250 mg/day), azathioprine (74 mg/day) and prednisolone (tapering doses). The procedure was uncomplicated and renal function was stable; however, the patient developed a fever of 39°C 1 month after transplantation. The patient’s general condition was good, and physical examination revealed no remarkable findings. Blood and urine culture, Wright agglutination and Widal tests were all negative. Serologies of cytomegalovirus, herpes simplex virus, Epstein–Barr virus, human immunodeficiency virus and hepatitis B and C viruses were also negative. The fever was persistent (>2 weeks), and the diagnosis of fever of unknown origin (FUO) was made. At the same time, the patient’s younger sister was diagnosed with FMF because of recent episodic fever and abdominal pain. Upon further questioning, the patient revealed that her older sister was also suffering from a similar condition and had been receiving long-term colchicine. With the presumptive diagnosis of FMF, colchicine (1 mg/day) was started. Her fever ceased within <24 h. After 3 years of renal transplantation and on a daily dose of colchicine, the patient is doing well, and no flare-up of systemic lupus erythematosus (SLE) or FMF has occurred. Her serum creatinine level is normal at around 1.2 mg/dl.

The FMF is a well-known cause of episodic FUO. It is said that serositis is almost always present in FMF [1]. In the present case, the persistent fever (>2 weeks) and absence of serositis were unusual findings. However, the positive family history and rapid cessation of fever with colchicine favoured FMF as the most likely diagnosis. Renal failure necessitating replacement therapy is a major complication of FMF [2]. However, FMF triggered by kidney transplantation is a very unusual scenario. Surprisingly, in the present case, the post-renal transplantation FMF was preceded by SLE. Whether vasculitis is an integral feature of FMF or is secondary to enhanced inflammatory response in this condition still remains to be clarified [2]. Braun et al. [6] reported a patient with acute systemic vasculitis superimposed on FMF. Schwartz et al. [5] found 50 patients with features of BD among 4000 known FMF patients.

We recommend that clinicians should consider FMF in the differential diagnosis of fever after renal transplantation. Association of FMF with vasculitis such as SLE should not be overlooked as well. Although, vasculitis has not yet been included among the criteria for diagnosis of FMF, we would like to speculate that a past history of vasculitis may be a positive clue for the diagnosis of FMF.

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