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Exceptional Case

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Minimal-change disease secondary to etanercept

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Abstract
Etanercept is a soluble tumor necrosis factor alpha (TNFα) receptor which is widely used in the treatment of rheumatoid arthritis, psoriasis and other autoimmune inflammatory disorders. It is known for its relative lack of nephrotoxicity; however, there are reports on the development of nephrotic syndrome associated with the treatment with TNFα antagonists. Here, we describe a patient with psoriasis who developed biopsy-proven minimal-change disease (MCD) shortly after initiating etanercept. Our case is unique in that the MCD resolved after discontinuation of this medication, notably without the use of corticosteroids, strongly suggesting a drug-related phenomenon.

Keywords: etanercept; minimal-change disease; nephrotic syndrome; podocyte

Introduction

Minimal-change disease (MCD) is a cause of nephrotic syndrome for which the exact pathophysiology is unclear, although a T-cell-mediated disorder has been proposed [1]. Most cases of MCD are idiopathic and not clearly associated with an underlying disease or event. Occasionally, MCD occurs in the setting of other T-cell disorders (i.e. thymoma, Hodgkin's lymphoma and eczema) or with medications (i.e. nonsteroidal anti-inflammatory drugs, antimicrobials, lithium, penicillamine, pamidronate and sulfasalazines). Tumor necrosis factor alpha (TNFα) is a Th1 cytokine which possesses broad inflammatory and immunoregulatory functions. TNFα inhibition has been shown to ameliorate a range of inflammatory autoimmune diseases, but rarely has been associated with the development of MCD and other glomerular diseases [2–4]. Here, we present the case of a patient with resistant psoriasis who developed acute-onset MCD shortly after the initiation of treatment with etanercept, which resolved spontaneously upon discontinuation of the medication.

Case Report

A 43-year-old man presented to the office with a 3-day history of generalized body swelling, weight gain and foamy urine. The patient's past medical history was significant for psoriasis (diagnosed at the age of 8) and ulcerative colitis (diagnosed at the age of 20), for which he underwent colectomy at age 33 years. His medication list included multivitamins, loperamide as needed, and etanercept 50 mg subcutaneously twice a week that was started 3 months prior to presentation. On physical examination, he had a newly elevated blood pressure of 140/95 mmHg with new 2+ pitting edema of the bilateral lower extremities. Laboratory workup revealed a serum creatinine of 0.9 mg/dL (68.6 μmol/L), spot urine protein–creatinine ratio of 2800 mg/g, serum albumin of 3.1 g/dL (31 g/L) which had fallen from 4.2 g/dL (42 g/L) 3 weeks prior and total cholesterol of 197 mg/dL (5.1 mmol/L) with an LDL-cholesterol of 125 mg/dL (3.2 mmol/L). Urine dipstick revealed 3+ protein and 1+ blood, and urine sediment demonstrated many hyaline casts, some granular casts and some sloughed tubular epithelial cells. Renal ultrasound revealed kidneys of normal size and morphology. Chest X-ray was clear. Viral hepatitis serology, antinuclear antibody, antineutrophil cytoplasmic antibody, rheumatoid factor, serum and urine protein electrophoresis and immunofixation were all negative.

Kidney biopsy was performed the day after presentation. On light microscopy, there were 31–45 glomeruli per level section, of which 1–2 were globally sclerosed. The glomeruli were without inflammatory cell infiltrates or segmental sclerosis, and the interstitium was without significant fibrosis, tubular atrophy or interstitial inflammation. Immunofluorescence revealed no significant staining of the glomeruli or tubules for IgG, IgA, IgM, C3, C1q, fibrinogen, kappa or lambda light chains or albumin. Electron microscopy demonstrated normal morphology of glomerular basement membranes, with no evidence of immune-type electron-dense deposits. Ultrastructural examination of nine glomeruli demonstrated extensive effacement of podocyte foot processes, consistent with MCD (Figure 1).

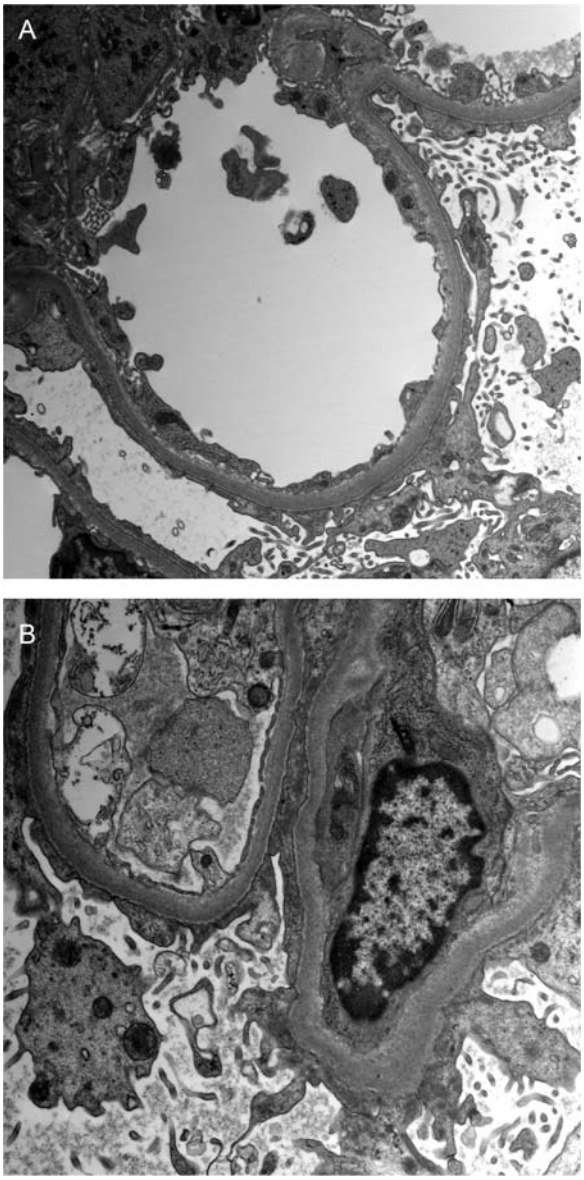

Fig. 1. (**A** and **B**) Electron microscopy reveals diffuse effacement of podocyte foot processes.

The patient was asked to stop taking his etanercept, and steroids were never given. Amlodipine 10 mg/valsartan 320 mg po qday, aliskiren 300 mg po qday, and furosemide 20 mg po bid were initiated for control of proteinuria, blood pressure, and edema. Within 2 weeks, the spot urine-protein ratio had decreased from 2800 mg/g to 1800 mg/g. By 4 weeks, the spot urine protein-creatinine ratio was <100 mg/g and a 24 h urine collection revealed a urine total protein of 200 mg/day in an adequate sample. This was associated with a marked improvement in his weight and peripheral edema. During the following 6 months, as his antihypertensive medications were discontinued, the patient had low grade proteinuria ranging from 200 to 1300 mg/g. At last review, 17 months after the patient's initial presentation, his proteinuria had completely resolved with an albumin to creatinine ratio of 9.8 mg/g (Figure 2).

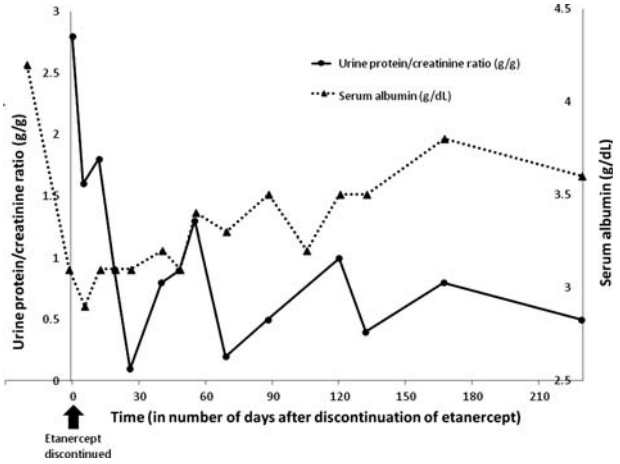

Fig. 2. Graph of serum albumin (g/dL) and urine protein/creatinine ratio (g/g) over time. Day 0 marks the day which etanercept was discontinued.

Discussion

We describe a 43-year-old man who developed MCD 3 months after commencing etanercept for psoriasis. The temporal relationship between the initiation of etanercept (3 months prior) and the subsequent development of biopsy-proven MCD, along with the resolution upon withdrawal of etanercept, notably without the use of steroids, suggests the possibility of a drug-related phenomenon. Although spontaneous remission of MCD has been described, this typically takes longer than 6 months [5–7]. One older study demonstrated that ∼30% of untreated patients achieved proteinuria reduction (<1 g/24 h) at one year, rising to ∼60% at 2 years [5]. MCD has also been reported in association with psoriasis [8] and ulcerative colitis [9]; however, these associations are rare, and may be coincidental. The association of nephrotic syndrome with treatment with TNFα antagonists has been previously described (both MCD [3, 4] and membranous nephropathy [2, 3]), but this case is unique in that the nephrotic syndrome resolved without the use of steroids or immunosuppression.

Etanercept is a soluble, dimeric, recombinant human TNFα receptor, fused to the Fc fragment of human immunoglobulin G1, which was developed for neutralization of circulating TNFα. TNFα is an inflammatory cytokine and is typically considered a mediator of glomerular injury. In experimental models of glomerulonephritis, mice that are deficient in TNFα receptor [10], and rats administered inhibitory TNFα antibodies [11] had reduced glomerular injury. In addition, TNFα may have direct injurious effects on the podocyte, the target of injury in nephrotic disorders. TNFα has been shown to downregulate nephrin, the key protein of the slit diaphragm [12], reorganize the actin cytoskeleton [13], and cause dedifferentiation and podocyte proliferation [6]. Furthermore, there are case reports of successful treatment of nephrotic syndrome with the use of TNFα inhibitors in association with high-dose steroids [14, 15].

While TNFα can be damaging, its protective immunoregulatory role within the kidney is less well appreciated. In experimental models of lupus nephritis, TNFα may play an immunosuppressive role at early stages of the disease. Replacement therapy with exogenous recombinant TNFα to (NZB × NZW)F1 mice, a model of SLE

characterized by low levels of TNFα, delayed the development of lupus nephritis [16]. Notably, therapeutic inhibition of TNFα with etanercept, as well as infliximab, has been associated with the development of SLE [17, 18]. In animal models, diminished expression of TNFα has been associated with emergence of other autoimmune disease such as multiple sclerosis [19] and diabetes mellitus [20]. The mechanisms of these immunoregulatory effects of TNFα may include TNFα-mediated T-cell apoptosis and downregulation of T-cell receptor signaling [21]. If TNFα plays a protective role in the kidney, blockade with etanercept may increase its susceptibility to autoimmune phenomena, including MCD.

Another possible role of TNFα in MCD is its function as a Th1 cytokine promoting cell-mediated immunity. T-helper cells may be subdivided into Th1 and Th2 subsets. Th1 cytokines (i.e. TNFα, IFNγ and IL-2) promote cell-mediated immunity, whereas Th2 cytokines (i.e. IL-4 and IL-13) promote humoral immunity, and are known to switch B-cell production toward IgG4 and IgE [22]. TNFα blockers have been shown to shift the T-helper cell response towards Th2, as decreased IFNγ [23] and increased IL-4 levels [24] have been seen in animals and patients receiving these medications. TNFα inhibition has been associated with various Th2-mediated conditions such as atopic dermatitis and urticarial skin reaction [25, 26]. While the exact pathophysiology of MCD remains unclear, it has long been considered to be a disorder of T-cell function [1], and more recently, a Th2-mediated disease process [27]. MCD is associated with elevated levels of various Th2 cytokines [28–30]. In particular, IL-13 has been implicated in the pathogenesis of MCD, as transgenic rats overexpressing this cytokine have been shown to develop proteinuria. IL-13 increases the podocyte expression of B7.1 (CD80) which may promote proteinuria [31] by inducing reorganization of the vital slit diaphragm proteins [32]. Overexpression of angiopoetin-like-4 (Angptl4) has recently been shown to induce steroid responsive proteinuria in rats, but the upstream factors leading to this have not been identified [33]. Blockade of TNFα may contribute to the Th2 polarization, and may have made our patient more susceptible to the development of MCD.

In conclusion, etanercept is an effective biologic therapy for many autoimmune diseases such as psoriasis and rheumatoid arthritis, and is recognized for its lack of nephrotoxicity. Indeed, the protective role of TNFα inhibition has been studied in the treatment in kidney diseases such as lupus nephritis and granulomatosis with polyangiitis [21] and rarely in the nephrotic syndrome [14, 15]. Our case and one other [4] describe the association of etanercept with the development of nephrotic syndrome, and highlight the dichotomous roles of this cytokine.

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Conflict of interest statement. None declared.

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