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Membranous glomerulonephritis, psoriasis and etanercept. A chance or causal association?

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ABSTRACT

Psoriasis is a cutaneous disease with systemic involvement. Tissue damage is considered to be immune-mediated, and etanercept currently provides effective treatment. Kidney injury arising from this condition has not yet been fully explained in the literature. We present a case of membranous nephropathy with C1q deposits followed by development of psoriasis. In this article we will review the possible association between these conditions and the response to that biological molecule.

Keywords: Psoriasis. Membranous nephropathy. Etanercept. Tumour necrosis factor alpha (TNF-alpha). C1q deposits. Proteinuria.

Glomerulonefritis membranosa, psoriasis y etanercept. ¿Asociación casual o causal?

RESUMEN

La psoriasis es una enfermedad cutánea con afectación sistémica, cuyo daño tisular se considera inmunomediado y que en la actualidad se trata eficazmente con etanercept. El daño renal de esta patología no está completamente aclarado en la literatura. Presentamos un caso de glomerulonefritis membranosa con depósitos de C1q que posteriormente desarrolló psoriasis. En este artículo hacemos una revisión de la posible asociación entre estas patologías y la respuesta a esta molécula biológica.

Palabras clave: *Psoriasis. Glomerulonefritis membranosa. Etanercept. Factor de necrosis tumoral alfa (TNF-alfa). Depósitos de C1q. Proteinuria.*

INTRODUCTION

Many authors now consider psoriasis to be an immune-mediated disease that primarily affects the skin. There is no consensus as to whether or not the disease has an impact on the kidneys directly, but the literature contains several cases of associated kidney diseases. Etanercept is a tumour necrosis factor alpha (TNF-alpha) inhibitor used to treat this condition and others. However, cases of kidney injury have been associated with this drug. In this study, we present the case of a patient with membranous nephropathy (MGN) who later developed psoriasis, which was treated with etanercept. We observed complete remission of proteinuria during this treatment.

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CASE STUDY

Male patient 43 years of age with hypercholesterolaemia treated with statins, non-hypertensive and non-diabetic. Smoker and occasional drinker. His nephrological symptoms began in April 2003, when he presented with clinical and laboratory signs of a nephrotic syndrome while being treated for an ear infection with amoxicillin and clavulanic acid. Since spontaneous partial remission of the syndrome occurred, with residual proteinuria levels of approximately 1g/24 hours and renal function normal at all times, he did not undergo a biopsy and was monitored by the Nephrology Department on an outpatient basis.

From that time on, proteinuria (selective) gradually increased to 14g/24h, with no changes in urinary sediment. An immunological study detected no antibodies, and complement levels were normal according to multiple studies throughout the follow-up period. The patient tested negative for hepatitis B, C and human immunodeficiency

virus. In October 2003, when renal function was normal, the patient underwent a kidney biopsy that showed stage II MGN. The immunofluorescence assay revealed intense granular parietal IgG, C3 and C1q deposits.

Prednisone treatment was started at doses of 1mg/kg/day, resulting in partial remission of proteinuria, which reached levels of 1.3-0.5g/24h. Treatment lasted 8 months, with a progressive decrease in steroid doses. At that time, we initiated antiproteinuric treatment with enalapril and candesartan; proteinuria persisted at levels of about 0.5g/24h.

In December 2006, the patient presented with scaly, erythematous lesions on his hands, feet and elbows, and was diagnosed with psoriasis in the Dermatology department. Treatment with acitretin failed and we decided to use an anti-TNF-alpha agent (etanercept) in April 2009; treatment continued for 9 months and skin lesions improved significantly before resolving completely. At the same time, proteinuria decreased and was in complete remission 6 months after starting the treatment described above.

The patient's glomerular syndrome remained in complete remission during 11 months, during which time no skin lesions were present. In December 2010, signs of psoriasis began to reappear slowly and progressively. Proteinuria was detected again at that time, at a level of 0.5g/24h.

Figure 1 summarises the evolution of the case.

DISCUSSION

This case led us to review three topics and the relationships between the two entities:

Psoriasis and renal conditions

Psoriasis is mainly a skin condition but it has some systemic repercussions.[1] It is characterised by the cutaneous infiltration of activated T cells and the proliferation of keratinocytes, dendritic cells and Langerhans cells, resulting in high concentrations of TNF-alpha in psoriatic lesions.[2] Decreasing intralesion and blood levels of TNF-alpha using agents that inhibit this cytokine is associated with clinical improvement.[3]

Most reviews conclude that compromised renal function in psoriasis is very rare, and may be directly related to a condition such as glomerulonephritis (mainly membranous glomerulonephritis and IgA nephropathy), microalbuminuria or secondary amyloidosis (the literature reports some 20 cases of associated amyloidosis[1]), or related to psoriasis treatment with cyclosporine, methotrexate or fumaric acid esters.[1,2,4-9] One study of 109 psoriasis patients and 178 controls observed that the former had significantly higher albuminuria levels and poorer creatinine clearance rates (110ml/min vs 109ml/min) measured using the Cockcroft-Gault formula. Nevertheless, the design and the discussion of that study are quite questionable; among other issues, there were no significant differences between subjects' serum creatinine levels.[10]

According to Zachariae, incidental renal biopsies performed in psoriasis patients were normal.[4]

As these patients' levels of beta 2-microglobulin in urine were within the upper limits of the normal range in 2 different analyses, we conclude that tubular function is not affected in psoriasis.[11,12]

In the Szepietowki study, the only renal anomaly detected was microalbuminuria, which was present in 22% of cases and in 42% of those with severe skin lesions.[13] These data are comparable to recent findings published by Dervisoglu, who found a correlation between proteinuria and the psoriasis activity/severity index in 24% of patients with microalbuminuria.[14] Cecchi demonstrated the presence of significant microalbuminuria (values >20μg/min) in 32 psoriasis patients compared to a control group, and these values were correlated with the extent of the skin lesions.[15]

Several cases of IgA nephropathy associated with psoriasis have been described.[7,16] IgA levels are elevated in 50% of psoriasis patients.[17] However, in view of new findings about this nephropathy, other factors must be at work in order for glomerular damage to occur.

Sakemi et al described a similar case to our own in which a patient with MGN and nephrotic syndrome subsequently developed psoriasis. These authors suggested that the immunological mechanism responsible for the association between systemic lupus erythematosus (SLE) or rheumatoid arthritis and secondary MGN could also be at work in psoriasis.[18]

There are currently several approaches to explaining MGN pathogenesis. One hypothesis is that it is caused by immune complexes (formed by IgG1 and IgG4 directed against antigens on the epithelial side of the glomerular basement membrane and in podocytes, associated with the complement) that would alter the permeability of the filtration barrier. Cellular immunity with increased TNF-alpha expression in the glomerulus[19-21] and high levels of circulating TNF-alpha contribute to this damage.[22,23] For that reason, inhibition of this cytokine is proposed as a treatment objective in this disease.[20]

The role played by tumour necrosis factor alpha

TNF-alpha is a cytokine produced by many cells having immunological activity in response to inflammation.[24] It is

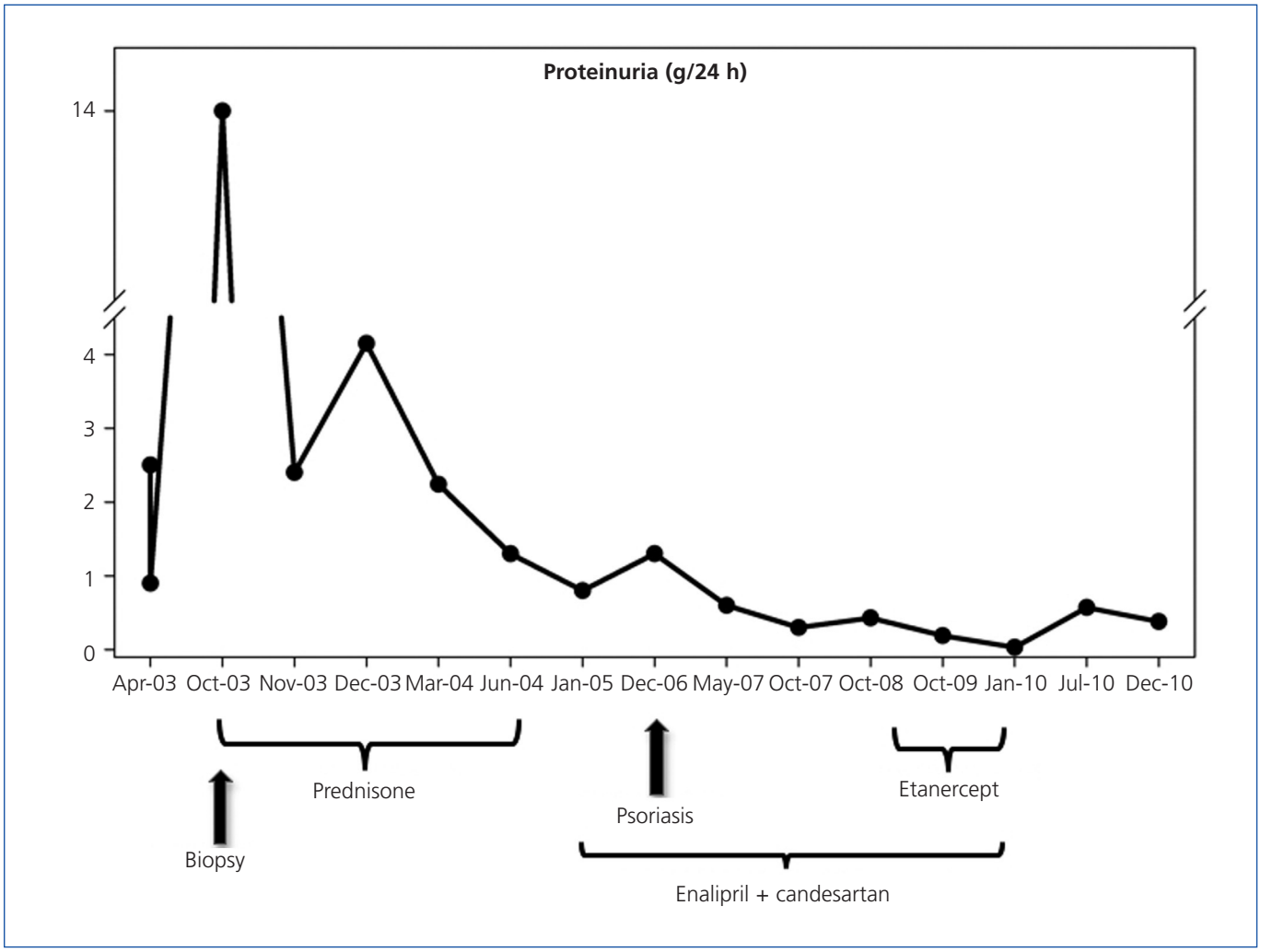

Figure 1. Evolution of the case described and treatment administered

the main pro-inflammatory cytokine, although there is evidence that it also acts as an immunomodulator.[25,26]

Etanercept is a dimeric molecule formed by the tumour necrosis factor receptor associated with the Fc region of IgG1. This human recombinant protein inhibits TNF-alpha by competing with it to bind to its receptors TNFR1 (55 kDa) and TNFR2 (75 kDa).[3,20]

Etanercept has been shown to be effective in treating psoriasis, rheumatoid arthritis and juvenile idiopathic arthritis.[3,27,28]

However, due to its complex interactions with other immune system agents, it has been found to stimulate autoimmunity. This was demonstrated in published cases involving the appearance of new autoimmune disorders, such as ANCA-positive vasculitis[26] and lupus-like syndromes,[29-33] during treatment with this drug. It has been observed that TNF-alpha plays an important role in the production of autoantibodies, since it has different (and sometimes contradictory) effects on B cells, dendritic cells, T cells and the process of apoptosis. These complex effects could explain the production of antinuclear antibodies (anti-DNA, anti-dsDNA) and anti-cardiolipin antibodies, which has been observed during treatment with anti-TNF-alpha.[26]

Despite the importance of TNF-alpha in MGN pathogenesis, TNF-alpha inhibition with etanercept was shown to decrease TNFR1 without any significant clinical improvement in a pilot study by Lionaki et al.[20] The authors concluded that this lack of efficacy could be caused by insufficient inhibition of TNF-alpha, caused mainly by an unknown pharmacokinetic mechanism in nephrotic syndrome.[20,34]

C1q and kidney injury

An unusual trait in this case was the presence of intense C1q deposits in the glomeruli.

C1q is a complement component that is very important in triggering activation of the classical pathway. When the Fc region of immune complexes (mainly IgG and IgM) binds to C1q, the molecule dividing C4 and C2 into their subfractions undergoes a conformational change. Among other functions, this change stimulates phagocytosis and increases the production of cytokines (TNF-alpha and IFN-gamma).[35] Unlike most complement proteins, it is synthesised by antigen-presenting cells instead of hepatocytes.[36]

The mechanisms by which C1q deposits are detected in renal biopsies are as follows: 1) C1q may bind to the Fc region of Ig or circulating immune complexes; 2) apoptotic debris may capture C1q and facilitate its clearance; 3) C1q may bind to C-reactive protein, amyloid protein or Ig trapped in the glomerulus; 4) C1q may bind directly and specifically to renal parenchymal cells: 5) passive trapping and 6) cross reaction with antigens similar to C1q. This explains why every time we encounter a nephropathy affecting the classical pathway of complement activation, we observe C1q deposits in the biopsy.[35]

It is only when the renal biopsy shows a predominance of C1q deposits that C1q nephropathy may be considered as a diagnosis. Its histological basis is highly variable, ranging from different types of proliferative lesions to membranous nephropathies.[37,38]

There are studies in the literature that report the presence of such deposits in IgM nephropathy, SLE,[34,35] transplant glomerulopathy,[35,36,39-43] and many other very different entities, such as nephrosclerosis, tubulointerstitial nephritis and even in two donor kidneys with no clinical or laboratory abnormalities (deposits are present in up to 19.4% of biopsies, according to the biopsy series by Vizjak et al[37]).

CONCLUSIONS

Based on its evolution, our case raises the question of a possible link between kidney injury and psoriasis; clinical evolution suggests that this could be a secondary form of MGN that goes into complete remission at the same time as the skin symptoms, with proteinuria reappearing when new psoriasis lesions are found on the skin. We cannot exclude the possible effect that suspending renin-angiotensin-aldosterone blockers may have had on the recurrence of proteinuria. Spontaneous, idiopathic MGN remission cannot be ruled out either. Given the presence of C1q, this could also be an SLE-associated disease, but it did not meet either clinical or laboratory criteria for SLE at any time during 9 years of follow-up. It is known that membranous nephropathy can manifest several years before SLE does. C1q nephropathy is an unlikely diagnosis in our case, since immunofluorescence does not show a predominance of these deposits.

No direct benefits of etanercept treatment have been described for MGN so far. In this case, treatment might have acted by controlling the primary illness.

Conflicts of interest

The authors affirm that they have no conflicts of interest related to the content of this article.

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