

From the Clinic

Anti-TNF- α therapy in membranous glomerulonephritis

A 43-year-old woman with a history of psoriasis vulgaris was admitted for nephrotic syndrome that had started 6 months before. Renal biopsy revealed membranous glomerulonephritis (MGN). She did not receive any therapy for MGN. Two months later she started therapy for psoriasis with adalimumab, which resulted in disappearance of psoriatic skin lesions with progressive reduction of 24-h proteinuria. This is the first report of therapeutic efficacy of adalimumab in MGN. Idiopathic membranous glomerulonephritis (MGN) is the most common cause of nephrotic syndrome in adults. It is considered an autoimmune disorder in which antibodies against some antigens result in generation of immune complex with subsequent activation of the complement cascade [1]. Recently, the M-type phospholipase A2 receptor (PLA2R), expressed in podocytes, has been identified as the auto-antigen [2]. Psoriasis is an immune-mediated chronic inflammatory skin disease with a strong genetic background. Chronic glomerulonephritis associated with psoriasis vulgaris has been reported in the literature [3]. However, because of the limited number of cases and the lack of specific histological findings, the pathogenetic mechanisms of these associations remain unclear [4].

In March 2011 a 43-year-old woman with a history of psoriasis vulgaris, without evidence of psoriatic arthropathy, was admitted to hospital for NS with a 6-month history of proteinuria (3.0 g/day). On admission, she presented severe peripheral oedema. Blood pressure was 110/70 mmHg. The laboratory test showed a creatinine clearance of 211 mL/min, urea 7.85 mmol/L, total protein 57 g/L, albumin 23.4 g/L and 24-h proteinuria 6.7 g/day. Serological tests for hepatitis B and C and for ANA, ENA and anti-DNA were all negative. Renal biopsy revealed MGN. In May 2011, she started therapy with adalimumab (40 mg every 15 days) for psoriasis. We decided to delay immunosuppressive therapy for NS because of contemporary treatment with anti-tumour necrosis factor- α (TNF- α). When adalimumab therapy started, 24-h proteinuria was 5.7 g/day. She was not on drugs acting on renin-angiotensin system because of low blood pressure. Therapy resulted in disappearance of psoriatic skin lesions (Figures 1 and 2) with an unexpected progressive reduction of 24-h proteinuria: July 2011 1.215 g/day and September 0.240 g/day (Figure 3). After 1 year, proteinuria is still absent (March 2012: 0.084 g/day).

The initiating event in the pathogenesis of MGN is mediated by the Th2 humoral immune response, leading to formation of IgG1 and IgG4 directed against antigens on the epithelial side of the glomerular basement membrane that would alter the permeability of the filtration barrier [5, 6]. Alteration in cellular immunity and pro-inflammatory cytokines may contribute to kidney injury. One of these cytokines is TNF- α , a 17-kd protein encoded in the major histocompatibility complex locus on chromosome 6. It is produced in response to various stimuli, not only by infiltrating monocytes-macrophages but also by



Fig. 1. Psoriatic skin lesions.



Fig. 2. Disappearance of skin lesions after adalimumab therapy.

glomerular and mesangial cells with pro-inflammatory activities [5, 7].

TNF- α also plays a pivotal role in the pathogenesis of psoriasis. TNF- α has been shown to act directly on keratinocytes, thereby inducing the production of various kinds

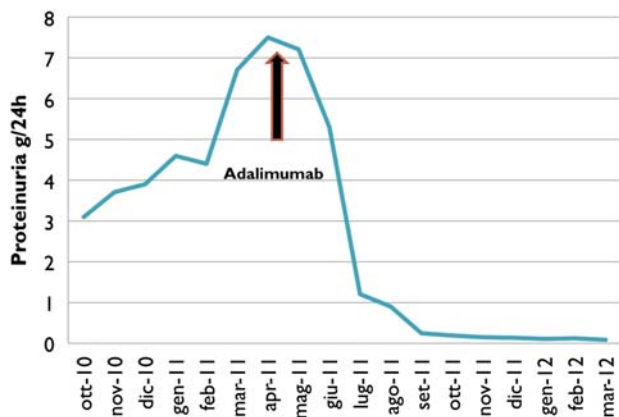


Fig. 3. Progressive reduction of 24h proteinuria after adalimumab therapy.

of chemokines, which contributes to the infiltration of leucocytes into the psoriatic lesions [8]. The immunologic injury of MGN leading to increased intrarenal TNF- α production is reflected by altered urinary TNF- α excretion [1]. TNF- α is directly cytotoxic to many glomerular cell types that express the receptor for TNF- α and can promote pro-coagulant activity with formation of microthrombi that could contribute to renal vein thrombosis associated with MGN[8]. It has been reported that TNF blockade severely impairs the induction of T cell-dependent humoral responses and, accordingly, may have a beneficial effect in antibody-mediated inflammatory pathologies [9]. These pathogenetic mechanisms would explain the possible therapeutic effect of anti-TNF- α monoclonal antibody. The administration of adalimumab might well have resulted in impaired induction of Th2 humoral responses, explaining the improvement of the proteinuria.

In this case, spontaneous remission might be considered rather than the efficacy of anti-TNF- α therapy, but the prolonged proteinuria (>6 months) and the close relationship with the start of adalimumab therapy favour the last one as the factor responsible for induction of remission. The role of anti-TNF- α for resistant FGSG (focal and segmental glomerulosclerosis), another cause of nephrotic syndrome, is under evaluation in a clinical trial (ClinicalTrials.gov Identifier: NCT00814255). This is the first report of the therapeutic efficacy of adalimumab in membranous glomerulonephritis.

Conflict of interest statement. None declared.

Department of Clinical and Experimental Medicine and Pharmacology, Unit of Diagnosis and Therapy of Glomerular Disease, University of Messina, Messina, Italy

Domenico Santoro
Adele Postorino
Giuseppe Costantino
Vincenzo Savica
Guido Bellinghieri

Correspondence and offprint requests to: Domenico Santoro;
E-mail: santisi@hotmail.com

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