Membranous nephropathy in rheumatoid arthritis: a case report

N. Maruotti, A. Corrado, A. Gaudio, F.P. Cantatore

Department of Rheumatology, University of Foggia Medical School, Foggia, Italy.

Nicola Maruotti, MD, PhD
Addolorata Corrado, MD
Annamaria Gaudio, MD
Francesco Paolo Cantatore, MD, PhD

Please address correspondence to: Prof. Francesco Paolo Cantatore, Rheumatology Clinic Mario Carrozzi, D’Avanzo Hospital, Viale degli Aviatori 1, I-71100 Foggia, Italy.
E-mail: fp.cantatore@unifg.it

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ABSTRACT

Rheumatoid arthritis (RA) is a chronic disease characterized by inflammation, abnormal cellular and humoral immune responses, synovial hyperplasia and rarely by renal involvement, characterized principally by secondary amyloidosis and nephrotoxic effects related to drugs, while renal lesions directly due to the disease itself are infrequent.

In this report we describe a patient with rheumatoid arthritis who developed membranous nephropathy associated with nephrotic syndrome while receiving adalimumab, an anti-tumour necrosis factor-α drug.

Introduction

Rheumatoid arthritis (RA) is a chronic disease characterized by inflammation, abnormal cellular and humoral immune responses, synovial hyperplasia and rarely by renal involvement.

The most common forms of renal involvement are secondary amyloidosis and nephrotoxic effects related to drugs such as D-penicillamine, bucillamine, cyclosporine, gold salt, non-steroidal anti-inflammatory drugs, and rarely anti-tumour necrosis factor (TNF-α) drugs (1-6). Although renal lesions directly due to the disease itself are infrequent, several reports demonstrated the presence of nephropathy peculiar to RA, including mesangial glomerulonephritis, membranous nephropathy, crescentic glomerulonephritis, fibrillary glomerulonephritis, and focal segmental necrotizing glomerulonephritis (1, 7-10).

In this report we describe a patient with RA who developed membranous nephropathy associated with nephrotic syndrome.

Case report

A 61-year-old woman had been suffering from RA, according to the criteria of American College of Rheumatology, since the age of 49 with inflammatory pain and swelling in metacarpophalangeal and interphalangeal joints of both her hands and painful flexion-extension-movement of both the wrists and ankles.

After diagnosis, her arthritis was treated with prednisone (5 mg/day), non-steroidal anti-inflammatory drugs, and methotrexate (10 mg/week), although this medication was discontinued after one year due to elevation of transaminases and gamma-glutamyl transpeptidase. In the following years, characterized by alternation of active-phases and inactive-phases of the disease, she received only low-dose steroid therapy (prednisone 5-10 mg/day). From the age of 53, the polyarthritis was gradually getting worse. Her arthritis was successfully treated with cyclosporine associated with corticosteroids (prednisone 5 mg/day) over the next 3 years.

From the age of 56, treatment with adalimumab in association with methotrexate (10 mg/week) and prednisone (5 mg/day) was started because active synovitis continued to affect her metacarpophalangeal and interphalangeal joints and wrists.

In June 2008, she was admitted to our clinic because of proteinuria and hematuria which she had developed in the course of a year.

The physical exam relieved tenosynovitis of the right wrist and decline oedema of inferior limbs she developed over one month.

Laboratory values were characterized by VES 101 mm (1 h), PCR 0.57 mg/dl, negative Waaler-Rose, increased levels of rheumatoid factor (86 U/ml; normal: 0-40); hemocromocytometic values and liver functional parameters were normal. Serum hepatitis B surface antigen and anti-hepatitis C virus antibody were negative and serum complement levels and circulating immune complexes were within normal limits. Anti-nuclear antibody (ANA), anti-double stranded (ds) DNA, anti-Ro(SS-A), anti-La(SS-B), anti-Sm, and anti-ribonucleoprotein (anti-RNP) antibodies were not detected and likewise anti-cyclic citrullinated (anti-CCP) and anti-neutrophil cytoplasmic antibodies (ANCA) were absent.

Her renal laboratory profile showed the following concentrations: creatinine, 0.8 mg/dl; blood urea nitrogen, 63 mg/dl; albumin, 2.6 g/dl; total protein, 4.5 g/dl. Urinalysis revealed proteinuria (6 g/day) and microscopic hematuria.

Bone erosions and symmetric joint space narrowing consistent with RA were defined by standard radiography of hands and feet.

Competing interests: none declared.
A renal biopsy was performed on June 16, 2008. Histological examination revealed membranous nephropathy (stage 2) characterized by basement membrane thickening, subepithelial proteic deposits, two areas of segmentary sclerosis, glomerular ischemia, tubular atrophy and interstitial fibrosis (Fig. 1). Immunofluorescent microscopy revealed deposits of IgG and C3 on the capillary wall (Fig. 2).

In July 2008, the patient underwent a 3-day course of steroid pulse treatment (intravenous methylprednisolone 1g/day). Subsequently, she was switched to oral prednisone 75 mg/day for 30 days, which was then tapered gradually until to the final dose of 5 mg/day. In August 2008, when she was seen at a follow-up visit, she did not complain of any symptoms and proteinuria was markedly decreased to 0.5 g per day. About 3 months later, her urinary protein excretion was below 0.2 g per day without evidence of progressive renal dysfunction.

**Discussion**

Considering the renal biopsy findings in RA patients with urinary abnormalities and/or kidney impairment, mesangial glomerulonephritis is the most frequent histological lesion (35-60%), followed by minimal change glomerulopathy (3-14%) and p-ANCA positive necrotizing crescentic glomerulonephritis (11). Regarding membranous nephropathy, it is generally accepted as the most frequent histological lesion during treatment with gold-salt, D-penicillamine and bucillamine, even if other authors have described a direct relation to RA (2, 3).

Membranous nephropathy occurs in our patient during the prolonged course of RA. We have considered the possibility of secondary glomerulonephritis due to connective diseases or vasculitides. Nevertheless, we have excluded these hypotheses because our patient has not presented cutaneous or mucosal lesions, hematological alterations, serositis or other visceral organs involvement. Moreover, serum complement levels were normal and ANA, anti-DNA, anti-Ro(SS-A), anti-La(SS-B), anti-Sm, anti-RNP, and ANCA were absent. Hepatitis-related glomerulopathy was excluded because hepatitis B surface antigen, and anti-hepatitis C antibody were negative.

Even if the presence of membranous nephropathy has been described in RA patients treated with D-penicillamine, bucillamine or gold salt, we excluded also these causes because our patient had never been treated with these drugs. Non-steroidal anti-inflammatory drugs are also been considered responsible for developing nephrotic syndrome in RA, but our patient has not showed the clinical features that may help to classify non-steroidal anti-inflammatory drug-related membranous nephropathy: the swift onset of symptoms, the swift remission after the non-steroidal anti-inflammatory drugs withdrawal, and the absence of recurrent disease (4).

Our patient was instead treated with adalimumab in association with methotrexate. We may exclude a correlation between methotrexate and the renal disease because methotrexate is usually related to minimal change glomerulopathy and acute tubular necrosis rather than to membranous nephropathy (12). On the contrary, we can not exclude a correlation between adalimumab and the renal disease. In fact, a correlation between adalimumab and renal diseases has already been described in three RA patients who developed focal proliferative lupus nephritis, necrotizing crescentic glomerulonephritis, and membranous nephropathy, respectively (5, 6, 13). Moreover, glomerulonephritis has also been described in RA patients receiving etanercept or infliximab, suggesting a
role for anti-TNF-α therapy (5). Even if the pathogenic mechanism is still unknown, it has been hypothesized that anti-TNF-α drugs may have immunogenic effects by inducing apoptosis and releasing immunogenic antigens, or by reducing C-reactive protein levels, which is involved in clearing apoptotic immunogenic debris (14). Furthermore, a recent observational study has demonstrated that vasculitis is more frequent in RA during anti-TNF-α treatment than without anti-TNF-α, even if it remains to be determined whether vasculitis is a consequence of anti-TNF-α therapy or whether it is related to more severe RA, considering that patients treated with anti-TNF-α have usually a more severe RA which is characterized by higher incidence of vasculitis (15).

In conclusion, the above-described relation between membranous nephropathy and RA, remains unclear. On one hand, membranous nephropathy may be directly related to RA. In fact, even if the pathogenesis of membranous nephropathy in RA is still unknown, it is hypothesized that the presence of circulating immune complexes and rheumatoid factor, or alteration in T cell immune response and the presence of pro-inflammatory cytokines may play a role in the pathogenesis of the nephropathy. On the other hand, we can not exclude a correlation between adalimumab and the renal disease. Even if there are only three previous reports about RA patients receiving treatment with adalimumab who developed renal diseases, a role of anti-TNF-α drugs in RA nephropathy is hypothesized because of the temporal relationship of the treatment with the onset of renal disease (5, 6, 13).

References