

## Case Report

# Idiopathic Membranous Nephropathy Preceding the Onset of Rheumatoid Arthritis: a Case Report

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## Abstract

**Introduction:** Membranous nephropathy (MN) in the context of rheumatoid arthritis (RA), is often an iatrogenic complication due to the nephrotoxic effects of antirheumatic drugs. Rare cases of non-iatrogenic association between these two diseases were reported in the literature.

**Case report:** A 30-year-old female patient presented in September 2005 with nephrotic syndrome. Renal biopsy showed features consistent with MN. Search for etiology was negative, particularly lupus serology which remained negative throughout the course of her illness. Accordingly, she was diagnosed as a case of idiopathic MN. Initially, she was treated with angiotensin converting enzyme inhibitors and angiotensin receptor blockers which maintained her protein excretion below nephrotic range for two years. Her nephrotic syndrome then relapsed and was treated with steroids and chlorambucil, according to the Ponticelli protocol. A few months later, she presented with early morning joint stiffness, polyarthritis involving the small joints of the hands, and strongly positive rheumatoid factor, fulfilling the diagnostic criteria of rheumatoid arthritis (RA). Her serum creatinine remained normal and a second renal biopsy revealed the same features of MN. Her RA was treated with pulsed methylprednisolone followed by oral steroids and methotrexate resulting in remission of the joints disease and the nephrotic syndrome. Remission was maintained for the last two years up to the time of this report.

**Conclusion:** We hereby report a case of secondary membranous nephropathy that preceded the onset of rheumatoid arthritis by three years.

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## Introduction

Membranous nephropathy (MN) is an important cause of adult nephrotic syndrome. It is characterized by fixation of immune deposits on the outer surface of the glomerular basement membrane followed by complement activation and damage to the basement membrane. The disease is commonly idiopathic, though secondary forms do exist [1]. Studies of MN in a murine model, Heymann's nephritis, concluded that the subepithelial immune deposits characterizing the disease are formed in situ, as a result of excretion of a target antigen megalin, from the basal surface of podocytes. Megalin, together with circulating anti-megalin antibodies leads to immune complex formation [2]. However, as megalin is not expressed in human podocytes, it was hypothesized that a similar process with an unknown antigen could be involved in human MN. Debiec *et al* [3] have confirmed the in situ formation of glomerular immune deposits in patients with MN. They described an allo-immune form of MN in newborns of mothers who are carriers of a deficit of a protein expressed on the podocytes, and to which they had been sensitized during previous pregnancies. Understanding the physiopathology of MN has improved lately by the discovery of a new target antigen that includes the M-Type Phospholipase A2 Receptor (PLA2R), which seems to play a key role in the pathology of human MN [4].

On the other hand, rheumatoid arthritis (RA) is the most common chronic inflammatory rheumatic diseases. It had been reported to occur in about 0.5% of the total population, with women being affected four times more often than men. The disease commonly presents between 35 to 55 years of age. It is characterized by chronic

inflammation of the synovial membranes of joints that gradually leads to the destruction of bone and cartilage and accordingly causes impairment of joints' function. Rheumatoid arthritis is also a systemic disease with extra-articular manifestations, particularly renal involvement. Affection of the kidneys often influences the prognosis of the disease [5].

MN in the context of RA is often an iatrogenic drug induced complication. It is mostly related to the use of gold, D-penicillamine and non-steroidal anti-inflammatory drugs. Rare cases demonstrating a non-iatrogenic association between these two pathologies has been reported in the literature. The existence of a causal link between the two entities is still in question. We report the clinical observation of a case of MN, considered idiopathic, that preceded the onset of RA by three years.

## Case Report

A 30-year-old female patient, with no previous history of medical problems and no history of taking medications was initially hospitalized in our Nephrology Department in September 2005 for the management of newly diagnosed nephrotic syndrome. Investigations showed inactive urinary sediment and negative immunological analysis for antinuclear antibodies, anti-dsDNA antibodies, anti-SSa antibodies, anti-SSb antibodies, anti-Smith antibodies, anti-phospholipid antibodies and anti-neutrophil cytoplasmic antibodies. Investigations also revealed normal C3 and C4 fractions of the serum complement, negative latex fixation test and Waaler Rose reaction, negative serological tests for bilharziasis, leishmaniasis, malaria, hydatidosis, hepatitis B and C viruses, negative Widal and Felix tests, normal chest X-ray and normal abdominal ultrasonography. Renal biopsy showed diffuse and moderate thickening of the glomerular basement membrane on light microscopy. Immunofluorescence study on a frozen fragment enclosing four glomeruli showed intense granular and diffuse staining with anti-IgG. Accordingly, the diagnosis of idiopathic MN was made. The patient was initially started on angiotensin converting enzyme inhibitors, angiotensin II receptor blockers and anti-platelets. Proteinuria diminished but was not eliminated, and was maintained in the sub-nephrotic range for two years. After that, a relapse of nephrotic syndrome occurred. The patient was switched to immunosuppressant therapy in the form of alternating corticosteroids and chlorambucil according to the Ponticelli protocol. Three months after initiation of immunosuppressant treatment, the patient presented with morning joint stiffness and polyarthritis,

mostly involving the metacarpophalangeal (MCP) and the proximal interphalangeal (PIP) joints while sparing the distal interphalangeal joints (DIP). The knee joints were also affected. Further laboratory investigations showed an elevated erythrocyte sedimentation rate of 65 mm at one hour, and a C-reactive protein level of 12 mg/L. The Latex fixation test and the Waaler Rose reaction exceeded 256 UI/L. Serological screening for lupus was negative. Her complete blood count as well as C3 and C4 fragments of serum complement were normal. Her proteinuria remained within the nephrotic range and her renal function tests were normal. A second renal biopsy was taken; it showed the same previous renal histological lesions.

These findings suggested the diagnosis of rheumatoid arthritis (RA) associated with idiopathic MN, given the presence of at least 4 diagnostic criteria according to the American College of Rheumatology (ACR), namely: morning joint stiffness lasting at least one hour, arthritis of at least 3 joint groups simultaneously, arthritis of at least one hand joint observed by a doctor and positive test for serum rheumatoid factor. At this early stage of the disease, imaging of the hands did not demonstrate significant erosive lesions. Furthermore, the diagnosis of RA was confirmed by the presence of strongly positive anti-cyclic citrullinated peptide antibodies (Anti-CCP) and anti-filaggrin antibodies by ELISA, with levels exceeding 340 UI/L and 10 UI/L, respectively.

The patient was thus given pulsed methylprednisolone followed by oral prednisolone and Methotrexate. Two months after initiation of therapy, there was great improvement in the joint symptomatology and resolution of the nephrotic syndrome. Her protein excretion significantly dropped to a mean value of  $0.5 \pm 0.3$  g/24h. Currently, two years after initiation of steroids and Methotrexate therapy, the patient remains in complete remission regarding her nephrotic syndrome as well as her joints' disease.

## Discussion

The question raised by this clinical observation concerns the causal link between MN and RA in the absence of an iatrogenic cause. The diagnosis of early RA is usually difficult, being mostly based on clinical observations. In 70% of cases the suspicion of RA is raised by the presence of distal oligo-arthritis, and suggested by its localization at the MCP and PIP joints [5]; that was the case in our patient. In RA, the autoimmune hypothesis

was first raised upon identification of the first known auto-antibody, the rheumatoid factor, and in the absence of etiological factors such as an infection preceding the disease. The presence of this auto-antibody and the specific consumption of the complement support the fact that RA is an immune complex-mediated disease appearing in predisposed individuals in response to a variety of inflammatory stimuli [6]. However, several questions remain unanswered, so far. It is not yet clear how an antibody directed against a ubiquitous antigen can lead to a pathology specific to joints. Also, the role of the rheumatoid factor, which differs from one disease to another, is not altogether understood. Furthermore, the mechanism for initiation of loss of self-tolerance remains unknown [6].

Renal abnormalities reported in patients with RA were mostly minimal change disease and MN. These were often related to the use of gold salts and D-penicillamine [7]. Outside the iatrogenic context, the most observed renal impairment in patients with RA is Type 1 Membranoproliferative Glomerulonephritis (MPGN) with predominance of IgM and/or IgA immune deposits, together with C3 and C1q. IgG deposits were rarely seen in patients with MPGN due to RA. Other glomerular affections reported in patients with RA include focal necrotizing glomerulonephritis and mesangial or fibrillary glomerulonephritis [8-11].

Observing MN in a patient with RA and in the absence of prior use of any disease-modifying therapy remains exceptional in the literature. Kobayashi reported a case in which MN preceded the onset of RA by two years [12]. Honkanen also reported four cases with a similar scenario [13]. In our patient, MN preceded the onset of RA by three years. A causal relationship between these two pathologies remains questionable. In fact, the autoimmune nature of the two diseases raise the possibility of auto-antibodies with antigenic targets prevalent in both MN and RA, that can provide an explanation for the possible association between the two conditions.

## Conclusion

We report a female patient with secondary MN due to RA, with the renal involvement preceding joints involvement by more than three years. It showed an abrupt response only to a disease modifying anti-rheumatic protocol.

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