

A membranous nephropathy case: Is it related to sulfasalazine?

Un nefropatía membranosa Caso: ¿Está relacionado con sulfasalazina?

Dear Editor,

In adult age group, the cause of membranous glomerulonephritis (MG) cannot be detected in about 75% of the patients. These cases are defined as idiopathic (primary) MG. MG associated with drugs and other diseases are defined as secondary MG.

Penicillamine and gold salts, formerly used in the treatment of rheumatoid arthritis (RA), are responsible for the development of MG. Amyloidosis, analgesic nephropathy, glomerulonephritis and rheumatoid vasculitis can be observed in RA.

In the literature sulfasalazine was reported to cause interstitial nephritis, nephrotic syndrome, acute renal failure, non-nephrotic proteinuria, hematuria, and leucocyturia.¹⁻⁴ Sulfasalazine 2000 mg/day, hydroxychloroquine, prednisolone 5 mg/day was started for a 55 year old non-diabetic man who was diagnosed as rheumatoid arthritis a year ago. He did not have a history of nonsteroidal antiinflammatory drug use. Proteinuria was detected a month later. Daily protein excretion was 14,725 mg/day and serum albumin was 2.8 g/dl. On physical examination, the patient was normotensive and had pitting oedema in his legs. The patient's blood urea nitrogen and creatinine level and C3, C4 was in normal range and HBsAg, AntiHCV, p-ANCA and c-ANCA was found to be negative. ANA was positive, but anti-ds DNA was found to be negative. Duodenal biopsy was negative for amyloid and percutaneous kidney biopsy was performed. In light microscopic examination, mild thickening of the glomerular basement membrane, mild interstitial inflammatory cell infiltration and hyaline material accumulation in some tubular spaces was observed. By immunofluorescence microscopy strong linear/granular IgG and complement deposition and mild granular, C3, C1q and kappa deposition in glomerular basal membranes was detected. These pathological findings suggested the diagnosis of membranous glomerulonephritis anti-phospholipase A2 receptor antibodies were negative. Considering this condition to be related to sulfasalazine, treatment was dropped out and prednisolone dosage was increased as 20 mg/day. In follow-up, two months later, 24-h urine protein excretion was found to be 389 mg/day and steroid dosage was tapered gradually. He is now being followed without proteinuria.

Although rare, case reports blaming sulfasalazine in the pathogenesis of parenchymal kidney injury, exist. Nevertheless, the US FDA placed a warning within the prescribing information for mesalazine products that stated "It is recommended that all patients have an evaluation of renal function prior to initiation of therapy and periodically while on treatment".⁵

5-Aminosalicylate (5-ASA) is blamed for the nephrotoxicity of these drugs. Nephrotoxicity is thought to be idiosyncratic rather than dose-related.⁶ Cases reported in the literature were mainly in the form of progressive interstitial nephritis. Following cessation of treatment, improvement of renal function can be observed in some cases, while steroid treatment can be indicated if improvement is not observed.⁷

In a cohort of ulcerative colitis 6 patients were reported to develop nephrotic syndrome. 3 of these patients were using mesalazine while 2 were using sulfasalazine and one patient was using both. In histological evaluation of the patients, 5 had minimal change disease and one patient had focal segmental glomerulosclerosis. All of the patients improved with steroid treatment.⁸ The pathogenesis of nephrotic syndrome associated with the use of sulfasalazine is not understood yet.⁹

The patient was also using hydroxychloroquine. This drug continued and remission of proteinuria existed, so the cause is not probably this drug. Also rheumatologic diseases can cause MN but proteinuria remission after discontinuation of the drug excluded this possibility.

In our case, the histopathologic diagnosis was membranous glomerulonephritis and this varies from case reports in the literature.

Drugs are one of the important causes of secondary membranous glomerulonephritis. By presenting this case we want to remind that sulfasalazine may be a cause of secondary membranous glomerulonephritis.

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^a Nephrology Department, Ankara Ataturk Research and Training Hospital, Turkey

^b Rheumatology Department, Ankara Ataturk Research and Training Hospital, Turkey

^c Nephrology Department, Corum Hitit University, Turkey

*Corresponding author.

E-mail addresses: ozlemderen2@hotmail.com (O. Bagdatoglu), ymaras@hotmail.com (Y. Maras), ozlemderen@hotmail.com (O. Yayar), beser374@mynet.com (B. Eser).

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Oktay Bagdatoglu^a, Yuksel Maras^b, Ozlem Yayar^{a,*}, Baris Eser^c

Complete remission of nephrotic syndrome in a woman with renal amyloidosis due to Familial Mediterranean Fever[☆]

Remisión completa de síndrome nefrótico en mujer con amiloidosis renal por fiebre mediterránea familiar

Dear Editor,

Chronic kidney disease due to AA amyloidosis is one of the main complications of Familial Mediterranean Fever (FMF).¹ In 2009, in the journal *Nefrología*, we presented the case of a 38-year-old woman of Armenian origin with severe nephrotic syndrome due to AA amyloidosis as a form of onset of FMF (with heterozygous M680I and M694V mutations in the MEFV gene). Given the severity of her proteinuria at diagnosis, deterioration in renal function and intolerance to antiproteinuric drugs, we started treatment with colchicine, at doses of 0.5 mg/8 h/day, and infliximab, at doses of 5 mg/kg IV at baseline, at 2 weeks and subsequently every 2 months. In the clinical follow-up performed in the first year of treatment to evaluate her response to this, we reported partial remission: clinical improvement and improvement in renal function, but with persistent nephrotic proteinuria.²

In this report we describe her mid-term clinical course. In the following 6 years, the patient has remained asymptomatic with no new episodes of hydropic decompensation or hospital admissions. [Table 1](#) shows the clinical course of both her laboratory values and the treatment followed. Starting from the second year of treatment, colchicine was sustained

continuously at doses of 1 mg/day. Given that her proteinuria progressively decreased, infliximab doses were increasingly spaced out, to intervals of 4–6 months, and this treatment was permanently suspended in 2011.

As a result of combination therapy with colchicine and infliximab, in the acute phase of diagnosis of AA amyloidosis due to FMF, clinical improvement and improvement in renal function were achieved, but nephrotic proteinuria persisted. Subsequent follow-up required us to modify our initial conclusions: her clinical improvement was maintained, without any new hydropic decompensation, in the context of resolution of her proteinuria.

Treatment with colchicine is effective in preventing amyloidosis in Armenian patients with FMF.³ In cases of colchicine resistance or intolerance, anti-TNF agents may be effective to treat these patients and manage symptoms associated with FMF.^{4,5} In our case, given the initial severity of nephrotic syndrome, together with the findings of AA amyloid in the renal parenchyma and the M694V mutation associated with the most serious cases, combination therapy was decided upon, with a partial response in the first year and subsequently a complete response sustained over time. Perhaps this combination treatment, as it prevented the onset of

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