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

Complete remission of nephrotic syndrome in a woman with renal amyloidosis due to familial mediterranean fever

Sr. Director:

La insuficiencia renal crónica por amiloidosis AA, es una de las principales complicaciones de la fiebre mediterránea familiar (FMF)[1]. En el año 2009, en la Revista Nefrología, presentábamos el caso de una mujer de 38 años, de origen armenio, con un síndrome nefrótico severo debido a una amiloidosis AA como forma de debut de la FMF (con presencia de mutaciones M680I y M694V en heterocigosis en el gen MEFV). Por la severidad de la proteinuria al diagnóstico, el deterioro de función renal, así como la intolerancia a fármacos antiproteinúricos, nos llevó a instaurar un tratamiento con colchicina, a dosis de 0,5 mg/8 h/día e infliximab a dosis de 5 mg/kg iv, de forma basal, a las 2 semanas y, posteriormente, cada 2 meses. En el seguimiento clínico realizado en el primer año de tratamiento, para evaluar la respuesta a este, comunicábamos una remisión parcial: mejoría clínica y de función renal, pero con persistencia de proteinuria nefrótica[2].

En esta comunicación damos a conocer la evolución a medio plazo. En los 6 años siguientes, la paciente ha permanecido asintomática sin presentar nuevos episodios de descompensación hidrópica ni ingresos hospitalarios. En la tabla 1 se expone tanto la evolución analítica como el tratamiento seguido. A partir del segundo año de tratamiento, la colchicina se ha mantenido de forma continuada a dosis de 1 mg/día. Y ante la disminución progresiva de la proteinuria, la dosis de infliximab se fue espaciando cada vez más a intervalos de 4-6 meses, suspendiéndose definitivamente este tratamiento en el año 2011.

La terapia combinada con colchicina e infliximab, en la fase aguda del diagnóstico de la amiloidosis AA por FMF, logró una mejoría clínica y de función renal, pero persistencia de proteinuria nefrótica. El seguimiento posterior nos obliga a modificar nuestras conclusiones iniciales: se mantiene la mejoría clínica, sin nuevas descompensaciones hidrópicas, todo ello, en el contexto de una desaparición de la proteinuria.

El tratamiento con colchicina es efectivo en prevenir amiloidosis en pacientes armenios con FMF[3]. En los casos de intolerancia o resistencia a esta, los agentes anti-TNF pueden ser efectivos para tratar a estos pacientes, así como para el control de síntomas asociados a la FMF[4,5]. En nuestro caso, dada la severidad inicial del síndrome nefrótico unido a los hallazgos de amiloide AA en parénquima renal, la presencia de la mutación M694V asociada a los casos más graves se decidió una terapia combinada, con respuesta parcial en el primer año y posteriormente completa mantenida en el tiempo. Quizás este tratamiento combinado, al evitar la aparición de nuevos episodios autoinflamatorios asociados a la FMF, evitaría que se depositara más amiloide en el tejido renal y, además, una regresión progresiva del acumulado, que, en este caso, no podemos confirmar, al carecer de nueva histología, aunque la clínica puede sugerirlo, al haberse logrado una desaparición de la proteinuria. Respecto a este hecho, en la literatura Kutlugün et al., también describen 2 casos de remisión completa del síndrome nefrótico con colchicina 1,5 mg/día, mantenido por un periodo de cerca de 30 años[6].

En conclusión, la principal complicación renal (insuficiencia renal crónica) asociada a la amiloidosis AA por FMF,