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Acute kidney injury due to granulomatous interstitial nephritis induced by tramadol administration☆

Fracaso renal agudo secundario a nefritis intersticial granulomatosa asociada al tratamiento con tramadol

Dear Editor,

Granulomatous interstitial nephritis (GIN) is a very rare condition present in <1% of kidney biopsies.[1–3] It is primarily associated with drugs (9–45%), sarcoidosis (9–29%), less commonly to mycobacterial or fungal infections and very rarely to inflammatory bowel diseases, microcrystals or paraproteinaemia. The causes of >40% of cases may remain unidentified.[4,5] The drugs which are most commonly involved are analgesics and anti-inflammatories, but we have not found being reported with tramadol, which is why we are presenting this case.

A 71-year-old woman with cervical arthrosis, diverticulitis *coli*, gonarthrosis with total prosthesis of the left knee and arterial hypertension (treated with telmisartan/hydrochlorothiazide). She attended A&E because of a history of nausea and poor fluid intake for several weeks with no diarrhoea, fever or cutaneous exanthema. The patient had been taking tramadol 200 mg/12 h Retard (prolonged-release) for 40 days for knee pain. In the initial tests, she presented with severe deterioration of kidney function (Table 1) which was attributed to sodium and water depletion, so she was hydrated and hydrochlorothiazide was withdrawn. She was admitted two weeks later as kidney function had not recovered and she presented with proteinuria with no significant albuminuria (Table 1). A kidney biopsy was performed and 3× 500-mg bolus of IV methylprednisolone were administered, and she was discharged with oral prednisone (1 mg/kg/day decreasing 10 mg in10 days) In a subsequent check-up (day +39), a clear improvement of kidney function was seen with reduced proteinuria. The bone marrow was sampled by fine-needle aspiration, ruling out myeloma, with only 2% of plasma cells being phenotypically mature.

The kidney biopsy showed: 10 glomeruli, 2 with total sclerosis; in six glomeruli there was expansion of the glomerular tuft with vascular congestion and slight hyperplasia of podocytes; capsular adhesions, areas of sclerosis or glomerular collapse was ruled out. The tubule–interstitial compartment showed a marked mixed inflammatory component which occupied 40% of the tissue sample, with predominance of lymphocytes, occasional non-necrotising epithelioid granulomas and incidental presence of giant cells. The Ziehl-Neelsen technique was negative. A degree of tubular atrophy was also seen, as well as degenerative and regenerative changes in tubules in unaffected areas. No tubular protein cylinders were detected. In the immunofluorescence, no immune deposits were seen, showing tubular reaction to both immunoglobulin light chains as well as to IgA and IgM. The histology ultimately suggested GIN, and the existence of a myeloma-related nephropathy was ruled out. The final blood test showed significant recovery of kidney function, although did not achieve the baseline Cr level (Cr 0.78 mg/dl)

GIN has been associated with a wide variety of drugs, including omeprazole, ibuprofen, triamterene, furosemide, fenofibrate, cotrimoxazole, penicillin, ketoprofen and paracetamol. The level of kidney insufficiency is usually mild or moderate, although some cases have required dialysis.[4,6] Accompanying clinical symptoms of fever, exanthema, haematuria or peripheral eosinophilia are rare.[7] The kidney biopsy revealed granulomas with no necrosis, no

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Table 1 – Changes in blood and urine chemistry.

	Baseline	+15 days	+39 days	+11 months
Creatinine	4.6–5 mg/dl	3.38 mg/dl	1.54 mg/dl	1.28 mg/dl
Albuminuria	37.7 mg/gCr	78.9 mg/gCr	14.7 mg/gCr	20.6 mg/gCr
Proteinuria	–	660 mg/gCr	241.8 mg/gCr	352 mg/gCr
Bence-Jones urine kappa	–	64.9 mg/l	17 mg/l	17.5 mg/l
Bence-Jones urine lambda	–	21 mg/l	0	0
IgG	–	1630 mg/dl	669 mg/dl	855 mg/dl
β2-microglobulin	–	8.1 μ/l	–	3.5 μ/l (normal)
Monoclonal peak	–	0.28 g/dl IgG lambda	–	0.14 g/dl IgM kappa

calcifications, no pattern of starry bodies and very few giant cells. The level of interstitial fibrosis is normally mild or moderate and mild or moderate inflammation may be seen, with rare presence of eosinophils.[4]

The recommended treatment is corticosteroids, which foster good and progressive recovery of kidney function, even in cases requiring dialysis.[4,6] The level of recovery bears no relation to age and is not clearly related to the level of fibrosis present in the biopsy. The doses of corticosteroids administered vary greatly, usually 0.5–1 mg/kg of prednisone, and it has even been suggested that lower doses could be just as effective.[3,4] The maintenance time of the treatment is usually >6 months and it is usually adjusted to the clinical course of kidney function recovery. In some cases, further deterioration of kidney function has been seen when the steroid dose is reduced. Administering immunosuppressants (mycophenolate) has even been tried to reduce steroids, with a good response.[8]

Myeloma may cause acute tubulointerstitial nephritis on rare occasions, with variable levels of tubulitis and, rarely, with eosinophils.[9] In our case, myeloma was ruled out. We also observed a rapid and clear recovery of kidney function with steroids, that was associated to reduction of with IgG or β2-microglobulin and Bence-Jones proteinuria indicating that they were an expression of an immunological stimulus.

The tramadol toxicity reported in the literature is more related with the opioid effects and we have found no reported cases of GIN. We have only found one case of a nephrotic syndrome due to tramadol with focal segmental glomerulosclerosis (*tip*-lesion), in which data of interstitial nephritis were seen, but with no formation of granulomas or presence of giant cells.[10]

We therefore present the first case described in the literature of GIN associated with tramadol, with recovery of kidney function after treatment with steroids.

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