

## Standard dose paracetamol-induced tubulointerstitial nephritis

Katherine Pose<sup>1</sup>, Margarita Tomás-Perez<sup>1,2</sup>

<sup>1</sup>Department of Allergy, La Paz University Hospital, Madrid, Spain

<sup>2</sup>Department of Allergy, La Paz University Hospital, Institute for Health Research (IdiPAZ), Madrid, Spain

To the Editor,

Paracetamol is widely used as an analgesic and antipyretic agent safe for all age groups and even for chronic kidney disease patients, freely prescribed by many physicians and available as an over-the-counter drug at pharmacies (1). Tubulointerstitial nephritis (TIN) is a group of immune-mediated inflammatory diseases that involve the interstitium and tubules. It is one of the most important and major causes of acute kidney injury that subsequently leads to renal failure. Drug-induced nephritis is the leading cause of TIN and its most important etiology is medication such as paracetamol and other NSAIDs (2). Histopathological view after the renal biopsy is the only definitive diagnosis and gold standard for TIN, which shows characteristic diffuse or focal inflammatory cells (2). The basic treatment is supportive therapy, such as body fluid and electrolyte management, discontinuation of drugs is the first line of treatment in drug-induced TIN with alternative drug administration to treat infections that often lead to the reversal of renal injury (2,3). Although the effectiveness of steroids is controversial, some studies have reported a more rapid and complete recovery of baseline renal function in those patients treated with steroids; its initiation in the early phase has shown efficacy (4). There are just a few cases reported on paracetamol-induced TIN with standard doses (5). None of the previous cases reported were confirmed by a lymphocyte transformation test (LTT). We present a case of acute tubulointerstitial nephritis induced by paracetamol confirmed by LTT.

A 25-year-old woman with a 72-hour bilateral lumbar pain radiating to the flanks, nausea, and vomiting. To relieve the pain she took 1 gram of paracetamol every 8 hours (previously tolerated without incidence), with a total of 5 pills taken in that time. Due to worsening symptoms, she went to the emergency room where she was finally admitted by Nephrology due to a non-oliguric AKIN 3 acute renal failure with a non-anion gap metabolic acidosis. Laboratory tests showed creatinine 6.05 mg/dL, urea 64 mg/dL, eosinophils 90/ $\mu$ L, and leukocytosis of 12770/ $\mu$ L. Glomerular filtration (CDK-EPI) 12 mL/min/1.73m<sup>2</sup>. The anion gap was 12. Urinary analysis showed sodium 61 mmol/L, chloride 50 mmol/L, potassium 23 mmol/L, and leukocyturia. Obstructive etiology was ruled out with the abdominal ultrasound, and the renal biopsy revealed tubulointerstitial nephritis, nephrocalcinosis, and tubular necrosis (Figure 1). She was then assessed by the department of allergology and we performed an LTT with paracetamol and started corticoids treatment. The patient completed a two-week course of systemic corticosteroids with good clinical evolution, restoring renal function. Briefly, the proliferation of lymphocytes from the allergic patient was measured as previously described (6). Fresh peripheral-blood mononuclear cells separated over a density gradient (Histopaque-1077, SigmaAldrich) and were incubated for 6 days at 10<sup>6</sup> cells/mL in triplicate with paracetamol (200, 100, 10, 1  $\mu$ g/mL). Phytohemagglutinin (5  $\mu$ g/mL) was the positive control. Proliferation was determined by the addition of [<sup>3</sup>H] thymidine (0.5 $\mu$ Ci/well) for the final 18 hours of the incubation period. Proliferative response was calculated as stimulation index (SI), defined as the ratio between the mean values of counts per minute in cultures with antigen and those obtained without antigen. A positive response, defined as an SI over 2, was obtained with the drug tested. In summary, the result of the LTT with paracetamol was positive with a stimulation index of 4.1, 2.4, 0.7 and 2.0 for 1, 10, 100 and 200  $\mu$ g/mL respectively. The LTT has been used previously to assess delayed allergic reactions and due to its safety on the assessment of a T-cell response to the drug, it can be used to evaluate this type of reactions. The chronology of symptoms in our patient, its resolution following the withdrawal of the drug, and corticosteroid therapy, in addition to the complementary tests,

suggests the diagnosis of paracetamol-induced acute tubulointerstitial nephritis, this being the first case reported that had been confirmed with LTT.

## REFERENCES

1. Higashi Y, Baba N, Yoshimine H, Sakaguchi I, Kanekura T. Late-onset interstitial nephritis in a patient with drug-induced hypersensitivity syndrome/drug reaction with eosinophilia and systemic symptoms. *J Dermatol*. 2020;47(2):174-177. DOI: 10.1111/1346-8138.15175
2. Bhandari J, Thada PK, Arif H. Tubulointerstitial Nephritis. In: *StatPearls*. StatPearls Publishing; 2022. Accessed January 20, 2023. <http://www.ncbi.nlm.nih.gov/books/NBK557537/>
3. Kodner CM, Kudrimoti A. Diagnosis and management of acute interstitial nephritis. *Am Fam Physician*. 2003;67(12):2527-2534. PMID: 12825841
4. González E, Gutiérrez E, Galeano C, Chevia C, de Sequera P, Bernis C, et al. Early steroid treatment improves the recovery of renal function in patients with drug-induced acute interstitial nephritis. *Kidney Int*. 2008;73(8):940-946. DOI: 10.1038/sj.ki.5002776
5. Tang Y, Yang L, Tao Y, Qin W. A case of acetaminophen-induced acute interstitial nephritis and other complications. *Clin Nephrol*. 2015;84(2):118-119. DOI: 10.5414/cn108440
6. Pichler WJ, Tilch J. The lymphocyte transformation tests in the diagnosis of drug hypersensitivity. *Allergy*. 2004;59:809-20. DOI: 10.1111/j.1398-9995.2004.00547.x

**Figure 1.** Patient's kidney biopsy findings. Patchy areas of interstitial edema and mixed inflammatory infiltrates with lymphocytes, neutrophils, and occasional eosinophils (arrowheads) are recognized. There are regenerative changes and vacuolization in the proximal convoluted tubules and foci of interstitial microhemorrhage (asterisk). Images of tubulitis are not identified. The glomeruli have fine and permeable capillary lumens and do not show significant histological alterations (arrows).

