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Acute tubulointerstitial nephritis due to the use of topical diclofenac in a pediatric patient: A case report

Cristhian David Peláez Cristancho [ID] [1]*, Mariangel Castillo Arteaga [ID] [2], Andrea Carolina Rueda Soto [ID] [2], Santiago Ortiz Ramírez [ID] [2]

1. Postgrado de Pediatría, Pontificia Universidad Javeriana, Bogotá, Colombia.
2. Servicio de Pediatría, Hospital Universitario San Ignacio, Bogotá, Colombia.

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Abstract

Introduction: Tubulointerstitial nephritis (TIN) is a histological diagnosis that can manifest with the classic triad: fever, rash, and eosinophilia. Among the leading causes is consuming nonsteroidal anti-inflammatory drugs (NSAIDs) and cyclooxygenase 2 (COX2) inhibitors. We present an unusual case of TIN development with topical NSAID exposure in an adolescent.

Clinical case: 16-year-old woman admitted for the study of acute abdomen with repeated emetic episodes. During hospitalization, he developed nonoliguric acute renal failure, hyperphosphatemia, proteinuria, metabolic acidosis, hyperuricemia, hyperparathyroidism, decreased vitamin D, and developed arterial hypertension.

Evolution: Required vitamin D, antihypertensives, allopurinol, and parenteral hydration. She did not require hemodialysis or steroids. Progressively, the patient improved and was discharged. The renal biopsy report was confirmed in the outpatient clinic as acute patchy tubulointerstitial nephritis.

Conclusion: It is essential to know that all NSAIDs have the potential risk of generating tubulointerstitial nephritis. This rule-out diagnosis should not be underestimated in clinical practice, even with topical NSAID treatment.

Keywords:

MESH: Nephritis, Interstitial; Anti-Inflammatory Agents, Non-Steroidal; Adolescent, Hospitalized; Case report.

* Corresponding author

Email: Cristhian David Peláez Cristancho < pelaez.c@javeriana.edu.co >/Address: Hospital Universitario San Ignacio, NIT 860.015.536-1. Kra 7 No. 40-62, Bogota, Colombia. Telephone: +57 5946161

Acute tubulointerstitial nephritis is a significant cause of acute kidney injury, accounting for approximately 5-15% of cases in pediatric and adult patients. It is histologically characterized by an inflammatory cell infiltrate, edema, and tubulitis at the level of the renal interstitium, which can progress to fibrosis and is usually accompanied by impaired renal function [1-3]. They have been reported to represent (in their acute or chronic form) the diagnosis of 1-7% of renal biopsies performed in pediatric patients [2].

Among the multiple triggers are infectious processes, genetic conditions, medications, and autoimmune diseases. However, 90% of reported cases are associated with medications, with nonsteroidal anti-inflammatory drugs (NSAIDs), antibiotics (e.g., beta-lactams), and proton pump inhibitors being the most common [1, 3].

NSAIDs have become an alternative for pain management. They provide higher local skin concentrations than plasma levels, generating a lower degree of systemic exposure and, therefore, a lower risk of systemic adverse effects than oral presentations [4]. Given the limited number of reports in the literature of possible adverse effects at the renal level, this case report was decided to be carried out.

Clinical case

A 16-year-old female adolescent with no pathological medical history consulted the emergency department due to a clinical picture of 8 hours of evolution consisting of multiple emetic episodes, initially managed with intravenous fluids and an antiemetic (ondansetron), with the improvement of symptoms, for which reason he was discharged. However, he returned 48 hours later due to colicky abdominal pain at the mesogastric level, which radiated in a band to the back, with an intensity of 6/10 on the analog scale of pain associated with nausea and hypoxia, managed at home with a single dose of 500 mg of acetaminophen. On admission, the patient was found to be in good general condition, with pain on palpation of the hypochondrium, right flank, and buoyant bilateral fist percussion, predominantly right, with no other findings on physical examination.

Diagnostic workshop

Due to the clinical picture of acute abdominal pain under study, paraclinical tests are requested, which show serum creatinine levels twice increased for the average value according to age at 1.63 mg/dl (expected average weight for age: 0.8 mg/dl), with a BUN of 26.8 mg/dl, a BUN/creatinine ratio of 16.44, with a urinary tract ultrasound showing kidneys without alterations in their size, shape or echogenicity, nor evidence of focal lesions in their parenchyma or dilation of the system's collectors; accompanied by a urinalysis with density 1.006, pH 6, protein 30 mg/dl, without leukocyturia, hematuria or bacteriuria.

Initially, it was considered a KDIGO 2 acute kidney injury, so extension paraclinical tests were requested to clarify its origin: ionogram with phosphorus levels in the upper limit (6.1 mg/dl), with a proteinuria/creatinuria ratio in the normal range. Moderate elevation: 1.6 (creatinuria and proteinuria in an isolated sample at 43 and 71 mg/dl, respectively), an average calciuria/proteinuria ratio (calciuria in an isolated test at 0.18 mg/dl), and venous gases with metabolic acidosis (pH: 7.36, pCO2: 23 mmHg, pO2: 20 mmHg, HCO3: 21.9 mmol/l, BE - 3 mmol/l).

Taking into account the associated emetic episodes and the patient's symptoms, a picture of acute kidney injury of presumed ischemic etiology was initially considered; however, the presence of proteinuria, age, sex, progressive increase in nitrogen gases, and the previously presented noxa indicated that a differential picture such as acute glomerulonephritis or toxic acute kidney injury was ruled out. Studies were completed showing an adverse autoimmunity profile (anti-DNA, ANAS, pANCA, cANCAS) with C3/C4 without alterations, lipid profile, normal glycemia, and glycosylated hemoglobin, complete blood count without dyscrasias, with peripheral blood smears showing occasional echinocytes, mild leukocytosis, without alteration in the platelet line, preserved coagulation times, normal LDH, with uric acid levels elevated by 10.6 mg/dl, increased PTH and phosphorus (87.4 pg/ml and 6.2 mg/dl, respectively), with vitamin D 25 Hydroxy decreased by 12.9 mg/dl, calcium, and alkaline phosphatase in ranges for age, eosinophils in urine at 0, proteinuria in 24 hours in the moderate content of elevation (13.2 mg/m2/hour) and a urinary tomography with the mild inflammatory phenomenon of right perirenal fat. In hyperuricemia, moderate proteinuria, and hyperparathyroidism secondary to nephropathy, management with intravenous fluids was continued, vitamin D supplementation was started, and control was achieved with allopurinol.

Evolution

During the hospital stay, the patient developed arterial hypertension. A Doppler ultrasound of the renal vessels was performed, which revealed a slight increase in the resistance indices of the proximal renal arteries with a nonspecific appearance. The clinical evolution was sluggish, with the progression of the kidney injury, with maximum serum creatinine levels of 3.12 mg/dl, which make up a KDIGO 3 acute kidney injury, for which a kidney biopsy was performed to establish the cause and determine the need for additional treatments.

The mother and patient are reinterrogated, who deny taking medications in recent months other than acetaminophen on the day of the consultation, and deny taking Chinese or homeopathic herbs. They only state that 3-4 weeks before the current clinical picture, he presented edema in the unilateral ulnar joint region in the right hand not associated with trauma, managed with daily topical diclofenac in the affected area for approximately three days with resolution of the picture, without symptoms or signs suggestive of autoimmunity.

Four days after hospitalization, the patient presented a resolution of the renal lesion and hyperuricemia; creatinine levels decreased to 0.77 mg/dl; without the need for additional management, such as systemic corticosteroids, it was decided to discontinue allopurinol, continuing with vitamin D and antihypertensive. The patient was discharged with a suspected diagnosis of tubulointerstitial nephritis secondary to topical NSAIDs.

The biopsy report was received on an outpatient basis by the pathology service, where no glomerular lesion was seen, an immune-mediated lesion was ruled out, and in a very isolated and focal manner, it exhibited a patchy lymphohistiocytic interstitial infiltrate with some eosinophils, suggesting a picture of tubulointerstitial nephritis in resolution possibly due to hypersensitivity, supporting diagnostic suspicion of discharge.

Discussion

The clinical manifestations of acute tubulointerstitial nephritis are nonspecific, making diagnosis difficult. It has a classic triad of extrarenal manifestations of fever, rash, and eosinophilia. However, only 5-10% of patients present all three findings simultaneously [2]. In a retrospective study carried out at the Great Ormond Street Hospital in London, they characterized 60 pediatric patients with diagnoses of tubulointerstitial nephritis by renal biopsy, finding that 11 (41%) had a fever, 9 (33%) presented low back pain, 4 (15%) showed a rash, and they did not report eosinophilia, with anorexia, vomiting, nausea, and general malaise being the most reported symptoms [5].

The renal level is characterized by nonoliguric acute kidney injury and rapidly deteriorating creatinine levels. Patients may have findings of pyuria, hematuria, and glycosuria, with loss of phosphorus and potassium, indicating a tubular lesion. Sometimes, these patients develop proteinuria in different degrees of severity; rarely, in the nephrotic range, they may present eosinophiluria and anemia. Arterial hypertension and edema are uncommon manifestations [1-3].

Decreased levels of vitamin 1.25 explained the development of hyperparathyroidism in the context of acute kidney injury and hypocalcemia related to an impaired glomerular filtration rate (GFR), which leads to an increase in parathyroid hormone (PTH) secretion and subsequently generates increased production of fibroblast growth factor 23 (FGF-23) as part of negative feedback [6].

Renal ultrasound may be routine or show increased cortical echogenicity or renal size. Biopsy findings are usually located at the level of the interstitium, with edema of variable degree, tubulitis, and an infiltrate of mononuclear cells, especially lymphocytes and macrophages. Glomeruli are commonly standard. However, in those caused by NSAIDs, minimal change in disease is occasionally seen [7, 8].

The exact pathophysiological mechanism by which NSAIDs generate tubulointerstitial nephritis is not well established; it is believed to be due to a delayed hypersensitivity reaction. It has also been described that the diversion of the metabolism of arachidonic acid to the formation of leukotrienes (by inhibition of cyclooxygenases) induces the activation of T lymphocytes, which will generate damage [7, 8]. Regarding the histological findings, it is not expected to find granular immune complex deposits at the level of the glomerular basement membrane; it is possible to show interstitial infiltrates with a significant percentage of T lymphocytes, accompanied by tubular injury of variable degree and sometimes granulomatous-mediated reactions by T lymphocytes and eosinophils, implying a high probability of cell-mediated immunity [9]. The presence of interstitial lymphohistiocytic infiltrate in patches with some eosinophils is described in our patient, which suggests the possibility of tubulointerstitial nephritis due to NSAIDs.

Treatment is based on the suspension of the etiologic agent and support management. The probability of spontaneous recovery will depend on the time of exposure to the drug; however, most are self-limited. The addition of systemic corticosteroids can be considered, but the evidence needs to be more conclusive and limited in the pediatric population [1, 3].

In the international literature, there are few described cases of acute tubulointerstitial nephritis due to topical NSAIDs; all of them occurred in adults with advanced ages, and there are no cases reported in the pediatric population [10-12].

Conclusion

In the present case of acute tubulointerstitial nephritis in an adolescent woman, the etiology attributed was the use of topical NSAIDs. Although the plasma concentrations achieved by a topical NSAID are low, there is a theoretical risk of generating systemic compromise. Given the difficulty of establishing possible causality, the possibility of kidney injury from this type of medication should be considered once other causes have been ruled out.

Abbreviations

NSAIDs: Nonsteroidal anti-inflammatory drugs.
FGF-23: Fibroblast Growth Factor 23
TIN: tubulointerstitial nephritis.
PTH: parathormone.

Supplementary information

Supplementary materials have not been declared.

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Author contributions

Cristhian David Peláez Cristancho: Data curation, Formal analysis, Fundraising, Research, Methodology, Project management, Resources, Software, Writing – original draft.
Mariangel Castillo Arteaga: Conceptualization, Supervision, Validation, Visualization, Writing: review and edition.
Andrea Carolina Rueda Soto: Conceptualization, Supervision, Validation, Visualization, Writing: review and edition.
Santiago Ortiz Ramírez: Conceptualization, Supervision, Validation, Visualization, Writing: review and edition.
All authors read and approved the final version of the manuscript.

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Author Information
Cristhian David Peláez Cristancho, Pediatric Resident Physician, Pontificia Universidad Javeriana, Bogotá, Colombia. San Ignacio University Hospital, Bogota, Colombia.
Mariangel Castillo Arteaga, Pediatric Nephrologist. San Ignacio University Hospital, Bogota, Colombia
Andrea Carolina Rueda Soto, Pediatrician. San Ignacio University Hospital, Bogota, Colombia.
Santiago Ortiz Ramírez, Internal Medicine, Fellow of Nephrology. Pontifical Javeriana University, Bogota, Colombia. San Ignacio University Hospital, Bogota, Colombia.

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