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Case Report

NSAID-Induced Tubulo-Interstical Nephritis, Case Report

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Abstract: We present a clinical case of acute renal failure due to acute tubulo-interstitial nephritis induced by NSAIDS without presenting the classic triad (fever, rash and eosinophilia), the withdrawal of the drug did not resolve renal failure, but had an excellent response to corticosteroid therapy until normalization of renal function.

Keywords: Acute interstitial nephritis, acute kidney injury, corticosteroids.

INTRODUCTION

Acute interstitial nephritis (AIN) is a poorly recognized and diagnosed cause of acute kidney injury (AKI). It is estimated to represent between 15 and 20% of cases of acute renal failure; it is the diagnosis reported in 2.8% of all renal biopsies and in 13.5% of biopsies performed specifically for acute renal failure [1].

Drug-induced acute interstitial nephritis (DI-AIN) is an idiosyncratic systemic hypersensitivity reaction to a drug, which by definition means that it is specific to the affected individual and not just the agent involved [2].

Although any drug can potentially cause DI-AIN, antibiotics, non-steroidal anti-inflammatory drugs, and proton pump inhibitors are the most frequent offenders [3]. The diagnosis of DI-AIN is obvious when the classic triad of rash, fever, and eosinophilia occurs a few days after the onset of a guilty drug. However, these findings occur in 10% of patients and the initiation of DI-AIN may be delayed weeks or months after drug initiation [4]. In addition, only half of all patients with biopsy-proven DI-AIN have AKI, while the rest have a slow and progressive loss of renal function that does not meet the AKI criteria [5]. Urinary abnormalities such as eosinophilia, pyuria, and white blood cell (WBC) cylinders, considered typical of DI-AIN, are also unreliable [4]. The diagnosis of DI-AIN is based on maintaining a high index of suspicion in people at risk of this disease and obtaining a kidney biopsy to establish the diagnosis.

PATHOLOGY

Drug-induced tubulointerstitial kidney injury can be pathologically classified into dose-dependent renal tubular epithelial injury (acute tubular injury or necrosis) or an idiosyncratic hypersensitivity reaction that predominantly causes an interstitial pattern of injury (AIN) with inflammation extending posteriorly into the tubular epithelial cells (tubulitis) [3].

Drug-induced AIN is an idiosyncratic B-type immune reaction not mediated by immunoglobulin E. Itis predominantly marked by an immune injury secondary to a cell-mediated process in the kidney.

Antigen Recognition Phase

The immunogenicity of drugs depends on their ability to participate in various processes as follows:

1) Most drugs are small molecules (<1000 Da) and, by themselves, are not immunogenic. However, they can bind to carrier proteins and become immunogenic, a process called haptenization [7]. These "hapten-carrier complexes" are capable of stimulating both T-cell and B-cell immune responses in the kidney where the drug binds to specific tubulointerstitial proteins of the kidney and sets the stage for acute interstitial nephritis to occur.
2) In some cases, however, the drug acts as a "prohapten" and requires metabolism into a reactive compound that can then bind to specific proteins to undergo haptenization [8]. Renal proximal tubule cells have the ability to hydrolyze and mix exogenous antigens and present them to the major histocompatibility complex (MHC), antigen-presenting cells within the kidney [6].
3) Drugs can sometimes produce 'neoantigens' that cause direct toxic damage to interstitial structures and render them 'foreign' and antigenic [9].
4) Drugs can elicit an immune response by antigenic mimicry.
5) Drugs can form circulating antigen-antibody complexes that can deposit in the kidney and cause immunological damage. This is possibly the least common form of drug-induced kidney injury and often causes more tubulointerstitial glomerular injury.

Antigen Presentation Phase

Tubular epithelial cells, when activated, also propagate further damage by inducing pro-inflammatory molecules such as cytokines, growth factors, adhesion molecules, and chemokines [11]. Thus, tubular cells are not only the target of injury in the NIA, but are also involved in inflammatory cell entry and T cell activation.

Antigen-presenting cells in the kidney process and present 'nephritogenic' antigens to helper T cells to activate the immune response, which ultimately leads to kidney injury. In addition, activated renal dendritic cells migrate to regional lymph nodes and activate naïve T cells which, when activated, return to the antigenic source in the kidney and induce immunologicalinjury [10].

Immunological Regulation Phase

Interstitial nephritis is a relatively rare immune response because the activation of nephritogenic immune responses is often self-limited by specific “protective” immunoregulatory events. These involve the activation of suppressor T cells and the down-regulation of MHC class II expression, the latter being necessary for the activation of cells T [12].

Effector Phase

Drug-specific T cells have been identified in the peripheral blood of patients with biopsy-proven DAIN with the simultaneous demonstration of these T cells in the renal interstitium in the immunohistochemical analysis of the respective renal biopsy samples [8]. T cells orchestrating the lesion can be locally activated in the kidney by resident antigen-presenting cells or migrate from neighbouring lymph nodes as explained above, to cause an inflammatory interstitial reaction cascade marked by cytokine release and subsequent tubulointerstitial injury [8- 13].

Diagnosis

The diagnosis of DI-AIN is based on its clinical and laboratory manifestations. Definitive diagnosis of AIS requires a renal biopsy, as well as clinical or laboratory identification of the causativefactor [1].

Treatment

In 2014, Muriithi and colleagues published their experience with 133 cases of biopsy-proven AIS, of which 95 (70%) were drug-induced [14]. All of these patients underwent renal biopsy for Aki with a mean maximum serum creatinine of 4.3 mg / dl. Steroid use was based on clinical judgment. Eighty-three patients were treated with corticosteroids (no specific regimen) for a relatively short period (an average of 5 weeks), while 12 patients were treated conservatively. Meanmaximum serum creatinine in the steroid group was 4.5 mg / dl and 3.0 mg / dl in the control group. At the mean follow-up of 6 months, there was no difference in serum.

Analysis of all patients receiving steroids revealed that a shorter interval from drug withdrawal to steroid administration (6 days against 14 days) was associated with recovery of renal function.

In addition, glucocorticoid treatment should be initiated immediately to limit the extent of damage caused by inflammation and improve the chances of recovery. If the biopsy can be performed on the same day as the initial evaluation, then it may be reasonable to wait to start glucocorticoids until immediately after the biopsy. However, dialysis may sometimes be necessary prior to biopsy to reduce the risk of bleeding complications. In such situations, glucocorticoids should be initiated prior to biopsy, as they should not alter the interpretability of thebiopsy [15].

Initially with 500 to 1000 mg intravenous methylprednisolone daily for three days, followed by oral prednisone at 1 mg / kg daily for definitive treatment of AIN. Others begin prednisone therapy without first administering intravenous methylprednisolone. Therefore, either approach is reasonable [15].

CASE REPORT

18-year-old female, onset of current condition 26.09.21 after ingesting 2,750 mg of naproxen and 3,000 mg of acetaminophen, was hospitalized on October 5, 2021 with the following laboratory reports: creatinine 1.6 mg/dl, bun 17.9 mg/dl, UREA 38.3 mg/dl, hemoglobin 13.9 g/dl, sodium 142 mmol/l, potassium 4.3 mmol/l, chlorine 101 mmol/l.

Continued deterioration of renal function laboratories October 7, 2021 creatinine 4.1 mg/dl, urinary albumin 961.9 mg/l, albumin/creatinine ratio 2477.2 mg/g, C3 supplement 86 mg/dl, C4 supplement 17 mg/dl. On 07.10.21 he requested voluntary discharge from a private hospital and hospitalization, where laboratories were requested to complete the study protocol.

Upon admission to the following laboratories on October 8, 2021: creatinine 3.8 mg/dl, bun 30 mg/dl, UREA 64 mg/dl, HB 12 g/dl, sodium 140 mmol/l, potassium 4.6 mmol/l, chlorine 108 mmol/l, P Anca and C Anca: NEGATIVE, AC ANTI SMITH: NEGATIVE, AC ANTI DOUBLE-STRANDED DNA: NEGATIVE, AC ANTI NUCLEAR(Ana): NEGATIVE. With serum creatinine decreased on October 10, 2021: creatinine 1.4 mg/dl, bun 22 mg/dl, UREA 47 mg/dl, HB 10.5 gr/dl, sodium 145 mmol/l, potassium 4.4 mmol/l, chlorine 117 mmol/l.

However, he presented a new increase in serum creatinine on October 11, 2021: CR 2.3 mg/dl, bun 29 mg/dl, UREA 64 mg/dl, hemoglobin 10.4 gr/dl, sodium 144 mmol/l, potassium 3.82 mmol/l, chlorine 116 mmol/l, proteinuria 700 mg in 24 hours.

Therefore, according to evolution time, it was considered the start of 3 boluses of methylprednisolone 1gr/every 24 hrs. With a decrease in serum creatinine within 24 hours of starting steroid treatment laboratories October 12, 2021: creatinine 1.2 mg/dl, bun 18.78 mg/dl, UREA 40 mg/dl, hemoglobin 10.9 gr/dl, sodium 142 mmol/l, potassium 3.95 mmol/l, chlorine 110.9 mmol/l. A FENA is calculated: 2.81%, URINARY OSMOLARITY: 266 mOsm/kg.

Renal ultrasound showed normal echo structure and size kidneys without ectasia of pathways, negative ANA, normal immunoglobulins and complement.

A renal biopsy was performed by percutaneous puncture on October 12, 2021, with a report on October 15, 2021:

- Active tubulo-interstitial nephritis with eosinophils with acute multifocal tubular injury and marked regenerative changes of the epithelium.
- The most significant histological changes in this material are tubulo-interstitial (AIN with multifocal acute tubular injury). The IFD study did not demonstrate the presence of immune complexes.
- Immunoreactant IGG positive with linear pattern, albumin positive with linear pattern, c3c positive in arteriolar walls.

Immunoreactant IGA, IGM, C1Q, C4C, FIBRINOGEN, KAPPA, LAMBDA ALL NEGATIVE. She is graduated by improvement under management with gradually decreasing prednisone, last control in outpatient consultation October 19, 2021: creatinine 0.7 mg/dl, BUN 14.00 mg/dl, UREA 30 mg/dl, glucose 98 mg/dl.

DISCUSSION

Given the underlying immune mechanism of DI-AIN, corticosteroid administration has been considered the treatment of choice along with early withdrawal of the offending drug. However, there are no randomized controlled trials of corticosteroids in DI-AIN. The bibliography is replete with case reports, case series, and retrospective studies examining corticosteroid treatment for this inflammatory kidney injury.

The patient did not develop the classic allergic DI-AIN with systemic manifestations, she only presented renal manifestations that did not allow to easily differentiate DI-AIN from other causes of AKI. In addition, he did not have resolution of DI-AIN only with the interruption of the drug and presented an aggravation of the AKI, due to inflammation and tubulointerstitial injury in progress despite the interruption of the drug. Therefore, treatment with methylprednisolone boluses was initiated and a gradual decrease in serum creatinine was observed within 24 hours of starting the steroid, with recovery of renal function.

Ethical Responsibilities

Protection of People and Animals: The authors declare that no experiments have been carried out on humans or animals for this research.

Data Confidentiality: The authors declare that they have followed their workplace's protocols regarding the publication of patient data.

Right to Privacy and Informed Consent

The authors have obtained informed consent from the patients and/or subjects referred to in the article. This document is in the possession of the corresponding author.

Use of Artificial Intelligence to Generate Texts

The authors declare that they have not used any type of generative artificial intelligence in the writing of this manuscript or for the creation of figures, graphs, tables or their corresponding captions or legends.

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