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What about NSAID and secondary minimal change disease in adult's people? A case report and review of the literature

Erica E Faure[1], Jorge H. Mukdsi[1*]

Abstract

Non-steroidal anti-inflammatory drugs (NSAIDs) have been used in the management of inflammatory disease for decades. The spectrum of nephrotoxicity attributed to NSAIDs includes mainly acute tubulointerstitial nephritis. However, much less attention has been given to drug-induced glomerular injury. NSAIDs treating patients presenting with nephrotic syndrome may have a variety of glomerular changes indistinguishable from those found in idiopathic minimal change disease (MCD), for example. The clinical presentation is typically abrupt with nephrotic syndrome while in the elderly it can present as acute renal failure from the beginning. We present an MCD-NSAID induced in elderly patient and discuss possible pathogenic mechanism, thinking about on the indiscriminate use of NSAIDs. Here we report the case of a 66-year-old woman with a history of nephrotic syndrome and hypertension without an apparent secondary etiology. However, an exhaustive history showed and indiscriminate use of NSAIDs. Renal biopsy showed a MCD with a mild interstitial nephritis. To our knowledge the morphology of drug-induced diseases often does not differ from the primary forms, making the distinction difficult. There are subtle clues, although the dialogue between clinician and pathologist is essential to reach an etiological diagnosis. Physicians should suspect glomerulonephritis in patients who receive drugs and its management must be determined based on the histological characteristics of the disease. Although corticosteroid therapy seems to be of value, the effectiveness of this approach must still be tested in randomized and multicentric clinical trials.

Keywords: Non-steroidal anti-inflammatory drugs, Minimal change disease, Adult

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Introduction

The kidneys are a frequent target by many drugs used in clinical practice that can exert significant damage in their structure and, therefore, in the function (1). The incidence of acute renal injury related to drugs can be greater than 60%, which can be very expensive and require multiple interventions, including hospitalization (2).

The drug injury could present 4 possible phenotypic forms: acute renal failure, glomerular lesion, tubular lesion or nephrolithiasis. The clinical presentation includes increased creatinine, proteinuria, glomerular hematuria, electrolyte abnormalities and ultrasonographic findings of nephrolithiasis, respectively (3). The spectrum of nephrotoxicity attributed to non-steroidal anti-inflammatory drugs (NSAIDs) includes acute tubular necrosis, acute tubulointerstitial nephritis, glomerulonephritis, papillary necrosis, chronic renal failure, sodium and water retention, hypertension, hyperkalemia and hyperreninemic hypoaldosteronism (4).

The most common is tubular or interstitial damage, resulting in acute tubular necrosis or acute interstitial nephritis, which are dose-dependent processes (5), although there are reports of subclinical renal dysfunction and, chronic renal insufficiency (4). Much less attention has been given to drug-induced glomerular injury (6,7).

NSAIDs patients treated presenting with nephrotic syndrome may have a variety of glomerular changes indistinguishable from those found in minimal change disease (MCD), membranous glomerulonephritis (MG), focal segmental glomerulosclerosis (FSGS). These complications have almost occurred in association with acute interstitial nephritis (8). The mechanisms of NSAIDs induced nephropathies have not been explained. Most authors consider that each of them is a separate entity with own mechanisms. Considering increasing use of these drugs, nephropathy is a rare complication. One possible explanation is that they have a common cause and that the pathogenic processes are modulated by secondary factors that can vary from one patient to another (9).

Case Presentation

A 66-year-old woman, with hypertension of 15 years of evolution, hearing loss and ex-smoking, begins in 2018

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[1]Universidad Nacional de Córdoba, Facultad de Ciencias Médica, Centro de Microscopía Electrónica, Córdoba, Argentina.
***Corresponding Author:** Jorge Mukdsi; Email: mukdsijorge@gmail.com, jorge.mukdsi@unc.edu.ar

Implication for health policy/practice/research/ medical education

Association between drugs and glomerulopathies is not uncommon. Minimal change disease induced by non-steroidal anti-inflammatory drugs is not different from idiopathic minimal change disease. The dialogue between clinician and pathologist is essential to reach an etiological diagnosis.

May with ankles and thighs edema and blood pressure values higher than usual. She is hospitalized in 2018 September due to edema and dyspnea, and she was studied for nephrotic syndrome without diagnosis. She received antiproteinuric drugs. Another nephrologist, requests a renal biopsy for nephrotic syndrome. An exhaustive history showed and indiscriminate use of NSAIDs

The laboratory showed: total cholesterol 405 mg/dL, triglycerides 267 mg/dL, proteinuria 5.5 g/24 h, albumin 2.2 g/dL, creatinine 3 mg/dL, HbA1c 5.5%. HBV viral serology negative. Autoimmune serology: ANCAc, ANCAp: negative. ANA 1/20. Urinary sediment without particularities. On the other hand, renal ultrasonography reported right and left kidney, both of 10x5x5 cm, with preserved corticomedullary relationship and without dilatation. The fundus showed a grade I hypertensive retinopathy.

The high-resolution optical microscopy showed three glomerular structures without major alterations, with slightly hypertrophic podocytes (Figure 1). The interstitium exhibited mild edema and few eosinophilic polymorphonuclear leukocytes, highlighting the presence of several of these in peritubular capillary lumens. Focal fibrosis and slight tubular atrophy, were observed.

The ultrastructural study reveals normal glomerular basement membranes with paramesangial folds by sectors. Podocytes exhibit very extensive and severe pedicel fusion with microvillus transformation and vesicularization of their cytoplasm (Figure 2). No tubulo-reticular inclusions are identified in cytoplasm of endothelial cells or clear deposits of immune complex type.

Discussion

The drug-induced glomerular disease is a poorly defined and recently reported entity (10) and, although is a rare condition, causes significant morbidity and mortality, with most of the drugs that cause it associated with MCD or MG (6).

Drug exposure glomerular lesion can be classified into two specific forms: direct cell toxicity and immune-mediated injury (11).

The immune-mediated injury includes antibodies formation induced by haptens, toxins against visceral epithelium or T cells with cytokine secretion and glomerular endothelial cells injury, contribute to glomerular disease after drug exposure (5).

Some NSAIDs can produce severe proteinuria and nephrotic syndrome associated with glomerular lesions identical to those seen in the MCD. In most, but not in all cases, there is a concomitant acute interstitial nephritis characterized by the influx of polyclonal B and T cells. Although interstitial inflammation could predict a drug-related MCD, some reports have indicated that the drugs can produce it without inflammation (12).

Secondary MCD accounts for 10% of all cases, mainly in adults, with only a few recognized causes, including drugs and Hodgkin's lymphoma. The primary defect in MCD and FSGS appears to be related to podocyte dysfunction with diffuse slough of pedicel processes and absence of immune deposits, as the main diagnostic features. The clinical presentation is typically abrupt with nephrotic syndrome and, rarely with hematuria or hypertension, while in the elderly it can present as acute renal failure from its beginning, as in our patient, presumably due to the existence of previous vascular disease. Warren et al reported that 5 of 55 cases of adult MCD were due to NSAIDs and interstitial nephritis was common in these

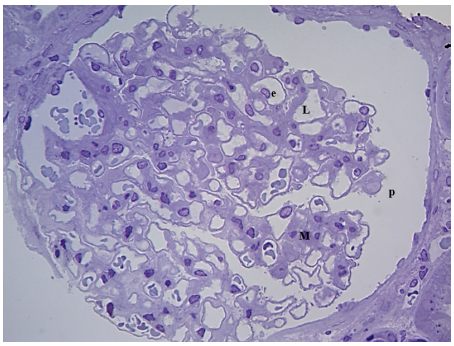

Figure1. High-resolution optical microscopy showed normal glomerulus with prominent podocyte (p). M: mesangium; e: endothelium. Original magnification ×400.

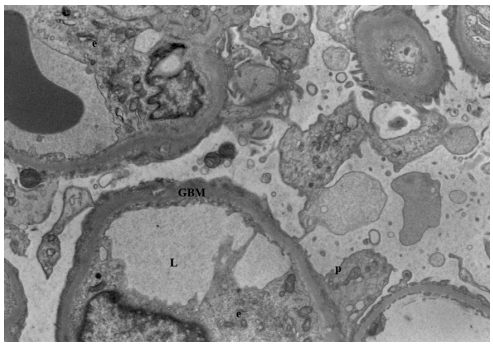

Figure 2. Electron microscopy shows diffuse foot process effacement. GBM: glomerular basement membrane; e: endothelium; L: capillary lumen. Original magnification ×7500.

biopsies (13).

Regarding physiopathogenic mechanism, a drug can directly affect a cell type, modifying the immune system or cell metabolism resulting in a specific pattern of glomerular injury. The glomerular drug-induced injury can primarily affect the immune system and lead to the production of autoantibodies, resulting in several drug-induced glomerulopathies (6).

The drugs that cause FSGS are, for the most part, similar to those that cause MCD. The systemic release of factors that increase the capillary perm-selectivity may be the basis for the association between drug exposure and MCD (5). However, Ravnskov consider that a toxic effect on the podocyte is unlikely because in other NSAIDs treated patients is not followed by proteinuria, and on contrary sometimes they have been used to reduce the nephrotic syndrome (9).

Although Markowitz et al argues that the available data do not support a relationship between NSAIDs and FSGS, many publications claim that drug-induced podocytopathies consist of MCD and FSGS, including both NOS and collapsing type. Although the relationship between MCD and FSGS has been a debate area and most patients with MCD do not progress to FSGS or vice versa, multiple therapeutic agents are associated with both conditions (6). Both diseases are associated with nephrotic syndrome and share diffuse changes in podocytes in the absence of immune deposits (1). Risk factors and mechanisms of NSAID-induced nephrotic syndrome have not been characterized, but it is known that the inhibition of cyclooxygenase by these drugs can result in vascular permeability increase in glomerular and peritubular capillaries and, consecutively, in proteinuria. Similarly, by the same mechanism, activated T cells secrete cytokines that can cause podocyte injury and increase glomerular permeability (1).

The classic renal findings of MCD are the presence of normal glomeruli without tubulointerstitial inflammatory changes (7). On the other hand, Feinfeld et al postulate that his patients represent the second case of nephrotic syndrome associated with NSAIDs with a pattern of MCD and absence of interstitial nephritis, suggesting that glomerular and interstitial lesions can occur independently (14).

The NSAID-induced MCD can be independent of the dose and can resolve spontaneously without medical intervention (7). The fact that the lesion appears only in a small proportion of patients, makes it unlikely that it is only due to a direct pharmacological effect of the drug. The glomerular changes are indistinguishable from those of the idiopathic "minimal change". Proteinuria of the nephrotic range has only been rarely reported in association with acute interstitial nephritis induced by drugs, caused by other drug classes than NSAIDs. Most cases of acute interstitial nephritis do not have concomitant glomerular proteinuria. The nephrotic syndrome of MCD, with or without associated interstitial nephritis, can probably be a complication of therapy with any NSAID. In the case of MG, immune complexes would be formed secondary to the increase in glomerular patency due to hyperactivity of the immune system (15,16). Since this drug-associated injury usually decrease spontaneously and rapidly in a few weeks (which is an unlikely event in a large number of patients with nephrotic syndrome due to idiopathic MCD), corticosteroid therapy in this adult population is probably not indicated initially. The withdrawal of the agent is usually associated with complete resolution, but corticosteroids can accelerate the rate of return to normal renal function and disappearance of proteinuria. However, a clear beneficial effect of steroids in the course of NSAID-induced MCD has not yet been established (5). If renal failure or nephrotic syndrome persists, corticosteroid therapy could be justified (14).

A drug-induced etiology should be considered in all forms of kidney disease. Careful attention to the timing of adverse events and a clinic-pathological correlation can provide insights into new and important patterns of drug-induced nephrotoxicity (5).

Despite of hypothesis about how some drugs can cause glomerular disease, there are no definitive biomarkers to distinguish between a patient with an idiopathic disease and a drug-induced disease (10).

Clinical, laboratory and pathological variations are more likely determined by the type and strength of the immune response and the magnitude of exposure to the drug (9).

It is important to highlight that these drugs, which are widely used due to their easy access, are a group of drugs that produce a number of alterations at the renal level, which confirms the importance of both health professionals and patients, know more in depth about the adverse effects that can be generated at this level, as well as in other organs and systems. In the same way, it is important to make all health personnel aware of the high susceptibility of the kidney as a potential target of drug and other xenobiotic toxicity, especially when it represents the main mechanism for the elimination of drugs and other substances from the body. The early recognition of patients with a particularly high risk of developing such events, will result in the optimal use of medications in terms of dosage schemes, possible combinations and monitoring, in order to minimize the impact of this frequent adverse effect and potentially serious (1), remembering that potentially offensive drugs should be discontinued before attributing the lesion to the "idiopathic" category (12).

Conclusion

To our knowledge the morphology of drug-induced diseases often does not differ from the primary forms, making the distinction difficult. There are subtle clues, although the dialogue between clinician and pathologist is essential to reach an etiological diagnosis.

Physicians should suspect glomerulonephritis in patients who receive drugs and who develop renal failure, proteinuria or active urinary sediment and its management must be determined based on the histological characteristics of the disease. The drug responsible should be discontinued immediately if glomerulopathy is suspected. Treatment modalities that are sometimes effective in other forms of glomerulopathies have been used empirically. Although corticosteroid therapy seems to be of value, the effectiveness of this approach must still be tested in randomized and multicentric clinical trials.

Authors' contribution

EEF have drafted the initial manuscript which was further modified by JHM. All authors have reviewed and agreed on the final version of this manuscript prior to submission.

Conflicts of interest

There is no conflict of interest in this case report.

Ethical considerations

Ethical issues including plagiarism, double publication, and redundancy have been completely observed by the authors. The patient has provided informed consent to publish as a case report.

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