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Original Scientific Paper

TIOPRONIN AND/OR NSAID? A CASE OF NEPHROTIC SYNDROME AND ACUTE INTERSTITIAL NEPHRITIS IN A YOUNG WOMAN WITH CYSTINURIA.

Luka Vidović[1], Josipa Josipović[1], Petar Šenjug[2] and Danica Galešić Ljubanović[2]

[1]Division of Nephrology, Department of Internal Medicine, Sestre milosrdnice University Hospital Center, Zagreb, Croatia; [2]Department of Pathology, University Hospital Dubrava, Zagreb

SUMMARY – Cystinuria is an autosomal recessive disease that leads to recurrent stone formation. Tiopronin, a glycine derivative with a free thiol similar to penicillamine, prevents stone formation and facilitates their dissolution. Nephrotic-range proteinuria is a serious and relatively uncommon adverse effect, reported in 6-10% of patients, most frequently during the first year of tiopronin use. Various patterns of morphologic kidney injury have been associated with tiopronin use, including MCD, MN, and MPGN. Acute interstitial nephritis can be caused virtually by any drug. Non-steroidal anti-inflammatory drugs (NSAIDs) may cause AIN, with or without nephrotic syndrome due to minimal change disease or membranous nephropathy.

Key words: *tiopronin, NSAID, acute interstitial nephritis*

Introduction

Cystinuria is an autosomal recessive disease that leads to recurrent stone formation. The therapy comprises dietary modification, reduction of salt intake, increased hydration, and urinary alkalinization. If these conservative measures are not effective, drugs may be used. Tiopronin, a glycine derivative with a free thiol similar to penicillamine, prevents stone formation and facilitates their dissolution. Nephrotic-range proteinuria is a serious and relatively uncommon adverse effect, reported in 6-10 % of patients, most frequently during the first year of tiopronin use.[1] Acute interstitial nephritis can be caused virtually by any drug.[2] It is a reversible disease characterized by inflammatory infiltrates within the renal interstitium (Fig.1, Fig. 2). Patients may present with nonspecific signs and symptoms of acute kidney dysfunction or without any symptoms at all. Patients usually do not have significant proteinuria, and nephrotic syndrome occurs in <1 percent of patients with AIN[3]. Non-steroidal anti-inflammatory drugs may cause AIN, with or without nephrotic syndrome due to minimal change disease or membranous nephropathy.[4]

Case report

We present a case of a 22-year-old woman with bilateral nephrolithiasis and cystinuria who was initially admitted to the ER due to bilateral upper eyelid edema. The patient had been taking tiopronin for 4 months. While initially treated as an allergic reaction, a dipstick urine test showed proteinuria (3+) and urinalysis showed microhematuria.

She had no skin rash. The patient was advised to discontinue tiopronin, upon which she was discharged and a nephrologist follow-up was scheduled in 3 days. She subsequently complained of weight gain and bilat-

Correspondence to: *Luka Vidović*, Division of Nephrology, Department of Internal Medicine, Sestre milosrdnice University Hospital Center, Zagreb, Croatia
E-mail: lukavidovic70@gmail.com

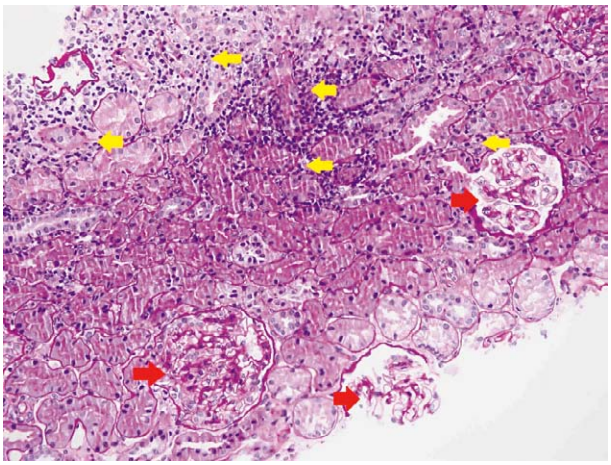

Figure 1. Mononuclear inflammatory infiltrate in renal cortex interstitium (yellow arrows). Glomeruli of normal morphology (red arrows). PAS, original magnification x200.

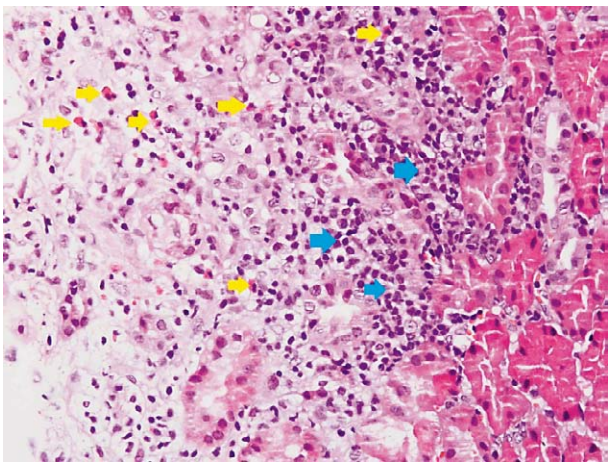

Figure 2. Mononuclear inflammatory infiltrate in renal cortex interstitium (blue arrows) with numerous eosinophils (yellow arrows). HE, original magnification x400.

eral leg swelling, also revealing recent bouts of colicky flank pain during the previous week, for which she had been taking a non-steroidal anti-inflammatory drug (ibuprofen) in an undisclosed dose regimen. 24-h urine analysis showed proteinuria of the nephrotic range 4.4 g/24 h, hypercholesterolemia, and normal eGFR, upon which she was admitted to hospital. Immunological workup (including ANA, ENA, ANCA, C3, C4) yielded negative results. A kidney biopsy was performed on the 2nd day of hospitalisation, with light microscopy and immunofluorescence showing acute interstitial nephritis. Electron microscope analysis showed no abnormalities. Discontinuation of tiopronin along with initiating prednisone 60 mg and furosemide 40 mg on the 1st day led to regression of edema and proteinuria to 0.4 g/24 h during the following 7 days (after which prednisone was discontinued) and the patient was discharged. A month later, she was hospitalised due to a bout of renal colic upon which she passed a kidney stone, as well as acute pyelonephritis.

Discussion

An important subtype of AIN is that induced by NSAIDs, which is associated with nephrotic syndrome in about 75% of cases.[5] AIN associated with nephrotic syndrome has also been reported after using such drugs as rifampin, ampicillin, and D-penicillamine.[6] Our patient has been taking tiopronin for 4 months. She was admitted to the ER with signs of fluid retention, which was mistaken for an allergic reaction. Since she had also been experiencing bouts of colicky back pain, she was taking NSAIDs for a couple of days. It remains unclear whether this combination of nephrotic syndrome and AIN was induced by tiopronin, NSAID, or both. Various patterns of morphologic kidney injury have been described with proteinuria associated with tiopronin use, including MCD, MN, and MPGN.[7,8] Tiopronin might interfere with podocyte function by an unclear mechanism. A genetic predisposition for proteinuria is suggested by associations with HLA-DR3 and HLA-B35 alleles.[9] Since histol-

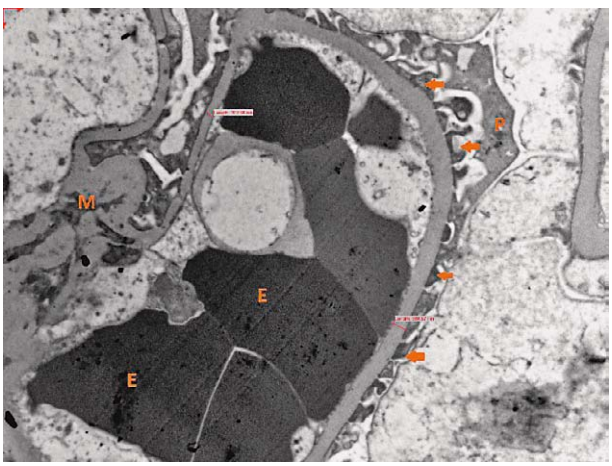

Figure 3. Intact podocyte foot processes by the GBM (arrows). M mesangium, E erythrocyte, P podocyte. TEM, original magnification x 8000.

ogy showed only signs of AIN, with the absence of pathological evidence of glomerular damage (Fig.3), it is reasonable to presume a functional disorder. It is also possible that ibuprofen may be the sole culprit drug. However, it cannot be ascertained since tiopronin was simultaneously discontinued, as recommended with the onset of proteinuria. Another possibility is that inflammatory cells in interstitial nephritis secrete some cytokine-like factor, with resultant permeability of glomerular basement membrane.[10] Since the incident, our patient has been hospitalized due to a bout of renal colic upon which she passed a kidney stone and acute pyelonephritis. With this in mind, the reintroduction of tiopronin remains an option to consider. In such an instance, more frequent urinalysis would be useful for early identification of proteinuria.[11]

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Sažetak

TIOPRONIN I/ILI NSAR? NEFROTSKI SINDROM I AKUTNI INTERSTICIJSKI NEFRITIS U MLADE ŽENE S CISTINURIJOM - PRIKAZ SLUČAJA

L. Vidović, J. Josipović, P. Šenjug i *D. Galešić Ljubanović*

Cistinurija je autosomno recesivna bolest koja dovodi do recidivirajućeg stvaranja kamenaca. Tiopronin, derivat glicina sa slobodnim tiolom, sličan penicilaminu, sprječava stvaranje kamenaca i čini ih topljivima. Proteinurija nefrotskog raspona ozbiljan je i relativno rijedak neželjeni učinak, zabilježen u 6-10% bolesnika, najčešće tijekom prve godine upotrebe tiopronina. Razni obrasci morfološke ozljede bubrega povezani su s upotrebom tiopronina, uključujući MCD, MN i MPGN. Akutni intersticijski nefritis može biti uzrokovan gotovo bilo kojim lijekom. Nesteroidni protuupalni lijekovi (NSAR) mogu uzrokovati AIN, s nefrotskim sindormom ili bez njega uzrokovanog bolešću minimalnih promjena ili membranskom nefropatijom.

Ključne riječi: *tiopronin, NSAR, akutni intersticijski nefritis*