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Case Report

Lornoxicam-induced acute interstitial nephritis

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Drug-induced acute interstitial nephritis (DI-AIN) is an important cause of reversible acute kidney injury.While antimicrobials and non-steroidal anti-inflammatory drugs are typically associated with drug-induced AIN,few reports have been made on the involvement of other analgesics.Side effects of nonsteroidal anti-inflammatory drugs (NSAIDs) most commonly affect the gastrointestinal tract and the kidney.This case report describes the first case of biopsy proven interstitial nephritis associated with acute renal failure in a patient treated withlornoxicamthe non-selective inhibitior of cyclo-oxygenase-1 and -2. She presented with clinical findings of acute renal failure that required dialysis.The renal biopsy showed acute interstitial nephritis with a prominent eosinophilic infiltrate in the interstitium.She recovered normal renal function three weeks after cessation of lornoxicam and use of a corticosteroid (1 mg/kg/day).A course of oral prednisolone (1 mg/kg/day) was commenced andrapidly tapered to zero within three weeks.The renal function improved, and the patient was discharged with a creatinine of 0,75mg/dl (67 µmol/L).In general, the prognosis for drug-induced AIN is good and at least partial recovery of kidney function is normally observed. Early recognition is crucial because patients can ultimately develop chronic kidney disease.

Keywords: Acute interstitial nephritis, lornoxicam, corticosteroids, hemodialysis, acute renal failure.

INTRODUCTİON

Acute interstitial nephritis (AIN) is an important cause of acute renal failure (ARF) (Haas et al.,2000).It is demonstratedin 2-3% of all native renal biopsies, increasing to 10-15%in the setting of acute kidney injury(Lopez-Gomez et al.,2008). This syndrome may result after exposure to antibiotics NSAIDs, anticonvulsants, diuretics, and other agents. The etiology ofat least two thirds of all cases is thought to be druginduced. The most common etiology of AIN is drug-induced disease, which is thought to underlie 60-70% of cases (Bakerand Pusey,2004).

NSAIDs are well known to cause fluid and electrolyte abnormalities and renal failure primarily by blocking normal renal regulatory mechanisms mediated through prostaglandin E2 and prostacyclin.NSAIDs act by reducing prostaglandin biosynthesis through inhibition of cyclooxygenase (COX) which exists as two isoforms (COX-1 and COX-2).NSAID-induced gastrointestinal toxicity is generally believed to occur through blockade of COX-1 activity, whereas the anti-inflammatory effects of NSAIDs are thought to occur primarily through inhibition of the inducible isoform, COX-2. However, the situation in the kidney may be somewhat different.Recent studies have demonstrated that COX-2 is constitutively expressed in renal tissues of all species; this isoform may, therefore, be intimately involved in prostaglandin-dependent renal homeostatic processes(Brater et al.,2001).

NSAIDs also may cause an acute allergic interstitial nephritis (AIN) and the nephrotic syndrome, characterized by histologic pathology consistent with minimal change disease evenin patients with previously normal renal function (Whelton,1999).Lornoxicam (trade names Xefo, Xafon, Lorcam, Acabel) is a NSAID that is used as a painkiller.Lornoxicam is one of the oxicam class of NSAIDs, producing analgesic and antipyretic effects in part through the non-selective inhibition of cyclo-oxygenase-1 and -2. It is prescribed for osteoarthritis, rheumatoid arthritis, acute lumbar-sciatica conditions and for postoperative pain management [Hall et al.,2009).

Rocha and Fernandez-Alonso, 2000 reported a case of AIN caused by rofecoxib.Henao et al.,2002 reported another case of AIN related with celecoxib,a selective COX-2 inhibitor.

This case report is, to our knowledge, the first report of AIN associated in lornoxicam.

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CASE

A 49-year-old female was admitted to the emergency unit with a twelve-hourhistory of nausea, vomiting, abdominal pain. She was using 8mg intramuscularlornoxicam for seven days prescribed by her orthopedist for chronic buttockpain due to L4/5 facet joint degeneration. The patient had no significant past medicalhistory.She denied using any other prescribedor over-the-counter medications. Family history was negative for any renal disease.

Physical examination was unremarkable. On admission, her blood pressure was 150/90 mm/Hg .Urine outputwas 50cc/day.

Laboratory investigations showed acute renal failure [urea131mg/dl,creatinine 8.3mg/dl (739.0 µmol/L)].Her laboratory valueson first day; Hgb:10. 8g/dl, Hct:31. 4 %, WBC count: 10,200/µl, platelet count :217.000/µl, uric acid:9mg/dl, P:8.8mg/dl,sedimentation rate :68mm/h, Na:144mmol/L, K: 3.6mmol/L, Ca:9.3mg/dl; autoimmune antibodies were negative (anti-Scl-70,anti-Jo-1, anti-glomerular basal membrane antibody, antinuclear and anticardiolipin antibodies, Antids-DNA , P-ANCA(myeloperoxidase-anti-neutrophil cytoplasmic antibody), C-ANCA(serine proteinase 3-anti-neutrophil cytoplasmic antibody).Serological evaluations for hepatitis B, hepatitis C viruses and human immunodeficiency virus were all negative.C3 and C4 levels were within normal range as well.Urinalysis demonstrated haematuria,leucocyturia and tubular proteinuria of 0.6 g/day (albumin +2, red bloood cells 8/hpf, white blood cells 3/hpf). The white cell count was normalwithout eosinophilia or lymphocytosis. Kidney ultrasound demonstrated a normal bladder and urinary tract with no obstruction. Both kidneys were normal in size.

Despite rehydration, kidney function did not improve and a session of haemodialysis wasperformed. The presentation was compatible with acute interstitial nephritis.Prednisone therapy was commenced. She wascommenced on a two-week course of prednisolone 1mg/kg/day, nifedipine60mg/day, calcium acetate 1000mg/day, allopurinol 300mg/day. Starting from the second day the urine output started to increase with improvement in serum creatinine and BUN levels. On fourteenth day urine output was 7000cc/day. Hemodialysis was discontinued when her serum creatinine level fell below 4mg/dl.

Anultrasound guided percutaneous renal biopsy was performed which revealed acute interstitial nephritis with lymphocytic and administration of eosinophilic infiltrate (Figure 1).Renal biopsy showed 10 glomeruli, one of which was globally sclerotic.Glomerular capillaries were open and basement membranes were normal;the tubules and interstitium showed marked interstitial oedema with an intense inflammatory infiltrate of lymphocytes and plasmocytes (Figure 2).Acute tubular necrosis was present with an infiltrateof polynuclear neutrophils and lymphocytes in the tubules.Immunohistochemistry for IgA, IgM IgG, C3,C4, kappa and lambda chains was completely negative.The immunofluorescence study did not show any specific deposits.Electron microscopy was not performed, due to the unambiguous diagnosis and the good clinical response.

The patient improved rapidly under corticosteroidtreatment. Kidney function recovered progressively over 3 weeks.She was discharged and folowed-up in the outpatient clinic. to cometo outpatient clinic.

To our knowledge,this is the first report of AIN associated with use of lornoxicam.

DISCUSSION

Acute interstitial nephritis (AIN) represents a frequent cause of acute kidney injury, accounting for 15–27% of renal biopsies performed because of this condition. The most common causes of drug-induced acute AIN in native kidneys are NSAIDs, antibiotics, especially penicillin derivatives and trimethoprim-sulfamethoxazole,diuretics, allopurinol, and phenytoin (Praga and González, 2010).

Common symptoms include asthenia, anorexia, nausea and vomiting.Classical triad in a patient with drug-induced AIN are fever, skin rash, and eosinophilia. However, this triad is seen in only one third of patients. Typical laboratory features are hematuria, proteinuria and eosinophilia.Renal failure is common at the time of diagnosis. Untreated AIN can cause irreversible interstitial fibrosis and chronic renal failure (Remuzzi et al.,2011).

Pathogenesis is based on an immunologic reaction against endogenous nephritogenic antigens or exogenous antigens processed by tubular cells, with cell-mediated immunity having a major pathogenic role.The infiltrates are largely composed of T cells, togetherwith some macrophages, plasma cells and eosinophils (Praga and González, 2010; Singh and Colvin, 2003).

Antibiotics and NSAIDs are the most frequently implicatedagents,but the list of drugs that can induce a DI-AIN iscontinuously increasing. The mechanism of injury ispostulated to involve cell mediated immunity andthe syndrome is often associated with extrarenal manifestationsof hypersensitivity, such as rash, fever andeosinophilia(Spanou et al., 2006; Clarkson et al., 2004).Theclinical presentation most suggestive of the diagnosis isthat of a sudden impairment of renal function associated with mild proteinuria and abnormal urine analysis in apatient with flank pain, normal blood pressure and noedema. Nevertheless, such a clinical picture is observedin less than one fourth of cases (Praga and González, 2010).

In cases of biopsy-proven as well as clinically suspectedAIN, the mainstay of management has been withdrawal ofthe potential aetiologic agent. Supportive therapies that include close monitoring of intravascular volume and maintenance of electrolyte balance are also essential.The therapeutic role of corticosteroids remain

Figure 1. Light microscopic appearance of the biopsy specimen. Kidney biopsy showing acute interstitial nephritis. The interstitium is oedematous and densely infiltrated by mononuclear inflammatory cells and eosinophils.

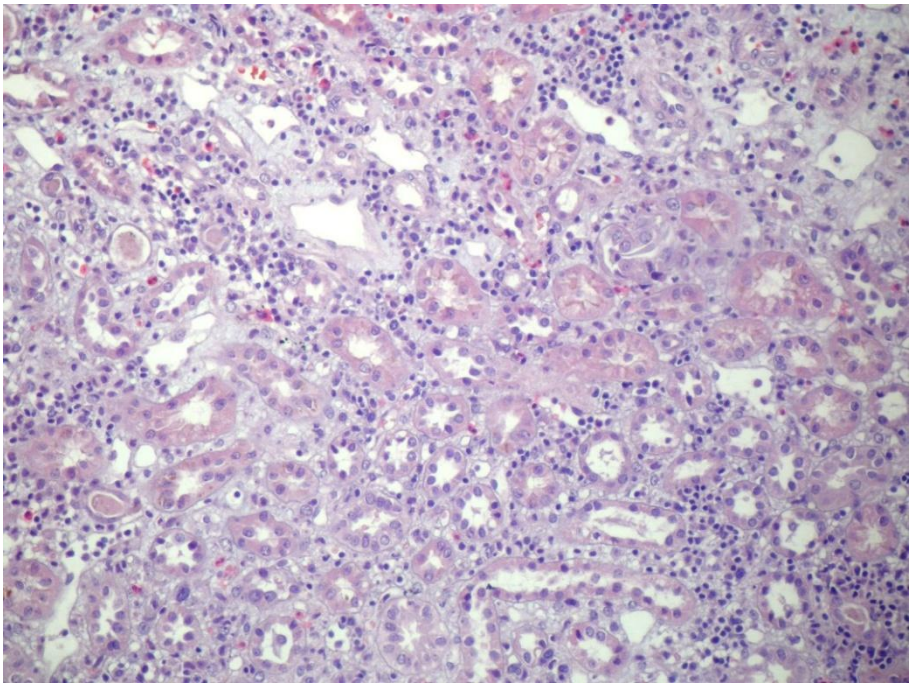
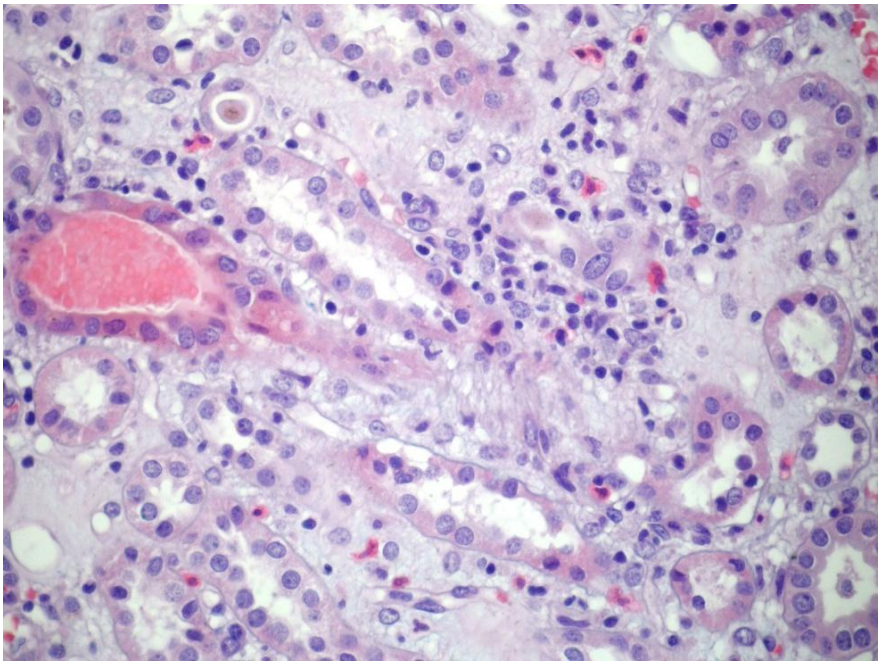


Figure 2. In addition to the intersititial inflammatory infiltrate there is mild tubulitis.



controversial.During recent decades, steroidtherapy was reported to be helpful in shortening the recoverytime and avoiding irreversibletubulointerstitialchanges.Gonzalez et al., 2008 reported a beneficial influence of corticosteroids on the outcome of drug-induced AIN in 61 patients.An earlier onset of use was associated with a better recovery of renal function. Clarkson et al.,2004 and Khaira and Mendonca, 2008 could not demonstrate any beneficial

effect ofcorticosteroids in a study of renal biopsy series. We report here on an informative casethat documents the effectiveness of steroids in the resolutionof interstitial nephritis.

Preddie et al.,2006 showed that mycophenolate mofetil has also been reported to be effectivein the treatment of interstitial nephritis.In cases of renal insufficiency, interstitial nephritis should always be included in the differential diagnosis and all drugs should be regarded as potential causative agents**.**

NSAIDsare among the most commonly prescribed drugs in the western world.

Several side effects have been reported including fluid and electrolyte abnormalities,nephrotic syndrome and renal failure as severe side effects (Alper et al., 2002). Kikuchi et al.,2014 reported a case of nephrotic-range proteinuria and acute interstitial nephritis caused by topical loxoprofen patch use.

Identification and removal of the offending drug are the mainstay of the treatment, but recent studies strongly suggest that early steroid administration (within 7 days after diagnosis) improves the recovery of renal function, decreasing the risk of chronic renal impairment. Delayed steroid treatment,when interstitial fibrosis has taken place, would have a less pronounced therapeutic benefit (Praga and González, 2010).

In conclusion, our case, documented by biopsy, shows that corticosteroids are effective in the treatment of drug induced interstitial nephritis.

Early diagnosis of interstitial nephritis by renal biopsy and identification of the causative drug and its withdrawal are essential in the treatment of interstitial nephritis to avoid irreversible renal damage. The additional use of steroids helps to eradicate inflammatory infiltrates rapidly and may thus be important to minimize chronic damage.

CONCLUSİON

Lornoxicam-induced AIN represents a reversible cause of acute kidney injury. The classical clinical features were absent in our patient and her renal function recovered fully despite dialysis dependency at presentation.Therefore increased vigilance is required to identify the emergence of new toxic compounds and early renal biopsy is recommended in cases of acute kidney injury in patients taking lornoxicam. The early use of corticosteroids should be considered in patients with lornoxicam induced AIN.

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REFERENCES

Alper ABJr, Meleg-Smith S, Krane NK (2002). Nephrotic syndrome and interstitial nephritisassociated with celecoxib. Am. J. Kidney Dis., 40(5):1086-90.

Baker RJ, Pusey CD (2004). The changing profile of acute tubulointerstitial nephritis. Nephrol. Dial.Transplant., 19(1):8-11.

Brater DC, Harris C, Redfern JS, Gertz BJ (2001). Renal effects of COX-2-selective inhibitors. Am. J. Nephrol.,21:1–15.

Clarkson MR, Giblin L, O'Connell FP,Walshe JJ, Conlon P, O'Meara Y, Dormon A, Campbell E, Donohoe J(2004). Acute interstitial nephritis: clinical features and response to corticosteroid therapy. Nephrol. Dial. Transplant., 19(11):2778-2783.

Gonzalez E, Gutierrez E, Galeano C, Chevia C, de Sequera P, Bernis C, Parra EG, Delgado R, Sanz M, Ortiz M, Goicoechea M, Quereda C, Olea T, Bouarich H, Hernández Y, Segovia B, Praga M; Grupo Madrileño De Nefritis Intersticiales(2008). Early steroid treatment improves the recovery of renal function in patients with drug-induced acute interstitial nephritis. Kidney Int., 73: 940–946.

Haas M, Spargo BH, Wit EJ, Meehan SM (2000). Etiologies and outcome of acute renal insufficiency in older adults: a renal biopsy study of 259 cases. Am. J. Kidney Dis., 35(3):433-447.

Hall PE, Derry S, Moore RA, McQuay HJ (2009). Single dose oral lornoxicam for acute postoperative pain in adults. Cochrane Database Syst Rev. 7;(4):CD007441. doi: 10.1002/14651858.CD007441.pub2. Review.

Henao J, Hisamuddin I, Nzerue CM, Vasandani G, Hewan-Lowe K (2002). Celecoxib- induced acute interstitial nephritis. Am. J. Kidney Dis., 39:1313–1317.

Khaira A, Mendonca S (2008). Steroids in acute interstitial nephritis: letter to the editor. Kidney Int., 74:971-972.

Kikuchi H, Aoyagi M, Nagahama K, Yajima Y, Yamamura C, Arai Y, Hirasawa S, Aki S, Inaba N, Tanaka H, Tamura T (2014). Nephrotic-range proteinuria and interstitial nephritis associated with the use of a topical loxoprofen patch. Intern. Med., 53(11):1131-1135.

Lopez-Gomez JM, Rivera F, Spanish (2008). Registry of Glomerulonephritis: Renal biopsy findings in acute renal failure in the cohort of patients in the Spanish Registry of Glomerulonephritis. Clin. J. Am. Soc. Nephrol.,3(3):674-681.

Praga M, González E (2010). Acute interstitial nephritis: A mini review .Kidney Int., 77: 956-961.

Preddie DC, Markowitz GS, Radhakrishnan J, Nickolas TL, D'Agati VD, Schwimmer JA, Gardenswartz M, Rosen R, Appel GB(2006). Mycophenolate mofetil for the treatment of interstitial nephritis. Clin. J. Am. Soc. Nephrol., 1(4): 718–722.

Remuzzi G, Perico N, De Broe ME (2011). Tubulointerstitial diseases. In: Brenner BM (ed.) Brenner and Rector's the kidney, 9th edn., pp. 1340-1343.

Rocha J, Fernandez-Alonso J (2000). Acute tubulointerstitial nephritis associated with the selective

COX-2 enzyme inhibitor, rofecoxib. Lancet. 357:1946–1947.

Singh AK, Colvin RB (2003). Case records of the Massachusetts General Hospital. Weekly clinicopathological exercises. Case 36-2003. A 68-year-old woman with impaired renal function. N. Engl. J. Med., 349(21):2055-2063.

Spanou Z, Keller M, Britschgi M,Yawalkar N, Fehr T, Neuweiler J, Gugger M, Mohaupt M, Pichler WJ(2006). Involvement of drug-specific T cells in acute drug-induced interstitial nephritis. J. Am. Soc. Nephrol., 17(10):2919-2927.

Whelton(1999). Nephrotoxicity of non-steroidal antiinflammatory drugs: Physiologic foundations and clinical implications. Am. J. Med., 106:13-24.