CASE REPORT

Cyclooxygenase-2 inhibitor-induced acute interstitial nephritis

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SUMMARY

A 64-year-old female patient presented to the emergency department with a 3-week history of persistent nausea and vomiting. Her serum creatine prior to admission was 118 $\mu\text{mol/L}$ and on presentation was elevated to 420 $\mu\text{mol/L}$. On clinical history, she indicated that 3 weeks prior, she had been initiated on a cyclooxygenase-2 (COX-2) inhibitor, celecoxib, for her osteoarthritis of her knees. Renal biopsy confirmed the diagnosis of acute interstitial nephritis (AIN). Celecoxib was discontinued and the patient's renal function improved to a discharge creatine of 205–220 $\mu\text{mol/L}$. Nine months later, her creatine had decreased to 195 $\mu\text{mol/L}$ and she was initiated on tapering doses of prednisone therapy for 4 months, after which time her creatine had improved further to 143 $\mu\text{mol/L}$. She was later transitioned to mycophenolatemofetil for 9 months and her creatine improved to 110 $\mu\text{mol/L}$. This report provides further evidence that COX-2 inhibitors are associated with AIN.

BACKGROUND

To our knowledge, this is the fourth reported case of acute interstitial nephritis occurring as a result of celecoxib use. The patient in our case developed an acute kidney injury (AKI), which resolved with the elimination of the offending drug and introduction of immunosuppressive medications.

CASE PRESENTATION

We report the case of a 64-year-old female patient who presented to the emergency department with a 3-week history of feeling unwell, reporting persistent nausea and vomiting. Her serum creatine 3 weeks prior was 118 $\mu\text{mol/L}$. Incidental labs drawn on arrival to the hospital showed an increase of creatine to 420 $\mu\text{mol/L}$. Due to the diagnosis of AKI, she was admitted to the hospital for further investigations.

On history, the patient denied any overt haematuria, blood stained sinus discharge, recent upper respiratory tract infections, haemoptysis, kidney stone disease, recent urinary tract infection and use of over-the-counter or herbal medications. She denied any fever or rash and any decline in her urine output. She has no prior history of any infective illnesses, systemic lupus erythematosus (SLE) or Sjogren's syndrome. She had taken no recent trips to a tropical climate. Previous to this admission, she was reasonably well and worked full time as a cashier at a grocery store.

A review of the patient's medical history included: hypertension, asthma/chronic obstructive pulmonary disease, depression, peripheral arterial disease and osteoarthritis. Medications included: celecoxib, citalopram, omeprazole, diltiazem, valsartan, hydrochlorothiazide, amitriptyline, acetylsalicylic acid and ventolin inhaler.

Other labs revealed: absence of blood but presence of protein on urine analysis, absence of red cells on urine microscopy and presence of white cells but no casts. The patient's creatine was serially followed during her course in hospital. Immunology screening including antinuclear antibody (ANA), antineutrophil cytoplasmic antibody (ANCA), antglomerular basement membrane antibody (anti-GBM), complement 3 and 4 (C3/C4) and antistreptolysin (ASOT) were all negative or within the normal range.

On the basis of AKI, the presence of protein in urine, urine microscopy changes in the clinical absence of infection and the history of recent introduction of celecoxib, a kidney biopsy was performed. There were three cores containing 17 glomeruli, five of which were sclerotic. On light microscopy, the glomeruli showed no increase in mesangial matrix or cellularity. The capillary walls appeared normal in thickness, with patent lumen and with diffuse interstitial infiltration of mononuclear inflammatory cells predominantly composed of plasma cells and lymphocytes. Inflammatory infiltrate accounted for >40% of the cortical surface. There was also presence of mild tubulitis as suggested by the presence of lymphocytes and plasma cells in the tubular epithelial cells. These changes were associated with 15% tubular atrophy and interstitial fibrosis reflecting prior renal injury. On immunofluorescence, there were two glomeruli with no obvious abnormalities. There was only one glomerulus on the electron micrographs, which showed a mild increase in mesangial matrix. The biopsy changes were felt to be consistent with the diagnosis of AIN.

Celecoxib was felt to be the culprit medication as it was introduced 3 weeks prior to her admission. The medication was discontinued and over the next 6 months, her creatine spontaneously improved to 195 $\mu\text{mol/L}$. As her creatine plateaued over the next 3 months, she was initiated on 30 mg of prednisone for 2 weeks, to be tapered further by 5 mg every 14 days. Following exposure to steroids for 3 months, her serum creatine improved further, to 165 $\mu\text{mol/L}$. At that point, she was transitioned to azathioprine as a steroid-sparing agent at a dose of

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1 mg/kg body weight. She unfortunately could not tolerate the medication due to reflux-like symptoms and was later changed to mycophenolate mofetil (MMF), which was continued for 1 year, with near-complete resolution in renal injury to a baseline creatine of 110 $\mu\text{mol/L}$. At that point, MMF was discontinued and she was observed for another 1 year, with sequential labs; her creatine stayed stable from 110 to 120 $\mu\text{mol/L}$.

INVESTIGATIONS

As documented above: Immunology screening, ANA, ANCA, anti-GBM, C3 and C4 and ASOT were negative or within the normal range.

Urine analysis: presence of protein but no evidence of blood.

Urine microscopy: presence of white cells (10–20/hpf) but no evidence of white cell casts.

DIFFERENTIAL DIAGNOSIS

The patient was on multiple drugs that have been associated with AIN.

Omeprazole

Proton-pump inhibitors (PPI) have been shown recently in multiple studies to have an association with AIN. A recent literature search showed that there were greater than 50 reported cases associated with omeprazole.¹ However, she was taking the medication for close to 36 months prior to the presentation. Therefore, the patient was continued on omeprazole. Her clinical recovery, despite being on the medication, rules out PPI-induced AIN.

Hydrochlorthiazide

A review of the literature on the association between thiazides and AIN is weak, with less than 10 reported cases. She was taking the medication for close to 10 years and the medication was left unchanged. Her clinical recovery on the medication makes it less likely that the ongoing use of diuretics were the cause of AIN.

TREATMENT

As documented above, celecoxib was stopped immediately, as it became evident that the timeline between initiation of the medication and AKI was 3 weeks. Six months after discontinuation of the medication, her serum creatine improved to 195 $\mu\text{mol/L}$ but remained at that value for a further 3 months. She was then initiated on prednisone at a dose of 30 mg per day, to be tapered over 3 months, which led to a further improvement in her serum creatine level to 140 $\mu\text{mol/L}$. As she had mild cushingoid changes (weight gain, acne), she was transitioned to azathioprine at a dose of 1 mg/kg of body weight. She could not tolerate the medication and was later changed to MMF, which was better tolerated and her creatine over the next 12 months improved to 110 $\mu\text{mol/L}$. MMF was then discontinued and she was observed for a further 12 months with sequential labs. She remained stable, with creatine values ranging from 110 to 120 $\mu\text{mol/L}$ during this time.

OUTCOME AND FOLLOW-UP

The patient was followed for a further 2 years at yearly intervals and remained stable.

DISCUSSION

AIN is an under-recognised and underdiagnosed cause of AKI. Since AKI is linked to untoward outcomes such as incident and progressive chronic kidney disease, end-stage renal disease and

death, it is all the more important to rapidly diagnose and treat the underlying condition. The recognition of AIN is important, as early discontinuation of the offending medication improves prognosis.^{1,2} The reported incidence of AIN ranges from 1% to 10% of the total biopsies examined, with an overall average of 2.8%.¹ The incidence of AIN increases among biopsies done specifically to evaluate acute renal failure of unknown origin, where it ranges from 6.5% to 35%, with an overall average of 13.5%.¹ As such, most estimates of the prevalence of AIN are based on retrospective reviews of biopsy registries, and the actual incidence of AIN goes grossly underestimated, in part, due to reluctance of the physicians, low index of suspicion and if the biochemical changes improve after discontinuation of the medication.³

The causes of AIN include allergic reactions, infections and systemic autoimmune diseases such as SLE and Sjogren's syndrome, tubulointerstitial nephritis with uveitis syndrome and immunoglobulin G4-related disease. Antibiotics, non-steroidal anti-inflammatory drugs (NSAIDs) and PPIs account for greater than 75% of the cases. Over 150 medications have been incriminated as a cause of AIN.¹

In a retrospective study by Clarkson *et al*⁴ of all cases of AIN in 2598 native renal biopsies over a 12-year period, the classic triad of rash, fever and eosinophilia was described in only 10% of cases. Agents such as NSAIDs and PPIs are less commonly associated with the classic triad in comparison to methicillin-induced AIN.⁴ COX-2 inhibitors have been long thought to be relatively safe in comparison to conventional non-selective cyclooxygenase inhibitors. Although the exact mechanism of action of COX-2 inhibitor-induced AIN is unknown, it has been shown that COX-2 has been found expressed in the renal vasculature, medullary interstitial cells and the macula densa. In contrast, COX-1 has been identified in the collecting ducts, thin loops of Henle and portions of the renal vasculature.⁵ COX-1 has typically been associated with renal haemodynamics and GFR, whereas COX-2 has been known to affect sodium secretion and water retention; however, there is overlap of these functions between the two isoforms.⁵ It has been postulated that the mechanism behind NSAID-induced AIN is related to the increased shunting of arachidonic acid, due to COX inhibition, towards pathways that produce leukotrienes.⁶

Leukotrienes are known to recruit T lymphocytes and promote the inflammatory process, as well as cause proteinuria via increased vascular permeability. Because non-selective NSAIDs inhibit both COX-1 and the constitutively expressed COX-2, as well as have similar physiological effects as COX-2 inhibitors at therapeutic doses, it is possible that the same mechanism of action may exist for selective COX-2 inhibitor-induced AIN.⁶

Case reports, such as this one, hopefully will lead to increased awareness and greater clinical suspicion, as this leads to earlier discontinuation of offending medications. It is imperative that we strive to determine the real-life incidence of adverse effects to best determine the risk:benefit ratio of a drug. As this medication is

Learning points

- ▶ Cyclooxygenase-2 inhibitors are associated with clinically significant side effects including acute kidney injury as a consequence of acute interstitial nephritis.
- ▶ Acute interstitial nephritis secondary to medications is a reversible cause of acute kidney injury, and its early identification and discontinuation of the offending drug improves renal prognosis.

widely prescribed, it is important to continually reassess its safety and associated adverse reactions.

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