CASE REPORT

Granulomatous tubulointerstitial nephritis secondary to omeprazole

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SUMMARY

Drug-induced interstitial nephritis is a common cause of acute kidney injury indicated by elevated serum creatinine. We report a case of omeprazole-induced acute granulomatous interstitial nephritis (GIN). Our patient developed acute GIN secondary to omeprazole ingestion requiring haemodialysis. Treatment with steroids and withdrawal of omeprazole was successful allowing the patient to discontinue haemodialysis in 3 months. She remains dialysis free with chronic kidney disease stage IV, reflected by a serum creatine of $191\text{ }\mu\text{mol/L}$ and estimated glomerular filtration rate of $23\text{ mL/min/1.73 m}^2$ at 5 years on follow-up.

BACKGROUND

Proton-pump inhibitors remain one of the most frequently prescribed medications in inpatient as well as outpatient settings. Omeprazole is a parent drug that has been widely used for multiple indications such as erosive oesophagitis, gastro-oesophageal reflux disease, gastric ulcers and active duodenal ulcers. It is also coprescribed with non-steroidal anti-inflammatory drugs (NSAIDs) and other drugs that are an irritant to the gastric mucosa. Side effects remain minimal and thus tolerated well by patients. Omeprazole is known to cause granulomatous interstitial nephritis (GIN). Acute GIN can be severe enough to necessitate renal replacement therapy. Prompt recognition of the offending agent, its withdrawal and treatment with steroids can help salvage renal function.

CASE PRESENTATION

A 53-year-old woman with a history of hypertension, chronic bronchiectasis with recurrent infective exacerbations necessitating lobectomy (performed 10 years ago), hypothyroidism and uterine fibroids was referred to the renal service with acute decline of renal function. Her medications included amlodipine and levothyroxine. Given her history of bronchiectasis, she had undergone several courses of antibiotics during exacerbations in the past. She presented to the emergency room with low-grade fever, nausea, decreased urine output and lower limb swelling, which had been deteriorating over 4 months. She reported low-grade fever but denied haemoptysis or joint pains. She denied NSAID's use and did not have any recent contrast studies. She is a non-smoker and family history was negative for renal disease. During her last outpatient visit she complained of symptoms suggestive of gastritis, so omeprazole 20 mg once daily was added empirically to her regular prescription, which she

had been taking for a total of 4 months prior to presentation. On examination she was conscious, oriented and alert with no apparent signs of distress. Her blood pressure was 156/81 mm Hg and she had a low-grade fever of 37.8°C . Respiratory rate was 22 per min and pulse rate was 82 bpm. There were no cutaneous signs suggestive of allergy and eye examination was within normal limits. Chest examination revealed bi-basal fine crepitations with decreased air entry in the left lower side. Cardiac examination revealed normal S1 and S2 with no murmurs, rubs or gallops. She had bilateral lower limb pitting oedema.

INVESTIGATIONS

Laboratory investigations revealed serum creatine of $642\text{ }\mu\text{mol/L}$, last documented serum creatine was $96\text{ }\mu\text{mol/L}$ 4 months earlier, during her last outpatient visit. Urea was 24.4 mmol/L , potassium 5.5 mmol/L , bicarbonate 14 mmol/L , calcium 2.27 mmol/L and albumin 33 g/L . White cell count was $10.29\times 10^9/\text{L}$, eosinophil count $0.65\times 10^9/\text{L}$, haemoglobin 86 g/L and platelet count $198\times 10^9/\text{L}$. Urinalysis revealed +1 protein, no red blood cells or white blood cells. 24 h proteinuria was 0.27 g . Serology for hepatitis B, hepatitis C and HIV was negative. Antinuclear antibody and antiglomerular basement membrane antibodies were negative. Complement C3 and C4 were normal. Antineutrophil cytoplasmic antibodies (ANCA) was negative. Cytoplasmic ANCA (C-ANCA) was 3.5 U/mL (range $0.0\text{--}10.0$), perinuclear ANCA (P-ANCA) was 3.1 U/mL (range $0.0\text{--}6.0$). Cryoglobulin was absent. Renal ultrasound was within normal limits. Serum and urine electrophoresis was normal. Chest X-ray revealed a mild left pleural effusion. Given the new onset peripheral eosinophilia and low-grade proteinuria presenting with acute kidney injury (AKI) and oligoanuria, we suspected a diagnosis of interstitial nephritis of recent onset. She required renal replacement therapy, so haemodialysis was initiated. We opted for an ultrasound-guided renal biopsy so that any reversible pathology could be identified. Biopsy revealed wide-spread interstitial inflammatory infiltrates composed predominantly of plasma cells, lymphocytes and monocytes with scattered eosinophils. There was one area showing the presence of granulomatous inflammation with histiocytes, lymphocytes and central amorphous eosinophilic material (figure 1). Trichrome stain revealed moderate interstitial fibrosis. The blood vessels showed mild to moderate subintimal sclerosis (25–50% occlusion of the lumen). Congo red stain was negative

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Figure 1 Encircled area showing granulomatous inflammation in a kidney biopsy.

for amyloid. There was no glomerular pathology and immunofluorescence was negative. Special stains for microorganisms including acid-fast bacilli were negative. Mantoux skin test and quantiferon were negative.

DIFFERENTIAL DIAGNOSIS

- ▶ Renal tuberculosis
- ▶ Renal sarcoidosis
- ▶ Drug-induced GIN
- ▶ Tubulointerstitial nephritis and uveitis (TINU)

TREATMENT

The patient was treated with prednisone 1 mg/kg/day with ranitidine 150 mg once daily while on dialysis and omeprazole was discontinued. Initiating ranitidine was not without risk, as it is also associated with interstitial nephritis and Fanconi syndrome.^{1 2} However, in our patient, who was already suffering from gastritis and was about to receive high-dose prednisone, we elected to use ranitidine. A repeat biopsy was performed 2 months after the first and it revealed complete resolution of the granulomatous lesions; again there was no glomerular pathology. The repeat biopsy was performed to look for chances of renal recovery. After a period of 3 months on steroids her urine output gradually improved with steady decline of serum creatinine, allowing her to discontinue dialysis; subsequently, prednisone was tapered off completely.

OUTCOME AND FOLLOW-UP

A diagnosis of sarcoidosis was ruled out on the basis of normal chest radiographs, eye examination, acceptable pulmonary function tests and features of the granuloma on renal biopsy that were not consistent with sarcoid granuloma. Based on the temporal relationship between the use of omeprazole and renal failure with no other identified cause in history and diagnostic workup, in addition to the characteristic granulomatous lesions on the biopsy, a diagnosis of AKI secondary to omeprazole-induced GIN was entertained. To date she is enjoying life free from dialysis with serum creatinine around 191 µmol/L and estimated glomerular filtration rate of 23 mL/min/1.73 m². Present follow-up is 5 years.

DISCUSSION

GIN is one of four distinct histopathological patterns of injury and has been defined based on the constitution of the inflammatory infiltrate in acute tubulointerstitial nephritis (ATIN). The

Table 1 Drugs causing granulomatous ATIN

Drug class	Name
Antimicrobials	Erythromycin ¹⁴
	Amoxicillin ¹⁴
	Clarithromycin ¹⁵
	Vancomycin ¹⁶
Diuretics	Hydrochlorothiazide/amiloride ¹⁷
Anticonvulsives	Carbamazepine ¹⁸
Bisphosphonates	Alendronate ¹⁹
Antigout	Allopurinol ²⁰
	ATRA ²¹
	Dihydrocodeine ¹⁴
TNF-α inhibitors	Phenylpropanolamine ¹⁴
	Adalimumab ²²
Prokinetic agents	Cinitapride ²³
Proton-pump inhibitors	Omeprazole ^{6 11 12 24–28}

ATIN, acute tubulointerstitial nephritis; ATRA, all-trans retinoic acid; TNF, tumor necrosis factor.

others are lymph-macrophagal, eosinophilic and plasmocytic ATIN.³ Several drugs have been attributed as a cause of GIN as shown in table 1. GIN remains a rare but treatable histopathological diagnosis and is present in 0.5 to 0.9% of native renal biopsies^{4 5} and in 0.6% of renal transplant biopsies.⁶ The pathophysiology of drug-induced ATIN remains poorly understood.⁷ It can present with varying magnitudes of renal impairment and low-grade proteinuria. In addition to drugs as a cause of GIN, it may be the initial manifestation of systemic diseases such as TINU or sarcoidosis. When AKI does not resolve after discontinuation of a suspected agent in a cause of ATIN and the cause of AKI remains unexplained, a renal biopsy is indicated for definitive diagnosis and management.⁸ Decision to biopsy the kidney should be performed after assessing the risk benefit ratio in each case and after reviewing the renal ultrasound to make sure there is adequate renal cortex, indicating that the kidney is salvageable. In our case we demonstrated complete disappearance of the granulomatous lesions on renal biopsy in 2 months

Learning points

- ▶ Drug-induced interstitial nephritis is a common clinical entity that can lead to a transient rise in serum creatine. When trying to identify the causative agent in a suspected case of acute tubulointerstitial nephritis (ATIN), drugs taken at the onset of acute kidney injury (AKI) should be considered as possible causes. When renal impairment is persistent or severe, other causes should be excluded.
- ▶ When AKI does not resolve after discontinuation of a suspected agent in a cause of ATIN and the cause of AKI remains unexplained, a renal biopsy is indicated for definitive diagnosis and management.⁸
- ▶ If granulomatous inflammation is present in a renal biopsy, the differential diagnosis includes renal tuberculosis, renal sarcoidosis, drug-induced granulomatous interstitial nephritis and tubulointerstitial nephritis and uveitis (TINU).
- ▶ When drug-induced interstitial nephritis is suspected, prompt identification and withdrawal of the offending agent is essential and a course of steroids should be considered.

of treatment. It is difficult to determine whether the improvement was based only on withdrawing omeprazole or if steroids used empirically did in fact play a crucial role as there are no scientific data to support their use. Based on similar published case reports^{9–12} and our experience it is safe to conclude that in addition to removal of the suspected offending agent, steroids should be considered, and the risk-benefit ratio explained on an individual basis. This offers a favourable outcome in patients with omeprazole-induced GIN, although the serum creatine may not return to normal. In fact, in our patient it spared her from a life on maintenance haemodialysis. In conclusion, this is a case where successful treatment of omeprazole-induced GIN resulted in sufficient renal recovery to allow dialysis independence with stable CKD stage IV. The Naranjo adverse drug reaction probability scale revealed a score of 6, suggesting that omeprazole as a cause is probable.¹³ This case highlights the importance of early recognition, renal biopsy, withdrawal of the suspected offending agent and prompt treatment with steroids despite advanced renal dysfunction requiring dialysis.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- 1 Neelakantappa K, Gallo GR, Lowenstein J. Ranitidine-associated interstitial nephritis and Fanconi syndrome. *Am J Kidney Dis* 1993;22:333–6.
- 2 Karras DJ. Severe low back pain secondary to acute interstitial nephritis following administration of ranitidine. *Am J Emerg Med* 1994;12:67–8.
- 3 Pospishil' lu O. [The pathomorphology of acute drug-induced tubulointerstitial nephritis]. *Lik Sprava* 1996;(5–6):94–6.
- 4 O'Riordan E, Willert RP, Reeve R, et al. Isolated sarcoid granulomatous interstitial nephritis: review of five cases at one center. *Clin Nephrol* 2001;55:297–302.
- 5 Mignon F, Mery JP, Mougnot B, et al. Granulomatous interstitial nephritis. *Adv Nephrol Necker Hosp* 1984;13:219–45.
- 6 Meehan SM, Josephson MA, Haas M. Granulomatous tubulointerstitial nephritis in the renal allograft. *Am J Kidney Dis* 2000;36:E27.
- 7 Wilson CB. Nephritogenic tubulointerstitial antigens. *Kidney Int* 1991;39:501–17.
- 8 Lo WK, Rolston KV, Rubenstein EB, et al. Ciprofloxacin-induced nephrotoxicity in patients with cancer. *Arch Intern Med* 1993;153:1258–62.
- 9 Jones B, Hewson E, Price A. Acute interstitial nephritis due to omeprazole. *Lancet* 1994;344:1017–18.
- 10 Assouad M, Vicks SL, Pokroy MV, et al. Recurrent acute interstitial nephritis on rechallenge with omeprazole. *Lancet* 1994;344:549.
- 11 Fleury D, Storkebaum H, Mougnot B, et al. Acute interstitial nephritis due to omeprazole. *Clin Nephrol* 1995;44:129.
- 12 Christensen PB, Albertsen KE, Jensen P. Renal failure after omeprazole. *Lancet* 1993;341:55.
- 13 Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther* 1981;30:239–45.
- 14 Singer DR, Simpson JG, Catto GR, et al. Drug hypersensitivity causing granulomatous interstitial nephritis. *Am J Kidney Dis* 1988;11:357–9.
- 15 Audimoolam VK, Bhandari S. Clarithromycin-induced granulomatous tubulointerstitial nephritis. *Nephrol Dial Transplant* 2006;21:2654–5.
- 16 Hong S, Valderama E, Mattana J, et al. Vancomycin-induced acute granulomatous interstitial nephritis: therapeutic options. *Am J Med Sci* 2007;334:296–300.
- 17 Enriquez R, Cabezuolo JB, Gonzalez C, et al. Granulomatous interstitial nephritis associated with hydrochlorothiazide/amiloride. *Am J Nephrol* 1995;15:270–3.
- 18 Hegarty J, Picton M, Agarwal G, et al. Carbamazepine-induced acute granulomatous interstitial nephritis. *Clin Nephrol* 2002;57:310–13.
- 19 Pena de la Vega L, Fervenza FC, Lager D, et al. Acute granulomatous interstitial nephritis secondary to bisphosphonate alendronate sodium. *Ren Fail* 2005;27:485–9.
- 20 Almirall J, Orellana R, Martinez Ocana JC, et al. [Allopurinol-induced chronic granulomatous interstitial nephritis]. *Nefrologia* 2006;26:741–4.
- 21 Tomita N, Kanamori H, Fujita H, et al. Granulomatous tubulointerstitial nephritis induced by all-trans retinoic acid. *Anticancer Drugs* 2001;12:677–80.
- 22 Korsten P, Sweiss NJ, Nagorsnik U, et al. Drug-induced granulomatous interstitial nephritis in a patient with ankylosing spondylitis during therapy with adalimumab. *Am J Kidney Dis* 2010;56:e17–21.
- 23 Fernandez Tagarro EJ, de Gracia Nunez R, Sanchez Villanueva RJ, et al. [Prokinetic agents as a cause of granulomatous interstitial nephritis]. *Gastroenterol Hepatol* 2007;30:583–4.
- 24 Lochs H, Egger-Schodl M, Schuh R, et al. Is tube feeding with elemental diets a primary therapy of Crohn's disease? *Klinische Wochenschrift* 1984;62:821–5.
- 25 Meryn S, Bauman WA. Use of the rapid octadecasilyl column method for purification of 125I-bovine pancreatic polypeptide compared with conventional methodology. *J Chromatogr* 1984;287:161–5.
- 26 Ruffenach SJ, Siskind MS, Lien YH. Acute interstitial nephritis due to omeprazole. *Am J Med* 1992;93:472–3.
- 27 Kuiper JJ. Omeprazole-induced acute interstitial nephritis. *Am J Med* 1993;95:248.
- 28 Lewis CR, Somerville C, Agar JW. Omeprazole induced acute interstitial nephritis. *Aust N Z J Med* 1994;24:578.

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