**Case Report**

**Hypercalcaemia and acute interstitial nephritis associated with omeprazole therapy**

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**Keywords:** acute interstitial nephritis; acute renal failure; hypercalcaemia; omeprazole

**Introduction**

Hypercalcaemia is a biochemical abnormality frequently encountered in clinical practice. Laboratory and radiological investigations appropriate to the clinical setting can usually determine the cause of this abnormality. Hypercalcaemia in the setting of acute renal failure (ARF) is not uncommon but is typically associated with rhabdomyolysis [1] and resolves spontaneously as renal function recovers. We report the case of a patient who developed hypercalcaemia several weeks after recovering from an episode of ARF. Despite extensive investigations, we were unable to find a cause for the patient’s hypercalcaemia. A renal biopsy performed to investigate persistent mild renal dysfunction finally revealed the reason for the patient’s renal impairment. We speculate that the renal lesion was also the cause of the associated hypercalcaemia.

**Case**

A 31-year-old female was admitted to a local maternity hospital in March 1998 at 35 weeks gestation complaining of severe nausea and vomiting that had become marked in the 3 weeks prior to hospital admission. The patient was normotensive with a normal blood glucose and negative dipstick urinalysis throughout pregnancy. Severe iron deficiency anaemia (haemoglobin 6.6 g/dl) developed at 24 weeks gestation. There was no past medical or surgical history of note. Medications included ferrous sulphate and calcium carbonate containing antacids (4–5 g daily). On admission, the patient was hypertensive (blood pressure (BP) 160/100 mmHg). Dipstick urinalysis revealed 1⁺ proteinuria. There was no clinical evidence of foetal distress. Omeprazole therapy was commenced. Investigations revealed: haemoglobin 8.4 g/dl, platelets 265 x 10⁹/l, urea 23.4 mmol/l, urate 534 mmol/l, ionized calcium 1.36 mmol/l (range 1.19–1.35) and serum creatinine 481 μmol/l (elevated from 140 μmol/l at 24 weeks gestation). Coagulation screens were normal. Urine microscopy revealed occasional granular and hyaline casts. Arterial blood gases revealed that the patient was profoundly alkalotic (pH 7.54, HCO₃⁻ 40 mmol/l), despite being uraemic, which correlated with the history of prolonged vomiting. A renal ultrasound revealed echogenic but normal sized kidneys. A presumptive diagnosis of pre-eclampsia was made. The patient underwent an emergency caesarean section and was delivered of a healthy baby girl. On the following day the patient was transferred to our renal unit for further management.

The patient was stabilized and anti-hypertensive therapy was introduced. Renal function improved without the need for dialysis. One week later on discharge from hospital the patient was normotensive (BP 140/80 mmHg) with a corrected serum calcium of 2.62 mmol/l (normal range 2.2–2.7 mmol/l). The only prescribed medications on discharge were omeprazole 20 mg daily and nifedipine LA 30 mg daily. On review in the clinic 1 week later, serum creatinine had normalized to 118 μmol/l with a corrected serum calcium of 2.49 mmol/l. During the next 8 weeks, asymptomatic hypercalcaemia developed and renal function deteriorated concomitantly (Figure 1). Of note, dietary calcium intake was normal. Hypertension worsened necessitating the introduction of atenolol. Investigations performed 1 week after the onset of hypercalcaemia revealed the following: serum calcium 3.22 mmol/l, serum creatinine 237 μmol/l, serum phosphate 1.59 mmol/l, parathyroid hormone (PTH) 18.7 pg/ml (range 10–65 pg/ml) and 25-hydroxycholecalciferol 9.9 ng/ml (range 6.7–52 ng/ml) both of which were at the lower limit of normal. Serum angiotensin-converting enzyme was 119 IU/l (normal range 25–113 IU/l). Thyroid function tests, serum cortisol and

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tumour markers (CEA, αFP, CA125) were all within normal limits. Immunological investigations including urine and serum protein electrophoresis were negative. Radiological investigations including a chest radiograph and a parathyroid gland uptake scan were normal. An abdominal ultrasound revealed normal sized kidneys with decreased corticomedullary differentiation. No clear cause for either the hypercalcaemia or recurrence of renal impairment could be determined.

In view of the patient’s persistent renal dysfunction, a percutaneous renal biopsy was performed 5 weeks after the onset of hypercalcaemia. This revealed a diffuse mixed inflammatory infiltrate with several non-caseating granulomata localized around damaged tubules. Lymphocytes were the predominant cell type, but numerous clusters of eosinophils were also present throughout the biopsy. The granulomata differed from those found in sarcoidosis and were typical of those encountered in a minority of cases of tubulointerstitial nephritis. Histocytes were immunoreactive for CD-68 and tubular epithelial cells stained positively for EMA and cytokeratin. Glomeruli were normal by light and immunofluorescence microscopy. Electron microscopy revealed moderate foot process effacement. A presumptive diagnosis of drug-induced granulomatous interstitial nephritis was made. At this point, the patient was receiving nifedipine LA 30 mg and atenolol 50 mg daily. The patient had discontinued omeprazole approximately 2 weeks prior to her renal biopsy. Prednisolone was commenced at a dose of 40 mg daily for 4 weeks and was subsequently tapered to stop by 12 weeks. One week after the introduction of corticosteroids, the patient’s serum calcium had normalized and the serum creatinine was 200 μmol/l with a serum phosphate of 1.19 mmol/l (Figure 1). Two weeks later the serum creatinine was 141 μmol/l, which we consider to be the patient’s baseline. After 18 months of clinical follow-up, the patient remains normocalcaemic with no clinical evidence of granulomatous disease. Mild renal dysfunction persists.

**Discussion**

The 31-year-old female patient in this study developed hypercalcaemia and persistent renal impairment following resolution of pregnancy-related ARF. The renal biopsy findings, in particular the intense eosinophilic infiltrates and tube-destructive granulomata, are most consistent with a drug-induced interstitial nephritis. The main differential diagnosis in this case was renal sarcoidosis, which is characterized microscopically by granulomata. However, the intense eosinophilic infiltrate, clinical presentation and subsequent lack of other organ involvement render this diagnosis unlikely.

Acute interstitial nephritis (AIN) is identified in up to 15% of patients who undergo a renal biopsy for investigation of ARF [2]. Drug hypersensitivity is a major cause of AIN with penicillins, cephalosporins and non-steroidal anti-inflammatory drugs (NSAIDs) being the most commonly implicated drugs [2]. At the time of renal biopsy, the patient was receiving nifedipine LA and atenolol for hypertension. Omeprazole was discontinued by the patient 2 weeks prior to the renal biopsy. Neither atenolol nor nifedipine are likely causal agents in this case. Atenolol was introduced following the onset of hypercalcaemia and renal impairment. Nifedipine was continued after cessation of corticosteroid therapy with no recurrence of hypercalcaemia or renal impairment. We consider omeprazole to be the most likely cause of this patient’s AIN even though the drug was discontinued 2 weeks prior to biopsy.
Omeprazole-induced AIN has been well documented with 16 cases reported to date in the world literature of which 11 were biopsy-confirmed [3–17]. A presumptive diagnosis of AIN was made in the five patients who had not had biopsies based on typical clinical and laboratory findings together with recovery of renal function following withdrawal of omeprazole therapy [5,7,13,14,17]. The classic clinical findings of drug induced AIN are fever, eosinophilia and/or eosinophiluria and a maculopapular rash. These findings are present in fewer than 30% of cases of drug-induced AIN and their absence does not exclude the diagnosis [2]. Fever and rash were not noted in our patient and have been reported in only six of the 16 patients with AIN due to omeprazole [7–10,13,17]. Eosinophilia was not sought prior to renal biopsy in our patient but was documented in only four of the 16 cases reported previously [8–10,13]. The time to development of AIN following omeprazole exposure can vary from 1 week to 6 months [13,14]. Renal impairment was present early in our patient and was initially ascribed to pre-eclampsia and possible mild pre-existing renal impairment in view of the finding of a raised serum creatinine at 20 weeks gestation. Drug withdrawal is the recommended treatment for drug-induced AIN but there is anecdotal evidence that concomitant steroid therapy may aid recovery of renal function [2]. Steroids were prescribed in eight of the 16 cases reported [3,7–12,17]. Complete recovery of renal function occurred in most patients within 4–8 weeks of the cessation of omeprazole. In this case, steroid therapy was prescribed as the patient had discontinued omeprazole 2 weeks prior to the renal biopsy but failed to show any recovery of renal function and remained hypercalcaemia.

To date, there have been no case reports of omeprazole therapy associated with hypercalcaemia. However, hypercalcaemia is a recognized feature of many granulomatous diseases. The usual mechanism involves PTH-independent calcitriol production by activated mononuclear cells within granulomata [18]. Occasionally granuloma-derived PTH-related peptide has been detected [19]. We speculate that a similar mechanism may have accounted for the development of hypercalcaemia in our patient and this is supported by the rapid normalization of our patient’s serum calcium with corticosteroid therapy. 1,25-dihydroxycholecalciferol levels were not measured but would have been useful in clarifying the pathophysiology of this patient’s hypercalcaemia.

A trial of corticosteroid therapy has been widely advocated in the acute management of hypercalcaemia. In this particular case, such a trial may well have proved effective and the underlying renal pathology might never have been revealed. Finally, as omeprazole is a widely prescribed drug, clinicians should be aware of its rare association with renal failure due to AIN.

References


Received for publication: 25.10.99
Accepted in revised form: 13.4.00