Case report

Acquired pyroglutamic acidosis due to long-term dicloxacillin and paracetamol use

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SUMMARY
An 85-year-old man with a background of transfusion-dependent chronic myelomonocytic leukaemia and chronic kidney disease stage III presented with symptomatic anaemia, acute kidney injury, sepsis and high anion gap metabolic acidosis (HAGMA). Initial treatment with intravenous antibiotics and blood transfusion was complicated by transfusion-associated circulatory overload, necessitating diuresis and non-invasive ventilation. Despite gradual clinical improvement, the patient’s HAGMA persisted, and no cause was identified on urine testing or renal ultrasound. As the patient was on long-term dicloxacillin for infective endocarditis prophylaxis and regular paracetamol, pyroglutamic acidosis (PGA) (5-oxoproline acidosis) was considered. This was later confirmed with elevated serum levels, and the HAGMA resolved following cessation of these medications. Although considered an uncommon cause of HAGMA, PGA is likely also under-recognised, and to our knowledge, this may be the second reported case in the context of dicloxacillin.

BACKGROUND
High anion gap metabolic acidosis (HAGMA) is a commonly encountered acid-base disturbance in patients in the hospital setting and is generally attributable to ketoacidosis, lactic acidosis, renal failure or ingestion of toxic substances (eg, salicylates, glycols and methanol).

Accumulation of pyroglutamic acidosis (PGA) (5-oxoproline) is a less commonly identified aetiology. This can occur in children with inborn errors of metabolism affecting enzymes in the γ-glutamyl cycle (eg, glutathione synthase deficiency), which produces the antioxidant glutathione, or it can be acquired.1 Acquired PGA occurs in association with glutathione and cysteine depletion, or as an adverse effect of certain medications (eg, fluvoxacinil and paracetamol).

Complications due to drug interactions in patients with hepatic and renal dysfunction can be difficult to identify, and unmanaged metabolic acidosis can contribute significantly to mortality.2 Given the common utilisation of paracetamol and penicillins, PGA may be an under-reported issue.

We report a case of an 85-year-old man with a complex medical history, who developed a multi-factorial HAGMA.

CASE PRESENTATION
An 85-year-old man was brought to emergency department following a fall at home while attempting to change his incontinence pad. He sustained no injuries from the fall; however, he reported a background of several days of worsening lethargy, a productive cough and decreased oral intake. His medical history was complex and included transfusion-dependent chronic myelomonocytic leukaemia type 1 (CMLM-1) (see baseline results in table 1), type II diabetes mellitus, atrial fibrillation with a permanent pacemaker, chronic kidney disease stage III (baseline creatinine 100–120 μmol/L), hypertension and a permanent suprapubic catheter due to neurogenic bladder and benign prostatic hypertrophy.

His medical history also included restless leg syndrome, duodenal ulcers, hypercholesterolaemia, renal calculi, pyelonephritis, infective endocarditis of the aortic valve, non-ST elevation myocardial infarction, polyvalmy rheumatoid arthritis and chronic obstructive pulmonary disease.

His chronic treatment consisted of irbesartan, digoxin, pantoprazole, bisoprolol, apixaban, sulfasalazine, pramipexole, domperidone, atorvastatin, cholecalciferol, mixed insulin, paracetamol and lifelong dicloxacillin (1g two times per day for the last 10 months) for suppression of infective endocarditis.

He had a low-grade fever (37.9°C), blood pressure of 131/47 mm Hg, heart rate of 70 bpm, respiratory rate of 21 and oxygen saturation of 93%. Clinical examination was notable only for some interstitial markings. He had a low-grade fever (37.9°C), blood pressure of 131/47 mm Hg, heart rate of 70 bpm, respiratory rate of 21 and oxygen saturation of 93%.

The initial point of care blood testing indicated a significant acute kidney injury (AKI) (creatinine 325 μmol/L, urea 28 mmol/L, estimated glomerular filtration rate (eGFR) 14 mL/min/1.73 m²). One month prior to this presentation, his eGFR had been 47 mL/min/1.73 m² and creatinine 120 μmol/L. His serum glucose was 14.2 mmol/L.

The full blood count showed a haemoglobin of 80g/L, platelets 103×10⁹/L, white cell count (WCC) 40.3×10⁹/L, neutrophils 22.91×10⁹/L and monocytes 13.43×10⁹/L (table 1). Occasional blasts were seen on the blood film.

Venous blood gas indicated a metabolic acidosis (pH 7.31, bicarbonate 14 mmol/L and lactate 1.3 mmol/L). Following correction for hypoalbuinaemia and hyperglycaemia, his anion gap was calculated to be 21 mmol/L (table 2). Chest X-ray showed patchy perihilar opacification and increased interstitial markings.

REFERENCES
1. Almuwais A, Gibbons H. BMJ Case Rep 2020;13:e233306. doi:10.1136/bcr-2019-233306.
positive response to diuresis; however, the acidosis persisted for diuresis and high-flow nasal prong oxygen up to 50 L/min. Adjusted for renal impairment, with the addition of furosemide.

Intravenous antibiotics were changed to piperacillin–tazobactam intravenously (4.5 g two times per day, dose-adjusted for renal impairment), with the addition of furosemide for diuresis and high-flow nasal prong oxygen up to 50 L/min.

Over the next 24 hours, the patient demonstrated a gradual positive response to diuresis; however, the acidosis persisted with an anion gap of 21.3 mmol/L. Various causes for HAGMA were excluded. Renal ultrasound showed multiple small calculi in the right kidney but no evidence of obstruction or hydronephrosis. Urine was highly positive for leukocytes, and culture grew Candida sp, but negative for eosinophils, casts, monoclonal immunoglobulin and Bence-Jones proteins.

In the context of sepsis, AKI and long-term treatment with dicloxacillin and paracetamol, PGA was considered. These medications were withheld on day 4 of admission and a request for blood pyrogglutamic acid levels was sent. Cephalexin was recommended by infectious diseases as the replacement for the dicloxacillin for long-term infective endocarditis suppression.

Given the patient’s history of CMML-1, acceleration phase of leukaemia or transformation to CMML-2, and spontaneous tumour lysis syndrome (sTLS) had to be considered as potential contributors to his clinical picture. He met two of the laboratory criteria for TLS (urate 1.28 mmol/L (reference 0.15–0.50) and phosphate 1.83 mmol/L (reference 0.75–1.50)), and at least one of the clinical criteria (increase in creatinine greater than or equal to 1.5 times the upper limit of normal).

Multiple sets of blood cultures eventually grew pan-sensitive Candida orthopsilosis, so he was commenced on a 2 week course of oral fluconazole (200 mg daily).

### OUTCOME AND FOLLOW-UP

Over the following weeks of his admission, the patient’s acidosis resolved with overall improvement in his clinical condition. His bicarbonate improved to 26 mmol/L with a calculated anion gap of 14.8 and his renal function stabilised (GFR 16 mL/min/1.73 m² and creatinine 292 μmol/L). His blood count differential also stabilised (WCC 20.1×10⁹/L, neutrophils 11.28×10⁹/L and basophils 0.20×10⁹/L) (table 1).

### Table 2

| Venous blood gas | Day 2 | Day 4 | Unit | Reference |
|------------------|-------|-------|------|-----------|
| pH               | 7.31  | 7.30  |      | 7.32–7.43 |
| Bicarbonate      | 14    | 14    | mmol/L | 22–33    |
| pCO₂             | 27    | 29    | mm Hg | 39–54    |
| Lactate          | 1.3   | 1.2   | mmol/L | 0.5–2.2  |
| Calculated anion gap | 21 | 21.3 | mmol/L | 8–16      |

pCO₂, partial pressure of CO₂.

### Table 3

| Arterial blood gas | Day 3 | Reference |
|--------------------|-------|-----------|
| pH                 | 7.26  | 7.35–7.45 |
| Bicarbonate        | 10    | 22–32     |
| pCO₂               | 23    | 32–48     |
| Lactate            | 1.1   | 0.5–2.2   |
| Calculated anion gap | 19.0 | 8–16       |

pCO₂, partial pressure of CO₂.
Drug-induced PGA is most commonly seen with chronic paracetamol use as it contributes to cysteine deficiency via direct conjugation and glutathione deficiency through its metabolite, N-acetyl benzoinoneimine, which irreversibly binds glutathione.12

PGA was retrospectively confirmed with blood levels of 62 μmol/L (reference 20–50 μmol/L). As the acidosis resolved following cessation of the paracetamol and dicloxacillin, PGA was likely the main contributor; however, sTLS could not be excluded. After further discussion with the patient and his family, he decided to discontinue the ongoing active treatment and was discharged to a residential aged care facility for symptomatic management and palliative care.

**DISCUSSION**

The cases of acquired PGA have been increasingly reported since 1989, generally in the context of glutathione deficient states.4 5 Risk factors for this condition have been well-defined in case reports and our case demonstrates some of these, namely advanced age, sepsis, malnutrition, chronic kidney disease, uncontrolled diabetes, isoxazolyl penicillin use and chronic paracetamol use.6–9 Other risk factors include chronic liver disease, female gender and the use of netilmicin or vigabatrin.5–10

PGA occurs in the presence of multiple risk factors and this is related to the underlying pathogenesis and the γ-glutamyl cycle. Depleted glutathione levels remove the negative feedback inhibition on γ-glutamylcysteine synthetase, resulting in the accumulation of γ-glutamylcysteine which can be metabolised to 5-oxoproline.11 Despite the increased activity of γ-glutamylcysteine synthetase, insufficient cysteine levels impair conversion of γ-glutamyl phosphate to γ-glutamyl cysteine, and it is converted instead to 5-oxoproline via a futile ATP-depleting cycle (figure 1).11

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5-oxoprolinase usually degrades 5-oxoproline to glutamate, but this enzyme can be inhibited by flucloxacillin, promoting 5-oxoproline accumulation and the associated acidemia.13 14 The vast majority of PGA cases associated with antibiotics involve flucloxacillin, and to our knowledge, our case may be the second reported in the context of dicloxacillin.6 Given the limited available evidence, it remains unclear if the association to PGA could represent a class effect of the isoxazolyl penicillins. However, there have been cases where flucloxacillin has been successfully substituted for other β-lactam penicillins, which would support this.15–17

A decline in renal function can further exacerbate PGA as 5-oxoproline, like other organic acids, is excreted in the urine (pyroglutamic aciduria).18 In our patient, deconditioning secondary to infection and declining oral intake likely precipitated his fall, and subsequently, sepsis, AKI and PGA were all contributing factors to the HAGMA.

The incidence of PGA is unknown, but it is likely underdiagnosed given the common utilisation of the associated medications and the prevalence of the risk factors. Definitive diagnosis can be made by blood pyroglutamic acid levels or urine organic acid profile; however, these tests are only performed in certain laboratories, which limit their practical application.19

In our case, the return of the blood levels was significantly delayed. PGA was an empirical diagnosis, based on the presence of risk factors and HAGMA, which prompted alterations to management (ie, cessation of dicloxacillin and paracetamol).

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**Learning points**

- Given that a large proportion of patients admitted to hospital are likely to be glutathione deficient, and paracetamol and isoxazolyl penicillins are commonly prescribed medications, pyroglutamic acidosis (PGA) should be considered as a differential diagnosis in patients with risk factors and an unexplained high anion gap metabolic acidosis.
- The mainstay of treatment involves cessation of medications that can influence the γ-glutamyl cycle or glutathione levels, and the implementation of supportive measures.
- The roles of bicarbonate and N-acetyl cysteine are still unclear, but have been used successfully to promote recovery in some cases.
- Further enquiry is required to determine whether the association of flucloxacillin and dicloxacillin with PGA represents an isoxazolyl penicillin class effect.
The differential diagnosis for the HAGMA is broad and, once the more common causes have been excluded, should be further expanded to include PGA in patients with the relevant risk factors. 19

Accumulation of 5-oxoproline was incorporated into the ‘GOLDMARK’ mnemonic, which was proposed to replace older mnemonics, for example ‘MUDPILES’, that incorporate causes of acidosis that have become exceedingly rare (table 4). 20

The mainstay of management of PGA is cessation of causative medications and supportive care. There have also been reports of bicarbonate supplementation and N-acetyl cysteine (NAC) being used successfully to promote recovery. 21 22 However, the effectiveness of NAC in treating PGA is not well established, and the potential risks associated with NAC administration in patients with septic shock are unclear. 23 24 There have also been cases of effective haemodialysis clearance of 5-oxoproline, which would have been appropriate in our patient’s situation given the concurrent haematologic crisis and renal impairment if he had opted for active management. 25

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REFERENCES
1 Mayatepek E. 5-Oxoprolinuria in patients with and without defects in the -glutamyl cycle. Eur J Pediatr 1999;158:221–5.
2 Berbee JK, Lammers LA, Krediet CTP et al. Metabolic acidosis caused by concomitant use of paracetamol (acetaminophen) and fluocoxacinil: A case report and a retrospective study. Eur J Clin Pharmacol 2017;73:1459–65.
3 Cairo MS, Bishop M. Tumour lysis syndrome: new therapeutic strategies and classification. Br J Haematol 2004;127:3–11.
4 Creer MH, Lau BW, Jones JD, et al. Pyroglutamic acidemia in an adult patient. Clin Chem 1989;35:884–6.
5 Bonth J, Rattenbury J, Meeks A, et al. Pyroglutamicaciduria from vigabatrin. The Lancet 1989;333:1452–4.
6 Pitt JJ, Hauser S. Transient 5-oxoprolinuria and high anion gap metabolic acidosis: clinical and biochemical findings in eleven subjects. Clin Chem 1998;44:1497–503.
7 Sekhar RV, McKay SV, Patel SG, et al. Glutathione synthesis is diminished in patients with uncontrolled diabetes and restored by dietary supplementation with cysteine and glycine. Diabetes Care 2011;34:162–7.
8 Pitt JJ, Brown GK, Clift V, et al. Atypical pyroglutamic aciduria: possible role of paracetamol. J Inherit Metab Dis 1990;13:755–6.
9 Croal BL, Glen ACA, Kelly CJG, et al. Transient 5-oxoprolinuria (pyroglutamic aciduria) with systemic acidosis in an adult receiving antibiotic therapy. Clin Chem 1998;44:336–40.
10 Dempsay GA, Lyall HJ, Corke CF, et al. Pyroglutamic acidemia: a cause of high anion gap metabolic acidosis. Crit Care Med 2000;28:1803–7.
11 Emmett M. Acetaminophen toxicity and 5-oxoproline (pyroglutamic acid): a tale of two cycles, one an ATP-depleting futile cycle and the other a useful cycle. Clin J Am Soc Nephrol 2014;9:191–200.
12 Liss DB, Paden MS, Schwarz ES, et al. What is the clinical significance of 5-oxoproline (pyroglutamic acid) in high anion gap metabolic acidosis following paracetamol (acetaminophen) exposure? Clin Toxicol 2013;51:817–27.
13 Lanoy C, Bouckaert Y. Metabolic acidosis and 5-oxoprolineuria induced by fluocoxacinil and acetaminophen: a case report. J Med Case Rep 2016;10:184.
14 Zand L, Murithi A, Greene EL, et al. Severe anion gap metabolic acidosis from acetaminophen use secondary to 5-oxoproline (pyroglutamic acid) accumulation. Am J Med Sci 2012;344:501–4.
15 EH A, Lam K, Umanathan M, et al. High anion gap metabolic acidosis: a case of pyroglutamic acidosis. Nephrology 2017;22:926.
16 Mo L, Liang DL, Madden A, et al. A case of delayed onset pyroglutamic acidosis in the sub-acute setting. Intern Med J 2016;46:747–9.
17 Thomas SD. High anion gap metabolic acidosis due to pyroglutamic aciduria (5-oxoprolinuria) in an elderly patient. Aust J Sci Med 2015;36:72.
18 Heinemam L, Mahieu B, Heibert M, et al. High anion gap metabolic acidosis induced by cumulation of ketones, L- and D-lactate, 5-oxoproline and acute renal failure. Acta Clin Belg 2018;73:313–6.
19 Myall K, Sidney J, Marsh A. Mind the gap! An unusual metabolic acidosis. The Lancet 2011;377:526.
20 (Meha AN, Emmett IB, Emmett M. Gold mark: an anion gap mnemonic for the 21st century. The Lancet 2008;372:892.
21 Spector SR, Mayan H, Loebstein R, et al. Pyroglutamic acidemia as a cause for high anion gap metabolic acidosis: a prospective study. Soc Rep 2019;9:3554.
22 Hunderger ML, Feneis AZ. Acquired 5-oxoproline acidemia successfully treated with N-acetylcysteine. Proc 2017;30:169–70.
23 Chertoff J. N-Acetylcysteine’s Role in Sepsis and Potential Benefit in Patients With Microcirculatory Derangements. J Intensive Care Med 2018;33:87–96.
24 Bavalurui RV, Turner JD, Jujjavarapu S, et al. An unusual case of severe high anion gap metabolic acidosis. Clin Kidney J 2011;4:80–2.
25 Luysau S, Wamelink MMC, Galanti L, et al. Pyroglutamic acid-induced metabolic acidosis: a case report. Acta Clin Belg 2014;69:221–3.