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Case report

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

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Accepted 13 March 2020

**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  $\gamma$ -glutamyl cycle (eg, glutathione synthase deficiency), which produces the antioxidant glutathione, or it can be acquired.<sup>1</sup> Acquired PGA occurs in association with glutathione and cysteine depletion, or as an adverse effect of certain medications (eg, flucloxacillin 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.<sup>2</sup> 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 multifactorial 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 (CMML-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  $\mu\text{mol/L}$ ), 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, polymyalgic 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 crackles at the lung bases bilaterally and massive splenomegaly (first noted 2 months earlier).

**INVESTIGATIONS**

The initial point of care blood testing indicated a significant acute kidney injury (AKI) (creatinine 325  $\mu\text{mol/L}$ , urea 28 mmol/L, estimated glomerular filtration rate (eGFR) 14 mL/min/1.73 m<sup>2</sup>). One month prior to this presentation, his eGFR had been 47 mL/min/1.73 m<sup>2</sup> and creatinine 120  $\mu\text{mol/L}$ . His serum glucose was 14.2 mmol/L.

The full blood count showed a haemoglobin of 80 g/L, platelets  $103 \times 10^9/\text{L}$ , white cell count (WCC)  $40.3 \times 10^9/\text{L}$ , neutrophils  $22.91 \times 10^9/\text{L}$  and monocytes  $13.43 \times 10^9/\text{L}$  ([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 hypoalbuminaemia 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.



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**To cite:** Zand Irani A, Almuwais A, Gibbons H. *BMJ Case Rep* 2020;**13**:e233306. doi:10.1136/bcr-2019-233306

**Table 1** Blood biochemistry results during admission

	Baseline results	Day 1	Day 2	Day 3	Day 20	Unit	Reference
Hb	94	80	78	116	86	g/L	125–175
Platelet	85	103	92	129	92	10 <sup>9</sup> /L	150–400
WCC	28.0	40.3	38.7	80.4	20.1	10 <sup>9</sup> /L	3.5–10.0
Neutrophils	17.4	22.91	22.42	53.22	11.28	10 <sup>9</sup> /L	1.5–6.0
Monocytes	6.7	13.43	12.37	17.61	5.84	10 <sup>9</sup> /L	0–0.9
Eosinophils	0.28	0.40	0.00	1.15	0.20	10 <sup>9</sup> /L	0–0.6
Basophils	0.00	0.00	0.00	0.38	0.20	10 <sup>9</sup> /L	0–0.15
eGFR	47	14	14	15	16	mL/min/1.73 m <sup>2</sup>	>59
Creatinine	120	325	319	310	292	µmol/L	60–110
CRP	5.8			165		mg/L	<5
BNP	452			1544		ng/L	<100
cTroponin I				<2.42		ng/L	<20

BNP

, brain natriuretic peptide; CRP, C-reactive protein ; eGFR, estimated glomerular filtration rate; Hb, haemoglobin; WCC, white cell count.

## TREATMENT

The initial working diagnosis was a chest and/or urinary infection, complicated by AKI. Medications with potential nephrotoxicity were withheld, his suprapubic catheter was flushed, and he was commenced on ceftriaxone 1g one time a day intravenously and doxycycline 100 mg two times per day orally.

Due to his low haemoglobin, he received two units of packed red cells. Eight hours following the transfusion, he developed tachypnoea (rate >40/min) and desaturated to 80% on 3 L nasal prongs. His blood pressure was 159/53 mm Hg, heart rate 70 bpm and temperature 39.0°C. He was clinically fluid overloaded with respiratory crackles to mid-zones bilaterally, and his urine output was poor.

Arterial blood gas showed significant metabolic acidosis (pH 7.26, bicarbonate 10 mmol/L, lactate 1.1 mmol/L and corrected anion gap 19 mmol/L) (table 3). His eGFR was 14 mL/min/1.73 m<sup>2</sup>, troponin 42 ng/L and brain natriuretic peptide 1544 ng/L (table 1).

Inflammatory markers were significantly raised with C-reactive protein 165 mg/L. WCC was 80.4×10<sup>9</sup>/L (neutrophils 53.22×10<sup>9</sup>/L, lymphocytes 6.13×10<sup>9</sup>/L, monocytes 17.61×10<sup>9</sup>/L, eosinophils 1.15×10<sup>9</sup>/L and basophils 0.38×10<sup>9</sup>/L) (table 1).

The patient declined dialysis and transfer to an intensive care unit, so non-invasive management was commenced for a provisional diagnosis of sepsis, transfusion-associated circulatory overload with pulmonary oedema and possible haematologic transformation. 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 pyroglutamic 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).<sup>3</sup>

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 m<sup>2</sup> and creatinine 292 µmol/L). His blood count differential also stabilised (WCC 20.1×10<sup>9</sup>/L, neutrophils 11.28×10<sup>9</sup>/L, monocytes 5.84×10<sup>9</sup>/L and basophils 0.20×10<sup>9</sup>/L) (table 1).

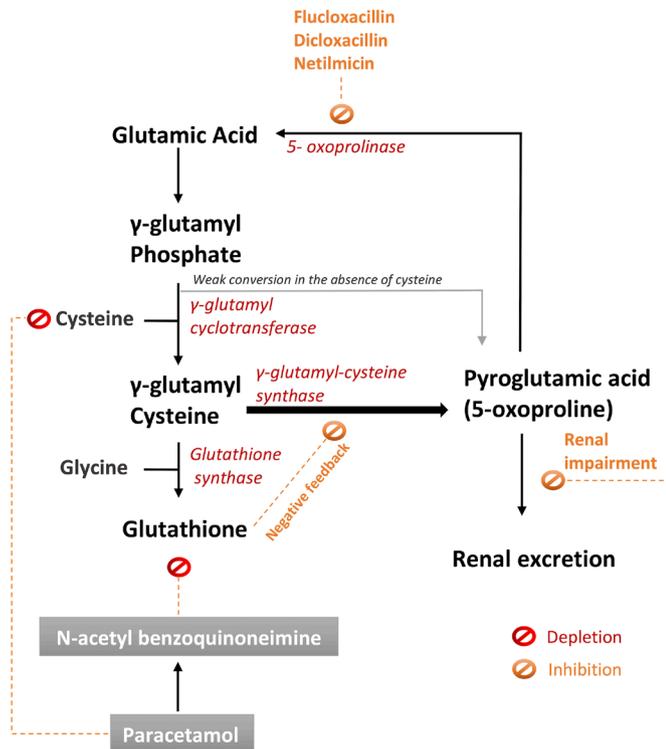
**Table 2** Venous blood gas in day 2 and day 4 of admission

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
pCO <sub>2</sub>	27	29	mm Hg	38–54
Lactate	1.3	1.2	mmol/L	0.5–2.2
Calculated anion gap	21	21.3	mmol/L	8–16

pCO<sub>2</sub>, partial pressure of CO<sub>2</sub>.**Table 3** Arterial blood gas in day 3 of admission

Arterial blood gas	Day 3	Reference
pH	7.26	7.35–7.45
Bicarbonate	10	22–32
pCO <sub>2</sub>	23	32–48
Lactate	1.1	0.5–2.2
Calculated anion gap	19.0	8–16

pCO<sub>2</sub>, partial pressure of CO<sub>2</sub>.



**Figure 1** The  $\gamma$ -glutamyl cycle. The effect of long-term dicloxacillin and paracetamol use in promoting 5-oxoproline accumulation.

PGA was retrospectively confirmed with blood levels of 62  $\mu\text{mol/L}$  (reference 20–50  $\mu\text{mol/L}$ ). 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.<sup>4,5</sup> 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.<sup>6–9</sup> Other risk factors include chronic liver disease, female gender and the use of netilmicin or vigabatrin.<sup>5–10</sup>

PGA occurs in the presence of multiple risk factors and this is related to the underlying pathogenesis and the  $\gamma$ -glutamyl cycle. Depleted glutathione levels remove the negative feedback inhibition on  $\gamma$ -glutamylcysteine synthetase, resulting in the accumulation of  $\gamma$ -glutamylcysteine which can be metabolised to 5-oxoproline.<sup>10</sup> Despite the increased activity of  $\gamma$ -glutamylcysteine synthetase, insufficient cysteine levels impair conversion of  $\gamma$ -glutamyl phosphate to  $\gamma$ -glutamyl cysteine, and it is converted instead to 5-oxoproline via a futile ATP-depleting cycle (figure 1).<sup>11</sup>

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 benzoquinone imine, which irreversibly binds glutathione.<sup>12</sup>

**Table 4** Main causes of high anion gap metabolic acidosis

High anion gap metabolic acidosis (GOLD MARK)	
G	Glycols (ethylene and propylene)
O	5-Oxoproline (pyroglutamic acid) chronic paracetamol use, EtOH, poor nutrition, vegetarian diet, renal failure, infection, flucloxacillin/dicloxacillin/netilmicin, Vigabatrin
L	Lactate
D	D-lactic acid Associated with short bowel syndrome
M	Methanol and other toxins (ethanol, Aldehyde)
A	Aspirin, salicylates
R	Renal failure
K	Ketoacidosis

EtOH, ethyl alcohol.

5-oxoprolinase usually degrades 5-oxoproline to glutamate, but this enzyme can be inhibited by flucloxacillin, promoting 5-oxoproline accumulation and the associated acidemia.<sup>13,14</sup> 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.<sup>6</sup> 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  $\beta$ -lactam penicillins, which would support this.<sup>15–17</sup>

A decline in renal function can further exacerbate PGA as 5-oxoproline, like other organic acids, is excreted in the urine (pyroglutamic aciduria).<sup>18</sup> 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.<sup>19</sup>

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).

## 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  $\gamma$ -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.<sup>19</sup>

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).<sup>20</sup>

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.<sup>21 22</sup> 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.<sup>23 24</sup> 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.<sup>25</sup>

**Contributors** Supervised by AZI. Patient was under the care of AI. Report was written by AZI, AA, HG.

**Funding** The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

**Competing interests** None declared.

**Patient consent for publication** Next of kin consent obtained.

**Provenance and peer review** Not commissioned; externally peer reviewed.

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