Pyroglutamic Acidosis – An Underrecognized Entity Associated with Acetaminophen Use

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Case Report

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Abstract

Pyroglutamic acidosis (PGA) is an underrecognized entity characterised by raised anion gap metabolic acidosis (RAGMA) and urinary hyper-excretion of pyroglutamic acid. It is frequently associated with chronic acetaminophen (APAP) ingestion. We report the case of a 73-year-old man with invasive pulmonary aspergillosis treated with voriconazole, and APAP for analgesia with a cumulative dose of 160g over 40 days. PGA was suspected as he developed severe RAGMA and which common causes were excluded. Diagnosis was confirmed by urinary organic acid analysis showing significant hyper-excretion of pyroglutamic acid. APAP was discontinued and *N*-acetylcysteine (NAC) was administered. His RAGMA rapidly resolved following treatment.

Introduction

Raised anion gap metabolic acidosis (RAGMA) is a commonly encountered acid-base disturbance in clinical practice. Aetiologies for RAGMA were previously represented by the popular mnemonic MUDPILES, which stands for Methanol, Uraemia, Diabetic ketoacidosis, Paraldehyde, Iron or Isoniazid, Lactic acidosis, Ethylene glycol and Salicylate. This old mnemonic has underrepresented lately identified but also important causes of RAGMA. The new mnemonic GOLDMARK was first introduced in *The Lancet*[1], an acronym for Glycols (ethylene and propylene glycol), Oxoproline, L-lactate, D-Lactate, Methanol, Aspirin, Renal failure and Ketoacidosis. “Oxoproline” refers to 5-oxoprolinuria which is also known as pyroglutamic acidosis (PGA). This increasingly recognised entity is caused by accumulation of the endogenous organic acid in the γ-glutamyl cycle, pyroglutamic acid (5-oxoproline). PGA is most frequently associated with chronic acetaminophen (APAP) use. We report a 73-year-old man with invasive pulmonary aspergillosis on long term voriconazole and chronic daily APAP ingestion for pain control during his hospital stay, who subsequently developed severe RAGMA.

Case Report

A 73-year-old man with inoperable adenocarcinoma of the right lung received concurrent chemoradiotherapy. The irradiated site developed *Salmonella* Group D necrotising pneumonia, which progressed to extra-thoracic extension and caused empyema necessitans, a year before the current admission to medical ward. In the index admission, the patient was admitted for haemoptysis and purulent discharge at the site of empyema necessitans. Invasive pulmonary aspergillosis (IPA) was suspected based on clinical symptom of haemoptysis and radiological finding of persistent cavitation on computed tomography (CT) of the thorax. Diagnosis of IPA was further supported by an elevated serum ß-D-glucan titre at 139 pg/ml (Positive ≥ 80 pg/ml), a positive serum galactomannan assay and growth of *Aspergillus niger* in his sputum. He was placed on a 6-week course of voriconazole 400mg/day to treat as probable IPA. Multiple intravenous antibiotics including cefoperazone-sulbactam, metronidazole, vancomycin, piperacillin-tazobactam and meropenem were administered at separate occasions as anti-bacterial coverage. He was also given acetaminophen (APAP) regularly at a therapeutic dose of 4g/day due to intractable pain at the cavitation site.

On day 40 of hospital stay, the patient developed acidotic breathing, and blood gas analysis showed severe metabolic acidosis with raised anion gap (Table 1). There was no lactic acidosis and serum osmolal gap was normal. There was no exposure to salicylate, toxic alcohols or glycols. Although both his creatinine and beta-hydroxybutyrate levels were moderately raised, these were not sufficient to account for the degree of metabolic acidosis. Urine anion gap (UAG) was grossly elevated which indicated increased excretion of unmeasured anions in urine. PGA was suspected at this point, in light of an unexplained RAGMA, positive UAG, and chronic APAP use since hospital admission with a total cumulative dose of 160g.

Table 1
Relevant laboratory studies on day of diagnosis

Parameter	Result	Reference interval
Venous blood		
Sodium, plasma (mmol/L)	142	137–144 mmol/L
Potassium, plasma (mmol/L)	4.4	3.5–4.5 mmol/L
Chloride, plasma (mmol/L)	107	98–107 mmol/L
Bicarbonate, plasma (mmol/L)	5.8 (L)	23–27 mmol/L
Anion gap* (mmol/L)	29 (H)	8–12 mmol/L
Albumin, plasma (g/L)	25 (L)	35–52 mmol/L
Total bilirubin, plasma (µmol/L)	5	< 19 µmol/L
ALP, plasma (U/L)	251 (H)	43–105 U/L
ALT, plasma (U/L)	11	< 53 U/L
Urea, plasma (mmol/L)	4.9	3.1–7.8 mmol/L
Creatinine, plasma (µmol/L)	176 (H)	65–109
eGFR(CKD-EPI) (mL/min/1.73m^2)	32	> 90 mL/min/1.73m^2
Lactate, plasma (mmol/L)	2.4 (H)	< 2.2 mmol/L
Beta-hydroxybutyrate, plasma (mmol/L)	2.92 (H)	≤ 0.30 mmol/L
Osmolality, serum (mOsm/kg)	294	274–295 mOsm/kg
Osmolal gap, plasma** (mOsm/kg)	3	< 10 mOsm/kg
Random glucose, plasma (mmol/L)	8.3	-
Acetaminophen, serum (µmol/L)	119	Therapeutic range: 66–199 µmol/L
Arterial blood		
pH	7.17 (L)	7.35–7.45
PaCO2 (kPa)	1.73	4.66–6.00 kPa
PaO2 (kPa)	12.4	10–13.33 kPa

Remarks: eGFR: estimated glomerular filtration rate; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration. *Plasma anion gap = (Plasma Na^+ + Plasma K^+) − (Plasma Cl^- - Plasma $HCO3^-$); **Osmolal gap = Measured osmolality − Calculated osmolality [2(Plasma $Na^{+)}$ + Plasma urea + Plasma glucose], ***Urine anion gap = Urine Na^+ + Urine K^+ - Urine Cl^-

Parameter	Result	Reference interval
Actual bicarbonate (mmol/L)	4.7 (L)	22–26 mmol/L
Base excess (mmol/L)	-21.7 (L)	-2.0 – +2.0 mmol/L
Spot urine		
Sodium, urine (mmol/L)	93	-
Potassium, urine (mmol/L)	26	-
Chloride, urine (mmol/L)	< 20	-
Urine anion gap*** (mmol/L)	> 99 (H)	< 10 mmol/L
Urine organic acids analysis by LC-MS/MS	Significant hyper-excretion of pyroglutamic acid. -	
Remarks: eGFR: estimated glomerular filtration rate; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration. *Plasma anion gap = (Plasma Na^+ + Plasma K^+) – (Plasma Cl^- - Plasma $HCO3^-$); **Osmolal gap = Measured osmolality – Calculated osmolality [2(Plasma $Na^{+)}$ + Plasma urea + Plasma glucose], ***Urine anion gap = Urine Na^+ + Urine K^+ - Urine Cl^-		

The prescription of APAP was immediately discontinued. Intravenous *N*-acetylcysteine (NAC) infusion was given according to the standard 3-bag regimen for acute APAP poisoning (150 mg/kg over the first hour, 50 mg/kg over the next 4 hours, 100 mg/kg over the next 16 hours). The patient was transferred to the Intensive Care Unit (ICU) for close monitoring. The acid-base imbalance rapidly improved (pH 7.38, $HCO3^-$ 19.9 mmol/L, BE – 4.7mmol/L) following treatment. He was discharged from ICU to the medical ward on day 43 of hospital stay. Urine organic acid profile revealed significant hyper-excretion of pyroglutamic acid, confirming the diagnosis of PGA retrospectively. Unfortunately, despite resolution of the PGA, the patient developed massive haemoptysis due to uncontrolled IPA and eventually died on day 61 of hospital stay.

Discussion

It has been widely recognised that in acute APAP overdose, saturation of sulfation and glucuronidation systems together with glutathione depletion results in accumulation of the toxic metabolite *N*-acetyl-*p*-benzoquinoneimine (NAPQI), which inhibits mitochondrial respiration and causes direct hepatocellular necrosis, resulting in severe lactic acidosis. On the other hand, chronic APAP ingestion, even within therapeutic doses, may nevertheless lead to toxicity in susceptible individuals by causing PGA. This is due to interruption of the γ-glutamyl cycle which governs the synthesis and metabolism of glutathione, probably via an ATP-depleting cycle of reactions as depicted in Fig. 1. In patients with debilitating illness and/or malnourishment who are on chronic APAP treatment, there may be depletions of both glutathione and cysteine stores. Glutathione depletion releases the negative feedback on γ-glutamyl-cysteine synthetase, which catalyses a two-step reaction for synthesis of γ-glutamyl-cysteine from glutamic acid.

Because of concomitant cysteine depletion, such reaction cannot be completed. Instead, γ-glutamyl-phosphate is formed at the expense of ATP, and is spontaneously hydrolysed into pyroglutamic acid. 5-oxoprolinase, with consumption of ATP, metabolises pyroglutamic acid back into glutamic acid. The newly formed glutamic acid may then be converted into γ-glutamyl-phosphate and subsequently pyroglutamic acid again. As such, an ATP-consuming futile cycle is established, and with ATP depletion, there will be subsequent accumulation of pyroglutamic acid leading to RAGMA[2].

Inherited forms of PGA are rare and mostly due to glutathione synthetase deficiency, which can manifest as severe metabolic acidosis, haemolytic anaemia and progressive encephalopathy. Acquired PGA, usually associated with chronic APAP intake, is more common and was first described in 1989. Additional risk factors for PGA include female sex, malnourishment, concomitant sepsis, hepatic and renal impairment[3,4]. These risk factors are prevalent and often co-existent in hospitalized patients. Therefore, PGA is likely to be an underrecognized and underdiagnosed condition. Concurrent use of the antibiotics flucloxacillin and netilmicin[5], and the anticonvulsant vigabatrin[6] have also been implicated in PGA. These drugs inhibit the enzyme 5-oxoprolinase, preventing breakdown of pyroglutamic acid into *L*-glutamate, resulting in accumulation of pyroglutamic acid[5].

Urine pyroglutamic acid to creatinine (Cr) ratio in our patient was estimated to be 1716 μmol/mmol Cr as measured by liquid chromatography tandem mass spectrometry (LC-MS/MS). This high level of urine pyroglutamic acid was at comparable levels as in reported PGA cases in the literature, ranging from 700 to 11000 μmol/mmol creatinine[7–9]. Because measurement of pyroglutamic acid is only available in specialised metabolic laboratories, it can be difficult to confirm the diagnosis of PGA. On the other hand, urine anion gap (UAG) is a readily available test which may provide a clue to the diagnosis. As in our patient, a positive UAG indicates increased excretion of unmeasured anions in urine, including pyroglutamic acid. Though such finding is non-specific, it would nevertheless be useful if interpreted in a proper clinical context. In addition, it must be noted that a therapeutic level of APAP does not rule out the diagnosis of PGA as the pathogenesis is different from acute overdose.

Apart from chronic APAP ingestion, additional risk factors are often present in patients with PGA. Our patient had chronic infection, prolonged hospitalisation and malnutrition, probably leading to depletion of glutathione and cysteine stores. His renal impairment likely also reduced clearance of pyroglutamic acid and contributed to its accumulation. The patient was also on chronic voriconazole, which has also been reported to cause glutathione depletion and have potential hepatotoxicity based on an animal study[10]. Recently, a 7-year-old patient with leukaemia who was given chronic APAP, antibiotics and antifungals including voriconazole has been reported to develop PGA[11].These suggest that voriconazole might be a contributing culprit. We would like to advise cautious use of APAP in susceptible individuals, particularly patients with multiple aforementioned risk factors. Prolonged use of APAP should be avoided and the dosages should be kept to a minimum, and alternative analgesics should be used where appropriate.

Treatment for PGA should be initiated based on clinical grounds and must not be delayed until laboratory confirmation. APAP and other offending agents should be withheld and alternative prescriptions should

be employed where appropriate. NAC is widely used as an antidote for acute APAP poisoning and is the standard treatment for hereditary glutathione synthetase deficiency. Its mechanism of action is by regeneration of glutathione and cysteine stores[12]. Although there has been limited experience with its use in acquired PGA and the optimal dosage is not uncertain, it appears to be safe and effective according to the published case reports[3,4,8,9]. We adopted the treatment protocol as in acute APAP poisoning, and demonstrated rapid reversal of acidosis without noticeable adverse effects after NAC administration in our patient.

This case illustrates acute severe RAGMA due to PGA in a patient on therapeutic doses of APAP. Extra caution should be exercised when administering repetitive doses of APAP in hospitalized patients at risk of glutathione depletion. Prolonged use of high therapeutic APAP doses, such as 4g/day in our case, should be avoided. PGA should be considered when patients develop unexplained RAGMA. Elevation of urine anion gap reflect urinary excretion of unmeasured organic acids and may be an informative adjunct to the diagnosis of PGA in an appropriate clinical context. Diagnosis of PGA should be confirmed by measuring organic acids in the serum and/or urine. However, testing may not be readily available and results are often delayed. High clinical suspicion in at-risk patients is the key to a timely diagnosis and effective treatment by withholding the offending agents and giving NAC empirically.

Declarations

Conflicts of interest: The authors declare that there are no conflicts of interest to disclose.

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Ethical statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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Figures

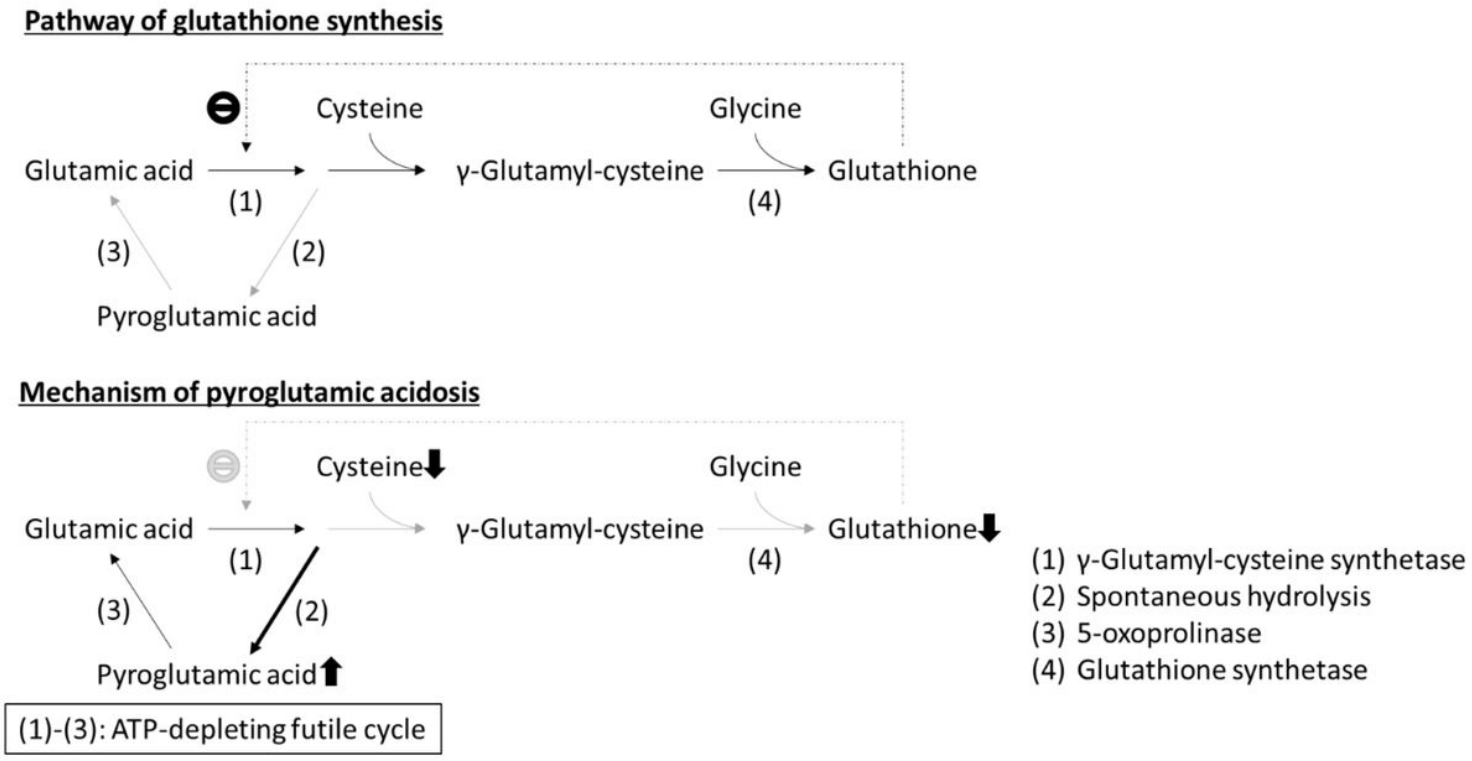

Figure 1

Pathway of glutathione synthesis and mechanism of pyroglutamic acidosis in cysteine and glutathione depletion.