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Case Report

An Unusual Case of Metabolic Acidosis: The GAP and Urine are the Clues

Lina M León-Machado[1,2], Begoña Rivas Becerra[1*], Cristina Vega[1], Yanieli Hernandez[1], Gema Fernandez-Juarez[1,2]

[1]Nephrology Unit, La Paz Hospital, Madrid, Spain

[2]Biomedical Research Foundation (Idipaz), Madrid, Spain

[*]**Corresponding author:** Begoña Rivas Becerra, Nephrology Unit, La Paz Hospital, Madrid, Spain.

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Abstract

Metabolic acidosis is a common disorder in hospitalized patients, even more in the intensive care unit, often representing a diagnostic challenge. It is classified as normal or high anion gap metabolic acidosis. High Anion Gap Metabolic Acidosis (AGMA) can result of increase in unmeasured anions such as lactic acid, keto acids, alcohol intoxication or more rarely pyroglutamic acid. Case presentation: A 19-year-old woman with no medical history presented to the emergency department due to bullous skin lesions with extensive involvement of the body surface suggestive of Steven Johnson Syndrome (SJS).During her stay in the ICU she presented acute endocarditis by methicillin -sensitive Staphylococcus aureus treated with cloxacillin, also she received acetaminophen for fever. After two months of admission, nephrology unit was consulted for hypokalemic metabolic acidosis with high requirements of intravenous sodium bicarbonate over 1000 mEq/day. High anion gap metabolic acidosis, hypokalemia, uroanalysis with elevated pH and positive urinary anion gap were indentified. Conclusion: AGMA by accumulation of pyroglutamic acid is a rare and underdiagnosed condition. It should be considered in all patients with unexplained AGMA who have risk factors that predispose them.

Keywords: Metabolic Acidosis; Anion GAP; Acetaminophen; Oxiproline

Introduction

Metabolic acidosis is a frequent disorder in the Intensive Care Unit (ICU), often representing a diagnostic challenge, due to the complexity of the critically ill patient which involves nutritional and electrolyte alterations that modify the usual interpretation of the acid-base status.

The most known causes of Anion Gap Metabolic Acidosis (AGMA) are alcohol intoxication, ketoacidosis status, lactic acidosis and impaired renal function.

Below we describe an unusual cause of high anion gap metabolic acidosis.

Objective

To describe a rare cause of AGMA with important clinical repercussions if delayed in diagnosis

Case Report

A 19-year-old woman with no medical history presented to the emergency department due to Bullous skin lesions with extensive involvement of the body surface, compatible with Steven Johnson Syndrome.

During her stay in the ICU she presented acute endocarditis on the mitral valve due to Staphylococcus aureus treated with cloxacillin for 60 days and valve replacement, also she received acetaminophen for fever.

She was also under treatment with enteral nutrition, because of digestive intolerance to enteral nutrition she remained with prolonged fasting periods.

After two months of admission, nephrology unit was consulted for hypokalemic metabolic acidosis with high requirements of intravenous sodium bicarbonate (>1000 mEq/day).

On admission to the ICU (Table 1), she did not present any abnormalities in acid-base or electrolyte status. Two months after admission to the ICU, marked respiratory alkalosis was observed as a consequence of fever and anxiety due to prolonged admission moreover hypokalemic AGMA. Hypokalemia was interpreted in the context of the use of diuretics.

Parameter (Normal values)	At admission in ICU	After 60 days of cloxaciline	Two weeks after cloxaciline ceased
Sodium (135-145 meq/l)	136	141	138
Potassium (3,5-5 meq/l)	4	3,3	4
Chloride (96-106 meq/l)	100	110	102
Bicarbonate (23-27 meq/l)	24	13	26
pH (7,35-7,35)	7,38	7,5	7,4
pC02 (mmhg)	40	19	37
Anion GAP	12	18	10
Albumin (g/dl)	4	2	4,5
Anion GAP corrected*	__	24	__
Osmol GAP	No data	-5	No data
Delta GAP/delta HCO3	__	1,2	__
Lactato(mmol/l)	0,8	1	1,3
Creatinine (mg/dl)	0,8	0,4	0,6
eGRF (ml/min/1,73)	>90	>90	>90
Glucose (mg/dl)	80	60	85
Urine sodium (meq/l)	__	181	___
Urine chloride (meq/l)	__	50	___
Urine potassium (meq/l)	__	22	___
Urine GAP	__	Positive (+153)	___
Ph urine	5,5	7,5	6
Cetones (urine dipstick)	Negative	Positive	Negative

Table 1: Supplementary tests. __: results not available

In the urinalysis, high urinary pH and positive urinary anion gap stood out, probably due to the administration of large amounts of bicarbonate and the elimination of non-measurable anions such as 5-oxyproline.

We consider in the differential diagnosis fasting ketoacidosis because the background of fasting periods and the presence of urinary ketones. The patient persisted with AGMA despite starting parenteral nutrition so it was excluded this etiology.

We exclude all other causes of AGMA, the most likely diagnosis was AGMA secondary to pyroglutamic acid due to treatment with cloxacillin and acetaminophen.

We decided to change antibiotic therapy to daptomycin and stop acetaminophen, after 2 weeks she presented resolution of AGMA without requirement of bicarbonate, which confirmed our suspected diagnosis.

Discussion

Pyroglutamic acid accumulation is a rare cause of AGMA by occurring as a result of hereditary or acquired defects by glutathione depletion [1] (Figure1).

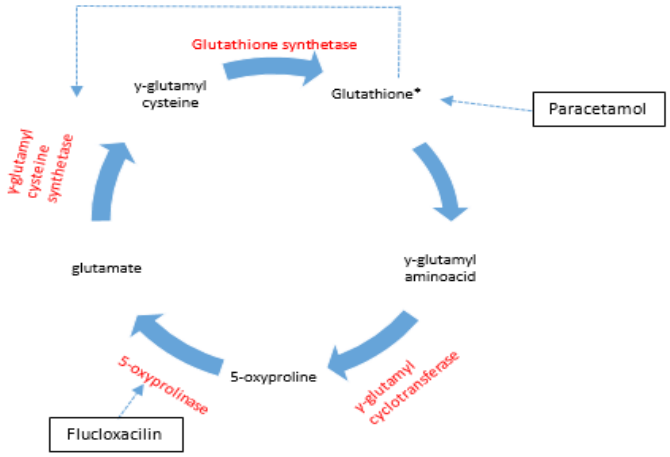

Figure 1: The γ - glutamyl cycle Paracetamol induces glutathione depletion and flucloxacilin inhibit 5-oxiprolinase causing disrupt of the cycle. *Glutathione synthesis is sensitive to dietary intake of cysteine. Dashed lines indicated inhibition [1].

Under normal circumstances, the activity of γ-glutamylcysteine synthetase is regulated by feedback inhibition by glutathione. Therefore, severe depletion of glutathione stores reduces the inhibition of y-glutamilcysteine synthetase resulting in increased production of y-glutamyl cysteine which is converted by γ-glutamyl cyclotransferase to 5-oxyproline [1,2].

Our patient had several reasons to have glutathione depletion: sex differences in glutathione transferese activity and lower gluthatione stores in women than in men, make woman more prone to elevation of pyroglytamic acid [2]; during critical illness is usual have an increase in oxidative stress for many reason like sepsis and malnourished which promoted gluthatione depletion ; administration of acetaminophen depletes gluthatione by metabolism of hepatic cytochrome P450 to oxidative metabolite N-acetyl-pbenoquinone imine [3]. Also some antibiotics like flucloxaciline inhibits the enzyme that convert 5-oxiproline in glutamate causing more pyroglutamic acid accumulation [4].

The treatment of AGMA by pyroglutamic acid involves stop offending drugs [5] in this case acetaminophen and cloxacilin was stop with improving in acid-base status until normalization values.

The utility of N-Acetilcysteine (NAC) for acute acetaminophen toxicity is well known. The benefit of NAC in cases of acquired 5-oxiprolinemia has been postulated based on evidence reported in cases with hereditary enzyme deficiency [5]. Theoretically NAC will replete the glutathione stores and should reestablish the feedback inhibition of γ-glutamic cysteine synthetase.

Reported evidence in the literature supporting the use of NAC for AGMA by pyraglutamic acid is limited [1-5].

To conclude, AGMA by pyro glutamic acid is a rare and underdiagnosed condition. It should be considered in all patients with unexplained AGMA who have risk factors that predispose them to depletion of glutathione reserves because the condition can be fatal and the treatment is easy that include suspend all suspected drugs and the administration of NAC to regenerate glutathione stores should be considered.

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