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CASE REPORT

The McKittrick-Wheelock Syndrome: A Case of Acute Renal Failure Due to Neoplastic Cholera

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The McKittrick Wheelock syndrome is characterized by severe electrolyte and fluid depletion as a result of rectal tumor hypersecretion. Typically, a metabolic acidosis ensues. We report the case of a 58-year-old man who presented with a mixed metabolic acidosis and alkalosis. He was hyponatremic, hypokalemic, and hypochloremic, with acute renal failure on blood testing. Following fluid resuscitation, a predominant alkalemia was observed. The patient was found to be passing 1.5 L of mucous per rectum per day, containing high concentrations of sodium and potassium, similar to that observed in cholera stool. A large rectal villous adenoma was discovered on sigmoidoscopy, and definitive management was achieved by removal of the tumor. This case provides a demonstration of the ranging metabolic disturbance associated with secretory diarrhea. Other endogenous and infective causes are discussed, and mechanisms compared with the case described.

Keywords cholera, delta anion gap, McKittrick-Wheelock syndrome, metabolic alkalosis, villous adenoma

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INTRODUCTION

Secretory diarrhoea is generally defined as any diarrheal illness in which intestinal fluid losses exceed 10 mL/kg/day. Causes are either infectious (such as cholera) or non-infectious (such as neoplasia).[1] The rare McKittrick-Wheelock syndrome, first described in 1954,[2] is characterized by severe electrolyte and fluid depletion secondary to mucous diarrhoea from rectal tumors, most notably villous adenomas.[3] Cases of mucus hypersecretion from villous adenomas causing dehydration, hyponatremia, hypokalemia, and hypochloremia have been reported.[3–8] The majority of these describe a concomitant metabolic acidosis, secondary to pre-renal failure.[4,5,7] More unusually, metabolic alkalosis, presumed secondary to hypokalemia, has been described in one case report.[9] We present a case of the McKittrick Wheelock syndrome in which a mixed acid-base disturbance was observed, with severe biochemical derangement.

CASE REPORT

A 58-year-old man presented to the casualty department with symptoms of progressive weakness, lethargy, and dizziness over the preceding two days. These

symptoms were sufficient to prevent him from getting out of bed on the day of admission. He described some loose stools for just a few days prior to admission. He had been diagnosed with gout one year previously, for which he was taking allopurinol.

There was clinical evidence of volume depletion, with dry mucous membranes, reduced skin turgor, and postural hypotension (fall in systolic blood pressure of 33 mmHg on standing). Examination was otherwise unremarkable.

Blood testing revealed renal failure with urea of 38.6 mM and creatinine of 619 μM, which was associated with good urine output of 80–100 mL/hour (see Table 1). Serum electrolytes were deranged with sodium of 114 mM, potassium of 2.3 mM, and chloride of 63 mM. There was concomitant complex acid base disturbance. Measured venous bicarbonate was 16 mM, and the anion gap was 37 mM. Thus, the delta anion gap/delta bicarbonate was calculated as 3.38, indicating the presence of a mixed metabolic acidosis and alkalosis:

$$\begin{aligned}\Delta \text{ Anion gap} / \Delta \text{ bicarbonate} &= (\text{anion gap} - 10) \\ &\quad \div (24\text{-bicarbonate}) \\ &= (37 - 10) \div (24 - 16) \\ &= +3.38\end{aligned}$$

Lactate was 2 mmol/L and there was no evidence of ketoacidosis or toxin ingestion with a normal osmolar gap (calculated osmolality 286 mOsm/L, measured 292 mOsm/L). Arterial blood gas analysis 90 minutes after commencing volume resuscitation revealed emerging systemic alkalemia (pH 7.51, pO_2 12.1 kPa [91 mmHg] and pCO_2 3.6 kPa [27.1 mmHg]).

Urinalysis demonstrated relatively concentrated urine (urine osmolality, 347 mosmol/kg; 24-hour urine osmolar excretion, 740 mosmol/day; plasma osmolality, 292 mosmol/kg) with urinary sodium 7 mmol/L, potassium 35.2 mmol/L (equivalent to 75 mmol/24hr), and chloride 5 mmol/L.

Table 1
Serum biochemistry during admission

Serum electrolytes	Days from admission					
	0	1	2	3	4	5
Sodium(mM)	114	124	131	135	135	137
Potassium (mM)	2.3	2.7	3.5	3.9	3.5	3.8
Chloride (mM)	63	73	99	105	103	101
Urea (mM)	38.6	37.6	33.5	19.4	10.3	7.4
Creatinine (μM)	619	563	281	142	121	110
Phosphate (mM)	4.05	3.62	1.24			
Bicarbonate (mM)	16	22	21	23		

There was a prolonged QT interval (532 msec) on electrocardiography, consistent with the presence of hypokalemia (Mg^{++} 1.66 mM Ca^{++} 2.23 mM). Chest radiograph and renal ultrasound scan were normal.

The patient was volume resuscitated with 8L 0.9% saline plus potassium in the first 48 hours, and serum biochemistry normalized within five days of admission (see Table 1). Although our patient denied significant gastrointestinal disturbance on initial questioning, it was noted on the night of his admission that he was passing large volumes of mucus per rectum. Over the next few days, it became evident that these volumes of mucus exceeded 1.5L a day. Analysis of the mucus confirmed high concentrations of electrolytes, responsible for the deranged serum biochemistry on admission (see Table 2). Sigmoidoscopy revealed a large rectal villous adenoma, 9 cm in size, occupying 75% of the luminal circumference (see Figure 1).

Following fluid and electrolyte resuscitation, the patient was initially discharged home with a future date for surgery. Unfortunately, he presented again one month after his initial presentation with a recurrence of acute renal failure secondary to losses from his rectal adenoma. Definitive management was achieved via proctectomy, and there was a good recovery with no further relapses. Histological analysis of the excised tissue demonstrated a sessile villous serrated adenoma with diffuse low-grade dysplasia but no evidence of invasive malignancy (see Figure 2).

DISCUSSION

Mucus produced by villous adenomas contains on average 120 mmol/L sodium, 44 mmol/L of potassium, and 123 mmmol/L of chloride.[10] Such extra-renal losses can lead to extreme electrolyte derangement, as demonstrated by this case. The associated complex and occasionally severe acid-base disturbances range from metabolic acidosis to metabolic alkalosis.[11] In the current case, a mixed picture ensued. In the absence of elevated lactate, ketosis or toxin ingestion, the observed increase in anion gap was almost certainly secondary to volume loss and

Table 2
Electrolyte content of rectal mucus in current case compared to that of cholera stool, normal saline, gelofusin, dioralyte solution, and normal plasma

	Case's stool	Cholera stool	Normal saline	Dioralyte solution	Normal plasma
Sodium (mM)	137	130	154	60	140
Potassium (mM)	28.9	120	0	20	4

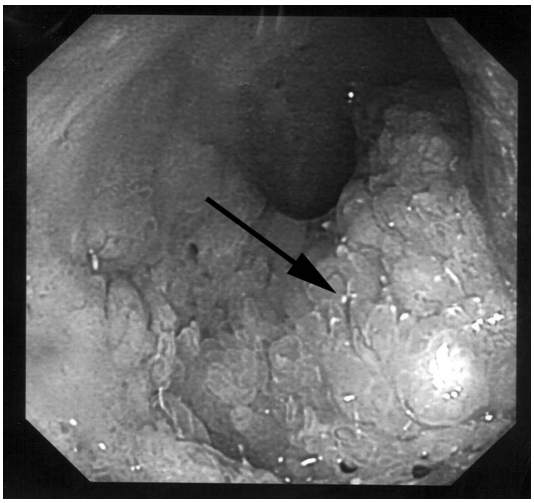

Figure 1. Sigmoidoscopic view of villous adenoma occluding approximately 75% of the rectal lumen.

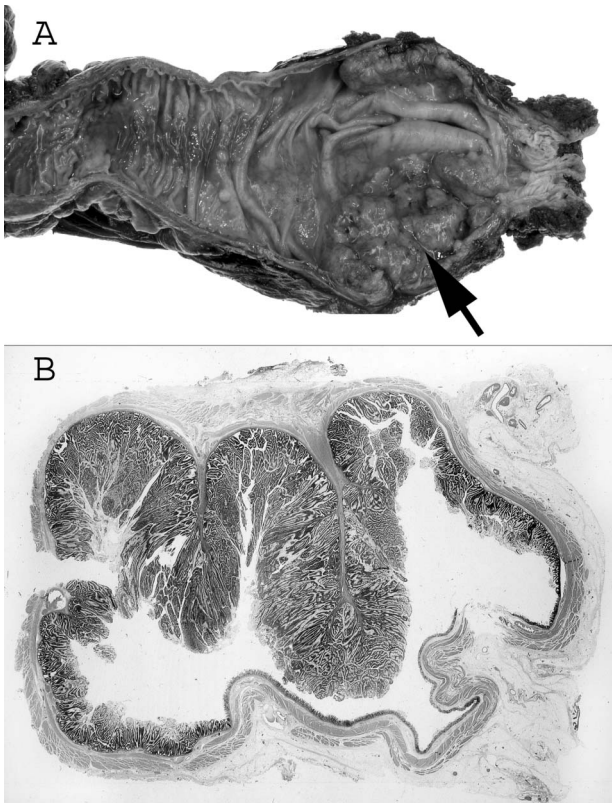

Figure 2. (a) Abdomino-perineal resection specimen showing a large sessile lesion just above the dentate line, measuring 9 cm in maximum dimension, on the anterior right and left lateral rectal wall. The lesion is partially obstructing the lumen, as evidenced by the marked dilatation of the proximal rectum. (b) Whole mount of a transverse section through the rectal wall shows a large sessile villous adenoma, with low-grade dysplasia and a serrated morphology producing large amounts of mucin. The adenoma occupies 75% of the luminal circumference and is confined to the rectal mucosa with no evidence of invasive malignancy. Hematoxylin & eosin stain.

pre-renal failure, with associated accumulation of organic acids, phosphate, and sulphate.

The use of the delta anion gap/delta bicarbonate equation in this case also revealed the presence of occult metabolic alkalemia, which was becoming evident on arterial blood gas analysis following partial volume resuscitation. This was probably driven primarily by chronic severe hypokalemia, which is thought to increase renal ammonia production and hydrogen ion excretion.[12] Hypochloremia also promotes metabolic alkalosis, as it is associated with a contraction of the extracellular fluid compartment, which reduces glomerular filtration rate and increases bicarbonate reabsorption.[13] Finally, the stimulation of the renin-angiotensin system by hypovolemia and hypochloremia in this case may also have contributed to the alkalosis, as hyperaldosteronism promotes hydrogen ion secretion in the distal renal tubules. Clearly, in this case, the various physiological mechanisms for preserving electrolyte and acid-base balance were pushed and pulled in numerous opposing ways.

Severe hypovolemia, leading to the secretion of antidiuretic hormone and activation of the renin-angiotensin system, resulted in the production of concentrated urine with elevated potassium level, extreme sodium avidity, and osmolality greater than that in serum. Although helping to prevent circulatory collapse, in this situation, the autoregulatory mechanisms worsened the degree of hypokalemia and hyponatremia, and further diluted all serum electrolytes. With regards to the patient's hypermagnesemia (1.66 mM), in the absence of exogenous magnesium administration or ingestion, this probably reflects the patient's underlying renal failure.

In the case described, there was a rapid therapeutic response to the administration of saline and potassium, as seen by a correction of his biochemistry and improvement in renal function. Metabolic alkalosis secondary to hyperaldosteronism is not always as easy to correct and may require anti-aldosterone treatment, such as with spironolactone.[5] Increased colonic mucosal cAMP and prostaglandin concentrations may be responsible for the fluid and electrolyte hypersecretion in the McKittrick-Wheelock syndrome.[14,15] Hence, non-steroidal anti-inflammatory drugs such as indomethacin, which reduce rectal prostaglandin E2 levels, can decrease rectal fluid and sodium losses.[16] Ultimately, however, definitive surgery in order to prevent further electrolyte disturbance is the most favorable long-term management option.

The McKittrick-Wheelock syndrome demonstrates one example of non-infectious secretory diarrhoea. However, the case described shared features with both other endogenous and infective diarrheal illnesses. One potentially fatal inherited condition is that of congenital chloride-losing diarrhea. In this condition, defective colonic Cl^-/HCO_3^- exchange results in copious, chloride-rich diarrhea, volume depletion, and systemic alkalemia. Reduced expression of the down-regulated in adenoma (DRA) gene linked with this condition is also found in colonic adenomas and adenocarcinomas.[17] Though unproven, we postulate that such genetic mutations may have contributed to the hypochloremic, alkalemic picture associated with a colonic villous adenoma in the case described.

As in the McKittrick-Wheelock syndrome, the cholera toxin leads to increased intracellular cAMP via sustained activation of adenylate cyclase, and the stimulation and synthesis of mucosal prostaglandin E2 via upregulation of COX-2 expression.[18,19] Subsequent intestinal fluid losses can exceed a litre per hour in adults, frequently leading to pre-renal failure and promoting metabolic acidosis. Mean potassium concentration of cholera stool is four to eight times that of plasma, resulting in profound whole body depletion. Serum potassium is usually raised at presentation, however, due to the severity of acidosis (as may be observed in diabetic ketoacidosis).

In non-infectious secretory diarrhea, the rate of fluid loss is seldom great enough to cause the hypovolemic shock characteristic of severe cholera, and hypokalemia and metabolic alkalosis are more likely to ensue. This process is augmented by hyperaldosteronism, which promotes sodium and water conservation by the gut at the expense of further potassium secretion.[1,20] In the case described, the patient was hypovolemic with a metabolic acidosis, which are common features of cholera diarrhea. It is likely however, that this acute decompensation occurred on a background of chronic potassium depletion and metabolic alkalosis, contributing to the complex acid base disturbance observed.

KEY POINTS

McKittrick-Wheelock syndrome and cholera are two causes of life-threatening secretory diarrhea, mediated by an increase in mucosal cAMP and prostaglandin E2.

Metabolic alkalosis secondary to hypokalemia occurs in the setting of chronic secretory diarrhea. This is a result of increased renal ammonia production and hydrogen ion excretion, augmented by hyperaldosteronism.

The equation

$$\text{Delta anion gap / delta bicarbonate} = \frac{(\text{anion gap} - 10)}{(24\text{-[bicarbonate]})}$$

evaluates the anion gap in proportion to the decrease in bicarbonate to assess for mixed acid-base disorders (normal: 1–1.6). A value less than 1 in the setting of a raised anion gap acidosis indicates that bicarbonate has decreased out of proportion to the elevation of the anion gap, suggesting the additional presence of a normal anion gap metabolic acidosis. A value exceeding 1.6 indicates a disproportionate rise in bicarbonate compared to the anion gap, which indicates a metabolic alkalosis is also present.

REFERENCES

1. Carpenter CC. The pathophysiology of secretory diarrheas. *Med Clin North Am.* 1982;66:597–610.
2. McKittrick LS, Wheelock FC. *Carcinoma of the Colon.* Springfield, Ill.: Charles C Thomas; 1954:61.
3. Lepur D, et al. McKittrick-Wheelock syndrome: A rare cause of diarrhoea. *Eur J Gastroenterol Hepatol.* 2006;18:557–559.
4. Shimada Y, et al. Villous tumor of the rectum that started secreting watery fluid after colectomy. *J Gastroenterol.* 2005;40:214–215.
5. Popescu A, Orban-Schiopu AM, Becheanu G, Diculescu M. McKittrick-Wheelock syndrome—a rare cause of acute renal failure. *Rom J Gastroenterol.* 2003;14:63–66.
6. Older J, Older P, Colker J, Brown R. Secretory villous adenomas that cause depletion syndrome. *Arch Intern Med.* 1999;159:879–880.
7. Ashman N, Yaqoob M. Metabolic acidosis, hypokalemia and acute renal failure with a normal urine output. *Nephrol Dial Transplant.* 2000;15:1083–1085.
8. Ranganath LR, Gould SR. Postural hypotension and electrolyte disturbances in a 61-year-old man. *Postgrad Med J.* 1999;75:185–187.
9. DuBose TD Jr. Acid-base disorders. In: Brenner BM, ed. *Brenner and Rector's The Kidney* 7th ed. Philadelphia: Saunders; 2004;921–996.
10. DaCruz GM, Gardner FJ, Peskin GW. Mechanism of diarrhea of villous adenomas. *Am J Surg.* 1968;115:203–208.
11. Babior BM. Villous adenoma of the colon. Study of a patient with severe fluid and electrolyte disturbances. *Am J Med.* 1966;41:615–621.
12. Tizianello A, et al. Renal ammoniagenesis in humans with chronic potassium depletion. *Kidney Int.* 1991;40:772–778.
13. Seldin DW, Rector FC Jr. Symposium on acid-base homeostasis. The generation and maintenance of metabolic alkalosis. *Kidney Int.* 1972;1:306–321.

14. Jacob H, Schlondorff D, St. Onge G, Bernstein LH. Villous adenoma depletion syndrome. Evidence for a cyclic nucleotide-mediated diarrhea. *Dig Dis Sci.* 1985;30:637–641.
15. Pugh S, Thomas GA. Patients with adenomatous polyps and carcinomas have increased colonic mucosal prostaglandin E2. *Gut.* 1994;35:675–678.
16. Steven K, Lange P, Bukhave K, & Rask-Madsen J. Prostaglandin E2-mediated secretory diarrhea in villous adenoma of rectum: Effect of treatment with indomethacin. *Gastroenterology*. 1981;80:1562–1566.
17. Schweinfest CW, Henderson KW, Suster S, Kondoh N, Papas TS. Identification of a colon mucosa gene that is down-regulated in colon adenomas and adenocarcinomas. *Proc Natl Acad Sci USA.* 1993;90(9):4166–4170.
18. Peterson JW, Ochoa LG. Role of prostaglandins and cAMP in the secretory effects of cholera toxin. *Science.* 1989;245:857–859.
19. Beubler E, Schuligoi R, Chopra AK, Ribardo DA, Peskar BA. Cholera toxin induces prostaglandin synthesis via post-transcriptional activation of cyclooxygenase-2 in the rat jejunum. *J Pharmacol Exp Ther*. 2001;297: 940–945.
20. Sladen G. Conservation of fluid and electrolytes by the human gut. *J Clin Path.* 1971;24(5):99–107.