CASE REPORT

Indomethacin therapy effective in a patient with depletion syndrome from secretory villous adenoma

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SUMMARY

This paper details the case of a 26-year-old woman with depletion syndrome and the effectiveness of her treatment with indomethacin. Villous adenomas are benign neoplasms with a high incidence of becoming malignant. A small percentage of villous adenomas are known to cause depletion syndrome, also referred to as the McKittrick-Wheelock syndrome, a condition characterised by secretory diarrhoea, dehydration, hyponatremia, hypokalaemia, hypochloraeaemia, metabolic acidosis and acute renal failure. Prostaglandin-E2 mediates the hypersecretion mechanism observed in depletion syndrome, and can be inhibited by cyclo-oxygenase inhibitors. This case study measured the effectiveness of prostaglandin inhibition on a patient with oral and parenteral electrolyte replacement refractory depletion syndrome. Fluid loss and prostaglandin levels were measured before and after pharmacological treatment. This case demonstrates a 49% decrease in rectal effluent and a marked commensurate decrease in daily replenishment requirements within 48 hours of indomethacin treatment initiation, resulting in subsequent electrolyte stabilisation.

BACKGROUND

Villous adenomas are benign neoplasms with a high incidence of becoming malignant, as high as 35–40%, when compared with the other types of adenomas.^{1 2} These adenomas are mostly located in the rectum and sigmoid colon, measuring even >4 cm.³ A small percentage of villous adenomas are known to cause an electrolyte depletion

syndrome characterised by secretory diarrhoea, dehydration, hyponatremia, hypokalaemia, hypochloraeaemia, metabolic acidosis and acute renal failure. The association between rectosigmoid villous adenomas and depletion syndrome was first described by McKittrick and Wheelock in 1954, and thus depletion syndrome is also referred to as the McKittrick-Wheelock syndrome.⁴ Studies have shown that Prostaglandin-E2 is the mediator for the hypersecretion mechanism observed in depletion syndrome, and that the hypersecretory state can be inhibited by cyclo-oxygenase inhibitors.^{5–7} While the only definitive cure for the McKittrick-Wheelock syndrome is surgical resection of the adenoma,^{3 8} surgical resection is not always feasible or prompt.

CASE PRESENTATION

A 26-year-old woman with medical history of chronic constipation since childhood presented to her primary care physician. One week prior to presentation, she began to feel bloated with diffuse, mild abdominal pressure. Four days prior to presentation, she began to have nausea and non-bloody, bilious emesis four to five times per day. Presently, she reported lightheadedness for 1 day, weakness and fatigue. Review of systems was otherwise normal.

Her primary care physician ran a β human chorionic gonadotropin, revealing the patient to be pregnant with an estimated gestational age of 8 weeks. An in-office chemistry panel revealed a potassium

Figure 1 Daily weight of nappy effluent in grams.

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level of 2.9 mEq/L. The patient was immediately instructed to go to the emergency department for treatment of hypokalaemia.

On presentation to the emergency department, the patient reported that her chronic constipation had worsened over the past 4 years. She reported bowel movements every 1–2 weeks. After using stool softeners per rectum, she had not defecated for 4 days. The patient endorsed rectal pain as well as leaking 'clear liquid' from her rectum earlier in the day.

On physical examination, the patient's vital signs were stable with a blood pressure of 95/55 mm Hg, pulse 90, respiratory rate 18, weight 40.8 kg and a temperature of 37°C. The patient's abdomen was soft, non-tender, non-distended, with no palpable masses. Digital rectal examination revealed soft stool and a clear gel-like substance mixed with blood in the rectal vault, but no masses. Anoscopy also revealed no masses. The patient's initial chemistry panel showed potassium 1.9 mEq/L, sodium 120 mEq/L, chloride 67 mEq/L, carbon dioxide 39 mEq/L, creatinine 1.72 mg/dL, blood urea nitrogen 46 mg/dL and an anion gap of 14 mEq/L.

The patient was admitted to the hospital for management of severe hypokalaemia, hyponatremia and acute kidney injury. Initial MRI of the abdomen and pelvis revealed constipation and faecal impaction in the rectosigmoid colon causing partial large bowel obstruction. The patient's electrolytes were replaced and stabilised, and she was treated for faecal impaction with enemas and laxatives. Once the patient had a bowel movement and her electrolytes were stable, she was discharged home.

Over the next 2 months, the patient had three presentations to the emergency department with two subsequent admissions to the hospital. Each time, the patient reported intractable vomiting, nausea and a clear liquid discharge from the rectum, variably mixed with small amounts of blood. The patient's electrolytes consistently showed hypokalaemia, hyponatremia and metabolic alkalosis. On the third admission, flexible sigmoidoscopy was introduced and revealed a mass in the rectum which was biopsied. After two biopsies did not yield sufficient tissue for pathological diagnosis, the mass was excised. The pathology report of the excised specimen revealed tubulovillous adenoma without high-grade dysplasia or invasion. On surgical removal of the visualised mass, a second larger mass was discovered 8 cm further superior to the anal verge. Surgical removal of the second mass was delayed due to concern for the pregnancy. The patient underwent transverse colon colectomy with right-sided stoma and left-sided mucous fistula creation as a temporising measure until definitive rectal surgery could be performed. She was transferred to a higher level of care for careful observation and eventual caesarean section at 37 weeks, after which the patient was discharged home with oral potassium supplementation and instructions to return in 6 weeks for removal of the second mass.

The patient presented to the emergency department with symptomatic hypokalaemia and accompanying hyponatremia an additional three times, and having failed maximum oral potassium supplementation and potassium infusions via peripherally inserted central catheter line, she was admitted until surgery could be performed.

INVESTIGATIONS

In the emergency department, her chemistry panel showed potassium 2.8 mEq/L, sodium 131 mEq/L, chloride 93 mEq/L, carbon dioxide 23 mEq/L, creatinine 1.39 mg/dL, blood urea nitrogen 47 mg/dL. While admitted, despite daily potassium supplementation by oral and intravenous routes, the patient consistently demonstrated hypokalaemia. At maximum, the patient was receiving potassium supplementation of 160 mEq by intravenous route and 220 mEq by oral route, for a total of 380 mEq daily. Rectal fluid prostaglandin level measured 1230 ng/mL.

DIFFERENTIAL DIAGNOSIS

Depletion syndrome

TREATMENT

The patient was initiated on spironolactone 25 mg by mouth daily. Indomethacin 25 mg by mouth three times a day was then introduced into her care regimen. The total amount of fluid lost per rectum as measured by adult nappy daily weights ([figure 1](#)) was initially 963.9 g and after 48 hours of indomethacin treatment, the amount of fluid lost was 473.4 g. Additionally, the patient's daily potassium requirement decreased from 380 mEq via oral and intravenous routes to 120 mEq per oral only. ([Figure 2](#)) Prostaglandin levels in the rectal fluid decreased from 1230 ng/mL to 1078 ng/mL after 4 days of treatment. Once stabilised, the patient was transferred to a higher level of care.

OUTCOME AND FOLLOW-UP

She underwent complete resection of a rectal villous adenoma, by a low anterior resection, coloanal anastomosis and diverting loop ileostomy. The rectal adenoma measured 13.2 cm in length by 2.5 cm in diameter according to final pathology. She subsequently required no further potassium supplementation.

DISCUSSION

Depletion syndrome was first described in 1954 by the name-sake surgeons McKittrick and Wheelock. Since that time, 1954–2015, a little over 100 case reports have been written pertaining to the condition. A meta-analysis of 18 studies showed that the prevalence of villous adenoma as the pathological type among all colonic polyps was 5.7%.⁹ Of these villous adenomas, a range from 0.76 to 2.4% of them will become secretory in

	BEFORE INDOMETHACIN	AFTER INDOMETHACIN*
Fluid per Rectum	963.9 grams	473.4 grams
Daily Potassium Requirements*	380 mEq IV and oral	120 mEq oral only
Rectal Fluid Prostaglandin Level	1,230 ng/L	1,078 ng/L
* Amount of potassium needed to maintain potassium with normal range		
** 48 hours after indomethacin treatment		

Figure 2 Pretreatment and post-treatment comparison.

nature,⁸ making the prevalence of secretory villous adenoma 0.01% of all colonic polyps.

Although depletion syndrome is characterised by a secretory villous adenoma causing diarrhoea, hypokalaemia, hyponatraemia, hypochloreaemia, metabolic acidosis and pre-renal acute kidney injury, there are many variations of presentation. Commonly, a patient will present with diarrhoea as some part of their history, but that diarrhoea may be chronic in nature occurring over 10–15 years,^{10 11} whereas others have a more recent onset of diarrhoea. The description of diarrhoea may change from patient to patient, with some reporting profuse diarrhoea of more than 10 loose, watery bowel movements per day, while others describe a rectal mucous discharge,¹² or clear mucus stools,¹³ instead of using the word 'diarrhoea'. Additionally, patients may present with signs of intestinal obstruction or pseudo-obstruction rather than diarrhoeal illness.^{14 15} Other presentations seen in the literature include:^{14 16} acute kidney injury, syncope, hypovolaemic shock, weakness, dermatomyositis, rectal prolapse or rectal intussusception. Regardless of the initial presentation, all patients exhibit massive fluid losses, up to 1.5–3.5 L per day, and the losses will increase as the adenoma grows.^{12 17} The secreted fluid is rich in sodium, potassium and chloride depleting these electrolytes in a very acute and severe manner.

Studies have shown that the background colonic mucosa that contains either an adenomatous polyp or adenocarcinoma have increased PGE2 synthesis when compared to control background colonic mucosa.¹⁸ Additionally, *Jacob et al* compared secretory villous adenomas against either carcinoma or non-secretory adenoma and found that the secretory adenoma had increased levels of adenylate cyclase and cAMP. The exact mechanism behind secretory villous adenomas is unknown; however, current belief is that the hyper-secretory state is due to a combination of PGE2 and adenylate cyclase pathways.¹⁹ It has also been shown that cyclo-oxygenase inhibitors such as indomethacin can effectively block PGE2 synthesis and in turn decrease the amount of fluid secreted by affected mucosa.^{6 7}

The definitive treatment is complete surgical resection of the adenoma. In the past, the mainstay surgical option was complete resection of the involved area of the colon or rectum. Today, numerous surgical options are being researched and considered, including endoscopic submucosal dissection.⁸ Even though surgical management is the definitive treatment, it is necessary to correct the severe electrolyte abnormalities that these patients exhibit. Most of the case reports reference using indomethacin as a theoretical option to decrease the fluid losses due to the PGE2-mediated secretory mechanism, but very few report a use of such treatment in their patients.²⁰ *Steven et al*, *Mila et al* and *Huchzermeyer et al* are several cases that detail the use of indomethacin as an electrolyte-stabilising measure for secretory adenoma, a technique that shows to be effective as *Mila et al* reports a decrease in secreted fluid from 1800 to 850 mL.^{7 21 22} Indomethacin may serve as a suitable option for poor surgical candidates or those with a delay in surgical correction, as was the case for our patient who was recently post partum and could not have rectal surgery for another 2 weeks. After she was started on indomethacin treatment, the amount of fluid lost per rectum dropped from 963.9 g to 473.4 g, and the amount of daily replacement of potassium was significantly reduced (figure 2).

Our patient had several unique features: First, she was only 26 years old when diagnosed, whereas the patients in all other reports have been 50 years of age or greater with most over the age of 60 years. Next, our patient presented predominantly with constipation instead of diarrhoea as a prominent feature of her history. After noting that the larger of the two rectal

adenomas was 13.2 cm in size and was obstructive to the colonoscope, she was most likely experiencing a mechanical bowel obstruction secondary to the adenomas. A third unique feature was that our patient repeatedly denied having diarrhoea, but described her experience as an uncontrollable 'leaking of clear fluid' from her rectum that was so severe that she had resorted to wearing adult nappies to catch the fluid.

Patient's perspective

I remember going into the hospital and the doctor started giving me some medications that helped make the leaking stop. I also remember the doctor and medical students collecting my nappies to weigh them. Sometimes I think of all of the people that I met and wonder how they are doing. I am so grateful to them all for saving my life. Our precious girl is healthy with no problems. I am healthy and my last check-up (colonoscopy) was perfectly normal.

Learning points

- ▶ Secretory villous adenomas may cause depletion syndrome.
- ▶ In this patient with depletion syndrome, daily potassium losses were overwhelming the mechanism for potassium replacement.
- ▶ Prostaglandin-E2 mediates the hypersecretion mechanism observed in depletion syndrome, and can be inhibited by cyclo-oxygenase inhibitors.
- ▶ Indomethacin effectively treats the replacement-refractory depletion syndrome and should be considered an early treatment option in secretory villous adenoma.

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