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## HAART toxicity masquerading as a surgical abdomen



Anthony Feghali\*, Yi Wang, Evelyn Irizarry, Meno Lueders

Lincoln Medical and Mental Health Center, Department of Surgery, United States

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## ABSTRACT

**INTRODUCTION:** Intussusception is a rare disease in adults and poses a challenge to identify and manage. In adults, surgical resection is the preferred treatment since half are due to malignancy. This case reveals an association between highly active antiretroviral therapy (HAART) and intussusception.

**PRESENTATION OF CASE:** A 44 year-old female with history of HIV on highly active antiretroviral therapy (HAART) presented with 3 month history of epigastric pain, nausea, emesis, weight loss, and lactic acidosis. CT of abdomen showed two small bowel intussusceptions and pericolic fat infiltration. A diagnosis of mitochondrial toxicity secondary to HAART medication was made. HAART medication was discontinued with resolution of symptoms. Further work-up to exclude a mechanical cause for her symptoms including colonoscopy, small bowel follow through, esophagogastroduodenoscopy, and repeat CT were performed. All established an absence of malignancy and intussusception.

**DISCUSSION:** Mitochondrial toxicity (MT) is a well-known complication of HAART. A hallmark of MT is lactic acidosis which when untreated can be fatal. Although MT is known to cause gastrointestinal symptoms, intussusception has not been previously reported. In our patient with MT, prolonged usage of HAART medication resulted in severe gastrointestinal symptoms and intussusception mimicking a surgical abdomen. Laparotomy has been recommended on adult patients with intussusceptions because of the high likelihood of identifying a pathologic lesion. The doctrine of adult intussusception is to operate for concern of malignancy.

**CONCLUSION:** Surgeons, gastroenterologist and internist caring for patients on HAART therapy must be aware of the possibility of MT when evaluating HIV patients for possible surgical abdomen.

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## 1. Introduction

Intussusception is a rare disease in the adult population and can be difficult to diagnosis and treat. It represents only 1% of all bowel obstructions [1,2]. About 0.003–0.02% of all hospital admission are due to intussusception. Due to its rarity in adults, it poses a challenge to identify and manage. In adults, surgical resection of the intussusception without reduction is the preferred treatment since approximately half are due to malignancy. We present here an unusual case of intussusception in an adult patient with human immunodeficiency virus (HIV) who developed intussusception secondary to highly active antiretroviral therapy (HARRT) manifesting as a pseudo-surgical abdomen.

## 2. Case presentation

A 44 year-old female with past medical history of human immunodeficiency virus (HIV) on highly active antiretroviral therapy (HAART) was referred to the gastroenterologist for a 6 month

history of epigastric pain associated with nausea, vomiting, and an unintentional 37 lb weight loss. She denied diarrhea or changes in her bowel movements. Her last CD4 count was >200 with a viral load of 33,000. She underwent a computed tomography (CT) of abdomen with oral and IV contrast which revealed two intussusceptions of the small bowel as well as circumferential fat halo within the descending colon, sigmoid colon, and rectal walls raising concern for new onset of inflammatory bowel disease [Fig. 1]. However before she could follow-up the pain worsened which prompted her to present to the Emergency Department.

In the emergency room her vital signs were within normal limits. Abdominal examination was significant for epigastric tenderness. Her labs were unremarkable and an abdominal X-ray was unremarkable. She was given intravenous fluids and Metoclopramide 10 mg IV and discharged home with a prescription for Zantac 150 mg twice a day. However she returned to the Emergency Department five days later with similar symptoms and inability to tolerate anything by mouth associated with non-bloody diarrhea. Again her vital signs were within normal limits and abdominal examination showed similar epigastric tenderness. She underwent a repeat computed tomography (CT) of abdomen with contrast which revealed a recurrent short segment of a non-obstructing intussusception of the small bowel [Fig. 2]. She was again given

\* Corresponding author.

E-mail address: [feghalia@upstate.edu](mailto:feghalia@upstate.edu) (A. Feghali).



**Fig. 1.** Initial computed tomography (CT) scan of the abdomen. Cross-sectional image of the mid portion of two intussusceptions (arrows) illustrates small bowel invagination of the small bowel. No evidence of bowel obstruction.

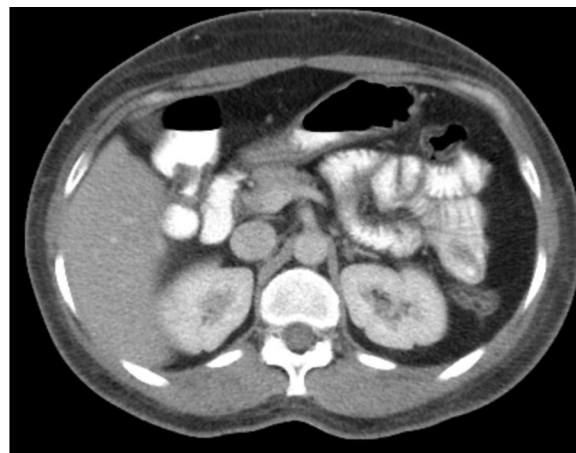


**Fig. 2.** Second computed tomography (CT) scan of the abdomen. Cross-sectional image of the mid portion of again shows recurrent short segment non-obstructing intussusception of the small bowel (arrow).

intravenous fluids and Metoclopramide 10 mg IV and discharged home.

Five days later she represented to the Emergency department with complaints of worsening abdominal pain, muscle pain and weakness, post-prandial vomiting and fatigue. Vital signs were significant for tachycardia and mild hypotension. Exam revealed a thin, ill-appearing woman, with dry mucus membranes, and a softly distended abdomen with moderate upper abdominal tenderness. Computed tomography (CT) of abdomen with contrast no longer visualized the previously seen intussusception [Fig. 3] but demonstrated edematous jejunal loops and diffuse deposition of fat in the colon with pericolic stranding and edema. Laboratory studies revealed a lactate of 4.6 mmol/L. The gastroenterologist recommended surgical consultation for consideration of surgical exploration and resection of the obstructing segment. The patient was admitted to the acute care surgery service with the differential diagnosis of dehydration, inflammatory bowel disease, or malignancy such as lymphoma.

Initial management was gastric decompression with nasogastric tube and intravenous fluid resuscitation. She remained unable to tolerate oral intake although a small bowel follow-through (SBFT) was unable to demonstrate mechanical occlusion. During the following days despite adequate fluid resuscitation a repeat lactate level was again abnormally high at 5.7 mmol/L. A source for type B lactic acidosis was entertained. A metabolic source was excluded



**Fig. 3.** Third computed tomography (CT) scan of the abdomen. The jejunal loops remain edematous but no further intussusceptions.

and drug toxicity or malignancies were considered the most likely sources. Upon further questioning the patient noted that shortly after a change in her HIV medications she was diagnosed with hypomotility and started on the prokinetic agent Doperidone. Her HAART medication was discontinued resulting in normalization of her lactate and regression of her symptoms.

She eventually underwent a flexible sigmoidoscopy, small bowel follow through (SBFT), and esophagogastroduodenoscopy (EGD). Her flexible sigmoidoscopy revealed normal appearing colonic mucosa with biopsies of sigmoid and rectum showing normal colonic mucosa. Further her SBFT was performed to evaluate proximal bowel which showed healthy bowel including both normal transit time and mucosa. Lastly, her EGD only revealed non-erosive gastritis. Capsule endoscopy was considered however with symptoms completely resolved and all other diagnostic workup negative, there was a low indication. Eventually the patient was advanced to a regular diet with no further abdominal pain or emesis, and discharged home with follow-up over the past year showing no further lactic acidosis or intestinal complaints.

### 3. Discussion

Intussusception was first reported by Barbette of Amsterdam in 1674 [1] who not only described the intestinal invagination but also the possibility of surgical reduction. Hunter [2] later defined intussusception as a rare form of bowel obstruction in the adult, which is the telescoping of proximal segment of bowel into a distal segment. However the first successful surgical correction of an intussusception was not described until 1871 by Hutchinson [3].

Today it is the most common abdominal emergency in children younger than two years of age [4], however in adults it's rarely seen. The child to adult ratio is more than 20:1 [5]. Intussusception in children is usually primary and idiopathic [6], while adults usually have intussusceptions secondary to an organic lesion in about 70–90% of cases of which about 20–50% of these cases are due to malignancy [7]. However it has yet to be associated with antiretroviral medications as was seen in this case.

In the colon, intussusceptions is most commonly caused by malignancy, metastatic lesions (from melanoma, breast and lung), leiomyosarcomas, malignant fibrous histiocytomas, lymphomas, carcinoid tumors, adenocarcinoma, Peutz–Jeghers syndrome, Henoch–Schönlein purpura, celiac disease, Crohn's disease. However in the small intestine, intussusception is more likely secondary to benign lesions, inflammatory fibrous polyps, lipomas, leiomyomas, haemangioma, or Meckel's diverticula. Some other reported causes of intussusceptions in adults include trauma and

operative factors (anastomosis sites, adhesions, suture lines, and feeding jejunostomy) [9]. Further adult intussusceptions can be associated with a systemic disease, such as AIDS.

Cases of adult intussusceptions have been commonly reported in HIV patients [10–12]. Wood et al. reported in their study that HIV- and AIDS-associated gastrointestinal pathology provide lead points for intussusception. These patients are at significant risk for intussusception. They conclude that intussusception should be a diagnostic consideration in an HIV-positive young adult with abdominal complaints. Established causes include the correlation between HIV and the increased incidence of pathologic small bowel processes [13] including intestinal Karposi-Sarcoma [14], lymphoma or infections [11]. Small bowel processes in AIDS patients may act as lead points of intussusceptions. In AIDS patients, hypersecretory infectious enteritis can cause intrinsic small bowel inflammation and lymphoid hyperplasia. A motility dysfunction of neuroendocrine origin has been proposed as a mechanism of intussusceptions in those cases where no lead point could be found.

However our patient proved to have no evidence of neoplastic or inflammatory causes of intussusception. Instead she was uniquely seen to have an association between her abdominal findings and her highly active antiretroviral therapy (HAART). Since the dawn of AIDS, gastrointestinal symptoms have been a common aspect of the disease. Despite the advent of HAART in 1995 [18] patients continue to have gastrointestinal symptoms. Of the toxicities associated with HAART, mitochondrial toxicity is recognized as one of the major adverse effects of nucleoside analogue treatments [19].

The exact mechanism of HAART toxicity is not completely known. Nucleoside analogs inhibit HIV replication due to their high affinity for viral enzyme reverse transcriptase, thus inhibiting HIV replication [20]. These nucleoside reverse transcriptase inhibitors (NRTIs) can also bind to other human DNA-polymerases in the mitochondrial DNA. This in turn leads to the impairment of oxidative phosphorylation which causes energy loss (decreased ATP) and an increase of electron leakage thus increasing the production of reactive oxygen species (ROS). As it was seen in our patient, she presented with a Type B lactic acidosis. With mitochondrial dysfunction, the metabolism of pyruvate is shifted to lactate with a decrease in energy production and cellular dysfunction [21]. This hyperlactatemia usually occurs in the absence of systemic hypoperfusion (Type A lactic acidosis). Clinical manifestations of these cellular events include lipodystrophy, myopathy, peripheral neuropathy, lactic acidosis, and hepatic steatosis. Left unrecognized death will ensue.

Intussusception has not been reported as a common effect of the medication. There have been reports of hepatic toxicity and gastrointestinal motility issues [22], yet this case report presents the first of its kind of HAART toxicity associated with intussusception.

One key to the diagnosis of mitochondrial toxicity in our patient was the recognition of a chronic lactic acidosis. Lactic acidosis has been classified by Cohen and Woods into 4 types [23,24]. Type A is hyperlactatemia caused by hypoperfusion and hypooxygenation as seen in shock states. Type B hyperlactatemia has three further subdivisions. Type B-1 is caused by systemic metabolic conditions such as diabetes, renal insufficiency, hepatic insufficiency or malignancies, especially leukemia and lymphoma. Type B-2 hyperlactatemia is secondary to drug toxicity. Well known examples include cyanide, phenformin, ethanol and now anti-retrovirals used in the treatment of HIV. Type B 3 are those hyperlactatenemias secondary to congenital metabolic disorders such as in pyruvate dehydrogenase deficiency.

This patient with a history of HIV on HAART, presented first with symptoms of enteral dysmotility which advanced to intussusception and a surgical abdomen. Initial resuscitation and discontinuation of HAART medications on the suspicion of mitochondrial toxicity were important steps in the recovery of this

patient. However given the risk of malignancy in this population we adhered and recommend that the algorithms for diagnosis and exclusion of a pathologic lesion be followed. Although CT is the most utilized diagnostic tool, studies have shown the benefit of barium enema tests with a diagnostic rate from 54 to 95% [17]. Despite the presentation of a surgical abdomen, the patient was noted to improve with the cessation of HAART. With this conservative management, the intussusceptions rapidly resolved both clinically and on imaging.

In our patient, it was seen that HAART medication, associated with mitochondrial toxicity caused both a lactic acidosis and intussusception. This is a unique case in which prolonged unrecognized toxicity caused by a HAART regimen resulted in severe gastrointestinal symptoms and intussusceptions mimicking a surgical abdomen. Laparotomy has been recommended on adult patients with intussusception because of the likelihood of identifying a pathologic lesion. It is imperative that the surgeon, gastroenterologist and internist caring for patients on HAART therapy are aware of the possibility of mitochondrial toxicity when evaluating HIV patients for possible surgical abdomen. This case challenges the doctrine of surgical intervention for all cases of intussusception particularly in the HIV patient who may be spared unnecessary surgery in mitochondrial toxicity associated cases.

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#### Ethical approval

Have obtained written consent from patient.

#### Author contribution

Feghali Anthon: primary author, composed paper. Wang Yi: performed literature search. Irizarry Evelyn: reviewed and edited paper. Lueders Meno: reviewed and edited paper.

#### Guarantor

Dr. Anthony Feghali.

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