Isolated Severe Gastropathy – an Unusual Presentation of Crohn's Disease in a Child

Roy Nattiv MD[1], Gabriel Dinari MD[1], Jacob Amir MD[2] and Yaron Avitzur MD[1,2]

[1]Institute of Pediatric Gastroenterology and Nutrition and [2]Department of Pediatrics C, Schneider Children's Medical Center of Israel, Petah Tikva, and Sackler Faculty of Medicine, Tel Aviv University, Ramat Aviv, Israel

Key words: gastropathy, stomach, Crohn's disease, infliximab, children

IMAJ 2008;10:322–324

Crohn's disease may involve any part of the gastrointestinal tract, but isolated involvement of the stomach is rare [1]. In common presentations, the diagnosis of Crohn's disease is usually based on a combination of typical clinical, laboratory, endoscopic and pathological findings. However, the diagnosis is difficult to establish in cases of atypical presentation as in isolated gastroduodenal disease. In such a scenario other possible etiologies must be systematically ruled out in order to establish the diagnosis. These may include H*elicobacter pylori* infection, tuberculosis, non-steroidal anti-inflammatory drugs, eosinophilic gastritis, Menetrier's disease, gastrinoma, collagen vascular disease, and lymphoma. Additional diagnostic strategy in atypical cases of inflammatory bowel disease is the use of anti-S*accharomyces cervisia* antibody. This serological marker can be a helpful adjunctive tool in the diagnostic process despite the test's limitations.

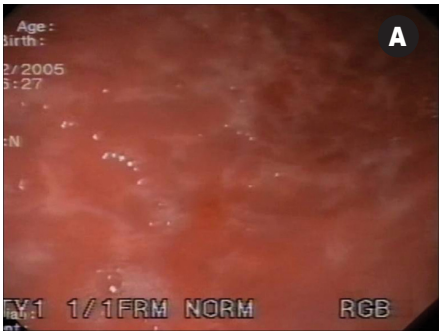
Treatment regimens for gastric Crohn's disease have been poorly studied. The routine treatment of inflammatory gastritis in Crohn's disease includes the concomitant use of acid-suppressive drugs and immunomodulators such as ASA products, or steroids. In recent years infliximab (anti-tumor necrosis factor-alpha) has become an important addition to the therapeutic options in Crohn's disease. The effectiveness of infliximab in isolated gastric Crohn's disease is limited to only a few case reports of adult patients and the long-term outcome is unknown [2,3]. We present a child with isolated gastric Crohn's disease and discuss the diagnostic and therapeutic implications of such a presentation. Ultimately, the diagnosis was supported by suggestive endoscopic and histological findings and the presence of ASCA as a serological marker. Treatment was refractory to steroids and treatment with infliximab resulted in marked gross clinical and endoscopic improvement.

ASCA = anti-S*accharomyces cervisia* antibody

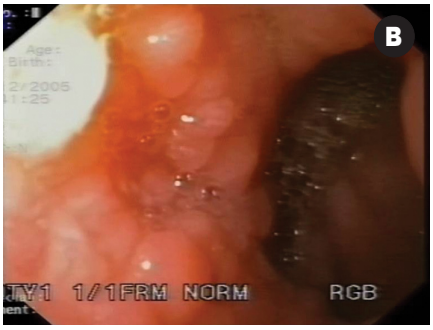
Patient Description

A 13 year old girl was admitted with symptoms of prominent epigastric pain, vomiting, bouts of both constipation and diarrhea, and anorexia with weight loss of 5 kg. For 9 months prior to her admission she was followed at an outside clinic for symptoms of recurrent epigastric pain and constipation. During that period erythrocyte sedimentation rate was elevated (54 mm/hour) while hemoglobin and albumin were within normal limits. Gastroscopy 2 months prior to her admission showed erythema and edema of the gastric mucosa, a single gastric ulcer, pseudopolyps and a cobblestone appearance of the mucosa. Chronic gastritis had been noted on corresponding biopsies; H. *pylori* had not been identified. Although the etiology of these findings was unclear, an empiric trial with prednisone was initiated but was unsuccessful. In addition, one month prior to the child's referral she underwent an appendectomy due to acute appendicitis. Pathological findings demonstrated appendicitis without granulomas. Her past medical history was otherwise normal.

Physical examination on admission revealed localized epigastric tenderness. The rest of the examination was normal. Initial blood work showed mildly elevated C-reactive protein (2.230 mg/dl, normal value 0.0–0.5), and normal ESR, complete blood count, ferritin, iron, and liver function tests. The lack of a definitive diagnosis prompted further endoscopic evaluation, which revealed mild esophageal edema and erythema, severe gastritis [Figure A], gastric pseudopolyps [Figure B], a single antral ulcer and edema with erythema in the duodenal bulb. The second part of the duodenum was normal. Colonoscopy was normal. Corresponding biopsies showed chronic active gastritis with erosion and

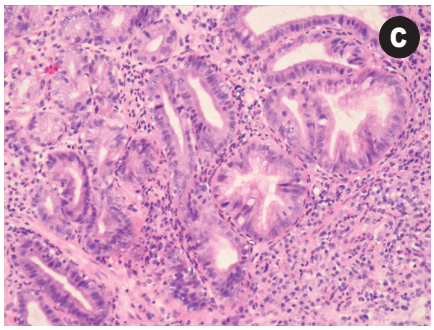


[A] Cobblestone appearance of the gastric body shown on gastroscopy.



[B] Gastroscopy showing antral nodularity and pseudopolyps.

ESR = erythrocyte sedimentation rate



[C] Histopathological stain of gastric mucosa showing moderate chronic active gastritis with regenerative changes (hematoxylin & eosin stain, original magnification x400)

marked regenerative changes; no granulomas were noted [Figure C]. Non-specific acute and chronic inflammatory changes were seen in the duodenal bulb. Colonic biopsies were normal.

Single-contrast barium follow-through showed non-specific findings isolated to the stomach, namely small protrusions and collaring in the lesser curvature of the stomach that may represent small fissures or ulcers and early cobblestoning. The remaining small intestine including the terminal ileum was normal. Further radiological investigation with computed tomography of the abdomen showed widening of the stomach and thickened edematous mucosa in the region of the pylorus without involvement of the remaining gut.

The findings of non-specific gastropathy without involvement of other parts of the intestine and lack of inflammatory markers prompted a systematic workup to rule out a number of possible etiologies including H. *pylori* infection, tuberculosis, Zollinger-Ellison syndrome, collagen vascular disease and lymphoma. Hence, the following tests were done and were found to be within normal limits: Mantoux skin test, silver stain for H. *pylori* on gastric biopsies, serum gastrin levels, serology for anti-neutrophil cytoplasmic antibody and antinuclear antibody, eye examination for signs of uveitis, and blood films. The only intriguing finding during this workup was consistently elevated ASCA titers (63 U/ml, normal range < 10 U/ml).

A diagnosis of isolated gastric Crohn's disease was made based on the endoscopic findings, the exclusion of other possible etiologies, and a positive ASCA test. Treatment with omeprazole and methylprednisolone (60 mg/day) was started but a 2 week course of intravenous steroids achieved only minimal clinical improvement. Second gastroscopy and biopsies following the 2 week treatment were essentially similar to the previous gastroscopy. Due to the lack of response to steroids, a course of infliximab at 0, 2 and 6 weeks was started with concomitant administration of azathioprine. Six weeks after the first dose the patient showed marked clinical and endoscopic improvement. Gastroscopy demonstrated only mild stomach wall nodularity with antral pseudopolyps. No ulcers or erythema were seen. Gastric biopsies showed amelioration of the chronic gastritis compared to the previous biopsies. Laboratory values showed normal ESR, normal hemoglobin, normal albumin and a C-reactive protein of 0.01 mg/dl. One year after the initiation of infliximab treatment the disease has not progressed to the remaining intestine and the child has resumed her normal daily activities. However, repeated infusions of infliximab were required due to recurrent bouts of epigastric pain and appearance of extra-intestinal manifestations including erythema nodosum and monoarthritis of the right wrist.

Comment

In most cases of Crohn's disease the presentation, workup and diagnosis run a familiar and substantiating course. Sometimes, however, this disease can manifest in an entirely non-specific and unusual manner. Uncommon presentations of Crohn's disease may manifest by a single symptom or sign, such as impairment of linear growth, delayed puberty, perianal disease, mouth ulcers, clubbing, chronic iron deficiency anemia – or extra-intestinal manifestations preceding the gastrointestinal symptoms, mainly arthritis or arthralgia, primary sclerosing cholangitis, pyoderma gangrenosum, and rarely osteoporosis. In such cases, the diagnosis is challenging and can remain elusive for some time.

The stomach is rarely the sole or predominant site of Crohn's disease. In a retrospective study of 230 pediatric Crohn's patients 30% of the children had lesions of the esophagus, stomach or duodenum, but only three of them had Crohn's disease isolated to the upper gastrointestinal tract [1]. Although histological changes in the stomach and duodenum may be seen in 20–40% of patients with Crohn's disease, clinically symptomatic proximal disease is only seen in 4% of patients [4]. Even in patients who initially presented with isolated gastroduodenal disease, the majority will develop distal disease over time. In a series of 72 patients with proximal Crohn's disease diagnosed on histopathology, all but one were eventually diagnosed with distal disease as well [5]. Similarly, in another study 56% of patients who presented initially with isolated gastroduodenal disease developed distal disease at a median follow-up of 11.7 years.

To date there are only a few documented case reports of adults with isolated gastric Crohn's disease and no reports in the pediatric population. In one case series, four adult patients with non-healing gastric ulcers refractory to conventional treatment were followed [2], and in another report a 37 year old woman with unusual gastric Crohn's disease was described [3]. In all cases the diagnosis of Crohn's disease was delayed for a long time due to the non-specific presentation of isolated gastropathy.

Normally, the diagnosis of Crohn's disease is based on clinical presentation, radiological abnormalities of the small bowel, gastroscopy and colonoscopy findings, and non-specific or typical pathological features. The abdominal pain and weight loss seen with our patient is by far one of the most common modes of presentation in Crohn's patients, although it is non-specific.

Radiology studies in gastroduodenal Crohn's normally demonstrate similar features to those found in more distal Crohn's disease, such as thickened folds, ulcers, nodularity, stenosis and distorted anatomy. Only mild ulceration of the stomach was noted on a gastrointestinal follow-through in our patient with no pathology found in the remaining gut. Upper endoscopy in gastric Crohn's

may be grossly normal, or it may reveal various combinations of edema, erythema, ulcers, nodularity and cobblestone appearance. The antrum is most frequently involved, while the proximal stomach is often spared. Gastric biopsies have poor specificity and the changes of non-specific gastritis may be seen in other conditions such as H. *pylori* infection. Discovery of granulomatous gastritis might help narrow the differential diagnosis to Crohn's disease, tuberculosis, malignancy, and collagen vascular disease. Interestingly, however, granulomas are only identified in 3–24% of the biopsies and repeat biopsies do not result in higher rates of granuloma discovery [5]. It is no surprise, therefore, that granulomas were absent on repeated biopsies in our patient. However, the marked edematous, inflamed and ulcerated regions with cobblestone appearance and inflammatory pseudopolyps found mainly in the antrum on endoscopy are at least suggestive of Crohn's disease.

In the absence of any other source of disease and in the presence of non-specific upper endoscopy and histological findings, serological testing can play a larger role in the diagnosis of atypical Crohn's disease. Recent studies have suggested that pANCA and ASCA may be used as additional diagnostic tools for patients with suspected inflammatory bowel disease and to help differentiate between Crohn's disease and ulcerative colitis. Indeed, ASCA is detected in 55–60% of children and adults with Crohn's disease and only 5–10% of controls with other gastrointestinal disorders. This finding highlights the relatively good specificity but poor sensitivity of ASCA as a marker for Crohn's disease. pANCA on the other hand is more specific to ulcerative colitis, and the combination of a positive ASCA test with a negative pANCA test has a positive predictive value of 96% and a specificity of 97% for Crohn's disease. In addition, some NOD2/CARD15 gene polymorphisms, particularly L1007P homozygocity, were found to be associated with gastroduodenal Crohn's disease and with younger age at diagnosis. It is possible that these genes might also help to support the diagnosis in the atypical presentation of Crohn's disease in the future.

Infliximab, a monoclonal antibody to TNFα, is often used in cases of steroid refractory Crohn's disease. The role of infliximab in treating patients with gastric Crohn's disease has scarcely been studied. In one case series, infliximab was effective in healing ulcers in two patients [2], but the development of chest cancer in one and surgery in the other necessitated stopping the treatment. In another case study the symptoms in a patient with diffuse mucosal thickening and ulceration throughout the antrum and duodenum continued despite prednisone and a twice-daily dose of a proton pump inhibitor. Treatment with infliximab led to marked improvement within one week [3]. Similarly, in our patient infliximab was effective in both controlling the symptoms and healing gastric ulceration. The effect was temporary and repeated administration of infliximab was needed. Our case and the others described suggest an important role for infliximab in steroid-resistant gastric Crohn's disease.

In summary, we describe a young girl with atypical presentation of isolated gastric Crohn's disease. In atypical cases with non-conclusive clinical, endoscopic and pathological findings, the ASCA test could be helpful in the diagnostic process. Infliximab may be an effective treatment in cases of severe isolated gastropathy due to Crohn's disease.

pANCA = perinuclear anti-neutrophil cytoplasmic antibody

TNFα = tumor necrosis factor-alpha

References

1. Lenaerts C, Roy CC, Vaillancourt M, Weber AM, Morin CL, Seidman E. High incidence of upper gastrointestinal tract involvement in children with Crohn's disease. *Pediatrics* 1989;83:777–81.
2. Grubel P, Choi Y, Schneider D, Knox TA, Cave DR. Severe isolated Crohn's-like disease of the gastroduodenal tract. *Dig Dis Sci* 2003;48:1360–5.
3. Firth MG, Prather CM. Unusual gastric Crohn's disease treated with infliximab – a case report. *Am J Gastroenterol* 2002;97 (Suppl 1):S190.
4. Akbulut S, Yavuz B, Koseoglu T, Gokoz A, Saritas U. Crohn's disease with isolated esophagus and gastric involvement. *Turk J Gastroenterol* 2004;15:196–200.
5. Wagtmans MJ, Verspaget HW, Lamers CB, van Hogezand RA. Clinical aspects of Crohn's disease of the upper gastrointestinal tract: a comparison with distal Crohn's disease. *Am J Gastroenterol* 1997; 92:1467–71.

Correspondence: Dr. Y. Avitzur, Institute of Pediatric Gastroenterology, Nutrition and Liver Diseases, Schneider Children's Medical Center of Israel, Petah Tikva 49202, Israel.
Phone: (972-3) 925-3673
Fax: (972-3) 925-3401
email: yarona@clalit.org.il