Gastric perforation in Crohn's disease in a young female: a case study

by

Rami Bayaa, MD student

St. James School of Medicine

Anguilla Campus

Adviser: Dr. Ramon Manglano, M.D., FACS.

Chicago, Illinois

April 16, 2014

Abstract

Crohn's disease an idiopathic, chronic inflammatory process that usually affects the ileum and the colon, but can occur anywhere along the digestive tract, from the mouth to the anus. Gastric perforations and subsequent generalized peritonitis in Crohn's disease is a rather rare and unusual event in the natural history of the disease. Hence, it is challenging to diagnose the condition clinically as it may mimic an acute abdomen secondary to other common causes such as perforated appendicitis.

There are only a few research articles that address the question of the incidence and prevalence of this life-threatening condition in Chron's disease, a few case-reports and no controlled, prospective treatment studies. We present a course of the disease in 27 year old Caucasian female with a past medical history of Crohn's disease who presented with severe, generalized abdominal pain and tenderness as well as abdominal rigidity from a subsequent generalized peritonitis. Emergency gastric perforation repair with Graham patch was performed. We will try to answer to the following questions: How common is a perforation in Crohn's disease, and where is the perforation most likely to occur? What could be the causes? What are the complications of a gastric perforation? Can they be prevented, and what are the chances of them recurring? Are medications used to treat Crohn's predispose the same one that pose a risk of the developing gastric perforations?

Key words: Chron's disease, Gastric perforation

Introduction

The isolated gastric Crohn's disease is very rare, and gastric perforation as a result of Crohn's almost never happens (2). Crohn's disease of the stomach can lead to mucosal ulcerations, pyloric deformities and even pyloric strictures, giving rise to gastric outlet obstruction. Considered a serious event and one of the indications for surgical intervention, free perforations occur in 1–3% of Crohn's disease patients as a first manifestation or later in the course of the disease (5). Early diagnosis of any perforation is crucial and determines the survival rate. Free air under the diaphragm on upright chest X-ray is indicative of a gastric perforation. A thorough physical exam is exceptionally indispensable in a physician's arsenal of diagnostic tools, and should always come first, even before imaging studies are performed. Thus, if the physician still has strong suspicions of a perforation following an unremarkable physical exam, a computed tomography (CT) of the abdomen should be the next step. The presence of gas or oral contrast outside the intestinal lumen may confirm the diagnosis of an intestinal perforation.

The actual cause of a gastric perforation in a patient with Crohn's disease may be difficult to determine. The ambiguity lies in the factors that lead to ulcerations in the first place. Is it really an isolated gastric involvement of Crohn's disease, or a combination of an acute flare-up compounded by steroid therapy? Free peritoneal perforation of the small or large bowel in Crohn's disease is by far more common than a gastric perforation; however, the mechanism is not entirely understood. Some authors have purported that bowel dilatation above a stenotic area with increasing intraluminal pressure could be the cause (5). Anti-inflammatory therapy such as

steroids and/or immunosuppresants have also been implicated in predisposing individuals to gastric perforations.

Case Report

This case study follows the course of a 27 year old Caucasian female with a past medical history of Crohn's disease who presented with severe, diffuse abdominal pain and tenderness as well as abdominal rigidity. The pain was non-radiating, and had an acute onset. The symptoms were severe, aching, constant and was getting worse. The patient stated that nothing ameliorated the pain, while any movement aggravated it. She had restarted her prednisone prior due to increased disease activity. The patient stated that her mother had given her some Motrin as well to help with the pain, but the pain persisted. Associated symptoms included light-headedness and diaphoresis. She denied any fever, chest pain, or shortness of breath. She has no past surgical history. Vital signs showed no hypotension or tachycardia. She claimed that this pain was not the usual pain she experiences from her Crohn's disease.

In the emergency room, her abdomen was markedly tender, with rebound tenderness. Bowel sounds were present, and there were no pulsating masses. There were no distinguishable features in her personal or family history. The rest of the examination was within normal limits. A CT scan of the abdomen showed antral perforation with mild to moderate amount of free air and free fluid, according to the radiologist report. The diagnosis of generalized peritonitis secondary to gastric

perforation was made. She underwent exploratory laparotomy and repair of gastric perforation with Graham patch.

During the procedure, a 1.5cm anterior gastric wall perforation at the antrum, within 1cm of the pylorus, was found. Upon incision of the abdomen, there was air pushing the peritoneum upward. Opening of the peritoneum revealed a significant amount of contamination due to spillage of stomach content into the abdominal cavity. The ulcer was repaired using a 3-0 Vicryl suture transversely, and a biopsy of the ulcer was sent to pathology. An omental patch was secured anteriorly over the repair, and was secured to the stomach with another 3-0 Vicryl suture. There were no abnormalities seen in the small or large intestines. Prior to closure of the incision, a 10 flat Jackson-Pratt drain was placed just anterior to the repair site and exited through a right lower quadrant incision and secured to the skin with a 2-0 nylon suture. The patient was started on antibiotics and was placed NPO. During her recovery, a nasogastric tube was placed due to abdominal discomfort, and was removed post-operative day 5. Her Jackson-Pratt drain was removed post-operative day 6, and the patient was discharged that same day. Follow-up visit to the clinic a few weeks later demonstrated marked improvement of symptoms, with the only complaint being mild incisional pain.

Discussion

Crohn's disease is an idiopathic, chronic inflammatory process that usually affects the ileum and the colon, but can occur anywhere along the digestive tract, from the mouth to the anus. It is a form of inflammatory bowel disease, not to be

confused with ulcerative colitis. Individuals with this condition often experience bouts of symptomatic relapse and remission. It affects both genders equally and has a bimodal incidence, occurring mostly in the 2nd to 3rd decade of life and, less frequently, during the 6th decade (3). Histologically, the initial lesion starts as a focal inflammatory infiltrate around the crypts, followed by ulceration of superficial mucosa. Later, inflammatory cells invade the mucosal layers and organize into noncaseating granulomas, which extend through all layers of the intestinal wall. The transmural nature of the disease can cause a localized perforation, which may be blocked by adjacent organs, and possibly give rise to fistulas (5). Longitudinal and circumferential fissures and ulcers separate islands of mucosa, giving it a cobblestone-like appearance.

Signs and symptoms of Crohn's disease include rectal bleeding, weight loss, fever, nausea, vomiting, and abdominal pain. Some patients will also experience insidious bouts of diarrhea or constipation. Crohn's disease can also present with extraintestinal manifestations such as erythema nodosum, pyoderma gangrenosum, arthralgias, primary sclerosing cholangitis, and rarely, osteoporosis (10, 14).

A combination of steroid, aspirin derivatives and monoclonal antibodies are the mainstay therapy for Crohn's disease. Those include mesalamine, corticosteroids, 6-mercaptopurine, and infliximab (13). Infliximab, a monoclonal antibody to TNF-α, is often used in cases of steroid refractory Crohn's disease, though its role of infliximab in treating patients with gastric Crohn's disease has scarcely been studied (10).

As mentioned earlier, Crohn's disease affects anywhere from the mouth to the anus, but isolated incidents of the stomach are very rare (10). In isolated Crohn's disease of the stomach, other parts of gastrointestinal tract are unremarkable.

Gastric perforation in Crohn's disease has been considered to be an even more uncommon complication of Crohn's, and usually occurs in association with another pathology, such as peptic ulcer disease. If it does occur, the perforated viscus can spill its contents into the abdominal cavity and irritate the parietal peritoneum, leading to peritonitis. This is characterized by severe generalized abdominal pain and tenderness, a rigid abdomen, fever and even hypovolemic shock, although massive hemorrhage is rare (4). Bowel sounds can be within normal limits or absent. Left untreated, it can lead to death. Hence, free perforation is one of the indications of emergency surgery. According to Werbin *et al*, perforative Crohn's disease is accompanied by more post-operative complications and poor anastamotic healing. Additionally, recurrent disease is more frequent in the short term (up to 5 years) follow-up than obstructive Crohn's disease (4).

During our research, we found a criteria developed by Nugent and Roy for diagnosing gastroduodenal Crohn's disease. They include either:

1) Histologic finding of noncaseating granulomatous inflammation of the stomach or duodenum, with or without concomitant Crohn's disease in the remaining gastrointestinal tract in the absence of other systemic granulomatous disorders;

or

2) Confirmed Crohn's disease of the gastrointestinal tract with radiographic or endoscopic imaging showing diffuse inflammation of the stomach or duodenum consistent with Crohn's disease (9).

Clinically significant gastroduodenal disease occurs in approximately 0.5% to 4% of all patients with Crohn's disease (9). Contiguous gastroduodenal involvement is the most common pattern, with about 60% of patients having diseased antrum, pylorus, and proximal duodenum (9). Since symptoms of gastric Crohn's disease and peptic ulcer disease are very similar, they can be mistaken for one another. Hence, it is vital for the physician to be able to distinguish between them. This is why a meticulous and detailed physical exam is of utmost importance to confirm the diagnosis.

The most common symptom is epigastric pain, nausea, vomiting, anorexia and weight loss (1, 3, 14). Pronounced, continuous abdominal pain associated with nausea and vomiting suggests gastric outlet obstruction due to eventual gastroduodenal stricture formation from chronic damage (9). Such strictures can predispose many to gastric outlet obstruction, for which surgery is required. Patients with peptic ulcer disease can also present with dyspepsia, nausea, vomiting, and epigastric discomfort. Their pain is usually made worse with food ingestion, and resolved with antacid therapy. In stark contrast to peptic ulcer disease, gastroduodenal Crohn's disease is not commonly associated with free perforations. Other differential diagnosis include carcinoma, lymphoma, tuberculosis, sarcoidosis, tuberculosis, eosinophilic gastroenteritis, Zollinger-Ellison syndrome, pancreatitis, and pancreatic cancer (9, 10). Left untreated, these can lead to

perforations. It is also important to rule out causes of gastritis. *Helicobacter pylori* is among the leading causes of gastritis and is responsible for the vast majority of duodenal ulcers. Because our patient had an unremarkable duodenum and had no symptoms of gastroesophageal reflux disease, *H. pylori* is an unlikely source of her perforation. The question still remains, was her gastric perforation a result of her recent steroid use, an active Crohn's flare-up, or a combination of both? According to her pathologist report, the biopsy obtained during surgery showed an ulcerated stomach with acute and chronic inflammation. No granulomas, malignancy or intact mucosa were identified.

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. Recent studies have suggested that perinuclear anti-neutrophil cytoplasmic antibody and anti-*Saccharomyces cervisia* antibody may be used as additional diagnostic tools (10). An upright chest X-ray will reveal free air under the diaphragm in a gastric perforation. Indeed, radiological, endoscopic, and histological findings are required to differentiate between the many differential diagnoses. Radiologic imaging studies normally demonstrate features such as thickened folds, ulcerations, nodularity, stenosis and distorted anatomy (10). A rare, albeit classic, radiographic finding is the funnel-shaped deformity of diseased antrum and duodenal bulb, known collectively as the "ram's horn" sign.

Endoscopy with biopsy, which is ideal for analyzing the mucosa, remains the gold standard in the diagnosis of gastroduodenal Crohn's disease. Microscopic

findings of non-necrotizing (("non-caseating") granulomas is most likely to identify early gastric and/or duodenal involvement (9).

We have found multiple literatures about isolated gastric involvement in Crohn's disease with subsequent perforations. Isolated gastropathies were relatively more common than gastric perforations associated with Crohn's disease. Kefalas (8) presented the case of a 43-year-old Caucasian male diagnosed with ileocolonic Crohn's disease who had undergone a proctocolectomy with resection of 9 cm of distal ileum and an ileostomy. The patient presented with a 2-month history of postprandial fullness, intermittent nausea and vomiting, and midepigastric, crampy abdominal pain that was non-radiating. His ileostomy was unremarkable and he was not taking any medication. The results of the physical exam and laboratory tests were within normal limits. An upper gastrointestinal X-ray demonstrated antral narrowing in addition to a pyloric stricture with narrowing of the second portion of the duodenum. The jejunum and ileum were unremarkable. Endoscopy revealed a normal esophagus. The distal stomach was characterized by mucosal nodularity ("cobblestoning"), scattered ulcerations, and narrowing of the antrum. The patient's duodenum was deformed and ulcerated as well. Biopsies revealed severe granulation tissue, with both acute and chronic inflammation in the stomach and duodenum. No granulomas or *H. pylori* were detected. The patient was treated with steroids and a proton pump inhibitor. The patient's symptoms improved, and repeat endoscopy with biopsies 2 weeks later demonstrated improvement in gastric and duodenal inflammation (9). Mucosal nodularity often arises in gastroduodenal Crohn's, a phenomenon termed "cobblestone."

In a series of 300 patients with Crohn's, Fielding and his colleagues found 12 patients with gastroduodenal involvement (8). In addition to those 12 patients, there were 24 with peptic ulcerations. No gastric perforations were observed.

Ibrahim and his colleagues presented the case of a 26-year-old woman with isolated gastric Crohn's disease. As a consequence of her disease, she had developed gastric outlet obstruction due to stricture formation (11). Again, gastric perforation did not develop in this patient.

We even came across a case study that describes an isolated espophagus and gastric Crohn's in a 35-year-old female who presented with dysphagia, fatigue, nausea and vomiting (13). Cary *et al* reported the case of a 52-year-old woman who was hospitalized because of nausea and vomiting (14). Her Crohn's disease had affected her entire stomach, while also developing a gastrosplenic fistula. The rest of the gastrointestinal tract was normal. Radiological studies showed extensive mucosal ulcerations with a deformed pylorus, while CT scans showed diffuse thickening of the entire stomach wall (14). No perforations were described.

Finally, the youngest patient we encountered in this researched included a 13-year-old girl with complaints of epigastric pain, bouts of diarrhea and constipation, anorexia, and weight loss (15). Endoscopic evaluation demonstrated esophageal erythema and edema, severe gastritis, an antral ucler, and a mildly erythematous duodenal bulb. Colonoscopy was normal. Once again, she did not perforate as a result of her gastropathy.

After an exhausting search for any gastric perforations associated with Crohn's disease, we finally found a few case reports. In one case, three separate episodes of free perforation of the duodenum and stomach are described in a 47-year-old Caucasian male with Crohn's disease, co-existing with peptic ulcer disease. In 1977, 1978, and 1982, three free perforations occurred first in the duodenum and then twice at the gastrojejunostomy site, which he underwent in 1972. This occurred while on continuous Cimetidine and steroids therapy, as well as after vagotomy. This unique situation of acid peptic perforation in the presence of active Crohn's disease poses an etiological dilemma and, according to the authors, signals the vulnerability of the diseased stomach and duodenum in transmural disease (16).

Perforations of the small and large intestines are slightly more common than gastric perforations. Crohn once stated that "free perforation of ileitis into the peritoneal cavity never occurs - or at least I have not seen it (1, 4)." However, it is now generally accepted that 1-3% of patients with Crohn's disease will present with a free perforation initially or eventually in the course of their disease (3, 4). It was interesting to note that free perforations in Japan have been increasing over the years, and the incidence of free perforations in Japan is higher than that of Western countries (17). The incidence of free perforation in Crohn's disease in Japan was between 2.9% and 10.5% (17). Crohn himself reported 7 cases of perforations in 1965 (4). Rai *et al* documented the case of a 23-year-old female who developed generalized peritonitis secondary to an acute perforation of a Crohn's ileitis (3). The true incidence of free perforation is quite difficult to assess, since it is indistinguishable from rupture of intraabdominal abscesses (1). A 10 year

retrospective study of 160 patients with documented Crohn's disease was conducted by Werbin *et al*. Of the 83 patients (52%) requiring surgical intervention, 13 (15.6%) underwent surgery due to free perforation. Their impression is that perforations have been presenting more frequently then they were 20 years ago (4).

According to most research articles we have come across, the vast majority of perforations that do occur have been almost invariably limited to the ileum or jejunum (1, 2, 18). Indeed, spontaneous free perforation was the presenting clinical feature of Crohn’s disease in 60% of the newly diagnosed cases of perforations of the small intestine (18). As stated earlier, isolated gastric involvement is rather rare. Other causes of perforations of the small and large intestines should be sought and ruled out, and they include exacerbation of chronic illness mainly in the distal colon complicated by stenotic disease and dilatation upstream, a fistula, or colorectal cancer associated with perforated Crohn's (5). Small bowel perforations are more common than their larger counterparts. Perforation of the colon may be secondary to toxic megacolon (2). According to Nasr *et al*, of their 41 patients with Crohn's disease, 29 had ileal perforations. Only 3 were in the jejunum (6). Steinberg and his colleagues found that of the 7 perforations documented, 4 were in the ileum, and one was jejuno-ileal in origin (1). Greenstein *et al* investigated the 21 cases of perforation in a study group of 1,415 patients with Crohn's disease. The incidence of perforation in diseased segments of small bowel was 1.0% (includes regional enteritis and ileocolitis), 3 jejunal perforations among 50 patients with jejunitis, jejunoileitis, or jejunoileocolitis (6.0%), and 8 ileal perforations among the 1,156 patients with jejunoileitis, ileitis, or ileocolitis (0.7%). The colon was the site of perforation in 1.3%

of the patients with Crohn's colitis or ileocolitis. There were no gastric perforations. The patient involved in Rai's case study developed a perforation in her terminal ileum.

Of the 13 patients who had perforated bowels in Werbin's study, ten had a perforation in the terminal ileum. Two had perforations of the mid-ileum, and one patient had a perforation of the left colon (4). Ikeuchi and his colleague documented free perforation in 126 patients in a study involving 89 men and 37 women, with ages ranging from 16 to 92 years (17). Free perforation was the presenting sign in 72 of those patients. Seven perforations occurred in the jejunum, 102 in the ileum, and 17 in the colon. Multiple perforations occurred in 13 patients; those patients with multiple perforations were associated with poor prognosis (17).

Though the underlying mechanism for free perforation may not be entirely understood, one explanation is the development of bowel distention with increased intraluminal pressure proximal to an obstruction (2, 5). Another hypothesis points to ischemia as the principal pathogenic factor, which can occur in some cases of toxic dilatation where intramural infarction can lead to perforation (2, 5). Moreover, enteritis of small blood vessels can also contribute to ischemia and an eventual perforation (5).

Anti-inflammatory medications such as non-steroidal anti-inflammatory drugs (NSAID), immunosuppressants, and steroids have been implicated in predisposing individuals with or without Crohn's to perforations. Steroids have been considered to contribute to a breakdown in immune defense mechanisms. The administration of

large doses of steroids may sometimes obscure the clinical picture. Their role in gastric ulcer development and subsequent perforation of the stomach has been well documented. They have been shown to break down the protective mucosal barriers in the stomach and increase acid production, leading to perforations in the long term. Immunosuppressants such as 6-mercaptopurine can compromise one's immune system and lead to opportunistic infections of the gastrointestinal tract and give rise to perforations. Devlin *et al* documented the case of a recurrent gastric perforation in a young male with Crohn's disease that was associated with mucormycosis due to immunosuppression medications he was taking (12). The authors concluded that the case highlights the fact that gastric perforations are rarely due to Crohn's disease, and that an alternate explanation should be sought (12). Steinberg and his colleagues showed that 152 of their 360 patients at risk for perforations in the Birmingham study had been receiving steroids, but stated that steroids were not an important factor in this complication (1). In addition, Rai and his colleagues also showed that their 23-year-old patient was not on steroids prior to her perforation of a Crohn's ileitis, indicating that steroids may not play a significant role as previously thought (3). Werbin *et al* attributed the perforations they encountered partly to the use of steroids as a consequence of prolonged medical treatment (4). Finally, 14 of the 21 patients with free perforations in Greenstein's study (2) had been on steroids before the perforation occurred.

Whether steroid therapy contributes to gastric perforation in those with Crohn's disease is controversial. It is difficult to determine whether the gastric perforation was the result of steroid therapy or from an isolated event from Crohn's disease, however

rare that may be. Ironically, inhaled corticosteroids are used to treat gastric Crohn's disease, and Ibrahim *et al* demonstrated that they appear to be a safe and effective alternative to oral steroid therapy in patients with the abovementioned condition (11). They observed that this approach may provide effective relief long-term while diminishing the side-effects of conventional steroid therapy. It is always prudent to obtain a clear history from the patient and discuss what medications they have been taking. In our case study, it is difficult to pinpoint the exact cause of her gastric perforation. We suspect that she experienced an acute Crohn's flare up that, combined with her steroid therapy and NSAID therapy, exacerbated her condition and may have led to the development of the perforation. It is important to emphasize that anti-inflammatory agents such as steroids or immunosuppressant drug use is not the direct cause of or is the major factor in the development of free perforation; rather, it is implicated in predisposing individuals to such perforations (7).

Surgical approach depends on the site of perforation. Patients should be optimized for surgical intervention, unless it is an emergency. Isolated Crohn's disease of the stomach can lead to pyloric strictures and gastric outlet obstruction, necessitating balloon dilatation. If this initial therapy fails, then surgery is indicated. In gastroduodenal perforations, debridement and primary repair is considered the best management option (5), since resections at this level are complex and require manipulation of the biliary tract. In jejunal–ileal perforations, resection and primary anastomosis is preferred; a diversion ileostomy may be performed if the need arises (5). The management of perforations of the colon will depend on whether the cause is due to toxic megacolon or segmental colitis. In the former case, the preference is

to perform a total colectomy and ileostomy, whereas a segmental resection is preferred isolated colonic disease (5).

However, we firmly believe that surgery should be the last resort to any complication, as it carries many risks and potential complications. That being said, surgery is no doubt indicated in patients with acute abdominal signs such as peritonitis from a perforation, those with multiple and frequent hospitalizations, patients who failed initial medical therapy, hemorrhage from bleeding ulcers, and those complicated fistulas.

Conclusion

Crohn's disease is an inflammatory bowel disease that affects any part of the gastrointestinal tract, from the mouth to the anus. It is characterized by abdominal pain, bloody stools, diarrhea and/or constipation, fever and even extraintestinal manifestations such as arthralgias, pyoderma gangrenosum, and primary sclerosing cholangitis. The disease involves marked inflammatory processes that invade all three layers of the mucosa, predisposing individuals to fistulas, and, quite rarely, a perforation of small or large bowel. Isolated gastric Crohn's disease is a very rare entity, and other differential diagnoses should be sought to rule out other causes of gastric pathologies because presentations are very similar. It is generally accepted that approximately 1-3% of those with Crohn's disease will develop a free perforation, with the small bowel being relatively more common. It is of paramount importance that a clinician be aware of the presenting signs and symptoms of peritonitis due to free perforation of a viscus, and be able to rapidly diagnose peritonitis from

perforation with a careful, concise physical exam. Left untreated, it can be fatal. A physician should be able to order the necessary tests if suspicion of a perforation remains, and promptly refer that patient to a surgeon for an emergency exploratory laparotomy and/or surgery should the diagnosis be confirmed.

This case was no doubt a unique and interesting one, complicated by the fact that the actual cause of the perforation still eludes us. Steroid therapy no doubt has been associated with gastric ulcers and perforations, but it is difficult to establish whether our patient's free perforation was caused by an acute flare of her Crohn's or the use of steroids and her recent NSAID use. Steroids are referenced in many anecdotal reports, but when analyzed critically, no clear association can be demonstrated.

According to our research, most cases of isolated Crohn's disease were treated with a combination of steroids and infliximab, and yielded dramatic improvement. Surgical therapy in gastric Crohn's disease is indicated for ulcers not responding to medical therapy, massive bleeding, in gastric outlet obstructions for which balloon dilatation therapy has failed, or in cases where gastric fistulas have developed (10). Surgical intervention is no doubt indicated in free perforation of any viscus that leads to generalized peritonitis.

Bibliography

1. Steinberg DM, Cooke WT, Alexander-Williams J. Free perforation in Crohn's disease. *Gut* 1973; 14:187-190.
2. Greenstein AJ, Sachar DB, Mann D, Lachman P, *et al*. Spontaneous free perforation and perforated abscess in 30 patients with Crohn's disease. *Ann Surg* 1987; 205:72-76.
3. Rai B, Rai SL, Mikhail M. Generalised peritonitis secondary to an acute perforation of Crohn's ileitis: A case report. *Internet Journal of Surgery* . 2014, Vol. 31 Issue 1, p1-1.
4. Werbin N., Haddad R., Greenberg R., Karin E., Skornick Y. Free perforation in Crohn's disease. *Israel Medical Association Journal*. 2003;5:175–177.
5. Leal RF, Ward M, Ayrizono MLS, Bellaguarda E, *et al*. Free peritoneal perforation in a patient with Crohn's disease - Report of a case. *Int J Surg Case Rep.* 2013; 4(3): 322–324.
6. Nasr, K., Morowitz, D. A., Anderson, J. G. D., and Kirsner, J. B. Free perforation in regional enteritis. *Gut* 1969; 10: 206-208.
7. Fielding JF, Toye DKM, Beton DC, Cooke WT. Crohn's disease of the stomach and duodenum. *Gut*, 1970; 11: 1001 -100
8. Kefalas CH. Gastroduodenal Crohn's disease. *Proc (Bayl Univ Med Cent).* April 2003; 16(2): 147-151.
9. Nugent FW, Richmond M, Park SK. Crohn's disease of the duodenum. *Gut*. 1977; 18:115–120.
10. Ingle SB, Hinge CR, Bhosale SS *et al.* Isolated gastric Crohn's disease. *World J Clin Cases.* May 2013; 1(2): 71-73.
11. Ibrahim SH, Smyrk TC, Faubion WA. Treatment of isolated gastric Crohn's disease with inhaled corticosteroids. *Case Rep Gastroenterol*. 2008 Sept-Dec; 2(3): 363-368.
12. Devlin SM, Hu B, Ippoliti A. Mucormycosis presenting as recurrent gastric perforation in a patient with Crohn's disease on glucocorticoid, 6-mercaptoprin, and infliximab therapy. *Dig Dis Sci* (2007) 52: 2078-2081.

13. Akbulut S, Yavuz B, Köseoğlu T, Gököz A, Saritaş U. Crohn's disease with isolated esophagus and gastric involvement. *Turk J Gastroenterol* 2004; 15 (3): 196-200.

14. Cary ER, Tremaine WJ, Banks PM, Nagorney DM. Isolated Crohn's disease of the stomach. *Mayo Clinic Proceedings.* July 1989; 64 (7): 776-779.

15. Nattiv R, Dinari G, Amir J, Avitzur Y. Isolated sever gastropathy - an unusual presentation of Crohn's disease in a child. *Israel Medical Association Journal* 2008; 10:322–324.

16. Katz S, Talansky A, Kahn E. Recurrent free perforation in gastroduodenal Crohn's disease. *Am J Gastroenterol*. 1983 Nov; 78 (11): 722-725.

17. Ikeuchi H, Yamamura T. Free perforation in Crohn's disease: a review of Japanese literature. *J Gastroenterol*. 2002; 37 (12): 1020-1027.

18. Henry JN, Tesfaye B, Tammana VS, Tyson C, Sanderson A. Jejunal perforation: an unusual presentation of Crohn's disease. *International Journal of Case Reports and Images,* Vol. 4 No. 7, July 2013.