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Short Running Title: GI lymphoma with colonic perforation

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SUMMARY

We present a rare case of primary gastrointestinal diffuse large B-cell lymphoma presenting as a perforation of the descending colon with subsequent retroperitoneal abscess formation. Non-Hodgkin’s lymphomas as a whole represent 0.3% of all colonic malignancies. These neoplasms usually present in older males, and are often associated with infection, autoimmune disease and immunosuppression. Presenting symptoms include non-specific findings such as abdominal pain, decreased appetite, weight loss and anemia. Several cases have reported colonic perforation or obstruction from primary colonic lymphoma, but these events often occur after treatment with chemotherapeutic agents.

A 65-year-old hepatitis C virus positive white male initially presented to a primary care clinic with chronic abdominal pain and recent weight loss of forty pounds. Computed tomography imaging of the abdomen showed an infiltrating locally invasive mass arising from the descending colon and extending into the perirenal space and abdominal wall with evidence of contained colonic rupture. Plans were made for a laparoscopic left hemicolectomy with possible left nephrectomy and abdominal wall resection.

One week after his initial presentation, the patient was admitted to the hospital for sepsis and gram-negative bacteremia. Emergent exploratory laparotomy was performed to remove the affected portions of the colon and debride the retroperitoneal abscess, as these were suspected to be the source of sepsis. Pathologic analysis of the surgical specimen revealed that the perforation was caused by a primary diffuse large B cell lymphoma of the colon. The patient was discharged home in stable condition and was scheduled to follow up with Oncology on an outpatient basis for lymphoma treatment.

Lymphoma should be considered in older men with a history of immunosuppression and viral infections, such as HCV, presenting with signs and symptoms of colon cancer. We emphasize that colonic perforation is a rare, yet important, initial presentation of primary colonic non-Hodgkin’s lymphoma. Surgical intervention is the primary treatment in this scenario to control bacteremia and sepsis, as seen in our patient.
TITLE: A case of primary gastrointestinal lymphoma presenting as colonic perforation

ABSTRACT

Introduction
Non-Hodgkin’s lymphoma represents 0.3% of colonic malignancies. It presents in older males with comorbid infection, autoimmune disease or immunosuppression. Presenting symptoms are often non-specific including abdominal pain, decreased appetite, weight loss and anemia. Colonic perforation or obstruction from primary colonic lymphoma is commonly reported after treatment with chemotherapeutic agents. We present a rare case of primary gastrointestinal lymphoma presenting with perforation of the descending colon causing retroperitoneal abscess formation.

Case Report
A 65-year-old, hepatitis C virus positive, white male presented to primary care with chronic abdominal pain and forty pound weight loss. Computed tomography of the abdomen showed a locally invasive mass arising from the descending colon and extending into both the perirenal space and abdominal wall with evidence of contained colonic rupture.

One week later, the patient presented to the hospital with sepsis. Emergent exploratory laparotomy was performed with removal of the affected colonic section and debridement of the retroperitoneal abscess to control the sepsis source. Surgical specimen pathologic analysis revealed primary diffuse large B cell lymphoma of the colon. The patient was discharged home in stable condition with scheduled outpatient oncologic treatment.

Conclusion
Lymphoma should be considered in older men with a history of immunosuppression and viral infections such as HCV presenting with signs and symptoms of colon cancer. We emphasize that colonic perforation is a rare, yet important, initial presentation of primary colonic non-Hodgkin’s lymphoma. Surgical intervention is the
primary treatment in this scenario to control bacteremia and sepsis, as seen in our patient.

**Keywords:** “diffuse large B cell lymphoma,” “gastrointestinal lymphoma,” “colonic perforation”
INTRODUCTION
Non-Hodgkin’s lymphoma (NHL) represents 0.3% of all colonic malignancies. Diffuse large B-cell lymphoma is the most common histologic subtype. This neoplasm usually presents in older males, and is often associated with infection, autoimmune disease and immunosuppression [1-3]. Presenting symptoms include non-specific findings such as abdominal pain, decreased appetite, weight loss and anemia [3]. Several cases have reported colonic perforation or obstruction from primary colonic lymphoma, but these events typically occur after treatment with chemotherapeutic agents [4-8]. To our knowledge, gastrointestinal diffuse large B-cell lymphoma presenting with colonic perforation has not been previously reported. We present a rare case of primary gastrointestinal lymphoma presenting as a perforation of the descending colon with subsequent retroperitoneal abscess formation.

CASE REPORT
A 65-year-old Caucasian man with a history of hepatitis C virus (HCV) infection, chronic kidney disease, hypertension, on anticoagulation presented to his primary care physician with chronic abdominal pain. The patient also reported a decreased appetite and a forty-pound weight loss over four months. No family history of gastrointestinal or hematological malignancy was noted. The patient had not been previously screened for colorectal cancer. Initial evaluation included abdominal radiographs and laboratory studies. Radiographs demonstrated a mass in the descending colon. Laboratory results were significant for leukocytosis of 14.3 k/uL with normal differential, decreased hemoglobin and hematocrit of 9.9 g/dL and 32.0%, and an abnormal iron study with iron of 16 ug/dL, transferrin of 172 mg/dL, total iron binding capacity of 240.8 ug/dL, and percent iron saturation of 6.6%. The patient’s most recent hepatitis C viral load was greater than seven million. Serum carcinoembryonic antigen and carbohydrate antigen 19-9 values were not measured during his initial workup. The patient was
referred for gastroenterology and surgical consultations along with computed
tomography (CT) and colonoscopic evaluation of the mass.

CT scan of the abdomen with contrast showed an infiltrating locally invasive mass
measuring 7.2 cm x 6.5 cm arising from the mid descending colon with extension
into the perirenal space and abdominal wall musculature. The scan also showed
colic rupture, fistulization to the posterior abdominal wall, and invasion into the left
perirenal space (Figure 1 A, B). Colonoscopy showed a circumferential, friable
obstructive mass in the descending colon fifty centimeters from the anal verge. A
biopsy of the mass was obtained and sent for pathology. Pathology results showed
mucosal ulceration with extensive necrosis and an atypical lymphoid infiltrate (Figure
2 A, B). The biopsy did not depict invasive carcinoma, demonstrated by negative
pankeratin immunohistochemistry. Although there was evidence of acute
inflammation in the biopsy, the biopsy results were concerning for lymphoma. The
majority of the inflammatory cells were lymphoid, predominantly B-cells positive for
CD20 and demonstrating a high proliferative rate as measured by Ki-67 staining.
There was equivocal positivity for BCL-2 and BCL-6. The lymphoid infiltrate was
negative for CD5, CD10, and Cyclin D1.

Chronic colonic perforation was strongly suspected from the imaging and pathology
results. However, the results did not differentiate an infectious versus neoplastic
etiology of the perforation. Further evaluation for suspected malignancy was
conducted because the clinical picture suggested colon cancer with left kidney and
abdominal wall invasion. The patient was referred to Hematology/Oncology and a
PET scan was ordered for further staging workup. PET scan showed a large
circumferential invasive left colon mass extending approximately fifteen centimeters
in length with intense FDG activity concerning for a primary malignancy. The mass
appeared to invade the left kidney cortex, left psoas muscle, and left posterior
abdominal wall muscles. The cecum and right colon showed intense circumferential
FDG activity with no definitive mass, likely secondary to an inflammatory/infectious
process. Plans were made for a laparoscopic left hemicolecction with a possible left
nephrectomy and abdominal wall resection.

One week prior to the scheduled surgery, the patient presented with acute on
chronic left flank pain unresponsive to hydrocodone. He was afebrile, but had a
leukocytosis (24,000) and was unable to ambulate independently. Physical exam revealed exquisite tenderness in the left flank without signs of peritoneal irritation. He was admitted for intravenous antibiotic treatment (piperacillin/tazobactam) and close clinical monitoring. Blood cultures were positive for gram negative rods, thought to be secondary to colonic perforation.

Emergent surgery was planned for retroperitoneal sepsis. The patient was sent to the operating room for an exploratory laparotomy. The entirety of the descending colon spanning from the splenic flexure to the sigmoid was removed and sent for pathologic analysis. During surgery, the descending colon was noted to be firmly stuck to the retroperitoneum and the lateral sidewall. A portion of the abscess cavity was excised and the cavity was debrided. Notably, the cavity had a thick rind with septations and contained gastrointestinal contents. Upon completion of debridement and confirmation of hemostasis, an omental flap was created and used to fill the cavity. A 10 French Jackson-Pratt drain was placed into the cavity. Due to the degree of contamination noted intraoperatively, decision was made to proceed with a Hartmann’s procedure rather than a primary anastomosis. The patient was stable throughout the procedure and was transferred to the surgical intensive care unit for recovery.

Intraoperative frozen section results from the colon specimen showed atypical leukocytes, suspicious for lymphoma. The colonic mucosa was noted to be ulcerated with an atypical small blue cell infiltrate, also suspicious for lymphoma. Definitive features of carcinoma were not identified. The official pathology report showed a final diagnosis of diffuse large B cell lymphoma (DLBCL, CD10 positive germinal center type) (Figure 2, 3). The lymphomatous process was noted to extend through the muscularis propria of the colon into the subserosal adipose tissue, causing subsequent colonic perforation and a left flank abscess (Figure 4). Immunohistochemical stains were positive for BCL-6, CD10 (diffuse, weak), CD79a, and BCL-2 (focal, weak) (Figure 5). The sample was negative for CD30 and Cyclin D1. CD3 and CD5 were positive in the surrounding background T lymphocytes. Ki-67 was markedly increased at 95-99%. Later oncology workup revealed that the patient had a Stage IE DLBCL.
Post-operatively, the patient progressed appropriately and was discharged on post-operative day eight. He was monitored closely for signs of sepsis, but remained afebrile with a steadily declining WBC. On discharge, the patient has normal ostomy function, was tolerating PO intake and had his pain well controlled on oral pain medications. The patient followed up with Hematology/Oncology as an outpatient for further medical treatment of his lymphoma.

DISCUSSION

The gastrointestinal tract is the most common site of primary extra-nodal non-Hodgkin’s lymphoma. The most commonly affected site is the stomach, followed by the small bowel, colon, and esophagus [9]. DLBCL is the most common histological subtype of NHL overall and the most common form of extra-nodal NHL seen in the gastrointestinal tract [10]. However, its low incidence and commonly non-specific symptoms often lead to delays in diagnosis, having a direct effect on morbidity and mortality [1, 11]. Uncommon presentations including colonic perforation increase the difficulty of diagnosis and delay treatment.

Family history, infections, environmental exposures, autoimmune disease, immunosuppression and immunodeficiency are important risk factors for the development of NHL. Specifically, HCV infection has been strongly associated with NHL. Four to 22 percent of patients diagnosed with NHL have a history of hepatitis C with B-cell lymphomas being the most commonly associated subtype [12-15]. Up to 60 percent of patients with DLBCL reported comorbid HCV infection with an average of 15 years between diagnoses [12]. This patient’s longstanding history of untreated HCV placed him at significantly increased risk for the development of NHL.

Evaluation of any patient with abdominal pain begins with a focused history and physical exam. However, the diagnostic accuracy of clinical findings alone is known to be poor [16]. In the setting of abdominal pain and a history of significant weight loss in an older male with HCV, evaluation is guided by a high suspicion for colorectal cancer. Laboratory tests including complete blood count with differential, complete metabolic panel, amylase, lipase, liver function tests, serum iron, total iron binding capacity and ferritin should be ordered. However, no diagnostic laboratory tests for colorectal cancer currently exist. Serum carcinoembryonic antigen (CEA)
and carbohydrate antigen 19-9 (CA 19-9) are commonly measured, but these tests are no longer recommended for colorectal cancer screening or diagnosis [17,18]. CT imaging and colonoscopy are the next diagnostic steps. CT imaging with contrast allows evaluation of the entire bowel and identification of sites of perforation. Colonoscopy allows follow-up localization, biopsy and possibly removal of suspected lesions. Unfortunately, endoscopic findings do not correlate to histologic subtypes of NHL and tissue biopsies are often non-diagnostic for NHL [19]. Diagnosis is often only made after surgical exploration with resection of affected bowel. Bone marrow biopsy is not recommended for extra nodal DLBCL.

Traditional therapy includes a combination of surgery, radiation, CHOP (Cyclophosphamide, doxorubicin, vincristine and prednisone) chemotherapy, and rituximab-based chemotherapy [20, 21]. Concomitant HCV infection necessitates the implementation of additional treatment strategies. Hepatitis C doubles the 5 year mortality in patients with DLBCL. Interferon-based antiretroviral therapy has been associated with an increase in mean survival from diagnosis, regression of indolent DLBCL without the use of chemotherapy, and greater success of first-line chemotherapy protocols [22]. This indicates the importance of screening for HCV infection in NHL patients and need for aggressive management once an infection is identified.

Surgical resection for gastrointestinal DLBCL is only performed in the setting of perforation, obstruction, bleeding, or resistant disease [20, 23]. Bowel perforation is a poor prognostic sign. A 30 percent mortality rate with a mean survival of less than 1 year is directly associated with perforation, particularly in patients suffering bowel perforation after chemotherapy [8]. However, no studies evaluated the prognosis of patients presenting with bowel perforation compared to non-perforated patients. The literature also does not delineate the outcomes of patients with colonic perforations before versus after radiation treatment. Further research is needed to clarify the treatment outcomes and prognosis of patients presenting with colonic perforation secondary to DLBCL.
CONCLUSION

Lymphoma represents a minority of primary gastrointestinal cancers and usually presents with an insidious onset of non-specific symptoms, such as weight loss, fatigue, anemia, and abdominal pain. Colonic lymphoma most commonly presents in older men, the same demographic as colonic adenocarcinoma. However, when an older man presents with signs and symptoms of colon cancer, lymphoma should be considered, particularly in patients with a history of immunosuppression and viral infections such as HCV. We also emphasize that colonic perforation is a rare, yet important, initial presentation of primary colonic non-Hodgkin’s lymphoma. This is a dangerous scenario that can lead to rapid development of bacteremia and sepsis, as seen in our patient. Timely surgical intervention is of utmost importance in these cases.

CONFLICT OF INTEREST

The authors have no ethical conflicts to disclose.

AUTHOR’S CONTRIBUTIONS

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Group 1 - Conception and design, Analysis and interpretation of data
Group 2 - Drafting the article, Critical revision of the article
Group 3 - Final approval of the version to be published

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REFERENCES


**FIGURE LEGEND**

Figure 1: (A, B) - Representative slices from computed tomography (CT) imaging showing an infiltrating, locally invasive mass measuring 7.2 cm x 6.5 cm arising from the mid descending colon. It extends posteriorly through the perirenal space to invade the left posterior abdominal wall musculature with colonic rupture, fistulation to the posterior abdominal wall, and invasion into the left perirenal space.
Figure 1: (A, B) - Representative slices from computed tomography (CT) imaging showing an infiltrating, locally invasive mass measuring 7.2 cm x 6.5 cm arising from the mid descending colon. It extends posteriorly through the perirenal space to invade the left posterior abdominal wall musculature with colonic rupture, fistulation to the posterior abdominal wall, and invasion into the left perirenal space.

Figure 2: Low power image of effaced atypical lymphoid proliferation consistent with lymphoma.

Figure 3: High power image of effaced malignant large B-cells consistent with lymphoma.

Figure 4: Low power image depicting lymphoma at area of colonic perforation.

Figure 5: CD79a B-cell immunohistochemistry demonstrating diffuse staining.

FIGURES
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