



CASE REPORT



An unusual presentation of non-IBD related colorectal primary extranodal diffuse large B cell lymphoma with a colo-colonic fistula

Rima Nakrani ^a, Ho-Man Yeung ^a, Matan Arnon^a, Alexandra Selby^a, Christine Burgert-Lon^b and Bhishak Kamat^c

^aDepartment of Medicine, Temple University Hospital, Philadelphia, PA, USA; ^bDepartment of Pathology, Temple University Hospital, Philadelphia, PA, USA; ^cDepartment of Radiology, Temple University Hospital, Philadelphia, PA, USA

ABSTRACT

Diffuse large B cell lymphoma of the sigmoid colon and rectum is relatively uncommon and aggressive. Due to its nonspecific symptomatology, patients are often diagnosed late into the disease and present with life-threatening complications, such as hemorrhage, obstruction, or perforation, requiring emergent surgical intervention. Patients with colorectal lymphoma typically have inflammatory bowel disease or immunosuppression. We present a case of a 79-year-old male with no known inflammatory bowel disease or immunosuppression, who had significant weight loss, diarrhea, and abdominal fullness, found by CT to have irregular wall thickening of the recto-sigmoid colon along with a colo-colonic fistula, concerning for bowel perforation. Endoscopic evaluation and biopsy confirmed the diagnosis of recto-sigmoid Diffuse large B cell lymphoma, with a PET/CT scan revealing stage IV disease. He had a partial response to six cycles of palliative reduced dose R-CHOP and is currently receiving palliative radiation to the sigmoid colon and rectum. Surgery and/or chemoradiation remain the mainstay therapy for this condition. Clinicians, however, must consider patient's functional, nutritional, and clinical status prior to choosing an optimal therapeutic regimen. This case illustrates a unique clinical presentation of this condition and the associated diagnostic and therapeutic challenges that arise in order to prevent life-threatening complications.

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1. Introduction



Diffuse Large B cell Lymphoma (DLBCL) is the most common type of non-Hodgkin lymphoma (NHL). It is a more aggressive form compared to the more indolent subtypes, such as follicular lymphoma [1]. DLBCL can present as nodal or extranodal disease. Among the extranodal sites, the gastrointestinal tract is the most common with colorectal involvement accounting for 10 to 20% of all GI lymphomas [2,3]. In contrast to the cecum being the most common site, recto-sigmoid involvement is relatively rare, accounting for approximately 10% of colorectal lymphoma cases [4]. The most important risk factors in the development of colorectal lymphoma include immunosuppression and inflammatory bowel disease (IBD) [4]. The symptomatology of colorectal lymphoma includes but is not limited to fevers, night sweats, fatigue, and weight loss. Depending on the colorectal portion compromised, patients may additionally present with a palpable mass, gastrointestinal bleeding, diarrhea, abdominal pain, change in bowel habits or obstruction. Histologic and flow cytometric analysis of the biopsied specimen remains the gold standard for diagnosis [5]. Due

to its nonspecific presentation and aggressiveness, diagnosis is often made late into the disease course.

Recto-sigmoid DLBCL is extremely rare and, as such, not many cases have been reported. Therefore, the scope of clinical presentations and its management have yet to be explored in its entirety. We present a case of a 79-year-old male with no history of IBD or immunosuppression who was found to have primary extranodal DLBCL of the sigmoid colon with a colo-colonic fistula upon presentation. This case demonstrates the variety of clinical presentations and diagnostic challenges of this rare disease.

2. Case presentation

A 79-year-old Caucasian male presented to his primary care physician for progressive weight loss and intermittent diarrhea. The patient experienced subjective weight loss of approximately 45 kg over a period of seven to eight months. While undergoing preparation for an outpatient colonoscopy, he experienced pre-syncope and presented to the emergency department. He endorsed nausea, diarrhea, and recent anorexia. He also complained of lower abdominal pressure without significant pain that began

CONTACT Rima Nakrani  Rima.Nakrani@tuhs.temple.edu  Department of Medicine, Temple University Hospital, 3401 N Broad St, Philadelphia, PA 19140

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several weeks prior to presentation. He denied any fevers, chills, night sweats, dysphagia, odynophagia, melena, hematochezia, or rectal pain. His bowel habits had been irregular, alternating between constipation and loose stools. In addition, he endorsed fecal urgency and occasional fecal incontinence.

His past medical history includes hypertension, hyperlipidemia, hypothyroidism, two cerebral arteriovenous malformations, and transient ischemic attack. He has a history of chronic tobacco use but denied alcohol or recreational drug use. He denied a family history of inflammatory bowel disease or hematological or oncological disorders. Four months prior to presentation, he underwent an emergency laparotomy for repair of a large strangulated umbilical hernia. His last colonoscopy was five years prior to presentation and was notable for severe sigmoid diverticular disease and a small benign polyp, although the preparation was suboptimal. On physical examination, he was awake, alert, and oriented to person, time, and place. He was in no acute distress, but thin appearing. Bowel sounds were normal. A midline laparotomy incision from his hernia repair appeared well healed and clean with well-approximated edges. His abdomen was soft with no palpable mass and he had suprapubic tenderness only to deep palpation. Laboratory results were significant

for a leukocytosis of 27 K/mm^3 , acute kidney injury with a creatinine of 1.55 mg/dL , and a lactic acidosis of 2.3 mmol/L .

A CT of the abdomen and pelvis with contrast revealed mass-like mural thickening of the sigmoid colon concerning for colorectal neoplasm with a new large stool-containing collection superimposed on matted loops of inflamed large bowel suspicious for a contained perforation and a colo-colonic fistula (Figure 1). In addition, bladder wall thickening was noted, which was felt to be due to reactive cystitis given the adjacent bowel findings and enlarged retroperitoneal lymphadenopathy (1.0 cm aortocaval lymph node, 1.0 cm left peri-aortic lymph node, 1.2 cm left pericolic lymph node noted adjacent to the left-psoas muscle) as well as indeterminate splenic lesions. These findings were suspicious for malignancy versus local inflammation, including possible diverticulitis. Compared to CT of the abdomen and pelvis four months prior, there had been an interval worsening of the irregular wall thickening of the recto-sigmoid colon and increase in bladder wall thickening (Figure 1). Gastroenterology and general surgery evaluated the patient and were concerned about an underlying malignant process versus perforated diverticulitis with subsequent abscess

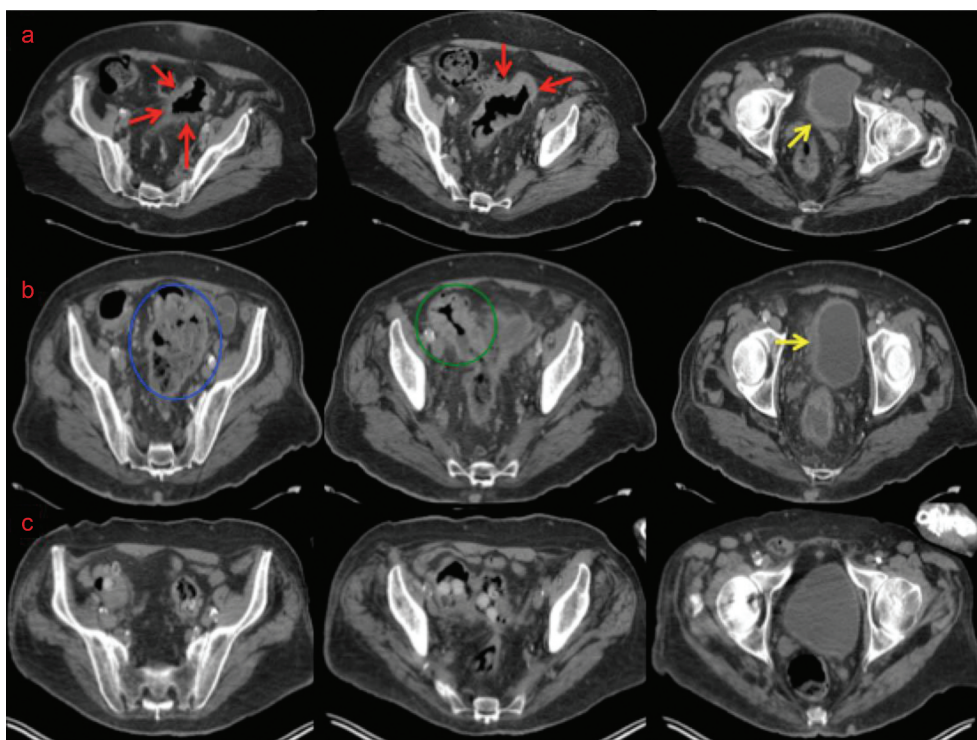


Figure 1. Row A: CT scan four months prior to recto-sigmoid DLBCL diagnosis showcasing mild irregular wall thickening of the recto-sigmoid colon (red arrows) and bladder (yellow arrow). Row B: CT at the time of diagnosis demonstrating significant irregular wall thickening of the recto-sigmoid colon with a large stool-containing collection superimposed on matted loops of inflamed large bowel (blue circle). Center image exhibits a colo-colonic fistula between cecum and rectum (green circle). Third image displays worsening circumferential wall thickening of the bladder (yellow arrow). Row C: Six months post-chemotherapy CT illustrates less wall thickening of the sigmoid colon in the colorectal junction with a smaller area of involvement. The tumor burden is moderately to significantly lower due to smaller soft tissue involvement.

formation, which may have drained spontaneously and now filled with stool since he had fairly severe sigmoid diverticular disease on his last colonoscopy. Clostridium difficile testing was negative. A carcinoembryonic antigen (CEA) level obtained at this time was normal at 0.9 ng/mL. An HIV fourth generation test was nonreactive. A flexible sigmoidoscopy revealed a circumferential mass in the recto-sigmoid extending 8 cm to 25 cm from the anal verge with necrotic tissue and mass-like features. Multiple biopsies were obtained from the sigmoid colon at 25 cm and 20 cm from the anal verge and the rectum at 8 cm from the anal verge.

Pathologic review revealed Diffuse large B-cell lymphoma (DLBCL), activated B-cell type (ABC, non-germinal center) in recto-sigmoid biopsies (Figure 2). Immunohistochemical stains demonstrated that the tumor cells were positive for PAX5, CD19, CD20, MUM1, BCL6 (about 40%) and c-Myc (about 30–40%). Tumor cells were negative for CD10, CD21, CD56, CD57 and BCL2. Ki-67 demonstrated a proliferative rate of about 60%. CD2, CD3, CD5 and CD7 highlighted T-cells. FISH studies were negative for t(8;14), BCL2-IGH t(14;18) and BCL6 (3q27) breakpoint translocations.

The patient improved during his hospital course, although he remained weak and malnourished. It was deemed that the patient was not a good surgical candidate, and he was discharged with home palliative care with a plan to proceed with oncologic evaluation for outpatient chemotherapy treatment. He was given metronidazole and cefuroxime to complete his antibiotic therapy and loperamide for diarrhea along with his home medications.

3. Follow up

The patient followed up with hematology-oncology as an outpatient and decided to proceed with chemotherapy. A PET/CT scan was obtained prior to initiation of chemotherapy to complete staging. PET scan revealed intense foci of FDG activity in the sigmoid colon and rectum, several pulmonary nodules, the left lateral posterior aspect of the prostate and mesenteric lymph nodes, suspicious for malignant involvement (Figure 3). Given extranodal and stage IV disease, there was no indication for a bone marrow biopsy prior to the treatment. Reduce-dose R-CHOP (rituximab-cyclophosphamide, doxorubicin, vincristine, and prednisone) therapy was recommended over conventional R-CHOP due to the patient's poor performance status (Eastern Cooperative Oncology Group 3) and advanced age. He required close monitoring while on chemotherapy due to high risk of colonic perforation and infectious complications, particularly given the presence of a colo-colonic fistula.

He tolerated six cycles with some fatigue and orthostatic hypotension requiring intravenous fluids. He received G-CSF support throughout his treatment with pegfilgrastim and prophylactic acyclovir. Following completion of six cycles of reduce-dose R-CHOP, repeat PET/CT showed decreased uptake and thickening of the sigmoid colon and colorectal junction. There was resolution of the small lesions in the lower abdomen and pelvis (Figure 3). This was consistent with partial response to chemotherapy with definite lower tumor burden. Following the completion of chemotherapy, patient was evaluated by radiation oncology and is currently undergoing

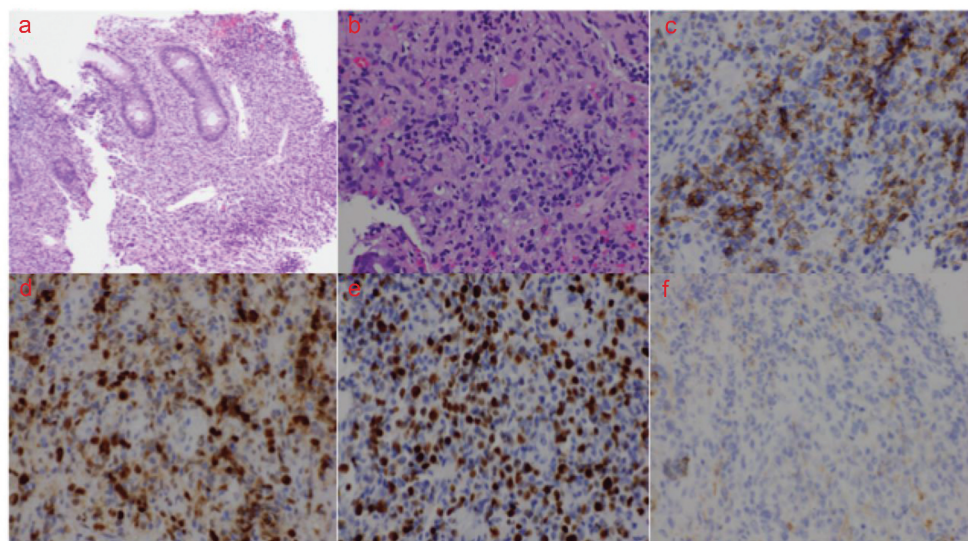


Figure 2. A, B: Sections of the rectosigmoid mass biopsies demonstrate ulcerated and inflamed colonic mucosa with a distinct population of large mononuclear cells within the lamina propria. Neoplastic cells are positive for C: CD20, D: BCL6 (~40%) and E: MUM1, and are negative for F: CD10 (hematoxylin-eosin, original magnification X100 [A] and X400 [B]; original magnification X400 [C, D, E, F]).

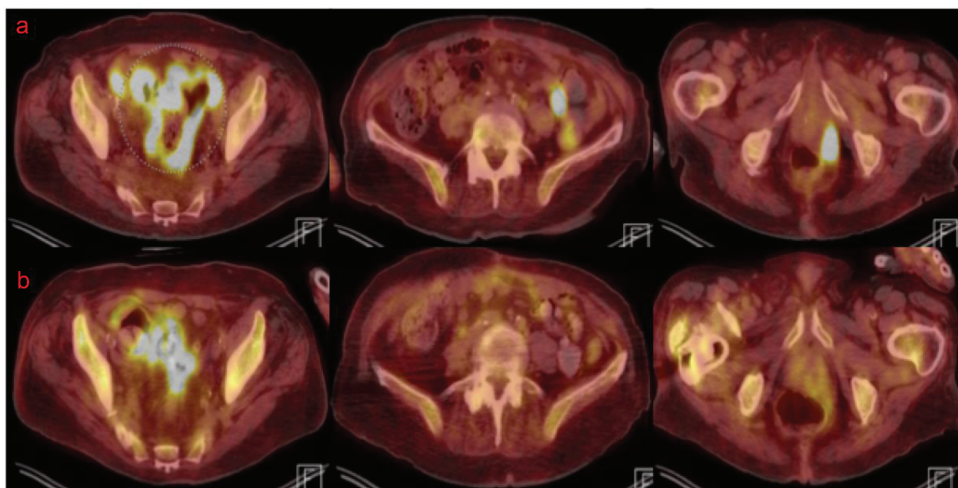


Figure 3. Row A: Pre-chemotherapy PET scan showed intense FDG activity in the sigmoid colon and rectum, mesenteric lymph nodes, and the left lateral posterior aspect of the prostate. Row B: Six months post-chemotherapy PET scan denotes decreased intensity of FDG activity in the sigmoid colon and colorectal junction and resolution of small lesions in the lower abdomen and pelvis.

consolidative radiation therapy, mainly targeting the recto-sigmoid colon.

4. Discussion

Primary colorectal DLBCL typically presents with vague and variable symptoms and as a result, the diagnosis can often be challenging [6]. The patient in our case exhibited prominent weight loss and a change in bowel habits concerning for colorectal malignancy. A CT of the abdomen/pelvis with contrast was initially concerning for perforated diverticulitis with abscess formation, especially in the setting of a history of diverticular disease. Relying solely on radiographic findings may have led to an incorrect diagnosis. Biopsies obtained via endoscopy remained the diagnostic gold standard. As colorectal lymphoma is difficult to diagnose, life-threatening complications such as obstruction, perforation, or hemorrhage may occur requiring emergent surgical intervention [7,8]. Thus, endoscopic evaluation is preferable in the absence of life-threatening complications or hemodynamic instability for all patients that present with alarming symptoms (i.e., significant unintentional weight loss or a change in bowel habits) rather than relying on imaging alone.

This case is unique due to its rapid progression within four months and the diagnosis of DLBCL with a colo-colonic fistula without a history of inflammatory bowel disease or immunosuppression. The handful of case reports on colorectal lymphoma causing fistulae formation denote associated risk factors (i.e., IBD, HIV, immunosuppressive therapy) or a life-threatening perforation at presentation, which was not the case for our patient [8–10]. The etiology of fistula formation is unknown; however, it has been

postulated that the absence of a desmoplastic reaction following full thickness bowel wall destruction in cases of primary colorectal lymphoma may underlie fistula creation [9]. Moreover, cytotoxicity from chemotherapy can also lead to fistula formation [11,12]. Fortunately, our patient did not experience infectious complications or perforation of his colo-colonic fistula while on chemotherapy. Our case demonstrates that early diagnosis can prevent life-threatening complications such as perforation, and close monitoring can prevent complications of treatment.

Primary colorectal DLBCL is a rare entity and effective frontline treatment of this condition (i.e., chemoradiotherapy or upfront surgery) has always remained a topic of controversy. Patients with complications, such as perforation, obstruction, or hemorrhage necessitate emergency surgery. Otherwise, clinical and tumor features should be taken into account in non-emergent cases [13]. Some investigators believe that surgery may provide better prognostication, enhance survival outcomes, and reduce the likelihood of future complications. Other authors believe that chemotherapy is adequate to achieve disease control [14]. However, localized disease (Stage I and II) fares better with surgical resection followed by R-CHOP chemotherapy, whereas unresectable disease (Stage III and IV) typically requires a full six cycles of R-CHOP chemotherapy followed by radiation for bulky disease [5]. Nevertheless, as with the treatment of all conditions, the risk and benefits must be weighted along with other factors including age, performance status, clinical condition and comorbidities, and patient/family preferences. In our case, the patient had advanced age, poor nutrition, poor performance status, and advanced stage IV disease. The patient and his

oncologist elected for chemoradiation with reduced dosage and close outpatient monitoring for potential complications.

5. Conclusion

We report this case to demonstrate a rather rare and aggressive presentation of primary colorectal Diffuse large B cell lymphoma associated with a colo-colonic fistula in a patient with no known risk factors. Colorectal DLBCL often has nonspecific symptoms and is diagnosed late into the disease course. Endoscopic evaluation and direct tissue biopsy is necessary for early diagnosis. Emergent surgical intervention is needed if the patient demonstrates evidence of perforation, hemodynamic instability, hemorrhage, or bowel obstruction. Close monitoring during chemoradiation is of utmost importance to further reduce the chances of infection or perforation when a fistula is present. R-CHOP remains the mainstay of systemic treatment. A thorough review of the risks and benefits of each treatment modality is imperative and must be carefully considered with each patient.

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RN, HY, MA drafted the manuscript. CB provided pathological images and pathologic description. All authors revised the manuscript and approved the submission of this draft.

ORCID

Rima Nakrani  <http://orcid.org/0000-0001-7820-9048>
Ho-Man Yeung  <http://orcid.org/0000-0002-7188-9738>

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