Gastrointestinal Perforation after Rituximab Therapy in Mantle Cell Lymphoma: A Case Report

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Abstract
Mantle cell lymphoma (MCL) is a rare form of non-Hodgkin lymphoma (NHL), responsible for 2.8% of all NHL cases within the United States. The majority of patients with MCL present with advanced disease, 10-20% of which have extra-nodal involvement at diagnosis. The gastrointestinal presence of lymphoma can lead to gastrointestinal perforation, resulting in significant morbidity from peritonitis and sepsis while prolonging hospitalizations and delaying treatment. In this case we discuss a 55-year-old male with newly diagnosed MCL who developed peritonitis 9 days after initiation of dose reduced rituximab due to gastrointestinal perforation. Although prognostication factors for MCL such as the mantle cell lymphoma international prognostic index (MIPI) score exist, further research is needed to stratify risk factors for morbid treatment complications such as gastrointestinal perforation.

Introduction
Mantle cell lymphoma (MCL) is a rare and incurable form of non-Hodgkin lymphoma (NHL), responsible for 2.8% of all NHL cases within the United States. MCL’s name stems from the originating neoplastic cells which occupy the ring of lymphocytes surrounding a germinal...
center called the mantle zone [1]. MCL occurs preferentially in both males (2:1 ratio) and adults, with a median age of diagnosis at 68 years old [2, 3]. MCL’s pathognomonic genetic signature is a single chromosomal translocation t(11;14)(q13;q32) that results in the overexpression of cyclin D1 protein that drives the pathogenesis of this lymphoma [4]. One of the most acute causes of sepsis and morbidity in treatment of intra-abdominal lymphomas is gastrointestinal perforation. Here we present a case of gastrointestinal perforation after initial treatment of MCL and review of pertinent literature.

**Case Report**

**Presentation**

A 55-year-old male presented to the emergency department with nausea, vomiting, abdominal discomfort and 18 kg unintentional weight loss over 6 months. He denied hematemesis, constipation, diarrhea, hematochezia and melena. The patient had no previous medical history, no family history of malignancy, and denied any history of alcohol or illegal drug use.

**Assessment**

On examination the patient’s vital signs were within normal limits. He was cachectic with bi-temporal wasting. His cardiopulmonary exam was normal; however, a palpable mass was identified in his right upper quadrant without rebound tenderness or distension. He had notable lymphadenopathy bilaterally in both his anterior and posterior cervical lymph nodes, all less than 1 cm, as well as bilateral inguinal lymphadenopathy. He had no pedal edema, and no focal neurologic deficits.

Initial complete blood count was notable for anemia with a hemoglobin of 10.4 g/dL (NR 13.2–18 g/dL), thrombocytosis of 566 K/mm³ (NR 150–450 K/mm³) and a normal white blood cell level of 10.7 K/mm³ (NR 4–11 K/mm³). Further laboratory testing revealed normal levels of carcinoembryonic antigen of 3.2 ng/mL (NR 0–5.0 ng/mL), cancer antigen 19–9 of 13.7 U/mL (NR 0–4.1 U/mL) and Beta 2 Microglobulin of 1.7 mg/L (NR 0.6–2.4 mg/L). He tested negative for human immunodeficiency virus as well as hepatitis B and C.

An abdominal computerized tomography (CT) scan (Fig. 1) revealed a large 13 × 10 × 12 cm mass in the right upper quadrant causing mass effect on adjacent structures as well as multiple mesenteric lesions, and a 1.5 cm left ureteral nephrolithiasis.

**Diagnosis**

A colonoscopy visualized a large polypoid tumor in the ascending colon and hepatic flexure (Fig. 2). The tumor was characterized as grossly nodular, friable, ulcerated and non-obstructive. Biopsies revealed a dense lymphoid infiltrate with monocytoid features infiltrating the lamina propria and extending to surrounding glandular elements. Histology (Fig. 3) was positive for significant CD20 staining, and CD43 co-expression on B cells. CD5 stained positive on scattered T cells, and both CD3 as well as CD10 were negative. Ki-67 stained 25–40% of the tissue sample. Fluorescent in situ hybridization using a dual color, dual fusion CCND1(BCL1)/IgH probe revealed t11;14 translocation with 34% double fusion (1R1G2F, normal <0.5% signal) indicative of mantle cell lymphoma. Bone marrow biopsy revealed an appropriately mixed population of maturing myeloid cells, B-cells and T-cells without increase of CD34+ blasts and 40% cellularity of the bone marrow.
Clinical Course

A CT scan of the chest with IV contrast revealed a 11 × 43 mm thrombi in the ascending thoracic aorta for which therapeutic enoxaparin 1 mg/kg twice daily was started. The patient’s Eastern Cooperative Oncology Group score rapidly increased from 1, a limited ability to perform daily strenuous activity, to 3, where the patient remained bedridden >50% of the day. The patient was advised of risks of chemotherapy, and agreed to proceed with rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone (R-CHOP).

The patient was given rituximab at 50% dose reduction, CHOP at 25% dose reduction and prophylactic allopurinol. He received multiple doses of filgrastim to mitigate neutropenia. Nine days later the patient developed feaculent emesis secondary to symptomatic bowel obstruction. CT imaging revealed free intraperitoneal air consistent with intestinal perforation. Enoxaparin was discontinued, and Piperacillin-Tazobactam started for treatment of presumed intra-abdominal bacterial seeding. The patient tested positive for multiple blood cultures of Escherichia coli without antibiotic resistance and was started intravenous nutrition on while on total bowel rest. Free abdominal air resolved within days, however a loculated fluid collection developed in the right hemipelvis and required placement of a percutaneous drain. With continued medical management the patient did well. Four months after his abdominal perforation the patient clinically improved and increased his weight from 50 kg on admission to 71.2 kg. A positron emission tomography after the first cycle of R-CHOP demonstrated a hypermetabolic solid intraluminal 9.2 × 8.4 × 10.8 cm mass, along with multiple <1 cm metabolically active retroperitoneal and mesenteric nodes.

Discussion

Unfortunately, at time of diagnosis approximately 75% of MCL patients present with Ann Arbor Stage III or IV disease, extensive lymphadenopathy and bone marrow involvement. Splenomegaly is present in approximately 80% of cases, and 10–20% of patients will have involvement of extra-nodal sites such as the gastrointestinal tract, breast, pleura or orbits [1, 3, 5]. Tissue pathology remains a standard for diagnosis, with histopathology playing a critical role. MCL typically expresses mature B cell markers as well as surface immunoglobulins IgM and/or IgD. MCL will stain positively for CD5, CD19, CD20, CD22, and CD23, while CD10 and BCL 6 will be negative [4].

Prognostication remains a challenge in many rare oncologic malignancies. MCL has been known to typically follow an aggressive course with median overall survival ranging from 3–5 years. Estimated 3-year survival was 44% for patients ≥ 60 years and of 81% for patients aged ≤ 60 years [2]. The mantle cell lymphoma international prognostic index (MIPI) score classifies MCL into three risk categories: low (median overall survival [OS] not reached), intermediate (median OS 51 months), and high risk (median OS 29 months). Included are age, leukocyte count, lactate dehydrogenase (LDH) level, and ECOG performance status. Histologic MIPI scoring includes Ki-67 proliferative index as well [6]. Predictors of poor outcome include the presence of night sweats, chills and weight loss prior to diagnosis, high risk MIPI scoring, elevated LDH, Ki67 >30%, and histology notable for complex karyotype, blastoid variance, and 17p/TP53 or SOX 11 mutations [7]. Ki67 has been a focus of study, and has been correlated to OS, with Ki67 expression <20% demonstrating OS of 53 months, 21–40% 33 months, 41–60% 19 months, and >60% 13 months [8]. This patient’s tumor was 25–40% positive for Ki67. TP53 was not tested in this patient, however the presence of a TP53 mutation has been shown.
to indicate both shorter time to treatment failure and lower OS, regardless of the corresponding Ki67 or SOX 11 scores [9].

Treatment regimens for MCL continue to evolve and are dependent on the patient’s ability to tolerate the regimen. For patients <65 with MCL in the intermediate to high risk MIPI category, autologous stem cell transplant with high dose chemotherapy composed of NORDIC alternating with AraC followed by BEAM or BEAC has been associated with median survival of 12.7 years. Rituximab plus hyper-CVAD alternating with MTX/Ara-C median survival is 13.4 years. These intensive regimens are however burdened by increased side effects and rate of secondary malignancies. Of patients who survive the more intensive treatment regimen, 9.4% develop solid tumors and between 3.1–6.2% experience MDS/leukemia [10]. However, given the median age of diagnosis is 68 years old, harm versus benefit ratio is often considered for the geriatric population, and observation alone in cases of indolent MCL or MCL with low MIPI score may be an option. In this population, more conventional CHOP or R-CHOP regimen and stem cell transplant are offered strong candidates.

Gastrointestinal lymphomas can be complicated by intestinal perforation, either at diagnosis or during the treatment phase. Perforation causes significant morbidity from peritonitis and sepsis while prolonging hospitalization and delaying further medical treatment. Approximately 9% of gastrointestinal lymphoma patients experience perforation [6]. Among lymphoma associated perforations, B cell lymphomas were associated with the highest perforation percentage of 59%, whereas MCL’s perforation rate was 2%. Of these gastrointestinal perforations, 49% occurred concurrently with chemotherapy, and most commonly with R-CHOP. Interestingly, only 32% of cases were within 1–2 weeks of chemotherapy initiation, and 12% in weeks 3–4. Unfortunately, in these patients the majority of bowel perforations resulted in death.

This patient’s abdominal perforation coincided with feculent emesis and symptoms of bowel obstruction. Abdominal CT scan confirmed intestinal perforation as well as intussusception. MCL with intussusception at diagnosis or as result of chemotherapy is rare, occurring only in 1% of MCL cases [5]. However, several cases of MCL complicated by intussusception have been published. Of these five cases identified in literature review, all suffered intussusception of the ileocecal region [11–15].

In conclusion, prognostication of MCL and anticipation of MCL treatment complications remain a challenge. Although the MIPI index may indicate time to treatment failure and overall survival, it has yet to be correlated to individual treatment complications, including gastrointestinal perforation. A high clinical suspicion for gastrointestinal perforation should be held in patients with a history of gastrointestinal lymphoma who demonstrate abdominal rebound tenderness with or without feculent emesis, and CT imaging of the abdomen should be obtained to evaluate for viscus perforation. Given the high mortality of gastrointestinal perforation in these patients, identification of delays in care toward medical and surgical treatment of gastrointestinal perforation may benefit this population. Current evidence suggest that gastrointestinal lymphoma associated perforations rarely occur less than two days after the initiation of chemotherapy, however approximately 48% of occur within the first month of treatment [12]. Thus we suggest that patients and their caretakers undergoing therapy for MCL with abdominal lymphadenopathy, or under treatment with history of abdominal lymphoma be educated on the symptoms of gastrointestinal perforation to minimize delays in seeking treatment.
Statement of Ethics

Informed consent was obtained from the patient for educational use of the below mentioned data and no personal patient information has been disclosed. This paper has been written in keeping with the principles of the Declaration of Helsinki.

Disclosure Statement

None of the authors have any financial or personal bias to declare.

Author Contributions

M. Adashek, A. Chan, and A. Medina completed the background research, drafted and edited the manuscript, and is the grantor of the publication.

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Fig. 1. Initial Abdominal Computerized Tomography Scan. A computerized tomography scan with intravenous contrast revealed a 13 × 10 × 12 cm mass in the right upper quadrant with mass effect on surrounding structures and small bowel obstruction.

Fig. 2. Colonoscopy Images. Colonoscopy revealed a large non-obstructing polypoid tumor in the ascending colon and hepatic flexure. This tumor was characterized during the procedure as nodular, friable and ulcerated (A, B, C).
Fig. 3. Histology Of Colonoscopy Biopsies. Colonoscopy biopsies showing dense lymphoid infiltrate with monocytoid features, staining positive for CD5 stain (A), CD20 (B), CD43 (C), and demonstrating cleaved morphology in haemotoxylin and eosin stain (D).