CLINICAL VIGNETTE

Malignant Cause of Diarrhea

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Case Presentation

A 79-year-old man with prior history of diabetes presented with diarrhea and weight loss. He was otherwise active and reported gradual loss of appetite and weight loss of 20 pounds over the last year. He also complained of loss of energy and needing to rest more frequently, and becoming less steady on his feet. One year ago, he had a normal stress test. His bowel habits have been alternating between solid and loose the last few months but have become mostly watery during the last month. He has never had an upper endoscopy or colonoscopy. The physical exam was normal. His BMI was 19.55 kg/m^2, labs we remarkable for low albumin at 3.8 g/dL, and elevated creatinine at 3.22 mg/dL. He had a normocytic anemia, with hemoglobin of 9.7 g/dL, hematocrit of 31.1 %, mean corpuscular volume of 98.4 and red cell distribution of 13.1%. Stool studies were negative for *Clostridium difficile* infection and enteric pathogens and he had a normal calprotectin value.

Endoscopy and colonoscopy were performed. The endoscopy showed normal mucosa in the esophagus, stomach and duodenum (Figure 1). In the colon, a small tubular adenoma was removed, but the colon and the terminal ileum otherwise appeared normal (Figures 2, 3). Random biopsies were obtained in the stomach, duodenum, terminal ileum, as well as the right and left colon. The biopsies in the duodenum and the left colon including descending colon, sigmoid colon and rectum showed Mantle cell lymphoma. Immunostains were positive for CD20, SOX11 and BCL2. The Ki67 proliferative index was low at 5%. FISH analysis was abnormal for t(11;14) translocation. Further staging work up, found extensive adenopathy above and below the diaphragm, as well as bone marrow involvement, making him stage IVB at time of diagnosis. Due to his stage 4 chronic kidney disease, medication selection was limited, and he was started on R-CHOP (rituximab, cyclophosphamide, hydroxydaunorubicin [adriamycin], oncovin [vincristine], prednisone). Unfortunately, after one dose he became significantly ill with pancytopenia, further weight loss and medication toxicity. He was then transitioned to rituximab and ibrutinib, which he has continued for a year. He is doing well with his current regimen; and understands that his current treatment is palliative.

Discussion

Mantle cell lymphoma (MCL) is a B-cell non-Hodgkin's lymphoma, which typically is aggressive and incurable, but has been reported to have heterogeneous clinical courses. MCL is defined by the translocation t(11;14)(a13;q32), which results in overexpression of cyclin D1, leading to dysregulation of the cell cycle.[1] Incidence has been rising in western countries. Presentation is often in older population, with median age of 68.[2] Different presentations can be attributed to different molecular pathways of MCL. Classical MCL, which is the most common, is made up of mature B cells that express transcription factor SOX11. Leukemic non-nodal MCL is less common and lacks SOX11 expression. The leukemic non-nodal subtype has a more indolent presentation.[1] Most cases, 70% to 80% of MCL present symptomatically, with nodal and extra-nodal involvement and require systemic therapy.[2]

Majority of patients present with involvement of multiple extra nodal areas including splenomegaly, kidneys, lymphadenopathy, cytopenias, and rarely with involvement of central nervous system. MCL is commonly present microscopically and macroscopically in the gastrointestinal tract. It has also commonly been found in biopsies of macroscopically normal mucosa. It has been noted microscopically in the lower gastrointestinal tract in 80% of cases and in the upper gastrointestinal tract in over 40% of cases. Gastrointestinal involvement, although common, has not been shown to change the course of disease nor management.[3]

Multiple factors affect MCL prognosis. Patients can be risk stratified into low-, intermediate-, and high-risk groups based on the MCL International Prognostic Index (MIPI), which includes age, performance status, lactated dehydrogenase (LDH) level and white blood cell count. Ki-67 proliferation index from non-bone marrow, lymphoma rich areas also predicts prognosis as Ki-67 over 30% is considered high risk.

Overall survival in low risk MCL is 60% at 5 years. Overall survival of intermediate and high risk has been reported as 29 months and 51 months, respectively.[2,4]

Treatment of MCL has significantly changed in the last 5 years with new medications improving both survival and minimizing adverse effects of therapy. Choice of treatment varies with patient presentation. Indolent courses have been considered for observation only. Symptomatic patients are considered for rituximab- and cytarabine-containing therapies, depending on age and co-morbidities. Several treatment regimens have the goal of maintenance rather than cure. Other agents can be considered in patients, who are not candidates for standard therapies or clinical trials.

Bruton's tyrosine kinase inhibitors, such as ibrutinib, have markedly improved outcomes and medication tolerance in MCL. Ibrutinib was the first oral agent to be approved by the US Food and Drug Administration for use in MCL. Uses include monotherapy and combination therapy, including with rituximab. Ibrutinib had better objective response rate, longer progression-free survival, and better tolerability than many other medications used in MCL. Potential serious adverse events of ibrutinib included atrial fibrillation and bleeding.[1,2]

Conclusion

MCL is a rare, incurable non-Hodgkin's type lymphoma associated with translocation t(11;14)(a13;q32), which results in overexpression of cyclin D1. It can present with an indolent course, but much more commonly is aggressive and symptomatic. Gastrointestinal involvement is common, especially microscopically, as in the patient described above. Gastrointestinal involvement does not alter the disease management or prognosis. Treatment of MCL has recently become more effective with medications such as Bruton's tyrosine kinase inhibitors, in addition to the rituximab-based regimens already being used. New trials are underway with many more treatments that promise to be more effective and with less adverse effects.

Figures

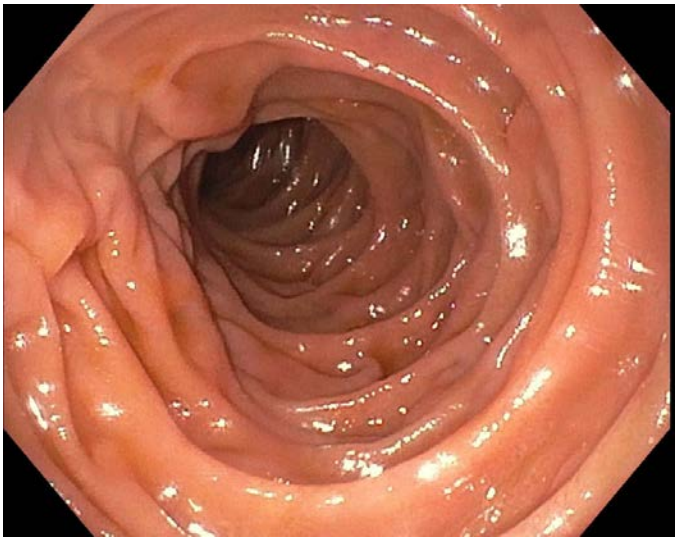

Figure 1. Endoscopically normal duodenum.

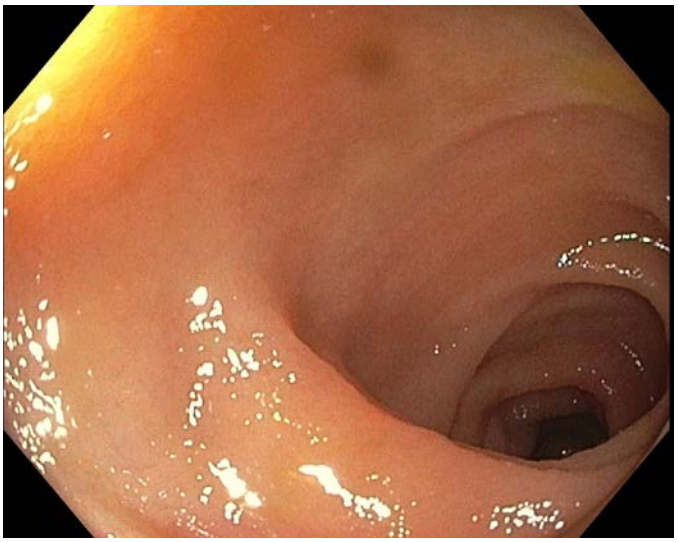

Figure 2. Endoscopically normal terminal ileum.

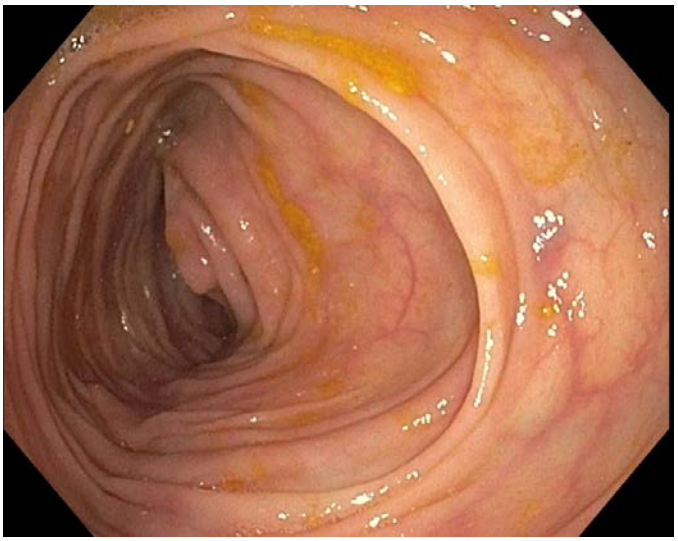

Figure 3. Endoscopically normal descending colon.

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