Celiac disease Associated with therapy for lymphoma: case report and review of the literature

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Case Report

Keywords: diffuse large B cell lymphoma (DLBCL), celiac disease, chemotherapy, CD20, case report

Posted Date: May 24th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1674507/v1

Abstract

Background

Celiac disease is an autoimmune enteropathy characterized by a reaction to gluten leading to autoantibodies that have deleterious effects on several organs. Most commonly, celiac disease affects the small bowel causing an inflammatory reaction that leads to villous atrophy and thus malabsorption.

While post-chemotherapy side effects are varied and affect several organ systems, one of the more common effects seen in patients is diarrhea. However, in some cases diarrhea is not an isolated event but rather a manifestation of new onset celiac disease. We propose that while celiac disease is a relatively rare condition, there may be an association with chemotherapy.

Case Presentation

A 66-year-old woman with a history of diffuse large B-cell lymphoma (DLBCL), immune idiopathic thrombocytopenia, and hypothyroidism, developed diarrhea and severe hypokalemia two years after completing a 6 cycle EPOCH-R chemotherapy regimen. EPOCH-R consisted of rituximab, etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin. Evaluation of the patient showed villous blunting and increased intraepithelial lymphocytes in the small intestine as well as increased levels of anti-TTG antibodies, endomysial IgA antibodies, and gliadin IgG antibodies indicating a diagnosis of celiac disease. The patient had no family history of celiac disease or other enteropathies and outside of a brief case of *Clostridium difficile* colitis, had not experienced any side effects in the immediate post-chemotherapy period. The patient responded well to a gluten-free diet with resolution of her diarrheal symptoms.

Conclusions

Celiac disease developing after completion of chemotherapy for DLBCL is a rare phenomenon with only a few examples found in the medical literature. Although diarrhea is a common side effect of chemotherapy for lymphoma, patients with delayed onset of diarrhea with failure to improve despite conventional management, should be evaluated for celiac disease.

Case Presentation

A 66-year-old woman who had a history of hypothyroidism and immune thrombocytopenia requiring splenectomy, in the summer of 2016, began experiencing symptoms of a persistent cough. Initially the symptoms were thought to be of infectious origin, and she was subsequently placed on oral antibiotics which proved ineffective. A CT scan of the chest eventually revealed a right hilar mass of 4.5cm diameter, along with a 4.2cm diameter hepatic mass, which both were FDG positive on PET scan. Ultrasound guided biopsy of the lesion and subsequent pathology revealed high grade B cell lymphoma. Immunohistochemistry showed expression of BCL6, CD20, and c-myc. Ki67 was elevated at >95% but

FISH studies did not reveal chromosomal abnormalities. The patient was subsequently started on the EPOCH-R regimen consisting of etoposide, prednisone, vincristine, cytoxan, and doxorubicin, and rituximab. She received pegfilgrastim as an outpatient. Her first cycle was complicated by *C. difficile* colitis as well as thrombocytopenia. In total she received 6 cycles of EPOCH-R ultimately achieving complete remission.

Although the patient's main side effect from the chemotherapy was worsening of her thrombocytopenia, she did not exhibit many other side effects in the immediate post chemotherapy period. However, approximately two years after completing chemotherapy the patient began experiencing persistent watery diarrhea and weight loss of approximately 30 lbs in 6 weeks which she initially attributed to a recent cholecystectomy. The patient had no family or prior personal history of enteropathies either in adulthood or childhood. The patient had been eating a normal diet without loss of appetite, but symptoms persisted. She eventually presented to the ED with palpitations and severe hypokalemia.

Evaluation included stool cultures which were negative for *C difficile*, campylobacter, entamoeba, giardia, salmonella, and shigella. Further evaluation showed elevated CRP and ferritin. She underwent endoscopic evaluation. Biopsy from the duodenum and stomach from EGD and colonoscopy revealed lymphocytic gastritis and small intestinal mucosa with total villous blunting and markedly increased intraepithelial lymphocytes, suggestive of gluten sensitive enteropathy. Serologic testing revealed elevated anti-TTG antibodies, endomysial IgA titers of 1:1,280 with an elevated gliadin IgG antibody level of 165.4 units/mL. A Prometheus Celiac Genetics Test was also performed which revealed a genotype of DQ2 homozygous, placing the patient at 31 times risk of developing celiac disease.

The patient was subsequently placed on a gluten free diet with rapid improvement of symptoms. When seen in the outpatient setting the patient gained weight without any further diarrheal symptoms. Five years after being in remission, the patient had an isolated recurrence of her lymphoma in the left cheek region and was started on mosunetuzumab and polatuzumab. She has responded well to treatment and has not had any further complications of her celiac disease.

Conclusions And Discussion

Celiac Disease followed by Lymphoma

Celiac disease is associated with an increased risk of lymphoma[3, 4]. Some studies estimate that the risk of lymphoma in patients with celiac disease may be as high as five times that of the general population.[4]. Theories behind the link between lymphoma and celiac disease include increased survival of intraepithelial lymphocytes secondary to IL-15 expression by enterocytes.[4] Lymphoma development can occur in 60-80% of patients with refractory celiac disease (RCD).[4] RCD represents a small portion of celiac disease patients (1-2%) and is defined as 6–12 months of continued enteropathy despite gluten free diet or return of symptoms after remission with gluten free diet.[5] However, in our patient, lymphoma and chemotherapy occurred prior to the development of celiac disease.

Another report describes the association of histologically proven celiac disease with lymphoma and other malignancies. In that study 133 of the 259 malignancies studied were lymphomas, further suggesting the link between lymphoma and celiac disease.[6] However, there is no mention of chemotherapy in these patients prior to their diagnosis of celiac disease, although 3 patients who survived more than 5 years after being diagnosed with lymphoma did receive chemotherapy.[6]

Lymphoma followed by Celiac Disease

We found one case describing a patient with lymphoma who developed celiac disease manifestations post-chemotherapy.[7] This patient was initially treated with BEMOP-CA (bleomycin, etoposide, vincristine, methotrexate, prednisolone/cyclophosphamide, doxorubicin), followed by 3 cycles DHAP (cisplatin, cytosine arabinoside and dexamethasone) one year later due to recurrent lymphadenopathy and B symptoms. The patient was treated with combination chemotherapy LACE (lomustine, cytarabine, cyclophosphamide, etoposide) after which the patient developed 6 weeks of diarrhea and was eventually found to be seropositive for IgG and IgA antigliadin antibodies without anti-endomysial antibodies, confirming a diagnosis of celiac disease.[7]

A retrospective chart review of patients at the Mayo Clinic examined the prevalence of diarrheal symptoms in cancer patients after treatment with chemotherapy and found that some cases of celiac diseases were unmasked due to chemotherapy. In this study, 15 of 27 patients were identified as having both celiac disease and some form of cancer including lymphoma prior to initiation of chemotherapy. 12 of 27 patients were diagnosed with celiac disease after chemotherapy but it was not clear how many of these patients had lymphoma.[8] Those with known celiac disease who were compliant with a gluten free diet prior to chemotherapy tolerated 5-fluorouracil without severe diarrhea. A majority of those with subsequently diagnosed CD on the same regimen experienced severe diarrhea more than 7 stools a day. Despite the small sample size of subjects, this paper suggests that chemotherapy possibly unmasked or caused celiac disease.

Both our patient and the patient in the previously described case report received chemotherapy regimens whose agents' primary mechanisms involved direct cytotoxic injury. Our patient also received rituximab, a monoclonal antibody targeting CD-20. CD-20 is a receptor found on the vast majority of B-lymphocytes and rituximab facilitates increased complement-mediated and antibody-dependent cell-mediated cytotoxicity. This binding leads to an immune response which in turn reduces the B-cell population. Due to the high number of gut-associated lymphoid tissue (GALT) it is possible that rituximab and other B-cell-targeting chemotherapy agents cause imbalance of secretion and absorption in the small intestine leading to the pathology seen in celiac disease.

While the role of intestinal B-cells is unclear in inflammatory bowel disease, in one patient with IBD treated with rituximab 6 months after chemotherapy, immunophenotyping of B-lymphocytes showed complete ablation of CD-20+ B-cells in circulation and in other tissues but not the colon.[9]

Although there has not been a well-established association between lymphoma and celiac disease, there are rare cases in which celiac disease has its onset well after chemotherapy, as seen with our patient. It may be prudent to evaluate patients with lymphoma for celiac disease should they present with delayed refractory diarrhea after chemotherapy.

Abbreviations

DLBCL, diffuse large B-cell lymphoma; CT, computed tomography; FDG, fluorodeoxyglucose; BCL-6, B-cell lymphoma 6; CD-20, B-lymphocyte antigen CD20; c-myc, cellular myelocytomatosis; Anti-TTG, Anti-transglutaminase antibodies; RCD, refractory celiac disease; GALT, gut-associated lymphoid tissue

Declarations

Availability of data and materials

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

Consent for publication

The authors obtained informed consent from the patient to publish information on their disease and clinical course. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Ethics Approval and consent to participate

The authors obtained the patient's consent to participate.

Competing Interests

The authors declare they have no competing interests

Funding

None applicable

Authors' contributions

The original manuscript was written by SR. All authors participated in drafting and editing the manuscript. All authors read and approved the final manuscript.

Acknowledgements

The administrative assistance of Joanne Aguiar is gratefully acknowledged.

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References

1. Tang I, MacFaul G, Madhotra R, Rostami K. Post pancreatitis/cholecystectomy gluten intolerance. Gastroenterol Hepatol Bed Bench. 2018;11(3):273–275.
2. Stein A, Voigt W, Jordan K. Chemotherapy-induced diarrhea: pathophysiology, frequency and guideline-based management. Ther Adv Med Oncol. 2010;2(1):51–63. doi:10.1177/1758834009355164
3. Catassi C, Fabiani E, Corrao G, Barbato M, De Renzo A, Carella AM, Gabrielli A, Leoni P, Carroccio A, Baldassarre M, Bertolani P, Caramaschi P, Sozzi M, Guariso G, Volta U, Corazza GR; Italian Working Group on Coeliac Disease and Non-Hodgkin's-Lymphoma. Risk of non-Hodgkin lymphoma in celiac disease. JAMA. 2002 Mar 20;287(11):1413-9. doi: 10.1001/jama.287.11.1413. PMID: 11903028.
4. Halfdanarson TR, Rubio-Tapia A, Ristow KM, Habermann TM, Murray JA, Inwards DJ. Patients with celiac disease and B-cell lymphoma have a better prognosis than those with T-cell lymphoma. Clin Gastroenterol Hepatol. 2010;8(12):1042–1047. doi:10.1016/j.cgh.2010.09.007
5. Chibbar R, Nostedt J, Mihalicz D, Deschenes J, McLean R, Dieleman LA. Refractory celiac disease type II: A case report and literature review. Frontiers in Medicine. 2020;7. doi:10.3389/fmed.2020.564875
6. Swinson CM, Slavin G, Coles EC, Booth CC. Coeliac disease and malignancy. Lancet. 1983 Jan 15;1(8316):111-5. doi: 10.1016/s0140-6736(83)91754-3. PMID: 6129425.
7. Stewart AJ, Southcott BM. Coeliac disease following high-dose chemotherapy. Clin Oncol (R Coll Radiol). 2002 Dec;14(6):494-6. doi: 10.1053/clon.2002.0079. PMID: 1251297
8. Robinson SI, Murray J, McWilliams RR. Celiac disease and chemotherapy. Journal of Clinical Oncology. 2007;25(18_suppl):19561–19561. doi:10.1200/jco.2007.25.18_suppl.19561

9. Uzzan M, Ko HM, Rosenstein AK, Pourmand K, Colombel JF, Mehandru S. Efficient long-term depletion of CD20 + B cells by rituximab does not affect gut-resident plasma cells. Ann N Y Acad Sci. 2018 Mar;1415(1):5–10. doi: 10.1111/nyas.13577. Epub 2017 Dec 31. PMID: 29291255; PMCID: PMC6368409.