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Idelalisib: a rare cause of enterocolitis

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Abstract

Idelalisib is an oral, phosphatidylinositol 3-kinase delta (PI3Kδ) inhibitor, approved by FDA since July 2014 for the treatment of relapsed follicular B-cell non-Hodgkin lymphoma. Data from three phases of the study involving idelalisib demonstrate diarrhea (47%) to be the common adverse effect. The other side effects are pyrexia (28%), fatigue (30%), nausea (29%), cough (29%), pneumonia (25%), abdominal pain (26%) and rash (21%). The characteristic histological findings of idelalisib colitis include intraepithelial lymphocytosis, neutrophilic cryptitis and epithelial cell apoptosis within the crypts. Histological findings help differentiate among other causes of diarrhea and entero-colitis. We present a female patient with recurrent follicular lymphoma treated with idelalisib and presented with diarrhea. She was found to have entero-colitis and was treated successfully with drug discontinuation and prednisone.

Keywords Idelalisib, enterocolitis, diarrhea

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Introduction

Idelalisib is an oral, phosphatidylinositol 3-kinase delta (PI3Kδ) inhibitor, approved by FDA in July 2014 for the treatment of relapsed follicular B-cell non-Hodgkin lymphoma in patients who have failed 2 or more systemic therapies. In this case report, we present a female patient with recurrent follicular lymphoma who was treated with idelalisib and presented with diarrhea. She was found to have entero-colitis and was treated with prednisone and improved symptomatically. We describe the mechanism of action of drug, side effects, grades of diarrhea, histological features, differentiation from other common causes of colitis and management of idelalisib-induced colitis.

Case report

A 72-year-old female presented with abdominal pain, non-bloody diarrhea for two months and 15-pound weight loss. Her frequency of bowel movements was 10-12 times a day with occasional nocturnal bowel movements. Her past history was significant for follicular lymphoma since 2009, treated with rituximab with remission until recurrence in 2012 when she was treated with R-CHOP and R-ICE regimens. Her disease continued to progress and she was started on oral idelalisib 10 months prior to this admission. Physical exam showed stable vital signs, non-tender abdomen without guarding. Initial lab findings showed potassium 2.8 mEq/L (normal: 3.5-5.0 mEq/L), chloride 98 mEq/L (normal 101-111 mEq/L), WBC 9.9, hemoglobin 12.5, TSH 2.56 mIU/L, morning cortisol 18 μg/dL and negative tissue IgA transglutaminase with normal immunoglobulin level. The patient was started on IV hydration with potassium supplementation. Stool studies were positive for occult blood, but negative for infectious organisms such as *Salmonella*, *Shigella*, *Campylobacter*, *Cyclospora*, *Microspora*, and *Clostridium difficile* PCR. CT abdomen and pelvis with and without contrast, mainly to rule out lymphadenopathy with her history of lymphoma, was normal. Upper endoscopy and duodenal biopsy were negative for celiac disease. Subsequent colonoscopy revealed ileitis (Fig. 1) and mild colitis. Random biopsies showed focal inflammation, crypt drop out cryptitis, increased lymphocytes, plasma cells and eosinophils in lamina propria in ileum (Fig. 2), and mild cryptitis (Fig. 3) in colon. Review of her medications revealed use of idelalisib, a known cause of chronic diarrhea and entero-colitis. The medication was discontinued and patient was started on prednisone 40 mg q.d. with slow tapering over 8 weeks leading to a significant improvement in patient's condition; idelalisib was then re-started with close monitoring of patient's symptoms.

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Conflict of Interest: None

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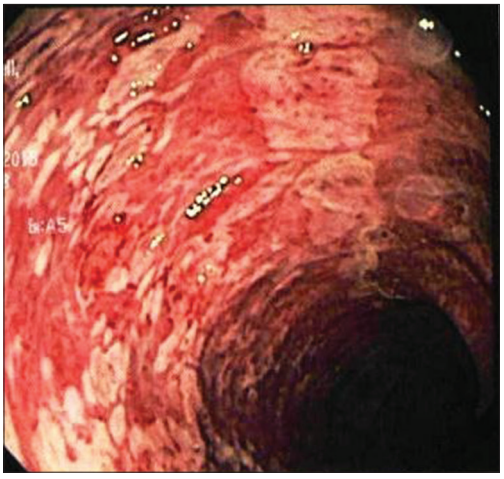

Figure 1 Colonoscopy with Ileum intubation showing changes of ileitis in terminal ileum

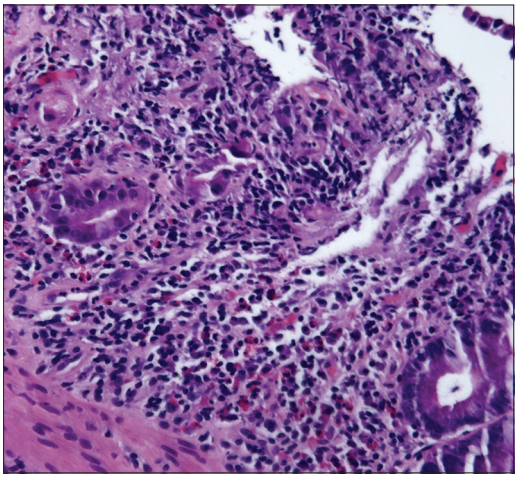

Figure 2 Terminal ileum biopsy with increased lymphocytes, plasma cells, and eosinophils in lamina propria. Note: Lymphocytes and plasma cells are expected in the lamina propria, but not to this degree, and eosinophils are more prominent here than normal

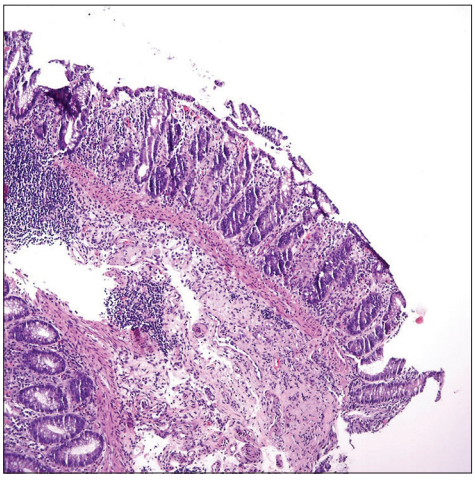

Figure 3 Colon biopsy showing mild cryptitis

Discussion

Idelalisib is a potent and selective inhibitor of PI3Kδ (Phosphatidyl Inositol 3, 4, 5-tri-phosphate: isoform delta, also known as p110δ). By inhibiting PI3δ, idelalisib inhibits proliferation, chemotaxis, motility, adhesion and survival of B cells and promotes apoptosis in cell lines derived from B-cell malignancies, including Chronic lymphocytic leukemia diffuse large B-cell lymphoma, multiple myeloma and Hodgkin lymphoma [1,2].

Data from phase 1, 2 and 3 studies involving idelalisib demonstrate diarrhea (47%) to be the common adverse effect [1]. The National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) evaluated and graded diarrhea by number of stools per day, incontinence, and increase in ostomy output compared to baseline [3]. The NCI CTCAE is widely accepted throughout the oncology community as the standard classification and severity grading scale for adverse events in cancer-related clinical trials and other oncology settings (NCI, 2009) [3]. Grades refer to the severity of the adverse events (AE). The CTCAE displays grades 1 through 5 with clinical description of severity for each AE based on general guideline. Grade 1 includes asymptomatic or mild symptoms, based on clinical or diagnostic observations, and intervention is not indicated. Grade 2 includes moderate symptoms and local or noninvasive intervention is indicated. Grade 3 includes severe or medically significant but not immediately life-threatening, and hospitalization is indicated. Grade 4 is a life-threatening consequence and requires urgent intervention. Grade 5 includes death related to AE. Among 146 patients with NHL who received idelalisib 150 mg monotherapy, any grade of diarrhea was reported in 47%, grade 3 diarrhea in 14% and grade 4 diarrhea in 11%. The median time to onset of any grade diarrhea or colitis was 1.9 months, of grade 1 or 2 was 1.5 months and of grade 3 or 4 was 7.1 months [1].

A recent randomized control trial comparing rituximab plus idelalisib with rituximab and placebo found similar rates of mild diarrhea in both arms [4,5]. However, in a similar trial only patients in rituximab plus idelalisib arm developed severe (grade >3) diarrhea suggesting mild diarrhea to be self-limited temporary effect of treatment. The pathophysiology of idelalisib induced diarrhea and colitis is unclear. However, proposed mechanism involves T cell dysregulation. Mesenteric B cells in mouse models were proved to protect intestinal mucosa by inhibiting T cells. Inhibition of B cells by idelalisib is thought to cause immune dysregulation causing damage via CD8 cytotoxic T cells [6].

The histological differential diagnosis of idelalisib-induced colitis involves autoimmune enteropathy, other medication side effects (ipulimumab, mycophenolate mofetil), Graft versus host disease, inflammatory bowel disease (IBD), infectious colitis, and celiac disease. Although clinical history can help eliminate most causes, there are few histological clues to differentiate. The characteristic histological findings of idelalisib colitis include intraepithelial lymphocytosis, neutrophilic cryptitis and epithelial cell apoptosis within the crypts [4,7]. Presence of

cryptitis and apoptosis is atypical for celiac disease. Although, severe crypt cell apoptosis can raise a suspicion for GVHD, pauci-inflammatory without intraepithelial lymphocytes, and absence of stem cell transplant history helps with exclusion. Certain infection such as CMV induced colitis closely resembles idelalisib colitis in form of cryptitis and cell apoptosis but viral inclusions are apparent in active disease [8]. It can be distinguished from IBD because of crypt apoptosis which is atypical for IBD. Colitis induced by other drugs rarely show epithelial cell apoptosis and usually have eosinophil rich infiltrate in lamina propria [4,7,8].

Management is usually intravenous or oral prednisone or budesonideafter excluding other causes [1]. Recommended dosage of budesonide is 9 mg q.d. or prednisone 1mg/kg with tapering dose after diarrhea returns to grade 1 [1]. For grade 2 diarrhea, FDA packet information recommends maintaining idelalisib dose and monitoring at least once weekly until resolution [9]. For grade 3 diarrhea or hospitalization due to diarrhea, FDA packet information recommends withholding idelalisib and monitoring at least once weekly until diarrhea resolves [9]. Once resolved, idelalisib may be resumed at a reduced dose. If life-threatening grade 4 diarrhea occurs, idelalisib should be permanently discontinued. The time to resolution of severe diarrhea appeared to be shorter with the initiation of budesonide and/or systemic corticosteroids (1-2 weeks) compared with idelalisib interruption alone (approximately 1 month) [1]. Our patient was treated with oral prednisone 40 mg q.d. with slow tapering over an 8-week period with improvement in her symptoms and she was re-started back on idelalisib at a reduced dose.

In conclusion, idelalisib has the propensity to cause diarrhea and gastrointestinal injury in the form of colitis. Since the FDA approval of idelalisib in 2014 for its use in recurrent follicular lymphoma and CLL, the drug has been widely used. Patients taking idelalisib should be evaluated for any grade of diarrhea. For those presenting with diarrhea, a thorough history, physical examination and necessary laboratory testing should be performed. Histological findings help differentiate among other causes of diarrhea and entero-colitis.

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