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Dasatinib-Induced Colitis in a Patient with Chronic Myeloid Leukemia (Chronic Phase)

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ABSTRACT

Chronic myeloid leukemia (CML) is a Philadelphia (Ph) chromosome-positive myeloproliferative neoplasm. The molecular consequence of reciprocal translocation t(9;22)(q34;q11) is the generation of the BCR–ABL fusion gene, which encodes a constitutively active tyrosine kinase signaling protein. The tyrosine kinase is responsible for the leukemia phenotype through the constitutive activation of multiple signaling pathways involved in the cell cycle and in adhesion and apoptosis. Dasatinib is an oral BCR-ABL tyrosine kinase inhibitor (TKI) which is mainly used for treating CML patients with resistance or intolerance to Imatinib. Dasatinib has several significant adverse reactions and gastrointestinal side effects including colitis. We report a case of a 33-year-old male, diagnosed with CML (Chronic Phase) who received Dasatinib as second-line therapy and developed chronic diarrhea and colitis attributed to Dasatinib and improved after stopping it.

Keywords: Dasatinib, Chronic myeloid leukemia, Colitis

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Background

Chronic myeloid leukemia (CML) is a myeloproliferative neoplasm characterized by the presence of the Philadelphia (Ph) chromosome resulting from the reciprocal translocation t(9;22)(q34;q11). The molecular consequence of this translocation is the generation of the BCR-ABL fusion gene, which encodes a constitutively active protein tyrosine kinase. (1-3) Dasatinib is multi-targeted kinase inhibitor and it is approved therapy for patients with imatinib-resistant or imatinib-intolerant CML or newly diagnosed CML (chronic phase).(4) This agent has been shown to exhibit broad off-target kinase inhibition and immunomodulating properties. These effects may be responsible for dasatinib's unique side effects including a distinctive form of hemorrhagic colitis.(5)

Case Presentation

A 33-year-old male, previously healthy, diagnosed incidentally to have CML 5 years ago and started on Imatinib as upfront therapy. On follow up, BCR ABL was 1.1% international scale (IS), so the patient was shifted to Dasatinib two years after achieving MMR.BCR-ABL 0.01 (IS). Two years after treatment with Dasatinib, the patient started to have persistent watery diarrhea. Neither blood nor mucus were detected. No fever or any abdominal pain. Stool for ova and parasites were negative, and stool culture was also negative. Therefore, Dasatinib was discontinued, and the patient underwent colonoscopy.

The biopsy was reported as severe active chronic inflammation with focal ulceration *(see Figure 1)*.

Serology for CMV (cytomegalovirus) was negative. Diarrhea improved after the Dasatinib discontinuation. The patient was kept on interferon subcutaneous weekly as a bridge before deciding whether to continue or to shift to another tyrosine kinase inhibitor. One month later, a repeat colonoscopy has been performed and showed a normal view *(see Figure 2)*. Patient re-counseled and started on Nilotinib 400 mg twice daily which was well tolerated.

Discussion

CML is a chronic myeloproliferative neoplasm characterized by the Philadelphia chromosome t(9;22)(q34;q11) and the *BCR-ABL1* fusion gene. The *BCR–ABL1* fusion gene codes for BCR–ABL1 transcripts and fusion proteins with high tyrosine kinase activity that is implicated in the pathogenesis of this disease (6). Tyrosine kinase inhibitors target the fusion protein BCR-ABL and members of the SRC tyrosine kinase family. Imatinib mesylate induces complete response in 91% of chronic phase CML patients. However, in later stages of the disease resistance is seen. Nilotinib and Dasatinib are designed to overcome Imatinib resistance in CML (7). Treatment with Dasatinib is associated with anemia, thrombocytopenia and neutropenia, and fluid retention and infertility (male infertility in patients with CML) (8). Bleeding diathesis in CML patients receiving Dasatinib therapy noted in more than 80% of all bleeding episodes were confined to the gastrointestinal tract (9). Diarrhea and nausea are generally observed in approximately about 30% of patients, during Dasatinib therapy. GI bleeding; mainly Lower Gastrointestinal Bleeding (LGB) may occur during treatment, but it’s less common than diarrhea (10). In phase II, multi-center studies, GI bleeding was reported to be around 14%, Grade 3: (Requiring transfusion, radiology, endoscopic or surgical intervention)and Grade 4(life-threatening) occurring in 7% and only 2% of patients with CML in the chronic phase reported grade 3-4 GI bleeding (11). Colitis caused by Dasatinib is reversible after stopping the drug and switching to other TKI is a reasonable option (12). Review of the literature suggests a 3-month median time to the onset of symptoms of colitis from the time of Dasatinib initiation (range 18 days to 3 years). It can occur in all age groups, and no gender predilection is found Histopathology evaluation of the biopsies in most patients showed a predominant CD3+ CD8+T cell lymphocytic infiltration of the colonic mucosa, but the exact pathogenesis of this

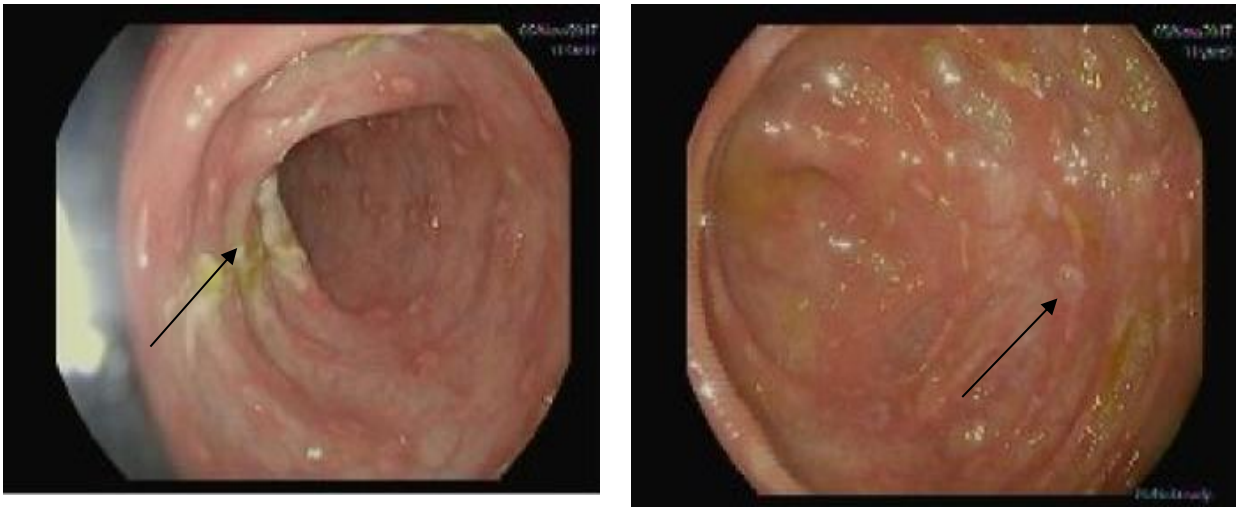

Figure 1. Colonoscopy: multiple aphthous ulcers with superficial exudate that is easily washed away distributed throughout the colon and ileum inc the rectum.endoscopic appearance suggestive of CMV colitis.

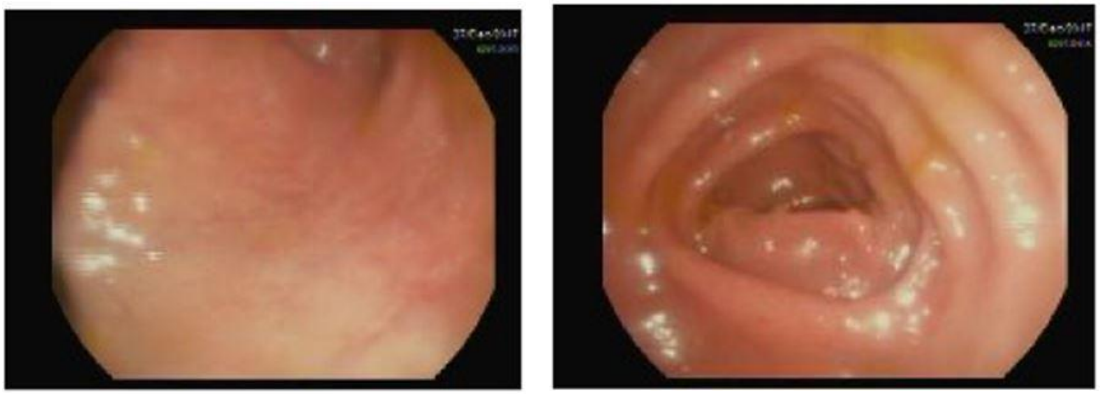

Figure 2. Colonoscopy: mild erythema in sigmoid, descending and transverse colon otherwise normal mucosa seen.

uncommon adverse drug effect is still unrevealed (5). One postulated mechanism is that Dasatinib inhibiting the proliferation and function of T regulatory cells by decreasing the expression of several contributing factors including; box P3 (a transcription factor), Glucocorticoid-induced tumour necrosis factor receptor (GITR), cytotoxic T-cell-associated protein 4 and inducing apoptosis in the G0/G1 phase of the cell cycle in T regulatory cells. Furthermore, two major studies have shown that Dasatinib suppresses the function of natural killer (NK) cells and T-cells by inhibiting SRC-family kinases (13, 14), therefore, Dasatinib may cause acute colitis by decreasing immune tolerance to intestinal microflora through reducing the number of immunoregulatory cells and inhibiting signal transduction pathways (15). Mustjoki and colleagues described an association between lymphocytosis secondary to significant expansion of clonal large granular lymphocytes and patients receiving Dasatinib. A large number of patients who developed colitis with Dasatinib were found to have LGL expansion, and therefore clonal LGL expansion may play a role in Dasatinib induced colitis (10). Other than the immunological mechanisms to cause colitis, Dasatinib has been reported to cause colitis by activation of cytomegalovirus, and even the hemorrhagic colitis that improves after stopping the drug. Gastrointestinal bleeding is consistent with the oral route of Dasatinib, which is eliminated in the feces. Consequently, the lower gastrointestinal tract

may be predominantly vulnerable to Dasatinib during the elimination phase and this may explain the existence of bleeding (2, 16).

Conclusion

Colitis presenting with diarrhea is a possible complication of treating CML patient with Dasatinib although this condition improves upon drug discontinuation. In such cases; prolonged diarrhea should be investigated thoroughly to rule out infectious conditions, mainly cytomegalovirus infection, which can occur simultaneously. Further prospective, large-scale, multisite studies are necessary to reveal the relationship between colitis and Dasatinib therapy.

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