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Brief Report

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Proven Cytomegalovirus Colitis Associated with Dasatinib Administration in Two Pediatric Allogeneic Hematopoietic Stem Cell Transplantation Recipients

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ABSTRACT

Gastrointestinal (GI) bleeding is a rare adverse event of dasatinib, which is known to be caused by dasatinib-induced colitis, severe thrombocytopenia, and platelet dysfunction. We present two cases of pediatric patients who developed hematochezia during treatment with dasatinib after hematopoietic stem cell transplantation (HSCT). A colonic tissue biopsy was performed to differentiate the cause of GI bleeding. Both patients were diagnosed with proven cytomegalovirus (CMV) colitis, but only one was treated with ganciclovir. The patient who did not receive antiviral therapy experienced recurrent GI bleeding during dasatinib administration, leading to multiple treatment interruptions. During dasatinib therapy after HSCT, patients with GI bleeding and confirmed CMV colitis may benefit from antiviral therapy to reduce interruptions in dasatinib therapy.

Keywords: Dasatinib; Cytomegalovirus; Child; Hematopoietic stem cell transplantation

INTRODUCTION

Since the introduction of imatinib, tyrosine kinase inhibitors (TKIs) have been used as key drugs for the treatment of chromic myeloid leukemia (CML) and relapsed or refractory Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) [1]. TKIs are also being actively used in the treatment of pediatric CML and Ph+ ALL and are of great help in improving patient prognosis [2]. TKIs must be selected by comprehensively judging the patient's diagnosis, age, risk, treatment response, and other complications; caution is required, as each TKI may show a different toxicity.

Dasatinib is a widely used second-generation TKI, as it shows superior potency to inhibiting BCR/ABL fusion protein compared to imatinib [3,4]. Dasatinib adverse events are mostly

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mild and self-limited, but severe ones, such as pleural effusion, pulmonary hypertension, prolonged QTc interval, and platelet dysfunction, may occur [5,6]. Furthermore, gastrointestinal (GI) bleeding is a relatively rare adverse event of dasatinib and is known to be caused by dasatinib-induced colitis, severe thrombocytopenia, and platelet dysfunction [7]. If GI bleeding occurs during the administration of dasatinib after allogeneic hematopoietic stem cell transplantation (HSCT), there are numerous possibilities which should be differentiated as its cause other than dasatinib-induced colitis, such as gut graft-versus-host disease (GvHD) and adverse events of immunosuppressants or conditioning regimen [8,9].

Cytomegalovirus (CMV) GI disease also presents with abdominal pain and hematochezia [10]. Because the onset usually overlaps with that of acute gut GvHD, as well as the timing of re-administration of dasatinib after HSCT, endoscopic gross evaluation and tissue biopsies are necessary to confirm the etiology and treat the cause of GI bleeding. We present two cases of pediatric patients who developed hematochezia during treatment with dasatinib after HSCT. A colonic tissue biopsy was performed to differentiate the cause of GI bleeding, and both patients were confirmed to have proven CMV colitis.

This study was approved by Seoul St. Mary's Hospital Institutional Review Board (No. KC22ZISI0560). Informed consent was waived by the board.

CASE REPORT

Case 1

A 6-year-old male patient was admitted for the evaluation of recurrent hematochezia after re-initiation of dasatinib post-HSCT. He was diagnosed with Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL, *BCR/ABL1* e1a2 minor relative ration 1.32, *IKZF1* exon4_7 deletion, *CDKN2A, 2B* partial deletion), and treatment with imatinib (GLIVEC®; Novartis) was initiated. After vincristine, prednisolone, daunorubicin, L-asparaginase chemotherapy, a follow up bone marrow study showed complete remission. The patient then received consolidation with cyclophosphamide, cytarabine, 6-mercaptopurinol, oncaspar, and vincristine regimen while maintaining imatinib. However, due to vomiting (grade 3), he was switched to dasatinib (SPRYCEL®; Bristol-Myers Squibb) and continued his 2nd to 12th week of consolidation chemotherapy.

Between induction and consolidation, a bone marrow biopsy showed detection of minimal residual disease (BCR/ABL1 RQ PCR ratio 0.00224). Therefore, he underwent familial mismatch peripheral blood stem cell transplantation (PBSCT) with fludarabine, busulfan, and low-dose antithymocyte globulin myeloablative preconditioning regimen while dasatinib was put on hold. Engraftment occurred 12 days after graft infusion, and the patient's day-28 lymphocyte subset panel showed an absolute CD4+ T-cell count 65.5×10^6/L, absolute CD8+ T-cell count 50.9×10^7/L, and absolute CD19+ B-cell count 36.4×10^6/L; he tested negative for CMV DNAemia. However, the patient began to complain of nausea, abdominal discomfort, vomiting, and poor oral intake. Thus, he underwent esophagogastroduoenoscopy, showing mild chronic gastritis suspicious for graft versus host disease (GvHD), and later tested negative for CMV immunohistochemistry (IHC). Therefore, tacrolimus was administered for the prevention of GvHD.

Two months post-transplant, dasatinib was resumed. However, within 4 weeks of recommencement, the patient presented with moderate amount of fresh blood along

with well-formed stool, which increased in frequency for 5 days. Upon stool examination, the patient was positive for *Clostrioides difficile* toxin. Therefore, under the impression of pseudomembranous colitis, he was given oral metronidazole for 10 days. During this time, he did not show any evidence of skin or gut GvHD. Even after a complete cycle of metronidazole therapy, the patient continued to show hematochezia up to three times daily. Thus, he was admitted for a colonoscopy at 3 months post-transplant.

The colonoscopy did not show any lesions from the terminal ileum to descending colon. However, erythematous changes with multiple erosions were observed from the sigmoid colon to the rectum, and the patient was diagnosed with probable dasatinib associated erosive colitis (**Fig. 1A–C**). A biopsy was performed from the terminal ileum to rectum, which showed mild lymphoplasma cell infiltration from all eight biopsy sites, and CMV immunohistochemistry stain was positive in the ascending, transverse, and descending colon tissue. The patient was therefore diagnosed with proven CMV GI colitis without gut GvHD. Furthermore, because his 3-month post-transplant lymphocyte subset showed robust immune reconstitution, no evidence of CMV retinitis, and did not have concurrent CMV DNAemia, the patient was not treated with an antiviral agent for CMV colitis. Thus, he was maintained on dasatinib.

At 4 months post-transplant, dasatinib was discontinued for 3 weeks due to a recurrence of hematochezia and abdominal pain. As symptoms subsided, dasatinib was restarted with a

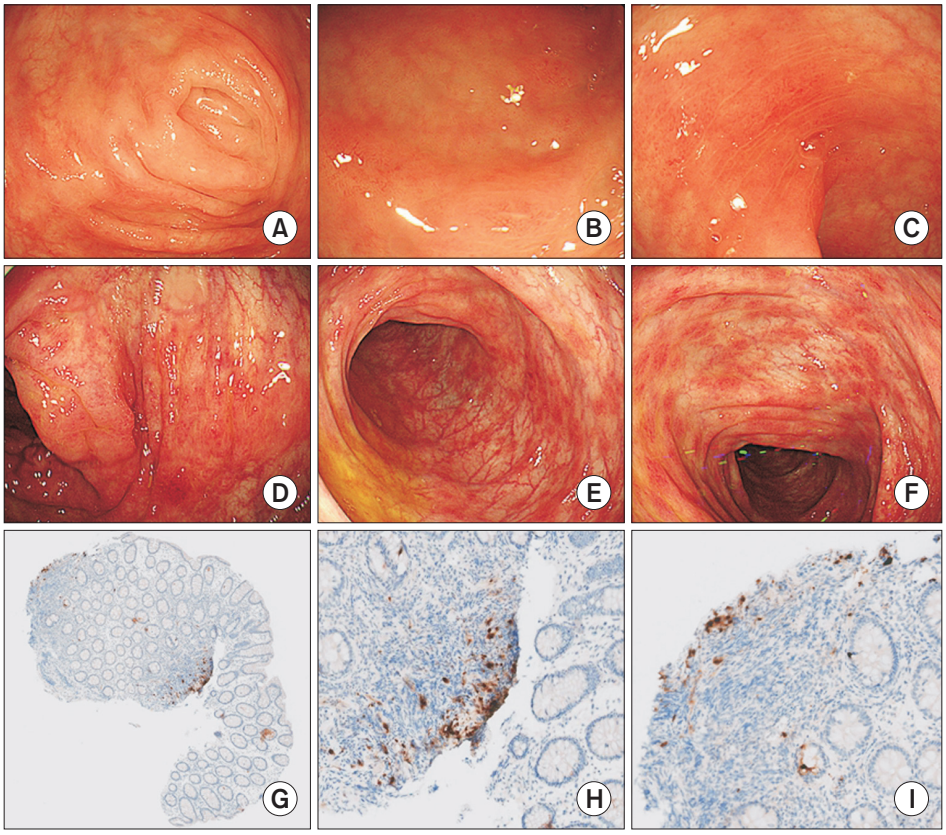

Fig. 1. (A–C) Colonoscopic findings of erythematous changes with multiple erosions in case 1. (D–F) Colonoscopic findings of multiple erythematous lesions and erosions from the cecum to the sigmoid colon in case 2. Ascending colon tissue biopsy histopathology showing positive for CMV IHC stain (G) at magnification×200 and (H), (I) magnification×400 in case 2. CMV: cytomegalovirus, IHC: immunohistochemistry.

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decreased dosage. Nevertheless, at 6 months post-transplant, dasatinib was withdrawn again dasatinib for another 4 weeks due to hematochezia.

At one-year post-transplant, the patient continued showing intermittent waxing and waning hematochezia; however, dasatinib was maintained with plans to discontinue it at 18 months post-transplant.

Case 2

A 16-year-old female patient was admitted for the evaluation of recurrent hematochezia after administration of dasatinib post-HSCT. She was diagnosed with chronic myeloid leukemia (major *BCR-ABL1* positive (b3a2); *BCR-ABL1* RQ-PCR 0.504) and myeloid blast phase, and dasatinib was initiated soon after diagnosis. Seven months after diagnosis, a follow up bone marrow biopsy showed complete hematologic response state (BCR-ABL1 RQ-PCR 0.00422), and the patient showed good molecular response. Therefore, 9 months after diagnosis, she underwent matched sibling donor PBSCT with busulfan and cyclophosphamide myeloablative conditioning regimen, and dasatinib administration was halted. Twelve days after graft infusion, engraftment occurred, and the patient's post-transplant day-28 lymphocyte subset panel showed absolute CD4+ T-cell count 256.4×10^6/L, absolute CD8+ T-cell count 19.0×10^7/L, and absolute CD19+ B-cell count 8.7×10^6/L. At day-120 post-transplant, dasatinib was resumed (BCR/ABL1 RQ-PCR 0.00021).

At 6 months post-transplant, the patient's plasma CMV viral load rose to 7,189 IU/mL; however, she did not show any other symptoms or signs of CMV end organ disease. Therefore, the patient was treated with preemptive valganciclovir for 3 weeks upon which her CMV DNA load became undetectable.

At 9 months post-transplant, the patient began to present with small amounts of fresh blood and mildly loose stool, but she did not complain of any abdominal pain or nausea/vomiting. However, the amount increased over a span of 2 weeks, and a complete blood cell count showed a hemoglobin drop to 5.5 mg/dL. Thus, the patient was admitted for further evaluation of hematochezia. Dasatinib was again put on hold due to the possibility of dasatinib associated colitis.

The patient underwent a colonoscopy showing multiple erythematous lesions and erosions from the cecum to the sigmoid colon (**Fig. 1D–F**) and was given a clinical diagnosis of probable dasatinib associated erosive colitis. A biopsy was taken from 8 different sites, starting from the ileocecal valve to the rectum; findings showed consistent grade 1 acute graft versus host disease from the cecum to the rectum. However, from the ascending colon tissue, CMV IHC stain was positive (**Fig. 1G–I**). The patient did not have concomitant CMV DNAemia; however, 2 weeks before hematochezia began, the patient had transient CMV DNAemia with a maximum plasma viral load of 1,974 IU/mL. Without antiviral therapy, the patient's viral load had become undetected on subsequent follow up, prior to the colonoscopy.

The patient was diagnosed with proven CMV colitis and grade I gut GvHD, and she did not show evidence of CMV rentinitis or other CMV end-organ involvement. Oral valganciclovir was initiated, and the patient's hematochezia subsided. Dasatinib was restarted after 3 weeks of valganciclovir treatment, and the patient no longer experienced hematochezia during the next 8 months. She was then diagnosed with CNS and molecular bone marrow relapse.

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DISCUSSION

Dasatinib-induced colitis is a rare drug adverse event which can present as GI bleeding. To date, there are only a paucity of studies related to GI bleeding during the administration of dasatinib in pediatric cancer patients. Because of the many possible etiologies of GI bleeding in these patients, thorough evaluation and prompt intervention are crucial for maintaining dasatinib for the treatment of underlying CML or PH+ ALL. We experienced two cases of CMV colitis in pediatric patients using dasatinib after HSCT, and this is the first case series reported in children.

The pathophysiologic mechanism of CMV reactivation or the development of CMV disease during dasatinib administration is not yet fully understood. Despite the significant effect of dasatinib on the immune system, a clear association with infectious complications has not been observed in large clinical studies [11]. However, previous studies in adults have reported several cases of CMV colitis after the use of dasatinib in adults and suggested that the use of dasatinib may increase the risk of CMV reactivation [12-14]. Other studies have reported more cases of dasatinib-induced colitis and CMV colitis occurring concomitantly compared to cases of CMV colitis alone during dasatinib therapy [13-15]. Furthermore, in patients with coexisting dasatinib-induced colitis and CMV colitis, discontinuation of dasatinib resulted in a short-term improvement of symptoms, such as GI bleeding. However, among the cases where CMV colitis was untreated, GI bleeding often recurred as dasatinib was recommenced, whereas those treated with anti-CMV agents experienced no recurrence of GI bleeding after dasatinib was readministered [13].

In these two cases, similar results were observed in children. In the first patient, CMV colitis was confirmed by CMV-specific IHC staining through a biopsy. However, GI bleeding improved immediately after dasatinib was discontinued, and CMV colitis was therefore not treated in this patient. After GI bleeding and GI symptoms improved, dasatinib was readministered, and intermittent bloody stools were repeatedly observed during the course of dasatinib treatment, leading to multiple interruptions and delays in the treatment of underlying disease. The second patient presented with hematochezia in large amounts, and there was a clear hemoglobin drop; CMV colitis was confirmed by CMV-specific IHC staining through endoscopic biopsy. After discontinuation of dasatinib, ganciclovir treatment was performed for CMV colitis, and the patient's symptoms subsided. When dasatinib was readministered, no further GI bleeding was observed; thus, dasatinib therapy continued without any interruptions. A major limitation of this study is that there is still an insufficient number of cases and studies to fully comprehend the clinical significance of CMV reactivation and colitis during dasatinib administration. However, the response and outcomes of children with concomitant dasatinib and CMV colitis were similar to previously published reports on adults, suggesting that patients may benefit from the treatment of CMV colitis by decreasing interruptions and delays in maintaining dasatinib therapy.

In conclusion, dasatinib treatment after HSCT may be a potential risk factor for CMV reactivation and colitis. When GI bleeding occurs during dasatinib treatment, it is necessary to consider the possibility of CMV colitis combined with dasatinib-induced colitis. Patients with GI bleeding and confirmed CMV colitis may benefit from antiviral therapy by reducing symptoms as well as interruptions in dasatinib therapy.

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