Non-resolving colitis in a patient with acute lymphoblastic leukaemia: looking further, digging deeper

Cherie Le Si Gan[1], Wei Qiang Leow[2], Mark Chang Chuen Cheah[3], Chieh Hwee Ang[4], Yeh Ching Linn[4], Shimin Jasmine Chung[1]
[1] Department of Infectious Diseases, Singapore General Hospital. [2] Department of Anatomical Pathology, Singapore General Hospital. [3] Department of Gastroenterology and Hepatology, Singapore General Hospital. [4] Department of Haematology, Singapore General Hospital.

INTRODUCTION

Dasatinib is a second-generation oral Tyrosine Kinase Inhibitor (TKI) of BCR-ABL used in the treatment of Chronic Myeloid Leukaemia and Philadelphia chromosome positive (Ph+) Acute Lymphoblastic Leukaemia (ALL)[1]. We report the case of a patient with Ph+ B-ALL on dasatinib, who had both cytomegalovirus (CMV) colitis and dasatinib-induced colitis.

CASE REPORT

A 58-year-old Chinese lady presented with a one-day history of fever, abdominal pain, diarrhoea and haematochezia. She had been on treatment for Ph+ B-ALL with dasatinib 70mg once daily for the past 4 months and recently received systemic chemotherapy and blinatumomab 47 days and 8 days respectively before her presentation. She had fever of 38.6°C and blood pressure 95/62 mmHg. Her abdomen was soft, non-tender with active bowel sounds. She had no lymphadenopathy or rash. Labs showed pancytopenia with haemoglobin 6.8g/dL, white cells 3.55x10^9/L, platelet 79x10^9/L, as well as raised transaminases with alanine transaminase 82u/L and aspartate transaminase 85u/L. A timeline of her progress and key images are presented on the right.

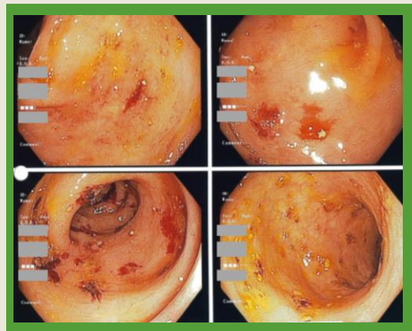

Figure 1. Images of the sigmoid colon from flexible sigmoidoscopy. Diffuse patchy colitis from the rectum till splenic flexure with erosions, contact bleeding and loss of vascular markings.

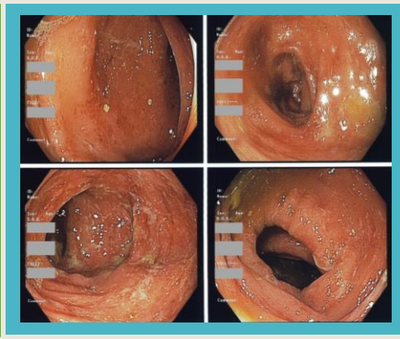

Figure 4. Images from 3rd colonoscopy, after 6 weeks of CMV treatment and treatment for *C difficile* colitis. **Persistent, and endoscopically worsening pancolitis**. Slough seen with markedly inflamed mucosa, and loss of vascular markings.

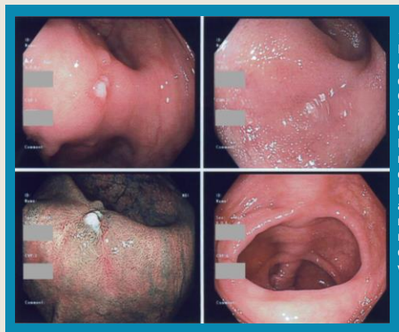

Figure 5. Images from final colonoscopy after completion of CMV treatment and cessation of dasatinib. Endoscopic resolution of colitis, with normal mucosa and vascular markings. Single resolving residual caecal ulcer visualised.

Week 1 of illness

- Symptoms: fever, diarrhoea, abdominal pain, haematochezia
- Plasma CMV PCR **12,229 IU/mL**
- Sigmoidoscopy [Fig. 1] and colon biopsies [Fig. 2] consistent with CMV colitis

IV foscarnet (90mg/kg BID)

Week 4 of illness

- Symptoms improved
- Plasma CMV PCR undetectable
- Discharged with PO valganciclovir
- Dasatinib continued throughout

PO valganciclovir (900mg BID)

Week 5 of illness

- Recurrence of diarrhoea and abdominal pain 7 days post discharge
- Colonoscopy: diffuse pan-colitis
- Biopsies negative for CMV [Fig. 3]
- Stool *C. difficile* toxins positive

PO vancomycin 125mg QID Valganciclovir → foscarnet

Week 7 of illness

- Symptoms persisted despite 6 weeks of CMV therapy + 10 days vancomycin for *C. difficile* colitis
- Workup for other etiologies non-yielding (stool bacterial/AFB cultures, stool parasite microscopy, plasma adenovirus PCR)
- 3rd colonoscopy: **worsening colitis** [Fig. 4]
- Biopsies: severe colitis but only single CMV inclusion (inflammation out of proportion to CMV cytopathic changes). Drug-induced colitis suspected → **dasatinib stopped**

Week 9 of illness and beyond

- Symptoms resolved 2 weeks after dasatinib cessation
- Final colonoscopy at end of 11 weeks of CMV treatment showed resolution of colitis [Fig. 5].
- Dasatinib switched to ponatinib, a third-generation TKI.
- She successfully underwent an allogenic stem cell transplant 3 months later, with no further recurrence of CMV disease

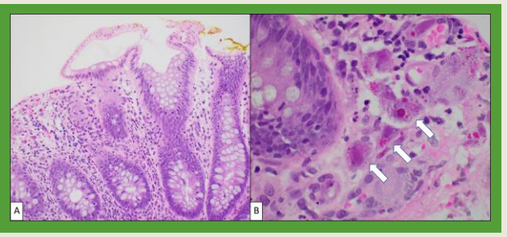

Figure 2. Histopathological examination of the colon biopsies (H&E stain).

Figure 2A (Left): descending colon mucosa with mild acute colitic changes (200x).

Figure 2B (Right): Multiple CMV viral inclusions (white arrows) within the more inflamed sigmoid colon mucosa (600x).

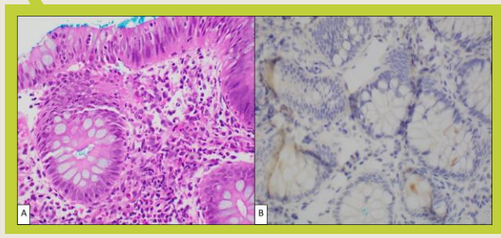

Figure 3. Histopathological examination of the caecal biopsies from colonoscopy after 4 weeks of CMV treatment (H&E stain)

Figure 3A (Left): Severe active colitis (400x).

Figure 3B (Right): Negative CMV immunohistochemical stain on caecal biopsy specimen (400x).

DISCUSSION

Dasatinib-induced colitis is an immune-mediated colitis which can occur a median of 3 months after dasatinib initiation (range 18 days to 3 years)[2]. It may be preceded by large-granular-lymphocytosis in peripheral blood, with clonal expansion of cytotoxic CD8+ T cells or Natural Killer (NK) cells[3]. Some authors postulate that dasatinib can cause such immune-mediated side effects due to its multiple off-target inhibitory activity against other kinases such as SRC family of kinases, which results in hyper-reactivity of CD8+ T cells or NK cells[3].

Dasatinib is associated with elevated infective risks. Neutropenia from drug-induced myelosuppression increases risk of bacterial or fungal infections[4]. Also, dasatinib impairs cell-mediated immunity, in particular cytotoxic T cells, increasing risk of viral infections or reactivations such as CMV[4, 5]. Literature review reveals multiple case reports of CMV colitis in patients on dasatinib[2,5,6]. Generally, successful treatment entails both CMV treatment and discontinuation of dasatinib; treating CMV alone without cessation of dasatinib is usually ineffective[2,6]. Dasatinib may be resumed after CMV colitis resolves[6].

CONCLUSION

Clinicians should evaluate for CMV colitis in patients on dasatinib who develop diarrhoea, abdominal pain or haematochezia. One should also be mindful of infective and non-infective differentials for colitis in immunocompromised hosts. Drug-induced colitis must be considered if infective work-up is non-yielding or the patient's response to anti-infectives is poor.

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