Dasatinib-induced colitis: a case report

Sir,

We report a case of subclinical colitis induced by dasatinib (a BCR/ABL tyrosine kinase inhibitor) in a 61-year-old female with chronic myelogenous leukaemia (CML) in chronic phase. CML was diagnosed in late 2013. Initial breakpoint cluster region-Abelson murine leukaemia (BCR-ABL) quantitative level was 26% prior to the commencement of treatment. Dasatinib 100 mg was started in December 2013. There was an excellent response with reduction in the BCR-ABL quantitative level to 0.18% by 3 months, and major molecular response after 6 months of dasatinib therapy.

After 9 months of therapy, it was noted that the patient had developed a microcytic blood film with iron deficiency; ferritin was 39 μg/L with a transferrin saturation of 10%. Physical examination was normal and she had no significant gastrointestinal symptoms or signs of gastrointestinal bleeding. A stool culture for common bacterial pathogens and parasites was negative. To investigate the patient's recent onset iron deficiency, a referral to a gastroenterologist was made and gastroscopy and colonoscopy were performed. Gastroscopy was unremarkable; however, the colonoscopy identified numerous, diminutive (<3 mm), pigmented nodules throughout the colon. Histology revealed a mild to moderate, active inflammation with cryptitis. The inflammatory infiltrate contained a mixture of lymphocytes, plasma cells, eosinophils and neutrophils. Very occasional branched crypts and borderline basal plasmacytosis were also features. Crypt abscesses were not seen. There was no ulceration or fibrosis. Pseudopyloric metaplasia was not a feature. There were no Paneth cells. Patchy surface mucin depletion was noted, probably representing regenerative changes.

The differential diagnoses for the observed endoscopic features include a drug reaction, infectious colitis (though this was excluded on stool testing), nodular lymphoid hyperplasia (more common in the small bowel), primary or secondary colonic malignancy (including squamous cell carcinoma or melanoma). Inflammatory bowel disease was thought to be less likely given the unusual appearances and lack of ulceration or associated endoscopic inflammation. In addition, the atypical features and lack of risk factors meant that an ischaemic cause was excluded.

These findings were thought to be related to dasatinib therapy. Despite this, as the patient had had an excellent response to dasatinib and a lack of clinically significant consequences of the colitis, the tyrosine kinase therapy was continued. She remained on dasatinib 100 mg with no clinical side effects of therapy and stable haematinics.

The nodules were found at a repeat colonoscopy 3 years later (performed due to positive faecal occult blood test) and biopsied (Fig. 1). The histological findings were more prominent on this occasion, and revealed a multifocal active pan-colitis with patchy borderline basal plasmacytosis. In view of the basal plasmacytosis and previous crypt architectural distortion, inflammatory bowel disease was considered (though based on clinical history and endoscopic appearances this was thought less likely). Histologically, diverticular disease related colitis could also give this pattern of inflammation.

A chronic infection was also a strong suggestion; however, stool culture was negative and selected organisms could not be found [periodic acid-Schiff (PAS) stain for amoebic organisms and CMV immunostain were negative].

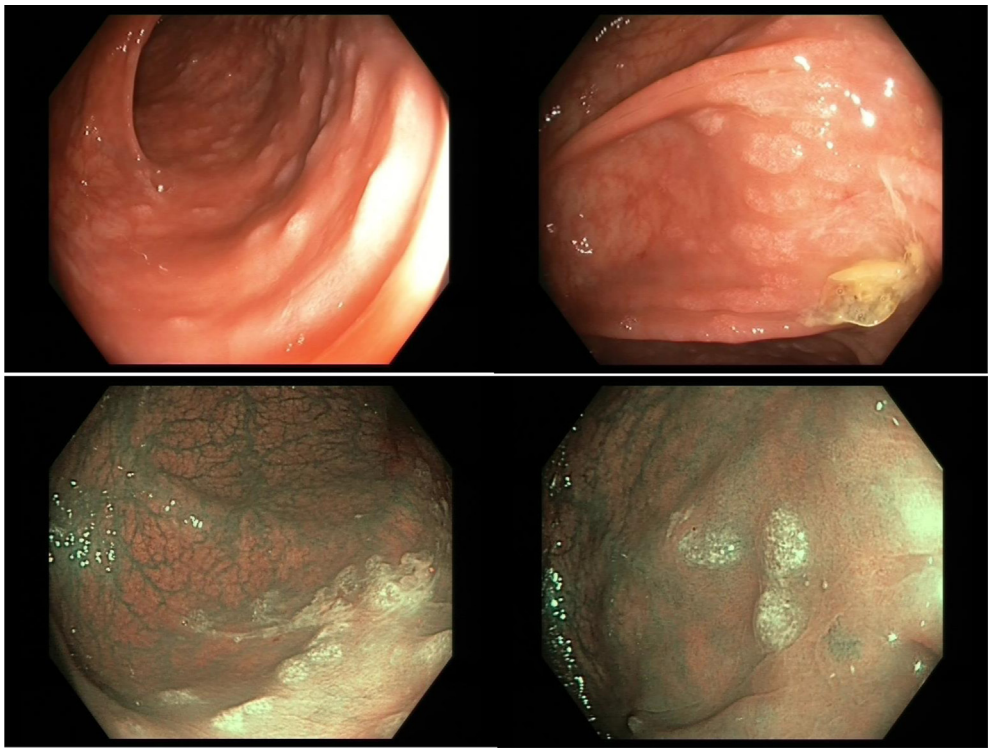

Fig. 1 Discrete, raised, discoloured nodules seen throughout the colon, which are more prominent when viewed with narrow-band imaging (NBI) as seen in the lower panel.

Pseudomembranous colitis or antibiotic related colitis was not entertained in the histological differential diagnosis as eruptive necrosis or pseudomembranes were not seen. Ischaemic colitis was unlikely in the absence of crypt withering or capillary thrombosis. There was no vasculitis or amyloid deposition (Congo red stain did not show interstitial or vessel wall pink deposits suggestive of amyloid). There were no features of GVHD such as crypt apoptosis. Immunohistochemistry demonstrated a predominantly T-cell lymphocytic infiltrate within the lamina propria which was enriched for CD8+ compared to CD4+ (Fig. 2). There were only very occasional FOXP3+ (expressed by regulatory T-cells) lymphocytes and virtually non-existent CD56+ lymphocytes.

These features are consistent with subclinical dasatinib-induced colitis. Given the lack of clinically significant symptoms and the excellent response to therapy, dasatinib therapy was continued.

The Philadelphia chromosome is the result of a translocation between chromosome 9 and 22, commonly denoted as t(9; 22) (q34; q11). This results in the fusion gene, *BCR-ABL1*, which produces a constitutively active tyrosine kinase. The continuous, unregulated activity of this tyrosine kinase results in unchecked proliferation of haematopoietic cells and leads to the development of chronic myelogenous leukaemia (CML).[1] Dasatinib is a second-generation tyrosine kinase inhibitor (TKI) which is approved as a first line treatment for CML.[2] Dasatinib is active against the ABL1 domain, but also has efficacy against the Src family kinases (Lck, Yes, Lyn and Fyn), c-KIT and platelet derived growth factor receptor-β (PDGFR-β). It has been shown to be effective in cases of resistance or intolerance to imatinib, due to more potent BCR-ABL antagonism. In first line therapy, dasatinib use is associated with faster and deeper levels of response compared with imatinib, with high levels of progression free, and overall, survival.[3] However, the activity of dasatinib against a broader range of targets compared with imatinib may contribute to its side effect profile.

Five year follow up of the phase III DASISION trial confirmed the safety and efficacy of dasatinib as first line therapy in CML.[3] However, gastrointestinal tract side effects have been noted with dasatinib therapy and it has been shown to cause occult gastrointestinal bleeding in 2−12% of cases.[4,5] Dasatinib affects platelet activation and aggregation (by inhibition of Src family kinases), as well as impairing the ability of megakaryocytes to form pro-platelets, exacerbating the patient's inability to achieve haemostasis.[6]

A recent prospective study investigated the frequency of dasatinib-induced colitis and the screening efficacy of faecal occult blood tests (FOBT).[7] Ten of 18 patients treated with dasatinib had a positive FOBT and went on to have colonoscopy and mucosal biopsy. Six of these patients (33%) had dasatinib-induced colitis and only one patient still had a positive FOBT when dasatinib was withheld. Another study reviewing the literature identified only 13 articles (10 case reports, 2 single centre case series and 1 multicentre series)

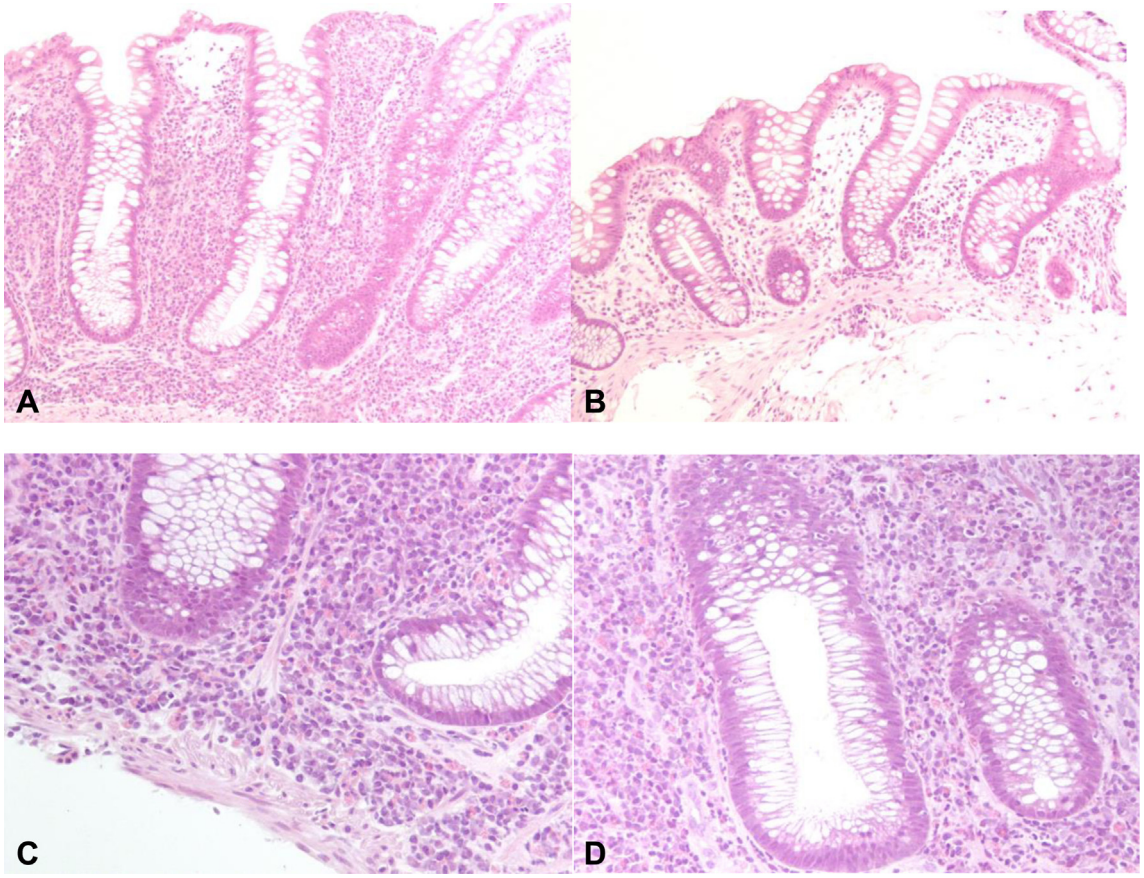

Fig. 2 (A) Mild to moderate active colitis with preserved crypt architecture. (B) Some fragments show a mild oedema without active inflammation. (C,D) Cryptitis and patchy basal plasmacytosis.

reporting colitis directly associated with dasatinib therapy.[8] However, this may be a result of under-reporting of this condition rather than a true reflection of its prevalence.

There have been various theories postulated as to the mechanism of dasatinib-induced colitis. It has been hypothesised that dasatinib reduces immune tolerance.[6] Dasatinib interrupts the Src family kinase signalling pathway and thereby reduces the number of regulatory T cells in the bowel. In this way, dasatinib limits host natural immune tolerance to commensal intestinal microflora.[6,9] This allows commensal microflora to become pathogenic and cause the colitis that we associate with dasatinib. In our case the targeted colonic biopsies showed a primarily T cell infiltrate, with an increased CD8+:CD4+ ratio. In addition, there was a relative lack of regulatory T cells and NK cells, as evidenced by the sparsity of FOXP3 staining cells and absence of CD56 staining cells. The lack of regulatory T cells and reduced numbers of NK cells are in keeping with the presumed mechanism of dasatinib-induced colitis.

Dasatinib may cause a drug-induced, immune-mediated colitis in susceptible patients. This seems to be a result of the drug's broad inhibition of off-target kinases involved in regulatory T cell and NK cell proliferation, causing impaired immune tolerance. The mechanism of immune dysregulation appears to be different from the inflammatory bowel disease model, where FOXP3+CD4+ T cells predominate. Dasatinib-induced colitis is a relatively uncommon phenomenon and reverses with drug cessation. However, in cases of milder colitis or those with limited alternative therapeutic options, continuation of dasatinib is acceptable. We report a case of subclinical dasatinib-induced colitis, to add to the developing body of literature relating to this pathological process.

Conflicts of interest and sources of funding: The authors state that there are no conflicts of interest to disclose.

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DOI: https://doi.org/10.1016/j.pathol.2019.07.013

Novel apolipoprotein AII mutation associated renal amyloidosis and fibrillary/immunotactoid cardiomyopathy

Sir,

We present the case of a novel apolipoprotein AII (apoAII) mutation related systemic deposition disease with both renal amyloidosis and cardiomyopathy with a fibrillary (F)/immunotactoid (IT) deposition pattern on electron microscopy (EM).

A 63-year-old man with end stage kidney disease secondary to amyloidosis was admitted to hospital for work-up prior to renal transplantation. Five years prior, an incidental finding of elevated creatinine and proteinuria had led to renal biopsy. In 2014 he had subsequent renal biopsies, which all showed similar features of amyloid deposition. On light microscopy (LM) there were amorphous, eosinophilic, extracellular deposits in the mesangium and arterial walls, which stained positively with Congo red and showed apple green birefringence under polarised light (Fig. 1A). Amyloid A immunoperoxidase (IPX) staining was positive (Biocare Medical, USA), while kappa and lambda immunoglobulin light chain IPX (Cell Marque, USA) showed no evidence of light chain restriction. EM confirmed the diagnosis of amyloid, demonstrating non-branching fibrils, randomly arranged, with a diameter of 8.7–12.0 nm (Fig. 1B). Genetic sequencing of lysozyme (exon 2), fibrinogen (exon 5), transthyretin (TTR, all coding exons) and apolipoprotein A1 (exon 3) failed to show any known or new DNA changes, which could be attributed to the diagnosis of hereditary amyloidosis. The patient was given a provisional diagnosis of amyloid AA, likely due to his recurrent, untreated gout.

Despite good control of his gout and normalisation of his serum amyloid A (SAA) protein levels with allopurinol, there was a progression of the renal impairment over the following years resulting in renal failure and the patient commencing peritoneal dialysis. During this time amyloid was detected in abdominal fat biopsies and incidentally in a transurethral resection of prostate. As the disease progressed, concern arose that the initial amyloid typing as AA may have been incorrect.

In the meantime, on the premise that the patient had amyloid AA and that the SAA was well controlled, the patient began work-up for renal transplant from a live dedicated donor.

A transthoracic echocardiogram (TTE), performed as part of his pre-transplant investigations, showed a moderate