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Case Report

Dasatinib-Induced Colitis: Risk of misdiagnosis of inflammatory bowel disease. A case report and review of the literature

Graziana Arborea[1]*, Anna Maria Valentini[1], Stefania Marangi[2], Nicoletta Labarile LT[1] and Maria Teresa Savino[1]

[1]Department of Pathology, National Institute of Gastroenterology "S. de Bellis", Research Hospital, Castellana Grotte, Bari, Italy

[2]Department of Gastroenterology, National Institute of Gastroenterology "S. de Bellis", Research Hospital, Castellana Grotte, Bari, Italy

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***Corresponding authors:** Graziana Arborea, MD, Department of Pathology, National Institute of Gastroenterology "S. de Bellis", Research Hospital, via Turi 27, 70013 Castellana Grotte, Bari, Italy,
E-mail: graziana.arborea@irccsdebellis.it

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Abstract

Dasatinib is a potent tyrosine kinase inhibitor, in disease states associated with BCR/ABL 1, approved in 2006 for chronic myeloid leukemia treatment. This agent has been shown to exhibit broad off-target kinase inhibition and immunomodulating properties. These effects may be responsible for common adverse reactions (> 15%) which include immunosuppression, cytopenias, pleural effusion and other fluid retention, diarrhea, and other gastrointestinal side effects.

Although gastrointestinal bleeding is a well-documented side effect, the presentation of colitis is an uncommon occurrence.

In most cases, it is hemorrhagic colitis, nonspecific colitis, or CMV-related colitis.

We report a 34-year-old male patient affected by CML in treatment with Dasatinib for approximately 1 year, who reported chronic diarrhea which progressed to suspected Dasatinib-induced colitis whose clinical, endoscopic, and histological findings overlapped those of Inflammatory Bowel Disease.

Introduction

Chronic Myeloid Leukemia (CML) is one of the most common leukemias occurring in the adult population. The course of CML presents three possible phases: the chronic phase, the acceleration phase, and the blast phase.

Pathophysiology of CML revolves around Philadelphia chromosome that constitutively activates tyrosine kinase through BCR-ABL1 oncoprotein. In the era of Tyrosine Kinase Inhibitors (TKIs), CML patients now have a similar life expectancy to people without CML, and it is now very rare for these patients to progress to the blast phase. Only a small proportion of CML patients have resistance to TKI, caused by BCR-ABL1 point mutations. CML patients with TKI resistance should be treated with second or third-generation TKI, depending on the BCR-ABL1 mutation [1].

Dasatinib (SPRYCEL, Bristol-Myers Squibb, NewYork, NY, USA)is a second-generation Tyrosine Kinase Inhibitor (TKI), which is approved as a first-line treatment for Chronic Myelogenous Leukemia (CML), obtaining faster and deeper levels of response compared with Imatinib [2], leading to high levels of progression-free and overall survival.

Dasatinib is also well tolerated and offers meaningful advantages for CML-CP patients [3].

The randomized, phase III DASISION trial demonstrated improved efficacy with dasatinib compared with imatinib in treatment-naïve CML-CP patients.

At 5 years, dasatinib 100 mg once daily has demonstrated superior outcomes compared to imatinib 400 mg once daily as initial therapy for CML. In addition, the 5-year analysis from the phase III Dasatinib Versus ImatinibStudy in Treatment-

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Naïve Chronic Myeloid Leukemia Patients (DASISION) trial, evaluated long-term efficacy and safety outcomes of patients with Chronic Myeloid Leukemia (CML) in Chronic Phase (CP) treated with dasatinib or imatinib.

Results from the final 5-year dasision study demonstrated that patients taking dasatinib had more rapid and profound MRs than those taking imatinib.

There are no new safety signals observed with dasatinib in long-term follow-up.

These results suggest that first-line dasatinib could still be considered a standard of first-line therapy for patients with newly diagnosed CML [4].

So, the phase III DASISION trial confirmed the safety and efficacy of Dasatinib as first-line therapy in CML but highlighted the possibility of gastrointestinal tract side effects: occult gastrointestinal bleeding occurs in 2% -12% of cases [5].

A survey looking at bleeding diathesis in CML patients receiving Dasatinib confirmed that it is in the gastrointestinal tract that 81% of all bleeding episodes occur [6]. Gastrointestinal bleeding is consistent with the oral route of Dasatinib and its subsequent elimination in the faeces [7]: exposure of the bowel to Dasatinib during its elimination may make the lower gastrointestinal tract particularly vulnerable, and this may explain the development of colitis in these patients [6].

Dasatinib treatment can lead to hemorrhagic colitis, which typically resolves after discontinuation of the drug [8].

A recent prospective study reports Dasatinib-induced haemorrhagic colitis in one-third of CML patients treated with Dasatinib [9,10].

The histologic pattern of active colitis, with acute cryptitis and crypt abscesses, is described in a few reported cases [11].

We present a case of Dasatinib-Induced Colitis in which the histological findings overlapped those of Inflammatory Bowel Disease (IBD).

Case report

A young 34-year-old male was diagnosed with Philadelphia chromosome positive-CML, and treated with Dasatinib at a daily dosage of 100 mg. Before the drug administration, he had no gastrointestinal symptoms such as vomiting, diarrhea, weight loss, or bleeding from any site. After approximately 1 year, he developed chronic diarrhea lasting for almost 3-4 months, so a gastroenterology appointment was scheduled.

Following this consultation, the medical team performed a bacteriological and parasitological stool examination that resulted in negative.

Subsequently, they performed a total colonoscopy due to suspected neutropenic or drug-induced colitis. Multiple shallow areas of mucosal erosion measuring 6-8 mm in the descending and sigmoid colon emerged in the investigation. Therefore, the team carried out biopsies of the ileum, colon – right and left- and rectum.

The histological examination revealed a mild to moderate active inflammation with mild cryptitis (Figure 1). The inflammatory infiltrate was composed of a mixture of lymphocytes, plasma cells, neutrophils, and increased numbers of eosinophils (> 20/HPF) (Figure 2).

Very occasional branched crypts (Figure 3), borderline basal plasmacytosis and focal surface microabscesses (Figure 4) and erosion (Figure 5) were also evident. No crypt abscesses were seen.

Immunohistochemical staining excluded CMV infection.

The observation of basal plasmocytosis and crypt architectural distortion raised the hypothesis of inflammatory

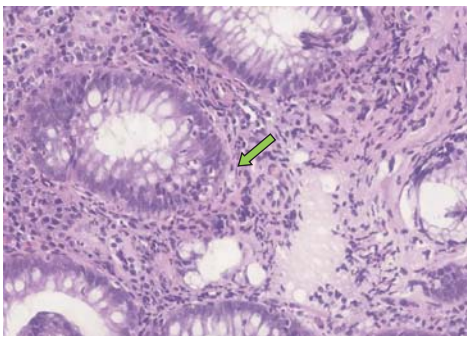

Figure 1: H&E 20x Mild cryptitis (green arrow).

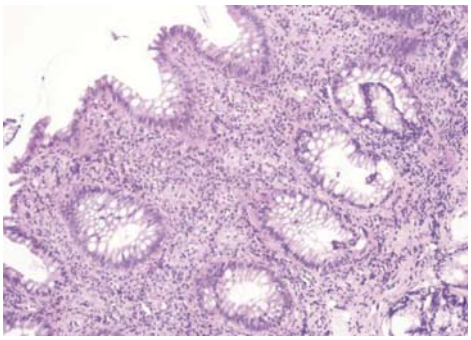

Figure 2: H&E 10x Mild to moderate active inflammatory infiltrate composed of a mixture of lymphocytes, plasmacells, neutrophils and an increased number of eosinophils.

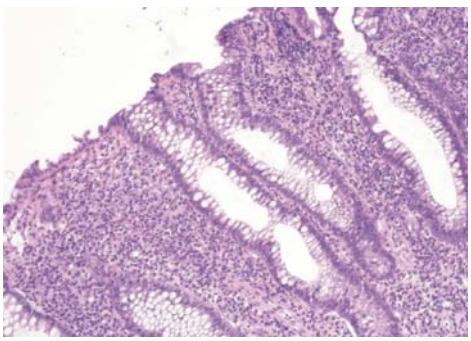

Figure 3: H&E 10x Occasional branched crypts.

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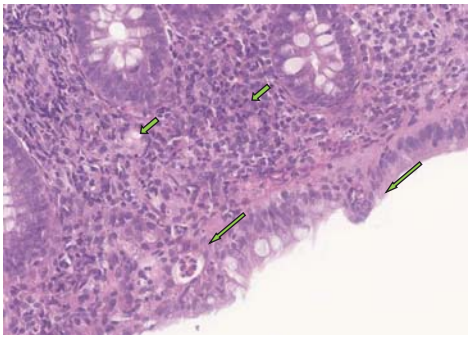

Figure 4: Focal surface microabscesses 20x).

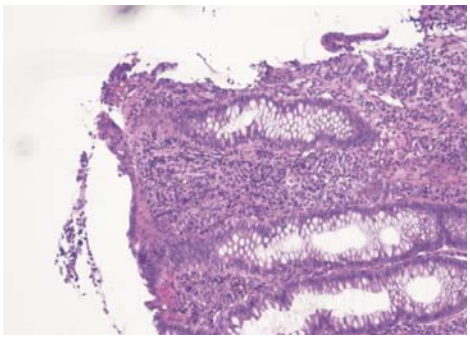

Figure 5: H&E 20x Focal surface erosion.

bowel disease but on the basis of the clinical information, we were able to diagnose DIC.

Although patients with drug-induced colitis typically need to suspend the therapy, Dasatinib was continued without interruption or dose adjustment in our patient due to the absence of important gastrointestinal symptoms such as bloody stool or abdominal pain.

Our study highlights the possibility that dasatinib-induced colitis may not only be of the hemorrhagic type or non-specific colitis, as the literature reports in the last decade but that it may mimic a chronic inflammatory bowel disease, thus opening scenarios diagnostically complex.

The limit of our work is certainly represented by the small number of cases. Recently, however, the working group of Drs Grillo and Dr Mastracci of the University of Genoa has published a short report, in which they describe a novel Crohn's-like histopathologic pattern of Dasatinib-induced colitis [12].

We look forward to a further evaluation of the incidence of these specific inflammatory manifestations affecting the intestinal mucosa during treatment with Dasatinib in the future.

Systematic review

We searched for all case reports, series, and literature reviews, published in the past decade, that reported gastrointestinal side effects in patients affected by chronic myeloid leukemia in treatment with Dasatinib, by using "Dasatinib-induced colitis" as keywords.

We found 28 cases of DIC, confirmed on pathology (Table 1).

References may be found on Pubmed

DIC occurred in the 33-69 years age range and there appeared to be no gender differences in morbidity. In the DIC cases reviewed, colitis symptoms onset occurred between one month and three years from the beginning of therapy, except for a single case in which colitis appeared after 6 years [13]. Most episodes occurred after 3-month drug exposure. These data suggest that this side effect usually follows a few weeks to some months after the initiation of therapy, but can also occur several years after treatment.

The symptomatology and clinical presentation of DIC are extremely variable, as shown by our review. Among the analyzed cases, six cases featured asymptomatic colitis, diagnosed through a histological examination conducted following FOB positivity [13,14], ten patients had chronic diarrhea -of which four with blood diarrhea [6,15-17], and two with watery diarrhea [18,19], two patients had the fever [18,20] and four patients had persistent abdominal pain [11,18,21,22], rectal bleeding was the chief complaint in four patients [22-25], hematochezia in seven patients [18,20,21,26].

Sigmoidoscopy/colonoscopy examination findings showed inflammatory changes in all cases, with shallow erosion and even haemorrhagic ulcers. Diffuse papular erythematous areas and diminutive nodules throughout the colon were identified in two cases [5,15].

The histopathological examination allowed haemorrhagic colitis to be identified in twelve patients and ulcerative colitis in only one [21]. Histology revealed four cases of active inflammation with cryptitis [5 11,13,14] and four cases with focal minimal active colitis [19,22,24], only one nonspecific colitis [16] and, in one case, mucosa with no significant pathological changes [6]. Five patients, during Dasatinib treatment, were diagnosed with CMV colitis, mimicking Dasatinib-induced haemorrhagic colitis [18]. CMV colitis is defined by the detection of the virus in a biopsy tissue, through microscopic finding and immunohistochemical staining. These cases suggest the possibility of CMV reactivation in patients on Dasatinib, so this reactivation should be considered in unexplained inflammatory responses during Dasatinib treatment [18]. Therefore DIC may have an association with CMV colitis, although the exact role of CMV in cases of Dasatinib-associated colitis remains unclear.

Discussion

The rearrangement of two particular chromosomes 9 and 22 in the BRC-ABL-1 fusion gene, known as the Philadelphia chromosome, is typically responsible for CML. This oncogene produces a constitutively activated enzyme (tyrosine kinase) responsible for the abnormally increased blood cell production in CML [5].

Dasatinib is a potent inhibitor of this kinase, as well as acting against Src kinases, c-kit, and PDGFR-beta (platelet-derived growth factor receptor-beta) [5,15].

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Table 1: Literature review of Dasatinib-induced colitis in the past decade and clinical-pathological features.

First Author [Ref]	Age / Sex	Time on Dasatinib	Clinical Presentation	Sigmoidoscopy	Pathology
Tamilarasan [5]	61 F	9 months	Iron deficiency without significant gastrointestinal symptoms	Numerous diminutive pigmented nodules throughout the colon	Moderate active inflammation with cryptitis
Maat [6]	34 F	7 months	Bloody diarrhoea	Patchy erythema and inflammation in the sigmoid colon with rectal sparing	Colonic mucosa with no significant pathological changes
Nishiwaki [9]	n.s.	n.s.	Asymptomatic	n.s.	Haemorrhagic colitis
	n.s.	n.s.	Asymptomatic	n.s.	Haemorrhagic colitis
	n.s.	n.s.	Asymptomatic	n.s.	Haemorrhagic colitis
	n.s.	n.s.	Asymptomatic	n.s.	Haemorrhagic colitis
	n.s.	n.s.	Asymptomatic	n.s.	Haemorrhagic colitis
	n.s.	n.s.	Asymptomatic	n.s.	Haemorrhagic colitis
Contino [11]	69 M	1 year	Abdominal pain diarrhoea and persistent anaemia	Erythematous angioctasias in the ascending colon, nodular erythematous mucosa with punctate white plaques in the descending and sigmoid colon	Active colitis, with acute cryptitis and crypt abscesses
Beltrán [13]	55 F	6 years	FOBT+, without significant gastrointestinal symptoms	Erythematous lesions on the colic mucosa with focal ulceration	Cryptitis with mild inflammation
Oshima [14]	56 F	1 year	Faecal occult blood in the absence of gastrointestinal symptoms	Multiple shallow areas of mucosal erosion with yellow exudate and congested erythematous lesions	Increased lymphocytes infiltration to the lamina propria with cryptitis
Chisti [15]	47 F	9 months	Bloody diarrhoea and pancytopenia	Inflammation of the descending colon	Haemorrhagic colitis
Perdigoto [16]	54 M	2,5 years	Bloody diarrhoea	Diffuse papular erythematous areas, more severe in the sigmoid colon	Nonspecific colitis
Yassin [17]	39F	30 months	Bloody diarrhoea	Multiple polypoid-like lesions all over the colon up to the hepatic flexure.	Haemorrhagic colitis
Choi [18]	67 M	14 months	Haematochezia	Edematous and friable mucosa along with a loss of vascularity from caecum to rectum. CMV-specific IHC staining positive	CMV colitis
	43 F	2 months	Watery diarrhoea and abdominal pain	Diffuse erythema and shallow ulcerations with spontaneous bleeding involving the rectum and sigmoid colon CMV-specific IHC staining positive	CMV colitis
	51 M	14 months	Hematochezia	Erythema, friability, and easy touch bleeding from the ileocecal valve to the sigmoid colon. CMV-specific IHC staining positive	CMV colitis
	54 M	3 months	Haematochezia and diarrhoea	Edematous mucosa and shallow erosions CMV-specific IHC staining positive	CMV colitis
	55 F	5 months	Haematochezia and fever	Mild erythema, ulceration with blood clot CMV specific IHC staining positive	CMV colitis
Riaz [19]	33 M	2 years	Watery diarrhoea	Severe active chronic inflammation with focal ulceration	Mild acute colitis
Ahn [20]	68 M	3 months	Hematochezia and fever	Several mucosal hyperemia spots and edema with spontaneous bleeding	Haemorrhagic colitis
Del Sordo [21]	58 M	3 years	Haematochezia and abdominalpain.	Isolated erythematous areas with mucosal erosions from the transverse to the descending colon and rectum	Moderate to severe ulcerative colitis
Aldoss [22]	47 M	108 days	Rectal bleeding	Inflammation	Focal, minimal active colitis
	47 M	3 months	Diarrhoea and abdominal pain	Inflammation	Mild acute colitis
Patodi [23]	59 M	3 years	Diarrhoea, rectal bleeding, and weight loss	Granular and congested mucosa in the rectus along with large ulcers on the descending colon	Haemorrhagic colitis
Shanshal [24]	43 F	3 months	Bright-red blood per rectum	The nodular patchy pattern of inflammation with a friable surface	Focallyactivecolitis
Nakaya [25]	69 M	2,5 years	Pleural effusion and rectal bleeding	Multiple haemorrhagic ulcers in the transverse colon	Haemorrhagic colitis
Yim [26]	54 M	1 month	Haematochezia is associated with a significant drop in hemoglobin levels	Multiple shallow ulcers with exudate and erythematous lesions on the mucosa involving the entire colon	Haemorrhagic colitis

n.s.: non specified

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Dasatinib has been approved for first-line therapy for CML, as well as second-line therapy when the patient exhibits intolerance or resistance, mainly to Imatinib therapy [15,27,28].

The randomized phase III DASISION trial demonstrated greater efficacy of Dasatinib compared to Imatinib in the treatment of CML [29]; in addition, Dasatinib is better tolerated and demonstrated a faster response within 3 months.

Although more effective and generally well tolerated, Dasatinib has a 22% incidence of local side effects [13]. Those are for the most part moderate and manageable, such as superficial edema, muscle cramps, skin rashes, nausea, and cytopenia [30] and include gastrointestinal disturbances, such as diarrhea and vomiting. In addition, systemic symptoms, such as anorexia and edema [15], are reported. In a high percentage of patients, gastrointestinal bleeding with faecal occult blood (FOB) is observed, unveiling a series of patients with active colitis [13].

Gastrointestinal bleeding has been reported in 2% - 9% of cases but although well documented in literature during Dasatinib therapy, Dasatinib-induced colitis (DIC) is a rare adverse event. In most cases DIC presents in haemorrhagic form, featuring bloody diarrhea which may appear from a few weeks to months after the start of therapy but also after a few years. This condition may require the suspension or a dosage reduction of the therapy [16]. DIC (except for cases of colitis-associated CMV) generally resolves within a few days after drug discontinuation but would recur within a short period of time, if the drug were reintroduced.

The mechanism underlying colitis is still unknown; theories advanced include an immune reaction, thrombocytopenia, platelet dysfunction, and impaired immune tolerance to the intestinal microbiota [11].

In particular, it is likely that this drug interferes with the activation and aggregation of platelets through the inhibition of the Src family, as well as preventing megakaryocytes from forming the platelet plug, thus preventing the activation of haemostasis [5]. This could act by reducing the number of T and NK lymphomonocytes [31] in the intestine, limiting the natural tolerance in the commensal intestinal bacterial flora and so causing DIC [21].

Our biopsies reveal changes indicative of chronic injury, in association with focal surface erosion and acute mild cryptitis. These histologic features cannot be differentiated pathologically from IBD and they appear as potential mimics of IBD. In our case, we were able to diagnose Dasatinib-induced colitis thanks to the clinical information. Without a pharmacological history, we could have concluded the onset of IBD.

Recognizing this Dasatinib-induced colitis has positive implications, such as avoiding overtreatment, including the use of specific IBD-drug therapy.

Conclusion

We present this interesting case of Dasatinib-induced Colitis in order to shed light on one hyperinflammation condition of the large bowl, drug-induced, which share clinical, endoscopic, and histologic features with IBD. The diagnosis of Ulcerative Colitis or Crohn's disease is straightforward, especially when patients have a typical presentation and characteristic histopathological features. Knowledge of the full clinical history is very important, particularly past and recent medical history and drug history. Accurate diagnosis of IBD and exclusion of IBD mimics are crucial for patient management. Serious errors in treatment could be the result. Close attention to the clinical picture, information on therapeutic treatment, and a careful approach to colo-rectal biopsy assessment by the pathologist should help reduce the chance of misdiagnosis of IBD.

Statement of ethics

This study was approved by both the local Scientific Committee and the Institutional Ethics Committee of the Oncologic Institute Research Hospital of Bari –Italy and was performed following the Declaration of Helsinki. The patient was compliant and willing to participate in the study. Written informed consent was obtained from the patient for laboratory investigations and clinical data recording.

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