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Single Case

Inflammatory Bowel Disease in a Patient Returning from Colombia: Association with Dipeptidyl Peptidase 4 Inhibitor?

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Keywords
Colitis · Drug-induced colitis · Dipeptidyl peptidase 4 inhibitor · Sitagliptin · Amebiasis

Abstract
Introduction: Recent-onset colitis poses a diagnostic challenge, necessitating a thorough evaluation to identify potential infectious and non-infectious etiologies. We considered inflammatory bowel disease (IBD) secondary to dipeptidyl peptidase 4 (DPP-4) inhibitor-induced colitis. ***Case Presentation:*** This case report details the presentation and management of a patient with persistent dysentery, refractory to conventional treatments, ultimately attributed to IBD possibly secondary to long-term DPP-4 inhibitor use. Following an episode of suspected amebiasis, the patient experienced prolonged bloody diarrhea with an endoscopic image compatible with ulcerative colitis. Extensive infectious diagnostics were negative. Ultimately, the cessation of sitagliptin therapy resulted in rapid symptom resolution and normalization of eosinophilia, as well as endoscopic improvement. However, after a few weeks, the patient was readmitted with diarrhea after continued cessation of sitagliptin. ***Conclusion:*** This case underscores the importance of considering IBD secondary to DPP-4 inhibitor use in the evaluation of patients with recent-onset IBD. Further research is needed to elucidate the pathophysiological mechanisms underlying the relationship between DPP-4 inhibitors and IBD.

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Introduction

Assessing patients with recent-onset colitis poses a relatively frequently encountered clinical dilemma. The initial risk evaluation takes factors such as travel history, medications, and human immunodeficiency virus (HIV) risk into account. This should be followed by a comprehensive clinical history, physical examination, stool studies, blood tests, and, in specific instances, endoscopic examination and serologic tests. Nevertheless, in some cases, the cause remains elusive after the initial analysis. In such scenarios, it is crucial to consider drug-induced colitis. In this report, we present a patient who was referred because of persistent dysentery for more than 4 weeks after being treated for suspected amebiasis with metronidazole (no contact amoebicides) in Colombia. However, with comprehensive diagnostics, all infectious causes were ruled out. We considered inflammatory bowel disease (IBD) secondary to dipeptidyl peptidase 4 (DPP-4) inhibitor-induced colitis.

Case Report

Herein we present a woman in her 60s with Colombian origin who recently came back from a 3-month stay in Colombia. In Colombia, she developed diarrhea, which started 3 h after consuming fish in a restaurant. The symptoms persisted for 4 weeks, and in November 2023 she presented to a local general practitioner who prescribed ciprofloxacin and diosmectin empirically. After 5 days without response, the patient was admitted with dehydration and hypokalemia in a hospital in Colombia (Fig. 1). A CT-scan showed inflammation, in particular proctocolitis and diverticulosis in the descending colon and sigmoid. The patient was treated with ceftriaxone and metronidazole, and in the following days a colonoscopy showed erythema and a cobblestone pattern in the descending colon. Furthermore, an inflammatory stenosis was observed between the sigmoid and colon descendens. Based on this finding, mesalazine was commenced. Colon biopsies showed colonic-type mucosa with a severe inflammatory process composed of lymphocytes, plasmacytes, neutrophils with formation of cryptic abscesses and up to 58 eosinophils per high-power field with ulceration and formation of degranulation tissue. There was mild focal glandular distortion and decreased mucus production, and small cells suggestive of trophozoites of *Entamoeba* spp. No granulomas were observed. The patient was treated with metronidazole for suspected amebiasis. The patient was further treated with sulbactam and mesalazine. The patient was admitted for approximately 4 weeks, after which she was discharged with persistent diarrhea. Three weeks later, she traveled back to the Netherlands, while still suffering from diarrhea. Upon returning to the Netherlands, she was admitted to the department of Internal Medicine, Amsterdam University Medical Centers, location Academic Medical Center. A comprehensive diagnostic panel was conducted to rule out infectious causes of diarrhea, including *Schistosoma*, *Strongyloides*, *Blastocystis*, *Cryptosporidium*, *Dientamoeba*, *Entamoeba histolytica*, HIV, Adenovirus, Astrovirus, Enterovirus, Norovirus, Parechovirus, Rotavirus, Sapovirus, CMV, *Mycobacterium tuberculosis*, *Plesiomonas*, *Campylobacter* spp., *Salmonella* spp., *STEC-1/2*, *Shigella* spp., *Y. enterocolitica*, *and Vibrio parahaemolyticus*. All tests returned negative results. Additionally, anti-tissue transglutaminase tests yielded negative results. A CT-scan revealed pancolitis without abscess formation. Subsequently, a colonoscopy (Fig. 2) detected severe inflammation and also a known inflammatory stenosis in the sigmoid colon that could not be passed by the colonoscope. In multiple biopsies of colonic mucosa, there was an increase in infiltration in the lamina propria with admixture of eosinophils. There were crypt abscesses and intraepithelial neutrophils granulocytes. The crypt epithelium is reactively changed. No entamoebae were seen (Fig. 3). CMV and TB staining were negative. Since 5.6% of

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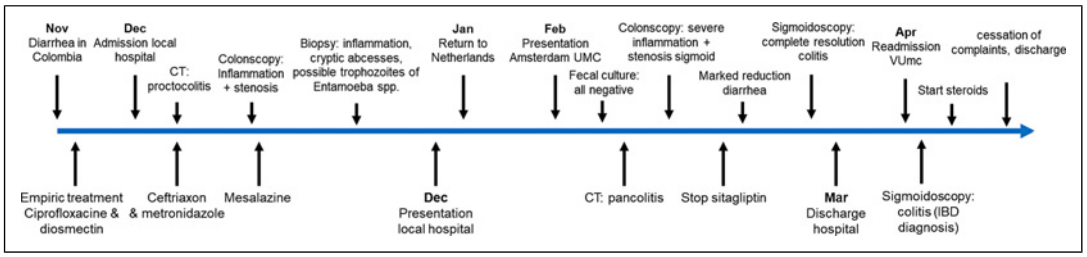

Fig. 1. Schematic overview of events that led to the diagnosis of IBD secondary to DPP-4 inhibitor use.

hospitalizations are related to iatrogenic disease, we have considered drug-induced colitis [1]. The patient was using amitriptyline, gliclazide, loperamide, semaglutide, alendronic acid, cholecalciferol, and sitagliptin. Based on a systematic review and meta-analysis by Radel et al. [2] which showed that in patients taking DPP-4 inhibitors, the risk of developing IBD was increased (RR = 3.01; 95% CI = 2.30–3.93) in a fixed-effects model, we considered a causal role of sitagliptin. Despite the observed eosinophilia, we considered a drug reaction with eosinophilia and systemic symptoms (DRESS) an unlikely diagnosis in our patient because of the absence of other systemic symptoms such as rash or other systemic involvement [3].

We stopped sitagliptin treatment, which the patient had been taking since July 2021. Remarkably, only 2 days after discontinuing sitagliptin, the frequency of diarrhea significantly decreased without any additional treatment. Four days post-discontinuation, the patient developed a urinary tract infection (urosepsis) caused by *Escherichia coli*, which was treated with ceftriaxone. Notably, the diarrhea had already ceased before the initiation of ceftriaxone treatment. During sitagliptin therapy, the patient exhibited eosinophilia (0.66×10^9/L), which resolved 4 days after the discontinuation of sitagliptin (0.02×10^9/L). Eleven days after cessation, the patient passed blood clots, prompting monitoring and transfusion of one unit of packed red blood cells. The patient underwent a sigmoidoscopy the following day, revealing the complete resolution of colitis (Fig. 2). The patient was discharged without any symptoms of diarrhea. However, after 4 weeks, the patient was readmitted to the hospital due to diarrhea complaints. Endoscopy showed features suitable for IBD. Steroid treatment was started with subsequent resolution of symptoms. Steroid therapy was tapered over time; however, the patient developed clinical signs of active disease, prompting induction therapy with steroids again, alongside a maintenance strategy with vedolizumab infusions. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000543680) [4].

Discussion

In this case report, we present a patient with DPP-4 inhibitor-associated colitis. Several arguments support a causative role of the DPP-4 inhibitor as a cause for IBD. First, the patient experienced diarrhea for 4 months without responding to various treatments, including 5-ASA treatment and multiple antibiotic regimens such as metronidazole and ceftriaxone. Following discontinuation of sitagliptin, the diarrhea rapidly resolved. Second, eosinophilia was observed during sitagliptin treatment and resolved 2 days after discontinuation, supporting a drug-induced origin [5]. Additionally, the initial biopsies revealed chronic inflammation that was non-specific for IBD and contained eosinophils. This atypical finding, combined with the presence of eosinophils, further suggests a drug-induced etiology [5, 6]. However, after stopping sitagliptin the patient developed diarrhea again, and after endoscopic

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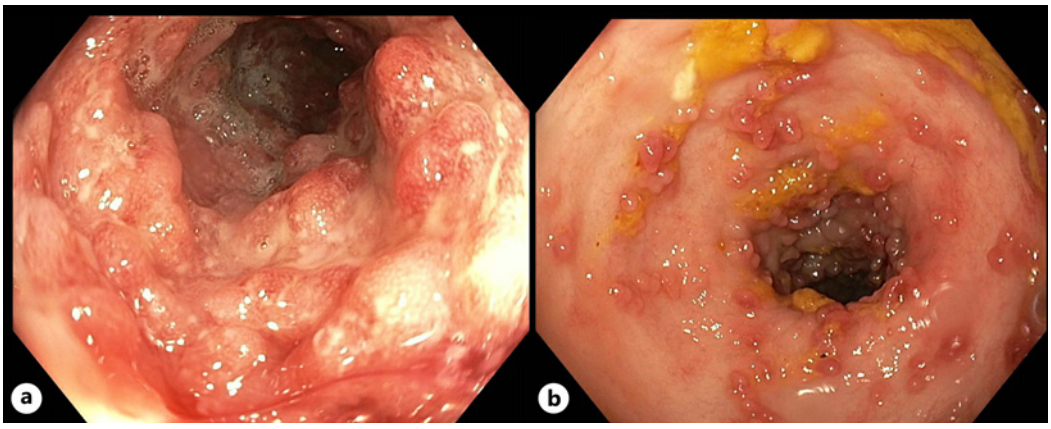

Fig. 2. Endoscopic images of prior to DPP-4 inhibitor cessation (on DPP-4 inhibitor therapy (**a**), 11 days after DPP-4 inhibitor cessation [13 days of first endoscopy] (**b**)). **a** Multiple hemorrhagic pseudopolyps suggesting colitis. **b** Marked endoscopic recovery after cessation of the DPP-4 inhibitor.

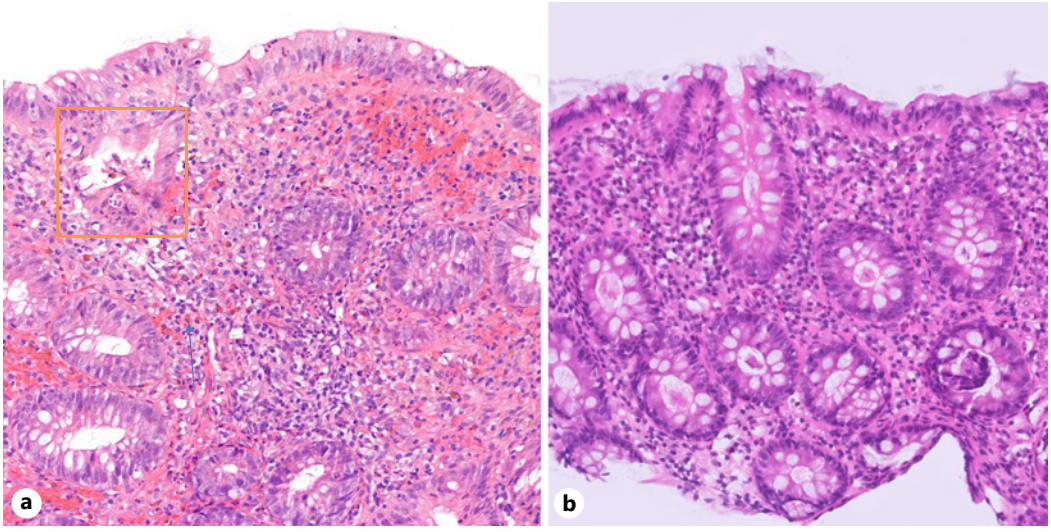

Fig. 3. Pathology images. **a** On DPP-4 inhibitor therapy, an increased infiltrate in the lamina propria with admixture of eosinophils (arrow) is seen. There is a crypt abscess and intraepithelial neutrophils granulocytes (square). **b** Biopsy taken after DPP-4 inhibitor cessation with a normal crypt pattern and a normal (physiological) infiltrate in the lamina propria with only occasional eosinophils. No active inflammation.

evaluation it became clear that the patient had developed IBD. So, this raised the question whether the initiation of IBD was related to the DPP-4 inhibitor [7]?

This is the second case report that reports on an association between DPP-4 inhibitor and colitis. Takedomi et al. [8] reported a case of a 60-year-old man with type II diabetes mellitus with sitagliptin who presented with refractory watery diarrhea. Similar to our case, this patient used sitagliptin and the onset of colitis was quite long (≈2.5 years) after initiation of therapy. This is in line with a population-based study showing that the overall risk of developing IBD was increased in patients using DPP-4 inhibitors (HR 1.75, 95% CI = 1.22–2.49) [9]. It was also shown that hazard ratios increased with longer duration of use, reaching a peak after 3–4 years of use (hazard ratio 2.90, 95% CI = 1.31–6.41), which adds evidence to a

drug-related cause of a duration-relationship. However, in contrast to our case, the patient of Takedomi et al. [8] presented with watery diarrhea without blood, and on biopsies collagenous colitis was shown. Drug-induced colitis may indeed present with different pathological findings [5].

The TECOS trial showed in sitagliptin-treated subjects with T2D [10] that plasma DPP-4 activity was markedly reduced at 12 months compared to those not treated with sitagliptin [11]. DPP-4 is an enzyme that degrades glucagon-like peptide-1 (GLP-1), thus directly promoting insulin secretion from β-cells which subsequently decreases glucose levels. In addition to the incretin hormones, there are over 45 identified DPP-4 substrates that influence various cellular functions. DPP-4 activates cytokines, chemokines and neuropeptides involved in inflammation [12]. In the literature, various reports suggest that DPP-4 may play a role in IBD pathophysiology. Jaenisch et al. [13] performed a cohort study with 220 IBD patients and 26 non-IBD controls, and found 30% lower total circulating DPP activity in active Crohn's disease (CD) patients compared with inactive disease. Furthermore, CD patients using sitagliptin had 21% lower circulating DPP-4 activity compared with non-IBD patients. Other authors also reported that the circulating DPP-4 expression is lower in CD patients compared to healthy controls [14]. Gene expression of DPP-4, FAP, and DPP8 was also significantly higher in colonic biopsies of patients with IBD compared with non-IBD patients, while total circulating DPP enzyme activity was lower, which may reflect the dysregulated IBD immune profile and aberrant activation of circulating lymphocytes [15].

Furthermore, decreased DPP-4 levels in serum and feces were reported in CD and ulcerative colitis (UC) patients [16]. In contrast to these studies that support that lower levels of circulating DPP-4 may be associated with increased IBD activity, various rodent reports were published that showed that DPP-4 inhibitors have a positive effect on induced colitis animal models through inhibition of T-cell proliferation and cytokine production and restoration of gut mucosal damage, respectively [17], which may reflect a species difference, as not all findings in mice can be translated to humans.

As mentioned in the introduction, Radel et al. [2] performed a meta-analysis on the association between DPP-4 inhibitors and the risk of developing IBD. They included 16 individual studies consisting of a total of 198,404 patients. In their primary random-effect analysis, DPP-4 inhibitor exposure resulted in a non-significant increase in the risk of IBD (RR = 1.52; 95% CI = 0.72–3.24; I^2 = 54.2%). Moreover, when a sensitivity analysis was performed using a fixed-effects model, an increased risk of developing IBD was demonstrated (RR = 3.01; 95% CI = 2.30–3.93). In their meta-analysis, the risk of IBD was primarily driven by one very large study that contained 141,170 patients by Abrahami et al. [9]. The authors of the meta-analysis provided a comprehensive discussion, wherein they mentioned that most of the trials that were performed had a median duration of 1.92 years, which was considered rather short. As described by Abrahami et al. [9] and also in line with our case, colitis may develop after prolonged use of DPP-4 inhibitors. Hence, the majority of RCTs that were included in the meta-analysis of Radel et al. [2] were unlikely to detect the true risk of DPP-4 inhibitor induced colitis. We concur with the conclusion of Radel et al. [2] that continued post-marketing surveillance of DPP-4 inhibitors, especially in the context of drug-induced colitis and IBD, is needed.

Conclusion

In summary, this case underscores the clinical challenge of diagnosing colitis associated with DPP-4 inhibitor use. In this instance, the patient used a DPP-4 inhibitor for an extended period, which has been reported to be linked to the onset of IBD. Differentiating between DPP-

4 inhibitor-associated IBD and regular IBD remains difficult. However, several factors suggest a possible association with the DPP-4 inhibitor, such as the initial rapid resolution of symptoms after discontinuing sitagliptin and the presence of eosinophilia during treatment. Clinicians should remain vigilant for adverse drug reactions and thoroughly evaluate medications in patients presenting with IBD.

Statement of Ethics

This retrospective review of patient data did not require ethical approval in accordance with Dutch National Guidelines (https://www.rijksoverheid.nl/documenten/rapporten/2020/02/14/niet-wmo-plichtigonderzoek-en-ethische-toetsing). Written informed consent was obtained from the patient for publication of the details of their medical case and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

A.B.B. and D.J.S. were clinically responsible for the patient, and wrote the case. G.M.C.M. and N.K.H.B. were responsible for gastroenterology-related care and provided the endoscopy images and reviewed the manuscript. A.N.-B. was responsible for the clinical pathology images.

Data Availability Statement

The data that support the findings of this study are not publicly available due they are containing information that could compromise the privacy of the patient but are available from the corresponding author, A.B.B., on request, but only anonymized data will be available.

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