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CASE REPORT | INFLAMMATORY BOWEL DISEASE

Nintedanib-Induced Colitis Can Mimic Inflammatory Bowel Disease

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ABSTRACT

Nintedanib is a medication that has been increasingly used for treatment of idiopathic and progressive pulmonary fibrosis. In this case series, we describe 3 patients with colitis symptoms associated with nintedanib use. Nintedanib discontinuation resulted in symptomatic resolution in all patients. Budesonide decreased symptoms in 1 patient. Clinicians should be vigilant in taking a thorough medication history and include nintedanib as a cause for gastrointestinal symptoms including colitis.

KEYWORDS: nintedanib-induced colitis; Ofev; diarrhea; IBD

INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is a prototype of chronic, progressive, and fibrotic lung disease.[1] The prevalence of IPF seems to be increasing, with reported range from 10 to 60 cases per 100,000.[2] In 1 study, the prevalence was 494 cases per 100,000 in 2011 among individuals older than 65 years, which was twice as high as the prevalence reported 10 years earlier.[3] Nintedanib (Ofev) was approved by the US Food and Drug Administration in October 2014 for treatment of IPF.[4] It is also approved for progressive pulmonary fibrosis and systemic sclerosis–associated interstitial lung disease. Nintedanib is a multitargeted tyrosine kinase inhibitor with antifibrotic and anti-inflammatory effects that inhibit key pathways leading to pulmonary fibrosis.[5] Nintedanib was shown to reduce the decline in forced vital capacity, which is a surrogate of slowing of IPF progression.[6] Nintedanib may cause a wide range of gastrointestinal adverse events. We describe 3 cases of nintedanib-induced colitis. A summary of the case presentations and management is shown in Table 1.

CASE REPORTS

Patient A: A 74-year-old White woman with a medical history significant for diabetes, hypertension, IPF, and biliary pancreatitis status post cholecystectomy. The patient presented to the office with complaints of anorexia, nausea, vomiting, abdominal pain, diarrhea, and weight loss. Her symptoms started approximately 4 months after nintedanib initiation. A cholecystectomy had been performed around the same time her symptoms started. She was prescribed cholestyramine, colesevelam, pancreatolipase, rifaximin, and diphenoxylate/atropine with minimal improvement of symptoms. Diagnostic studies included negative stool studies for an infectious etiology and normal complete blood count (CBC). Computed tomography (CT) of her abdomen showed mild circumferential intestinal wall thickening extending from the transverse colon to the rectum. Subsequent colonoscopy showed patchy colitis, with biopsies noting mild-moderate acute and chronic inflammation with focal areas of cryptitis with no evidence of microscopic colitis, collagenous colitis, or inflammatory bowel disease (IBD). Given unclear etiology, she underwent repeat CT of the abdomen that showed persistent circumferential intestinal wall thickening and mucosal hyperenhancement of the rectum and colon. Given temporal relationship, her presentation was felt to be due to nintedanib-induced colitis, so she was instructed to stop the medication. Three days later, the patient reported complete symptomatic resolution.

Patient B: A 63-year-old White man with a medical history significant for scleroderma, systemic sclerosis–associated interstitial lung disease, atrial fibrillation, and liver cirrhosis presented with anorexia, nausea, vomiting, abdominal pain, diarrhea, and weight

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Table 1. Summary of the case presentations and management

	Patient A	Patient B	Patient C
Age/gender/race	74/F/White	63/M/White	69/F/White
Past medical history	Diabetes Hypertension IPF Biliary pancreatitis status post cholecystectomy	Scleroderma Systemic sclerosis–associated ILD (diagnosed 3 months before nintedanib initiation) Atrial fibrillation Cryptogenic decompensated liver cirrhosis with low MELD score	Hypertension Lung cancer status post resection IPF
Clinical features	Onset: 4 months after nintedanib initiation Symptoms: anorexia, nausea, vomiting, abdominal pain, diarrhea, and weight loss (22% of body weight)	Onset: 5 months after nintedanib initiation Symptoms: anorexia, nausea, vomiting, abdominal pain, diarrhea, and weight loss (10% of body weight)	Onset: unclear Symptoms: anorexia, nausea, vomiting, diarrhea, and weight loss
Relevant laboratory data	Normal CBC; stool studies for infectious causes were negative	Normal CBC except for anemia with hemoglobin of 10.4 g/dL; stool studies were not obtained	Normal CBC; stool studies for infectious causes were negative
Imaging	Left-sided colitis then pancolitis	Right-sided colitis	Pancolitis
Endoscopy	Colonoscopy: moderately erythematous mucosa in ascending, hepatic flexure, transverse, and sigmoid colon	Colonoscopy: no gross abnormalities seen	Colonoscopy: mild pancolitis
Colon biopsies	Mild-moderate acute and chronic inflammation with focal area of cryptitis	No biopsies were taken	Ulceration with patchy granular mucosa
Management	Patient treated with cholestyramine, colesevelam, pancreatolipase, rifaximin, and diphenoxylate/atropine for question of postcholecystectomy syndrome and chronic pancreatitis without significant benefit Nintedanib was discontinued with complete resolution of symptoms. A lower dose of nintedanib was later introduced with recurrence of GI symptoms	Patient treated with loperamide and simethicone without relief Nintedanib was discontinued with complete resolution of symptoms	Budesonide treatment was associated with partial improvement; PRN use of loperamide and diphenoxylate/atropine Nintedanib was discontinued with complete resolution of symptoms

CBC, complete blood count; GI, gastrointestinal; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; MELD, model for end-stage liver disease; PRN, pro re nata.

loss 5 months after starting nintedanib. CBC was normal except for anemia. Stool studies were not obtained. CT of the abdomen was notable for right colon wall thickening and enhancement (Figure 1). Subsequent colonoscopy was unremarkable. No biopsies were obtained. He was taking loperamide and simethicone without symptomatic relief. His clinical presentation was felt to be due to nintedanib, with discontinuation leading to complete symptomatic resolution.

Patient C: A 69-year-old White woman with a medical history significant for hypertension, lung cancer status post resection, and IPF on nintedanib presented with complaints of anorexia, nausea, vomiting, diarrhea, and weight loss, which had been ongoing for a few years. Diagnostic studies included negative stool studies for an infectious etiology and normal CBC. A diagnosis of IBD was initially entertained. Colonoscopy showed pancolitis with ulceration with patchy granular mucosa in the sigmoid colon. Pathology results were not suggestive of IBD. Subsequent CT of the abdomen on 2 occasions demonstrated persistent pancolitis (Figure 2). She was prescribed budesonide 9 mg with partial improvement of gastrointestinal symptoms but developed dermatological side effects. She was also on loperamide and diphenoxylate/atropine with minimal benefit. Because of concern for

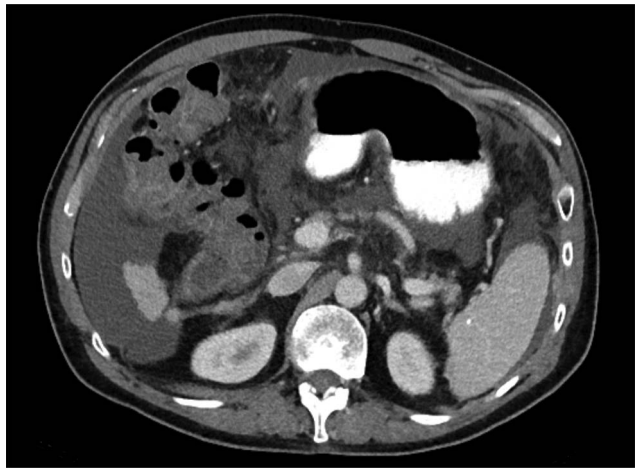

Figure 1. Computed tomography of the abdomen of patient B showing right-sided colitis.

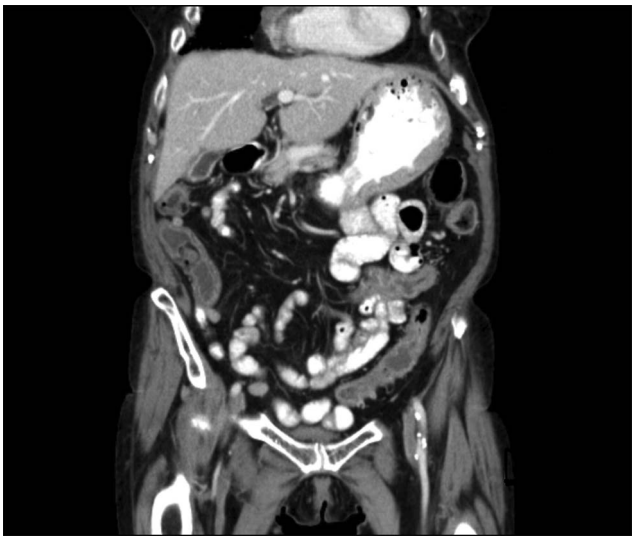

Figure 2. Computed tomography of the abdomen of patient C showing pancolitis.

nintedanib-induced colitis, nintedanib was discontinued with resolution of gastrointestinal symptoms.

DISCUSSION

Subsequent to its approval in 2014, nintedanib has been increasingly used in the treatment of IPF among other conditions. Nintedanib may cause gastrointestinal adverse effects, with diarrhea being the most common.[7] A literature search identified 9 cases of nintedanib-induced colitis.[8–15]

Our study of 3 patients with nintedanib-induced colitis significantly adds to the limited literature on this topic (summarized in Table 1). In our patients, the average age was 69 years, with 67% being female. The most common presenting symptoms were nausea, vomiting, diarrhea, anorexia, and weight loss (100%) followed by abdominal pain (67%). All patients were noted to have a normal CBC except 1 patient who was anemic. Of the 3 patients, 2 had stool studies negative for an infectious etiology, whereas stool studies were not obtained for patient B. Initial CT scan of the abdomen and pelvis demonstrated bowel wall thickening with mucosal enhancement in all patients, with 1 patient noting pancolitis, whereas the remaining 2 patients had right- or left-sided colitis. Endoscopic evidence of colitis was seen in 2 patients. All patients discontinued nintedanib with rapid improvement in abdominal symptoms.

The current 3 patient presentations are consistent with the 9 previously reported cases of nintedanib-induced colitis, including radiographic, endoscopic, or histologic evidence of colitis associated with nintedanib use.[8–15] In previous literature, the average age was 68 years, with 89% being male. Gastrointestinal adverse effects began a few days after starting therapy to as long as to 1.5 years[8] after initiation of nintedanib. Most cases in the literature demonstrated symptomatic improvement in gastrointestinal symptoms after nintedanib discontinuation except 1 patient whose symptoms improved only after oral prednisone was prescribed.[8] He, however, had recurrence of symptoms when he was rechallenged with the standard dose of nintedanib. Two of the 9 patients elected to continue nintedanib with 1 having symptomatic improvement with budesonide 9 mg,[11] whereas the other improved on *Bifidobacterium infantis* and loperamide.[10] IBD was one of the differentials in multiple case reports,[8,12,13] but none of the patients had confirmatory evidence to suggest IBD. Two patients had histological findings consistent with ischemic colitis,[13,14] whereas 2 others had subepithelial eosinophilic material in their pathology.[15]

Nintedanib-induced colitis can cause debilitating symptoms with a decreased quality of life and serious complications. It can also mimic IBD in some cases.[12] Clinicians should be vigilant in taking a history and including nintedanib as a cause of gastrointestinal symptoms including colitis.

DISCLOSURES

Author contributions: T. Odah drafted the article. C. Karime and JG Hashash revised the article for intellectual content. FA Farraye revised the article for intellectual content and is the article guarantor.

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Informed verbal consent was obtained for 1 patient; 1 cannot be reached, whereas the remaining patient was deceased. No identifying details are reported in the manuscript.

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