# Characterization of intractable diarrhea resulting from vismodegib treatment for basal cell nevus syndrome

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## INTRODUCTION

Basal cell carcinoma (BCC) is the most common type of skin cancer. Most BCC cases are slow-growing and are effectively treated with surgery, topical therapy, or radiation therapy.[1] However, certain BCCs can be aggressive and locally advanced or metastatic, rendering conventional treatment inadequate. Abnormal activation of the hedgehog signaling pathway is a key driver for BCC pathogenesis.[2] Vismodegib (Erivedge, Genentech) is a Food and Drug Administration–approved systemic hedgehog inhibitor used in the treatment of advanced BCCs, including the multiple BCCs found in Gorlin syndrome. Labeled indications of vismodegib are patients with metastatic BCC, patients with recurrent locally advanced BCC, or patients who are not candidates for surgery or radiation.[3]

Clinical studies have demonstrated that common adverse effects (≥15% incidence) of vismodegib include muscle spasms, alopecia, dysgeusia, weight loss, fatigue, nausea, and diarrhea. In a prospective study of 119 patients, 25% of patients had any grade of diarrhea and 1.6% of patients had grade 3 or grade 4 diarrhea.[4] Several studies have outlined the severity and timing of diarrhea occurrence during vismodegib therapy, which may lead to medication discontinuation. Colonoscopy is an integral part of the investigation of chronic diarrhea, and knowledge of the pathologic changes in medication-associated diarrhea can inform the differential diagnosis. We report previously undescribed endoscopic findings in a patient experiencing diarrhea because of vismodegib.

*Abbreviations used:*

BCC: basal cell carcinoma
IBD: inflammatory bowel disease

## CASE REPORT

We present a case of a 66-year-old man with a past medical history of locally advanced BCCs and metastatic BCC in the context of Gorlin syndrome and a 10-year history of vismodegib use (150 mg by mouth daily) with excellent response who developed diarrhea, requiring holding vismodegib.

He had a history of loose stools 2 or 3 times daily that began 2 years after starting vismodegib, consistent with Common Terminology Criteria for Adverse Events grade 1 diarrhea. There were no interruptions in vismodegib use before or during diarrheal episodes. A colonoscopy performed 5 years after starting vismodegib therapy was unremarkable. A colonoscopy performed 9 years after starting vismodegib showed mildly granular mucosa with loss of vascular pattern in the ascending and transverse colon. Random colon biopsies demonstrated chronic inactive colitis with focal architectural distortion. There were no signs of mucosal erosions or ulcers, viral inclusions, parasites, granulomas, metaplasia, dysplasia, or malignancy.

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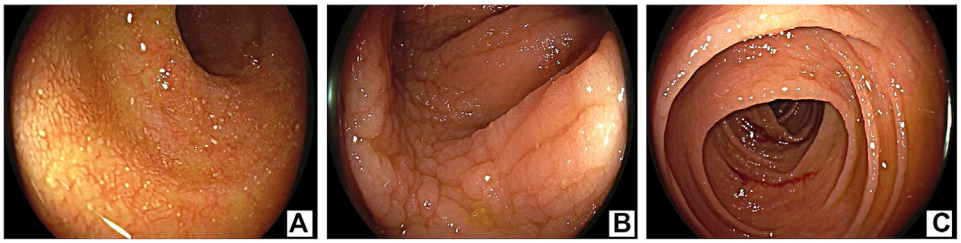


**Fig 1.** Colonoscopy findings of vismodegib-induced diarrhea showing (**A**) ilium with mucosal edema and granularity, (**B**) transverse colon with mildly granular mucosa and loss of vascular pattern, and (**C**) descending colon showing mildly granular mucosa with loss of vascular pattern.

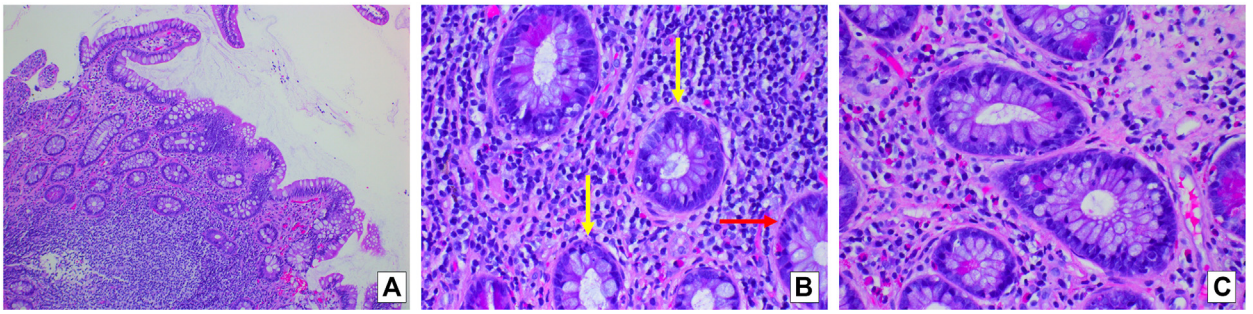


**Fig 2.** Microscopic findings of vismodegib-induced diarrhea in the ileum. Ileum biopsy sepcimens showing (**A**) mild villous blunting, (**B**) focal epithelial apoptosis (*yellow arrows*) and active ileitis (*red arrow*), and (**C**) focal active ileitis. **A** to **C,** Hematoxylin-eosin stain; original magnifications: **A,** ×10; **B,** ×40; **C,** ×40.

The patient most recently presented (10 years after starting vismodegib) with worsening watery diarrhea, consistent with Common Terminology Criteria for Adverse Events grade 2, which only partially resolved with loperamide (2 mg) up to 5 times daily. He had associated alopecia, dysgeusia, and muscle spasms, although these did not correlate time-wise with his diarrhea. He denied experiencing any abdominal pain, associated symptoms, or unintentional weight loss. Physical examination and workup, including blood count, a comprehensive metabolic panel, including electrolytes, thyroid stimulating hormone, tissue transglutaminase antibody, immunoglobulin A, and an infectious gastrointestinal panel through stool testing by polymerase chain reaction for bacterial (*Campylobacter, Clostridium, Escherichia coli, Salmonella, Shigella, Vibrio, Cryptosporidium, Cyclospora, Entamoeba, and Yersinia*) and viral (adenovirus, astrovirus, norovirus, rotavirus, and sapovirus) causes, were unremarkable.

A repeat colonoscopy showed diffuse mild ileal changes of congestion (edema) and granularity with punctate tiny erosions and exudate. Colonic edema, granularity, and a diffuse loss of vascular pattern were found (Fig 1).

The biopsy showed active ileitis with villous blunting and diffusely increased chronic inflammation in the lamina propria. Epithelial apoptosis of the crypts was noted (Fig 2).

Biopsies of the right colon, left colon, and rectum showed various degrees of crypt architectural distortion, mixed inflammation, epithelial apoptosis, and a crypt abscess (Fig 3). Immunostains for cytomegalovirus were negative.

Through correlation of clinical, endoscopic, and pathologic findings, the etiology of adverse drug effects were favored. To manage symptoms, 10 mg loperamide and 2 bismuth subsalicylate tablets daily were prescribed. Vismodegib therapy was held for 10 weeks, with resolution of diarrhea. After 10 weeks, vismodegib was restarted with continued tumor response. Diarrhea has not yet recurred 3 months after restarting vismodegib.

## DISCUSSION

Basal cell nevus syndrome (Gorlin syndrome) is caused by an inactivating mutation of the main inhibitor of the hedgehog pathway, resulting in the development of hundreds of BCCs. In a study of patients with Gorlin syndrome, patients receiving vismodegib had a significantly decreased number of new BCCs and reduced size of existing clinically significant BCCs.[5-7] After the first month of vismodegib treatment, hedgehog target-gene expression by BCC reduced by 90%.[7]

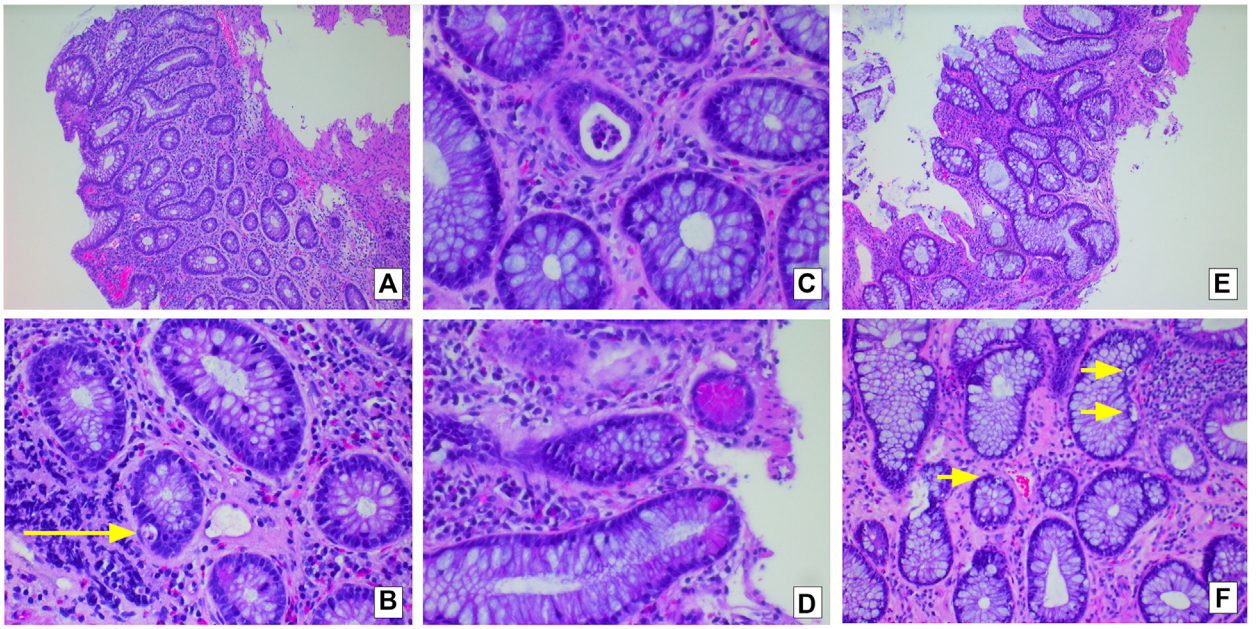


**Fig 3.** Microscopic findings of vismodegib-induced diarrhea in the colon. Colon biopsy sepcimen showing (**A**) the right colon with mild crypt branching and irregularity; (**B**) the right colon with epithelial apoptosis and mildly increased eosinophils (the *yellow arrow* highlights a focus of epithelial apoptosis); (**C**) the left colon with active inflammation with neutrophils and eosinophils within an atrophic crypt, (**D**) the left colon with Paneth cell metaplasia, indicative of chronic damage; (**E**) the rectum demonstrating architectural distortion with crypt branching and irregular crypts; (**F**) the rectum demonstrating that epithelial apoptosis was present (*yellow arrows* highlights foci of epithelial apoptosis). **A** to **F,** Hematoxylin-eosin stain; original magnifications: **A,** ×10; **B,** ×40; **C,** ×40; **D,** ×40; **E,** ×10; **F,** ×40.

However, the adverse events of vismodegib prevent many patients from long-term use. In 1 study, >50% of patients discontinued treatment because of adverse events, noting alopecia, weight loss, muscle cramps, and dysgeusia.[7] Diarrhea is a common adverse reaction, with approximately 25% of patients experiencing diarrhea during vismodegib therapy.[4] In an update to the ERIVANCE BCC study, of the 104 patients assessed, 26.9 % of patients had any grade of diarrhea, with 24.8% with grade 1 or 2 and 2.9% with grade 3 diarrhea.[8] Dose reduction has been shown to reduce the severity of adverse events in 55% of patients while maintaining the therapeutic benefit of vismodegib.[9]

The time to onset of diarrhea after initiation of vismodegib therapy and the severity of diarrhea are worthy of consideration, especially because the patient was not on any other medications. In a study with 119 patients in the safety-evaluable population receiving vismodegib, the median time to diarrhea onset was 38 days (95% CI 22-116). There were 23.5% of patients with grade 1 or 2 diarrhea and 1.6% of patients with grade 3 or 4 diarrhea.[4] An increased duration of exposure results in an increased occurrence and severity of diarrhea, with 20.8% of patients experiencing diarrhea of any grade within the first 12 months of exposure compared with 32.1% of patients who experience diarrhea >12 months of exposure.[8] Our patient had a unique case of late-onset diarrhea beginning 2 years after starting vismodegib, and this highlights that diarrhea does not always correlate with other common side effects, such as alopecia, muscle spasms, and dysgeusia.

The nonspecific histologic findings in this case yield a broad differential diagnosis of infectious causes (including viral infections), ischemia, graft-versus-host disease, inflammatory bowel disease (IBD), and medication/drug effects. However, the presence of epithelial apoptosis raises the likelihood of a medication-related etiology because epithelial apoptosis is characteristically associated with medication effects, graft-versus-host disease, and viral infections. The changes seen are not entirely specific, and many of the changes could also be seen in association with viral infections, which were included in the differential diagnosis. However, the presence of striking apoptosis can also be seen in association with medication/drug effects. In addition, the result of polymerase chain reaction–based testing for infectious etiologies (including bacterial and viral entities) was negative. A cytomegalovirus

stain performed on the tissue was also negative. There were no clinical symptoms warranting workup for malabsorption, such as weight loss or oily stool. These findings led us to conclude that a medication/drug effect was the most likely etiology. Inhibition of the sonic hedgehog pathway, such as in vismodegib use, has been associated with the inhibition of cell turnover.[10] Hedgehog protein and RNA expression are present in the colon, and data suggest that the hedgehog pathway is involved in the remodeling of the damaged epithelium through the effects of immune cells, such as $CD4^+$ T lymphocytes and macrophages.[11] Recent findings also suggest an upregulation of the hedgehog pathway during chronic inflammation.[11] In patients who use vismodegib, this pathway is inhibited, which could contribute to poor remodeling of the damaged epithelium. These findings and their association with vismodegib are important to recognize to prevent misdiagnosis of IBD because IBD presents with similar symptoms with chronic damage and architectural distortion. However, IBD typically presents with a more pronounced active inflammatory infiltrate and lack of epithelial apoptosis.

In conclusion, vismodegib remains an important treatment for patients with Gorlin syndrome. Diarrhea is a frequently encountered adverse event with unpredictable timing, and physicians should consider vismodegib-induced diarrhea in a patient with no signs of infectious or ischemic etiology, even if the timing of diarrhea does not correlate with other adverse effects. Villous blunting in the terminal ileum with crypt architectural distortion, increased inflammation, and epithelial apoptosis in the colon may support that the underlying etiology is an adverse drug effect from vismodegib. Temporary holding of vismodegib for 3 months resulted in the resolution of symptoms, and the patient has not had a recurrence of his diarrhea after resuming the standard 150 mg dose of vismodegib.

**Conflicts of interest**

None disclosed.

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