Accelerated Colorectal Polyposis in an Immunosuppressed Patient With a Small Bowel Transplant Treated With Teduglutide: Case Report and Review of Literature

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Clinical Practice Points

- Teduglutide is a dipeptidyl peptidase-4-resistant analogue of glucagon-like peptide 2 that is United States Food and Drug Administration-approved for patients with intestinal failure dependent on parenteral nutrition via its intestinotrophic properties.
- Various preclinical models suggest a possible role of glucagon-like peptide 2 in intestinal polyposis and carcinogenesis; however, available human trials have not demonstrated this conclusively.
- We present a case of accelerated colorectal polyposis in an immunosuppressed patient with a small bowel transplant. With 17 doses of teduglutide, colonoscopy at 4 months revealed 6 new polyps, the largest of which was 8 mm and 4 of which classified as tubular adenomas. High-grade dysplasia or malignancy was absent.
- We recommend screening colonoscopy every 3 months in teduglutide-treated immunosuppressed patients with a small bowel transplant until the drug is discontinued, given the accelerated polyposis observed in this case. This contrasts with the manufacturer's listed screening protocol, which recommends a colonoscopy 6 months prior to initiating teduglutide therapy and at 1 year of therapy, with subsequent colonoscopies at least every 5 years or more if indicated. Instead, greater caution is advised in this population.
- Further studies are needed to assess the longer-term safety and efficacy of teduglutide, especially in patient populations not originally included in the prior teduglutide trials, such as the patient presented in this case.

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Introduction

Short bowel syndrome (SBS) results from the loss of intestinal absorptive capacity owing to surgical resection, congenital defect, or malabsorptive disease. Common etiologies for SBS include extensive surgical resection for vascular disease, Crohn's disease, trauma, or cancer.[1] Patients with SBS are unable to maintain a nutrient-balanced state because of the decreased surface area and length of the remaining bowel. The subset of patients who are no longer able to meet their nutritional requirements via enteral support alone have intestinal failure and require nutrient supplementation.[1]

Patients with SBS who have lost nutritional autonomy must be carefully managed to compensate for their malabsorption. If dietary and pharmacologic therapies are insufficient management, parenteral nutrition (PN) is required. Although a mainstay of treatment, long-term PN is inconvenient, expensive, and can lead to life-threatening complications such as bloodstream infections, renal failure, and liver disease.[1] In cases of severe intestinal failure that are also associated with PN-related complications, intestinal transplantation may be considered.[2]

This work is dedicated to the life and loved ones of the patient presented in this report, serving as the longest surviving small bowel transplant recipient at our institution whose brief life furthered our knowledge of this unique population.

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Hormonal therapy has increasingly garnered interest in promoting intestinal adaptation in patients with SBS. The peptide hormone glucagon-like-peptide-2 (GLP-2) demonstrates the capacity to stimulate growth of enterocytes in the small and large intestines. A GLP-2 analog resistant to dipeptidyl peptidase-4 (DPP4) degradation, teduglutide, was shown to reduce consequences of malabsorption (eg, diarrhea, abdominal pain) and PN dependence in patients with SBS, improving patient quality of life.[3-8] However, immunosuppressed recipients of small bowel transplants were not included in these studies, and the effects of teduglutide in this subset of patients who may remain PN-dependent remain uncertain.

Case Description

A 44-year-old man with a history of SBS and PN dependence underwent cadaveric small bowel transplantation in 2015 owing to chronic rejection that developed 14 years after receiving a living donor small bowel transplant for significant blunt abdominal trauma in 1998. His postoperative course was complicated by gastric perforation, intraabdominal sepsis, and leakage of the gastrojejunal anastomosis. He was discharged 2 months later on a general diet, J-tube feedings, and PN. By 3 months posttransplant, he was able to support his nutritional requirements by general oral diet alone, and he returned by 4 months posttransplant for takedown of his loop ileostomy. Although his daily immunosuppressive regimen for his prior graft involved tacrolimus 6 mg, sirolimus 3 mg, and prednisone 10 mg, the daily regimen for his second graft included tacrolimus 5 mg, azathioprine 100 mg, and prednisone 10 mg, as well as an intravenous infusion of basiliximab 20 mg every 2 months.

Two years posttransplant, the patient presented with fatigue and 30-pound weight loss over the past several months. He was admitted to the hospital where computed tomography (CT) findings of dilated loops were suggestive of small intestinal bacterial overgrowth, a well-known complication in the small bowel transplant population. The patient was reinitiated on PN owing to bowel dysfunction and severe malnutrition, and he was provided intravenous antibiotics during admission to treat small intestinal bacterial overgrowth. A transjugular liver biopsy at this time revealed PN-induced changes with stage II fibrosis, severe steatohepatitis, and chronic cholestasis but was negative for acute changes related to alcohol. These changes were consistent from a liver biopsy 4 years prior when the patient was also PN-dependent.

Although recipients of small bowel transplant were excluded from the trials that assessed teduglutide efficacy and safety, the patient with small bowel transplant that presented in this case continued to experience nutrient malabsorption and PN dependence, and it was determined to attempt a trial therapy of teduglutide off-label to improve absorption and facilitate weaning off PN. The benefit of achieving PN independence and avoiding its complications, especially in this immunosuppressed patient with significant liver disease, outweighed the potential risks associated with the proliferative effects of teduglutide. Therefore, following a year of PN dependence, the patient underwent a colonoscopy prior to initiating therapy. The entire examined colon appeared normal, and therapy was started with 0.05 mg/kg/day teduglutide daily. However, he reported several side effects such as severe abdominal pain, constipation, and anorexia that made the medication difficult to tolerate and prevented its regular use. A 50% reduction in the dose and changing the administration frequency from daily to every other day did not improve tolerance to the medication. By 4 months, the patient ultimately received a total of 17 doses of teduglutide. At that time, the patient was admitted for hyperammonemia and underwent an upper endoscopy and colonoscopy to evaluate the viability of the patient's small bowel graft by assessing for mucosal changes, anastomotic integrity, post-biopsy bleeding, and microscopic changes via histopathology. Biopsies taken of the proximal graft and neo-terminal ileum with cold forceps were negative for acute and chronic cellular rejection, but colonoscopy revealed a total of 6 polyps, 4 of which were tubular adenomas in the rectum, sigmoid, and descending colon, the largest being 8 millimeters (Figure 1). All were negative for high-grade dysplasia and malignancy (Figure 2). A CT scan of the abdomen and pelvis as well as a small bowel follow-through study did not demonstrate any additional polyps or masses. Of note, the patient had a single 6-mm tubular adenoma detected at the age of 41 while he was immunosuppressed for his prior small bowel transplant.

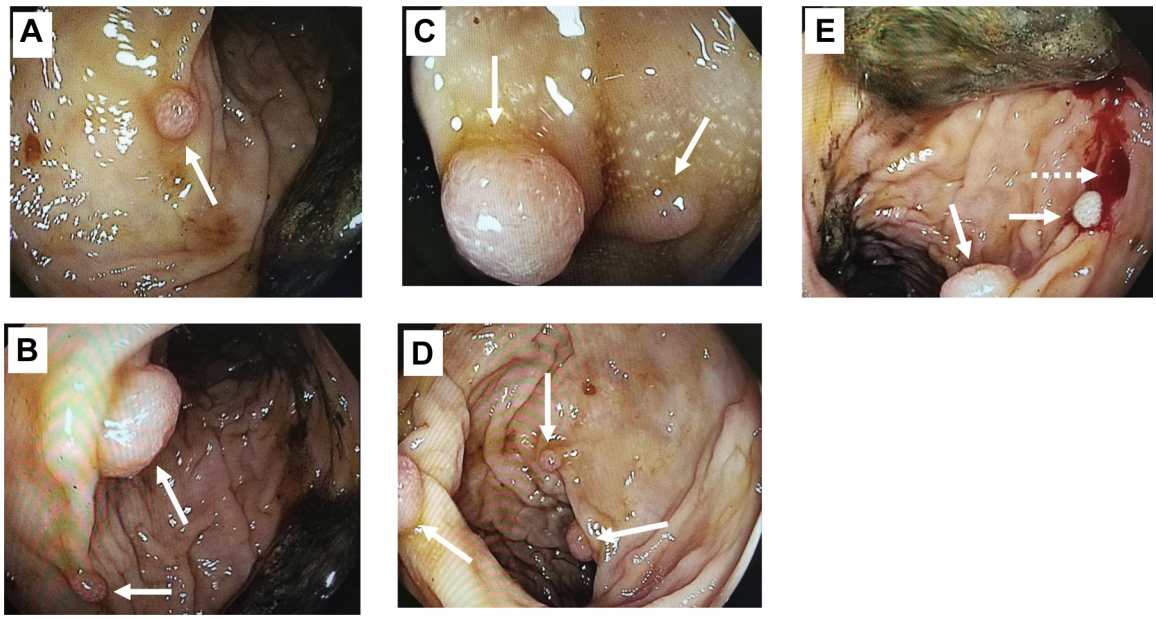
Discussion

In this case, we report a novel finding on the potential augmentation of the proliferative effects of teduglutide in the immunosuppressed patient with a small bowel transplant. This patient developed 6 polyps, the largest being nearly 1 cm in diameter, in a period of less than 4 months. The rapidity of adenoma pathogenesis may be attributed to the synergistic effects of supplementing a growth factor like teduglutide in an immunosuppressed patient.

Some reports suggest a relationship between colorectal carcinoma incidence and recipients of solid organ transplants on immunosuppressive therapy. It has been reported that recipients of solid organ transplants exhibited a faster progression of colorectal adenomas than control in a study of 287 kidney and 73 liver transplants.[9] Compared with control, these transplant recipients had significantly more colorectal adenomas classified as advanced (20:3) and those greater than or equal to 1 cm (19:3).[9] There were no significant differences between the types of solid organ transplant regarding the number of patients with adenomas or advanced adenomas. Consistent with these findings, other studies describe an earlier development of colorectal carcinoma and decreased 5-year survival in solid organ transplant recipients.[10,11] The mechanism underlying the more rapid polyposis is unclear, although immunosuppression is likely a factor.

Preclinical animal models sensitized with carcinogens demonstrated accelerated adenoma pathogenesis with prolonged GLP-2R activation. In azoxymethane-treated mice, treatment with 1.5 μg teduglutide twice daily for 4 weeks resulted in significantly increased aberrant crypt foci, mucin-depleted foci, polyp formation, and β-catenin expression in the neoplastic tissue compared with treatment with a GLP-2 antagonist and control.[12] Similarly, 1,2-dimethylhydrazine-treated mice had significantly increased development of small and large polyps with teduglutide treatment for 1 month compared with control.[13] In an inflammation-associated colon cancer model, rats fed a high-fat diet, administered the carcinogen 2-Amino-1-methyl-6-phenylimidazo[4,5-b]

Figure 1 Endoscopic Images of Colonic Polyps. Polyps Were Discovered in the Descending Colon, Sigmoid Colon, and Rectum (A-E, Solid Arrows). Biopsies Were Obtained With Normal Post-biopsy Bleeding (E, Dashed Arrow)



pyridine (PhIP), and treated with teduglutide had significantly increased aberrant crypt foci and a 22% incidence of colon cancer at 51 weeks compared with 0% in vehicle-treated rats.[14] In addition, azoxymethane- and dextran sodium-sulfate-treated mice had a 64% colon cancer incidence with teduglutide treatment compared with 56% in vehicle-treated or 46% with treatment with a GLP-2 antagonist.[14] Conversely, models non-sensitized with chemical carcinogens suggest less significance of GLP-2 in carcinogenesis. In $Apc^{Min/+}$ mice treated with 5-μg GLP-2 daily for 7 weeks, there was no difference in adenoma number or size compared with control.[15] Nevertheless, jejunal crypt and villous height was shown to be significantly increased in GLP-2-treated $Apc^{Min/+}$ and wild-type mice, suggesting intact GLP-2 intestinotrophic function.[15] Moreover, litters of $Apc^{Min/+}$ mice bred with $Glp2r^{+/+}$, $Glp2r^{+/-}$, or $Glp2r^{-/-}$ mice demonstrated no significant difference in polyp size or total number in the small and large intestines at 14 to 15 weeks of age, suggesting endogenous GLP-2 signaling is independent of intestinal polyposis in $Apc^{Min/+}$ mice.[15] In the same study, nude mice subcutaneously implanted with GLP-2R-positive human colon cancers were treated with 5 μg GLP-2 twice daily for 6 weeks and

Figure 2 Histopathology of Resected Colonic Tubular Adenoma. Of the 6 Newly Detected Polyps, 4 Were Classified as Tubular Adenomas, Negative for High-grade Dysplasia or Malignancy. A Representative Image is Shown (A) and With 55× Magnification (B)

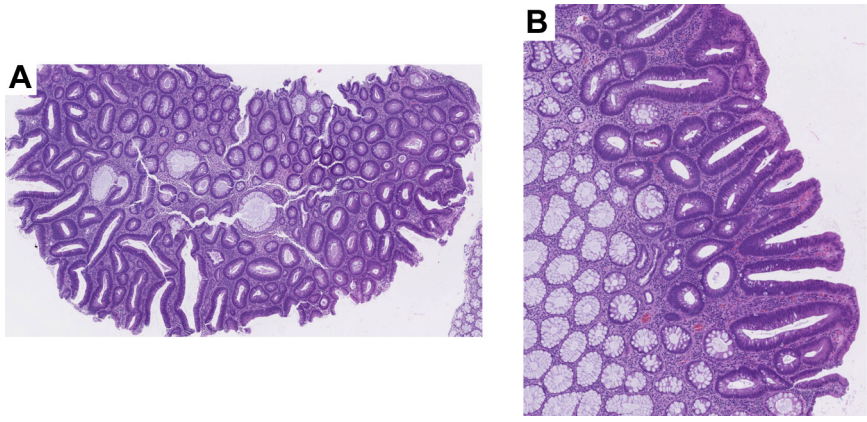


Table 1 Endoscopic and Histopathologic Findings of Colorectal Polyposis in Human Trials of Teduglutide

Study	Teduglutide Protocol	Colonoscopy Protocol	Colonoscopy Findings	Histopathologic Findings
Jeppesen et al[3]	0.05 mg/kg/d or 0.1 mg/kg/d for 24 weeks	At baseline and at 24 weeks	No polyps discovered	Of 390 individual biopsies, no dysplasia noted.
O'Keefe et al[5] (28-wk extension of Jeppesen et al[3])	0.05 mg/kg/d or 0.1 mg/kg/d for 52 weeks	At 24 weeks and at 52 weeks	1 polyp	Hyperplastic polyp. No adenomatous polyps identified.
Jeppesen et al[4]	0.05 mg/kg/d for 24 weeks	At baseline		
Schwartz et al[6] (24-mo extension of Jeppesen et al[4])	0.05 mg/kg/d for 24 or 30 months	At baseline and at 24 or 30 months 50 patients screened by end of study	Polyps in 6 patients with 24-month treatment. Polyps in 3 patients with 30-month treatment.	5 adenoma, 1 hyperplastic, 1 rectal inflammatory, 2 unclassified. No dysplasia or malignancy
Seidner et al[7] (12-mo extension of Schwartz et al[6])	0.05 mg/kg/d for 36 or 42 months	At 24 or 30 months (baseline) and at 36 or 42 months. Four patients had both, 3 patients had former only, and 3 patients had unscheduled colonoscopy.	At end of 12-month study (36 or 42 months total treatment), new polyps found in 2 patients.	1 adenoma, 1 unclassified

Colonoscopies were completed in patients with a preserved colon.

yielded no significant effect on tumor development.[15] Therefore, whether teduglutide induces cancers or advances already existing lesions seems to depend on the experimental model used. The patient presented in this case did not have any known exposures chronically to carcinogens nor did he have a personal or family history of malignancy.

Human studies are ongoing in evaluating the continued efficacy and safety of teduglutide. As noted in Table 1, 5 of 50 screened patients developed adenomas with 24 or 30 months of 0.05 mg/kg/d teduglutide.[6] Moreover, 2 of 4 patients screened at the end of a 1-year extension of the prior study developed polyps, 1 being an adenoma and the other remained unclassified.[7] Although the authors maintain that their reported adenoma prevalence corresponds to the adenoma detection rate in first-time colonoscopies, these were not first-time colonoscopies as all patients received a colonoscopy at baseline. Although the number and size of polyps discovered in each patient are not specified in these reports, the development of 4 tubular adenomas within 4 months of teduglutide therapy with an isolated history of a single adenoma 6 years prior is substantial. Human studies have also described 3 cases of malignancy while on teduglutide therapy. Two patients with significant smoking histories were diagnosed with lung cancer (squamous, non–small-cell) on 12 and 3 months of therapy, respectively. The third reported case involved metastatic adenocarcinoma with unknown primary after 11 months of therapy in a patient with previous Hodgkin lymphoma treated with chemotherapy and abdominal radiation. Only the case of metastatic disease was considered related to teduglutide treatment as it could not be ruled out.[6] There is also a report describing the incidence of hamartomatous polyps in a patient treated with teduglutide following extensive postoperative small bowel necrosis.[16] Although an upper endoscopy at 7 months of therapy was reported as normal, one completed at 26 months of therapy demonstrated 2 large (> 1 cm) and 10 small (< 5 mm) polyps in the duodenum, and a double balloon enteroscopy showed no additional polyps beyond. Colonoscopies before and at 10 months of therapy were normal. The authors report that, 15 months after identifying the duodenal polyps, there was a 30% to 50% increase in polyp size, with subsequent removal and histopathology demonstrating hamartomatous polyps without dysplasia.[16] The patient we are reporting in the present case, however, did not demonstrate any additional polyps or masses with upper endoscopy, CT of the abdomen and pelvis, and a small bowel follow-through. Although capsule endoscopy has reportedly been used in screening the total length of the small bowel graft for mucosal changes in transplant recipients,[17,18] it is not routinely used at our institution owing to a greater risk of capsule entrapment and resultant small bowel obstruction with the extensive adhesions we observe involving small bowel grafts. This may also be exacerbated by the known predisposition patients on teduglutide therapy have to small bowel obstruction from its hypertrophic effects. Capsule retention would require double balloon enteroscopy or even surgical intervention for retrieval, resulting in greater morbidity. Furthermore, capsule endoscopy is generally not performed at our institution for even stronger indications, such as obscure gastrointestinal bleeding. As small bowel polyps have not been reported beyond the duodenum of teduglutide-treated patients, and those that have been reported in the small bowel are not considered premalignant, the remaining small bowel in this patient was not further assessed. Moreover, no recommendations currently exist in screening for small bowel polyps or neoplasia in teduglutide-treated patients.

Of note, our institution has also treated 2 other immunosuppressed patients with small bowel transplants with a remnant colon off-label with teduglutide. Both patients received their graft in the third decade of life and were started on teduglutide shortly after, totaling over 2 years of therapy. Immunosuppressive therapies for both included tacrolimus, basiliximab, prednisone, and either everolimus or infliximab. Neither patient developed colorectal polyps throughout their teduglutide course as seen with multiple colonoscopies performed each year for 3 years. Age contributes significantly to colorectal carcinogenesis and is likely one of the factors that allow younger patients such as these 2 to better tolerate teduglutide. Smoking, alcohol consumption, obesity, diet, family history, and concomitant medications must also be considered.

Conclusion

Published trials on the effects of teduglutide in humans have suggested the sustained efficacy, tolerability, and safety of the drug[3-8];

however, the longer term studies were limited by small study populations and lack of a control arm.[6,7] The uncertainty regarding the proliferative effects of teduglutide on immunocompromised patients warrant continued vigilance, frequent screening, and caution. Per the manufacturer, current screening recommendations include obtaining a colonoscopy 6 months prior to teduglutide therapy and at 1 year of therapy with subsequent colonoscopies at least every 5 years or more frequently if polyps are detected, per current polyp follow-up guidelines. Discontinuation is indicated in cases of colorectal or small bowel cancers. Laboratory assessments are also recommended every 6 months with appropriate diagnostic workup as needed. This report demonstrates that a trial of teduglutide in this patient population should only be considered if the benefits outweigh the risks, as the warning and precaution section of the label stipulates. We recommend screening colonoscopy every 3 months in teduglutide-treated immunosuppressed patients with a small bowel transplant until the drug is discontinued. Nevertheless, larger, prospective studies should be conducted to more accurately evaluate these risks and optimize the pharmacologic management of patients with SBS. A 10-year ongoing database, of which our institution is a part, has been established by the manufacturer Shire-NPS Pharmaceuticals, Inc to better understand and detect the long-standing consequences of teduglutide therapy (Clinicaltrials.gov identifier: NCT01990040). The patient discussed in this report has been enrolled into this study.

Disclosure

The authors have stated that they have no conflicts of interest.

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