INTRODUCTION

GLP-2 (Glucagon-like peptide-2) is a 33-amino acid peptide hormone secreted by L-cells in the ileum and large intestine that acts as an intestinal growth factor. Once this hormone reaches its target, it induces Akt phosphorylation through currently unknown mechanisms and eventually results in a decrease in apoptosis, increase in proliferation, and deepening of the crypts of the intestinal mucosa. In light of these effects, this hormone has been a focus of interest for the treatment of a variety of intestinal diseases.

Glucagon-like peptide-2 has a short half-life due to its renal clearance and degradation by dipeptidyl peptidase-IV. However, recombinant analogues of this hormone have been synthesized and successfully utilized in the treatment short bowel syndrome. The administration of this drug has been shown to increase the absorptive properties of the residual bowel and reduce the need for parenteral nutrition.

The use of GLP-2 agonists has been approached cautiously due to concern for potential side effects, including cancers, due to its growth stimulating effects. However, a study following the use of GLP-2 analogues for a period of 2 years demonstrated no cancers or polyps attributable to the use of the drug. Other studies have demonstrated a variety of side effects including an increase in lean body mass and pancreatic enzymes. The increase in pancreatic enzymes has been demonstrated in few reports, including one study examining pediatric short bowel syndrome where a dose-dependent increase of amylase was found in response to varying levels of GLP-2 analogue administration. In this case report, an adult patient with a dose-dependent increase of amylase levels with the administration of teduglutide (GLP-2 analogue) will be described.

CASE

A 70-year-old female with Crohn's disease and short bowel syndrome has been followed in the clinic for weight loss and nutrition management. She was first diagnosed with Crohn's Disease at age 25 and had undergone total colectomy, ileostomy, and multiple small bowel surgeries, which have resulted in intestine length of between 1.0 and 1.5 m. She has required Total Parenteral Nutrition (TPN) to manage her...
short bowel syndrome, weight loss, and multiple micronutrient deficiencies, as well as octreotide and frequent normal saline infusions to treat dehydration from high stool output. She denied any history of alcohol or illicit drug use.

She had been started on TPN 4 days per week, while tolerating oral diet well and maintaining her weight at a stable level. Six months after starting TPN, she was started on teduglutide for management of short bowel syndrome. Before the initiation of this treatment, she received ileoscopy for gastrointestinal malignancy screening. Within 2 months of teduglutide administration, the patient showed improvements in symptoms; she reported thickening of stool and decreased stoma output, which allowed her to stop taking diluted tincture of opium (DTO) for loose stools. She also reported improvement in energy level without abdominal pain. The frequency of TPN administration was reduced gradually, then was completely discontinued (Figure 1). She gained nine lbs of weight during the first 2 months of teduglutide treatment.

One year after initiation of teduglutide, the patient’s lipase and amylase levels were shown to be elevated in a dose-dependent manner during the teduglutide administration (Figure 2). In response to these values, her teduglutide dose was decreased to one half of the original dose. The patient did not have any clinical signs of pancreatic stimulation when her lipase level was greater than 10 times the upper limit of normal range. Liver function tests, serum bilirubin, and alkaline phosphatase levels remained in a normal range during the treatment. Interestingly, lipase and amylase levels
continued to show intermittent spikes even after reduction of teduglutide dose, which led to temporary discontinuations of the medication (Figure 3).

3 | DISCUSSION

Teduglutide has been used for patients with short bowel syndrome. The principal target cells of teduglutide are enteroendocrine cells in the colon and the small intestine. Teduglutide can stimulate GLP-2 receptors, and it can enhance the intestinal functions by increasing the intestinal surface area.6 Both GLP-1 (Glucagon-like peptide-1) and GLP-2 derive from the same peptide which is proglucagon. However, distribution of the GLP1 and GLP-2 receptors is different. While GLP-2 receptor expressions are very limited and localized to the gastrointestinal tract and central nervous system, the GLP-1 receptors are widely expressed in human organs including the brain, pancreas, liver, intestine, heart, lung, and muscle. More specifically, pancreatic expression of GLP-2 receptor has not been reported.13,14 Therefore, acute or chronic pancreatitis is not a commonly reported complication from GLP-2 analogue treatment for short bowel syndrome.

In our case, amylase and lipase have been dose-dependently elevated by administration of teduglutide and the patient did not have clinical signs of pancreatitis during the treatment of teduglutide. It was a benign abnormality without any clinical pathologic findings. Amylase and lipase activities can be found not only in pancreas but also in the stomach, small intestine, extrahepatic duct, and gallbladder. Therefore, the origin of the enzymes did not give any clues as to whether it was from the pancreas or nonpancreatic organs.15,16 GLP-2 receptors were not founded in the patient's pancreas, so it is possible that the enzyme was originated from the nonpancreatic organ in this case.

Management of hyperamylasemia and hyperlipasemia after teduglutide treatment has not been established yet. The clinical outcomes of elevated pancreatic enzymes without clinical symptoms and functional pancreatic disorder are still unknown. Gullo et al reported nonpathological elevation of amylase and lipase, and further diagnostic test and treatments were not recommended in these cases.16 However, in our case, GLP-2 analogue is a dose-dependent triggering factor to increase the enzymes. We observed that the enzymes were trending down by temporarily discontinuing or decreasing the dose of GLP-2 analogue. Therefore, we still recommend that the treatment dose of GLP-2 analogue should be reduced or adjusted for patients with elevated enzyme levels. Currently, serum amylase and lipase levels are not included in mandatory screening laboratory tests before initiation of the treatment. We strongly recommend checking amylase and lipase levels before the initiation of the treatment and continuing to monitor them routinely in patients with GLP-2 analogue treatment.

**FIGURE 3** A graph showing a 2-y period of lipase and amylase levels overlapped with teduglutide doses. Spikes of lipase and amylase level elevation are visible which correspond with the times of discontinuations of teduglutide.
AUTHOR CONTRIBUTION

DK took care of the patient and supervised the manuscript as the corresponding author. JL, MK, and DK followed up the patient and wrote the manuscript.

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