

Successful reversal of intestinal obstruction by PRRT: two case reports and literature review of PRRT in Small Intestinal Neuroendocrine Tumors with mesenteric fibrosis

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Abstract

Small intestinal neuroendocrine tumors (SI-NETs) typically follow an indolent disease course and are often accompanied by mesenteric lymph node metastases upon diagnosis. These tumors can incite a fibroblastic reaction within the mesenteric root. Here, we present two cases of patients with symptomatic small bowel obstruction due to such mesenteric involvement. These patients underwent peptide receptor radionuclide therapy (PRRT), resulting in the stabilization of the mesenteric mass and remarkable improvements in obstructive symptoms. They experienced a return to oral intake and were able to discontinue parenteral nutrition.

Despite some controversies, PRRT emerges as a promising tool in managing the mesenteric mass and achieving a reversal of debilitating complications such as obstruction and mesenteric ischemia. (*Acta gastroenterol. belg.*, 2024, 87, 517-520).

Keywords: neuroendocrine tumor; mesenteric fibrosis; obstruction; primary tumor resection; PRRT; 177Lu-DOTATATE.

Introduction

Small intestinal neuroendocrine tumors (SI-NETs) constitute a rare subset of neoplasms known for their slow growth. They are frequently detected at an advanced stage, often accompanied by lymphadenopathies and mesenteric masses (1). Patients are at risk of developing mesenteric fibrosis, leading to a range of problems such as postprandial abdominal pain, diarrhea, weight loss, and malnutrition. Complications such as bowel obstruction and ischemia may occur due to compression of the superior mesenteric vessels (2,3). Radiologically, SI-NETs typically exhibit a spoke-wheel appearance on the mesenteric root with linear soft tissue extending from a central mesenteric mass. Somatostatin receptor (SSTR) PET/CT scans usually depict positivity in the mass or a portion of it (3). Managing SI-NETs with nodal masses poses a challenge, with surgery playing a pivotal role (2,4). Long-acting somatostatin analogues (SSAs), everolimus and peptide receptor radionuclide therapy (PRRT) have demonstrated efficacy in progressive SI-NETs, although their impact on mesenteric fibrosis remains less clear (5).

Case report 1

In 2011, a 66-year-old female patient was diagnosed with a SI-NET grade 2 (Ki-67 index 3%), accompanied

by mesenteric and retroperitoneal involvement. Her initial treatment included a partial enterectomy (R1 resection) and long acting SSAs. In October 2019 she developed obstructive symptoms attributed to tumor growth of the mesenteric mass with encasement of mesenteric vessels and congestion of the small bowel. SSTR PET/CT imaging with 68Ga-DOTANOC showed intense SSTR expression in the mesenteric mass and retroperitoneal lymph nodes (Figure 1). Treatment with everolimus was initiated alongside parenteral nutrition awaiting PRRT. The first cycle of PRRT with 177Lu-DOTATATE (7.4 GBq/cycle) was given in May 2020. The evening after administration, the patient experienced an exacerbation of obstructive symptoms. Conservative measures were taken and a nasogastric tube was inserted. When symptoms persisted, corticosteroids and short-acting SSAs were added. Over the next six months, the patient received three additional PRRT cycles at eight-week intervals, with the last cycle in October 2020. During PRRT her obstructive symptoms gradually decreased, allowing for the cessation of parenteral nutrition by November 2020. Follow-up imaging with 68Ga-DOTATATE after completing PRRT indicated stable disease. In mid 2021, the patient reported increased abdominal pain due to venous congestion, for which opioids were prescribed. Despite these symptoms, no further obstructive episodes occurred, and no additional nutritional support was required. Subsequent 68Ga-DOTATATE imaging, conducted every six months, continued to show a stable response of the mesenteric mass to PRRT three years post-treatment.

Case report 2

A 57-year-old male was diagnosed with a grade 1 ileal neuroendocrine tumor with a mesenteric fibrotic mass, along with liver and peritoneal metastases (Ki-67 index 2%). Palliative derivation between the distal jejunum and terminal ileum was performed due to small bowel obstruction, followed by medical therapy with SSAs

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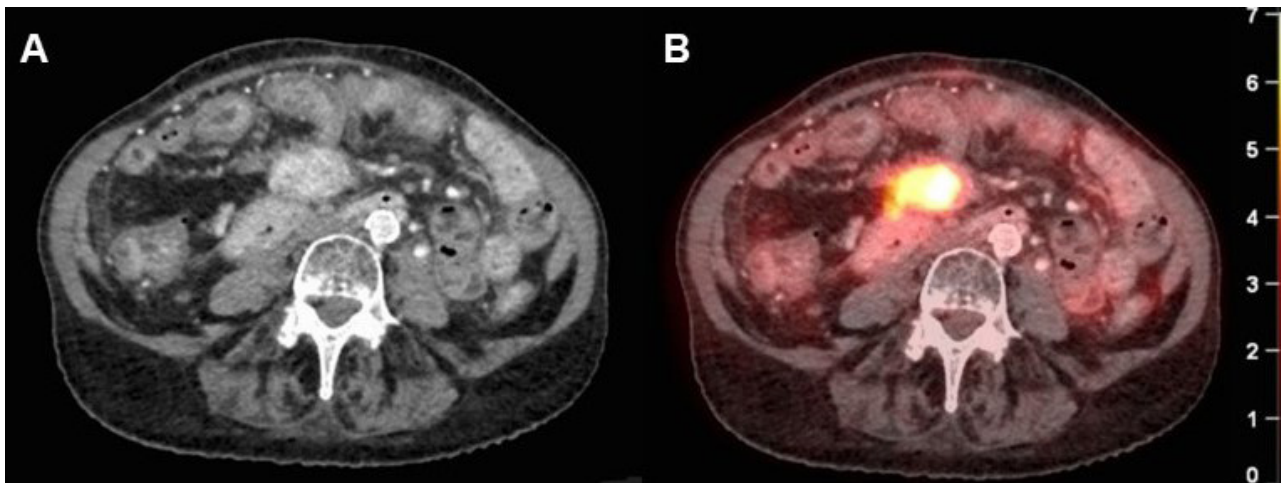


Figure 1. — CT (A) and ^{68}Ga -DOTANOC PET/CT fusion (B) before peptide receptor radionuclide therapy (PRRT). CT shows a large mesenteric mass with fibrotic bands radiating in the mesenteric fat. PET/CT imaging shows intense somatostatin receptor (SSTR) expression in the mesenteric mass. Color scale is standardized uptake value (SUV).

and everolimus. ^{68}Ga -DOTATATE PET/CT revealed intense SSTR expression on the primary tumor located in the mesogastrium (Krenning score grade 3), along with smaller adjacent mesenteric and retroperitoneal lymphadenopathies (Krenning score grade 2). ^{18}F -FDG PET/CT showed moderate uptake in a portion of the mesogastric mass (metabolic grade 2). Subsequently, the patient received 4 cycles of ^{177}Lu -DOTATATE PRRT at 7.4 GBq/cycle, administered every eight weeks between October 2017 and March 2018. After the second cycle, he developed subobstructive symptoms and malnutrition, necessitating the use of opioids and the initiation of parenteral nutrition. A follow-up ^{68}Ga -DOTATATE PET/CT in October 2018 demonstrated a mixed response, showing decreased uptake in the primary tumor, but a slight increase in the adjacent and retroperitoneal lymph nodes (Figure 2). No metabolic activity was observed on ^{18}F -FDG PET/CT. Clinically, the patient exhibited significant improvement, with decreased postprandial abdominal pain allowing for a gradual reduction and eventual discontinuation of parenteral nutrition. Two years post-treatment, subobstructive symptoms recurred intermittently on a monthly basis, resolving spontaneously without necessitating hospital admission. It was not until October 2023 that ^{18}F -NOTA-Octreotide SSTR PET/CT revealed increased SSTR expression in the mesogastric mass, lymphadenopathies, liver and peritoneal metastases. Everolimus was reintroduced and the patient was relisted for salvage PRRT.

Discussion

Up to 88% of patients diagnosed with SI-NETs have mesenteric lymph node metastases (1,2), triggering a desmoplastic reaction within the mesenteric root. This reaction can encase and obstruct the superior mesenteric vessels, leading to mesenteric angina, ischemia, and intestinal obstruction (2,3,6).

The exact pathophysiology of mesenteric fibrosis in SI-NETs remains elusive. While serotonin has long been proposed as a primary driver, the extent of fibrosis does not consistently correlate with systemic serotonin circulation (6,7). Recent research into pathogenesis suggests that the interaction between tumor cells and their microenvironment significantly influences tumor growth and fibrosis (7,8).

The debate over resecting the primary tumor and mesenteric lymphadenopathies in SI-NETs with metastatic disease persists (4,6). Guidelines from the European Neuroendocrine Tumor Society propose potential benefits of prophylactic surgery to avert locoregional complications and potentially enhance oncologic outcomes (9). A cohort study by Bennett et al. demonstrated that early resection of the primary tumor in metastatic SI-NETs resulted in improved patient-related outcomes, with fewer acute care admissions and reduced need for re-intervention compared to non-operative management (10). However, the associated complications of mesentery root dissection and postoperative morbidity, such as short bowel syndrome, warrant consideration (11). In both of our cases, complete resection of mesenteric involvement was unachievable.

While optimizing anti-tumoral therapies is vital for reducing tumor growth, their impact on mesenteric fibrosis remains uncertain (5,7). Retrospective studies suggest that mesenteric desmoplastic masses generally do not exhibit morphological responses to PRRT (12,13,14). Nevertheless, PRRT may aid in stabilizing mesenteric metastases, thereby averting further symptoms and complications, as indicated by recent multicenter study. In this study, 12 out of 26 patients with symptoms related to mesenteric masses showed partial or complete clinical response to PRRT, with 42% experiencing persistence of this response 6 months after treatment cessation (12). Concerns exist that PRRT may elevate the risk of intestinal obstruction, possibly due to radiation-induced

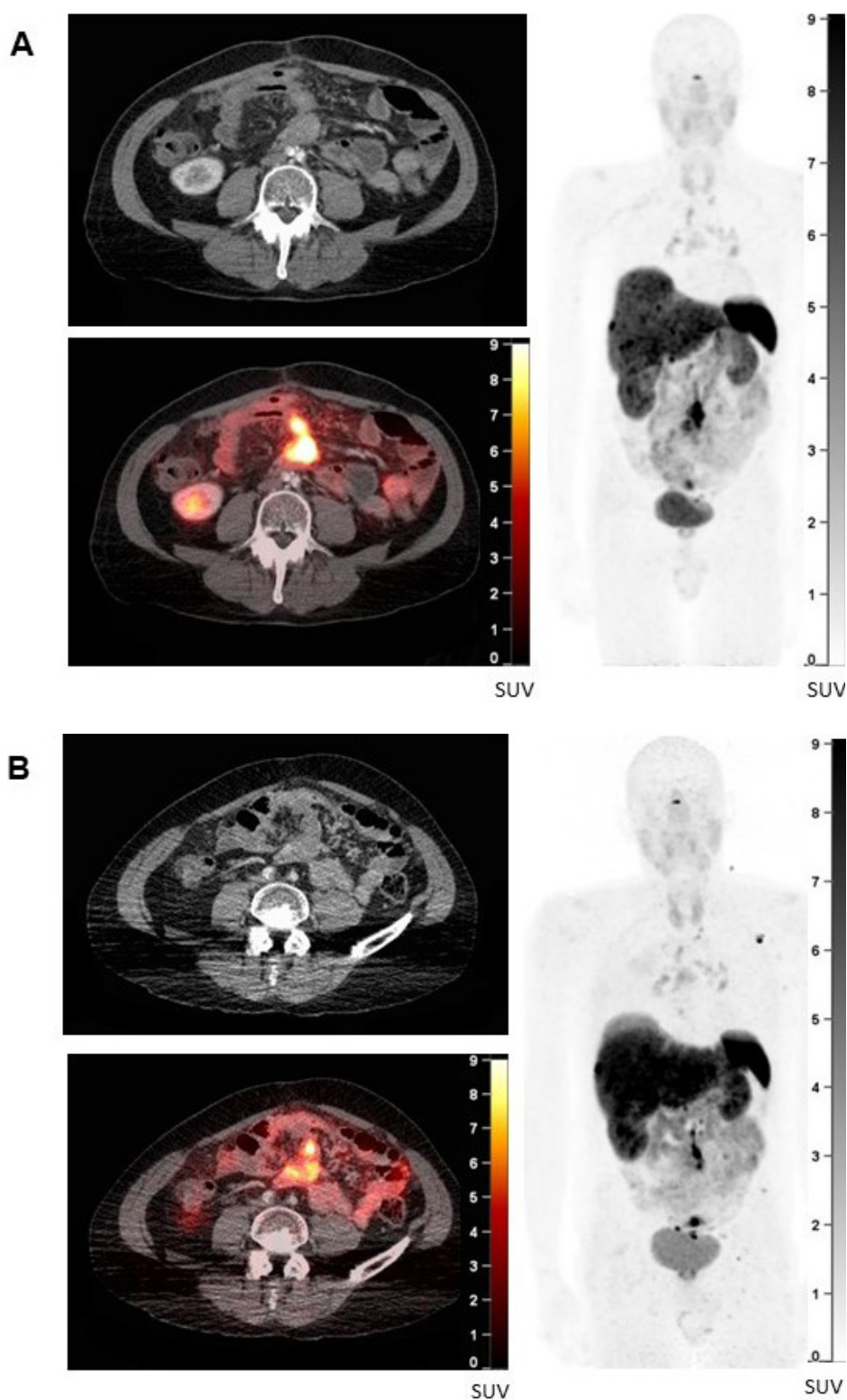


Figure 2. — CT, ^{68}Ga -DOTATATE PET/CT fusion and maximal intensity projection (MIP) images before (A) and after (B) PRRT. PET/CT imaging shows intense SSTR expression in the mesenteric mass with mixed disease response after PRRT (B).

inflammation. Strosberg et al. reported 5 out of 81 patients experiencing bowel obstruction within 3 months of PRRT treatment; however, these patients had progressive mesenterial or peritoneal disease at PRRT initiation, thus bearing a high risk for spontaneous obstruction (15). Al

Mansour et al. found only one patient developing bowel obstruction during PRRT (12). In our cases as well, there was an initial exacerbation of obstructive symptoms during PRRT, followed by clinical improvement with prolonged persistence. Corticosteroids may reverse or

mitigate obstruction, potentially serving a preventive role in high-risk patients (15).

In conclusion, PRRT emerges as a valuable treatment option for patients with SI-NETs and mesenterial mass-associated fibrosis. It may contribute to stabilizing tumor growth, thereby relieving symptoms and enhancing patient quality of life, despite the transient increased risk of intestinal obstruction. Prospective trials are imperative to further delineate the role of PRRT.

Conflict of interest statement

ED: none; RG: none; HL: none; CMD: CMD is/has been a consultant for: Sirtex, Advanced Accelerator Applications, Novartis, Ipsen, Terumo, PSI CRO and Immedica Pharma. He has received travel fees from: GE Healthcare, Sirtex; CV: consultant for Sirtex, Ipsen, Servier, MSD and Roche.

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