

## Recurrent gastrointestinal bleeding after Peptide Receptor Radionuclide Therapy for a small intestine neuroendocrine tumor

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### Abstract

We report a case of a patient who received three cycles of Peptide Receptor Radionuclide Therapy (PRRT) with [<sup>177</sup>Lu]Lu-DOTATATE for a small intestine neuroendocrine tumor (siNET) and developed recurrent GI (gastrointestinal) bleeding. These complications required four admissions on intensive care unit (ICU), transfusion of fourteen units of packed cells and finally surgery. Radiation safety precautions were respected at all hospital wards. Histopathology of the culprit lesion did not reveal tumor, but showed a large-caliber angiodysplastic lesion. The somatostatin receptor (SSTR) positive tumor consisted of a confluent mass of adenopathies invading the mesenteric vein. We hypothesize the amino-acid infusion, which is supportive therapy given prior to PRRT, caused vasodilatation in the pre-existing angiodysplastic lesion. The vasodilatation together with the high venous pressure due to tumoral invasion of the mesenteric vein may have aggravated bleeding symptoms. (*Acta gastroenterol belg.*, 2026, 89, 83-86).

**Keywords:** Neuroendocrine tumor, radionuclide therapy, gastrointestinal bleeding, radiation protection.

### Introduction

Neuroendocrine tumors (NETs) are tumors with a relatively low incidence arising from the diffuse neuroendocrine system, primarily located in the pancreas, small intestine and lungs. In low grade NETs with progression under somatostatin analogues (SSA), peptide receptor radionuclide therapy (PRRT) with lutetium-177 containing DOTATATE ([<sup>177</sup>Lu]Lu-DOTATATE) is an evidence-based targeted type of radionuclide therapy (RNT). In general PRRT has a mild toxicity profile, but severe adverse events may rarely occur.

### Case history

We present a case of a 66-year-old female with a medical history of a curatively treated breast carcinoma.

During follow-up of the breast carcinoma, a mesenterial mass with retroperitoneal extension was detected on computed tomography (CT). Biopsy revealed a grade 1 NET with a Ki67-index of less than 1%.

Subsequently, the patient underwent two partial debulkings (including a partial enterectomy). Initially SSAs were started because of carcinoid symptoms (flushing) with a good effect. 5-hydroxyindoleacetic acid was not measured but the good response of SSAs on symptoms together with retroperitoneal adenopathies

suggest carcinoid disease. Six years later flushing aggravated despite maximalizing the dose of SSA and a trial with everolimus. Therefore, the patient was referred for PRRT. SSTR positron emission tomography (SSR-PET) with [<sup>18</sup>F]AlF-NOTA-octreotide at that time point showed a confluent mass of adjacent adenopathies around the superior mesenteric artery and vein as well as the celiac trunk as the major tumor bulk (Fig. 1A).

All PRRT cycles were administered in dedicated RNT rooms at the nuclear medicine ward with a stringent protocol concerning radiation protection. Two hours after the first PRRT treatment the patient developed severe hematochezia with evolution to hypovolemic shock. CT showed high-grade mesenteric vein stenosis due to invasion by malignant mesenteric adenopathies but could not demonstrate an active bleeding. Subsequently she was admitted to intensive care unit (ICU) for monitoring.

A few days later a new episode of hematochezia occurred with hypotension and anemia. A new CT could again not demonstrate an active bleeding. A gastroscopy and ileocolonoscopy could not reveal a culprit lesion. The patient was readmitted to ICU where two units of packed cells were administered.

During the second PRRT cycle no overt GI bleeding occurred, the patient remained weak and the iron-deficiency anemia persisted despite transfusion of one unit of packed cells.

Two months later the patient underwent a third cycle of PRRT. One day later, the patient presented to the emergency department with hematochezia. Hemoglobin was 5.5 g/dL, prompting transfusion of three units of packed cells. Gastro- and sigmoidoscopy revealed no bleeding source. CT showed active contrast extravasation at the preterminal ileum. Interventional angiography was performed but was negative. The patient was monitored in the ICU, where she received two additional units of packed cells. After two days, she was transferred to the general ward but developed a new episode of GI bleeding

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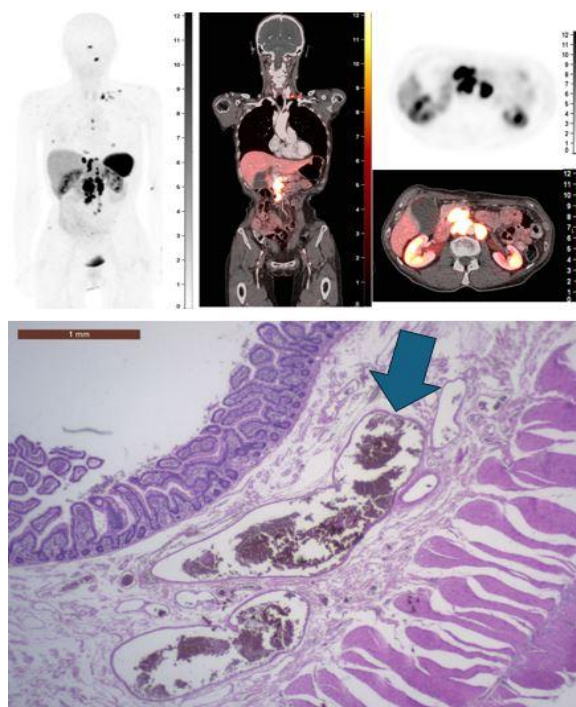


Figure 1. — Clinical images.

A. From left to right: (A) SSTR PET ( $^{18}\text{F}$ ]AlF-NOTA-octreotide) maximum intensity projection image showing intense SSTR expressing abdominal lymph nodes; (B) coronal PET-CT fusion image showing the relationship between the SSTR positive lesions and the mesenteric vein; (C) axial PET image; (D) axial PET-CT fusion image.

B. Histopathology of the resected specimen. The arrow shows a large-caliber thin-walled venous blood vessel in the submucosa.

with hemodynamic instability later that evening for which she was readmitted to the ICU for vasopression and blood transfusion. A new CT was again negative.

Throughout all episodes, no severe thrombocytopenia nor coagulation disorders were observed. No medication affecting coagulation or aggregation was administered.

In summary the patient experienced recurrent GI bleedings requiring four ICU admissions, four CT scans, one angiography, two endoscopies and transfusion of fourteen packed cells, with diagnostic uncertainty remaining. In that point of view abdominal surgeons performed an ileocecal resection including the entero-enteral anastomosis of the previous surgery. Histopathology revealed a conglomerate of large-caliber thin-walled venous submucosal blood vessels consistent with an angiodysplastic-like lesion (Fig. 1B). The patient recovered well. No further PRRT cycles were administered. Treatment with SSA was continued. No new episodes of GI bleeding occurred. The oncologic disease remains stable on CT and no carcinoid symptoms are present.

Radiation protection measures were implemented in all conventional wards, the ICU and the operating theater up to the first week after administration of PRRT and after dedicated radioactivity measurement of the room and patient. The radiation protection officer was involved at all different time points and was responsible

for collecting waste. Amongst others, personal protection equipment (double gloves, mask, gown, overshoes) for personnel was applied and a bladder catheter was placed at different wards, with specific instructions to deal with the collected urine. A spill kit was present at the ICU.

## Discussion

NETs are tumors that arise from the diffuse neuroendocrine cell system and originate mostly in pancreas, small intestine and lung. siNETs account for 25% of all NETs (1).

In first-line SSA is recommended for grade 1 and 2 small intestine and pancreatic NETs (2,3). In case of progressive disease under SSA and high SSTR overexpression, which is a hallmark of NETs, PRRT treatment can be prescribed (4).  $^{177}\text{Lu}$ ]Lu-DOTATATE, a therapeutic SSTR agonist radiopharmaceutical, binds to the SSTR, after which the complex internalizes into the cell. The emitted beta particles resulting from the lutetium-177 decay deposit energy along their path, resulting in DNA damage and ultimately cell death (5).

The toxicity profile of PRRT is generally mild. Common acute adverse events include nausea and vomiting (due to amino acid infusion), fatigue, and, rarely, carcinoid storm. Long-term adverse effects

are rare and include hematotoxicity (potentially progressing to myelodysplasia or, very rarely, secondary leukemia) and nephrotoxicity (1,5).

Only one case of GI bleeding after PRRT has been reported. This bleeding was related to PRRT-induced thrombopenia (6).

In our case, there is a clear time-based relationship between PRRT administration and GI bleeding. However, the bleeding is likely an indirect consequence of PRRT as histopathology revealed no tumor tissue but only an angiodysplastic lesion. It is likely that PRRT triggered the GI bleeding, as both the mesenteric vein stenosis and the angiodysplastic lesion were pre-existing before the PRRT and a GI bleeding never occurred before. We hypothesize that not the radiopharmaceutical but the amino-acid infusion, which is given before every PRRT cycle, may be the culprit. Amino-acid infusion is administrated systematically before infusion of the radiopharmaceutical because of its nephroprotective properties. As an exogenous source of nitric oxide, it causes vasodilatation of the splanchnic vasculature (5). In our case recurrent GI bleeding at the pre-existing angiodysplastic lesion may be explained by (a) vasodilatation of the splanchnic vasculature due to the amino-acid infusion and (b) venous congestion due to tumoral invasion of the mesenteric vein. Given the limited expression of SSTR2 on endothelial cells and the relatively low dose delivered to them by the administered [<sup>177</sup>Lu]Lu-DOTATATE at the time of the bleeding, we do not consider a direct effect of PRRT on the endothelium a likely explanation for the bleeding complications observed in this case.

PRRT requires a hospital stay in a dedicated radionuclide therapy room according to the current

radioprotection framework in Belgium. Patients need to spend one night in a dedicated therapy room with collection of urinary excreted radiopharmaceutical. Exposure of other persons by patients who have received RNT in general can occur upon (a) external irradiation of persons close to the patient and (b) internal contamination of persons due to excreted radionuclides (for [<sup>177</sup>Lu]Lu-DOTATATE) and/or contact with blood (7). Standard operation procedures should be available to protect personnel and the environment. A radiation protection officer should permanently be reachable. The procedures must cover the following areas: collecting excreta (in particular urine, which poses the greatest contamination risk due to urinary excretion of [<sup>177</sup>Lu]Lu-DOTATATE), management of radioactive waste, criteria for patient's discharge, contamination checks and decontamination procedure, personal protection equipment, labeling and transport of human samples (blood, urine, faeces in particular in case of GI bleeding) (8). The most important practical considerations to ensure radiation protection safety after PRRT are listed in Figure 2.

In summary, this case highlights the rarity of GI bleeding after PRRT, the side effects of the supportive therapy given prior to PRRT, the necessity of dedicated radioprotection and emergency protocols to ensure safety of personnel and environment and the importance of interdisciplinary collaboration in NET patients care, in particular during PRRT.

**Declarations**

*Competing interests:* All authors declare no conflicts of interest.

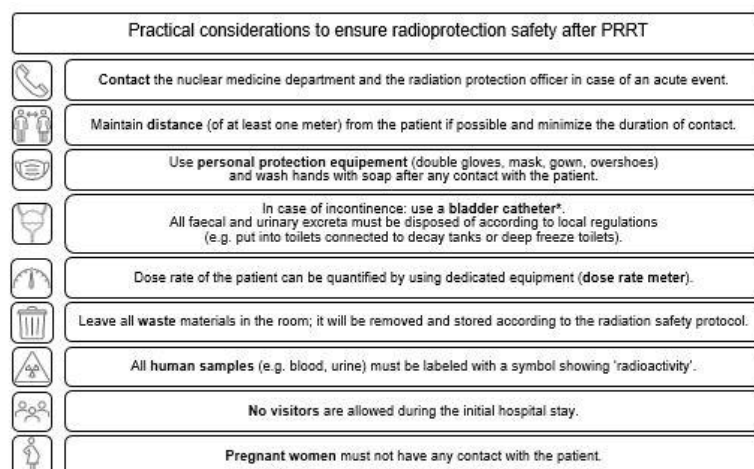


Figure 2. — Practical considerations that need to be respected to ensure radioprotection safety after PRRT.

\*Urine to be considered as highly radioactive; collection bag to be handled according to dedicated protocol.

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