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Severe Thrombocytopenia in Patients With Advanced Neuroendocrine Tumor Treated With Peptide Receptor Radioligand Therapy

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Background: Peptide receptor radioligand therapy (PRRT) was Food and Drug Administration approved in 2018 for the treatment of unresectable somatostatin receptor–positive gastroenteropancreatic neuroendocrine tumors (NETs) and provides an important option for patients with advanced disease. A known adverse effect of this treatment is hematologic toxicity, although usually transient. We present 3 patients with metastatic gastroenteropancreatic NETs treated with PRRT who were evaluated for severe persistent thrombocytopenia.

Methods: Three patients who commenced therapy with PRRT were known to proceed to a bone marrow (BM) biopsy for persistent severe thrombocytopenia and were included in this study. These patients were identified retrospectively and evaluated for their tumor properties, including immunohistochemical markers, treatment modalities, and clinical outcomes.

Results: All 3 patients had metastatic NETs that progressed on prior lines of therapy and were treated with 1 to 4 doses of ^{177}Lu-DOTATATE 7.4 GBq (200 mCi) before developing grade 3 (25,000 to 50,000/μL) refractory thrombocytopenia. All patients had concurrent bone metastases, and 2 of the 3 had baseline grade 1 thrombocytopenia. In all 3 cases, BM biopsy documented widespread tumor infiltration.

Conclusions: Severe refractory thrombocytopenia after PRRT is rare and may result from numerous known causes, including radiation-induced myelotoxicity, myelodysplastic syndrome, and tumor BM infiltration. We present 3 cases of thrombocytopenia related to persistent or progressive BM metastasis. Although known bone metastasis is not a contraindication to PRRT, thrombocytopenia may be a manifestation of tumor progression and should be considered when making decisions about continuation of therapy.

Key Words: neuroendocrine, tumor, PRRT, adverse, cytopenia

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Neuroendocrine tumors (NETs) are a rare and heterogenous group of neoplasms that arise from neuroendocrine cells. The gastrointestinal (GI) tract and lungs are the most common primary tumor sites,[1] although NETs have been described in the central nervous system, thyroid, and breast.[2] By 1 estimate, there has been a 6-fold increase in the age-adjusted annual incidence, possibly due to improved detection strategies.[3] Patient survival with NETs has improved, particularly in those with GI involvement, largely because of therapeutic advances such as tyrosine kinase inhibitors such as sunitinib[4] and everolimus,[5] as well as the recently approved ^{177}Lu-DOTATATE.

Peptide receptor radioligand therapy (PRRT) relies on systemic administration of radiolabeled somatostatin analogs, commonly ^{177}Lu-DOTATATE, or ^{90}Y, that delivers radionuclides to tumor cells.[6–11] In a trial of 310 patients with gastroenteropancreatic (GP) NETs treated with ^{177}Lu, investigators demonstrated a 28% partial response, a 2% complete response,[6] and median progression-free survival of 33 months. Recently, the Food and Drug Administration approved ^{177}Lu for the treatment of somatostatin receptor–positive GP NETs based on the NETTER-1 trial, a multicenter study, which evaluated the efficacy and safety of ^{177}Lu versus high-dose octreotide long-acting repeatable in patients with advanced somatostatin receptor–positive NETs. Patients who received PRRT demonstrated longer progression-free survival (65% at month 20 vs 11% in the control arm) and greater response rates (18% vs 3% in the control group).[12] A known adverse effect of this treatment is grade ≥3 hematologic toxicity, including thrombocytopenia and neutropenia, reported in up to 8% of cases.[13–19] Although often transient, some patients have cytopenias lasting months, necessitating transfusions.[13] Here we present 3 cases of patients with advanced, progressive NETs who underwent PRRT and developed persistent thrombocytopenia.

METHODS

Between January 2018 and June 2020, a total of 110 patients commenced therapy with PRRT at a large single-institution cancer treatment center. Of these, 3 were known to proceed to a bone marrow (BM) biopsy for persistent severe thrombocytopenia and were included in this study. These patients were identified retrospectively and evaluated for their demographic details, histopathological examination results, and tumor properties, including immunohistochemical markers, stage at diagnosis, treatment modalities, and clinical outcomes. Hematologic toxicity was evaluated using National Cancer Institute–Common Terminology Criteria for Adverse Events version 5.0 score.

Immunohistochemistry

The following primary antibodies were used: anti–SSTR-2 (clone UMB1; Abcam, Cambridge, United Kingdom) and antichromogranin A (clone DAK-A3; Denmark). AntiSSTR-2 was performed on Ventana Benchmark Ultra with a titer of 1:100. Antichromogranin was performed on Agilent Omnis Envision Flex with a titer of 1:100.v.

RESULTS

Case 1

A 66-year-old man, never-smoker, presented with a persistent cough. Initial evaluation demonstrated a left lung mass for which he underwent an upper lobe wedge resection. Pathology

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TABLE 1. The Clinical and Histopathological Findings, Treatments, and Laboratory Values Among Patients With NETs

Case	Age, y	Date of Diagnosis	Tumor Histology	Grade	Stage	Origin	Prior Therapy	Baseline Platelet Count	Date of PRRT Initiation	No. PRRT Doses	Date of BM Biopsy
1	66	12/2003	WD	WHO grade 2	T1, NX M1, G2	Unknown	Octreotide LAR, lanreotide, hepatic resections, ^{90}Y ablations	133	6/2020	2	12/2020
2	75	9/2015	WD	WHO grade 1	T1, NX, M1, G1	Unknown	Octreotide LAR, ^{90}Y ablations, XRT to spine/R humerus, everolimus	200	8/2020	1	12/2020
3	78	5/2013	WD	WHO grade 2	T2 NX M1, G2	Pancreas	Everolimus, octreotide, Zometa, palliative femur XRT	145	9/2018	4	2/2020

was consistent with metastatic NET of unknown origin. He was routinely monitored, and a subsequent CT scan demonstrated multiple nodules in the right hepatic lobe, with increased uptake on an octreotide scan. Biopsy revealed low-grade metastatic neuroendocrine carcinoma, which was surgically resected with residual disease, followed by octreotide long-acting release (LAR). He was actively monitored, and a second hepatic lesion was found and subsequently resected. Pathology revealed well-differentiated NETs, with a Ki-67 of 5% to 10% (Table 1). He underwent ^{90}Y ablations followed by lanreotide and telotristat. Serial MRIs of the pelvis and spine showed progressive nodal disease, and routine laboratory tests demonstrated increasing serum chromogranin A. Imaging with ^{68}Ga-DOTATATE PET/CT showed multiple foci of increased uptake in the left perihilar region and posterolateral ribcage (Figs. 1B, D), along with multiple hepatic metastases (Figs. 1C, E).

He began experiencing anorexia, lower extremity edema, recurring episodes of disorientation, bone pain, and worsening carcinoid syndrome. Therapy with ^{177}Lu-DOTATATE was started

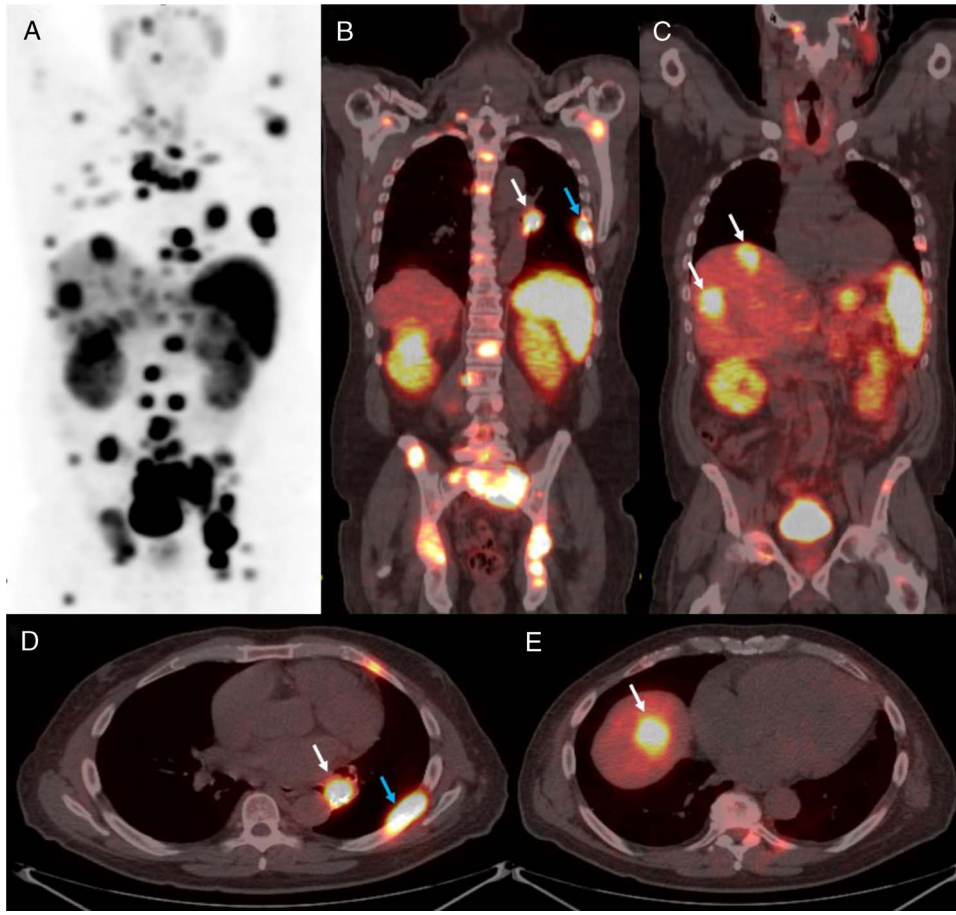

FIGURE 1. PET/CT before PRRT. **A**, FDG PET with multiple hot spots. **B** and **D**, PET/CT with left perihilar soft tissue nodule (white arrow) and left posterolateral sclerotic lesion (blue arrow) of seventh rib. **C** and **E**, PET/CT with multiple hepatic metastases (white arrow).

resulting in improved bone pain initially. After 2 doses of ^{177}Lu-DOTATATE 7.4 GBq, he presented to the emergency department with chest pain. Laboratory tests revealed a slightly elevated troponin, and grade 3 thrombocytopenia (Fig. 2) based on Common Terminology Criteria for Adverse Events version 5.0. Because of persistent thrombocytopenia, a BM biopsy was arranged and revealed extensive infiltration with malignant NET cells (Fig. 3). The marrow was normocellular (30%–40%) for age, exhibiting trilineage hematopoiesis without blasts. Iron storage was indeterminate, and there was diffusely increased reticulin fibrosis. Given the concern for lack of therapeutic benefit, a poor performance status, and hematologic toxicity, PRRT therapy was discontinued. Further systemic therapy was limited due to prolonged thrombocytopenia and was not pursued.

Case 2

A 75-year-old man presented with severe abdominal pain to the local emergency department and was diagnosed with acute pancreatitis. Subsequent CT scan showed multiple liver and bony lesions. Liver biopsy revealed intermediate grade, well-differentiated NET. He was started on octreotide LAR and underwent 2 ^{90}Y hepatic embolizations. Over time, he developed severe bone pain related to metastasis, treated with CyberKnife and external beam radiation therapy to the lumbosacral region and proximal right humerus. The pain was relieved for several months before recurring.

He was started on everolimus, which he initially tolerated well, but then experienced severe diarrhea and progressive carcinoid syndrome. CT imaging showed disease progression with a new right medial lobe lesion, and everolimus was discontinued. He received radiation for the right medial lobe mass, and octreotide LAR injections were increased to 40 mg every 3 weeks. A subsequent CT scan revealed progression of metastatic disease in the right lung, thoracic lymph nodes, liver, spleen, peritoneum, and diffuse bony involvement. ^{68}Ga-DOTATATE PET/CT confirmed increased uptake in all sites of metastases with additional somatostatin receptor–avid metastases in the posterior neck and infraorbital left eye muscles.

PRRT with ^{177}Lu-DOTATATE was started, and subsequent laboratory tests over the next 4 months documented an absolute neutrophil count of 0.7×10^9/L and grade 4 thrombocytopenia (Fig. 2). A BM biopsy showed NET infiltration and hypocellular marrow (less than 5%) with severely diminished trilineage

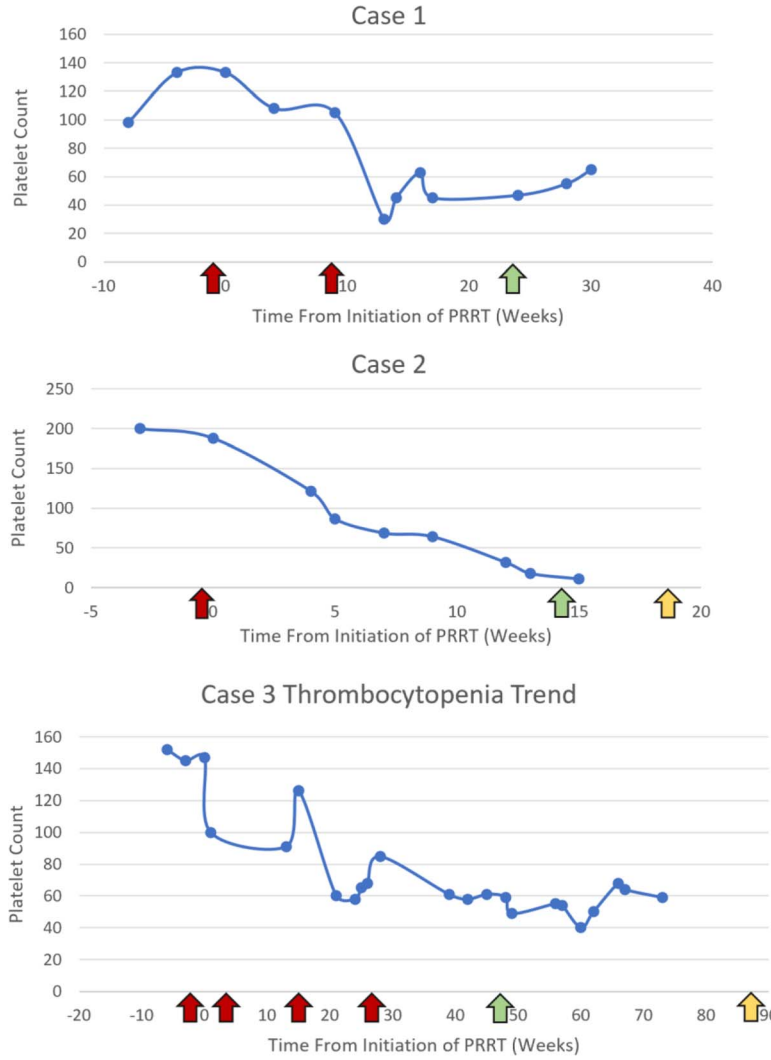

FIGURE 2. Platelet counts (in thousands) for each patient in correlation with PRRT treatments (red arrows), BM biopsies (green arrows), and time of death (yellow arrows). Of note, the patient in case 1 is currently alive but no longer pursuing further treatment.

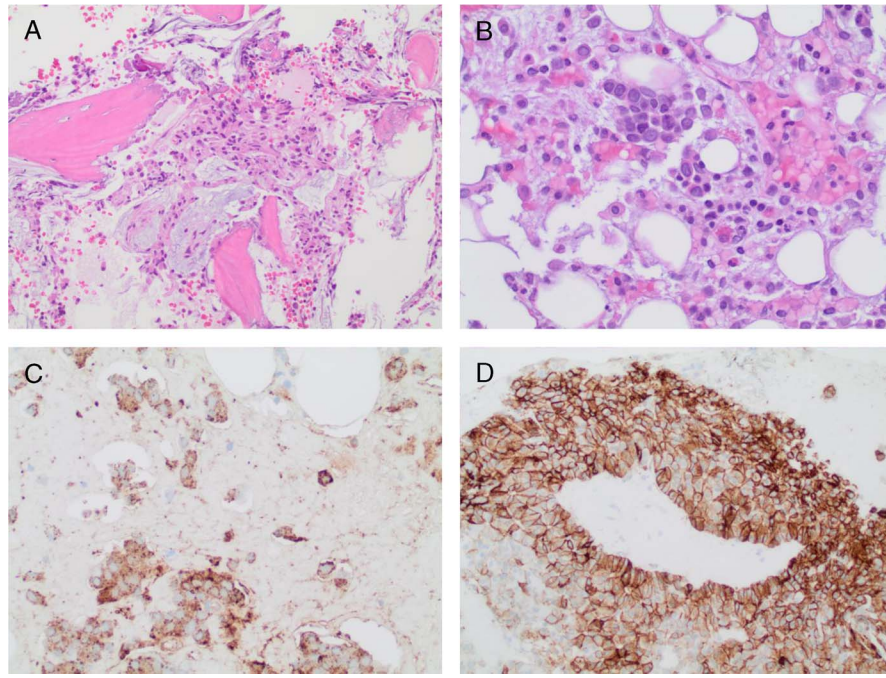

FIGURE 3. Photomicrographs of stained sections from BM biopsy of case 1. **A**, Hematoxylin-eosin, ×10. Reveals infiltration of BM by NET. **B**, Hematoxylin-eosin, ×20. Higher magnification revealing nests of well-differentiated NET cells. **C**, Chromogranin immunohistochemistry highlights a majority of tumor cells. **D**, SSTR-2 immunohistochemistry reveals strong membranous and cytoplasmic immunoreactivity in a majority of tumor cells.

hematopoiesis. After 1 dose of ^{177}Lu-DOTATATE, treatment was discontinued due to progressive disease and the patient unfortunately died 3 weeks later.

Case 3

A 76-year-old woman presented to an urgent care clinic with right upper quadrant pain, nausea, and vomiting. Further workup revealed leukocytosis and an elevated alkaline phosphatase. Liver ultrasound showed a 16-cm lesion in the right hepatic lobe with multiple satellite lesions. The largest mass was initially suspicious for hepatocellular carcinoma based on biopsy and CT scan, and transarterial chemoembolization was recommended. She underwent 4 rounds of transarterial chemoembolization and tolerated the treatments well. However, on routine follow-up imaging, there were multiple new liver lesions, as well as a 3-cm enhancing mass in the pancreatic body, and sclerotic bone lesions in T9 and L1. Biopsies from the liver and pancreatic lesions were consistent with a well-differentiated NET, likely of pancreatic origin. Ki-67 was 5%, and immunohistochemical (IHC) markers were positive for synaptophysin and chromogranin. She was started on everolimus. However, within a year, she showed further disease progression and was switched to octreotide LAR. This was effective for nearly 2 years before subsequent progression.

Her case was presented at a multidisciplinary tumor board conference, and given her nonsecretory tumor, with worsening hepatic and bony metastases despite extensive treatment, she was deemed a candidate for PRRT. After 1 cycle of ^{177}Lu-DOTATATE, she experienced a reduction in bone pain. ^{68}Ga PET/CT after 3 cycles of PRRT demonstrated a reduction in uptake of the osseous and pancreatic tail lesions. Because of progressive thrombocytopenia (Fig. 2), the fourth cycle of PRRT was given at a 50% reduced dose. After completion of therapy, she experienced prolonged fatigue, and worsening lower extremity edema. She developed neutropenia, anemia, and experienced multiple GI bleeds, eventually requiring ablation therapy. Repeat CT scans showed stable disease. A BM biopsy was performed given persistent pancytopenia, which showed infiltrative well-differentiated, WHO grade 2 NET. Her clinical condition continued to deteriorate, and a ^{68}Ga-DOTATATE PET/CT done 30 weeks after the fourth cycle of PRRT showed considerable progression of disease, and she unfortunately died several weeks later.

DISCUSSION

We present 3 cases of NETs treated with PRRT that developed persistent thrombocytopenia. In all 3 cases, BM biopsy revealed tumor infiltration, an underdescribed finding in the literature. In a small retrospective analysis of 5 patients with diffuse BM metastases on diagnosis who underwent at least 3 cycles of therapy with ^{177}Lu, no hematological toxicity was observed, suggesting that PRRT was well tolerated by this particular subgroup.[20] In the present study, despite tumor infiltration of BM, 1 patient was still able to receive clinically significant doses of PRRT. In the other 2 cases, thrombocytopenia was a manifestation of treatment failure and disease progression.

For patients with metastatic NETs that progress on first-line therapies, PRRT may prove a valuable next option. Hematologic toxicity is a known adverse effect that can delay and potentially limit subsequent treatments for these patients. Treatment-induced myelodysplastic syndrome has been reported in 1% to 2% of patients treated with ^{177}Lu-based PRRT,[15,18] and potentially higher in those pretreated with alkylating agents.[21] This raises the possibility of PRRT-induced myelodysplastic syndrome as another potential cause of thrombocytopenia in this setting. However, examination of BM biopsies ruled this out.

The value of SSTR-2 immunohistochemistry has been explored for clinical use in patients with GEP-NETs. Generally, initial studies indicate that SSTR-2 IHC has no additional value compared with somatostatin receptor scintigraphy in predicting tumor response after PRRT.[22] Furthermore, the results have not shown any consistent

relationship between patient outcome and SSTR-2 immunohistochemistry with variable results between low and high expressing SSTR-2 and outcome.[23,24] Therefore, at this time, SSTR-2 IHC is not used for clinical use for prediction of tumor response or patient outcome.

Certain characteristics were present in all patients of this study, including extensive bone metastases. Two of the 3 patients had a grade 1 thrombocytopenia before PRRT but >100, making them eligible for PRRT. Importantly, these findings are in line with recent studies showing patients with low WBC count, bony metastases, extensive tumor mass, high tumor somatostatin receptor level expression on OctreoScan and ^{68}Ga-DOTATATE, impaired renal function, and/or advanced age are more likely to develop grade 3 or 4 hematologic toxicity with PRRT.[13,15,18,25] Notably, none of the 3 patients presented here had impaired renal function. Also within this cohort, the number of treatment cycles before severe thrombocytopenia was variable. Interestingly, 1 patient experienced a radiologic response with decreased uptake in sclerotic osseous metastases and decreased liver lesion size despite progressive pancytopenia. The other 2 patients showed progressive metastatic disease alongside the hematologic toxicity, consistent with treatment failure on PRRT.

All patients had diffuse bony involvement before PRRT. Previously, investigators have shown that bone metastases are present in 8% to 15% of metastatic GP NETs,[26–32] with decreasing marrow function.[33] This higher frequency of hematologic toxicity has been attributed to their proximity to active BM, resulting in more pronounced radiation-induced myelotoxicity. However, advanced osseous disease is not a contraindication to PRRT, and our findings are consistent with other studies showing an overall favorable safety profile and promising response rates.[32,34–36] Although known bone metastasis is not a contraindication to PRRT, thrombocytopenia may be a manifestation of tumor progression and should be considered when making decisions about continuation of therapy.

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