

Everolimus in poorly differentiated neuroendocrine carcinoma of unknown primary: A case report

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Abstract

Malignancies with unknown primaries contribute to a small yet significant percentage of overall tumors. Neuroendocrine carcinomas, a rare disease with a poor prognosis, have been known to present as an unknown primary. Treatment consists of cytotoxic chemotherapy but given the latter's high toxicity profile new treatment options are being explored. In this case report, we describe a case of a patient with poorly differentiated neuroendocrine carcinoma of unknown primary treated with compassionate oral everolimus after his refusal of intravenous chemotherapy.

Keywords

Everolimus, hematology, oncology, poorly differentiated neuroendocrine carcinoma

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Introduction

About 5% of invasive cancers are of unknown primary,¹ with less than 5% of those being neuroendocrine carcinomas,² rendering this entity a very rare disease, with poor prognosis.^{3,4}

Treatment of poorly differentiated neuroendocrine carcinoma (PDNEC) is based on intravenous chemotherapy combining platinum compounds and etoposide, with high toxicity risk especially in the elderly, or enrollment into a clinical trial.^{3,4} In this case report, we describe a case of a patient with PDNEC of unknown primary treated with compassionate oral everolimus after his refusal of intravenous chemotherapy.

Case presentation

A 63-year-old male patient, non-smoker, with a history of type II diabetes and peripheral vascular disease presented for left flank pain. He was admitted for management of left obstructive kidney stone by JJ insertion. On physical examination, the patient was found to have multiple enlarged lymph nodes, predominantly in the cervical and right inguinal areas. Initial computed tomography (CT) scan that aided in the diagnosis of obstructive pyelonephritis was consistent with the physical examination findings of generalized lymphadenopathy. It revealed enlarged cervical, axillary,

mediastinal, hilar, mesenteric, retroperitoneal, and pelvic adenopathies. Splenic hypodensities and adrenal nodules were also discovered (Figure 1).

An excisional biopsy of the right inguinal lymph node was performed. Histopathology showed a lymph node entirely occupied by a malignant neoplasm with high mitotic index and patchy areas of necrosis. The neoplastic cells were CK7 (cytoplasmic paranuclear dots), CD56, TTF1, and synaptophysin positive, whereas they were CK20 and chromogranin negative. Ki-67 index was 80%. A diagnosis of PDNEC was made (Figure 2 and figure 3).

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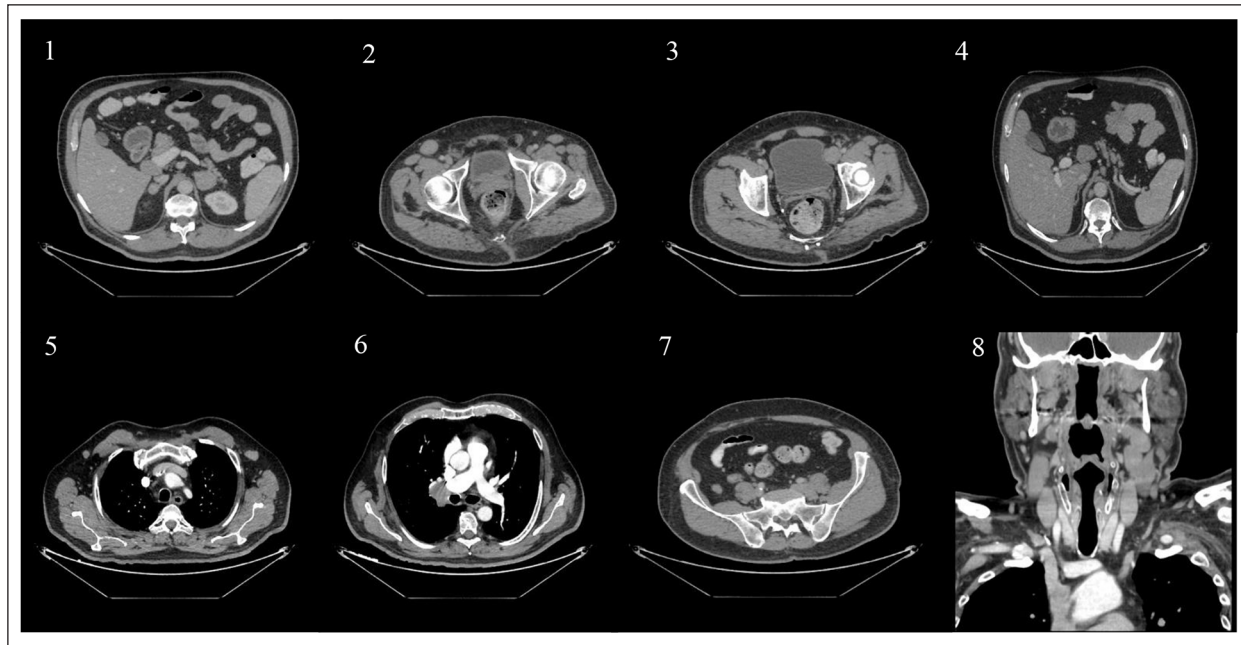


Figure 1. Coronal scans of the adrenals (1), inguinal region (2), pelvic area (3), portocaval (4), axillary (5), hilar (6), and peri-psoas muscle areas (7). Sagittal scan of the cervical area (8).

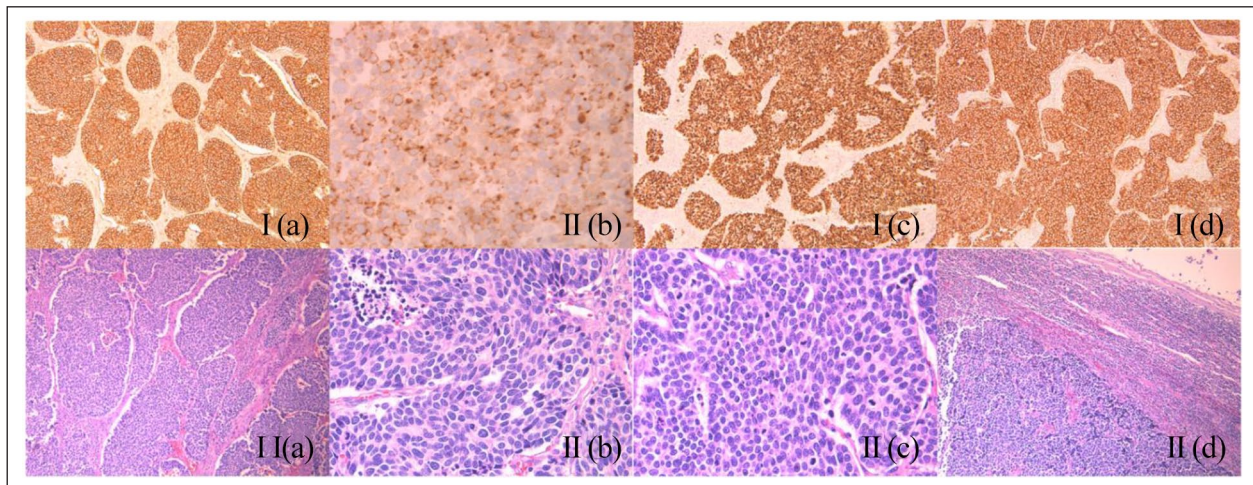


Figure 2. I(a): CD56 $\times 100$; Positive membranous staining. I(b): CK7 $\times 400$; Positive cytoplasmic staining of tumor cells with characteristic perinuclear dots. I(c): TTF1 $\times 100$; Positive nuclear staining. I(d): Synaptophysin $\times 100$; Positive cytoplasmic staining. II(a): HE $\times 100$; The tumor cells are arranged in nests of variable size and shape, some of which exhibiting peripheral nuclear palisading, set within a desmoplastic stroma. II(b): HE $\times 400$; Mitotic figures are also easily detected. II(c): HE $\times 400$; Tumor cells have high nuclear to cytoplasmic ratio and exhibit an oval to round nucleus with finely granular chromatin. Occasional necrotic areas are present (left upper area). II(d): HE $\times 40$; Sheets of metastatic small cell carcinoma cells (left lower half) in a lymph node (residual lymphocytes at the periphery).

Whole-body fluoro deoxy glucose (FDG) PET was performed for initial staging (Figure 4) showing increased FDG uptake in bilateral cervical nodes with an SUV=6.7, a solitary liver lesion with an SUV max of 5.5, bilateral adrenal foci and metastatic bone disease—in the right acetabulum and right iliac bone—with an SUV=8.6. Scattered FDG avid retroperitoneal and pelvic adenopathies with an SUV max of 7.1 and 5.7, respectively. A satellite lesion in

the right lower lung lobe was also noted with an SUV=6.9 (Figure 4).

The patient vigorously declined intravenous chemotherapy despite being in good general health status. He was started on compassionate everolimus 10mg daily. Clinical follow-up at 2 and 4 months revealed stable cervical and inguinal lymph nodes. The patient maintained a good performance status (ECOG PS=1) that allowed him to keep on

with his usual physical activities. Follow-up FDG PET at 6 months showed disease progression with mainly peri-portals lymphadenopathies using RECIST 1.1 criteria. Everolimus was stopped as the patient was complaining of diarrhea along with numbness and tingling his feet bilaterally. The

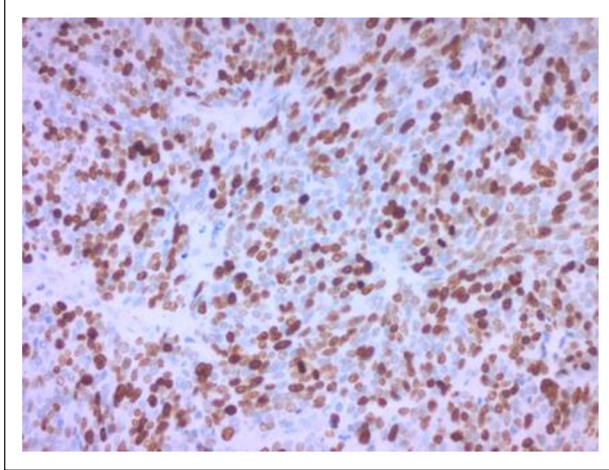


Figure 3. Ki-67 immunohistochemical stain revealing expression by approximately 80% of the neoplastic cells. Original magnification 200 \times .

patient still refused intravenous chemotherapy and death occurred 8 months after diagnosis from a complicated myocardial infarction.

Discussion

The biological and clinical features of PDNEC resemble small cell lung carcinoma with respect to their rapid growth, morphological and biological heterogeneity as well as the relatively high sensitivity to platinum-based chemotherapy.⁵

Following the 2019 WHO classification and grading of neuroendocrine neoplasms of the gastrointestinal tract and hepato-pancreato-biliary organs, NET G1, G2, and G3 are well-differentiated tumors with a low, intermediate, and high grade, respectively, have a mitotic rate of <2 mitoses/2 mm², 2–20 mitoses/2 mm², and >20 mitoses/2 mm², respectively, and a Ki67 index of <3%, 3–20%, and >20%, respectively. Small-cell type and large-cell type neuroendocrine carcinomas are poorly differentiated and considered high grade with a mitotic rate of >20 mitoses/2 mm² and a ki-67 index of >20%.⁶

PDNECs' response to platinum agents significantly fluctuates. A hallmark of PDNEC is the key loss of function mutations in tumor suppressor genes, PTEN and/or TSC and, as a result, the PI3K/AKT/mTOR pathway becomes

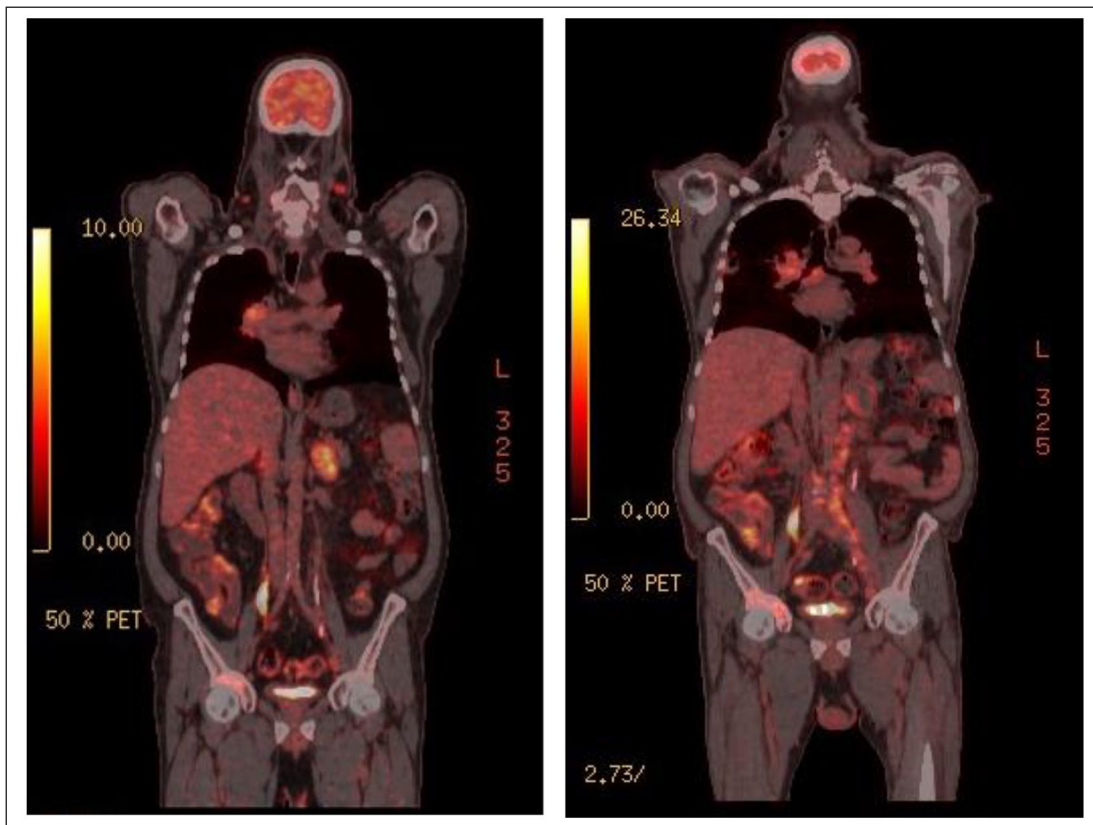


Figure 4. Initial (left) FDG-PET showing increased uptake in several organs versus mild progress seen in a comparable image 6 months later (right).

highly active.⁷ This presents an opportunity for tyrosine kinase inhibitors (TKIs) and mammalian target of rapamycin (mTOR) inhibitors, which target the PI3K/AKT/mTOR pathway.

The recent WHO classification recognized two distinct morphological subtypes of PDNEC: the small cell type and the large-cell type. Despite the current treatments, based on the combination etoposide-cisplatin, the prognosis of both subtypes is poor, with median survival durations in patients with localized, regional, and distant disease of 34, 14, and 5 months, respectively.^{8,9} Lindholm et al.¹⁰ revealed the efficacy of temozolomide, an alkylating agent, along with bevacizumab, a monoclonal antibody targeting tumor angiogenesis, after etoposide-cisplatin failed. There is a huge potential for future targeted therapies to be evaluated in PDNECs.

mTOR signaling pathway has a crucial role in controlling cancer cell-cycle and growth.¹¹ The activation of the mTOR pathway plays a major role in the pathogenesis of NETs.¹² Shida et al.¹³ assessed the expression of phospho-mTOR between well-differentiated and poorly differentiated neuroendocrine neoplasms. More than 65% of PDNECs had a high expression of phospho-mTOR as compared to only 27% well-differentiated NETs and carcinomas. Furthermore, Catena et al.¹⁴ were able to reveal that 80% of tumors in 36 patients diagnosed with PDNECs had a high expression of phospho-mTOR.

The RADIANT trials were clinical studies that studied the efficacy and safety of everolimus, an oral inhibitor of the mTOR pathway in patients with NETs of different origins.^{15–18} They showed significant clinical benefit of everolimus in patients with well and moderately differentiated advanced pancreatic, lung, and gastrointestinal NET's. Duran et al. evaluated the efficacy of temsirolimus, another mTOR inhibitor, in advanced neuroendocrine carcinoma. In this phase II study, having a higher baseline level of phospho-mTOR was predictive of tumor response and a decrease in phospho-mTOR after temsirolimus treatment was associated with increased time to progression.¹⁹ Bollard et al.²⁰ also demonstrated a strong expression of phospho-mTOR in several cases of PDNECs. After utilizing xenografted mice with everolimus, a decrease in the number of nodules as well as the mean surface and total tumor surface was observed. This was explained by a decrease in proliferation rather than an increase in apoptosis as a decrease in Ki67 index between control and treated animals was observed, but there was a difference in the percentage of cells expressing active caspase 3.^{9,20}

Gilabert et al.²¹ report a case series of six patients newly diagnosed (4 males and 2 females, median age 55 years (range 40–70)) with a metastatic PDNEC that refused chemotherapy or deteriorated at the time of the diagnosis and underwent targeted therapies, either sunitinib or everolimus.

Panzuto et al.²² investigated the use of everolimus in well-moderately differentiated pancreatic neuroendocrine carcinoma in 15 patients with a median Ki67 of 30% and Eastern Cooperative Oncology Group performance status 0 to 1. Of these, 11 had been pretreated with chemotherapy or peptide receptor radionuclide therapy and only four received everolimus as first-line therapy. Median progression-free survival was 6 months, and median overall survival was 28 months. At 3 months follow-up, 11 patients achieved disease stabilization. Six patients (40%) maintained the latter for at least 12 months. Three of four patients who received everolimus as first-line therapy had sustained disease stabilization, progression-free survival, 12, 17, and 22 months.

Chemotherapeutic agents or other targeted therapies should be used in combination with mTOR inhibitors. In addition, a stronger efficacy is expected if the mTOR pathway is targeted at several levels, such as PI3kinase and mTOR levels, by using new inhibitors targeting both complexes mTORC1 and mTORC2, or by targeting several pathways simultaneously (mTOR and MAPkinase pathways).^{23,11} A completed phase II study, NCT02248012, evaluated the use of everolimus or temozolomide as therapies in the first-line setting in gastroenteropancreatic neuroendocrine carcinomas, and we are awaiting its result.²⁴

Table 1 summarizes the use of everolimus in neuroendocrine carcinoma.

Conclusion

The standard treatment for PDNEC is chemotherapy with platinum-based regimens. PDNEC was shown to exhibit high expression and activation of mTOR in immunohistochemical analyses. Everolimus was shown to have an anti-proliferative effect in these tumors in a preclinical study. In this case report, the patient had a PDNEC of unknown primary origin with a very poor prognosis. He maintained a good performance status and a stable disease for 6 months before progression. Another case report described a patient with a poorly differentiated pancreatic neuroendocrine carcinoma treated successfully with everolimus for 15 months with a survival of more than 2 years following diagnosis.

Everolimus could be an interesting palliative treatment option for patients with PDNEC of unknown primary. Unfortunately, given the rarity of the disease, confirming this hypothesis with multicentered phase III studies can be very challenging, and data from individual case reports and case series may remain the only objective evidence to rely on for the time being.

In conclusion, mTOR inhibitors are known as effective treatment modality for well and moderately differentiated NEC. Studies should be conducted to assess efficacy in PDNEC especially of unknown primary.

Table 1. RADIANT trials findings and case reports of everolimus use in neuroendocrine carcinoma.

Authors	Study type	Summary
Yao et al. ¹⁷	Radiant 1 trial	Daily everolimus, with or without concomitant octreotide LAR, demonstrates antitumor activity as measured by objective response rate and PFS and is well tolerated in patients with advanced pancreatic NETs after failure of prior systemic chemotherapy.
Pavel et al. ¹⁶	Radiant 2 trial	Everolimus plus octreotide LAR, compared with placebo plus octreotide LAR, improved progression-free survival in patients with advanced neuroendocrine tumors associated with carcinoid syndrome.
Yao et al. ⁸	Radiant 3 trial	Everolimus, as compared with placebo, improves progression-free survival in patients with advanced pancreatic neuroendocrine tumors. Grade 1 and 2 adverse events with everolimus.
Yao et al. ¹⁷	Radiant 4 trial	Treatment with everolimus was associated with significant improvement in progression-free survival in patients with progressive lung or gastrointestinal neuroendocrine tumors. Acceptable tolerability of everolimus.
Bollard et al. ²⁰	Case report	Anti-proliferative effect of everolimus in PDNEC tumor in a patient with PDNEC of unknown primary origin. He maintained a good performance status and a stable disease for 6 months before progression
Gilbert et al. ²¹	Case Report	Poorly differentiated pancreatic neuroendocrine carcinoma treated successfully with everolimus for 15 months with a survival of more than 2 years following diagnosis
Panzuto et al. ²²	Retrospective study	Everolimus is active in well-differentiated neuroendocrine carcinoma G3 with Ki67 less than 55%. Seventy-five percent of the patients receiving everolimus as a first line had a progression-free survival of 12, 17, and 22 months.

PDNEC: poorly differentiated neuroendocrine carcinoma.

LAR: long-acting repeatable.

PFS: progression free survival.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical approval

Our institution does not require ethical approval for reporting individual cases or case series.

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