Sustained response to anlotinib in advanced pancreatic neuroendocrine carcinoma: A case report

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Received September 19, 2023; Accepted January 9, 2024

DOI: 10.3892/ol.2024.14271

Abstract. Pancreatic neuroendocrine carcinoma (pNEC) is a type of pancreatic neuroendocrine neoplasm with a poor prognosis, and patients with metastatic pNEC have a survival time of only 8-12 months. The treatment options for pNEC are minimal, and the prognosis is unfavorable. The present study reports the case of a 56-year-old male who was diagnosed with advanced pNEC with bone metastases in June 2018. The patient was treated with oral anlotinib after eight cycles of first-line etoposide + cisplatin (EP) chemotherapy until July 2022. The adverse events that occurred during the treatment period were resolved with symptomatic management or drug dose reduction. At the time of writing this report, the patient's survival time was almost 60 months, which is rare for patients with pNEC. This case report suggests that patients with pNEC treated with first-line EP regimen chemotherapy may have a sustained response to anlotinib.

Introduction

Neuroendocrine neoplasms (NEN) are rare and highly heterogeneous, accounting for only ~2% of all malignant tumours diagnosed in the Western world (1). The pancreas is one of the common sites of occurrence. In 2019, the World Health Organization (WHO) classified NENs into highly differentiated neuroendocrine tumors (NETs), hypodifferentiated neuroendocrine carcinoma (NEC) and mixed neuroendocrine non-NETs (2). NENs can be further classified into functional NEN and non-functional NEN according to whether they have neuroendocrine function. pNEN, although relatively rare, has shown an increasing incidence trend in recent years (3).

pNEC is highly aggressive and has a poor prognosis, with survival times in patients with pNEC usually recorded as <1 year (3). Currently, whether to perform surgery on patients with pNEC is still controversial, and palliative surgery is generally performed only to prevent or treat tumor-related complications. Systemic therapy is the primary treatment for pNEC. The 2021 National Comprehensive Cancer Network guidelines recommend platinum-based combination chemotherapy as the first-line chemotherapy regimen for pNEC, including etoposide + cisplatin (EP), etoposide + carboplatin, and irinotecan + cisplatin. The EP protocol is most commonly used in pNEC, with an objective response rate of ~30% and a median survival time of ~1 year. One study reported that the EP regimen has only marginal antitumor activity and relatively heavy toxicity in pNEC compared with the same regimen in extra-pulmonary NEC (4). After failure of the EP plan, second-line chemotherapy options are limited and the overall efficiency is low, not exceeding 18%. The immunotherapy in NENs is still in the clinical exploratory phase, and its efficacy, particularly with regard to immune checkpoint inhibitors, has shown mixed results in NENs (5). Similarly, targeted therapy has not entered the standard treatment regimen. In conclusion, the treatment options for pNEC are minimal, and the prognosis is unfavorable.

Case report

In January 2018, a 57-year-old man visited The 900th Hospital of the Chinese People's Liberation Army Joint Logistic Support Force (Fuzhou, China) for recurrent back pain that had persisted for 6 months. The patient had not previously visited other hospitals and was self-administering oral pain medication as required. The patient had no specific past medical history. Bone emission computed tomography suggested an abnormal radiological concentration in the second and third lumbar spine, and further examinations were recommended.

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Key words: pancreatic neuroendocrine carcinoma, anlotinib, targeted therapy, neuroendocrine neoplasm, neoplasm

However, the patient did not continue the consultation for personal reasons.

In June 2018, the patient was hospitalized in the Department of Oncology of The 900th Hospital of the Chinese People's Liberation Army Joint Logistic Support Force due to worsening back pain, and a whole-body 18F-fluorodeoxyglucose positron emission tomography-CT scan revealed that the body and tail of the pancreas were slightly thickened and hypermetabolic, suggesting a pancreatic malignant tumor (Fig. 1). The scan also indicated multiple bone destruction in the thoracic spine, lumbar spine and pelvis, with hypermetabolism, which was considered tumor metastasis; and multiple enlarged lymph node shadows in the bilateral supraclavicular fossa, intra-mediastinum, both lung hila and the retroperitoneum, with hypermetabolism, which was considered tumor metastasis. An enhanced magnetic resonance imaging (MRI) examination of the upper abdomen and the pelvic cavity also suggested pancreatic malignancy with bone and multiple lymph node metastases.

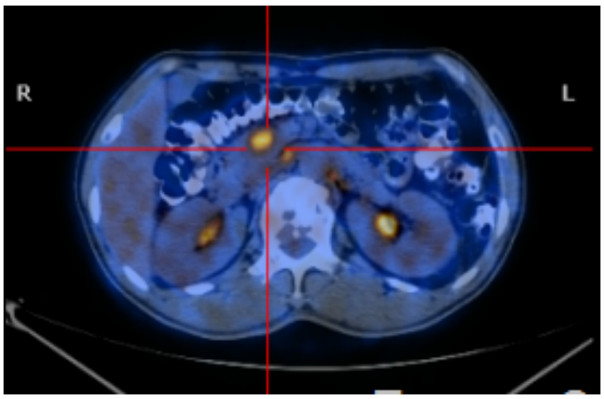

Figure 1. 18F-fluorodeoxyglucose positron emission tomography-CT analysis. A whole-body 18F-fluorodeoxyglucose PET-CT scan revealed that the body and tail of the pancreas were slightly thickened and hypermetabolic, indicating a pancreatic malignant tumor. CT, computed tomography.

To clarify the diagnosis, the patient underwent a bone marrow biopsy. Hematoxylin and eosin (H&E) and immunohistochemical staining were performed and results were examined using a light microscope. Tumor specimens were fixed in 10% neutral formalin for ~48 h at room temperature and embedded in paraffin, and then cut into 4-μm thick sections for H&E staining (hematoxylin for 5 min and eosin for 5 min at room temperature). For immunohistochemistry, the tissue was fixed in 4% formalin for 48 h at room temperature, embedded in paraffin and then cut into 3-μm sections. These sections were then rehydrated in a descending alcohol series (xylene, 100% ethanol, 95% ethanol, 85% ethanol and ethanol-free water) and underwent antigen retrieval using EDTA antigen retrieval treatment (cat. no. MVS0098; Fuzhou Maixin Biotechnology Co., Ltd.) in a microwave on high heat for 2 min, followed by incubation at room temperature for 8 min. Endogenous peroxidase activity was quenched with 3% hydrogen peroxide in methanol before incubation with primary antibodies. Immunohistochemical staining was performed overnight at 4˚C using the following primary antibodies (prediluted; Fuzhou Maixin Biotechnology Co., Ltd.): Synaptophysin (Syn; cat. no. MAB0742), chromogranin A (CgA; cat. no. RMA0548), neuron-specific enolase (NSE; cat. no. MAB0791) and Ki-67 (cat. no. RMA0731). The secondary antibody was obtained from the M&R HRP/DAB Detection IHC Kit (prediluted; cat. no. HC301-01; Vazyme Biotech Co., Ltd.) and was used to treat sections at room temperature for 30 min. Subsequently, a chromogen detection reagent was applied (M&R HRP/DAB Detection IHC Kit; cat. no. HC301-01; Vazyme Biotech Co., Ltd.). The IHC staining results demonstrated that the bone marrow tissue expressed Syn, CgA, NSE and Ki-67 (60%). The H&E and immunohistochemistry examinations (Fig. 2) were suggestive of pNEC invading the bone marrow. Since The 900th Hospital of the Chinese People's Liberation Army Joint Logistic Support Force was unable to conduct second-generation genetic testing, after full communication with the patient's family, the patient's family sent the patient's venous blood samples at their own expense to Shanghai Yikang Medical Laboratory Co., Ltd. The result showed that tumor mutation burden was 1.44 mutations/Mb. A total of 25 mutations in 23 genes were detected in the sample, of which no variants were detected that could be associated with clinical use.

Combining the results, the patient was diagnosed with pNEC, T2N1M1 stage IV, according to the American Joint Committee on Cancer 8th edition (6). In July 2018, the patient started to receive intravenous chemotherapy with the EP regimen (160 mg etoposide on days 1-3; 40 mg cisplatin on day 1) for 3-week cycles. In August 2018, after two cycles of chemotherapy, the patient's white blood cell count dropped to $2.3x10^9$/l (normal range, 3.5-$9.5x10^9$/l) [Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 grade 2; https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf], before returning to normal after symptomatic management, so the dose of etoposide was adjusted to 140 mg starting with the third cycle. However, at the end of the third cycle of chemotherapy, the patient's white blood cell count dropped to $1.5x10^9$/l (CTCAE version 5.0 grade 3), so the dose of etoposide was adjusted again to 100 mg. In total, eight cycles of therapy were administered. During chemotherapy, CT of the upper abdomen was performed twice and the efficacy was assessed as stable. Following the completion of chemotherapy, the patient received maintenance treatment with oral anlotinib (12 mg on days 1-14 every 3 weeks) in January 2019 and remained on this regimen until July 2022, when the patient experienced disease progression. To prevent severe bone destruction, the patient was intravenously administered 4 mg ibandronate every 4 weeks. Between 2019 and 2022, the patient underwent multiple MRI examinations of the upper abdomen, and the efficacy was assessed as stable disease. Until July 2022, the CT scan of the chest and upper abdomen was repeated, and the disease was considered to be progressive, with imaging suggestive of adrenal, lung, pleural and liver metastases, and a progression-free survival time of 48 months.

The patient was not treated further due to financial reasons. In January 2023, the patient was again hospitalized in the Department of Oncology of The 900th Hospital of the Chinese People's Liberation Army Joint Logistic Support Force and underwent a liver puncture. The H&E and immunohistochemistry examinations (Fig. 3) showed the following results: Syn(++++), CgA(+), somatostatin receptor 2(-) (prediluted;

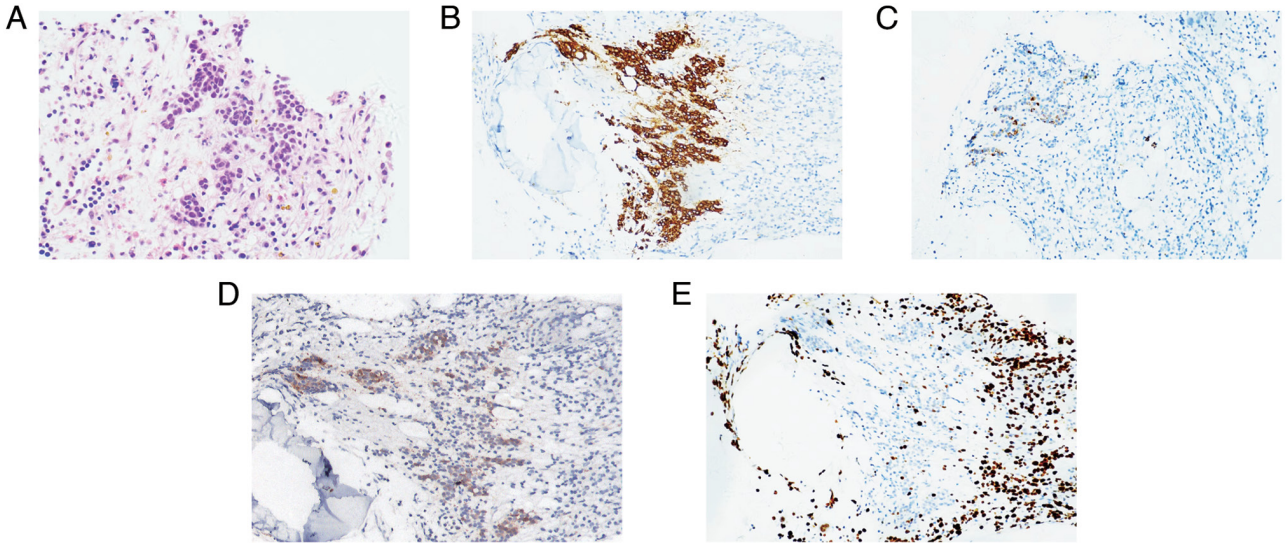

Figure 2. Histopathological (magnification, x400) and immunohistochemical (magnification, x200) features of pancreatic neuroendocrine carcinoma. (A) Histopathological examination of bone marrow biopsies using hematoxylin and eosin staining. (B) Tumor cells displaying synaptophysin expression (++). (C) Tumor cells showing chromogranin A expression (+). (D) Tumor cells exhibiting neuron-specific enolase expression (+). (E) High expression of Ki-67, with a positive index of ~60%.

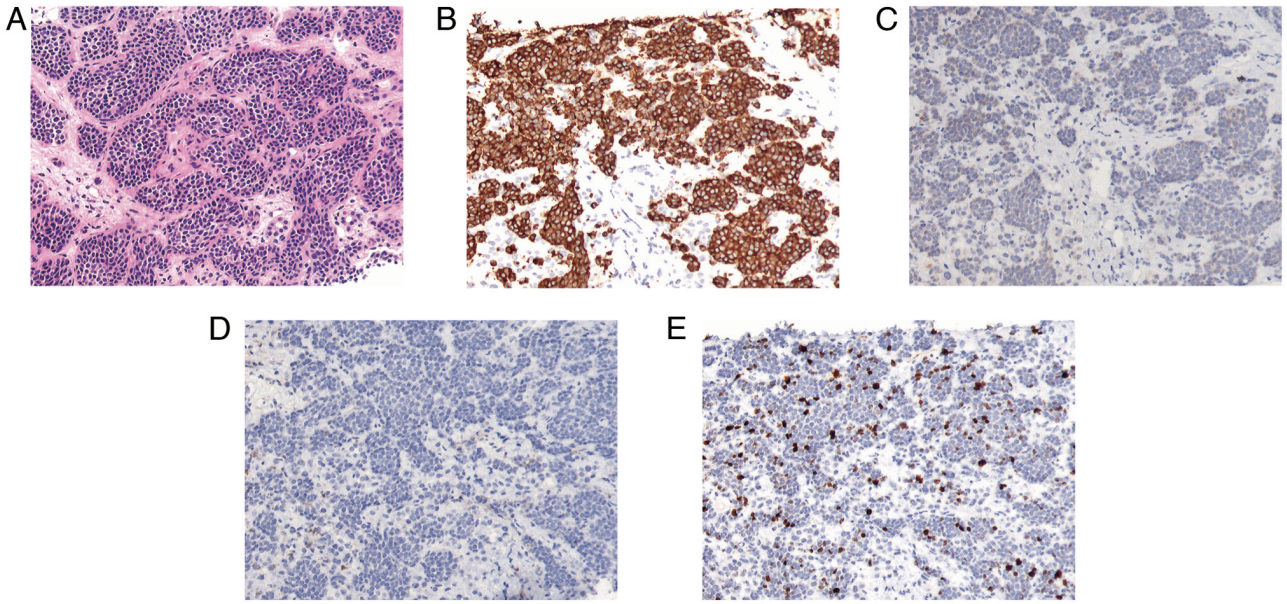

Figure 3. Histopathological and immunohistochemical features of a pancreatic neuroendocrine tumor (magnification, x100). (A) Histopathological examination of liver lesion biopsies using hematoxylin and eosin staining. (B) Tumor cells displaying synaptophysin expression (++++). (C) Tumor cells showing chromogranin A expression (+). (D) Tumor cells exhibiting somatostatin receptor 2 negativity. (E) High expression of Ki-67, with a positive index of ~15%.

cat. no. RMA0867; Fuzhou Maixin Biotechnology Co., Ltd.) and Ki-67 (15%). This was suggestive of a pancreatic (p)NET (grade 2 in the WHO grading system) (2). As the patient's disease continued to progress, treatment regimens were changed several times, including the use of irinotecan (200-mg intravenous drip on day 1 every 14 days) for 1 cycle, sunitinib (37.5 mg orally each day) in combination with mitotane (2,000 mg orally each day) for 1 month, and capecitabine (1 g orally twice a day on days 1-14 every 3 weeks) in combination with temozolomide (200 mg orally on days 1-5 every 3 weeks) for 1 cycle. However, the treatment was not as effective as it could have been.

Starting in April 2023, the patient developed pneumonia, which did not improve with antibiotics. After consultation with respiratory physicians, it was considered that the patient's pneumonia may be related to tumor invasion of the lungs, which resulted in destruction of the lung structure, and that the patient's pneumonia might continue to progress if the tumor progression could not be controlled. After fully communicating with the patient's family, the patient's family decided to discontinue antitumor treatment and chose to return to the local hospital for supportive care. The patient passed away a month after being discharged from the hospital.

Discussion

In the present case, the patient had multiple bone metastases at the time of the initial diagnosis. For pNEN with distant metastasis, the value and significance of surgery should be comprehensively evaluated by considering the age of the patient, their general condition, the functional characteristics of the tumor, the pathological grade, and the number and distribution of the metastases. In the present case, the NEC was non-functional, and the patient had already developed multiple bone metastases throughout the body, so the significance of local surgery was not great. Furthermore, after informing them about the situation, the patient and their family wanted to continue conservative treatment. Therefore, after eight cycles of chemotherapy, the patient was not treated with surgery. However, there is no standard recommendation on whether to continue treatment after first-line chemotherapy and which plan to use. At present, the lack of sizeable genetic mapping studies of pNEC, the limited number of patients with pNEC and the few clinical trials on targeted therapy in pNEC have all limited the application of targeted therapy in pNEC. The patient's genetic test results also did not identify clinically significant mutations.

Sunitinib is primarily recommended for advanced, well-differentiated pNETs (7). However, no studies have reported the efficacy of sunitinib in the treatment of pNEC. In the present study, the attempt at second-line treatment with anlotinib monotherapy was based on the ALTER 1202 study (8). This was a randomized, double-blind, placebo-controlled, multicenter phase II study that enrolled patients aged 18-75 years with histologically confirmed small cell lung cancer. The study also required that enrolled patients had received at least second-line chemotherapy in the past. Enrolled patients were randomized 2:1 to receive either anlotinib or a placebo. At the 2018 World Lung Cancer Congress, Professor Ying Cheng orally reported the PFS results of the ALTER 1202 study. Data was officially available as of June 2018, and the median PFS time in the anlotinib group was 4.1 months, which was significantly higher than the 0.7 months in the placebo group. The study was ultimately published in the British Journal of Cancer (8). Given that small cell lung cancer and pNEC are both NENs, after group discussion, second-line treatment with anlotinib monotherapy was eventually attempted in the present case.

Anlotinib is a multi-targeted oral small molecule tyrosine kinase receptor inhibitor that targets vascular endothelial growth factor receptor-1 (VEGFR1), VEGFR2/KDR, VEGFR3, stem cell factor receptor, platelet-derived growth factor β, fibroblast growth factor receptor-1 (FGFR1), FGFR2 and FGFR3, and also inhibits tumor angiogenesis and tumor cell proliferation (9,10). The anti-angiogenic activity of anlotinib is more potent than that of the other three anti-angiogenic drugs, including sunitinib, sorafenib and nintedanib (11). Compared with sunitinib, anlotinib has a broader and better antitumor effect. Furthermore, anlotinib is well tolerated and most adverse effects can be managed with medical intervention. Clinical trials of anlotinib in pNEC have not yet been conducted, and to the best of our knowledge, no case using anlotinib for pNEC has previously been reported.

The particularity of the present patient was that bone destruction had already developed in 2018, and the biological behavior of the tumor was relatively inert during a period of almost 4 years. In 2022, the disease progressed rapidly, with multiple metastases in the adrenal glands, lungs and liver. Unlike other tumors, while the pathological findings in the bone marrow suggested pNEC, the result in the liver was pNET. A limitation to the study was that no biopsies were performed on the different sites of metastases in the liver. Furthermore, the biopsied tissue from the liver was not genetically tested to investigate whether disease progression was associated with emerging genetic mutations.

In conclusion, as a relatively rare, highly aggressive malignancy with a poor prognosis, pNEC currently has limited therapeutic options, with only platinum-containing chemotherapy as the standard treatment option, and the therapeutic outcome is poor. The application of targeted therapy or immunotherapy in pNEC is still pending the results a series of clinical studies and trials. The present case report, as the first case of EP chemotherapy followed by targeted therapy with anlotinib, with a survival time of almost 60 months, may provide some ideas for the development of clinical trials related to pNEC.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

YZ, YW, XC and JL were responsible for study conception and design. Administrative support was provided by XC and JL. YZ, YW and JW provided study materials or patients. Collection and assembly of data was performed by JW and ZZ. Data analysis and interpretation was performed by ZZ and JL. All authors were involved in manuscript writing. All authors read and approved the final manuscript. YZ, YW, JW, ZZ, JL and XC confirm the authenticity of all the raw data.

Ethics approval and consent to participate

The study was conducted in accordance with the ethical standards from the 1964 Declaration of Helsinki and its later amendments. Local ethical approval was obtained from the Ethics Committee of the 900th Hospital of the Chinese People's Liberation Army Joint Logistic Support Force (Fuzhou, China; approval no. 2023-062).

Patient consent for publication

Written informed consent was obtained from the patient for the case information and images to be published in this case report.

Competing interests

The authors declare that they have no competing interests.

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