A Neuroendocrine Tumor of Unknown Primary Origin that Responded to Treatment Based on Tumor Grade Progression: A Case Report

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Abstract:
The standard chemotherapies for neuroendocrine tumors (NETs) are somatostatin analog (SSA) and targeted-agents for NET G1/G2 and platinum-based chemotherapy for neuroendocrine carcinoma (NEC), classified according to the WHO criteria of 2010. We report a case of NET, in which tumors were successfully treated with platinum-containing chemotherapy after remarkable progression with SSA. A 46-year-old man with multiple lymph nodes and liver metastases of unknown primary origin was diagnosed with NET G2 based on the examination of a biopsy specimen. His tumors were stable with SSA for a year, but rapidly became enlarged. A second biopsy revealed NEC. He received cisplatin plus etoposide, and his tumors showed a marked reduction in size.

Key words: neuroendocrine tumor, NET G3, biopsy, somatostatin analog, chemotherapy


Introduction

Gastrointestinal neuroendocrine tumors (NETs) and NETs of unknown primary origin were included in the World Health Organization (WHO) grading system in 2010. The system defines 3 grades of NET based on the Ki-67 labeling index and the mitotic count (1): G1, mitotic count <2 per 10 high power fields (HPF) and/or a Ki-67 index of ≤2%; G2, mitotic count 2-20 per 10 HPF and/or a Ki-67 index of 3-20%; and G3, mitotic count >20 per 10 HPF and/or a Ki-67 index of >20%. Clinicopathologically, NETs G1 and G2 show low proliferative activity, whereas G3, which is neuroendocrine carcinoma (NEC), shows high proliferative and metastatic low proliferative, as well as a poorly differentiated morphology, which results in a poor clinical prognosis (2-4).

Recently, it has been reported that NEC in the WHO 2010 classification could be divided into well-differentiated and high-proliferative tumors as NET G3, and poorly differentiated tumors as NEC G3; however, this only covers pancreatic NET (8).

Unresectable advanced NETs G1/G2 are generally treated with somatostatin analogs (SSAs), such as octreotide and lanreotide, peptide receptor radionuclide therapy, and targeted-agents, such as everolimus and sunitinib (9-12). In contrast, unresectable NEC is treated with systemic chemotherapy, commonly using a platinum-containing regimen (4, 13). Streptozotocin plus 5-fluorouracil or temozolomide plus capecitabine is recommended for unresectable advanced pancreatic NET G3 (14, 15). The treatment strategy is commonly chosen based on tumor grade at the initial diagnosis. However, it is unknown whether the treatment strategy for NET with slow growth should be changed based on the results of re-biopsy when the tumor grade progresses rapidly during treatment.

We present a case in which progression from NET G2 to NEC (WHO 2010) was observed by repeated tumor biop-

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Received: July 10, 2018; Accepted: July 26, 2018; Advance Publication by J-STAGE: December 18, 2018
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Figure 1. The immunohistochemical features of the first-time biopsy (lymph node lesion). A) Hematoxylin and Eosin staining shows an eosinophilic cytoplasm with irregular geographic growth. Tumor cells are diffusely positive for B) chromogranin-A, C) synaptophysin, and D) CD56 immunostaining. E) The Ki-67 index is 3.5%. Magnification ×400.

Case Report

A 46-year-old man was admitted to a local hospital primarily because of cervical lymph node swelling. Contrast-enhanced computed tomography revealed left supraclavicular, portal, and para-aortic lymph node swelling, and multiple liver tumors. He was referred to our department 2 months after his first visit to the hospital. His medical history included subacute thyroiditis, which occurred 2 years previously; he had no relevant social history. His father had died of hepatocellular carcinoma. A blood test showed no abnormalities, including tumor markers such as carcinoembryonic antigen, carbohydrate antigen 19-9, carbohydrate antigen 125, α-fetoprotein, and prostate-specific antigen. Neither hepatitis B nor C virus antibodies were detected. No primary lesion was found on upper, lower, or capsule digestive endoscopy, or positron emission tomography. Biopsy of the left supraclavicular lymph node revealed tumor cells with irregular geographic growth. Immunohistochemical staining of the specimen was positive for chromogranin A, synaptophysin, and CD56, and the Ki-67 index was 3.5% (Fig. 1). According to the WHO criteria 2010, his tumor was diagnosed as non-functioning NET G2. Despite the use of various types of diagnostic imaging, the primary site was
The patient received intramuscular octreotide long-acting repeatable (LAR; 30 mg) every 4 weeks for 1 year (Fig. 2). Thereafter, he refused to take it due to slight increases in the size of the metastatic lesions of the liver and lymph nodes. However, severe abdominal pain was caused because of the further progression of liver metastasis. This was accompanied by an increase in his serum neuron specific enolase (NSE) level (345.7 ng/mL). We added cisplatin (80 mg/m² on day 1) and etoposide (100 mg/m² on days 1 to 3), every 3 weeks. His symptoms resolved soon after the first treatment cycle, and the metastatic lesions shrank after 4 cycles (Fig. 2). At 5 months after the last administration of chemotherapy, the patient’s metastatic lymph nodes became enlarged and bone metastasis newly developed in the thoracic spine. Although everolimus was combined with octreotide LAR, it was soon discontinued due to severe anemia. While we considered subsequent chemotherapy, the patient died suddenly from an unknown cause, and no pathological evaluation was performed. His overall survival time from the time of the initial treatment was 32 months.

**Discussion**

In the present case, the patient was initially diagnosed with NET G2 according to the WHO 2010 classification and showed stable disease with octreotide. However, rapid tumor progression occurred, and re-biopsy changed the diagnosis to NEC after the short-term discontinuation of octreotide. Then, the reintroduction of octreotide followed by cisplatin plus etoposide was effective. To our knowledge there are no previous reports of the experience of systemic chemotherapy based on the results of re-biopsy of NET G2 that progresses with a high tumor burden. It was difficult to diagnose and treat this case. The proper grading of NETs is essential for predicting the prognosis and making therapeutic decisions in such cases. Re-biopsy revealed that this tumor contained a high proliferative component. Repeated biopsy may be useful for appropriately diagnosing and grading well-differentiated NETs, especially when the tumor progresses abruptly and intra-tumor heterogeneity is suspected.

Recently, several reports have indicated that NECs were more heterogeneous than expected in the WHO classification of 2010 (16, 17). It is increasingly recognized that NEC in the WHO 2010 classification includes well-differentiated tumors with a high-grade component and poorly-differentiated tumors. Both are categorized as WHO-NEC because of their high Ki-67 labeling index (5-7). Basturk et al. reported that 42 of 107 patients who had undergone surgical resection and who had a pathological diagnosis of pancreatic NEC were re-diagnosed with morphologically well-
differentiated NET (5). Thus, in the WHO classification of pancreatic neuroendocrine neoplasms, which was revised in 2017, the NECs of the WHO 2010 classification are now divided into well-differentiated neoplasms with a high Ki-67 labeling index (NET G3) and poorly differentiated NEC (NEC G3) (8), while the grade category is not yet formally recognized in NETs of other primary organs. The prognosis of NET G3 is worse than that of NET G2 and better than that of NEC G3 (18-20). These two tumors are reported to have distinct genotypes: RB, TP53, and KRAS gene mutations have been found in NEC G3 but not in NET G3 (6, 19, 21), and well-differentiated NETs sometimes contain a high-grade component because of their heterogeneity, but NEC G3 rarely includes a low-grade component (6). Although no tumor genes were analyzed in our case, we hypothesize that the tumor was an NET G2 with an NET G3 component (according to the WHO 2017 criteria of pancreatic NETs). In fact, only a few case reports have described the clinical progression from NET G2 to NEC G3 (22, 23); these cases might have included an NET G3 component, the same as in the present case.

SSA and molecular targeted drugs are the standard treatment for unresectable NET G1/G2 (9-12), and platinum-based regimens have been used as a standard therapy for NECs (4, 13) in both the pancreas and other primary organs. Streptozotocin plus 5-FU or temozolomide plus capecitabine has been recommended for pancreatic NET G3. In the present case, although cisplatin plus etoposide seemed to be effective for the growing NET G3 component, and octreotide stabilized the NET G2 component, treatment regimens for pancreatic NET G3 should also be considered in cases of NET G3 of other primary organs.

This case report is associated with some limitations. First, the organs in the first and second biopsies were different. Moreover, the area of the tumor in the biopsy specimen obtained from the liver was limited because of multiple small and diffuse metastases. However, the therapeutic effect appeared to be similar at all sites of metastasis. Second, we could not analyze potential aberrations of tumor genes. Finally, we did not examine the serum NSE level until the second biopsy.

We reported a case of NET with a high proliferative component that was successfully treated with SSA and platinum-containing chemotherapy. Further studies are needed to improve the care for such cases.

The authors state that they have no Conflict of Interest (COI).
References


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