Unknown-primary neuroendocrine neoplasms diagnosed by short-acting somatostatin test: Case series in one institution

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Received June 21, 2022; Accepted September 21, 2022

DOI: 10.3892/etm.2022.11708

Abstract. Neuroendocrine neoplasms (NENs) are a rare heterogeneous group of neoplasms that arise from neuroendocrine cells. Unknown-primary NENs (UP-NENs) are particularly challenging to diagnose and treat. Techniques such as immunohistochemical stains, functional imaging studies, and molecular cancer classifier assays may help clinicians identify the origin of a tumor. However, numerous medical facilities lack the necessary medical equipment, such as functional imaging scanning, to provide patients with a complete primary tumor survey. Even these tests are not enough to determine the original tumor in some cases. The present case series described the diagnosis and treatment outcomes of patients with UP-NEN in a single institution. The medical records of four patients treated between November 2012 and January 2022 were retrospectively reviewed and clinical symptoms, diagnostic methods, image findings and treatment modalities were considered. All patients were diagnosed having functional UP-NENs by using a short-acting somatostatin test. These patients were treated with long-acting release somatostatin analogs along with a positive result. Short-acting somatostatin is an alternatively simple method to determine if a patient has UP-NENs that are functional or expresses somatostatin receptors in the absence of imaging scanning.

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Key words: unknown-primary, neuroendocrine neoplasms, short-acting somatostatin test, diagnosis, treatment

Introduction

Neuroendocrine neoplasms (NENs) are a rare heterogeneous group of neoplasms that arise from neuroendocrine cells. The majority of NENs arise in the gastrointestinal tract and bronchopulmonary system. Yao *et al* (1) reported that the incidence of these tumors has increased in United States from 1.09 per 100,000 in 1973 to 5.25 per 100,000 in 2004 by using the data from Surveillance, Epidemiology, and End Results (SEER) program. In Taiwan, the incidence increased from 0.30 per 100,000 in 1996 to 1.51 per 100,000 in 2008 (2). Unknown-primary NENs (UP-NENs) account for 10-14% of all NENs and are clinically challenging to diagnose and treat (1,3,4). Patients can be diagnosed having NEN either by clinical manifestations and laboratory test or by pathologic proof from metastatic tumor. When the anatomic site of primary tumor is not known after the available diagnostic imaging study, these patients may be categorized as having UP-NENs. Patients with UP-NENs have a poorer prognosis than patients with NENs of definite origin. In addition to the high prevalence of metastatic lesions in most patients with UP-NENs, curative treatment by surgical resection of the primary tumor is often difficult. Somatostatin receptors (SSR) are widely expressed by NENs and are essential targets for diagnosis and treatment (5). Using functional imaging, including SSR scintigraphy or positron emission tomography with newer SSR-targeting radiotracers, can provide more information about the primary tumor location than traditional cross-sectional imaging alone (6). In contrast to functional imaging, immunohistochemical (IHC) staining and molecular cancer classifier assay (MCCA) are unable to pinpoint the definite location of tumors, but these tests can help identify tumors with neuroendocrine origin and their potential locations (7-9). However, not all medical facilities are

Table I. Demographic data of the study patients.

Case	Sex	Age, years	Date of diagnosis	Clinical manifestations	Endoscopic study	Cross-section imaging study
1	Female	61	May 2015	Recurrent abdominal bloating and discomfort	EGD; inflammatory polyp at antrum (4 mm)	MRI; cholelithiasis with cholecystitis
2	Male	68	November 2012	Epigastralgia and jaundice	EUS; duodenal bulb submucosal tumor (5.3 mm)	MRI; no evidence of gastrinoma
3	Male	63	August 2015	Epigastralgia and recurrent gastric ulcer	EGD; gastric and esophageal varices, multiple ulcers	MRI; liver cirrhosis, liver nodule at S8 (1.5 cm), dysplastic suspected nodule
4	Female	59	March 2019	Epigastralgia, diarrhea, body weight loss and lower gastrointestinal bleeding	EUS; negative findings	MRI; multiple hypervascular nodules at S2, S6 and S7, suspected perfusion anomalies

EGD, esophagogastroduodenoscopy; EUS, endoscopic ultrasound; MRI, magnetic resonance imaging.

equipped to offer these tests and for some patients the original tumor still might not be found. The present case series details clinical experience of diagnosing and treating UP-NENs in patients in a single institution.

Materials and methods

Case presentation. From November 2012 to January 2022, four patients with UP-NENs were encountered, accounting for 3% of patients with NENs in Kaohsiung Medical University Hospital. The selection criteria included patients with clinically suspected NENs for whom there was a failure to identify the primary site of tumor after every available examination. The clinical symptoms, diagnostic methods, image findings, and treatment modalities for each patient were retrospectively reviewed based on their medical charts (Table I). The four patients were all middle aged (from 59-68 years old). Two patients were male and two were female. Patient 1 had recurrent abdominal bloating and discomfort without association with meals and she also denied having any aggravating or relieving factors. Patient 2 suffered from chronic epigastric pain and presented to Kaohsiung Medical University Hospital to seek a second opinion with newly developed jaundice which had been diagnosed at another hospital. The measurement of hepatobiliary function was within normal range following general laboratory analysis, and imaging studies did not reveal any specific obstructive lesion related to jaundice. When his jaundice appeared to be improving, patient 2 refused invasive procedure (such as liver biopsy) to determine if it was hepatic jaundice. Patient 3 had refractory peptic ulcer disease causing chronic epigastric pain, and his upper gastrointestinal endoscopy revealed multiple ulcers over gastric antrum and duodenum. He also had regular surveillance for liver cirrhosis with gastric and esophageal varices. Patient 4 had suffered from chronic epigastric pain, diarrhea, and loss of body weight (~20% of usual body weight) over two years. Having failed to diagnose the primary site of suspected carcinoid syndrome caused by NENs at another hospital, she was presented to our hospital for seeking second opinion due to lower gastrointestinal bleeding. These four patients had recurrent symptoms, with or without peptic ulcers, and were clinically diagnosed as having Zollinger-Ellison Syndrome (ZES) without imaging evidence of the primary tumor site. All patients received available imaging studies in Kaohsiung Medical University Hospital including computed tomography, magnetic resonance imaging and endoscopy with or without endoscopic ultrasonography. All the patients were excluded from having multiple endocrine neoplasia. As SSR functional imaging tools were unavailable in our hospital, Patient 1 was referred to another hospital for further functional imaging. However, the primary tumor was still not identified. The endoscopic ultrasonography of patient 2 revealed a submucosal tumor sized 5.3 mm at duodenal bulb. The endoscopic needle biopsy was not able to obtain an adequate specimen. A surgical exploration of gastrinoma triangle was recommended based on these four patients' clinical manifestations and excessive gastrin level during fasting. As these four patients were unwilling to undergo extensive surgical exploration to find the primary tumor, they were accordingly diagnosed as having UP-NENs. These four patients had functional NENs and their pretherapeutic serum chromogranin A (CgA) and gastrin levels exceeded normal limits. The present study involving human participants was reviewed and approved by Institutional Review Board of Kaohsiung Medical University Hospital (approval no. KMUHIRB-20130022). The waiver of informed consent form was approved.

Short-acting somatostatin test. If the patient has ZES and is treated with H2 blocker or proton pump inhibitor, these

Table II. Clinical data of the study patients.

Case	Tumor markers (before treatment) CgA (ng/ml)	Tumor markers (before treatment) Gastrin (pg/ml)	Tumor markers (after treatment) CgA (ng/ml)	Tumor markers (after treatment) Gastrin (pg/ml)	Short-acting somatostatin test	Alive	Overall survival, months
1	1,063.7	140.97	25.9	72.6	Yes, positive	Yes	85
2	506.0	636.69	263.5	52.56	Yes, positive	Yes	115
3	464.3	62.06	28.8	35.89	Yes, positive	Yes	81
4	394.2	615.04	252.6	140.99	Yes, positive	Yes	39

CgA, chromogranin A (reference level: CgA: <101.9 ng/ml; Gastrin: 28~115 pg/ml).

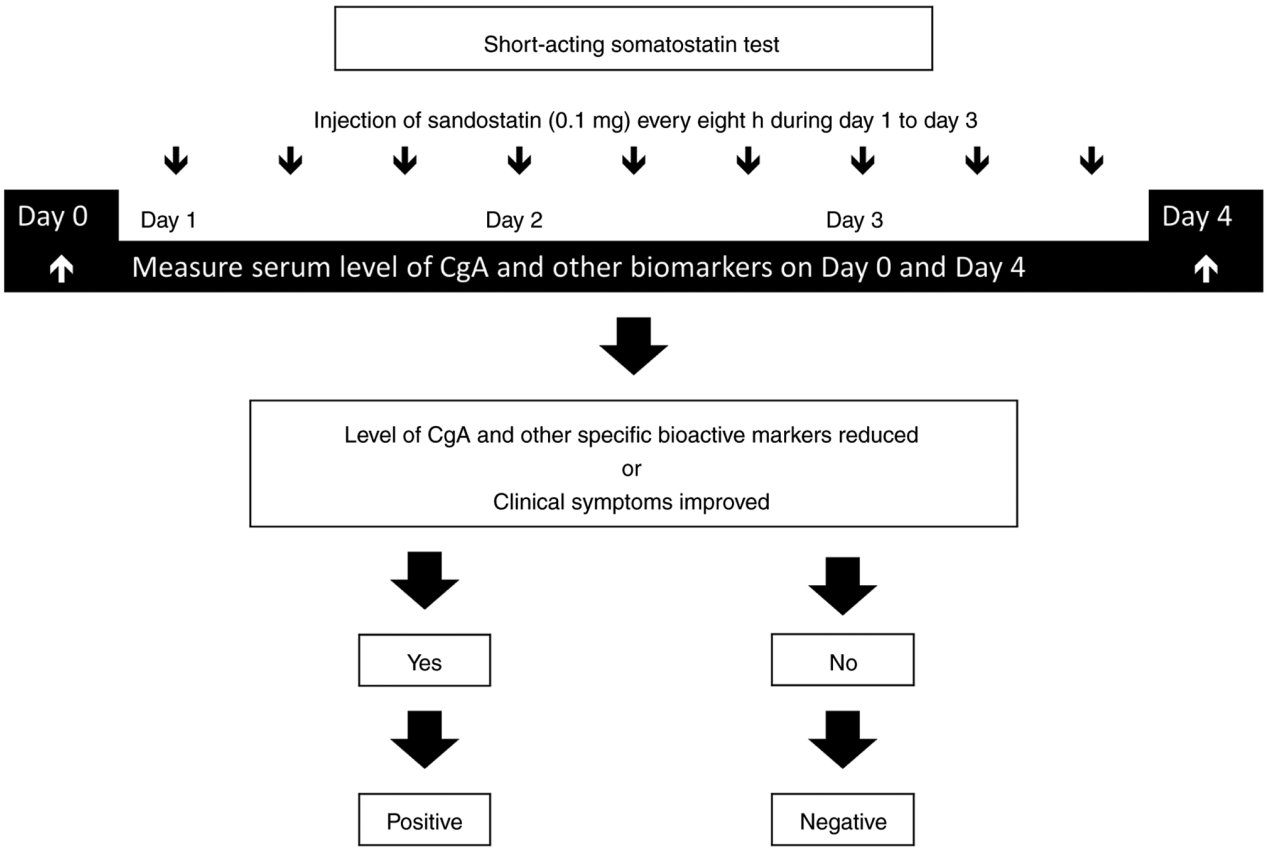

Figure 1. Schematic diagram of short-acting somatostatin test (Day 0: Within 24 h prior to the injection of sandostatin). CgA, chromogranin A; other specific bioactive markers, bioactive markers which associated with patient's clinical symptoms, such as gastrin and insulin.

medications should be discontinued for at least two weeks before serum CgA levels is measured. After admission to the hospital, the patient's serum CgA level as well as other specific bioactive markers (such as gastrin) were measured and then the patients prescribed short-acting somatostatin analogs on day one through day three. Sandostatin (Novartis Pharma Stein AG) is injected at a dose of 0.1 mg subcutaneously every 8 h for 3 days in Kaohsiung Medical University Hospital. The bioactive markers were collected again on day four and compared to pretherapeutic data. A positive outcome was defined as a reduced level of bioactive markers or improved clinical symptoms; otherwise, it was described as a negative result (Fig. 1). A positive result indicated that the patient had functional NENs or NENs that express SSRs and that long-acting release somatostatin analogs should be used as first line therapy consideringly.

Results

A total of four patients were given a short-acting somatostatin test and their serum CgA and gastrin levels were decreased significantly on day four. They also felt their clinical symptoms improve. In a median follow-up of 81 months, these four patients were prescribed long-acting release somatostatin

analogs (sandostatin LAR; Novartis Pharma Stein AG) 20-30 mg every four weeks to control their disease and they remain symptom-free at the time of writing. These patients were routinely followed up and no evidence of disease progression was seen from traditional imaging scans or serum bioactive markers (Table II).

The condition of patients with UP-NENs was assessed every 3 months using history-taking, physical examination, and measurements of bioactive markers (such as CgA and gastrin). Cross-sectional imaging surveys are performed annually or as clinically indicated.

Discussion

UP-NENs can be divided into two categories by the histology: Poorly differentiated and well-differentiated. Patients with poorly differentiated tumors are treated as having poorly differentiated neuroendocrine carcinoma (10-12). Patients with well differentiated UP-NENs usually have liver metastasis and the tumor's production of bioactive substances may cause readily apparent clinical syndromes (3). An initial evaluation of patients who have clinical symptoms or signs of a functional tumor should include not only a thorough physical examination and history-taking but also tests such as cross-sectional imaging, SSR imaging and an assay for blood or urine tumor markers. The presence of SSRs in well-differentiated NENs not only causes the tumor to be visible in SSR imaging but also indicates that somatostatin analog treatments will be effective. SSR functional imaging (68-Ga DOTATATE imaging or SSR scintigraphy) should be performed not only because it demonstrates superior performance to conventional imaging in the setting of initial detection, staging, detection of recurrent tumor and detection of unknown primary in the setting of known metastatic disease, but also if treatment with somatostatin analogs is to be considered (6,13,14).

As Kaohsiung Medical University Hospital lacks SSR functional imaging equipment, it was unable to perform these tests for all patients and one patient was referred to another hospital for further functional imaging, with a negative result. For those patients who did undergo functional imaging, it was still impossible to identify the primary tumor. All four patients also refused extensive surgical exploration for a definite diagnosis. Due to limitations noted above, it was impossible to obtain specimens for IHC staining or administer functional imaging to determine whether patients had SSR-expressing tumors. A short-acting somatostatin test was used to determine whether the patients had SSR-expressing or functional NENs. Based on the short-acting somatostatin test results, those patients with positive results should be treated with long-acting release somatostatin analogs to relieve their symptoms and control their tumor growth.

Surgical resection of the primary tumor is the curative management of NENs. Resection of the metastatic tumors also improves patient prognosis (15,16); however, curative resection is usually difficult for UP-NENs because the primary tumor site is unknown or because the patient is unwilling to undergo extensive surgical resection. It is reasonable to treat these patients by controlling tumor growth and relieving their clinical symptoms. If there is a difficulty diagnosing or treating UP-NEN patients, such as a lack of pathologic examination (IHC stain or MCCA) or functional imaging scanning, a short-acting somatostatin test may be an alternative method to determine the patient's condition if he or she has SSR-expressing or functional NENs. In addition, long-acting release somatostatin analogs are relatively expensive drugs, which may cause a financial burden on patients. A short-acting somatostatin test will choose the patient with a response without severe side effects to receive long-acting release somatostatin analogs.

The present study has several limitations: First, the small number of cases limited the strength of evidence for the effectiveness of short-acting somatostatin test for diagnosing UP-NENs. By sharing our experience, the authors aimed to share how to diagnose SSR-expressing or functional UP-NENs in the absence of advanced imaging (68Ga-DOTATATE PET scan) or pathological examinations. Second, it is essential to surgically explore the gastrinoma triangle to diagnose patients with ZES without obvious primary tumors. The patients in the present study were unwilling to take the risk of further surgical exploration thus limiting diagnosis. Third, in patient with UP-NENs, short-acting somatostatin test is unable to add additionally diagnostic value in localization of primary lesions. However, it can help clinician to evaluate the efficacy and cost-effectiveness of somatostatin analogs on patient with UP-NENs.

In summary, the accurate identification of NEN subtypes is critical for developing a targeted treatment plan. Multimodal diagnostic methods are often used to identify NEN subtypes. Short-acting somatostatin test is an alternatively simple method to determine if a patient has UP-NEN that is functional or expresses SSRs as well as to consider long-acting release somatostatin analogs as first line treatment.

Acknowledgements

Not applicable.

Funding

The present study was supported by grants from the Ministry of Science and Technology (grant nos. MOST 109-2314-B-037-046-MY3, MOST110-2314-B-037-097, MOST 111-2314-B-037-070-MY3 and MOST 111-2314-B-037-049), the Ministry of Health and Welfare (grant no. MOHW111-TDU-B-221-114014), the health and welfare surcharge of on tobacco products, the Kaohsiung Medical University Hospital [grant nos. KMUH110-0R37, KMUH110-0R38, KMUH110-0M34, KMUH110-0M35, KMUH110-0M36 and KMUH-DK(B)110004-3], the KMU Center for Cancer Research (grant no. KMU-TC111A04-1) and KMU Office for Industry-Academic Collaboration (grant no. S109036), Kaohsiung Medical University. In addition, this study was supported a Grant from Taiwan Precision Medicine Initiative and Taiwan Biobank, Academia Sinica, Taiwan, R.O.C.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

TC designed the present study, analyzed the data, and wrote the manuscript. WS, YC, PC, CL, YY, CH and HT made substantial contributions in terms of the data acquisition, interpretation and statistical analyses, in addition to assisting with the manuscript preparation. CH and HT confirm the authenticity of all the raw data. JW also participated in the study design and coordination, in addition to making critical revisions to the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The present study involving human participants was reviewed and approved by Institutional Review Board of Kaohsiung Medical University Hospital (approval no. KMUHIRB-20130022). The waiver of informed consent form was approved.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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