Professional Leaders of Asia in NEUROENDOCRINE TUMORS

PLANET
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Welcome Message

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PLANET is a webzine sponsored by the Korean Society of Gastrointestinal Cancer to be provided to the neuroendocrine tumor specialists of Korea, China, Taiwan and Japan. It was designed to not only provide the medium for the exchange of the latest knowledge on the diagnosis and treatment of gastroenteropancreatic neuroendocrine tumor (GEP-NET) but also for sharing the experiences of GEP-NET in Asian ethnic groups.

It will be published biannually, and each issue will carry several GEP-NET cases from the participating countries. In addition, there will also be online surveys asking for the opinions of international readers on some of these cases.

In this era where cancer diagnosis and therapy are individualized, the various cases in PLANET will be a valuable reference providing academic experience which is difficult to find in textbooks. Also, we expect the webzine of PLANET to allow a more interactive interchange of knowledge between the eastern Asian countries.

Director of the Council of the Neuroendocrine Tumor Research
Korean Society of Gastrointestinal Cancer
Professor Jae Hee Cho
Dear Reader,

It is with much joy that we celebrate the joint launch of PLANET in Korea, China, Taiwan and Japan as a webzine specializing in neuroendocrine tumors.

The disease incidence of neuroendocrine tumors has been increasing. In an effort to keep pace with the trend, we have not only increased our understanding of the pathology of neuroendocrine diseases but also vastly developed targeted cancer therapies and surgical techniques through a large amount of research in the past few years.

However, there is still a need for more academic research and interest on the relatively rare neuroendocrine tumors, for which a multidisciplinary approach is crucial. Korean Society of Gastrointestinal Cancer has been striving to confront the chronological changes to the best of our abilities by expanding opportunities for professional exchange through numerous academic events and workshops. Also, from this year, we will be publishing the webzine PLANET as a medium to allow exchanges and discussion of the latest knowledge on the area of neuroendocrine tumors between the Asian specialists.

I take this opportunity to thank the efforts of “Council of the Neuroendocrine Tumor Research” and all of whom have greatly contributed to the foundation of this webzine. I hope PLANET will be of great assistance to the neuroendocrine tumor specialists of each country for treatment and research. I would also like to encourage interest and contribution from the readers. Comments and suggestions are welcome. Thank you.

President of Korean Society of Gastrointestinal Cancer

Professor Si Young Song, MD, PhD

It is my great pleasure to celebrate the joint launch of webzine neuroendocrine tumors focused on such kind of rare tumors in Korea and China. Over the past three decades, the incidence of NEN has significantly increased - from 1.09/100,000 to 5.25/100,000 in western countries. There are still no epidemiological data of NEN based on the population of mainland China. However, an investigation from Taiwan showed that the incidence of NEN also increased 5 folds from 0.3/100,000 in 1996 to 1.5/100,000 in 2008.

Gastroenteropancreatic Neuroendocrine Neoplasm (GEP-NEN) is the most common type of NEN which accounts for 65%–75% of NEN from all sites. A multicenter retrospective pathological study in mainland China indicates pancreas and rectum as the most common sites. Treatment of NEN patients should be an individualized and multidisciplinary comprehensive management, including operation (under endoscopy and surgery), interventional therapy and nuclide therapy, chemotherapy, biotherapy and molecular target therapy, etc. Compared to other tumors, more specialized departments should be involved in the diagnosis and treatment of NEN.

Chinese doctors began to pay attention to these rare tumors in 2010 when the nomenclature and classification of neuroendocrine tumors of the digestive system were updated by WHO. Thereafter, various professional societies/studies (including the disciplines of pathology, gastroenterology, oncology and pancreatic surgery) have released several related guidelines/consensuses for NEN respectively. Considering the current situation of diagnosis, management and research of NEN in China, an increasing number of experts from NEN-related disciplines and fields have gradually gathered together and formed several professional NEN study groups. For instance, the Chinese Study Group for Neuroendocrine Tumors (CSNET), founded in 2015, is the first nation-wide interdisciplinary alliance of NET experts in China, including experts in various fields, such as medical oncology, gastroenterology, surgery, endocrinology, pathology, radiology and nuclear medicine.

As a specialized Chinese NET study group, we are looking forward to collaborating with the Korean NET study group. And the first step of the collaboration will be publishing this webzine as a bridge between Chinese and Korean specialists. I hope this webzine will be of great help for the diagnosis and treatment of neuroendocrine tumors in each country.

Chair of the Chinese Study group for Neuroendocrine Tumors

Professor Jie Chen
CASE DESCRIPTION

An 11-year-old girl presented with severe hypoglycemia. Abdominal MRI demonstrated a 2 cm sized mass in the tail of the pancreas. She underwent distal pancreatectomy and the pathologic analysis confirmed grade 2 neuroendocrine tumor. Postoperatively, her fasting blood glucose concentrations returned to the normal level. Three months after surgery, abdominal MRI demonstrated scattered sub-centimeter lesions in both lobes of the liver. She was referred to our hospital for evaluation of the liver lesions (Figure 1). Physical examination was unremarkable. Serum glucose level was 116 mg/dL (normal range 70-110 mg/dL) and serum chromogranin A (CgA) level measured by enzyme-linked immunosorbent assay was 65.32 ng/mL (normal range 27-94 ng/mL). US-guided percutaneous liver biopsy revealed no tumor.

However, she experienced multiple episodes of hypoglycemia 3 years after the initial surgery. Serum glucose level determined in the emergency department was 38 mg/dL. Serum insulin level was 30.9 µU/mL (normal range 2.6-24.9 µU/mL). Serum C-peptide level remained normal [5.14 ng/mL (normal fasting levels 1.07 to 3.51)] and antibody against insulin was not found. The CgA level remained normal (52.27 ng/mL). Follow-up MRI showed no gross interval change of multiple small enhancing lesions in the liver. Endoscopic ultrasonography showed no tumor in the remnant pancreas. Repeated US-guided percutaneous liver biopsy revealed metastatic neuroendocrine carcinoma. She was transferred to another hospital and received transhepatic arterial chemoembolization (TACE) and everolimus administration.

DISCUSSION

Insulinoma is a rare pancreatic endocrine tumor that is typically sporadic, solitary, and less than 2 cm in diameter. The common clinical manifestation of the insulinoma is fasting hypoglycemia, with discrete episodes of neuroglycopenic symptoms.1 Surgical removal is the treatment of choice. However, in the cases observed from 1927 to 1986, 196 patients were free of symptoms after the initial removal of the insulinoma, whereas 11 patients (6%) had recurrent hypoglycemia. Six patients had pathologic confirmation of recurrent insulinoma.2 Among the 4 patients with malignant insulinoma who were symptom-free for six or more months after the initial operation, 2 patients had recurrences at 4 and 9 years respectively. The diagnosis of insulinoma is suggested by endogenous hyperinsulinemia in the presence of hypoglycemia and reversal of the symptoms by administration of glucose. Diagnosis relies on clinical features along with laboratory tests and imaging investigations to aid in localization.3 Sometimes it is not easy to make the correct diagnosis.

She was not a candidate for surgical resection. The therapeutic choices to prevent symptomatic hypoglycemia include diazoxide, somatostatin analogues, verapamil and phenytoin. Although experience is limited, at least some data suggest that everolimus, an inhibitor of the mammalian target of rapamycin, may be of particular value in patients with functioning insulinomas and refractory hypoglycemia.4,5 TACE can be another option as palliative technique in patients with symptomatic hepatic metastasis who are not candidates for surgical resection. Liver transplantation in patients with liver metastasis of neuroendocrine tumor has proved effective for selected patients for whom standard surgical and medical therapies have failed. However, judgments regarding transplant therapy remain based on limited evidence6.

FIGURE

Abdominal MRI finding

It demonstrates scattered sub-centimeter lesions in both lobes of the liver (arrow head).
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A case of ampulla of Vater neuroendocrine tumor with liver metastasis showing discordance between mitotic count and Ki-67 index

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Category: Upper GI

CASE DESCRIPTION

A 75-year-old man was admitted with fever and right upper quadrant (RUQ) pain for 3 days. He had hypertension which was well-controlled with medication, and had no family history of cancer. Physical examination on admission revealed mild direct tenderness on RUQ area. The laboratory findings were as follows: white blood cells, 4,890 × 10^3/μL (3.8-10.0 × 10^3/μL); total bilirubin, 1.1 mg/dL (0.3-1.2 mg/dL); aspartate aminotransaminase, 147 U/L (normal range 5-40 U/L); alanine aminophosphatase, 43 U/L (10-40 U/L); alkaline phosphatase (ALP), 278 U/L (35-123 U/L); and gamma-glutamyltranspeptidase, 426 U/L (0-72 U/L). Carbohydrate antigen 19-9 (CA19-9) and carcinoembryonic antigen (CEA) were normal.

Transabdominal ultrasonography showed mild extrahepatic bile duct dilation, and computed tomography (CT) also revealed the mild bile duct dilation with a suspicious ampullary mass. Endoscopic retrograde cholangiography (ERC) demonstrated an ulceroinfiltrative mass of ampulla of Vater (AoV) and endoscopic biopsy was performed (Figure 1). Histologic examination showed small round cell tumor with mitotic activity less than 20/10 high power field (HPF) (WHO 2010 grade, G2), and additional immunohistochemical findings indicated that the tumor cells were immuno-positive for neuroendocrine markers such as synaptophysin and chromogranin (Figure 2). Although CT scan showed no metastatic lesion, PET-CT scan for staging work-up revealed the suspected metastatic lesion in liver (Figure 3) and ultrasound-guided liver biopsy was performed at 9 mm sized nodule in S6 (Figure 4). Histologic examination of liver biopsy showed small round cell tumor which was immuno-positive with chromogranin and synaptophysin with mitotic activity less than 20/10 HPF (WHO 2010 grade, G2). However, Ki-67 labelling index was calculated up to 25% (WHO 2010 grade, G3). The patient was finally diagnosed with WHO 2010 grade 3 metastatic AoV neuroendocrine carcinoma showing discordance between mitotic count (G2) and Ki-67 index (G3). Palliative combination chemotherapy with cisplatin and etoposide was planned, but the patient refused further treatment except conservative care. After 7 months of discharge, the patient was readmitted with disease progression and died of hepatic failure.

DISCUSSION

Biliary neuroendocrine tumor (NET) is very rare disease and it comprises less than 1 percent of all gastroenterohepatic (GEP) NETs. Because most of studies for biliary NETs consist of case reports, little is known about their clinicopathologic features, clinical behavior and prognosis. "The Society of Korean Gastrointestinal Cancer" created a retrospective registry of GEP-NETs between 2002 and 2012 in Korea. In terms of the analysis of biliary NETs (n=53) with this registry, we found that ampulla of Vater was the most common site (n=32) and 15% of them had liver metastasis on the initial staging work-up. Histologic grades and various classifications have evolved in the attempt to stratify NETs into different prognostic groups. The WHO 2010 grading system has been proposed in order to define a new pathologic grade stratification, and the system categorizes neuroendocrine tumors into low (G1), intermediate (G2), and high-grade (G3) based on their proliferative rate using the mitotic activity and/or a Ki-67 index.1,2 GEP-NETs are heterogeneous group of neoplasms which includes different nature of disease and the biologic behavior according to morphology and proliferative rate. Poorly differentiated neuroendocrine carcinomas are often related to rapid progression, while well-differentiated GEP-NETs have a much better prognosis.

Proliferative rate of NETs are determined by mitotic activity and/or Ki-67 index, however the best method to establish the proliferative rate is not fully established. Mitotic counting can be easily performed without immunohistochemical stain, however it is required that at least 40 HPFs should be counted. Thus, mitotic activity has a low availability for limited specimen. On the other hand, the Ki-67 index is determined on the areas of highest labeling zone, so it is more easily found in limited specimen such as aspiration and biopsy tissue which includes only a few available microscopic HPF.3 In addition, because it is a proportional comparison value and its localized amount changes with the cell cycle, it may give more objective results with discrepancies among different pathologists. However, Ki-67 index also has a limitation in representing the true grade of NETs, which is why there is intra-tumoral heterogeneity of proliferative rate.

If there is a discordance between these two measures of proliferation, the WHO classification recommends using the higher grade, which was validated in a study of discordant NETs.4 Basturk et al reported that there was a small subset of pancreas NETs (pNETs) that appeared histologically well-differentiated (less than 20 mitoses/10 HPFs, G2), but was associated with high Ki-67 proliferation index (>20%, G3). The clinical behavior of these grade-discordant pNETs was likely to be worse than grade-concordant G2 pNETs (median survival 54 vs. 68 months, and five-year survival 29 vs. 62%). And patients with grade-discordant pNETs had significantly longer survival when compared with poorly differentiated pNEC (median survival 54 months vs. 11 months, and five-year survival 29% vs. 16%).5 These findings suggested that the current WHO G3 category is heterogeneous group which contains two distinct neoplasms of well-differentiated pNET with an elevated proliferative index and poorly differentiated NEC.
As it was found in the latest study of other NETs, we presented a case of metastatic ampulla of Vater (AoV) NET with discordance between mitotic count and Ki-67 Index. Further study is warranted to elucidate the clinicopathologic characteristics of discordant GEP-NETs according to different primary sites.

FIGURES

![Figure 1](image1.jpg)

**FIGURE 1** Endoscopic retrograde cholangiography findings
A. Endoscopic image reveals an ulceroinfiltrative mass lesion on the ampulla of Vater.
B. Fluoroscopic image shows mild common bile duct dilation.

![Figure 2](image2.jpg)

**FIGURE 2** Histologic and immunohistochemical findings of the endoscopic biopsy of the ampulla of Vater mass
A. H & E staining shows high cellularity small round cell tumor with mitotic activity less than 20/10 HPFs.
B. Immunohistochemical staining shows immuno-positive with chromogranin.

![Figure 3](image3.jpg)

**FIGURE 3** PET-CT scan findings
It shows focal hypermetabolic area in the ampulla of Vater area (SUV 6.97) and several hypermetabolic lesions in the liver.
FIGURE 4  Transabdominal ultrasound finding
It reveals several hypo-echoic nodules in liver, and liver biopsy was performed to the 9 mm-sized nodule in S6.

FIGURE 5  Histologic and immunohistochemical findings of the liver biopsy
A. H & E staining shows small round tumor cells with irregular pleomorphic nuclei and prominent nucleoli. Mitotic activity is calculated less than 20/10 HPFs.
B. Immunohistochemical staining shows immuno-positive with chromogranin and synaptophysin, and the positive staining of Ki-67 index is up to 25%.

REFERENCES

A case of small intestinal neuroendocrine neoplasm with carcinoid syndrome, carcinoid heart disease and carcinoid crisis occurring sequentially

**CASE DESCRIPTION**

A 57-year-old man was referred to our hospital in November 2012 because of diarrhea, abdominal pain, intermittent flushing and a weight loss of 6 kg over one year. Physical examination revealed flushing on cheeks and chest (Figure 1A, 1B), hepatomegaly, and a firm and immobile mass (about 3×4 cm in size) under the left side of the navel. Serum CgA level was 1,586 ng/mL (normal range <95 ng/mL). CT scans showed a 4.6×2.9 cm mass in the mesenteric region (Figure 1C), numerous metastasis throughout the liver (Figure 1D), multiple lymph node enlargements including the retroperitoneal (Figure 1C), right portopulmonary and mediastinal lymph nodes. We also performed a somatostatin scintigraphy (octreotide scan) for the patient and reviewed the pathological section (two months before this admission, a liver biopsy was performed in another hospital). The octreotide scan was weakly positive in the mesenteric region and histopathology of the liver biopsy confirmed the diagnosis of grade 2 neuroendocrine tumor with mitotic count of 2/10 HPFs, and positive staining for Syn, CgA, CDX-2, SSTR2, SSTR5 (Figure 1E, 1F) and a Ki-67 proliferation index of 3%. The diagnosis of this patient was confirmed as metastatic small intestinal neuroendocrine tumor with carcinoid syndrome. We then treated this patient with long-acting octreotide (intramuscular injection, 30 mg every 4 weeks) and remittance of the carcinoid syndrome began soon afterwards. Symptoms were controlled and stable disease (SD) was achieved for 24 weeks until more symptoms occurred.

In October 2013, the patient manifested chest distress and gasp with post-activity exacerbation while diarrhea and flushing worsened. Echocardiography revealed severe tricuspid insufficiency, pulmonary incompetence and right atrial enlargement which suggested the diagnosis of carcinoid heart disease (CHD). Besides diuretic therapy, we increased the frequency of octreotide to every 3 weeks. Under such treatment, symptoms except flushing alleviated slightly.

On May 27th, 2014, the patient was referred to our hospital again via an ambulance. One month before this admission, coughing and expectorating occurred in the patient due to a common cold and 3 days ago, severe cyanosis arose while diarrhea and flushing worsened. Physical examination revealed low blood pressure of 90/58 mmHg, flushing, severely cyanotic lips (Figure 2A) and fingertips, ronchi and crackles of the lung, bicuspid and tricuspid diastolic murmur and hepatomegaly. Blood gas analysis suggested type I respiratory failure. Serum CgA level increased to 753 ng/mL, but a CT scan and echocardiography did not indicate disease progress. Based on these signs and findings, diagnosis of carcinoid crisis was confirmed. Besides oxygen inhalation and airway spasm relieving therapy, high dosage of short-acting octreotide (1.2 mg-1.4 mg I.V. drip/day) was used. After this treatment, symptoms were relieved (Figure 2B) and hypoxemia improved significantly. Considering the high tumor burden and excessive hormone secretion, we increased the dosage of the long-acting octreotide to 60 mg every 3 weeks since June 6th, 2014.

After being discharged from our hospital, the patient still repeatedly manifested chest distress and gasp, thus an increased dosage of octreotide was used in a local hospital. Because the disease was exacerbated, the dosage of long-acting octreotide was increased to 90 mg every 3 weeks from September 2015. Hypoxia still occasionally occurred and gradually worsened (Figure 3), and the dosage of short-acting octreotide was increased to 1.6 mg in October 2015. On December 28th, 2015, the patient died due to severe and uncontrollable hypoxemia in a local hospital.

**DISCUSSION**

In western countries, small intestinal neuroendocrine neoplasm (SI-NEN), including NEN of duodenum, jejunum and ileum, accounts for 18%-26% of NEN from all sites. However, in the Asian population, SI-NEN is not common. An epidemiologic investigation from Taiwan showed that SI-NEN only accounts for 5% of NEN. Furthermore, SI-NEN with carcinoid syndrome, carcinoid heart disease and carcinoid crisis occurring sequentially in one patient is much rarer in the Asian population.

Surgery is the sole curative option for patients with SI-NEN. However, 46.4%-70% of the patients manifested lymph node and liver metastasis when diagnosed. Although the recent ENETS guideline recommends that for patients whose distant metastasis can be curatively resected, resection for primary tumor should be performed, there are still many SI-NEN patients with distant metastasis who need more medical treatment, such as our patient. Somatostatin analogues (SSA), including octreotide, lanreotide, pasireotide, are the major drugs used in SI-NEN.

SSA was firstly applied to palliate symptoms of carcinoid syndrome such as diarrhea and flushing. However, more studies have shown that SSA can delay tumor growth in SI-NEN. Furthermore, a high dosage of short-acting SSA is essential when carcinoid crisis occurs. We administrated SSA (long-acting octreotide) to our patient, and diarrhea and flushing remitted significantly after treatment. Moreover, long-acting octreotide can also delay tumor growth in this patient who endured a relatively long progress-free survival. When carcinoid crisis occurred, a high dosage of short-acting SSA also helped to relieve symptoms and improve hypoxemia.

SI-NEN is rare in the Asian population, but many patients with SI-NEN have advanced disease. Although SSA may help slow down tumor growth, more effective regimens for antitumor therapy are needed and more attention from Asian countries should be paid to this rare tumor in the rare site.
FIGURES

FIGURE 1  Clinical manifestation and tumor detection
A. Flushing on the cheeks of the patient, B. Flushing on the chest of the patient, C. Primary tumor and retroperitoneal lymph node enlargement (arrow), D. Numerous metastasis throughout the liver (arrow), E. Positive staining of SSTR2, F. Positive staining of SSTR5.

FIGURE 2  Cyanotic lips
A. Before short-acting octreotide was used, B. After treating with short-acting octreotide

FIGURE 3  Severely cyanotic fingers

REFERENCES


CASE DESCRIPTION

A 67-year-old man was admitted with upper quadrant pain for 2 months. He had no family history of cancer. Physical examination on admission revealed mild direct tenderness in the middle upper quadrant area. The laboratory findings were as follows: CA19-9, 10.56 U/mL; CA125, 17.82 U/mL; CA15-3, 9.85 U/mL; AFP, 4.00 ng/mL; CEA, 4.25 ng/mL. Computed tomography (CT) showed the tumor involved the neck of the pancreas and multiple hepatic metastasis (Figure 1). Somatostatin receptor scintigraphy (SRS) also revealed the pancreas tumor and multiple hepatic metastasis with overexpression of somatostatin receptor (Figure 2). The results of additional serological examination were as follows: NSE, 14.39 ng/mL; Insulin, 24.5 pmol/L; CgA, 264.5 ng/mL. Endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) of primary tumor was performed according to the NCCN guidelines (Figure 3), and the pathologic diagnosis was well differentiated pancreatic neuroendocrine tumor G2 (Ki-67 5%).

Palliative surgery (distal pancreatectomy, splenectomy, partial hepatectomy and radiofrequency ablation for liver metastasis) was performed on 4th Jan 2016. Post-operative histological findings confirmed p-NET G2 with multiple liver metastasis (Ki-67 5%). Post-operative recovery was uneventful. He left the hospital 15 days after the surgery. Post-operative baseline examination showed >90% tumor was removed (Figure 4). From 28th Jan 2016, the patient started to receive octreotide LAR 30 mg every 4 weeks. After a 5-month follow-up, the patient is still alive.

DISCUSSION

Pancreatic neuroendocrine neoplasms (p-NENs) are slowly growing tumors with frequent liver metastasis. Various approaches for the treatment of non-functional pancreatic neuroendocrine neoplasms with synchronous liver metastasis (p-NENLM) create controversy over which is the optimal treatment.

For more specific and individualized treatment of p-NENLM, Frilling et al. classified p-NENLM into three radiological types and suggested the treatment selection should be based on these three localization types.

According to computed tomography (CT) and somatostatin receptor scintigraphy (SRS) results, metastatic lesions of this patient were defined as type II liver metastasis. According to ENETS guidelines 2012, pathological classification should be confirmed before the treatment in patients with liver metastasis because operation is only recommended for G1/G2. This patient underwent a EUS-FNA of primary tumor, and a pathological diagnosis was made before surgery.

Updated ENETS guidelines 2016 and NCCN guidelines 2016 both recommend the non-curative debulking surgery if at least 90% of the tumor can be surgically removed. In a retrospective study from the Mayo Clinic, there was no difference in overall survival between the 72 patients with metastatic nonfunctional p-NETs undergoing cytoreductive surgery and the patients undergoing R0 resections despite a higher incidence of tumor recurrence in the cytoreductive surgery group. Furthermore, cytoreductive surgery in combination with liver-directed therapies is also recommended in ENSTS and NCCN guidelines. A recent study reported that cytoreductive surgery combined with ablation demonstrated 5-year survival of around 75% in p-NETs patients, which was comparable to patients undergoing R0 resection. This patient recovered from a relatively invasive surgery (distal pancreatectomy, splenectomy, partial hepatectomy and radiofrequency ablation for liver metastasis). Therefore, it is worth noting that surgery for p-NENLM has become a feasible approach due to the improvement of technic.


