A case of pancreatic neuroendocrine tumors

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Abstract Pancreatic neuroendocrine tumors (pNETs) are an uncommon malignancy arising from the neuroendocrine cells of pancreas. Most cases of pNETs present with metastatic disease, but there are few reports in the literature describing pNETs metastasis to the lung and mediastinal lymph nodes [1]. Moreover, although a multimodal treatment including surgical resection and chemotherapy is acceptable for management of pNETs, advanced pNETs still remain a difficult therapeutic challenge [2, 3]. Radiotherapy or combined chemoradiotherapy has not been standard in the treatment of pNETs. An 80-year-old female was admitted to our hospital with cough and anorexia. She had been diagnosed and resected pNETs 8 years ago. Mass shadow was pointed out with chest X-ray, and endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) was performed. Pathological examination revealed neuroendocrine tumors, so the lung mass was considered as metastasis of pNETs. Then, we

discussed her treatment at Cancer Board, and radiotherapy was chosen. We hope this case suggests that radiotherapy will be one of the treatment options for metastatic pNETs.

Keywords Neuroendocrine tumor · Lung metastasis · Mediastinal lymph nodes swelling · Radiotherapy

Case presentation

Dr. Moriyama (conference chairperson, medical oncologist)

Good evening, everybody. Welcome to the Cancer Board Conference. Today we would like to discuss a case of pancreatic neuroendocrine tumors (pNETs). Dr. Takano, please begin the case presentation.

Dr. Takano (digestive surgeon)

This patient is an 80-year-old female. As to her history of present illness, she underwent pancreaticoduodenectomy for pancreatic head tumor at 72 years of age. Pathological examination revealed pNETs. 6 years later, a computed tomography (CT) demonstrated a mass lesion at the residual pancreas. She had undergone reoperation and was pathologically diagnosed with pNETs grade 2. In February 2015, 8 years after the initial operation, the patient visited a medical practitioner because of cough, anorexia, and weight loss. A mass shadow was pointed out by chest X-ray. She consulted the respiratory medicine in our hospital. A biopsy by endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) revealed neuroendocrine tumor. Thus, the lung mass was considered as metastasis of pNETs. Now the patient is admitted to our

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department. Please discuss the treatment strategies for this patient.

Dr. Moriyama

Thank you very much. How about the performance status of this patient?

Dr. Takano

Her performance status is 0–1. She is ambulatory and capable of all self-care, but has gradually been losing her appetite due to cough. She also has occasional bloody sputum after admission.

Dr. Moriyama

Thank you. Please read the radiological findings.

Dr. Ikeda (radiologist)

A contrast-enhanced CT of the chest shows a tumor with a diameter of 5 cm in the upper lobe of the left lung S3 (Fig. 1a). This image will not contradict lung metastasis of pNETs. Swelling of left parathoracheal lymph nodes is noted near the aorta, and these lymph nodes affect the thoracic and esophageal stenosis (Fig. 1b). No obvious tumor is detected in the residual pancreas or the liver.

Dr. Saijo (medical oncologist)

I have one question. Did the pathological examination of EBUS-TBLB also reveal pNETs grade 2?

Dr. Takano

We are currently confirming that with the pathologist now, but the report has not been in time for today.

Treatment choice

Dr. Moriyama

Now, we would like to start the discussion. In order to choose the treatment strategy, we have to consider the additional information of mediastinal lymph nodes. At first, I want to ask Dr. Sato about the surgical indication.

Dr. Sato (thoracic surgeon)

This is a case of metastasis to the left lung and mediastinal lymph nodes of pNET. The metastatic mediastinal lymph node seems to invade the esophagus directly, so it will be difficult for us to remove these lymph nodes completely.

Fig. 1 A contrast-enhanced CT of the chest shows a tumor in the upper lobe of the *left* lung S3 (a). Swelling of *left* parathoracheal lymph nodes is noted near the aorta, and affected the trachea and esophagus (b)

Dr. Moriyama

Thank you. How about the chemotherapy?

Dr. Matsumoto (medical oncologist)

Considering the patient's age, I think the administration of sunitinib will not be safe. But we cannot expect reduction of the tumor size with octreotide. Taking into account her symptoms, if possible, I think we may execute radiotherapy before chemotherapy.

Dr. Moriyama

OK. Then, how about possibility of the radiotherapy?

Dr. Yamana (radiation oncologist)

Irradiation therapy will be acceptable for this patient. Because she has bloody sputum, and the tumor lesion infiltrates to the respiratory tract, perforation or hemoptysis could occur during irradiation therapy. Looking back at these conditions and if irradiation therapy is required for this patient, the dose of 30 Gy/10 fractions (Fr) will be appropriate.

Dr. Ayukawa (radiation oncologist)

We do not have an experience in the irradiation for pNETS, thus we cannot say anything definite to effect at present.

Dr. Saijo

How about everolimus for this patient? I think everolimus is better than sunitinib in both efficacy and safety.

Dr. Matsumoto

I am not sure whether reduction of tumors is obtained promptly in everolimus or octreotide. Because she already has the symptoms such as hemoptysis and anorexia, I think it is better to do radiotherapy at first to improve her symptoms, and then administration of an appropriate chemotherapeutic agent should be considered sequentially.

Dr. Abe (radiation oncologist)

If the irradiation is not effective as expected or only shows temporary effect, it would cause the stenosis of left main bronchus in the near future. In addition, we worry about the invasion to esophagus from lymph node metastatic lesion.

Dr. Takano

We will perform esophagogastroduodenoscopy as soon as possible.

Dr. Abe

We will adopt palliative radiation at dose of 30 Gy/10Fr, but her symptoms may get worse during the irradiation.

Dr. Moriyama

Please explain to the patient about a possible risk with treatments by irradiation, consult the radiotherapist and start radiotherapy at first. After completion of irradiation, we will discuss about chemotherapy.

Thank you for your participation. I think we had a helpful discussion about this case.

Follow-up

We discussed the case of pNETs, which revealed lung and mediastinal lymph node metastasis. For more information about the mediastinal lymph node biopsy, tumor cells were strongly positive for chromogranin, synaptophysin, and CD56, low mitotic activity and 15 % Ki-67 index. The specimen was pathologically diagnosed as pNETs with grade 2 (Table 1) [4, 5]. In addition, direct invasion of the esophagus was not found at EGD. Large mediastinal lymph nodes metastasis contacted the aorta, and also a possible invasion into the trachea. We thought that the patient required immediate treatment and chose the radiotherapy at first.

There are few reports of the radiotherapy for pNETs, and external beam radiotherapy may relieve bone pain from metastasis. Lee et al. published the efficacy of radiotherapy in combination with surgery [6]. There were few reports of radiotherapy to the lesion of orbit metastasis and ethmoid sinuses, showing good results [7, 8].

We are going to administer an appropriate chemotherapeutic agent sequentially. The ProMid study reported that octreotide long-acting release (LAR) has a substantial antitumor effect, with longer progression-free survival (PFS) compared with placebo in patients with well-differentiated neuroendocrine tumors and low tumor burden [9]. Caplin et al. also published about efficacy of somatostatin analogues. They reported that lanreotide was associated with significantly prolonged PFS among patients with metastatic enteropancreatic neuroendocrine tumors of grade 1 or 2 [10].

Table 1 2010 WHO grading system for pNETs

	Grade 1 (G1)	Grade 2 (G2)	Grade 3 (G3)
Ki-67 index (%)	<3	3–20	>20
Mitotic count	<2/10 HPF	2–20/10 HPF	>20/10 HPF
Differentiation	Well differentiated	Well differentiated	Poorly differentiated
5-year survival rate (%)	85	78	9

WHO World Health Organization, HPF high power field, pNETs pancreatic neuroendocrine tumors

The multitargeted tyrosine kinase inhibitor sunitinib has shown activity against pNETs. Raymond et al. reported that continuous daily administration of sunitinib improved PFS, overall survival (OS), and the objective response rate (ORR) as compared with placebo among patients with advanced pNETs. Meanwhile, the most common adverse events associated with sunitinib were diarrhea, nausea, asthenia, vomiting, fatigue, and the most common grade 3 or 4 adverse events in patients were neutropenia (12 %) and hypertension (10 %) [11]. So we thought it is difficult to administrate sunitinib for our case, because of her general condition.

Everolimus, an oral inhibitor of mammalian target of rapamycin (mTOR), has also shown antitumor activity in patients with advanced pNETs. As compared with placebo, everolimus prolonged PFS among patients with progressive advanced pNETs and was associated with a low rate of severe adverse events [12].

We hope the radiotherapy would control local advance and relief symptoms, then the extension of survival is obtained by chemotherapy subsequent to it.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Research involving Human Participants and/or Animals This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent For this type of manuscript, formal consent is not required.

References

1. Satahoo-Dawes S, Palmer J, Iii EW et al (2011) Breast and lung metastasis from pancreatic neuroendocrine carcinoma. *World J Radiol* 3:32–37
2. Ramage JK, Ahmed A, Ardill J et al (2012) Guidelines for the management of gastroenteropancreatic neuroendocrine (including carcinoid) tumours (NETs). *Gut* 61:6–32
3. Kos-Kudła B, Blicharz-Dorniak J, Handkiewicz-Junak D et al (2013) Diagnostic and therapeutic guidelines for gastro-enteropancreatic neuroendocrine neoplasms (recommended by the Polish Network of Neuroendocrine Tumours). *Endokrynol Pol* 64:418–443
4. McKenna LR, Edil BH (2014) Update on pancreatic neuroendocrine tumors. *Gland Surg* 3:258–275
5. Ellison TA, Wolfgang CL, Shi C et al (2014) A single institution's 26-year experience with nonfunctional pancreatic neuroendocrine tumors: a validation of current staging systems and a new prognostic nomogram. *Ann Surg* 259:204–212
6. Lee J, Choi J, Choi C et al (2013) Role of radiotherapy for pancreaticobiliary neuroendocrine tumors. *Radiat Oncol J* 31:125–130
7. Peixoto RD, Lim HJ, Cheung WY (2013) Neuroendocrine tumor metastatic to the orbit treated with radiotherapy. *World J Gastrointest Oncol* 5:177–180
8. Flavahan PW, Keir J, Srinivasan V (2012) Neuroendocrine carcinoma of the ethmoid sinuses treated with radiotherapy alone. *J Laryngol Otol* 126:1066–1068
9. Oberg K (2010) Cancer: antitumor effects of octreotide LAR, a somatostatin analog. *Nat Rev Endocrinol* 6:188–189
10. Caplin ME, Pavel M, Ćwikła JB et al (2014) Lanreotide in metastatic enteropancreatic neuroendocrine tumors. *N Engl J Med* 371:224–233
11. Raymond E, Dahan L, Raoul JL et al (2011) Sunitinib malate for the treatment of pancreatic neuroendocrine tumors. *N Engl J Med* 364:501–513
12. Yao JC, Shah MH, Ito T et al (2011) Everolimus for advanced pancreatic neuroendocrine tumors. *N Engl J Med* 364:514–523