Neuroendocrine tumor in the mandible: a case report with imaging and histopathologic findings

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Neuroendocrine tumors (NETs) arise from neuroendocrine cells and are mostly observed in the gastrointestinal tract, pancreas, and lungs. NETs in the oral and maxillofacial region are extremely rare. We report a case of a 59-year-old woman with an NET in the mandible. The patient did not show any symptoms except for remarkable swelling and bleeding. The lesion appeared as a radiolucent honeycomb abnormality with bone destruction on panoramic radiography. The histopathologic diagnosis following a biopsy was NET. Contrast-enhanced computed tomography (CT), ^{18}F-fluorodeoxyglucose positron emission computed tomography (^{18}F-FDG PET/CT), and adrenal scintigraphy-labeled meta-iodobenylguanidine were the modalities added to identify the primary site. Multiple lesions were confirmed in the gastrointestinal tract. Endoscopy was performed to identify the lesions, and several lesions were observed protruding from the mucous membranes. However, the endoscopy specimens did not yield an accurate diagnosis because adequate samples were not acquired. Blood and urine tests revealed no functional activity caused by the tumors. Although the origin was not histopathologically confirmed with endoscopy, this patient was situationally diagnosed with nonfunctional NET originating from the duodenum, as demonstrated by the metastases in the mandible. (Oral Surg Oral Med Oral Pathol Oral Radiol 2015;119:e41-e48)

Neuroendocrine tumors (NETs) originate from hormone-producing cells. Neuroendocrine cells are found throughout the body in such organs as the gastrointestinal tract, pancreas, and lungs. Well-differentiated NET was previously described as "carcinoid" until this labeling was clarified by the World Health Organization (WHO) classification. In 2010, the WHO indicated a new classification of NETs based on both the mitotic count and Ki67 index and introduced a grading system (Grade 1 to Grade 3). The European Neuroendocrine Tumor Society (ENETS) also proposed a grading system (G1, G2, and G3).[1-3] According to their proliferative activity, G1 and G2 neuroendocrine tumors are well differentiated, and G3 tumors are poorly differentiated and are called carcinomas (NECs). The diagnosis of a NET is based on the histopathology of tumor specimens, circulating biomarkers, and imaging.[2]

Most NETs are located in the gastrointestinal tract and the pancreas. The incidence has been estimated to range from 1 to 2 per 100,000 people in Western countries.[4,5] In Japan, the latest report on the status of gastroenteropancreatic NETs (GEP-NETs) in 2005 estimated their prevalence to be 3.45 in 100,000 persons, with an annual onset incidence of 2.10 in

Statement of Clinical Relevance

Neuroendocrine tumors (NETs) are extremely rare and arise from the secretory cells of diffuse neuroendocrine cells. These tumors are particularly rare in the oral and maxillofacial region, and only a few cases have been reported. NETs are classified as malignant tumors because of their metastatic character. However, the malignant features are difficult to diagnose from the imaging findings in well-differentiated NETs because the tumors grow very slowly and the patients lack severe clinical symptoms. In this article, we report a case of NET (Grade 2 in the World Health Organization 2010 classification) in the mandible.

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Received for publication Mar 28, 2014; returned for revision Jul 22, 2014; accepted for publication Sep 21, 2014.

2212-4403/$ - see front matter
http://dx.doi.org/10.1016/j.oooo.2014.09.024

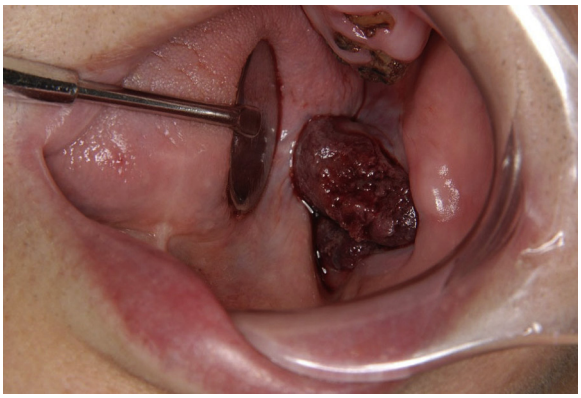

Fig. 1. Intraoral photography revealing an easily bleeding mass in the left buccal mucosa.

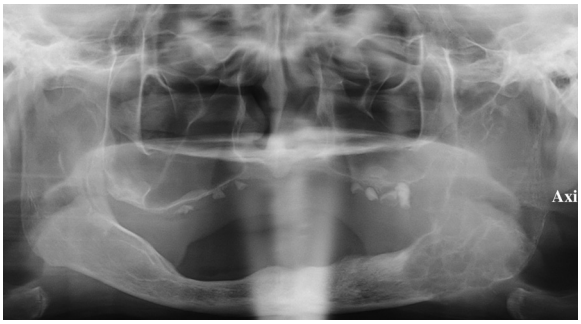

Fig. 2. Panoramic radiograph showing a large, ill-defined, soap bubble−like radiolucency of the left mandible extending from the retromolar area to the ramus.

100,000.[6] The increase in the incidence of GEP-NETs during the last 30 years can be attributed to the increase in the detection rate due to advances in endoscopic and imaging methods.[7-9]

This report describes an NET in the mandible and includes imaging and pathologic findings, symptoms, and the process leading up to diagnosis. In this case, despite having extensive bone swelling and resorption, the patient did not have numb chin syndrome or trismus. Hence, this lesion was difficult to diagnose as a malignancy. NETs in the head and neck region, particularly the well-differentiated types, are often underdiagnosed.[10]

CASE REPORT

A 58-year-old woman visited a dental practitioner for a new denture and was taken for a dental impression. After 10 days, she visited the dentist again because a bleeding mass had appeared in the left buccal mucosa. She was referred to a hospital for further examination.

Her left cheek was swollen, and a 20 × 15 × 15 mm reddish brown bleeding mass (Figure 1) was observed on the left buccal mucosa. Trismus, paresthesia, and spontaneous pain were absent, and her lymph nodes were not palpable. She had a history of hypertension and hyperthyroidism. Her father had died at 83 years of age from pancreatic cancer, and her sister had died of colorectal cancer.

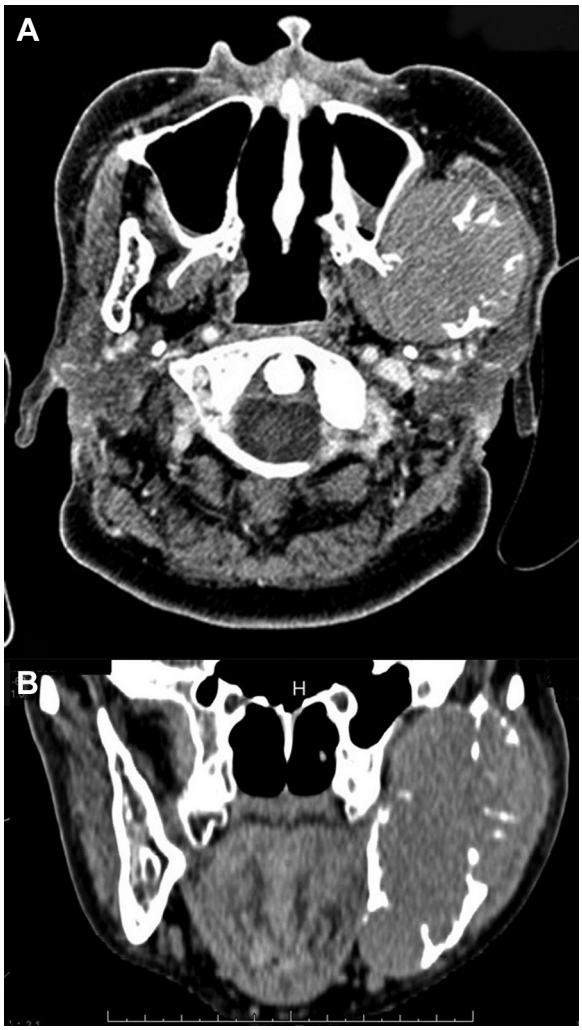

Fig. 3. Contrast-enhanced CT showing a very large osteolytic lesion in the left ramus. **A**, axial image. **B**, coronal image.

Panoramic radiography revealed an ill-circumscribed, multilocular, radiolucent area in a honeycomb pattern around the left ramus of the mandible, which was bulging and displaying a thin cortical bone (Figure 2). Contrast-enhanced CT demonstrated a weakly enhanced lesion, which had a relatively clear boundary, around the left ramus. Moreover, the lesion was accompanied by sporadic bone destruction enlarged in the lingual and buccal directions, along with compressive bone resorption at the posterior part of the maxilla (Figure 3).

The patient had undergone magnetic resonance imaging (MRI) for torticollis 3 years ago, and a mass had been confirmed in the left mandibular ramus at that time. The lesion was observed as a round, homogeneous, well-demarcated mass on the T1-weighted image. Furthermore, the lesion showed iso-signal intensity to the parotid gland on a T2-weighted image (Figure 4, A and B).

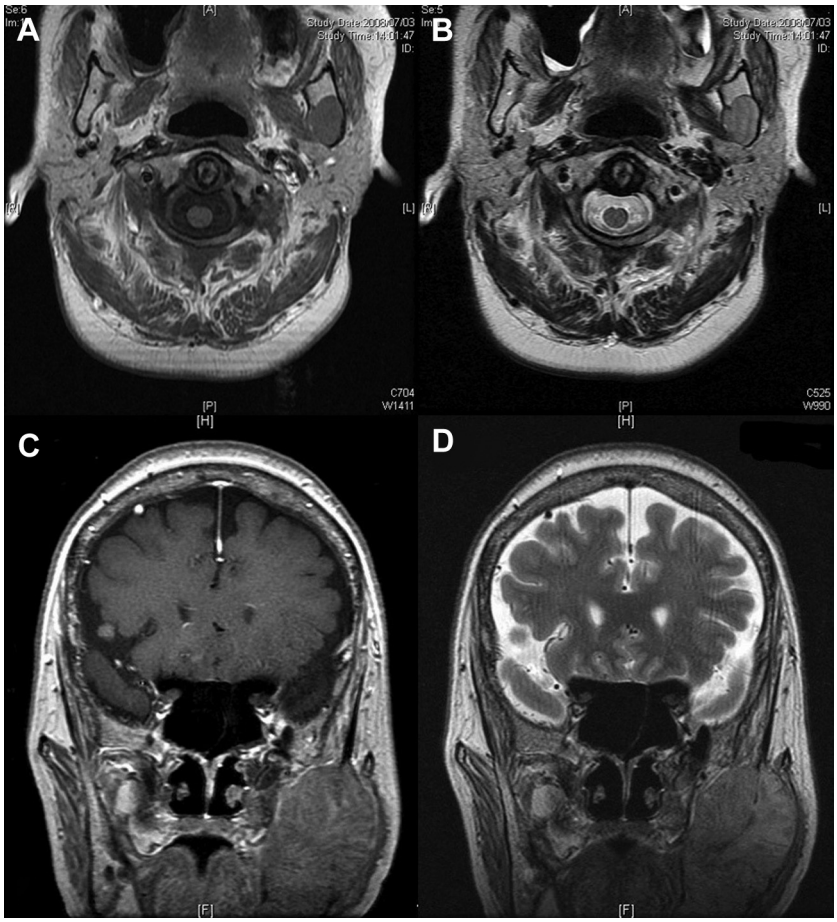

Fig. 4. Magnetic resonance imaging scans, taken 3 years before (**A** and **B**) and during this consultation (**C** and **D**). **B**, T1-weighted image by fast spin echo method. **B**, T2-weighted image by fast recovery fast spin echo method. **C**, Gadolinium-enhanced T1-weighted image by spin echo method. **D**, T2-weightened image by fast spin echo method.

In this consultation, MRI was used to determine if the patient's hyperthyroidism was the result of a malfunctioning pituitary gland (see Figure 4, C and D). Although the mandibular lesion was not imaged, its total volume had remarkably increased compared with the volume of the lesion observed on MRI 3 years ago. The lesion was comparatively homogeneous and had a comparatively well-demarcated margin with a capsule, despite the remarkable bulging. These findings were similar to those found on CT (Figure 3).

On the basis of the clinical features and these imaging findings, the lesion likely originated from the intraosseous component of the mandible and was a benign or mildly malignant tumor, such as a hemangioma (arteriovenous malformation), odontogenic myxoma, keratocystic odontogenic tumor, or ameloblastoma.

A biopsy of the mandible was performed. Diffuse growth of tumor cells with nesting or necrosis was found. The cytoplasm of large tumor cells was clear or granular, and abnormal nuclei and mitoses were detected. The fibrosis and proliferation of the capillary vessels were clearly evident in the stroma. In addition, the immunohistochemical staining was positive for synaptophysin, chromogranin A, CAM5.2, S100, Ki-67 (10%), and vimentin, but not for CD 34, factor VIII, or αSMA (Figure 5, A-E; and Table I). On the basis of these results, the intraoral lesion was diagnosed as Grade 2 NET based on the 2010 WHO classification (Table II). In addition, an immunohistologic study of somatostatin receptors (SSTR) was added to determine the treatment plan, and the specimen was positive for SSTR type 2 A (see Table I).

After establishing the diagnosis, an extensive search for the primary site was conducted. Using positron emission tomography (PET)-CT with 2-[fluorine 18] fluoro-2-deoxy-D-glucose (^{18}F-FDG), the accumulation of FDG in the lesion was observed. The standardized uptake value ranged from 2.3 to 5.2. The maximum standardized uptake value of 5.2 was observed in the posterior wall of the maxillary sinus (Figure 6). Some nodular lesions were observed near the left posterior diaphragm and the posterior vestibular part of the stomach but did not show ^{18}F-FDG accumulation. Subsequently, abdominal contrast-enhanced CT and gastrointestinal endoscopy were performed. On the endoscopy, intramural multiple masses were observed in the gastrointestinal tract. The overlying gastrointestinal mucosa was intact at some sites, and some masses showed focal ulceration. However, an adequate tissue sample for pathologic evaluation was not obtained from the endoscopy.

Considering the possibility of a paraganglion tumor, labeled meta-iodobenzylguanidine (MIBG) scintigraphy was

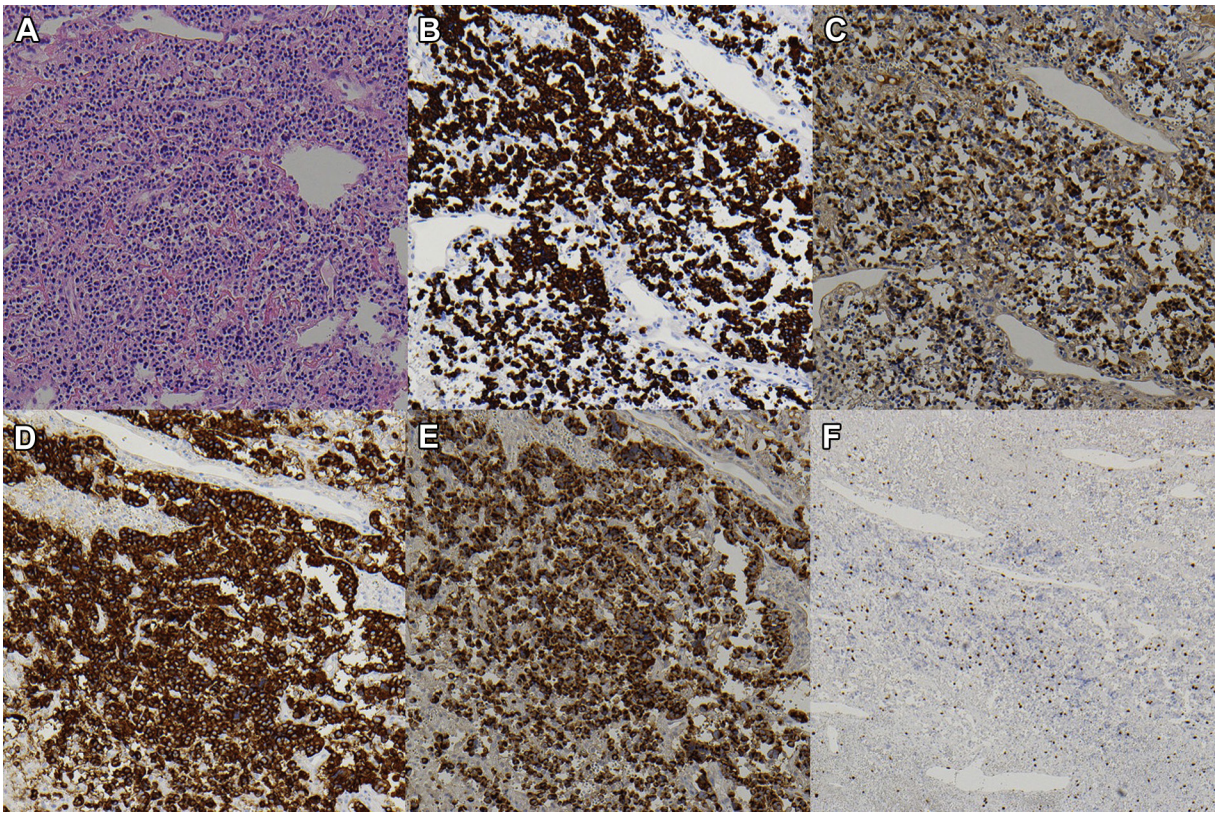

Fig. 5. Histopathologic findings. **A**, Hematoxylin and eosin stain (magnification ×100). **B**, Cytokeratin (CAM2.5) (magnification ×100). **C**, S100 (magnification ×100). **D**, Synaptophysin (magnification ×100). **E**, Chromogranin A (magnification ×100). **F**, Ki67 (magnification ×40).

subsequently performed. On MIBG scintigraphy, the uptake was observed at the adrenal medulla (Figure 7). However, investigations for amine secretions, including urinary normetanephrine and metanephrine, which are the metabolites of normetanephrine and epinephrine, and 5-hydroxy indol acetic acid, were within normal ranges. Therefore, pheochromocytoma, paraganglioma, and carcinoid tumors were excluded. The blood hormone levels were normal; thus, a nonfunctional neuroendocrine tumor of the gastrointestinal tract was unlikely. Urine and hematologic assessment showed normal functional activity. No signs of paraneoplastic syndrome, such as hormone production, were observed.

Table I. Results of immunostaining

Immunostaining	*Result*
Synaptophisin	Positive
Chromogranin A	Positive
S100	Positive
CAM 5.2	Positive
EMA	Weak positive
Vimentin	Positive
Ki67	10% positive
CD34	Negative
Factor VIII	Negative
α SMA	Negative
Somatostatin receptor 2A	Positive
Somatostatin receptor 5	Negative

The first-choice treatment for NET is resection. However, in this case, the oral tumor was too large to be removed. Attempted surgery would have reduced important functions, such as deglutition, speech, and eating, and affected the patient's quality of life. Instead, hormonal therapy was selected. The intraoral specimen was positive for SSTR. Hence, a somatostatin analog was administered during hospitalization around one month. A subcutaneous injection of 100 μg sandostatin was given twice daily. After the patient was discharged from the hospital, the injection was changed to the intramuscular long-acting Sandostatin LAR at 30 mg once a month. The patient continues to receive this therapy.

At present, the tumor has not reduced in size and no abnormalities in the hormone levels have been observed.

DISCUSSION

Definition

NETs are extremely rare tumors arising from the neuroendocrine cells. All NETs are potentially malignant but differ in their biologic characteristics and the probability of metastatic disease.[11] Neuroendocrine tumor cells secrete a variety of (poly-) peptide hormones, neuropeptides, and neurotransmitters. Functional tumors cause typical hypersecretion-related symptoms, which are directly related to the hormones secreted by

Table II. Grading System for GEP−Neuroendocrine Tumors (ENETS, WHO)

	Grade	*Proliferation degree*
Low	Grade 1 (G1)	<2 mitoses/10 hpf and <3 % Ki67 index
Intermediate	Grade 2 (G2)	2-20 mitoses/10 hpf or <3-20 % Ki67 index
High	Grade 3 (G3) small cell carcinma	>20 mitoses/10 hpf or >20 % Ki67 index
	Grade 3 (G3) largel cell neuroendocrine carcinma	

GEP, gastroenteropancreatic; *ENETS*, European Neuroendocrine Tumor Society; *WHO*, World Health Organization; *hpf*, high-power fields.
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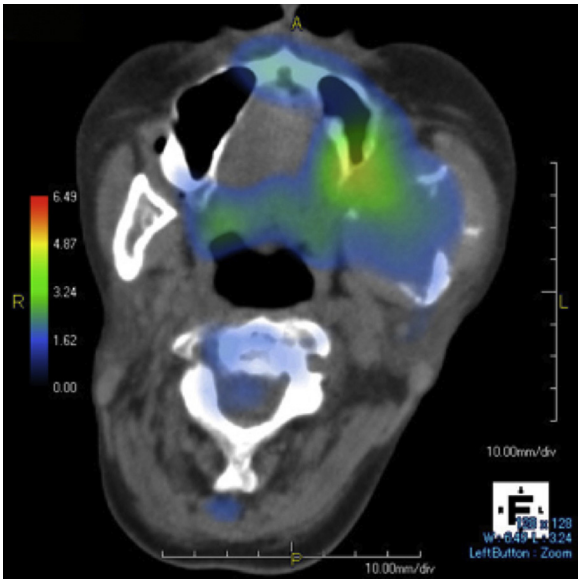

Fig. 6. The ^{18}F-fluorodeoxyglucose positron emission computed tomography shows the standardized uptake value maximum at 5.2 around the posterior wall of the maxilla.

the tumor, such as gastrinoma, insulinoma, glucagonoma in the pancreas, or carcinoid syndrome in patients with NETs of the ileum. Nonfunctional tumors do not secrete a hormone that results in a clinical syndrome. On the other hand, as nonfunctional tumors do not secrete a hoemone, they are usually asymptomatic. Thus, diagnosis of nonfunctional NETs tend to be difficult when they are small.

Classification

In 2010, the WHO defined low- to high-grade neuroendocrine cancer types under the broad category of neuroendocrine neoplasms. The proposed WHO 2010 grading system places them into three classes based on both mitotic count and Ki67 index.[1,2] The ENETS issued a GEP-NETs Ki67 labeling index.[12] Table II shows the grading systems of GEP-NETs based on the ENETS and WHO guidelines. Grade 1 shows a low proliferative index (Ki67 <3% or <2 mitoses per 10 high-power field), Grade 2 shows a moderate proliferative index (Ki67 3%-20% or 2-20 mitoses per 10 high-power fields [hpf]), and Grade 3 shows a high proliferative index (ki67 >20% or >20 mitoses per 10 hpf). The Ki-67 protein is a cellular marker of proliferation[13]; it is strongly associated with cell proliferation. Ki-67 protein is present during all active phases, such as the G1, S, G2, and M phases of the cell cycle, but is absent in resting cells (G0 phase).[13] In addition, Ki67 protein and the degree of the malignancy of the tumor are closely related; thus, Ki67 is a useful marker to detect proliferation in the tumor. The proliferative rate can also be assessed on the basis of the number of mitoses per unit area of tumor (mitoses per 10 hpf or per 2 mm^2). Ki67 is the biologic marker of cell proliferation, and the mitotic count represents morphologic changes in the nucleus. Ki67 is somewhat easier to evaluate than the mitotic count and more useful when the volume of tissue is limited.

Etiology

The incidence of NETs has been estimated to range from 1 to 2 per 100,000 people in Western countries.[4,5] In Japan, the latest report on the status of GEP-NETs in 2005 estimated the prevalence at 3.45 per 100,000, with an annual onset incidence of 2.10 per 100,000.[6] With regard to prognosis, Panzuto et al. reported that the overall 5-year survival rate of patients with NETs was 77.5%, and the major negative prognostic factors are pancreatic site, a poor degree of tumor cell differentiation, and distant extrahepatic metastases.[14] Furthermore, Pape et al. reported that the overall 2-year, 5-year, and 10-year survival rates were 87%, 75%, and 64%, respectively.[4]

According to Ito et al., the age of onset of gastrointestinal NETs is 50 to 70 years in 70.9% of patients, and mean age of onset was 59.8 years (males, 61.3; females, 57.3). Of the patients in the study, 64% were male and 32.3% were female, and 3.6% did not have information on the gender.[6] In a survival analysis of NETs classified according to the WHO grading system, the survival period was significantly poorer for patients who had G3 tumors than for those who had G1 and G2 tumors.[4]

Imaging diagnosis

The role of imaging with regard to functional NETs is mainly to detect the number of tumors and their locations

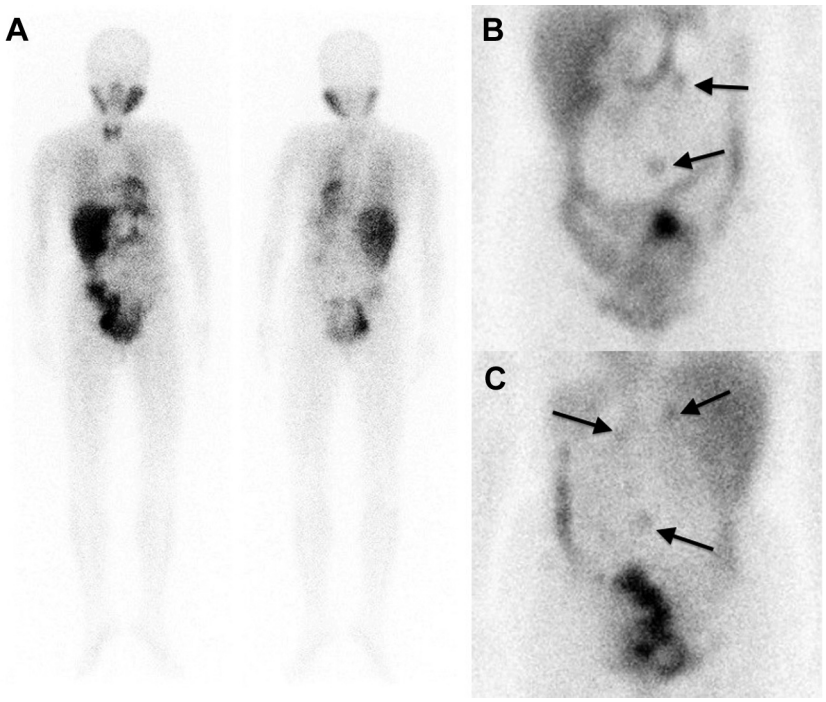

Fig. 7. Adrenal scintigraphy labeled meta-iodobenylguanidine. **A**, Full body image (*left: frontal view; right: posterior view*). **B**, Enlargement of abdominal area (*frontal view*). **C**, Enlargement of abdominal area (*posterior view*). Other than the liver and gastrointestinal physiologic uptake, multiple uptakes were observed at the abdominal nodules, which were also observed in the computed tomography examination. Although uptake at the left parotid area was observed, it was unclear whether this uptake was caused by the tumor itself or was due to a physiologic change in the parotid caused by the tumor.

because clinical symptoms are already apparent due to the hormones secreted by the tumor. In contrast, with nonfunctional NETs, which manifest late as large masses that cause compression syndromes or incidental findings, imaging is not primarily aimed at tumor detection.[15] Nonfunctional tumors frequently present late with mass effects, as they lack accompanying clinical syndromes. Once functional or nonfunctional NETs are suspected or diagnosed, a systemic whole body examination using PET/CT and scintigraphy is needed to identify a primary tumor or a metastatic tumor.

In the present case, we initially did not consider the lesion to be malignant. On radiographic examination, remarkable bone destruction and swelling of the left side of the mandible were observed. On CT, the border of the tumor was relatively clear, and compressive bone resorption in the posterior bone wall of the left maxilla was observed, rather than invasive destruction, which is a sign of malignancy. Furthermore, the patient did not have clinical manifestations, such as mandibular nerve paralysis, trismus, and pain, despite the extensive bone destruction. According to these imaging and clinical findings, we diagnosed the lesion as a benign tumor that originated from the mandible, such as an arteriovenous malformation, odontogenic myxoma, keratocystic odontogenic tumor, or ameloblastoma. Because the lesion was clarified as an NET on biopsy, whole-body scanning was performed. We finally detected the primary site using [^{18} F] FDG-PET-CT. Some nodular lesions in the gastrointestinal tract were confirmed on CT, although the mass did not show [^{18}F] FDG uptake. However, a previous report indicated that PET with ^{18}F-FDG is not useful for NETs, except for highly aggressive tumors.[16,17] Castano et al. stated that the vast majority of NETs with low Ki67 expression are, indeed, [^{18}F] FDG PET negative.[18] In the present case, PET-CT was useful in detecting the primary sites and staging the NETs. Various nodular lesions were found in the duodenum on PET/CT; thus, endoscopy was added. PET-CT can reveal both anatomic and metabolic information, irrespective of FDG uptake. Therefore, we suggest the use of PET/CT as a sensitive first-line imaging modality to detect the primary sites when a neuroendocrine tumor is suspected. Even though FDG was used for PET/CT at our institution, a new tracer for the diagnosis of NETs deserves attention. New PET tracers, such as ^{68}Ga-DOTATOC, ^{68}Ga-DOTATATE, and ^{68}Ga-DOTANOC, which utilize somatostatin receptors as the target, have been developed.[19]

Somatostatin receptor scintigraphy is a standard method to image NETs in some countries but not in Japan. This imaging method uses In-111 pentereotide, which is a homolog of somatostatin and can detect somatostatin receptors SSTR2 and SSTR5) developing

in tumor secretions. It is the only imaging method that can specifically depict NETs, and its introduction is expected soon in Japan.

Histopathologic diagnosis

An immunohistopathologic analysis is required to confirm the diagnosis of NETs. The current guidelines recommend immunolabeling for general neuroendocrine markers for the diagnosis,[20,21] such as synaptophysin and chromogranin A, which are the most sensitive and specific general immunolabeling makers for neuroendocrine tumors.[22,23] Chromogranin A is the major member of a family of acidic glycoproteins that are secreted from almost all endocrine and neuroendocrine cells of mammalian tissue, including the adrenal gland, endocrine pancreas, gastrointestinal endocrine system, thyroid gland, parathyroid gland, and pituitary gland.[24,25] Synaptophysin has been identified as a component of the membrane in presynaptic vesicles and a sensitive marker for neuroendocrine tumors.[26] Chromogranin A is the most widely used marker of neuroendocrine differentiation,[21] and synaptophysin is a sensitive but nonspecific marker expressed by adenomas and carcinomas of the adrenal cortex and normal cells.[23] Recently, the plasma levels of chromogranin A were reported to be the most consistent general marker of NETs, showing high sensitivity and specificity and reflecting the clinical evolution of the disease.[27]

Treatment

At present, the early detection and surgical resection of the tumor represents the best chance for a cure.[28] However, the majority of patients with sporadic GEP-NETs present with locally advanced, unresectable disease, frequently with distant metastases, and currently, there is no curative therapy.[28] Other available treatments include chemotherapy, interferon, somatostatin analogues, and targeted therapies.[29-33]

For treatment with somatostatin analogs, the distinction of the somatostatin receptor (SSTR5 or SSTR2) is very important. Somatostatin, which is a peptide hormone produced by the hypothalamus, inhibits the release of growth hormones and other secretory proteins.[34] Somatostatin analogs are the best therapeutic option for functional NETs because they reduce hormone-related symptoms and also have antitumor effects.[35] Somatostatin analogs are considered optional for treating nonfunctional tumors. They were found to have disease-stabilizing effects,[36] but data from a placebo-controlled trial in pNET are still pending (CLARINET study [Controlled study of Lanreotide Antiproliferative Response In NeuroEndocrine Tumors]). In the present case, the lesion that metastasized to the mandible was very large and could not be removed. Thus, somatostatin analog therapy was selected, even though the tumor was not a nonfunctional tumor.

The oral cavity is a rare site for a primary neuroendocrine tumor,[10] and only a few cases reported in the English language literature include metastatic cases.[37-40] The most common sites of NETs in the head and neck region are the larynx, followed by the salivary glands.[41] Reports of NETs in the mandible are few; in these cases, NETs were found in the retromolar region and the mandible.[37,39,40] The sites of the lesions are the most likely areas of metastases. Hence, without whole-body imaging, the origin of these lesions (i.e., primary or metastatic) was ambiguous. A NET of the mandible was reported by Colman et al.; however, it did not have the histologic or immunohistochemical characteristics of a paraganglioma, and the cell of origin was unknown.[37] The authors presumed that the tumor must have originated from immature, functionally uncommitted endocrine cells that were derived from the most proximal part of the foregut.[37] This case was very similar to our present case, and we doubt that it was a metastatic case. If a systemic search had been carried out, the origin of the NET might have been proven.

The current report describes a neuroendocrine tumor in the mandible. The tumor had grown to a very large size and caused destruction to the mandible, but the bone destruction was rather benign. Furthermore, the patient did not report symptoms, such as pain or paresthesia. The diagnosis of a neuroendocrine tumor is very difficult malignant bone destruction and clinical signs cannot be detected, and most dentists are not familiar with NETs.

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