CASE REPORT

Detection of Neuroendocrine Tumour of Sphenoid Sinus on the Gallium-68 DOTATATE PET/CT: A Rare Entity

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ABSTRACT

Neuroendocrine tumours (NETs) are a category of neoplasm that is characterised by its phenotypic and heterogeneity. The occurrence of this type of neoplasm in the nasal cavity and paranasal sinuses is extremely rare accounting for only 0.2-0.8% of all cancers. NET tends to expresses somatostatin receptors (SSTR) and owning to this unique characteristic, molecular imaging has been able to detect these tumours using radiolabelled somatostatin analogue agent. Gallium-68 (Ga-68) DOTATATE PET/CT is an example of SSTR imaging and has been shown to be of importance in the assessment and staging of NET. We present a case of a rare sphenoid sinus NET in a 45-year-old gentleman whom initially presented with persistent left eye pain which led to visual loss. We described the utilization of Ga-68 DOTATATE PET/CT in the diagnosis and staging of this patient which in turn dictated treatment approach.

Keywords: Neuroendocrine tumours, Gallium-68 DOTATATE, Positron Emission Tomography Computed Tomography, Sphenoid sinus

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INTRODUCTION

Neuroendocrine tumours (NETs) are distinctive neoplasms known for their phenotypic and molecular heterogeneity. NETs can be functional and non-functional, based on their ability to produce certain hormones and these tumours can be classified as either low grade or high grade, based on several histopathological characteristics such as Ki-67 and mitotic index. Sinonasal malignancy is a rare form of malignancy which account for 0.2-0.8% of all cancers and involvement of sphenoid accounts for about 1 to 2% of all paranasal sinus tumours, majority of the cases being squamous cell carcinoma and adenocarcinoma (1). Sinonasal NET is even rarer with only a handful in the literatures describing this tumour type. The rarity, diversity and intricacy of this tumour makes the diagnosis workup and subsequent management even more challenging as there is no clear guideline or consensus available for reference. However, NETs do possess some unique characteristic whereby these tumours tend to show over expression of somatostatin receptors (SSTR) on its surface hence allowing this SSTR to be targeted for both diagnostic and therapeutic purposes (2). Gallium-68 (Ga-68) DOTA-peptide is a form of radiolabelled molecular imaging that targets SSTR and this has improved lesion detectability and enhanced staging via positron emission tomography (PET) coupled with computed tomography (CT) (2). It has also been shown to have significant impact on the management of patients with somatostatin-avid malignancies (2).

CASE REPORT

A 45-year-old male presented with a 6-month history of bilateral nasal congestion and persistent left eye pain which led to visual loss. On physical examination, the patient had positive relative afferent pupillary defect (RAPD) of left eye with impaired function of the cranial nerve I, II and VI without evidence of other neurological deficits.

A contrast enhanced computed tomography (CECT) neck showed locally invasive soft tissue lesion arising from sphenoid sinus with resultant direct infiltration into the ipsilateral orbital fossa. Anteriorly, the mass extends to the paranasal sinuses and encroaches into the bilateral maxillary sinuses and anterior portion of the

optic nerves. Superiorly, it erodes the sella turcica and extends into the cavernous sinus, suprasellar cistern and appears to compress on the medial part of the temporal lobe bilaterally. Magnetic resonance imaging (MRI) of the brain revealed further mass infiltration into the pituitary gland and cavernous sinus.

Hence, biopsy of the tumour was done and histopathological examination (HPE) noted findings of NET with low proliferation index of 7/10hpf and Ki-67 index of 5-10% (Fig. 1). Furthermore, immunohistochemical staining showed expression of CKAE1/AE3, synaptophysin and chromogranin (Fig. 2).

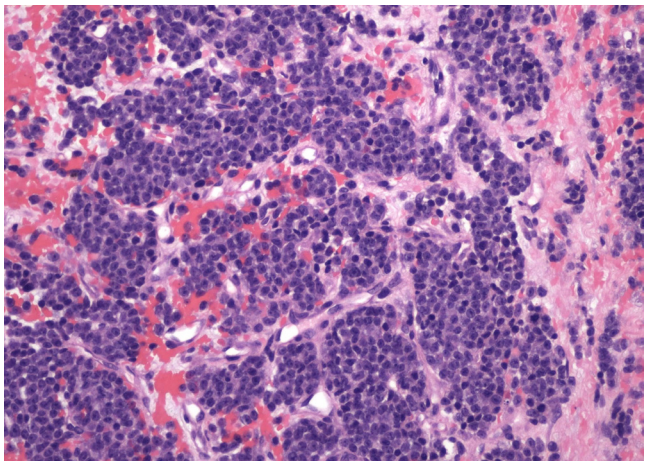

Figure 1: Microsopic examination (Haemotoxylin and Eosin, x 200). Nest and clusters of medium size round cells with moderate amount of eosinophilic cytoplasm forming rosette.

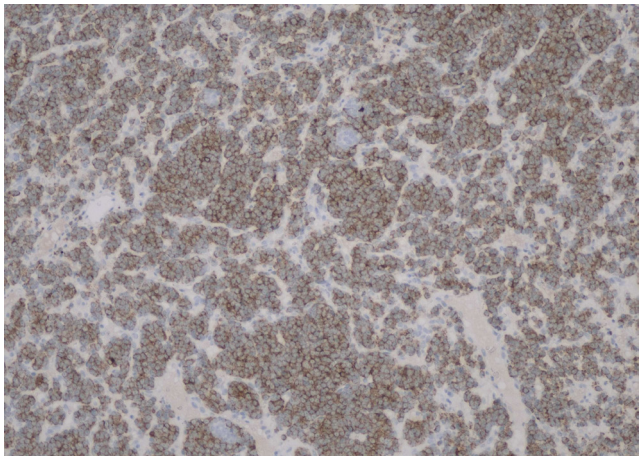

Figure 2: Immunohistochemical stains (x100). Neuroendocrine cells showing synaptophysin positivity.

In light of the histopathological findings of NET, a Ga-68 DOTA-peptide PET/CT was ordered to further stage this patient and to rule out distant metastasis. Ga-68 DOTATATE PET/CT confirmed evidence of SSTR-avid mass in the sphenoid sinus region (Fig. 3).

Due to the nature and local extent of the disease, surgery with radiation therapy preceded by chemotherapy was initially considered. Patient ultimately received initial 6-cycles of neo-adjuvant chemotherapy. Unfortunately,

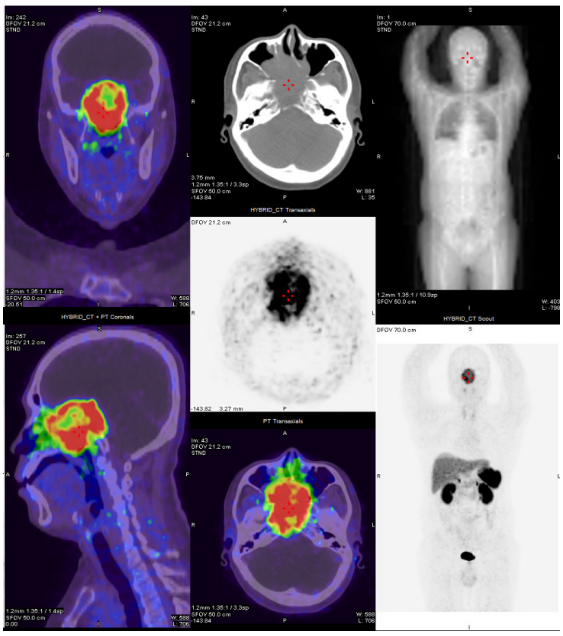

Figure 3: Gallium-68 DOTATATE PET/CT showed somatostatin receptor avid disease in the sphenoid region. Hetergenous Ga-68 DOTATATE uptake is seen at the large heterogenous soft tissue mass at the skull base likely arising from the sphenoid sinus region (highest SUVmax 17.0) with higher intensity of uptake seen at the peripheries and associated ametobolic area seen mainly centrally corresponding to hypodense necrotic areas. This mass measures approximately 6.9x5.3x5.6cm on CT. Anteriorly the mass extends to the paranasal sinuses and encroaches into the bilateral maxillary sinuses and anterior part of the nasopharynx as well as the bilateral optic canal and appears to compress the intra-cannalicular portion of the optic nerves. It also involves the pterygoid plate, sphenoid, ethmoid, petrous-temporal bone medially and anterior part of clivus. Superiorly it erodes the sella turcica and extends into the cavernous sinuses, suprasellar cistern and appears to compress on the medial part of the temporal lobes bilaterally.

during the last cycle of chemotherapy, patient developed perforated peptic ulcer which required surgical intervention. However, patient eventually succumbed to the post-operative complications.

DISCUSSION

SSTR are expressed by NETs on their cell membrane. SSTR density and expression is closely related to Ki-67 proliferation index whereby SSTR density decreases as the Ki-67 index increases. The Ki-67 proliferation index and degree of differentiation as well as mitotic index (mitoses in 10 high-power-field) are used by the World Health Organization (WHO) to classify NETs to either well-differentiated NETs G1 (Ki-67 <3%, mitoses/10HPF <2), G2 (Ki-67 3-20%, mitoses/10HPF <2-20), G3 (Ki-67 >20%, mitoses/10HPF >20) or poorly-differentiated neuroendocrine carcinomas (NECs) (Ki-67 >20%, mitoses/10HPF >20) (3). Differentiation of tumour type specifically in the sinonasal region is paramount in ensuring effective treatment. Sinonasal NETs has to be differentiated from other malignancies of the sinus such as squamous cell carcinoma, lymphoma or

melanoma. Traditionally, microscopic examination and cell characteristics such as pseudoglands and rosette formation have form the basis of diagnosis however more often than not, this may be insufficient thus immunohistochemistry studies are invariably needed for accurate diagnosis. For NETs, typical differentiating markers are chromogranin, synaptophysin, and neuron-specific enolase (4). As seen in this patient, microscopic examination noted rosette formations of nest and clusters of round cells with eosinophilic cytoplasm and further immunohistochemistry study revealed strong positivity of synaptophysin and chromogranin hence confirming the diagnosis of NET. Determination of tumour type, characteristic and grading are not just essential but also helps to prognosticate patients which would directly influence subsequent management plan.

The mechanism of radionuclide imaging such as Ga-68 DOTA-peptide PET/CT relies on the binding of the radiolabelled peptide to the SSTR with low grade tumour (G1-2) showing higher affinity for Ga-68 DOTA-peptide as compared to higher grade of NETs (G3) or NECs. This is in contrast to frequently used oncological PET/CT imaging with fluorodeoxyglucose (FDG) which utilizes metabolic activity and glucose metabolism differentiation between benign and malignant tissues. NETs often show slow metabolic activity during its initial stages hence they are not extremely avid with Fluorine-18 (F-18) FDG PET/CT. However, the uptake trend can change in the late state as the tumour characteristics change from well-differentiated to poorly-differentiated. In this scenario, tumour and metastatic sites display low uptake of Ga-68 DOTA-peptide due to lower SSTR-2 expression but strong uptake of F-18 FDG PET/CT (2). Ga-68 DOTATATE PET/CT was performed in this patient as the biopsy of the primary sinonasal tumour yielded NET with low mitotic index and Ki-67 proliferative index of 5-10% thus categorizing it as G2.

Interestingly, a study by Fanti el al., which dwelled on the usefulness of Ga-68 DOTA-peptide PET/CT in rare subtype of NETs such as NET of the uterus, prostate as well as ears demonstrated that Ga-68 DOTA-peptide PET/CT provided useful clinical information in 50% of cases and became significant determinant in subsequent treatment strategies in 57% of cases (10). However, most of these studies focus on GEP-NET and to the best of our knowledge, no published literature available on comparison of various imaging modality specifically in sinonasal NET, likely due to its rarity. Nevertheless, the findings by Fanti et al. on usefulness of Ga-68 DOTA-peptide PET/CT for rare NET subtypes have provided the platform and form the basis for utilization of Ga-68 DOTATATE PET/CT in addition to conventional imaging modalities in sinonasal NET particularly in this patient.
The emphasis of complete staging of this type of tumour is crucial considering the limited and lack of accomplished treatment strategies. Treatment options which include surgery, chemotherapy, radiotherapy or combination of these treatment modalities depend on the size and extent of involvement as well as presence or absence of distant metastasis. Surgery is usually reserved for cases where complete tumour resection can be safely achieved whereas chemotherapy is often prescribed in metastatic setting. SSTR imaging such as Ga-68 DOTATATE PET/CT allows for complete staging and assessment of tumour burden. Low grade NET often metastasize without inciting obvious anatomical changes hence presence of distant metastasis could have been missed by conventional CT. Ga-68 DOTA-peptide PET/CT has been shown to alter treatment strategy by either expanding surgical field to include detected SSTR-avid nodes or spared from surgery as PET/CT demonstrated more extensive disease than did the conventional imaging (10). In this patient, presence of distant metastasis was excluded with high degree of confidence as the Ga-68 DOTATATE PET/CT showed no SSTR-avid lesion elsewhere hence curative surgery was considered.

CONCLUSION

Gallium-68 DOTATATE PET/CT is a very useful non-invasive imaging tool for detection and staging of NETs and other somatostatin-avid malignancies. It provides an incremental diagnostic information as well as tumour grade analysis in addition providing valuable information in terms of assessing tumour burden in dictating subsequent treatment strategies.

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