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Poorly differentiated Neuroendocrine carcinoma (small cell) of Parotid Gland and 'Moderately differentiated' Hepatic metastases: a Discordant Histopathology clarified by dual tracer PET-CT (^{68}Ga-DOTATATE and ^{18}F-FDG) for predicting tumor biology and treatment decision-making

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ABSTRACT

Metastatic neuroendocrine neoplasms (NEN) of parotid gland, with discordant histopathology reports between primary parotid tumor (poorly differentiated small cell neuroendocrine carcinoma) and large hepatic metastasis (atypical carcinoid with moderately differentiation status, Ki-67 15-20%), and the value of dual tracer PET-CT imaging (^{68}Ga-DOTATATE and ^{18}F-FDG) features in such clinical setting are illustrated. Minimal ^{68}Ga-DOTATATE and high grade ^{18}FDG uptake of the lesions indicated a poor differentiation status helped in clarifying tumor biology, with its potential implications for subsequent treatment-decision individualization in favor of chemotherapy. The findings underscore the clinical utility of dual tracer PET-CT in appropriating the assessment in patients/situations with conflicting or discordant histopathology at two sites in an individual.

INTRODUCTION

Small cell neuroendocrine carcinoma (SCNEC) of the salivary glands account for about 2% of all salivary glands malignancies, and is the commonest form of salivary gland NENs, most commonly arising in parotid glands. Histologically, they are very similar to small cell carcinoma of the lung and are composed of sheets, ribbons. Well-differentiated NENs of salivary glands are exceedingly rare, with only seven cases reported till date, that include two reports of typical carcinoid and five atypical carcinoid *[1]*, all occurring in parotid glands.

Akin to what is observed in GEP-NENs, identifying predictors of tumor biology is of substantial importance in salivary gland NENs to predict clinical behavior of the tumor and guide appropriate treatment strategies. Grade determination often relies on previously resected primary tumor, or biopsy of a single metastatic lesion that may not be consistent with primary, reflecting tumor heterogeneity and biology *[2, 3]*. In a typical case scenario, the lower grade NENs should show high SSTR expression (imaged on ^{68}Ga-DOTATATE PET/CT) more than glucose transporter expression and metabolism (on ^{18}F-FDG PET/CT) and vice versa with poorly differentiated neoplasms *[2, 3]*.

CASE REPORT

A 39 years old female, apparently diagnosed with malignant round cell neoplasm of right parotid gland on biopsy, had undergone right radical parotidectomy two years previously, final histopathology suggestive of poorly differentiated NEN (small cell variant) with positive inked margins. Post-operatively she received adjuvant radiotherapy and four cycles of systemic chemotherapy (carboplatin-etoposide regimen). At 2 years follow-up, there was an isoechoic SOL (7.4 x 6.1 cm) in right lobe of liver on USG (abdomen), confirmed by triple phase ceCT with additional mention of large portocaval lymphadenopathy. Liver biopsy was indicative of moderately differentiated carcinoid tumour. The immunohistochemistry supported neuroendocrine origin, positive for synaptophysin, chromogranin and CK, and negative for Hepatocyte Specific Antigen (HSA or Hep Par 1) and Ki-67 of 15-20%, the features compatible with atypical carcinoid WHO grade 2.

The dual tracer PET/CT (^{68}Ga-DOTATATE and ^{18}FDG) evaluation (Fig 1 & 2) before treatment decision-making, demonstrated intense FDG uptake in liver SOL (SUVmax-23.92) and porto-caval lymph nodes (SUVmax-16.9) with minimal ^{68}Ga-DOTATATE avidity, suggestive of low SSTR expression compatible with diagnosis of poorly differentiated NEC, rather than moderately differentiated atypical carcinoid. The scan findings thus helped in clarifying the tumor biology: important in such cases, where histopathology was conflicting between two sites and alone not sufficient.

Discussion

A relatively rare entity, NENs of head and neck region pose diagnostic and therapeutic challenges; with the availability of multimodal treatment and the recently developed importance of PRRT in metastatic NENs, adequate patient selection for a particular treatment is important for subsequent management. Ki-67 index is useful for predicting tumor biology, metastasis and for deciding the multimodal approach towards therapy. From the standpoint of tumor aggressiveness, poorly differentiated NENs, atypical carcinoids (moderately differentiated) and typical carcinoid are stratified in decreasing order with implications for appropriate treatment assignment. In the present case, low/minimal ^{68}Ga-

DOTATATE uptake and high grade uptake of ^{18}FDG (despite the liver biopsy reported Ki-67 of 15-20%) in the lesions favored poorly differentiated/G3 tumor, usual characteristic of this subtype. This was commensurate with commonly observed spectrum of salivary gland NENs, primarily poorly differentiated NECs of small cell and large cell types, with very few cases of well-differentiated NENs (carcinoids) reported [*2, 3*].

Tumor SUVmax on SSTR based PET is predictive of response to SSTR-targeted therapies e.g. PRRT, while high FDG uptake has been employed as the basis for choosing chemotherapy. Dual-tracer PET-CT is thus potentially helpful for such tumor stratification and treatment decision-making. In the described patient, the tumor biology as evident from dual tracer PET/CT, was consistent with histopathology of the primary tumor (i.e. SCNEC of parotid) and chemotherapy was considered the preferred option rather than PRRT.

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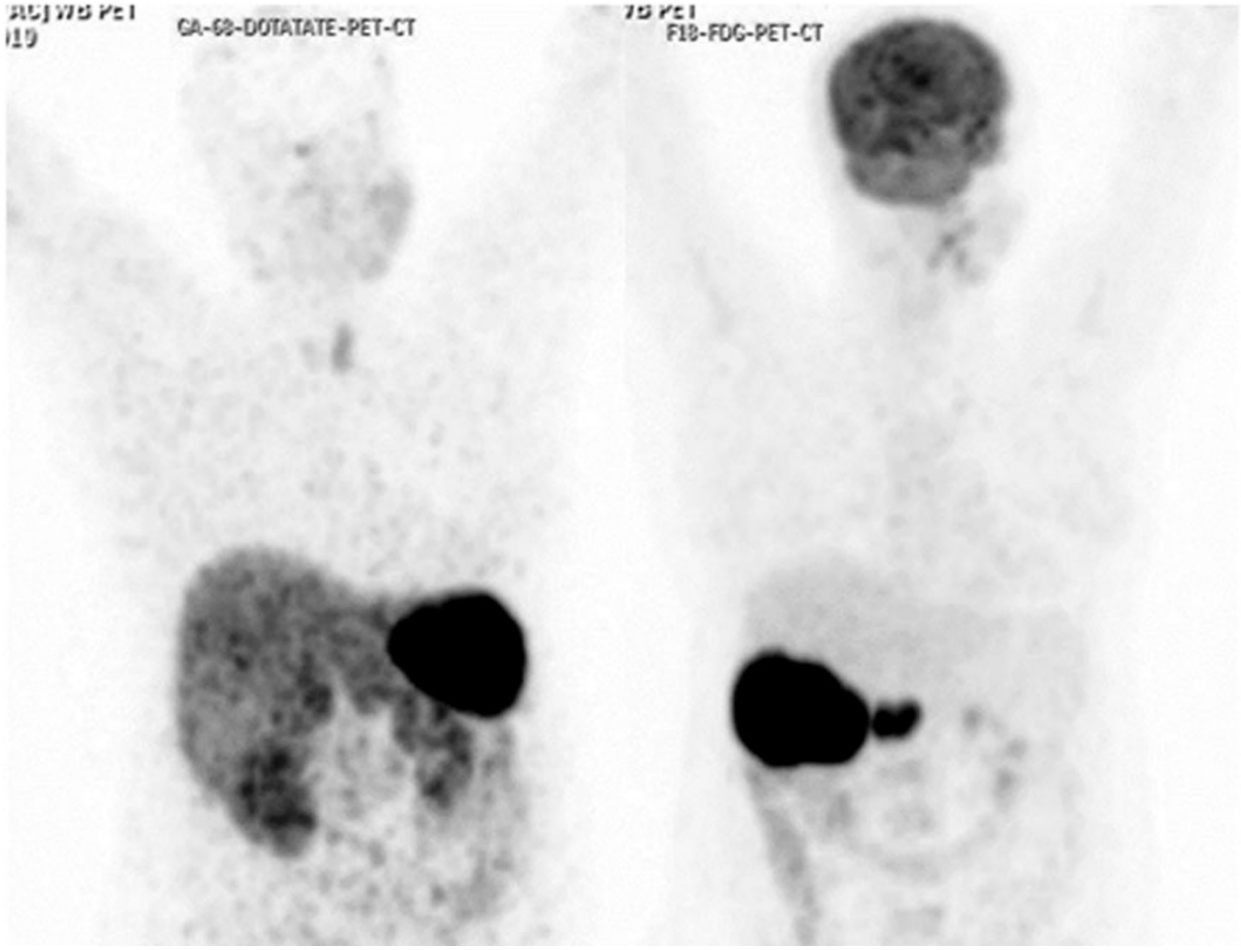

Fig 1. ^{68}Ga-DOTATATE and ^{18}FDG-PET-CT (MIP images) demonstrating high uptake of FDG in the metastatic liver lesion and porto-caval lymphadenopathy and low/minimal uptake on SSTR based ^{68}Ga-DOTATATE PET-CT.

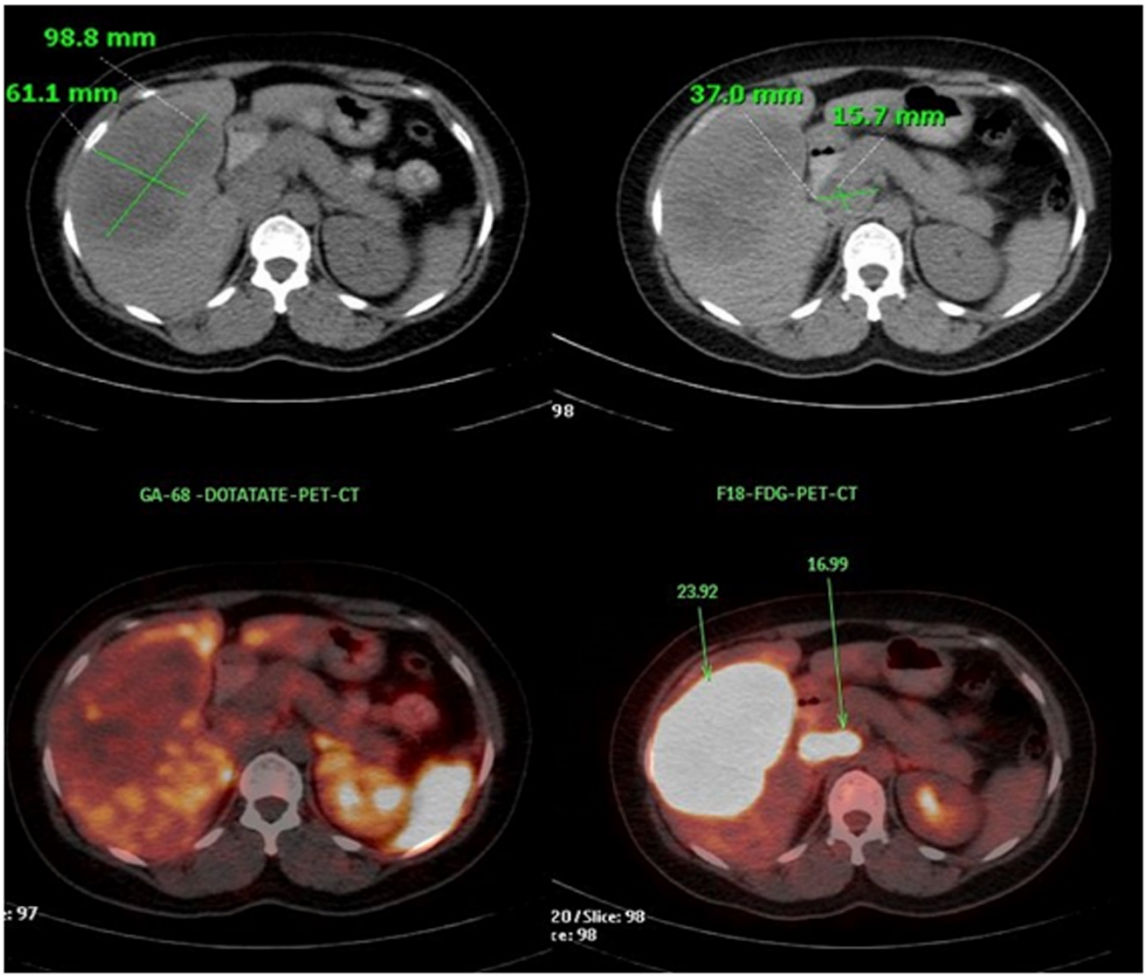

Fig 2. Axial fused PET-CT demonstrating limited ^{68}Ga-DOTATATE uptake in metastatic liver lesion (left panel) and porto-caval lymph nodes but prominent ^{18}FDG uptake (right panel).