

Case Report

Pituitary carcinoma: A case report and discussion of potential value of combined use of Ga-68 DOTATATE and F-18 FDG PET/CT scan to better choose therapy

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Abstract

Background: Pituitary carcinoma is extremely rare and carries a very poor prognosis. In most cases, apparently indolent tumors become malignant; however, there are no satisfactory biomarkers for predicting tumor behavior. Thus, scientific advances in the search for new biological markers, diagnostic methods, and therapies are needed to improve the prognosis of these patients.

Case Description: We report the case of a woman with initial diagnosis of nonfunctioning pituitary adenoma which evolved to carcinoma after 4 years. Diagnosis was confirmed after biopsy of metastatic pulmonary nodules, in which neoplastic cells were immunohistochemically positive for chromogranin, synaptophysin, prolactin, and growth hormone. Investigation with conventional somatostatin receptor scintigraphy, positron emission tomography-computed tomography (PET-CT) with Ga-68 DOTATATE and F-18 fluorodeoxyglucose (FDG) are showed. During temozolomide therapy, our patient had severe pancytopenia resulting in death from generalized infection despite 10 days of intensive care.

Conclusion: The present case of an aggressive pituitary carcinoma rising from a typical adenoma illustrates the importance of developing new prognostic biomarkers in these cases. In addition to demonstrating a serious side effect with the use of temozolomide, our case report suggests that the combined use of Ga-68 DOTATATE and F-18 FDG PET-CT scan may scale somatostatin receptors vs. tumor aggressiveness, therefore, helping to better choose the therapy for aggressive pituitary tumors.

Key Words: Ga-68 DOTATATE PET/CT, pituitary carcinoma, temozolomide

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INTRODUCTION

Pituitary carcinoma accounts for only 0.1% of all pituitary tumors, representing less than 200 cases in the English language literature. This entity is defined by a primary sellar tumor associated with noncontiguous intracranial lesions or metastasis to distant sites.^[6,19] Pituitary carcinoma is almost invariably first diagnosed in adults as a benign tumor, which after a time becomes aggressive. This period of latency ranges from 4 months to 18 years.^[14] The World Health Organization (WHO) proposes the utilization of Ki-67 index, elevated nuclear P53 expression, and mitotic figures to indicate tumor aggressiveness.^[3] However, these markers have not been able to define at an early stage which adenoma will change its natural course to become a carcinoma.^[3] So far, there are no satisfactory biomarkers for predicting tumor behavior.^[16] The prognosis of pituitary carcinoma is very poor. Most of the cases described in the current literature show rapid evolution after confirmation of metastasis, despite use of aggressive treatments available.^[18]

In this report, the authors describe the case of a young woman with primary diagnosis of a nonfunctioning pituitary adenoma, which evolved into carcinoma after 4 years of follow-up.

Although several studies have demonstrated security with the use of temozolomide concurrent with radiation therapy,^[1,8] our patient presented with severe collateral damage and eventual death due to irreversible pancytopenia and infection despite 10 days of intensive care.

The investigation with conventional somatostatin receptor scintigraphy, positron emission tomography-computed tomography (PET-CT) with Ga-68 DOTATATE and F-18 fluorodeoxyglucose (FDG), treatment, and fatal outcome of this aggressive pituitary carcinoma are discussed.

CASE REPORT

A 32-year-old Caucasian woman was referred to the endocrinology department with 18-month history of right temporal headache, which was accompanied by visual acuity reduction as well as amenorrhea and galactorrhea. She also reported fatigue, weakness, nausea, and sporadic vomiting. Visual field evaluation demonstrated left eye amaurosis and temporal hemianopsia and lower nasal quadrantanopsia in the right eye. Hormonal evaluation was compatible with panhypopituitarism, and the patient was started on cortisol and T4 replacement therapy.

Magnetic resonance imaging (MRI) showed a 4.0 cm diameter solid lobulated lesion with sellar and suprasellar components, predominantly isointense on T1 and hypointense on T2-weighted images and extension to both the cavernous sinuses and optic

chiasm. Given that the lesion was associated with optic tract compression, a transesfenoidal surgery for nonfunctioning pituitary macroadenoma was performed. The pathological evaluation revealed pituitary adenoma. Immunohistochemistry demonstrated that Ki-67 was positive in 3% of the cells and supporting the diagnosis of a canonical pituitary adenoma. In addition, p53 staining was positive in rare cells.

Although the headache persisted, the patient visual acuity significantly improved, as demonstrated by a striking improvement in visual field examination. The patient was started on cabergoline 0.5 mg 6 cps/week and remained free of progression for 4 years, when in a follow-up chest CT multiple pulmonary nodules with soft tissue density in both lung fields were detected, measuring 0.5–1.2 cm [Figure 1]. In accordance with the hypothesis of lung metastasis.

F-18 FDG images showed a markedly increased uptake in the pituitary (SUV 33) as well as in multiple lung nodules (SUV 11.1), pancreas (SUV 6), liver lesions (SUV 10.4) and right kidney nodule (SUV 8.5). Lung biopsy via bronchoscopy confirmed a moderately differentiated neuroendocrine tumor immunohistochemically positive for chromogranin, synaptophysin, prolactin, and growth hormone. Ki-67 was positive in approximately 10% of the cells [Figure 2]. Despite a normal chromogranin dosage and of whole body scintigraphy after Tc-99m HYNIC-octreotide injection showing no abnormal uptake in sellar region, the 3D PET/CT Ga-68 DOTATATE images showed moderate uptake in large pituitary lesion (SUV 4.4) and very mild uptake in some of the lung lesions; however, no increased tracer uptake was detected in the liver, pancreas, and right kidney lesions [Figures 3-5].

Given the presence of a pancreatic lump, the diagnosis of a primary pancreatic neuroendocrine tumor was

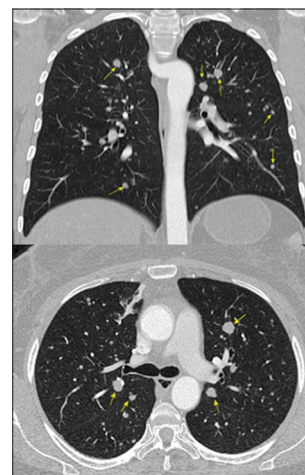


Figure 1: Multiple pulmonary nodules. Lesions indicated by arrows were confirmed in adjoining planes in the original CT scan to rule out that they might represent vessels

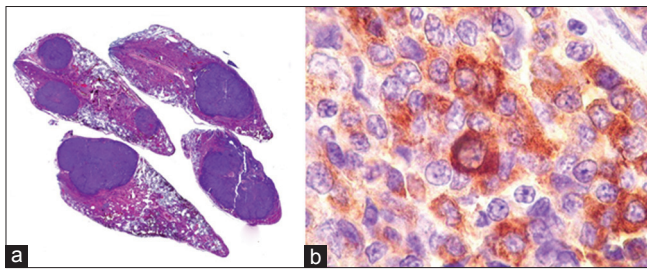


Figure 2: (a) Scanned slide of lung biopsy obtained via bronchoscopy, stained with hematoxylin and eosin: Multiple well-defined rounded, strongly basophilic lesions in the lung parenchyma. **(b)** Cytoplasmic positivity for chromogranin in part of neoplastic cells indicates neurosecretory character

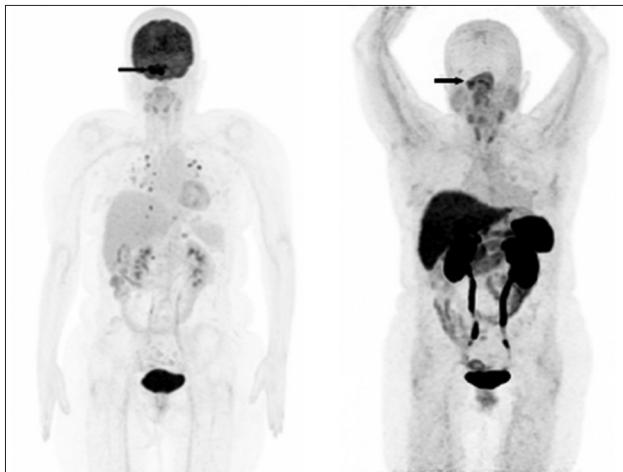


Figure 4: 3D images after F-18 FDG injection show physiologic brain uptake and markedly increased uptake in the pituitary and in multiple lung and liver lesions (left). Ga-68 DOTATATE show less impressive sellar uptake and very mild uptake in lung lesions (right)

considered, however, the turcica sella MRI showed significantly increased tumor size and signs of chiasm and right optic nerve compression [Figure 6]; the patient was submitted to a transcranial neurosurgery, but only partial removal of the tumor was possible because of hardened consistency.

Tumor tissue of this second sample showed small neoplastic epithelial cells either cubic or polygonal, with slight to moderate nuclear pleomorphism, dense chromatin, and scant pink cytoplasm. The cells were arranged in dense blocks amid fibrous tissue, with extensive necrotic areas, which also showed phagocytosed hemosiderin granules and hematoidin crystals. Mitosis were rare. The diagnosis of pituitary adenocarcinoma was based on the previous lung biopsy which disclosed a metastatic neuroendocrine tumor. The extensive necrotic areas in the pituitary tumor also supported the diagnosis of malignancy [Figure 7]. However, Ki-67 was positive only in approximately 4% and p53 in 3% of these cells.

After the diagnosis of pituitary carcinoma and based on PET-CT images obtained with F-18 FDG and Ga-68

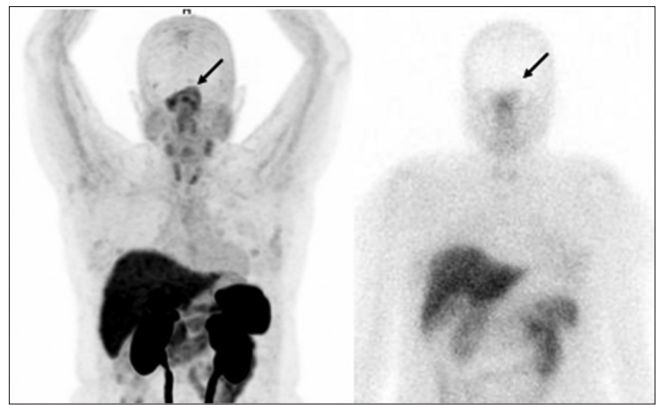


Figure 3: Left: 3D PET/CT Ga-68 DOTATATE showing moderate uptake in large pituitary lesion (SUV = 4.4). Right: Scintigraphy after Tc-99m HYNIC-octreotide showing no abnormal uptake in sellar region. The mild radiotracer uptake in the nasopharynx may be considered nonspecific

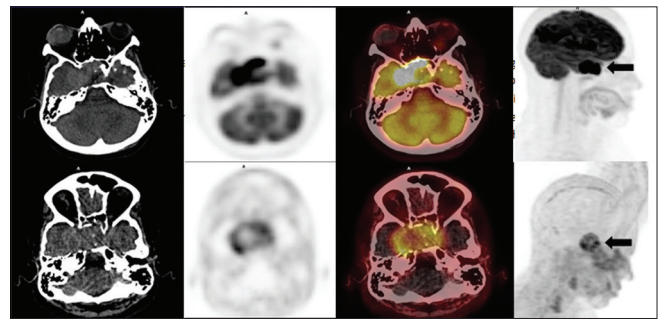


Figure 5: CT, PET, PET/CT and 3D-PET transaxial images. Superior row: F-18 FDG images show intense tracer uptake in the pituitary lesion (SUV33, black arrow). Inferior row: Ga-68 DOTATATE images show much less uptake with peripheral enhancement in the lesion (SUV4.4)

DOTATATE, the oncology team indicated concomitant radiochemotherapy. The planned radiotherapy was a total of 5400 cGy (180 cGy \times 30 days) plus temozolomide 75 mg/m²/day during the period of radiotherapy. However, on the 19th day of the treatment, the patient returned reporting of fatigue, sore throat, dry cough, and ecchymoses. Blood examination revealed pancytopenia, and despite intensive treatment, the patient died after 10 days due to generalized infection. A postmortem examination was not performed.

DISCUSSION

Because only 25% of the nonfunctioning macroadenomas increase in size significantly during follow-up^[2,9] after the first surgery, we opted for clinical follow-up for this patient. Moreover, it is known that the extent of tumor removal has no impact at mortality in these patients.^[10] During 4 years, the tumor remained stable and did not induce significant clinical changes despite continuous headache.

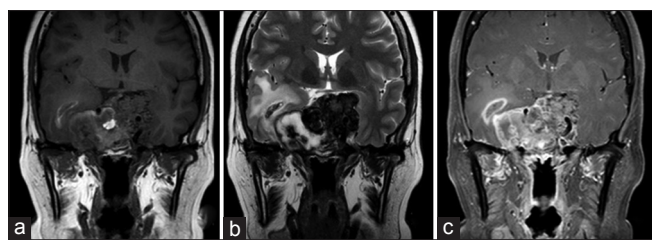


Figure 6: MRI after enlargement of the lesion: Solid lobulated lesion with hyperintense components on T1 without gadolinium (hemorrhage) (a) and on T2-weighted (b). Heterogeneous enhancement on T1-weighted after gadolinium (c) with extension to both cavernous sinuses and right temporal lobe

Some pituitary tumors that will become carcinoma demonstrate their aggressive behavior early, recur quickly after surgical debulking, and progress rapidly to carcinoma; on the other hand, certain tumors progress to carcinoma after many years of follow-up.^[14] Interestingly, despite persistent biochemical markers elevation in the absence of sellar tumor residual, pituitary carcinoma can go unnoticed for many years in a patient who later had cervical adenopathy proven to be GH-immunopositive neuroendocrine tumor on biopsy.^[13]

Even without significant growth of the tumor, the disease evolved with the emergence of metastases, showing the need for early markers of evolution in these cases. Histopathological diagnosis in the first surgery was pituitary adenoma, and there were no histological and immunohistochemical features of aggressiveness. Although some studies have shown a strong relationship between Ki-67 index and tumor aggressiveness (mean of 11.9 ± 3.4 for carcinomas to 1.4 ± 0.15 for adenomas),^[3,17] other studies have not proven such a significant association.^[15] Some authors have suggested that Ki-67 index appear to increase in conjunction with tumor transformation, however, in our case, even after the tumor growth and diagnosis of carcinoma was confirmed, Ki-67 and p53 continued to be hypoexpressed in tumor tissue.^[4] Interestingly, in our case pituitary Ki-67 never increased despite a 10% Ki-67 staining was detected in lung nodule, suggesting that the precursor adenoma presented a clonal dedifferentiation associated with early metastasis.

The presence of metastasis of a neuroendocrine tumor may indicate pituitary carcinoma, however, the presence of a pancreatic lump in our patient left a doubt regarding the possibility of a neuroendocrine tumor of the pancreas, hindering and delaying the diagnosis of pituitary carcinoma.

Whole body scintigraphy after Tc-99m HYNIC-octreotide injection was less sensitive to detect lesions with increased somatostatin receptors expression than three-dimensional PET-CT Ga-68 DOTATATE images in our patient, it can be verified that the former is more sensitive to detect somatostatin receptors expression. This greater sensitivity

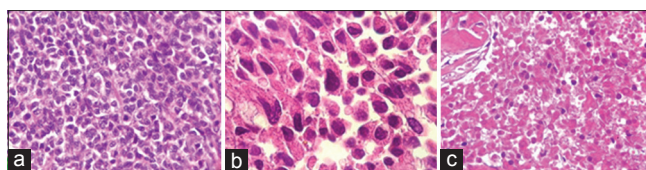


Figure 7: HE (a) Pituitary tumor at first Surgery: Regular small cells in solid arrangement. Absence of mitosis or necrosis. (b) Second surgery: Nuclear atypia and hyperchromasia are more pronounced. (c) Extensive areas of coagulation necrosis, not observed in the original sample

has already been described for neuroendocrine tumors,^[12] however, the literature does not show a comparison between these two exams in pituitary carcinomas. Although no SPECT/CT images were available for direct comparison, these images show that higher affinity of Ga-68 DOTATATE for the somatostatin receptors made it possible to easily detect the lesion even when only the functional image (PET) is shown.

In our patient, the concomitant evaluation of PET-CT scan using F-18 FDG and Ga-68 DOTATATE showed an uptake almost eight times more intense with F-18 FDG. This different uptake is probably related with the high aggressiveness of the lesion. Carrying out these two examinations has the potential to define the aggressiveness of the tumor and thus help to indicate which is the better therapy, e.g., molecular-targeted therapy using somatostatin analogs and peptide receptor radionuclide therapy targeting somatostatin receptors or chemotherapy. A recent study showed that in a patient with a PET-CT scan showing multiple foci of increased Ga-68 DOTATATE uptake in pituitary and posterior fossa lesions, the tumor remained stable over 4 years after Lu-177 DOTATATE therapy.^[11] In accordance with the need to individualize the therapy for these patients, Lu-177 DOTATATE therapy showed distinct results in three patients.^[7]

In contrast to a recently published study that showed high uptake of Ga-68 DOTATATE in a patient with pituitary carcinoma that the authors proposed Lu-177 DOTATATE therapy, the rationale to use temozolomide in our patient was a lower uptake with Ga-68 DOTATATE associated with high F-18 FDG uptake compatible with tumoral aggressiveness.^[20]

The prognosis for the patient of pituitary carcinoma is very poor. Most of the cases described in the current literature show rapid evolution after confirmation of metastasis, despite using aggressive treatments available.^[18] Although several studies have demonstrated that the use of temozolomide concurrent or not with radiation therapy is safe,^[1,5,8] our patient had severe pancytopenia secondary to the use of temozolomide resulting in death from generalized infection despite 10 days of intensive care.

In conclusion, the present case of an aggressive pituitary carcinoma arising from a typical adenoma show how a benign disease can transform into a devastating one. Thus, the development of new prognostic biomarkers should be an imperative task to better control aggressive pituitary tumors. In addition to demonstrating a serious side effect with the use of temozolomide, our case report suggests that the combined use of Ga-68 DOTATATE and F-18 FDG PET/CT scan may scale somatostatin receptors vs. tumor aggressiveness, therefore helping to better choose the therapy for pituitary carcinoma.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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