Pituitary Carcinoma in a Patient with Cowden Syndrome

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Patient: Female, 58-year-old
Final Diagnosis: Pituitary carcinoma
Symptoms: Headache • left temporal lower quadrantanopia • right temporal hemianopia
Medication: —
Clinical Procedure: —
Specialty: Neurology • Neurosurgery • Radiology • Pathology

Objective: Rare coexistence of disease or pathology
Background: Pituitary carcinomas are rare tumors that are histologically indistinguishable from pituitary adenoma. This report describes an extremely rare case of pituitary carcinoma in a patient with clinically diagnosed Cowden syndrome (CS). CS is a rare multisystemic hereditary disease with increased risks of cancer and benign overgrowth of different types of tissues.

Case Report: A 52-year-old woman with history of CS presented with pituitary adenoma and multiple meningiomata. After surgical resection, there was recurrence of the pituitary tumor. Partial resection of the recurrent pituitary tumor revealed an adenoma. Radiotherapy was administered due to the histopathological aggressive features of the resected pituitary tumor and growth of the residual pituitary tumor on follow-up. Although the pituitary tumor shrank after radiotherapy, there was development of multiple new intracranial extra-axial lesions. Resection of a rapidly growing extra-axial tumor in the parietal convexity region was performed. Given the similar histopathological features of the convexity tumor with the prior pituitary specimen, the diagnosis of pituitary carcinoma was established. A subsequent MRI scan showed metastatic deposits along the spine. The patient’s condition deteriorated and she died shortly after the last surgery.

Conclusions: To the best of our knowledge, there is no prior report of pituitary carcinoma in a patient with CS in the literature. Pituitary carcinomas frequently spread within the craniospinal axis, in addition to hematogenous dissemination. Given the high risks of developing malignant tumors in patients with CS, multidisciplinary management including diagnostic imaging and close surveillance are of paramount importance in patient management.

Keywords: Cowden-Like Syndrome • Meningioma • Pituitary Neoplasms

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Background

Pituitary carcinomas are rare tumors that are indistinguishable from pituitary adenomas and are defined by the presence of central nervous system (CNS) or systemic metastases [1]. The incidence of pituitary carcinomas is very low. Most pituitary neoplasms are benign adenomas, and the overall estimated prevalence in the general population is 16.7% (14.4% in autopsy studies, 22.5% in neuroimaging studies) [2]. In a large database from 3489 pituitary adenomas, only 5 of the cases (0.12%) were classified as pituitary carcinoma; even this incidence may be overestimated since it comes from a selected series of surgically treated patients [2].

Cowden syndrome (CS) is a rare hereditary multisystemic disease with increase risks of cancer involving various organs (particularly breast, thyroid, and endometrium) and benign overgrowth of different types of tissues (eg, skin, colon, thyroid). It is part of phosphate and tensin homolog (PTEN) hamartoma tumor syndrome (PHS). The PTEN mutations germline were first reported in individuals with CS in 1997 [3,4]. The latest edition of the diagnostic criteria for CS was published in 2013. It was subsequently accepted by the U.S. National Comprehensive Cancer Network (NCCN) in 2017 [5,6].

In this report, we describe an extremely rare case of pituitary carcinoma in a patient with clinically diagnosed CS. Besides imaging review, we discuss the pathogenesis of pituitary carcinoma and CS, including patient management strategies.

Case Report

A 52-year-old woman presented with right temporal hemianopia, left temporal lower quadrant anopia, and headache in 2015. She had a history of CS with macrocephaly, multiple mucocutaneous lesions, multinodular goiter, and breast fibroadenoma.

Figure 1. MRI brain in 2015 with right temporal hemianopia, left temporal lower quadrant anopia and headache. (A) Coronal T1-weighted image shows a large pituitary tumor (arrow) displacing the optic apparatus and a simultaneous left convexity extra-axial tumor, presumably a meningioma (arrow head). (B) Sagittal T1-weighted image shows the large pituitary tumor (arrow) displacing the optic apparatus and indenting the hypothalamus and the floor of third ventricle. (C) Coronal T1-weighted image shows left frontal and left sphenoid ridge meningiomata (arrow heads).
She also underwent surgery and chemotherapy for endometrial adenocarcinoma. These were part of the patient’s clinical diagnosis of CS based on the NCCN criteria.

On examination, she was conscious and alert. Apart from the known visual field defect, she had no motor weakness on examination. There was no clinical evidence of hormonal hypersecretion.

Magnetic resonance imaging (MRI) of the brain revealed a large and heterogeneous enhancing stalk mass with suprasellar and cavernous sinus extension. There was significant mass effect with compression and superior displacement of the optic chiasm and hypothalamus. In addition, there were multiple dural-based lesions with homogeneous enhancement at the left frontal convexity, tuberculum sella and left sphenoid ridge (Figure 1). Serum prolactin (PRL), adrenocorticotropic hormone (ACTH), and thyroid function test results were within normal limits. There was no clinical evidence of Cushing syndrome or acromegaly.

The patient declined surgery in 2015. Owing to increasing episodes of headache and visual deficits, she subsequently agreed to undergo surgery in 2018. Given the different locations of the convexity and stalk tumors, it was decided to use a 2-stage surgical approach. Left frontotemporal craniotomy was initially performed with removal of dural-based lesions, which were later found to be compatible with meningioma on microscopic examination. She subsequently underwent trans-sphenoidal surgery with partial resection of the stalk mass about 4 months later. The histology revealed an adenoma with positive ACTH and negative PRL staining. There was no significant cellular pleomorphism or mitotic activity, and the Ki-67 index was 1%. The serum hormone test results were within normal range.

A few months later in 2019, there was recurrence of the stalk-suprasellar tumor (Figure 2). The patient underwent bifrontal craniotomy and resection of the recurrent tumor (Figure 3). The histopathology revealed recurrent pituitary adenoma...
with positive ACTH staining and negative PRL and synaptophysin staining. However, there were increased cellular pleomorphism and mitotic activity, as well as elevated Ki-67 index (5%). Postoperative stereotactic radiotherapy (SRT) was administered with subsequent reduction in size of the remnant pituitary tumor. A follow-up MRI brain showed new extra-axial tumors scattered over bilateral cerebral convexities and in the left posterior fossa (Figure 3). The extra-axial tumors showed homogeneous enhancement, presumed to be meningiomata. Within a few months, there was rapid growth of the largest extra-axial mass over the left frontotemporal convexity (Figure 4). The patient subsequently underwent craniotomy for resection of the left convexity tumor in 2021. Histopathology revealed a well-circumscribed tumor arranged in sheets of polygonal cells exhibiting increased cellular pleomorphism, high mitotic activity, and an elevated Ki-67 index (10%) (Figure 5). The ACTH, synaptophysin, SSTR2, and MNF116 were positive, and PRL, EMA, and p53 were negative on the specimen. The histology and morphology of the convexity tumor was similar to that of the previously resected pituitary tumor (Figure 6). With regards to her history of CS, there were no other new tumors detected since 2015. However, no genetic pathology test was performed on the tumor samples. A subsequent whole MRI spine revealed multiple intradural extramedullary enhancing metastatic deposits along the thoracic and lumbar spine (Figure 4). Pituitary carcinoma was diagnosed based on the multiplicity of tumors with similar histopathological features, in different intracranial locations. Her condition deteriorated after the surgery and no further treatment could be administered. She was given palliative care and died a few weeks later from heart failure.

**Discussion**

Pituitary carcinoma, also termed metastatic pituitary neuroendocrine tumor, is strictly defined as a tumor of adenohypophysial cells that metastasize craniospinally and/or systemically. The definition depends on the behavior instead of the histological appearance. Pituitary carcinoma commonly originates...
from benign macroadenoma. In our case, the tumor recurred within 8 months after initial resection of pituitary macroadenoma. The resected specimen showed aggressive biological behavior with increased mitotic activity and elevated Ki-67 index. The histology could have been that of “atypical pituitary adenoma” but this entity was removed from the WHO Classification of Endocrine Tumors in 2017 due to incompletely defined histologic criteria and relatively few cases in the literature [7]. Hence, our patient was initially diagnosed with pituitary macroadenoma. When she developed tumor recurrence with intracranial and intraspinal metastases in 2021, the histologic diagnosis was subsequently reviewed and amended to pituitary carcinoma after reviewing the histology of all the resected tumor specimens.

Most pituitary carcinomas are hormonally active or functioning. The ACTH- and/or PRL-secretion are the most frequent types [8]. In our case, it was an ACTH immunoreactive type of tumor with elevated Ki-67 index, indicating the presence of high mitotic activity and potential risk of recurrence. The Ki-67 index is therefore useful for guiding treatment planning and tumor surveillance [9]. In our patient’s case, immunohistochemistry tests did not contribute to the diagnosis of pituitary carcinoma. There were no histomorphological or immunohistochemical criteria that could reliably predict any malignant transformation of pituitary adenomas. Moreover, immunohistochemical characteristics are not part of the diagnostic criteria for pituitary carcinoma. The diagnosis of a pituitary carcinoma requires evidence of metastatic spread outside the CNS or any separate noncontiguous lesions within the CNS [10].

Metastases of pituitary carcinoma frequently occur within the craniospinal axis as the result of dissemination in the subarachnoid space besides hematogenous dissemination via the petrosal sinus [9]. Brain metastases are often seen in the cerebral cortex and cerebellum [10]. Systemic metastases frequently involve the bones, liver, and lungs [9]. Lymph
Figure 5. Photomicrographs of resected left frontotemporal tumor of the woman with pituitary carcinoma in 2021. (A) Hematoxylin-eosin stained low-power view shows the tumor comprising of sheets of polygonal cells with eosinophilic granular cytoplasm. (B) Hematoxylin-eosin-stained high-power view shows moderate nuclear atypia and increased mitotic activity of the tumor cells. (C) Immunohistochemical Ki67 staining demonstrates 10% elevation of the index, indicating mitotic activity of the tumor cells.

Figure 6. Immunohistochemical staining of the resected left frontotemporal tumor of the woman with pituitary carcinoma in 2021. The tumor shows high positivity for (A) synaptophysin and (B) ACTH. This confirms the pituitary origin of the tumor. (C) Epithelial membrane antigen (EMA) is negative, thus excluding the possibility of meningioma.
node involvement can only occur from invasion of the skull and soft tissue, as the pituitary gland itself has no lymphatic vessels [11]. Tissue manipulation during surgery is unlikely to contribute to dissemination.

Multidisciplinary treatment strategy for pituitary carcinoma includes neurosurgery, radiotherapy, chemotherapy, and/or medical therapy. Surgery can provide tissues for histological diagnosis, but is unlikely to be curative. Our patient had 3 prior surgeries for tumor recurrence and metastases, and the diagnosis of pituitary carcinoma was only confirmed after the last surgery. Studies suggest that radiotherapy reduces the risk of tumor regrowth for non-functioning pituitary tumors significantly when administered within 12 months after the initial surgery [12]. However, there is no evidence to suggest that radiotherapy can improve survival in patients with pituitary carcinoma. Moreover, radiotherapy may be related to malignant transformation of brain tumors, especially in younger patients [13].

Temozolomide (TMZ) is the most widely used alkylating agent for treatment of pituitary carcinomas [14,15]. Historical data show that before the use of TMZ, the overall survival (OS) of pituitary carcinoma was less than 4 years [10]. A systemic review revealed that TMZ seemed to have improved the 5-year OS to 56.2% in patients with pituitary carcinomas [16]. Variable response rates with TMZ ranging from 31% to 51% have also been reported in some other studies [15,17]. Based on the evidences available so far, TMZ is recommended as the first-line chemotherapy for pituitary carcinomas [18]. In our patient’s case, TMZ could not be administered in time due her clinical deterioration after the last surgery. It is uncertain if administration of TMZ would have made a difference in our patient’s outcome.

TMZ with radiotherapy, the so-called “Stupp protocol”, is recommended to treat rapid growing tumors in patients who have not reached maximal doses of radiotherapy [18]. Other chemotherapy agents, such as fluorouracil (5-FU), carboplatin, cisplatin, lomustine, and etoposide, have been used in treating pituitary carcinoma [18]. Standard medical treatment, for example, cabergoline for prolactinomas, pasireotide for corticotropic tumors, and somatostatin analogs for somatotroph tumors and thyrotroph tumors, has been recommended, with maximally tolerated doses [18].

The relationship between CS and pituitary carcinoma is unknown and has never been reported. In the literature, there are only a few cases of pituitary adenoma [19,20] and meningioma [21,22] reportedly associated with CS. Interestingly, they occurred in young to middle-aged women, including our case. Having been clinically diagnosed with CS, our patient subsequently developed pituitary carcinoma and multiple meningiomas.

CS is characterized by a high risk of both benign and cancerous tumors of different organs, mainly the breast, thyroid, endometrium (uterus), colon, kidney, and skin. The well-recognized brain anomalies are macrocephaly, Lhermitte-Duclos disease or dysplastic gangliocytoma of the cerebellum, and developmental venous anomalies. Revised clinical diagnostic criteria in 2015 suggested that meningioma and gangliocytoma should be considered one of the major diagnostic criteria for CS [22], but these criteria have not yet gained wide acceptance.

Nevertheless, it is important to obtain detailed patient’s family and personal medical history in the diagnosis of CS. Patient management of CS should include a comprehensive multidisciplinary team approach and close surveillance. Diagnostic imaging therefore plays a vital role in early detection of new and malignant tumors in CS, with particular attention to the intracranial compartments, including the pituitary fossa.

Conclusions

This is the first report of a case of pituitary carcinoma in a patient with clinically diagnosed CS. Metastases of pituitary carcinoma frequently occur within the craniospinal axis, in addition to extraneural hematogenous dissemination. TMZ is advocated as the first-line chemotherapy in pituitary carcinoma, and the “Stupp protocol” can be considered for those with rapid tumor growth and who were suboptimally irradiated. Given the high risks of malignant tumor growth in CS, patient management should include a comprehensive multidisciplinary approach including diagnostic imaging, which inevitably plays a vital role in early tumor detection and surveillance.

Declaration of Figures’ Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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