Clinical Management of Pituitary Carcinomas

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KEYWORDS

• Pituitary carcinoma • Atypical pituitary adenoma • Invasive pituitary adenoma • Pituitary adenoma • Temozolomide

KEY POINTS

- Pituitary carcinomas are rare, with one study reporting only 165 cases reported in the English literature as of 2011.[1]
- Pituitary carcinomas make up only 0.1% to 0.2% of all pituitary adenomas.
- Diagnosis of pituitary carcinoma requires presence of metastases distant from the primary tumor in the sella, as local invasion is common (approximately 35%–40% of pituitary adenomas) and cannot be used to diagnose pituitary carcinomas.
- Most patients with pituitary carcinomas present initially with an invasive pituitary adenoma, although rarely, patients can present with primary pituitary carcinomas without a previous history of pituitary tumor.[2,3]
- Studies implementing histology, immunohistochemistry, genetic analysis, and ultrastructural imaging with electron microscopy cannot consistently distinguish pituitary carcinomas from adenomas and should be used only to supplement the diagnosis.

INTRODUCTION

Pituitary tumors represent 10% to 15% of primary intracranial neoplasms[4,5] and the overwhelming majority are benign adenomas. Pituitary carcinomas are very rare and consist of 0.1% to 0.2% of all pituitary tumors.[1,6–8] According to the 2004 World Health Organization (WHO) classification of endocrine tumors, tumors of the adenohypophysis are classified into benign pituitary adenomas, atypical pituitary adenomas, and pituitary carcinomas.[9,10] It is not clear whether pituitary carcinomas arise de novo as distinct malignant tumors or are malignant transformation of typical or atypical pituitary adenomas.

Whether there are clinically useful molecular, genetic or pathologic, differences among the 3 WHO classes of pituitary tumors are not known at this time. The histologic, immunohistochemical, radiographical, and ultrastructural analyses are limited in distinguishing typical and atypical adenomas, and malignant carcinomas.

Pituitary carcinomas portend a poor prognosis. They are mostly endocrine active tumors with very aggressive clinical features and rapid progression, often unresponsive to conventional therapies that are often effective against hormonally active adenomas. Clinical progression includes severe medical morbidities related to hormone overproduction (ie, Cushing's disease) and mass effects from sellar and distant tumor expansion. Current treatment paradigms include multiple surgical resections, although complete resection may be unrealistic given the extent of

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invasion or with multiple metastatic lesions. Other alternatives, such as radiation therapy, systemic chemotherapy, and medical therapies to treat hormone overproduction are also of limited help (ie, dopamine agonist therapy). Despite aggressive treatments, all of these treatments have proven to be palliative at best. Cytotoxic chemotherapies have yielded disappointing results, despite high proliferative index of pituitary carcinomas. Recurrence with rapid tumor growth is often evident following radiation therapy. Recently, however, some strides have been made with the use of temozolomide,[11,12] a methylating alkylator agent commonly used to treat malignant gliomas. Here, we review the histopathologic features of pituitary carcinomas relative to benign and atypical pituitary adenomas, how pituitary carcinomas are best managed in the modern era, and the future directions that will hopefully lead to better treatment for this aggressive malignant disease.

HISTOPATHOLOGIC DEFINITIONS AND FEATURES

Definition of atypical pituitary adenomas is currently made on histologic grounds, while the definition of pituitary carcinoma requires the presence of metastases distant from the primary tumor in the sella.[1,7,8,10,13–15] Atypical pituitary adenomas are defined as pituitary adenomas with elevated mitotic index, Ki-67 labeling index greater than 3%, and excessive p53 immunoreactivity.[10] However, cytologic features of pituitary carcinoma can be quite similar to and often indistinguishable from adenomas (**Fig. 1**).

These WHO definitions focus on histologic evidence of mutations and proliferation (atypical adenomas) or distant metastases (pituitary carcinomas), but they ignore other aspects of pituitary tumor behavior–like invasion. This is because gross evidence of local invasion during surgery is demonstrated in approximately 35% to 40% of pituitary adenomas,[15,16] meaning that the presence of invasion alone is not sufficiently restrictive to be included in the definition of atypical adenoma or carcinoma. Recent studies suggested that atypical pituitary adenomas show higher rates of local invasion by imaging compared with "typical" pituitary adenomas.[17] Thus, local invasion is a feature common to both typical and atypical pituitary adenomas, especially in large macroadenomas, but not enough to

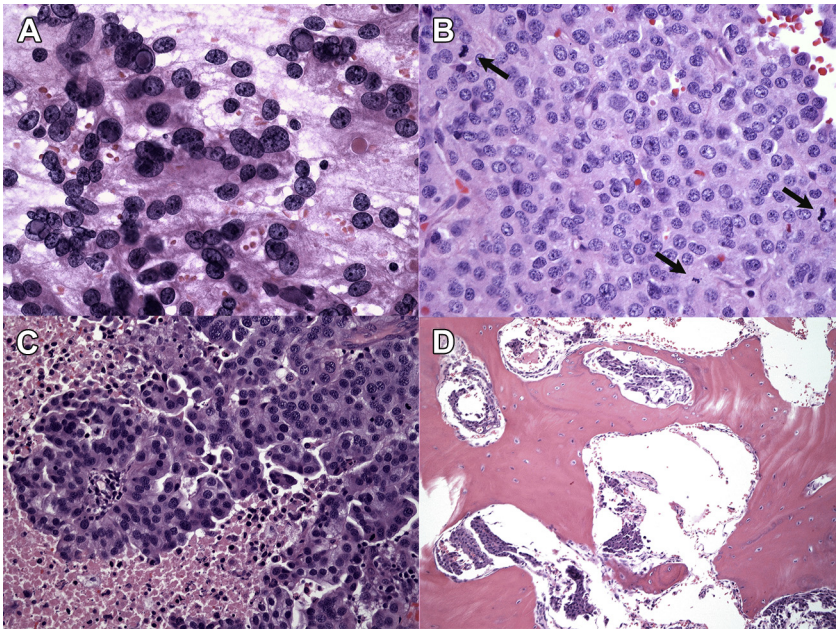

Fig. 1. (*A*) Cytologic features of pituitary carcinoma can be indistinguishable from some adenomas but typically show an increased hyperchromasia and nuclear pleomorphism (hematoxylin-eosin, original magnification ×600). (*B*) Most pituitary adenomas are indistinguishable from other epithelial carcinomas with variable degrees of pleomorphism, increased mitotic figures, and prominent nucleoli (*arrows*). However, these features are neither necessary nor sufficient for the diagnosis of pituitary carcinoma on histologic grounds (hematoxylin-eosin, original magnification ×400). (*C*) Loss of normal acinar architecture along with cytologic anaplasia and necrosis can be seen in most pituitary carcinomas (hematoxylin-eosin, original magnification ×200) (*D*) Bone invasion and invasion of adjacent tissues can be seen in both adenomas and in carcinomas of the pituitary gland. This image demonstrates invasion of the sphenoid bone by a pituitary carcinoma (hematoxylin-eosin, original magnification ×40).

render it diagnostic criteria for atypical adenomas. On the other hand, distant metastases are quite rare and thus represent an extremely restrictive criteria, making pituitary carcinoma a rare diagnostic entity. Some argue that there must be mutation(s) predisposing to metastatic ability, the presence of which might allow widening the diagnostic criteria to include pituitary tumors that look highly aggressive under a microscope without systemic metastases, but no such mutation(s) have been identified to date. Thus, although there is a clear need for well-validated genetic or histologic markers to better distinguish pituitary tumors by clinical aggressiveness, clinicians for the moment must recognize the 3 WHO classes of pituitary tumors defined as described previously.

EPIDEMIOLOGY OF PITUITARY CARCINOMA

Pituitary carcinomas are very rare, with one study reporting only 165 cases reported in the English literature as of 2011.[1] Although the evidence of local invasion is found intraoperative in 35% to 40% of cases,[15,16] pituitary carcinomas make up only 0.1% to 0.2% of all pituitary adenomas. By comparison, atypical pituitary adenomas represent approximately 15% of all pituitary adenomas.[17] Thus, the transformation that allows a pituitary carcinoma to form (ie, metastases) from either a pituitary adenoma, directly from normal pituitary gland tissue, or from an as yet unidentified precursor state is a rare event.

Both genders are equally affected by pituitary carcinomas with a mean age at presentation in the fifth decade. By contrast, pituitary adenomas, especially of prolactinomas, are more common in women,[18,19] possibly because of the ease of detecting endocrine symptoms in women compared with men.

Pituitary carcinoma seems to affect only the adult population, although one case report of pituitary carcinoma in a 9-year-old girl with widespread metastases to the craniospinal axis has been reported.[20] In one study of 15 patients (8 males and 7 females) with pituitary carcinoma,[6] the mean age was 56 with a range of 34 to 71.

Most (88%) pituitary carcinomas are hormonally active tumors.[1,6–8,21] The incidence of nonfunctioning pituitary carcinomas has been very low in recent years.[6,22] According to a study, hormonally active pituitary carcinomas predominantly consist of adrenocorticotropic hormone (ACTH) (42%) and prolactin-secreting (33%) carcinomas, followed by growth hormone (6%), gonadotropic hormones (5%), and thyroid-stimulating hormones (1%).[7] Null-cell pituitary carcinomas represent approximately 12%.[7]

PATHOPHYSIOLOGY OF PITUITARY CARCINOMAS

Etiology of Pituitary Carcinomas: De Novo Versus Malignant Transformation of Invasive Pituitary Adenomas

Whether pituitary carcinomas occur de novo or progress from invasive, typical, or atypical pituitary adenomas is unknown. Pituitary carcinomas without evidence of a prior benign lesion have been reported, suggesting the possibility of de novo occurrences.[2,3] As an entirely speculative possibility, pituitary carcinomas may start out as atypical adenomas that undergo malignant transformation. Typically, histologic features of aggressive pituitary adenomas as well as pituitary carcinomas remain more or less similar throughout the disease course (see **Fig. 1**). Recurrence of pituitary carcinoma is common, and may require repeated surgical resections, more aggressive medical therapy, and radiation therapy. Despite these aggressive measures, most tumors progress and result in the demise of the patient.

Some investigators believe that pituitary carcinomas progress from invasive pituitary adenomas, possibly with the atypical pituitary adenomas being the most likely culprit. Others have speculated dissemination of aggressive adenomas following surgical resection, but this hypothesis has not been adequately supported in the literature. Similarly, malignant transformation caused by radiation therapy has not received a wide support, although there are reports of sarcomatous changes in pituitary adenomas following radiation therapy.[23] A review of 36 cases of pituitary carcinoma in 1989 found that fewer than half (18 of 38) of patients with pituitary carcinomas were previously treated with radiation therapy.[24] The risk of developing secondary brain tumors following external beam radiotherapy for pituitary adenoma is also relatively low at 1.3% at 10 years and 1.9% at 20 years following treatment with a relative risk of 9.38 compared with the normal population.[25] Although these rates seem higher than the progression rates of pituitary adenomas to carcinomas (0.1%–0.2%), in the same study, there were no malignant transformations of pituitary adenomas in 3760 observed patient years.[25] Thus, it appears that radiation treatment does not significantly increase the risk of carcinomatous transformation of pituitary adenomas.

Local Invasion: A Step Toward Metastatic Transformation?

Pituitary adenomas commonly invade through local structures, such as dura, bone, cavernous sinus, and even blood vessels and nerve sheaths

(see **Fig. 1**D). Although evidence of local invasion by gross observation during surgery ranges from 35% to 40%,[15,16] microscopic demonstration of dural invasion can be demonstrated in up to 85% of patients with pituitary adenomas.[16] Atypical adenomas have significantly higher rates of local invasion (83%) by imaging compared with "typical" adenomas (45%).[17]

The natural expansion of an adenohypophysial tumor involves the dura mater. Therefore, it is not surprising to find dural invasion increasing in frequency with increasing tumor size. In one study, microadenomas, macroadenomas, and tumors with suprasellar extension had 69%, 88%, and 94% incidence of dural invasion by microscopic evaluation, respectively.[16] In a larger cohort study consisting of 354 patients treated with trans-sphenoidal surgery, percentage of tumors with dural invasion correlated with increasing tumor size: 24% for 10 mm or smaller, 35% for 10 to 20 mm, 55% for 20 to 40 mm, and 70% dural invasion for larger than 40 mm tumor size.[26] Whether dural invasion should be considered similar to invasion of surrounding soft tissues is debatable. There is still much work needed to correlate the extent of dural invasion with evidence of biologic aggressiveness not related to simple tumor growth rate. Currently, there is no evidence to suggest that dural invasion is independent of tumor size or growth rate as a prognostic indicator.

Evidence against this suggestion is the observation that local invasion, including dural invasion, does not confer malignancy or predict future transformation to pituitary carcinomas, as most invasive pituitary adenomas do not metastasize. For example, a recent study found that although dural invasion was significantly more common in the repeated trans-sphenoidal surgery group (69%) compared with the primary surgery group (41%), it is not a predictive factor for recurrence.[26] This study also found that mortality rates were higher in the group with dural invasion (9%) compared with the group with no invasion (0%) at the end of a 6-year follow-up.[26] However, this mortality rate is very small compared with the typical mortality rate in pituitary carcinomas, where 66% of patients with pituitary carcinoma die within the first year of diagnosis.[6] Furthermore, determination of dural invasion does not appear to be independent of tumor size or growth rate. It is still possible that invasive features may predict a more aggressive clinical course and may portend a higher risk, especially in hormonally active tumors. Most importantly, however, invasive features do not consistently predict malignant transformation.

Further evidence suggesting that local invasion does not consistently confer malignancy comes from studies looking at hormonal profiles of pituitary adenomas. For example, dural invasion is most frequently found in the nonfunctioning pituitary adenomas at 54.2%,[26] whereas most pituitary carcinomas are endocrine active.[1,6–8,21] By comparison, only 30% to 35% of endocrine-active tumors have dural invasion.[26] Most of the invasive nonfunctioning pituitary adenomas will never progress to pituitary carcinomas. In another study, 50% of atypical pituitary adenomas were nonfunctioning lesions,[17] suggesting the possibility that only a small percentage of endocrine-active, atypical pituitary adenomas could transform into pituitary carcinomas. The factors that determine which tumors progress to pituitary carcinomas remain elusive at this time, although invasive, atypical macroadenomas that are endocrine active are the most likely candidates.

The evidence for malignant transformation of pituitary adenomas rather than de novo pituitary carcinoma formation include the following:

- Most pituitary carcinomas initially present as aggressive pituitary tumors with multiple recurrences that "escape" medical, surgical, and radiation treatments[1,6–8,13,14,21];
- The latency of transformation from pituitary adenomas to carcinomas usually takes months to years. In the setting of Nelson syndrome, in which ACTH-secreting carcinoma develops following bilateral adrenalectomy for Cushing syndrome, the mean interval between the diagnosis of adenoma and carcinoma is 15.3 years[6];
- There is no histologic distinction between pituitary carcinomas and invasive macroadenomas. The decision of a pituitary carcinoma is made only after a metastatic focus is discovered.

Genetic, Molecular, and Ultrastructural Make-Up of Pituitary Carcinomas

Numerous studies have attempted to distinguish the genetic, molecular, and ultrastructural make-up of pituitary carcinomas from adenomas. Although some trends are important to note, generally the case-to-case variability has been so large that all of these features have failed to consistently distinguish among benign, invasive, and malignant pituitary tumors. Histologic features that define malignancy in other brain tumors, such as necrosis, invasion of surrounding structures, hypercellularity, increased mitotic activity, and pleomorphism, are found in benign and atypical pituitary adenomas, as well as pituitary carcinomas.[14]

Studies indicate that proliferative and mitotic activities are generally higher in carcinomas

compared with invasive adenomas. In one study, Ki-67 cell cycle–specific nuclear antigen detected by MIB-1 antibody was increased in the order of invasiveness: mean Ki-67 fractions were 1.37%, 4.66%, and 11.91% for noninvasive adenomas, invasive adenomas, and pituitary carcinomas, respectively.[27] Setting the Ki-67 labeling index threshold at 3% allows one to distinguish noninvasive from invasive tumors with 97% specificity and 73% sensitivity.[27] However, other studies have not found such clear correlation of Ki-67 labeling with the invasive potential of tumors.[28] Evaluation of mitotic figures[29,30] and proliferating cell nuclear antigen[31] have shown increased proliferation index in more invasive, higher grade tumors as well.

Molecular oncogenes that are often altered in other malignancies, such as p53, p27, Ras, retinoblastoma gene, MEN-1, gsp, nm23, and HER-2/neu, are also found to be affected in pituitary carcinomas, but not consistently enough to allow differentiation from benign adenomas.[1,6–8,13,14,21] In one study, p53 was expressed in a larger fraction in higher-grade pituitary tumors with 0%, 15.2%, and 100% expression in noninvasive adenomas, invasive adenomas, and pituitary carcinomas, respectively.[32] Interestingly, a higher fraction of metastatic lesions (83%) expressed p53 compared with primary sellar lesions (57%), suggesting that metastatic lesions may have accumulated more genetic abnormalities that make them able to metastasize.

An ultrastructural study using transmission electron microscopy also confirmed significant cellular atypia and mitotic activity in most pituitary carcinomas, but concluded that pituitary adenomas and carcinomas cannot be distinguished on ultrastructural features alone.[33] A detailed summary of histologic, immunohistochemical, and genetic alternations; proliferation indices; and ultrastructural studies of pituitary carcinomas have been thoroughly reviewed elsewhere.[1,6–8,13–15,21]

CLINICAL PRESENTATION AND PROGRESSION OF PITUITARY CARCINOMA

Clinical Presentation

Most patients with pituitary carcinomas present initially with an invasive pituitary adenoma, although rarely, patients can present with primary pituitary carcinomas without a previous history of pituitary tumor (**Fig. 2**).[2,3] Transformation of pituitary adenomas to pituitary carcinomas usually takes 6 to 8 years.[6,34] Clinical progression includes symptoms related to hormone overproduction (ie, Cushing disease), symptoms of local mass effect from tumor expansion of the sellar and suprasellar space, or symptoms of systemic metastases. Mass effects near the sellar region consist of symptoms similar to those found in macroadenomas, including visual field deficits and decreased visual acuity owing to compression of optic chiasm; headaches from stretching of the nearby dura or diaphragm sella; cranial neuropathies from compression of cranial nerves in the cavernous sinus; and hypopituitarism owing to compression of portal vessels, pituitary stalk, and/or pituitary gland. The most common presentation of pituitary carcinoma occurs in the setting of a patient with a history of invasive pituitary neoplasm, often with multiple surgical resections or previous radiation therapy, who undergoes rapid recurrence with resistance to medical therapy, as evidenced by rising serum hormone levels. Metastases away from the primary pituitary tumor must be confirmed on imaging.

Patients with functional pituitary carcinomas present with symptoms similar to those in respective functional adenomas,[1,7,13,14,21] but possibly with higher serum hormone levels. Patients with ACTH-secreting carcinomas present with Cushing disease with typical features of hypercortisolism, including round facies, thin skin with delayed wound healing, hirsutism, striae, central obesity, supraclavicular and dorsocervical fat pads, fatigue, muscle atrophy, hypertension, osteoporosis, immunosuppression, and psychiatric problems, including depression and cognitive impairment. Serum ACTH levels ranged from 145 to 280,000 pg/mL (normal 0–60 pg/mL) in one study with 4 of 7 patients presenting in the setting of Nelson syndrome, where patients have previously undergone bilateral adrenalectomy for Cushing syndrome.[6] Extremely high levels of ACTH are common with ACTH-secreting pituitary carcinomas.[35]

Prolactin-secreting carcinomas often release very high levels of prolactin, despite dopamine agonist therapy, ranging from 6 to 21,560 ng/mL (normal <13 ng/mL in men and <27 ng/mL in women; 21,560 ng/mL was obtained in one patient during treatment with bromocriptine).[6] Elevated prolactin levels, however, are often seen in macroadenomas that are unresponsive to dopamine agonists, making the diagnosis based on prolactin levels alone unfeasible. Although patients with prolactin-secreting carcinomas may be responsive to dopamine agonists like bromocriptine or cabergoline initially, their disease eventually becomes unresponsive to medical treatment, and tumors grow despite aggressive therapies. In one study, dopamine D2 receptors (through which the dopamine agonists exert their negative trophic effects) were expressed in initial surgically resected tumor tissues but absent in postmortem

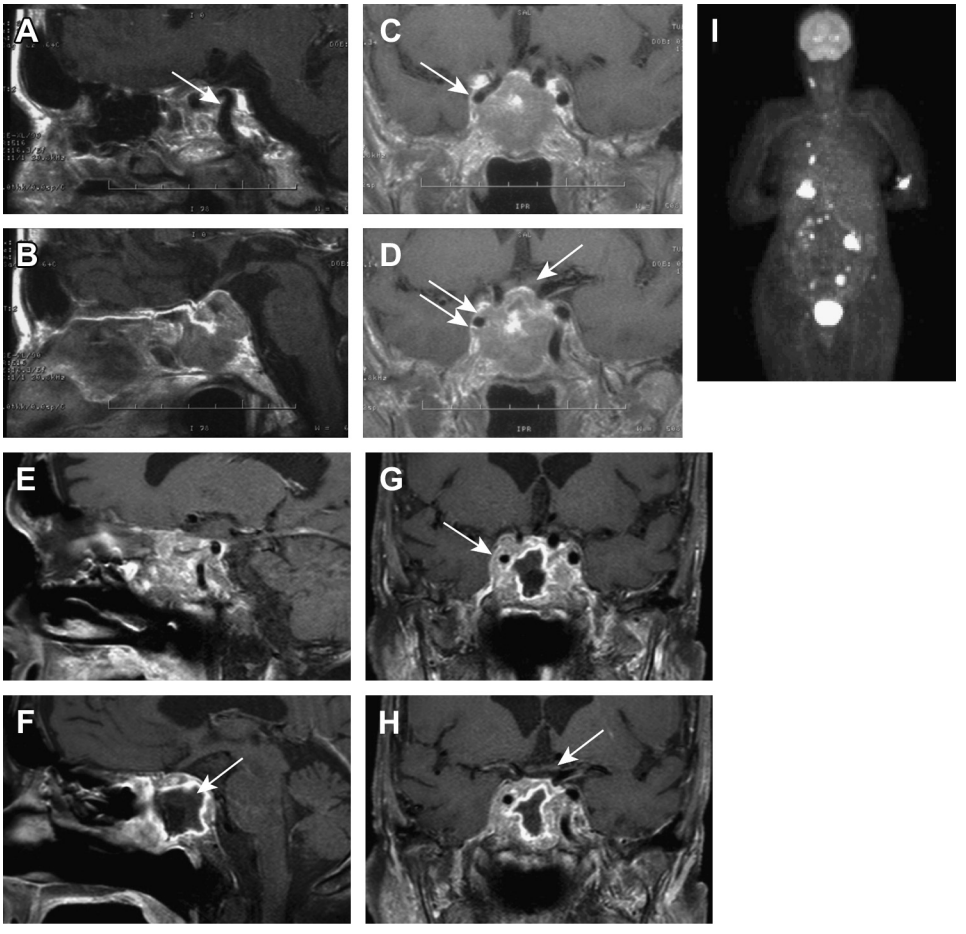

Fig. 2. A 71-year-old woman with a 3-year history of pituitary adenoma, initially diagnosed by imaging and followed with serial images without surgery, presented with 20-pound weight loss, fatigue, right ptosis with third cranial nerve palsy, and right sixth cranial nerve weakness. MRI of the brain was obtained (*A–D*, preoperative images). T1-weighted images with gadolinium enhancement (*A–H*) showed significant expansion of the pituitary tumor encasing the carotid arteries (*A, C, arrows*), a suprasellar extension and the compression of optic chiasm (*D, single arrow*), invasion into sphenoid sinus and clivus (*B*), and invasion of cavernous sinuses, which explains the cranial nerve deficits (*D, double arrows*). The patient underwent trans-sphenoidal decompression with debulking of the tumor, and the MRI obtained about a month following surgery (*E–H*, postoperative images) shows further expansion of the tumor (compare *arrows* in *G* vs *C*) but decompression of the optic chiasm (*H, arrow*). Pathologic specimen revealed MIB-1 (Ki-67) labeling of 54.4%, suggestive of very aggressive tumor. Follow-up whole-body PET scan with 2-(F-18) fluoro-2-deoxy-D-glucose confirmed the diagnosis of pituitary carcinoma with systemic metastases (*I*). Multiple systemic metastases were evident with signals in the right neck (lymph node), right superior mediastinum (hilar lymph nodes), liver, left subdiaphragmatic space, left ovary, left arm, and multiple lymph nodes in the abdomen. The patient succumbed to her disease approximately 3 months after the diagnosis of pituitary carcinoma.

tissues obtained after the diagnosis of metastatic pituitary carcinoma.[36] Thus, loss of dopamine D2 receptor expression could be one potential mechanism of resistance to dopamine agonists in prolactin-secreting carcinomas.

Endocrine symptoms of prolactin-secreting carcinomas are similar to those found in pituitary adenomas, which include decreased libido, galactorrhea, gynecomastia, amenorrhea, and infertility. Growth hormone–secreting tumors present as acromegaly, and gonadotroph and thyroid-stimulating hormone–secreting carcinomas are extremely rare.[1,6–8,13,14,21]

Metastasis can occur in the subarachnoid space, leptomeninges, or parenchyma of the central nervous system including both brain and spinal cord, or systemically with invasion into bone, liver, lymph nodes, ovary, heart, and lung. Patients with systemic metastases are thought to have a worse prognosis compared with those

with craniospinal metastases. Most (75%) patients who died within 1 year following the diagnosis of pituitary carcinoma had systemic metastases.[6]

The latency of transformation of invasive pituitary adenoma to pituitary carcinoma can range from months to years. Some studies have reported transformation to pituitary carcinoma after more than a 20-year latency period.[34] In one large series with 15 patients, mean latency period was 6.6 years (median 5.0 years) with a range of 0.3 to 18.0 years.[6] In another large cohort with 15 patients, mean latency period was 7.8 years (median 5 years) with a range of 0 to 24 years.[34] The patients with Nelson syndrome, which is attributable to proliferation of ACTH-secreting tumor following bilateral adrenalectomy for Cushing syndrome, had the longest latency period with a mean of 15.3 years.[6] Interestingly, in the same study, prolactin-secreting tumors transformed to pituitary carcinomas twice as fast compared with ACTH-secreting tumors (4.7 vs 9.5 years, respectively). It is unclear currently what factors determine how quickly pituitary adenomas transform into pituitary carcinomas. It is also unclear what factors allow certain adenomas to transform into pituitary carcinomas, while most other adenomas remain benign. Clinically, patients with long-standing pituitary adenomas who rapidly progress with recurrence and develop new resistance to current therapy warrant a close monitoring for possible malignant transformation.

Diagnosis

According to the 2004 WHO classification of endocrine tumors, the diagnosis of pituitary carcinoma requires primary pituitary tumor with either systemic or craniospinal metastases.[10] Pituitary carcinomas are diagnosed by radiographic imaging with detection of metastases, followed by pathologic confirmation of pituitary origin of the metastases. The pathologic confirmation is critical, because metastatic lesions from elsewhere, including breast, bronchus, kidney, and colon cancers, can metastasize to the sellar region.[21] Thus, other metastatic disease with non-pituitary primary must be considered in the differential.

Imaging Methods

Magnetic resonance imaging (MRI) studies show pituitary carcinomas with characteristics similar to invasive macroadenomas (see **Fig. 2**A–H). T1-weighted images with gadolinium provide the best imaging to evaluate for pituitary carcinomas, which may show suprasellar extension, parasellar cavernous sinus invasion, and/or other intracranial lesions. The primary pituitary tumor and metastases may have similar imaging characteristics on MRI.[37] In one study, the signal intensity and characteristics of the pituitary tumor and the extra-axial spinal metastatic lesion were found to be the same, suggesting similar vascularity and stroma in the 2 tumor tissues.[37]

Positron emission tomography (PET) scans and radionucleotide scans have been used, although not routinely (see **Fig. 2**I). There are reports of these studies being used for diagnosis and to determine the extent of metastases and response to therapy. In one study, dopamine D2 receptor binding and tumor amino acid metabolism were studied using PET scans. Malignant prolactinoma with high D2 receptor binding and tumor amino acid metabolism initially showed decreased D2 receptor binding, decreased tumor amino acid metabolism, and decreased tumor size in response to bromocriptine.[38] In another case report, malignant prolactinoma was diagnosed with dopamine D2 receptor scintigraphy using [^{123}Iodine]epidepride to detect multiple metastatic lesions in the ribs, femur, and spine in the absence of recurrent pituitary lesion.[39] Growth hormone–secreting pituitary carcinoma has been diagnosed with metastases in the neck without a recurrent pituitary mass using [^{111}Indium]pentetreotide.[40] These studies exemplify the feasibility of PET studies in aiding diagnosis, determining the extent and locations of metastases, and response to therapy in patients with pituitary carcinoma, especially those without a recurrent lesion in the sellar region.[39,40]

Studies implementing histology, immunohistochemistry, genetic analysis, and ultrastructural imaging with electron microscopy cannot consistently distinguish pituitary carcinomas from adenomas and should be used only to supplement the diagnosis. Further studies are needed to determine which targets (ie, histologic features, genetic mutation, oncogene or tumor suppressor gene expression, chromosomal abnormality) provide useful information toward prognosis or predict beneficial response to different treatment modalities.

Prognosis of Pituitary Carcinoma

Pituitary carcinomas portend a poor prognosis with a mean survival of 1.9 years with a range of 3 months to 8 years following the diagnosis of pituitary carcinoma.[6] They are mostly endocrine-active tumors with very aggressive clinical features and rapid progression, typically unresponsive to conventional therapies that are effective for benign adenomas. Despite aggressive multimodal treatment including surgery, radiation therapy, hormonally targeted therapies, and systemic chemotherapy, all of these treatments have

proven to be palliative at best. Overall, 66% of patients died within 1 year following diagnosis, with most deaths (75%) in the first year occurring in patients with systemic metastases.[6] Systemic metastases conveys worse prognosis compared with craniospinal metastases, with the median survival with systemic metastases of 1.0 year compared with 2.6 years with craniospinal metastases.[14] Although rare, long-term survivors have been reported.[41] Although no systematic analysis has been performed, negative prognostic factors include loss of response to medical therapies with extremely high serum hormone levels, rapidly expanding tumor despite aggressive treatment, and systemic metastases.

MANAGEMENT OF PITUITARY CARCINOMAS

Because of the rarity of pituitary carcinomas, there are no studies comparing different treatment modalities. The principles applied to treating benign pituitary tumors are also applied to carcinomas. Treatment modalities include surgical resection for the primary pituitary mass and the accessible, symptomatic metastases, medical therapy, radiation therapy, and chemotherapy.

Surgical Resection

First-line therapy for pituitary carcinoma consists of surgical resection, although usually gross-total resection is not achievable because of invasion of pituitary mass into surrounding structures with multiple distant metastases. The most important value of surgical debulking in the sellar region is to decompress the important structures nearby, such as optic chiasm, pituitary stalk, pituitary gland, cranial nerves, and major cerebral blood vessels. Surgical decompression can be critical for metastases to the spine to relieve compression on the spinal cord or nerve roots. Although there are no controlled studies showing long-term benefits of surgery, anecdotal evidence suggests that surgery can provide immediate relief of symptoms.[21] Cases of complete resection of sellar lesion and metastases have been reported previously[42,43]; although the long-term control in these patients has not been followed. In series reported by Pernicone and colleagues,[6] of 15 patients, 14 underwent resection of their pituitary mass with 7 craniotomy, 6 trans-sphenoidal resection, and 1 biopsy with radiation. One patient underwent bilateral adrenalectomy with radiation.

Hormone-Targeted Therapies for Pituitary Carcinomas

The medical therapy for pituitary carcinoma consists of dopamine agonist therapy for prolactinomas and somatostatin analogs for growth hormone–secreting carcinomas. Up to 80% to 95% of prolactinomas can be controlled, both in terms of hormonal normalization and tumor reduction, with either bromocriptine or cabergoline.[44,45] More often, higher doses of drugs are needed to achieve similar results in pituitary carcinomas; however, these drugs are often ineffective for carcinomas, given that most patients are diagnosed once they become unresponsive to medical treatments with increasing serum hormone levels.[14,21,46] Good response to dopamine agonists have been reported for some patients,[38] although effects are temporary in most patients. One case report of growth hormone–secreting carcinoma responsive to bromocriptine has been described as well, in which the patient showed marked improvement in symptoms, including visual field deficits.[24] Despite this symptomatic relief, the patient became unresponsive to treatment and succumbed to the disease about a year later.

Other medical therapies for pituitary carcinomas include somatostatin analog octreotide for growth hormone– and ACTH-secreting carcinomas. Remission rates in benign growth hormone–secreting adenomas are similar for octreotide treatment compared with the surgery group, although 48-week remission rate is slightly higher in the surgery group (39% vs 28%).[47] However, the effects for carcinomas are usually temporary, with a rapid disease progression. There is also a report of thyrotropin-secreting pituitary carcinoma that was temporarily responsive to octreotide.[48] Other drugs used for benign pituitary adenomas, such as ketoconazole and pasireotide (SOM230) for recurrent Cushing disease and pegvisomant for acromegaly, need further testing for pituitary carcinomas.

Radiation Therapy for Pituitary Carcinomas

There are no systemic analyses evaluating the efficacy of radiation therapy to pituitary carcinomas, and the number of reported cases with systemic chemotherapy is low, mostly with poor results.[22] Although fractionated radiotherapy and stereotactic radiosurgery have been generally successful for pituitary adenomas resistant to medical and/or surgical therapies, there are no large series reported for pituitary carcinomas.[14] Most reported cases portray short-term control at best with poor long-term results.[1,7,14]

Systemic Chemotherapy for Pituitary Carcinoma

Despite the high proliferative index of pituitary carcinomas, systemic chemotherapy has yielded

disappointing results for pituitary carcinoma, possibly because of the well-differentiated characteristics of pituitary carcinoma cells. Although there are a few reports of short-term stabilization with systemic chemotherapy,[6,24,46,49] most combinations of cytotoxic agents have yielded poor long-term benefits. The most commonly used treatment consists of combination therapy with CCNU and 5-fluorouracil, whereas carboplatin, either alone or in combination with 5-fluorouracil or interferon-α, and dacarbasine have also been used.[22] Recently, temozolomide, a methylating alkylator agent commonly used in malignant gliomas, has shown benefit in some patients with pituitary carcinomas.[11,12]

Temozolomide

Temozolomide (Temodar) is an orally administered agent that readily crosses the blood-brain barrier. It methylates DNA at the O^6 position of guanine, causing mismatch and eventually apoptosis. It is currently used in conjunction with radiation therapy following surgical resection for malignant gliomas,[50] as well as advanced malignant neuroendocrine tumors.[51] The effect of temozolomide is opposed by the expression of O^6-methylguanine DNA methyltransferase (MGMT), which is a DNA repair enzyme. Malignant gliomas that express low levels of MGMT via MGMT promoter methylation[52] are more susceptible to temozolomide-induced tumor suppression and increased survival.[53,54]

The first report of efficacy of temozolomide in 2 patients with pituitary carcinoma was presented in 2006.[55] The first patient had luteinizing hormone–secreting tumor with intradural metastases to the spine, and the second patient had prolactin-secreting macroadenoma that progressed to carcinoma with metastases to the spine, despite dopamine agonist therapy and proton beam radiation therapy. Both patients' symptoms improved shortly after starting therapy with temozolomide with significant improvement in visual field deficits for well over 1 year after the therapy.[55] Temozolomide treatment in prolactinoma has been confirmed to cause necrosis, hemorrhage, focal inflammatory infiltration, marked changes in morphologic features, and reduction in growth potential by histologic, immunohistochemical, and electron microscopic studies.[56]

Since these initial cases reported in 2006, additional studies have reported the use of temozolomide in pituitary carcinomas with encouraging outcomes.[34,56–68] Thus far, 40 patients with aggressive pituitary tumors treated with temozolomide have been reported, consisting of 16 patients with pituitary carcinoma,[11,12,58,65] most recently reviewed by McCormack and colleagues.[11] Of these 40 patients, 24 (60%) had good outcomes following temozolomide therapy with the highest response rates in prolactinomas (73%), followed by ACTH-secreting tumors (60%) and nonfunctioning tumors (40%).[11] Among the 16 pituitary carcinomas, 11 patients (68.8%) showed good response to temozolomide, whereas 2 patients (12.5%) showed no response and 3 patients (18.8%) showed progressive disease.[11]

Interestingly, patients with low MGMT expression seem to respond better to temozolomide.[11,12,61,63] Approximately 50% to 57% of pituitary carcinomas express low levels of MGMT.[34,69] In a most recent review, 76% of patients with aggressive pituitary tumors with low MGMT expression showed high response to temozolomide, whereas patients with high MGMT expression did not.[11] Among patients with pituitary carcinoma, 5 (62.5%) of 8 patients with absent to intermediate MGMT expression had good response to temozolomide, whereas only 1 (33.3%) of 3 patients with high MGMT expression had good response.[11] However, these results must be interpreted with caution because (1) some studies did not find an association of low MGMT expression with better temozolomide response,[58,65] (2) MGMT promoter methylation status is not correlated with temozolomide response,[11] and (3) the sample size is too small in the current studies. Clearly, further studies with more patients and analysis of MGMT expression and promoter methylation status are needed to make more definitive conclusions. Moreover, studies testing the combination therapies with temozolomide and other drugs, such as dopamine agonists, used for pituitary tumors should be further explored.[57,64,68]

Potential Novel Therapeutic Agents

Although results with the use of temozolomide in pituitary carcinomas and invasive adenomas are encouraging, it is clear that more research is needed to develop novel approaches to treat pituitary tumors resistant to conventional therapeutic modalities, such as surgery, medical therapy, radiation, and chemotherapy. Novel targeted therapies used for other brain and neuroendocrine tumors need further testing to evaluate their efficacy against pituitary carcinomas. One such candidate is the antiangiogenic agent bevacizumab (Avastin), which is a monoclonal antibody that binds and potently blocks vascular endothelial growth factor. As a potent inhibitor of angiogenesis, it is known to delay tumor growth and has been approved for use in metastatic colon cancer,

advanced non–small-cell lung cancer, metastatic renal cell carcinoma, and recurrent glioblastoma multiforme.[70] Recently, a 44-year-old man with aggressive silent corticotroph cell pituitary adenoma that progressed to carcinoma despite multiple surgeries, radiation, and temozolomide treatment was treated with bevacizumab. After 16 months of treatment, the disease stabilized with long-term control (26 months) of disease.[71] Another agent that warrants a further review is everolimus (Afinitor), an inhibitor of mammalian target of rapamycin (mTOR). Pituitary adenomas upregulate the PI3 K/Akt/mTOR pathway,[72] and everolimus has been shown to prolong progression-free survival in patients with advanced pancreatic neuroendocrine tumors.[73] A case report of use of everolimus in combination with a somatostatin analog, octreotide, has been presented recently, although the combined therapy failed to control an aggressive ACTH-secreting pituitary carcinoma.[74] More experience with other patients with pituitary carcinomas or invasive adenomas resistant to conventional therapies is needed before any definitive conclusion can be made.

SUMMARY

Pituitary carcinomas are rare malignant pituitary tumors with poor overall survival. Although effective medical, surgical, and radiation therapies are available for pituitary adenomas, such therapies are deemed only palliative for pituitary carcinomas. Although preliminary, results from the use of novel therapeutic agents, such as temozolomide, are encouraging and warrant further investigation for pituitary carcinomas and aggressive, invasive pituitary adenomas that are unresponsive to conventional therapies.

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