Pituitary carcinoma: a review of the literature

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Pituitary carcinomas, defined as distant metastases of a pituitary neoplasm, are rare; fewer than 140 reports exist in the English literature. The initial presenting pituitary tumor is usually a secreting, invasive macroadenoma, with adrenocorticotropic hormone (ACTH)– and prolactin (PRL)–secreting tumors being the most common. The latency period between the diagnosis of a pituitary tumor and the diagnosis of a pituitary carcinoma is 9.5 years for ACTH-producing lesions and 4.7 years for PRL-secreting tumors. Survival after documentation of metastatic disease is poor; 66% of patients die within 1 year. Treatment options include additional surgery, radiotherapy, and chemotherapy, all of which are associated with poor results. Future studies will focus on identifying those invasive pituitary tumors most likely to metastasize and treating them aggressively before they progress to pituitary carcinomas.

DEFINITION AND INCIDENCE OF PITUITARY CARCINOMAS

The hallmark of a pituitary carcinoma is distant metastases. Pituitary tumors grow by expansion and displacement of adjacent structures, with dural invasion noted in 45% of all cases in one large study. Nevertheless, histological invasion does not confer the diagnosis of pituitary carcinoma.

Pituitary carcinomas are rare tumors constituting only 0.1 or 0.2% of pituitary tumors. To date, approximately 140 well-documented examples have been reported in the English literature. The vast majority of reported pituitary carcinomas are endocrinologically active (88%), with 59 (42%) of the reported lesions producing ACTH, 1,5, 6,11,13,17,19,20,22,23,25–27,34,36,37,40,42,43,46–48,53,56,60,64,67,72,77,80,81,87,91,99,100,102, 107,111,118,46 (33%) producing PRL, 3,4,7,9,12,28,30,38,43–45,52,55,59, 69,75,80,84–86,92,94,96,98,99,103,113,114,116,117,119 nine (6%) producing GH, 2,32,35,54,68,70,73,76,106 seven (5%) producing LH or FSH, 55, 73,83,90,105 and only one (1%) producing TSH. Null-cell pituitary carcinomas represent 17 (12%) of the reported cases. No sex predominance has been reported. Before the 1970s, PRL levels were not measured and immunohistochemical staining was not performed. Therefore, a significant number of PRL-producing carcinomas were probably unrecognized, making data from older literature somewhat unreliable. Sites of pituitary tumor metastasis include the brain, spinal cord, leptomeninges, bone, liver, lymph nodes, ovary, heart, and lung. Of note, systemic spread of the disease is postulated to occur by way of venous circulation to the lungs. Nevertheless, pulmonary sites for the metastasis of pituitary carcinomas are rarely seen.

LATENCY PERIOD AND PATIENT SURVIVAL

In a series of 15 pituitary carcinomas, the latency period between the presentation of a sellar adenoma and the manifestation of metastasis was approximately half as long in PRL-producing tumors (mean 4.7 years) as in ACTH-producing lesions (mean 9.3–9.5 years). The overall latency period in cases of pituitary carcinoma has a surprisingly wide range: from a few months to 18 years (median 5 years). The longest latency interval (15.3 years) occurred for patients with Nelson syndrome. Eighty percent of patients in the series died of metastatic disease between 7 days and 8 years after diagnosis of carcinoma; of these, 66% died within 1 year. The mean survival time for the entire study population was approximately 2 years (range 0.25–8 years), with patients who had craniospinal and systemic metastatic diseases surviving 2.6 years and 1 year, respectively. Sironi, et al., reviewed the literature on 33 patients with PRL-secreting carcinomas; all but eight patients died with or as a result of their pituitary carcinoma, with a mean survival time of 2.4 years.

Abbreviations used in this paper: ACTH = adrenocorticotropic hormone; BrdU = 5-bromodeoxyuridine; CNS = central nervous system; FSH = follicle-stimulating hormone; GH = growth hormone; LH = luteinizing hormone; LI = labeling index; MR = magnetic resonance; PRL = prolactin; Rb = retinoblastoma; TSH = thyroid-stimulating hormone.
METASTATIC SPREAD OF THE DISEASE

Pituitary carcinomas have been reported to metastasize to the cerebral cortex, cerebellum, spinal cord, leptomeninges, cervical lymph nodes, liver, ovaries, and bone. All pituitary carcinomas have displayed a greater tendency toward systemic metastasis than craniospinal metastasis; the rate of systemic metastasis was 71% for PRL-producing tumors and 57% for ACTH-producing lesions. Thirteen percent of tumors have demonstrated both patterns of metastasis.

CLINICAL FEATURES OF PITUITARY CARCINOMAS

Symptoms and Signs

Nearly all pituitary carcinomas present as hormone-secreting, invasive macroadenomas with symptoms of mass effect including visual changes, diplopia, and headache. Nonsecreting carcinomas present with mass effect.

Corticotroph Carcinoma

Most ACTH-producing tumors present with Cushing syndrome; only a few cases of silent corticotroph carcinomas have been reported. Of the seven ACTH-producing adenomas reported in one large series four occurred in the setting of Nelson syndrome and the serum ACTH levels ranged from 145 to 280,000 pg/ml (normal level 0–60 pg/ml). Nelson syndrome is the clinical manifestation of an ACTH-secreting adenohypophysial neoplasm that occurs in patients who have undergone adrenalectomy for Cushing syndrome. In its typical form, the syndrome is characterized by the development of an ACTH-secreting adenohypophysial neoplasm that occurs in patients who have undergone adrenalectomy for Cushing syndrome. In its typical form, the syndrome is characterized by the development of an ACTH-producing pituitary tumor with fasting ACTH levels exceeding 200 pmol/L and hyperpigmentation of the skin. This secretion of ACTH and related melanotrophic peptides results in hyperpigmentation. Roncaroli, et al., reported on patients with clinically silent corticotroph tumors, noting that these pituitary carcinomas presented as invasive macroadenomas with symptoms of mass effect. The outcome for the patients harboring these five tumors was similar to that of patients presenting with Cushing disease.

Prolactin-Secreting Pituitary Carcinomas

As expected, PRL-producing tumors present with amenorrhea, galactorrhea, or impotence. Initially serum PRL levels can range from 6 to 22,000 ng/ml, with increasing serum levels noted in the presence of tumor recurrence and metastasis.

Gonadotroph Carcinomas

Gonadotroph tumors comprise approximately 30% of clinically nonfunctioning pituitary tumors and usually present as macroadenomas with suprasellar extension. In one large series, only 20% of these pituitary tumors demonstrated invasion on neuroimaging studies or at the time of the operation. Gonadotroph carcinomas are rare, with only a few published examples. Elevated serum levels of the glycoproteins LH and FSH, and of the α-subunit of glycoprotein hormones, a 92-amino-acid chain, is a component of glycoproteins produced by the adenohypophysis (LH, FSH, and TSH).

Growth Hormone–Secreting Carcinoma

The GH-secreting pituitary carcinomas present as invasive macroadenomas with acromegaly. Elevated serum levels for GH and insulin-like growth factor–I have been noted in several cases.

IMAGING FINDINGS

Pituitary carcinomas almost always present as invasive macroadenomas that metastasize both to the CNS and systematically. For disease of the CNS, MR imaging is the best diagnostic imaging method for defining the extent of the disease. Pituitary carcinomas usually occur in the setting of a known invasive macroadenoma. The intrasellar component is typically displayed as an aggressive pituitary tumor with suprasellar extension and possible invasion of the cavernous sinus. Within the CNS, pituitary carcinomas metastasize to the cerebral lobes, cerebellum, spinal cord, leptomeninges, and subarachnoid space. Interestingly, dural sites of metastasis can mimic meningiomas (for example, a homogeneously enhancing dural-based lesion). Matsuki, et al., compared the MR imaging characteristics of both primary intrasellar pituitary tumor and metastatic lesions on T1- and T2-weighted images, noting similar signal intensities. These MR imaging findings reflect the similar vascularity and stroma of the primary pituitary tumor and the metastatic lesion. Muhr, et al., used positron emission tomography and dopamine D2–receptor binding to assess tumor amino acid metabolism (11C-labeled L-methionine) in vivo in a patient with multiple intracranial metastases of a PRL-producing pituitary carcinoma. They demonstrated a high level of dopamine D2–receptor binding and a high amino acid metabolism within the tumor. After institution of bromocriptine injections, repeated PET imaging was performed and demonstrated decreases in tumor D2–receptor binding and amino acid metabolism. These findings correlated with a decrease in circulating serum PRL. This illustrates PET imaging as a possible in vivo tool in tracking patients with aggressive prolactinomas.

Radionuclide scintigraphy performed using indium 111–octreotide can detect active neuroendocrine neoplasias with somatostatin receptors, such as pituitary tumors, islet cell tumors, medullary thyroid carcinomas, pheochromocytomas, carcinoids, and parangangiomas. Octreotide is an eight-chain amino acid analog of somatostatin that, when combined with a radioactive isotope, is used for radionuclide scintigraphy. This novel imaging examination allows for the identification of distant pituitary metastasis.

HISTOPATHOLOGY OF PITUITARY CARCINOMAS

Histological Analysis

The histological and cytological characteristics of pituitary carcinomas vary from bland and monotonous to...
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frankly malignant. Fifty percent of primary tumors and the majority of metastases display nuclear pleomorphism and/or hyperchromasia. An increased number of mitotic figures are seen in pituitary carcinomas (Fig. 1); however, the mitotic index for all pituitary tumors (such as pituitary adenomas, invasive adenomas, and pituitary carcinomas) is low with a mean mitotic index of only 0.016%. Therefore, mitotic figures do not necessarily provide an indication of a tumor’s invasive potential. Histologically, features of frank pituitary malignancy appear suspicious for a metastatic disease from a systemic organ, with breast being the most common. Immunohistochemically these tumors exhibit staining patterns similar to that of the primary intrasellar adenoma. In general, as pituitary tumors become more aggressive they exhibit a trend for increased microvascular density and increased MIB-1 (Ki-67) and p53 staining (Fig. 2).

Microvascular Density

Vidal, et al., evaluated microvascular density in 157 pituitary tumors and seven pituitary carcinomas by using the vascular endothelial marker CD-34 antigen. This study showed a trend toward increased vascularity with more invasive tumors, but the trend did not reach statistical significance. No correlation was found between the MIB-1 LI and microvessel density.

Immunohistochemical Analysis

Typical antibodies used to recognize pituitary hormones include those to ACTH, PRL, GH, FSH, LH, TSH, and the α-subunit of the glycoprotein hormones (LH, FSH, and TSH). Other markers aiding in the diagnosis of pituitary origin tumors are cytokeratin, epithelial membrane antigen, glial fibrillary acidic protein, and chromogranin A.

Electron Microscopy

An ultrastructural study of 11 pituitary carcinomas showed that metastatic lesions maintain some of their basic ultrastructural markers. Ultrastructural investigation of pituitary carcinomas confirms their endocrine nature and, in most but not all cases, reveals their functional differentiation. In most cases, significant cellular atypia and mitotic activity were observed. A unique feature in two ACTH-producing carcinomas was the variable admixture of a smooth endoplasmic reticulum with intermediate (cytokeratin) filaments. In two cases, both involving PRL-producing carcinomas, the cell type comprising the tumor...
could not be identified on an ultrastructural basis alone. Indeed, the distinction between pituitary adenomas and carcinomas cannot be made on ultrastructural analysis alone.95

PROLIFERATIVE MARKERS

Pituitary carcinomas show an increased mitotic LI, compared with that of the intrasellar pituitary tumor. These mitotic LIs include both the MIB-1 LI and the BrdU LI (Table 1).

The MIB-1 (Ki-67) LI

Expression of the Ki-67 antigen occurs during the S, M, and G phases of the cell cycle and is demonstrated using the MIB-1 antibody. The resulting LI quantifies the proportion of mitotically active cells. Shibuya, et al.,101 stained 65 pituitary masses, revealing that primary pituitary tumors had a lower amount of Ki-67 (0.8%) when compared with recurrent tumors (3.6%, p < 0.005). In pituitary tumors MIB-1 labeling has produced consistently higher MIB-1 LIs in higher-grade tumors. The MIB-1 LIs for invasive tumors range from 1.7 to 4.66% for invasive adenoma, compared with those for pituitary carcinomas, which range from 7.8 to 11.91% (Table 1).26,80,109

The BrdU LI

The BrdU LI is used to identify only those cells in the DNA synthesis phase (S phase). The BrdU is administered 1 hour before surgery via an intravenous infusion (200 mg/m²).71 Excised tumor specimens are fixed in 70% ethanol and stained using the indirect peroxidase method in which anti–BrdU monoclonal antibody is used as the first antibody.71 This provides a more accurate index of DNA synthesis than Ki-67 labeling, and BrdU labeling typically yields lower values, reflecting its greater specificity. One study of 65 tumors showed a significant difference between the BrdU LI of primary and recurrent tumors (0.3% compared with 1.4%, p < 0.005).101 Nagashima, et al.,71 performed BrdU labeling on 21 pituitary tumors and found less than a 1% LI for all except two cases of Nelson syndrome, which exhibited LIs greater than 1%. No statistically significant association has been found between the BrdU LI and clinical findings of malignancy.39,71

MOLECULAR PATHOGENESIS AND CYTOGENETICS

The molecular pathogenesis of pituitary carcinoma and other pituitary tumors is being determined. In particular, the Gsp gene may play an important role in approximately 40% of GH-producing tumors and the Ras oncogene may play a role in anaplastic progression. The MEN-1 gene, which has been cloned, is associated with familial adenomas.84 The importance of the Gsp and MEN-1 genes in the evolution of pituitary carcinomas still remains to be elucidated.
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Presence of the p53 Gene

Immunohistochemical staining studies of p53 gene expression in pituitary carcinomas, as opposed to invasive and noninvasive pituitary tumors, show a marked increase in staining as the pituitary lesion progresses to a pituitary carcinoma (Table 1).\(^{10}\) One quantitative immunohistochemical analysis of p53 expression in pituitary tumors demonstrated labeling in 0% of noninvasive tumors, 15.2% of invasive tumors, and 100% of metastatic lesions.\(^{10}\) Another study of four ACTH-secreting pituitary carcinomas showed progressively stronger staining of p53 in metastatic lesions, with a mean LI in the metastasis group of 49.9% compared with 37.3% in the primary pituitary tumor group.\(^{26}\) Kumar, et al.,\(^{50}\) reported a case of metastatic pituitary tumor in which there was an absence of p53.

Genomic Instability—Gains of Chromosomes 5, 7p, and 14q and Losses of Chromosomes 1p, 3p, 10q, 11q, and 22q

Rickert, et al.,\(^{87}\) studied four metastatic pituitary carcinomas by using comparative genomic hybridization. Chromosomal gains were found in all four metastatic carcinomas. Overall, metastatic pituitary carcinomas were found to have a mean of 8.3 chromosomal imbalances per tumor (7 gains compared with 1.3 losses): 10 in metastatic PRL-producing carcinoma (7.5 gains compared with 2.5 losses) and 6.5 in metastatic ACTH-producing carcinoma (6.5 gains compared with 0 losses). The most common changes were gains of chromosome 5, 7p, and 14q (in three tumors each). High-level gains were found on 13q22 and 14q (two cases each) and on 1q, 3p, 7, 8, 9p, and 21q (one case each). Bates, et al.,\(^{6}\) genetically analyzed a metastatic ACTH-producing pituitary carcinoma and compared it with a previous sellar recurrence from the same patient, finding a loss of heterozygosity at loci on autosomes 1p, 3p, 10q26, 11q13, and 22q12. Genetic analysis of invasive masses and pituitary carcinomas may enable better prediction of those tumors associated with a poor prognosis.

The H-ras Gene Point Mutations

Pei, et al.,\(^{78}\) studied the molecular mechanisms of pituitary tumorigenesis by using polymerase chain reaction single-stranded conformational polymorphism with DNA sequencing to identify H-ras point mutations. Point mutations of H-ras were identified in three distant metastatic pituitary tumors, but not in their respective primary pituitary carcinomas or in six invasive adenomas. Two of the mutations included a guanine-to-cytosine substitution at codon 12 and a guanine-to-adenine substitution at codon 18, resulting in a glycine-to-arginine and an alanine-to-threonine change at these amino acids, respectively. A third mutation involved a single base-pair (adenine) deletion in codon 3 of H-ras, which causes a frame shift, resulting in a termination signal at codon 19. Point mutations of the H-ras gene may be important in the formation and/or growth of pituitary metastases.\(^{78}\)

Loss of Dopamine D-2 Receptors in a Malignant Prolactinoma

Winkelmann, et al.,\(^{119}\) studied the presence of D-2 receptors at the messenger RNA and protein level, in a patient whose PRL-producing macroadenoma eventually progressed to a pituitary carcinoma. By comparing tumor specimens obtained at neurosurgical operations with those obtained postmortem, the authors were able to show the presence of the D-2 receptor messenger RNA in all specimens, but the absence of D-2 receptor protein from the metastatic pituitary lesions. This indicates a posttranscriptional mechanism by which malignant pituitary tumors develop a resistance to dopamine.\(^{119}\)

Telomerase Activity and Cellular Immortality

The telomerase activity responsible for cellular immortality may participate in the development of human cancers. Telomerase is a multisubunit ribonucleoprotein composed of at least three components: hTERT, hTERC, and TEP1. In a single case of PRL-producing pituitary carcinoma Harada, et al.,\(^{33}\) showed that the metastatic tumor cells had acquired immortality by demonstrating an increase in telomerase activity and hTERT expression.

Expression and Gene Amplification of HER-2/neu

The HER-2/neu protein is a protooncogene located on chromosome 17q that encodes a 185-kDa transmembrane tyrosine kinase receptor belonging to the epidermal growth factor receptor family. Studies have demonstrated overexpression of HER-2/neu in pituitary tumors.\(^{90}\) Roncaroli, et al.,\(^{90}\) analyzed two cases of gonadotropin pituitary carcinoma for HER-2/neu with immunohistochemical staining, fluorescence in situ hybridization, and chromogenic in situ hybridization. Results of the HER-2/neu analysis showed low-level amplification in pituitary recurrence and metastasis, indicating an association between HER-2/neu and more aggressive pituitary tumors.\(^{90}\)

Retinoblastoma Gene

Involvement of the Rb gene has been suggested based on the frequent occurrence of pituitary carcinomas in studies of mice with heterozygous deletions of the Rb gene.\(^{34,118}\) Hinton, et al.,\(^{36}\) described a patient with two adjacent but histologically discrete pituitary tumors, one a benign ACTH-positive adenoma and the other an ACTH-positive carcinoma that metastasized. The tumor was found to express the Rb gene, but the carcinoma did not, indicating a loss of Rb expression in the pathogenesis of pituitary carcinomas.\(^{36}\)

GENETIC SUSCEPTIBILITY OF PATIENTS

The MEN-1 gene predisposes patients to pituitary tumors; however, this gene does not appear to increase the risk for developing pituitary carcinomas.

CAUSES OF PITUITARY CARCINOMAS AND PREDICTIVE FACTORS

Several possible causes have been proposed for the pathogenesis of pituitary carcinomas. These hypotheses include the following: 1) consequence of previous irradiation in the treatment of a pituitary tumor; 2) microscopic tumor seeding from a previous pituitary surgery; 3) malignant progression of a pituitary tumor; and 4) de novo car-
cinoma. Brada, et al., analyzed 334 patients with pituitary tumors who were treated with surgery and radiotherapy (median dose 45 Gy) and observed for a total of 3760 patient years. In five of these patients, a second brain tumor developed: two astrocytomas, two meningiomas, and one meningeal sarcoma. No case of malignant transformation of the pituitary tumor was reported. Tumor seeding from opening of the subarachnoid space during previous pituitary surgery has been suggested, but no definitive correlation has yet been made. Many authors favor a progression of an adenoma-to-carcinoma sequence, based on their laboratory observations of similar histological findings, molecular markers, and result of a loss-of-heterozygosity analysis between pituitary tumors and metastases. Nevertheless, in a recent case report the authors described a genetic analysis in which the primary and metastatic pituitary lesions were distinct clones, indicating either a de novo pituitary tumorigenesis or a separate clonal expansion from the original tumor. There are several long-term survivors of pituitary carcinoma, however, no identifiable factors have been noted to correlate with increased survival.

TREATMENT

Treatment options for pituitary carcinoma include resection, dopamine agonists (for PRL-producing tumors), somatostatin analogs (for GH-producing tumors), radiotherapy, and chemotherapy. These treatments are palliative only and the mean survival time for these patients ranges from 2 to 2.4 years, although several reports of long-term survivors have been published.

Dopamine Agonists

The dopamine agonists bromocriptine, pergolide, quinagolide, and cabergoline offer only palliation in the treatment of metastatic PRL-producing tumors. Initially, these agonists induce decreases in serum PRL levels and retard tumor growth. Unfortunately, these pituitary carcinomas will typically “escape” dopamine suppression and PRL levels may rise as high as 20,000 ng/ml (normal PRL levels 4–30 ng/ml in female patients and 4–23 ng/ml in male patients).

Somatostatin Analogs

The medical approach to patients with GH-secreting or clinically nonfunctioning pituitary tumor has made considerable progress thanks to the use of new somatostatin analogs such as octreotide. These agents were first used to treat acromegaly in the mid-1980s and numerous studies have shown a reduction in GH concentration in more than 90% of patients with this disorder. Good results were also obtained using slow-release analog treatment for TSH-secreting tumors, whereas the therapeutic efficacy of these peptides for clinically nonfunctioning tumors remains controversial. Treatment with somatostatin analogs improves the patient’s symptoms, normalizes hormone secretion, and in some cases may induce a reduction in the volume of the pituitary tumors. Scintigraphy with octreotide may be useful in selecting patients who respond to this form of treatment.

Radiation Therapy

Radiation treatment directed to the sella and to distant metastases is a common adjuvant therapy used after pituitary resection. Unfortunately, it does not appear to change disease outcome. The sella and the parasellar region are initially treated by fractionated, limited-field irradiation, with total radiation doses between 45 and 55 Gy. Whole-brain radiation therapy is reserved for intracranial metastasis. Recently, stereotactic radiosurgery (gamma knife surgery) was used in the treatment of a PRL-secreting carcinoma, although no mention of benefit was made in that report. The radiation regimen used in an ACTH-secreting pituitary carcinoma harbored by a long-term survivor was initial radiotherapy to the sella turcica (56 Gy), followed by whole-brain radiotherapy (24 Gy) after the discovery of craniospinal metastasis.

Chemotherapy Protocols

To date, a number of different chemotherapy protocols have been used with disappointing results. The agents used in these protocols have included carmustine, hydroxyurea, 5-fluorouracil, and dexamethasone (to suppress ACTH-producing tumors); bromocriptine and cabergoline (to suppress PRL-producing tumors); and the St. Bart protocol, consisting of 5-fluorouracil with folinic acid and α-interferon (for neuroendocrine tumors).

References

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