Corticotroph carcinoma of the pituitary: a clinicopathological study

Report of four cases

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Pituitary carcinomas are exceedingly rare tumors defined as primary adenohypophyseal neoplasms that have undergone cerebrospinal or systemic metastasis. Their prevalence, based on a review of more than 3000 adenohypophyseal tumors resected at the Mayo Clinic, is 0.2%. Fewer than 100 cases appear in the English literature and, thus, little is known about the clinicopathological or molecular biological features of these lesions. We report four cases of corticotroph (ACTH-producing cell) carcinomas. All tumors were endocrinologically functional, with three associated with Nelson syndrome and one with Cushing disease. The cases were analyzed by reviewing clinical and endocrinological data, imaging, imaging techniques, and determining of mitotic activity. The DNA content of the specimens was assessed using Feulgen stain. Reactivities were quantified by digital image analysis. Primary/recurrent lesions and metastatic tumors differed according to their respective mean mitotic indices (1.2/10 hpf compared with 4.3/10 hpf), MIB-1 labeling (1.7% compared with 8%), p53 staining (37.3% compared with 49.9%), and p27 labeling (48% compared with 25%). Cyclin D1 immunoreactivity provided no prognostically significant information. Glucocorticoid receptor mRNA was detected in all cases. Results of a ploidy analysis were variable and nonprognostic. In keeping with the 2000 World Health Organization classification of endocrine neoplasms, our findings support the concept that primary tumors that exhibit mitotic activity, an increased (> 3%) MIB-1 labeling index, and/or p53 immunoreactivity should be termed “atypical adenomas” to denote their aggressive potential and the possibility of future malignant transformation.
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ernous sinus. During transsphenoidal surgery, a gross total resection was achieved.

Postoperatively, the patient’s ACTH levels decreased to within normal limits. Although she enjoyed health for months, an exacerbation of her Cushing disease later occurred with development of marked skin hyperpigmentation. Shortly after she underwent a bilateral adrenalectomy in mid-1992, the patient displayed a sixth nerve palsy and diplopia. Both CT and MR images again revealed a pituitary mass with extension into the right cavernous sinus. Radiotherapy to the patient’s skull base (54 Gy) resulted in resolution of the diplopia for a period of 2 years. Nonetheless, the tumor grew and extended into the right cavernous sinus and Meckel cave. In mid-1994, minimal diplopia was again noted. Stereotactic gamma knife surgery (15 Gy delivered to the tumor rim and 30 Gy to its center) was undertaken in June 1995. Although the patient’s diplopia again resolved, an MR image obtained 6 months later revealed residual tumor encasing and narrowing of the intracranial carotid artery.

Within a year and despite no apparent tumor growth, the patient’s blood ACTH levels became markedly elevated (3000 pg/ml). In early 1997, abdominal pain prompted an emergency ultrasonography study that revealed not only cholecystitis but also three liver nodules. During cholecystectomy, a liver biopsy disclosed metastatic pituitary carcinoma. Postoperatively, the patient’s blood ACTH level rose to 33,000 pg/ml. An aggressive but palliative resection of the liver metastases was undertaken. Resected segment 2 and segments 6 and 7 contained two metastases measuring 3.5 × 5.2 cm and 2.3 × 1.2 cm, respectively.

Shortly after the patient’s postoperative recovery, diplopia was again noted in her right lateral gaze. It progressed despite treatment with octreotide (150 mg three times per day). The blood ACTH level was again markedly elevated (3000 pg/ml). An eight-cycle chemotherapy regimen, which included cyclophosphamide, vincristine, and dacarbazine, effectively lowered the ACTH level to 450 pg/ml. As of late 1998, the patient remained alive without progression of cranial or liver disease according to MR imaging. Recent measurements of ACTH levels remain stable at 310 pg/ml.

Case 2

In 1985, this 35-year-old woman began to experience fatigue, easy bruisability, weight gain, amenorrhea, and hirsutism, all within a period of 1.5 years. An elevated ACTH level of 80 pg/ml (normal 0–60 pg/ml) was detected and an intrasellar pituitary macroadenoma (1.3 cm in diameter) was demonstrated on CT scans. In April 1987, the patient underwent transsphenoidal adenectomy. Postoperatively, the patient’s blood cortisol levels fell to 4 μg/dl.

The patient fared well for 3 years before signs of Cushing disease again became evident. In 1992, her blood ACTH level was 110 pg/ml and mild hypertension was noted. An MR image revealed small foci of recurrent tumor abutting both cavernous sinuses. A transsphenoidal resection succeeded in removing all visible tumor. Immunostaining of all specimens again confirmed the diagnosis of corticotroph adenoma. Following surgery, the patient’s ACTH level decreased from 290 to 21 pg/ml. Due to persistent hypercortisolemia, however, a bilateral adrenalectomy was performed that same year. In addition, postoperative radiation therapy was administered (50.4 Gy in 28 fractions).

From 1993 to 1995, the patient’s blood ACTH levels fluctuated from 20 to 140 pg/ml. In September 1995, it increased to 1110 pg/ml, despite the fact that results of CT scans were nondiagnostic. In June 1996, after onset of severe headaches, the patient became somnolent and abruptly dysarthric. An MR image revealed a 5-cm mass in the right posterior fossa that was compressing the cervicomedullary junction. The woman’s blood ACTH had now risen to 3000 pg/ml. An emergency right-sided suboccipital craniotomy was performed and a diagnosis of pituitary carcinoma was confirmed.

Postoperative images revealed two additional, smaller posterior fossa lesions suggestive of metastases. Standard radiotherapy (40 Gy) was administered and followed by a booster dose (10 Gy). The patient’s blood ACTH levels steadily increased (3000 pg/ml in 1996, 4915 pg/ml in March 1999, and 9605 pg/ml in August 1999). One month later, the patient experienced progressive bowel and bladder dysfunction. An MR image revealed multiple intraspinal metastases. In January 2000, the patient succumbed to carcinomatous meningitis, a diagnosis confirmed at autopsy.

Case 3

In 1987, this 63-year-old woman underwent a bilateral adrenalectomy when signs and symptoms of Cushing disease had become apparent, but neuroimaging had revealed no pituitary tumor. Preoperative petrosal sinus sampling was also unrevealing. In 1990, she was found to have a large, invasive sellar tumor. A transsphenoidal hypophysectomy was performed and the diagnosis of ACTH adenoma was confirmed. Eight years later she presented with memory loss and dysphasia. An MR image of the head demonstrated multiple enhancing extraaxial lesions in addition to one large (7 × 5 × 4–cm) temporoparietal tumor associated with mass effect and uncal herniation. In addition, residual tumor in the cavernous sinus was seen to encase the right internal carotid artery. Debunking of the dural lesion was undertaken in August 1999 followed by radiation therapy (50 Gy).

Case 4

This woman first presented in 1984 at 17 years of age with a clinically nonfunctional pituitary macroadenoma. It was treated by transethmoidal resection. A postoperative MR image indicated the presence of residual tumor adjacent to the left internal carotid artery. The patient’s subsequent clinical course was marked by multiple episodes of local tumor recurrence, which required surgical debulking in 1990, 1997, and 1998. During the first surgery for recurrent disease, it was apparent that a complete resection was not possible. Postoperatively, the patient underwent a course of radiotherapy (50 Gy).

Biochemical evidence and the clinical stigmata of Cushing disease did not develop until 1995, 11 years after the patient’s initial presentation. Shortly thereafter, a bone scan revealed multiple osseous lesions; the sites of involvement included the sacrum, T-10 vertebral body, left hip, and ribs. A CT-guided biopsy of the sacral lesion demonstrated a non–small cell carcinoma, which was later shown to be
ACTH immunopositive. Despite extensive clinical investigation, no other primary tumor was identified. Palliative radiotherapy was delivered to the various osseous sites. Further debulking of the sellar tumor was performed in 1997. One year later, an additional resection was prompted by the patient's visual deterioration. Two years after the first indication of a metastasis, the patient remains alive with residual sellar and metastatic disease.

**Materials and Methods**

The tissue specimens from the four patients in this report were obtained from the consultation files of three of the authors (B.W.S., P.C.B., and P.R.). Two patients experienced craniospinal and dural metastasis (Cases 2 and 3), whereas in the others there was systemic spread to the liver (Case 1) or bone (Case 4). Three patients presented with Cushing disease and one patient exhibited Cushing disease only after an 11-year period of functional silence. Three patients (Cases 1, 2, and 3) displayed Nelson syndrome when, due to recurrence of their adenomas or inability to detect the sellar lesion, they underwent bilateral adrenalectomy. Multiple specimens were examined in each case. All tumors were fixed in buffered formalin, routinely

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**Fig. 1.** Photomicrographs. A and B: Case 2. Specimens of metastasis displaying only minor atypia in the form of prominent nucleoli. Mitotic activity is scant (arrow). C and D: Case 1. A significant increase in atypia can be observed between the primary lesion which was distinguishable from a benign pituitary adenoma (C), and the histologically malignant metastasis, which featured abundant mitotic activity (D, arrows). H & E, original magnifications × 200 (A), × 400 (B and C), and × 100 (D).
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processed, embedded in paraffin, and sectioned at 5-μm widths. Sections stained with hematoxylin and eosin were assessed for cytological atypia and mitotic activity, expressed as number of mitoses per 10 hpf (magnification × 400). During immunostaining, performed using the avidin–biotin peroxidase complex method, 18 we applied a battery of antisera to pituitary hormones (growth hormone, prolactin, ACTH, follicle-stimulating hormone, luteinizing hormone, thyrotropin, and α subunit). Sources and dilutions of these antisera as well as details of control methods were previously published. 24, 26 All specimens were stained to detect expression of Ki-67 (MIB-1 monoclonal antibody, dilution 1:100), p53 (monoclonal antibody, dilution 1:100), p27 (monoclonal antibody, dilution 1:1000), cyclins D1, D2, and D3 (monoclonal antibodies, dilution 1:500). In addition, all specimens were stained for the presence of glucocorticoid receptor mRNA by using a riboprobe generated by reverse transcription–polymerase chain reaction and Topo II subcloning. In all instances, positive and negative control agents were applied and reacted appropriately.

Nuclear LIs of MIB-1 antigen, p53, and p27 were quantified with the aid of an automated cell analysis system by using a method previously described. 23 Approximately 15 to 20 hpf were analyzed per specimen. Labeling indices were expressed as the percentage of nuclear staining. The same analysis system was applied to Feulgen-stained sections for determination of DNA ploidy. 54

For ultrastructural study, 1 to 2 mm of tissue was fixed in 2.5% glutaraldehyde, postfixed in 1% osmium tetroxide, dehydrated in a graded series of ethanol solutions, processed through propylene oxide, and embedded in an Epon–Araldite mixture. After they were stained with uranyl acetate and lead citrate, ultrathin sections were examined with the aid of a transmission electron microscope.

Sources of Supplies and Equipment

The antibodies used in this study included MIB-1 obtained from Immunotech Inc. (Marseilles, France), p53 antibody from Cambridge Biomedical (Norwich, UK), p27 antibody from Transduction Laboratory (Lexington, KY), and cyclins D1, D2, and D3 antibodies from Neomarkers (Fremont, CA). The CAS 200 automated cell analysis system was acquired from Bacus Laboratories (Lombard, IL), and the model 410 LS transmission electron microscope from Philips (Amsterdam, The Netherlands).

Results

As defined by the 2000 WHO classification of endocrine tumors, 55 the primary tumors included one benign adenoma (Case 4) and two atypical adenomas (Cases 1 and 2), that is, tumors featuring prominent nucleoli and occasional mitotic figures (Fig. 1A and B). The primary tumor excised from the patient in Case 3 was not available for assessment. Metastatic lesions were similar to the primary tumor in appearance in only one instance (Case 2), in which the histological characteristics of atypical adenoma were again evident. In the other two cases, a benign adenoma (Case 4) and an atypical adenoma (Case 1) transitioned to histological malignancy (Fig. 1C and D). The principal feature of these metastases was brisk mitotic activity (> 5 mitoses/10 hpf; Table 1). Because nuclear pleomorphism and necrosis are unreliable indicators of malignant behavior, only proliferative activity (mitoses in addition to high MIB-1 LIs) and p53 staining were considered valid in the assessment of atypia and/or histological malignancy.

All tumors, primary and metastatic, were ACTH immunoreactive. The overall immunophenotype of the tumors is summarized in Table 1. The MIB-1 LIs (Table 1) were found to correlate with mitotic activity, being obviously increased in the metastases of histologically malignant lesions (Cases 1 and 4). The same was true of p53 staining, which was moderate in the atypical adenoma-like metastasis (14.5% in Case 2) and marked in the two histologically malignant metastases (35% in Case 1 and 90% in Case 4). No correlation was observed between the histological characteristics of the lesions and p27 or cyclin D1 staining (Fig. 2).

Ultrastructural features indicative of corticotrophic differentiation were noted in the two tumors under investigation (Cases 1 and 4). These included cytoplasmic bundles of intermediate filaments (Fig. 3) and irregular secretory granules varying in electron density (Fig. 4). In addition, the tumor in Case 4 exhibited perinuclear smooth endoplasmic reticulum, a feature not heretofore described (Fig. 4).

Discussion

Predicting the biological behavior of pituitary adenomas remains an elusive goal. Fully 35% of these tumors have been recognized radiographically or grossly as invading perisellar structures. 52 It has been well documented that the frequency of invasion varies with tumor subtype and that endocrinologically functional tumors are more often invasive. 7,52 Pituitary carcinomas, defined as adenohypophyseal tumors that have undergone craniospinal or distant metastasis, 35 almost always present as invasive macroadenomas. 24 Although in theory they might arise from any of the well-known adenohypophyseal cell types, in the largest re-

| Table 1 Summary of findings among four corticotroph carcinomas* |
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| Case No. | Year at Surgery | Lesion Resected at Surgery | MIB-1 LI (%) | p53 (%) | Cyclin D1 p27 (%) | Mitotic Index† |
| 1 | 1991 | primary tumor | D | 1.43 | 23.86 | 24.49 | 1.89 | 2 |
| 2 | 1997 | liver metastasis | D | 10.28 | 34.92 | 8.99 | 0.29 | 7 |
| 2 | 1991 | primary tumor | D | 0.00 | 1.39 | 57.34 | 31.68 | 2 |
| 1992 | recurrence of primary tumor | D | 1.54 | 1.25 | 52.89 | 24.8 | 2 |
| 1996 | posterior fossa metastasis | A | 2.54 | 14.51 | 19.81 | 1.37 | 2 |
| 3 | 1999 | dural metastasis | A | 8.24 | 60.09 | 34.66 | 0.5 | 5 |
| 4 | 1984 | primary tumor | A | 3.57 | 77.10 | 54.73 | 2.25 | 0 |
| 1990 | recurrence of primary tumor | A | 1.94 | 82.92 | NR | NR | 0 |
| 1997 | recurrence of primary tumor | A | 11.06 | 90.04 | 35.22 | 33.67 | 3 |

* In all cases, the glucocorticoid receptor mRNA was present. Abbreviations: A = aneuploid; D = diploid; NR = no reaction.
† Number of mitoses per 10 hpf (magnification × 400).
ported series ACTH- and prolactin-secreting carcinomas each accounted for 46% of all cases. It is noteworthy that the older literature is misleading with respect to the frequency of carcinoma subtypes: because prolactin was not measured or immunohistochemically demonstrated before the 1970s, a significant number of prolactin-producing cell carcinomas no doubt were unrecognized.

Among ACTH-producing adenomas, 78% are noninvasive microadenomas, whereas 21% (mostly macroadenomas) are grossly invasive of perisellar structures. Particularly aggressive are those tumors occurring in the setting of Nelson syndrome. Although they represent less than 1% of all pituitary adenomas, carcinomas associated with Nelson syndrome accounted for three of the four tumors included in this study and four of the seven ACTH-producing cell carcinomas in the series of Pernicone, et al. Also noted for their high frequency of invasion (approximately 80%) are the two endocrinologically nonfunctional forms of ACTH-producing adenoma, the so-called silent corticotroph adenomas of subtypes I and II.

Fig. 2. Photomicrographs demonstrating that staining for cyclin D1 is mainly cytoplasmic (A, Case 1), whereas staining for cyclin D3 is focal and primarily nuclear (B, Case 2). In all cases, in situ hybridization for glucocorticoid receptor mRNA displayed a strong cytoplasmic signal (C, Case 2). Original magnifications × 100 (A), × 400 (B), and × 200 (C).

Fig. 3. Case 1. Electron micrograph showing a corticotroph carcinoma as hepatic metastasis. The tumor cells, one in mitosis, display prominent corticotroph characteristics. The cytokeratin microfilaments are present as small, fine bundles. Original magnification × 6900.
On balance, the clinical aspects of the four cases that we have reported parallel those of the 15 cases of pituitary carcinomas reported by Pernicone, et al. In that larger series, all patients presented with tumors that were operatively and/or radiographically shown to be invasive, but none presented with a metastasis. In our cases, the mean latency period between diagnosis of the primary pituitary tumor and discovery of the metastasis was 9.3 years (range 6–13 years), a figure comparable to the mean 9.5-year latency observed among the seven ACTH-producing carcinomas reported by Pernicone, et al. Despite variation, once metastases occur, the long-term survival of patients is uniformly poor. No doubt this is due to the fact that no uniform approach to treatment has been developed. In the report issued by Pernicone, et al., fully 80% (12 of 15 total) of all patients with pituitary carcinomas died of metastatic disease within 1.5 years.

With respect to our series, routine light microscopy revealed a trend toward increased mitotic activity in the transition from localized sellar disease to metastasis. Although all specimens in this report were found to contain nuclear atypia, one cannot rely on the conventional cytological hallmarks of atypia to predict tumor behavior. Indeed both adenomas and carcinomas may demonstrate cellular pleomorphism and/or marked nuclear abnormalities. To complicate matters further, some pituitary carcinomas display neither characteristic. In our series, the mitotic index averaged 1.2/10 hpf in primary/recurrent tumor specimens and 4.3/10 hpf in metastatic deposits. This is consistent with the recent observation by Thapar, et al., that mitotic activity is significantly increased in pituitary carcinomas, compared with noninvasive and invasive adenomas. Thus, finding more than the rare mitotic figure in a tumor suggests aggressive potential, because mitoses are uncommon in pituitary adenomas, increase in frequency in invasive tumors, and are often readily apparent in carcinomas.

Investigators continue the search for molecular markers of prognostic value. Some have studied MIB-1, p53, and p27 immunolabeling in relation to adenoma invasive-ness. Another group has examined D-type cyclin expression in pituitary tissues in experimental animals. To our knowledge, none has assessed these markers in the evolution of invasive adenoma to pituitary carcinoma.

The immunohistochemical marker of cell proliferation that we selected, MIB-1, is expressed in all replicating cells. In the recent systematic study conducted by Thapar, et al., mean MIB-1 LIs were found to be increased (> 3%) in invasive adenomas and increased still higher (11.9%) in pituitary carcinomas. Similarly, in the series conducted by Pernicone, et al., MIB-1 LIs were observed to increase from a mean of 11% in primary sellar tumors to 16% in metastases. The same was true in our small series, wherein progressive elevation in MIB-1 LIs was a definite trend; the mean LI in primary/recurrent tumors was 1.7% and that in metastases was 8%. It is noteworthy that, in one instance (Case 2), the MIB-1 LI in the metastatic lesion was only 2.5%. If this was not an artifact or the result of a treatment effect, it suggests that occasional carcinomas may have LIs even lower than the published 3% threshold for invasive tumors. In any event, we recommend using LIs as loose guides rather than establishing a rigid threshold corresponding to malignancy.

As a member of the Kip family of cyclin–cdk complex cell cycle inhibitors, p27 is known to induce termination of cell growth. Not surprisingly, its deficiency has been shown
to correlate with tumor development in experimental animals. Although authors of a recent study of p27 expression and its relation to pituitary tumor invasiveness found no significant correlation, in our study the mean p27 LI was 48% in primary/recurrent tumors, compared with 25% in metastatic tumors. Although we observed a consistent decrease in p27 labeling between the primary/recurrent group and the metastatic tumor group, there does not seem to be a cutoff level on which to distinguish reliably primary lesions (range 24.49–57.24) from metastatic tumors (range 8.99–35.22). Perhaps a larger study of premetastatic and disseminated tumors will establish a threshold value.

Overexpression of the oncprotein p53 is observed in a number of tumors, including carcinomas of the endometrium, lung, esophagus, stomach, liver, and urinary bladder. One quantitative immunohistochemical study of p53 expression in pituitary tumors demonstrated labeling in 0% of noninvasive adenomas, 15% of invasive adenomas, and 100% of metastases. Our study, like that of Pernicone, et al., supports the finding of universal, often strong p53 immunoreactivity in metastases. The mean p53 LI for our metastasis group was 49.9% (range 14.5–90.04%), compared with strong staining of 37.3% of cells (range 1.25–82.92%) in the primary/recurrent tumor group. It is noteworthy that what appears to be a rather narrow difference in means is due to an extraordinarily high p53 LI in the primary tumor of one case (Table 1, Case 4), wherein values ranged from a high of 77% in primary tumor specimens to 90% in a postmetastasis sellar recurrence (Fig. 4). Other cases in our study showed less robust p53 staining.

The D-type cyclins are expressed in normal pituitary tissue, with the D1 and D2 types being most often represented. According to a previous report, D-type cyclins have been found to vary with cell type, with the ACTH-producing cells containing the lowest levels. Because cyclin D1 is thought to interact with p27 by forming cytoplasmic complexes, it has been postulated that an elevation of D1 may correlate with aggressive behavior. Stains for cyclins D1, D2, and D3 were applied to all specimens in our study; preparations displayed uniform D1 cytoplasmic staining in each, lack of D2 staining in all cases, and a nuclear pattern of D3 staining that varied from case to case (Fig. 2B). Although D3 expression generally decreased as primary, sellar tumors metastasized, the decline was not striking. The exceptionally high value found in the 1997 specimen obtained in Case 4 is remarkable and perhaps a reflection of previous radiation therapy.

Our study of DNA ploidy, in which we used the Feulgen method and digital image analysis, revealed that the tumor in Case 1 remained diploid throughout its evolution and the tumors in Cases 3 and 4 remained aneuploid. Only the tumor in Case 2 demonstrated transition from diploidy to aneuploidy with metastasis. It is noteworthy that the authors of one previous study found aneuploidy to be common in cases of pituitary adenomas. That being the case, our limited findings and those of Pernicone, et al., suggest that ploidy determination is of little prognostic significance, particularly with reference to the prediction of metastatic behavior.

Any study of pituitary carcinomas must address the issue of the nature of the primary sellar lesion, that is, specifically whether it represents an adenoma that undergoes progressive changes to attain metastatic capacity, or a carcinoma de novo that is simply held in check by various surveillance mechanisms during its latency period. At present, this question cannot be firmly answered, but preliminary results from our laboratories, the present study, and investigations of others favor a progressive adenoma-to-carcinoma sequence.

We believe that the definition of pituitary carcinoma serves to hinder diagnostic and therapeutic progress. The current definition of pituitary carcinoma rests on documenting the presence of a discontinuous spread of tumor within the neuraxis or to systemic sites. Although this approach is pragmatic, it is unsatisfactory because it detracts from efforts to understand the nature of the primary sellar lesion and retards aggressive treatment until late in the course of the disease, a time when therapies are prone to fail and survival is short. Indeed, the prognosis of patients with pituitary carcinoma is poor, with their mean length of survival being only 1.9 years once metastases are demonstrated. Efforts have been made to identify pathological parameters predictive of which neoplasms will behave in a malignant (metastasizing) fashion. These are reflected in the 2000 WHO classification of pituitary tumors, which defines as atypical those adenohypophysyal tumors exhibiting all or various combinations of increased mitotic activity, elevation in the MIB-1 LI (>3%), and p53 immunoreactivity. These findings are said to warrant the atypical designation and should prompt careful reassessment of a case as well as the long-term follow-up plan. The results of our study certainly support this conclusion.

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