Cerebellar metastasis from a prolactinoma during treatment with bromocriptine

Case report

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A 31-year-old woman developed a cerebellar metastasis from an invasive prolactin-secreting pituitary adenoma while undergoing treatment with bromocriptine. The metastatic tumor was totally excised. Metastatic spread of pituitary tumors within the central nervous system is reviewed briefly.

KEY WORDS • pituitary tumor • prolactinoma • bromocriptine • metastatic tumor

Pituitary adenomas characteristically grow as a mass that deforms, displaces, and compresses adjacent structures. A minority of these tumors, however, behave in a more aggressive fashion, invading surrounding structures and, rarely, metastasizing to remote areas of the central nervous system (CNS) and to extracranial sites. This case illustrates the clinical and pathological features of a cerebellar metastasis from a prolactin-secreting adenoma. It is notable, in light of recent reports of pituitary tumor regression during bromocriptine therapy, that the patient developed the metastasis while being treated with bromocriptine.

Case Report

This 31-year-old woman failed to resume normal menses after discontinuing use of oral contraceptives in November, 1974. She had taken them for 2½ years. In December, 1974, she noted blurred vision in her right eye. Ophthalmological evaluation revealed decreased visual acuity in the right eye and a bitemporal hemianopsia. Skull x-ray films showed enlargement and erosion of the sella turcica.

She was admitted to the Neurological Surgery Service, University of California, San Francisco, on February 17, 1975, for evaluation. Physical examination revealed no clinical signs of Cushing's disease or acromegaly. There was no galactorrhea. Her visual acuity was 20/200 in the right eye and 20/20 in the left; she had a bitemporal hemianopsia, and the fundi were normal. The neurological examination showed no other abnormality. The general laboratory evaluation was unremarkable. Endocrinological testing revealed panhypopituitarism; an assay for prolactin was not available at that time. Polytomography of the sella turcica revealed deepening and erosion of the floor. Pneumoencephalography demonstrated suprasellar extension of an intrasellar mass and compression of the anterior third ventricle.

On February 20, 1975, the patient underwent a transsphenoidal procedure for removal of a pituitary tumor. Resection was incomplete because the tumor invaded the right cavernous sinus, but decompression of the right optic nerve and chiasm was achieved. Histological examination showed that the tumor was composed of polygonal cells with nongranular cytoplasm (Fig. 1). The nuclei contained evenly distributed chromatin. Mild nuclear pleomorphism was apparent; no mitotic figures were seen. A diagnosis of pituitary adenoma was made.

The postoperative course was complicated only by diabetes insipidus, which was controlled by Diapid nasal spray (lypressin) four times daily. Hormone replacement therapy consisted of levothyroxine (0.1
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mg once daily) and hydrocortisone (10 mg three times daily). Because of the known presence of residual tumor, radiation therapy (4500 rads, calculated tumor dose) was administered in March and April, 1975. A follow-up evaluation on April 18, 1975, showed that visual acuity in the right eye had improved to 20/25, and that the visual fields were normal. Her serum prolactin level was determined at this time; it was significantly elevated (412 ng/ml; normal range, 2 to 24 ng/ml).

The patient continued on hormone replacement therapy and did well until December, 1978, when she noted right retro-orbital headache and diplopia on left gaze. She developed progressive ptosis of the right eyelid. On February 18, 1979, the patient was readmitted to our service. The general physical examination was again unremarkable. Neurological examination revealed an incomplete right third-nerve palsy with pupillary involvement. Her visual acuity, visual fields, and facial sensation were normal. Laboratory evaluation documented a markedly elevated serum prolactin level (2417 ng/ml). Polytomography of the sella revealed further sellar enlargement and erosion of the right anterior clinoid process. Pneumoencephalography demonstrated slight suprasellar extension of the intrasellar mass. A cranial computerized tomography (CT) scan showed an enhancing intrasellar mass with extension into the right middle cranial fossa (Fig. 2).

On February 23, 1979, a right frontotemporal craniotomy was performed. Tumor filled the right cavernous sinus and extended into the suprasellar cistern. A biopsy specimen was obtained, and as much tumor as possible was resected. The histology of the specimen was similar to that of the previous pituitary tumor specimen. Rare mitotic figures and mild nuclear pleomorphism were apparent. The postoperative course was uneventful, and the patient was discharged receiving levothyroxine (0.15 mg once daily), hydrocortisone (25 mg each morning and 15 mg each evening), and Diapid nasal spray (two to four times daily). Bromocriptine (2.5 mg four times daily) was begun at the time of her discharge and was increased after 2 weeks (to 5 mg four times daily).

A review of the prior course of radiation therapy revealed that the recurrent tumor lay outside the previously irradiated field. A second course of radiation therapy, consisting of 4316 rads to the area of recurrence was given from March 3, 1979, to April 14, 1979. On April 11, 1979, reexamination showed nearly complete resolution of the right third-nerve palsy. Bromocriptine was continued; the serum prolactin level had dropped from the preoperative level of 2417 ng/ml, but it was still well above normal (1253 ng/ml on June 11, 1979).

Fig. 1. Photomicrograph of the pituitary tumor resected in 1975. The appearance is typical of an adenoma. H & E, × 1440.

Fig. 2. Computerized tomography scan through the sellar region after intravenous injection of contrast material. This axial section shows tumor invasion of the right cavernous sinus.
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She had no further neurological or endocrine symptoms until January, 1980, when she noted morning suboccipital headaches and postural light-headedness. Her next follow-up evaluation was in March, 1980. Despite continued treatment with bromocriptine (20 mg daily), her serum prolactin level had risen to 1604 ng/ml. A CT scan revealed that the sellar tumor was unchanged from its February, 1979, appearance; however, the scan showed a large, enhancing, posterior cerebellar mass (Fig. 3). The patient was readmitted on April 6, 1980. Bromocriptine treatment had been discontinued several weeks before her readmission; her serum prolactin level while she was not taking bromocriptine was 5700 ng/ml. The general physical examination was unremarkable. Visual acuity and visual fields were normal. There was no sign of residual third-nerve palsy. The only positive finding on neurological examination was mild truncal ataxia.

The patient underwent exploration of the posterior fossa on April 8, 1980. A well circumscribed, vascular tumor replaced the posterior vermis, extending from the region of the torcular herophili to the foramen magnum. The mass was dissected from the cerebellum and removed intact. The tumor weighed 15.8 gm. Microscopically, sheets of neoplastic cells resembling those of the previous tumor sections were separated by vascular sinusoids (Fig. 4). In contrast to the specimens obtained in 1975 and 1979, the tumor showed increased cellularity, and contained numerous mitotic figures. Electron microscopy demonstrated numerous electron-dense secretory granules within the tumor cells (Fig. 5). Immunofluorescent techniques showed prolactin-specific cytoplasmic staining of tumor cells, establishing that the tumor was a metastatic prolactinoma.

The patient's postoperative recovery was uncomplicated. A postoperative CT scan confirmed complete removal of the posterior fossa tumor; she did not receive further radiation therapy. A CSF specimen obtained by lumbar puncture after operation did not contain tumor cells. Her serum prolactin level fell to 545 ng/ml postoperatively. Bromocriptine therapy was not resumed.

Discussion

The terminology for aggressive pituitary tumors remains controversial. Tumors that invade adjacent structures and show the histological features of malignancy were designated "malignant adenomas" by Bailey and Cutler, and by Jefferson, Feiring, et al., and King, however, favored the term "pituitary carcinoma" for these tumors. Martins, et al., and Rub-
instein reserved the diagnosis of malignancy for pituitary neoplasms that had metastasized outside the CNS, and called the locally infiltrative tumors "invasive adenomas."

There is, in fact, an inconsistent correlation between histological appearance and malignancy in pituitary tumors. Noninvasive pituitary tumors, like benign endocrine tumors of other types, may show cellular pleomorphism and significant mitotic activity, but there are several reports of distant metastases originating from histologically benign pituitary adenomas. Landolt, in an electron microscopy study, found no distinct ultrastructural differences between invasive and noninvasive tumors. It seems apparent that biological behavior, rather than histopathological criteria, establishes the diagnosis of malignancy in pituitary tumors.

Critical review of the English language literature yields 11 reported cases of pituitary tumor metastases to the CNS (Table 1). Included in the reviewed cases are two growth hormone-secreting tumors and two adrenocorticotropic hormone (ACTH)-secreting primary tumors. The remaining tumors showed no endocrine activity. The metastases occurred throughout the CNS, and several cases showed multiple metastatic sites. Supratentorial metastases were demonstrated in seven cases, posterior fossa metastases in two cases, and spinal subarachnoid metastases in four cases. Our report describes the 12th such case of pituitary tumor metastasis to the CNS, and it is the first instance in which hormone production by the metastatic tumor has been demonstrated.

Metastases within the CNS probably result from spread of tumor cells by the cerebrospinal fluid (CSF) circulation. Tumor invasion or surgical violation of the basilar cisterns provides neoplastic cells with access to the subarachnoid space. Surgery preceded the finding of metastases in our patient and in seven of the cases reviewed. In these eight cases, radiation therapy also preceded dissemination. Although radiation therapy has been implicated in the development of intrasellar fibrosarcoma, it has not been demonstrated to cause malignant transformation in pituitary adenomas.

Landolt recently collected 25 cases of metastatic pituitary tumors from the literature, several of which are included in our review. Thirteen of the patients had hematogenous metastases to extracranial sites. The extracranial metastases are remarkable for the relative frequency of their association with Cushing's

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**Table 1**

<table>
<thead>
<tr>
<th>Authors, Year</th>
<th>Age (yrs), Sex</th>
<th>Endocrine Types</th>
<th>Sites</th>
<th>Surgery</th>
<th>Radiation Therapy</th>
</tr>
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<tr>
<td>Cairns &amp; Russell, 1931</td>
<td>25, F</td>
<td>inactive</td>
<td>spinal cord</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Feiring, et al., 1953</td>
<td>38, M</td>
<td>Cushing's disease</td>
<td>frontal lobe</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Salassa, et al., 1959</td>
<td>46, M</td>
<td>Cushing's disease (liver)</td>
<td>spinal cord</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Graf, et al., 1962</td>
<td>7, F</td>
<td>inactive (liver, lung)</td>
<td>frontal lobe</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Newton, et al., 1962</td>
<td>27, F</td>
<td>acromegaly</td>
<td>temporal lobe</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Madonick, et al., 1963</td>
<td>75, M</td>
<td>inactive lobes, medulla</td>
<td>frontal &amp; temporal</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Epstein, et al., 1964</td>
<td>29, M</td>
<td>inactive</td>
<td>cauda equina</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Solitaire &amp; Jatlow, 1967</td>
<td>66, F</td>
<td>inactive</td>
<td>frontal lobe</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Fleisher, et al., 1972</td>
<td>50, M</td>
<td>inactive</td>
<td>pons</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Ogilvy &amp; Jakubowski, 1973-4</td>
<td>58, M</td>
<td>inactive spinal cord</td>
<td>parietal lobe</td>
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<td>+</td>
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<tr>
<td>Ogilvy &amp; Jakubowski, 1973-4</td>
<td>49, F</td>
<td>acromegaly</td>
<td>olfactory tract, temporal lobe</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

* A + indicates that surgery or radiation therapy was administered before the development of metastasis; a - indicates that it was not administered.

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FIG. 5. Electron micrograph of the cerebellar metastasis. Secretory granules are apparent. X 19,000.
Metastatic prolactinoma
disease (four cases), and for the predilection of the metastases to reside in the liver (nine cases).

Our case is the second in which total excision of a metastatic pituitary tumor has been accomplished. Ogilvy and Jakubowski reported a case of resection of a parietal parasagittal metastasis from an inactive adenoma; there was no evidence of a parietal recurrence at autopsy 2 years later. When surgical removal of a metastasis is not possible, radiation therapy is a viable therapeutic alternative. Epstein, et al., noted significant clinical improvement after irradiation of symptomatic cauda equina metastases from a pituitary tumor.

The value of bromocriptine therapy in reversing hyperprolactinemia and its secondary endocrine effects has been established. In addition, bromocriptine therapy has apparently resulted in a reduction in pituitary tumor size in several recently reported cases. It is therefore interesting to note, in our case, the appearance of a large cerebellar metastasis during treatment with bromocriptine. Further experience with bromocriptine should clarify the indications for bromocriptine as an antitumor agent.

Cytological examination of CSF may prove useful in the follow-up examination of patients with CNS metastases from pituitary tumors. Ogilvy and Jakubowski examined the lumbar CSF from 20 patients with pituitary tumors. Tumor cells were found in only two specimens—those from their two patients who had CNS metastases. Cairns and Russell also noted abnormal cells in the CSF from their patient with spinal subarachnoid metastases. As CSF cytology after the last operation was negative in our patient, myelographic search for spinal deposits was deferred. Radiation therapy will be reserved for demonstrated cerebellar recurrence, and bromocriptine treatment for symptomatic hyperprolactinemia.

References
1. Bailey OT, Cutler EC: Malignant adenomas of the chromophobe cells of the pituitary body. Arch Pathol 29:368–399, 1940