Cushing's Disease Due to Pituitary Carcinoma

M. Saeed Zafar
R. C. Mellinger
J. L. Chason

Follow this and additional works at: https://scholarlycommons.henryford.com/hfhmedjournal

Part of the Life Sciences Commons, Medical Specialties Commons, and the Public Health Commons

Recommended Citation

This Article is brought to you for free and open access by Henry Ford Health System Scholarly Commons. It has been accepted for inclusion in Henry Ford Hospital Medical Journal by an authorized editor of Henry Ford Health System Scholarly Commons.
Criteria for the diagnosis of pituitary carcinoma are subject to controversy. Some authors do not accept the demonstration of cellular anaplasia alone as sufficient to establish the diagnosis but require evidence of metastatic disease in order to label a pituitary tumor as malignant. However, pituitary tumors can metastasize even in the absence of anaplasia. The present case of Cushing's disease and pituitary carcinoma had no clinical evidence of metastases when first reported. Partial surgical removal of the tumor followed by irradiation resulted in clinical remission of the Cushing's syndrome, but two years later progressive uncontrollable recurrence of the disease ended in death. At autopsy, evidence of metastatic pituitary carcinoma was found throughout the central nervous system. This case illustrates that the diagnosis of pituitary carcinoma can be made correctly even in the absence of demonstrable metastases on the basis of cytological and clinical criteria.

Pituitary carcinoma that causes Cushing's syndrome is a rare disorder. Because histologic confirmation of this entity is a subject of great controversy, some insist on the presence of metastases by the pituitary neoplasm before accepting the morphologic appearance alone as indicative of malignancy. However, some intrasellar pituitary neoplasms producing Cushing's disease are locally invasive, are resistant to treatment, and have a rapidly fatal outcome. Accordingly, demonstrated cytologic characteristics of malignancy justify the diagnosis of carcinoma even before metastases occur.

In 1980 we reported a patient who had Cushing's disease caused by a pituitary tumor whose histology was interpreted as that of a pituitary carcinoma (1). The patient had very high adrenocorticotropic hormone (ACTH) levels and was initially thought to have an ectopic ACTH syndrome. After subtotal removal of the tumor by craniotomy and cobalt radiation, the patient enjoyed a period of clinical remission. His disease recurred subsequently and proved to be uncontrollable. He died with extensive central nervous system metastases of the functioning pituitary tumor, but no extracranial neoplasm was demonstrated. The present report details the subsequent course of this patient with an ACTH-secreting pituitary carcinoma.

Initial laboratory tests disclosed both hyperglycemia and hypokalemia. The suspected diagnosis, Cushing's syndrome, was confirmed by plasma cortisol levels that varied between 40 and 60 μg/dl, and multiple determinations of plasma ACTH disclosed values greater than 2000 pg/ml.

Following the ultimate demonstration of an intrasellar neoplasm, right frontal craniotomy was performed, and the invasive pituitary tumor was partially removed. ACTH levels fell to 421 pg/ml, and the patient was treated with cobalt radiation (6000r) to the tumor area.

The patient improved very gradually, and the abnormal levels of ACTH and Cortisol slowly declined. By the end of 1978, the 24-hour urinary Cortisol level was less than 100 μg, and the patient's blood pressure, blood sugar, and serum potassium were normal. In 1979 he was able to return to his work as a draftsman.

Studies performed during this period of apparent remission demonstrated a continued abnormal response to administered dexamethasone and to metyrapone (Table I). Early in 1981 the patient's hypertension recurred. His weight began to increase, and his facial contour became fuller. Urinary cortisol rose to 190 μg/24 hr by June 1981.

---

Case Report

The patient, a 56-year-old white man, became ill in 1977 when he experienced weight loss, weakness, progressive confusion, back pain, increasingly easy bruisability, rounding of his facial contours, increased skin pigmentation, and edema.
TABLE I
ACTH and Adrenal Steroid Levels

<table>
<thead>
<tr>
<th>Date</th>
<th>Condition</th>
<th>Plasma ACTH (pg/ml)</th>
<th>Plasma Cortisol (ug/dl)</th>
<th>Desoxy cortisol (ug/dl)</th>
<th>Urinary Cortisol ug/24 hrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>June 1981</td>
<td>Clinical relapse</td>
<td>2445</td>
<td>36.0</td>
<td>465</td>
<td>655</td>
</tr>
<tr>
<td>Oct 1981</td>
<td>Metyrapone 3 grams daily x 20 weeks</td>
<td>2203</td>
<td>48.9</td>
<td>1585</td>
<td>1530</td>
</tr>
<tr>
<td>Mar 1982</td>
<td>Aminogluthethimide 1 gram daily x 8 weeks</td>
<td>275</td>
<td>9.6</td>
<td>99</td>
<td></td>
</tr>
<tr>
<td>Aug 1982</td>
<td>No therapy</td>
<td>165</td>
<td>12.3</td>
<td>63</td>
<td></td>
</tr>
<tr>
<td>Nov 1982</td>
<td>Mitotane 6 grams daily x 30 days</td>
<td>167</td>
<td>3.4</td>
<td>9.6</td>
<td></td>
</tr>
<tr>
<td>Dec 1982</td>
<td>Mitotane (6 gm) and Decadron (16 mg) x 5 days</td>
<td>85</td>
<td>4.1</td>
<td>1.2</td>
<td></td>
</tr>
<tr>
<td>Normal values</td>
<td>20-100</td>
<td>11-22</td>
<td>1.0</td>
<td>25-125</td>
<td></td>
</tr>
</tbody>
</table>

*Normal values after 2 gm of metyrapone administered intravenously at night = 5-25 ug/dl

but cerebral computerized tomography (CT) failed to reveal a recurrent intrasellar tumor. His clinical condition continued to deteriorate, and subsequent cerebral CT with metrizamide contrast medium disclosed slight elevation of the suprasellar cistern. The patient was advised to have repeat pituitary surgery but refused.

In an attempt to control the Cushing's syndrome pharmacologically, first metyrapone and then aminogluthethamide were administered chronically. Only the latter drug had an apparent effect on urinary cortisol levels, but the patient refused to take increasing doses and discontinued all medication in the belief that these agents were contributing to his mental confusion.

The features of the disease rapidly worsened, and the urinary cortisol rose to 2,442 ug/24 hr. Treatment with o,p'-DDD* (mitotane) in a dose of 6 gm daily was associated with a fall in cortisol levels, but the patient's confusion increased. He became delirious, aspirated vomitus, and died. During his terminal illness, dexamethasone (4 mg every 6 hrs) was administered along with o,p'-DDD. With this regimen the plasma cortisol was recorded at 1.2 ug/dl (Table II).

Autopsy disclosed that the residual pituitary carcinoma had infiltrated the base of the brain near the optic chiasm and extended into the third ventricle (Fig. 1). Tumor implants were present in all ventricles, in the leptomeninges of the medulla, pons, and in the cervical cord. The lower cervical cord was compressed by a large tumor implant, resulting in necrosis of the cord at this level along with secondary ascending and descending Wallerian tract degeneration (Fig. 2). The residual neoplasm was highly anaplastic, and, like the original tumor, was composed of polygonal cells with bizarre hyperchromatic nuclei and basophilic granular cyto-

---

*o,p'-DDD is 1,1 dichloro-2(o-chlorophenyl)-2(p-chlorophenyl)ethane.
**avidin-biotin complex-peroxidase-antiperoxidase.
Cushing's Disease Due to Pituitary Carcinoma

plasm (Fig. 3). With the ABC-PAP method, a strongly positive reaction to ACTH was demonstrated in the neoplasm was highly anaplastic and, like the original anterior lobe hormones capable of being tested (Fig. 4). These findings were consistent with that of the original neoplasm.

**Hormone Levels**

Plasma and urinary cortisol and plasma desoxyocortisol were measured by standard radioimmunoassay techniques in the Richmond W. Smith Endocrinology Research Laboratory of Henry Ford Hospital. Plasma ACTH was assayed by radioimmunoassay by a reference laboratory (Sera, Inc., Columbus, OH). All plasma and urinary studies were performed under standard control conditions. Dexamethasone suppression tests were performed after administration of dexamethasone (8 mg/24 hours for 48 hours). Metyrapone testing was carried out by the administration of 2 gm of the drug as a single intravenous bolus at midnight. Blood samples obtained the morning before and the morning after metyrapone administration were analysed for ACTH, desoxycortisol, and cortisol.

During the clinical remission of 1980, the urinary cortisol excretion declined into the normal range, and plasma cortisol levels were normal with less than usual diurnal variation. ACTH concentrations remained above normal during this time but were strikingly less than pretreatment values of 1977 and 1978. The ACTH levels did not decrease during the administration of dexamethasone (8 mg/day), although urinary cortisol and plasma cortisol were somewhat lower than on the control day. After the administration of metyrapone, the ACTH level fell from a control level of 159 to 85 pg/ml. However, concomitant plasma cortisol concentration also fell from 7.6 to 4.1 ug/dl, while the desoxycortisol value rose from 0.39 to 3.7 ug/dl (Table I).

During the weeks of the final relapse and terminal illness, administration of metyrapone (3 gm daily) failed to lower urinary cortisol, the values rising from 180 to 405 ug/24 hrs during its administration. When aminoglutethimide was administered in a dose of 3 g daily, the value did fall to 214 ug/dl. However, after the patient abandoned his medical therapy, the 24-hour urinary cortisol level rose to 2,442 ug/24 hrs. Associated plasma cortisol at that time was 42.1 ug/dl, and ACTH was 279 pg/ml. ACTH values never returned to the very high levels recorded during the initial observations (Table II).

**Discussion**

ACTH-secreting carcinoma of the pituitary gland is a rare entity, and the criteria for its diagnosis are in dispute. Some authors consider such cellular features as pleomorphism, nuclear hyperchromasia, and mitotic figures to be insufficient for such a diagnosis: evidence of metastasis is considered essential to establish the diagnosis of pituitary carcinoma.

Of the 12 cases of Cushing’s disease produced by pituitary carcinoma reported in the English literature, 10 had cytological features of malignancy, but two of these had no metastases when reported (1-12). One of the latter, the present case, subsequently developed evidence of metastatic disease. Two patients had metastases without any evidence of anaplasia (Table III). Six tumors metastasized to the central nervous system, six had blood-borne metastases chiefly to the liver, one to a lymph node and one to an adrenal gland.

Consideration of some characteristics of the pituitary may explain some of these features. The gland is confined to an enclosed space adjacent to the central nervous system, with a unique vascular system and no lymphatics (13). Furthermore, functioning tumors of the pituitary gland
may respond to hypothalamic factors which stimulate the pituitary neurotransmitters and the releasing hormones. This fact may be relevant to their tendency for local invasiveness as well as for distant spread even in the absence of evident anaplasia. Similar behavior is well known to occur with functioning tumors of other endocrine glands.

While there can be no doubt that a pituitary neoplasm which metastasizes is malignant, the present case demonstrates that cytological characteristics combined with such functional features as very high ACTH and cortisol concentrations can lead to a correct diagnosis of pituitary carcinoma. Autopsy findings in the patient reported support this conclusion.

Pituitary tumors that produce Cushing's disease may be usefully classified according to their cytological characteristics and the presence or absence of metastases:

- Adenoma: Cytologically benign
  - a. Circumscribed or encapsulated
  - b. Locally invasive without metastases
- Malignant adenoma: Cytologically benign
  - a. Locally invasive and metastasizing
- Carcinoma: Anaplastic
  - a. Locally invasive or localized
  - b. Metastatic

This classification emphasizes that pituitary tumors with cellular features of malignancy have great potential for local invasion and distant spread. In addition, some cytologically benign tumors may also have this potential.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Cellular Atypia</th>
<th>Metastasis</th>
<th>Duration of Disease</th>
<th>Cause of Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fachnie, et al (1)</td>
<td>yes</td>
<td>None at initial presentation</td>
<td>3 years</td>
<td>Pneumonitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Central nervous system at autopsy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cohen and Dibble (2)</td>
<td>yes</td>
<td>Liver</td>
<td>2 years</td>
<td>Pneumonia</td>
</tr>
<tr>
<td>Forbes (3)</td>
<td>yes</td>
<td>Liver</td>
<td>1 year</td>
<td>Congestive heart failure</td>
</tr>
<tr>
<td>Feiring, et al (4)</td>
<td>yes</td>
<td>Anterior cranial fossa</td>
<td>5 years</td>
<td>Unclear</td>
</tr>
<tr>
<td>Sheldon, et al (5)</td>
<td>yes</td>
<td>Liver</td>
<td>2 years</td>
<td>Anesthesia</td>
</tr>
<tr>
<td>Salassa, et al (6)</td>
<td>yes</td>
<td>Central nervous system</td>
<td>4 years</td>
<td>—</td>
</tr>
<tr>
<td>Haugen and Loken (7)</td>
<td>yes</td>
<td>No</td>
<td>2 years</td>
<td>Cushing’s Dx</td>
</tr>
<tr>
<td>Scholz, et al (8)</td>
<td>Minimal</td>
<td>Lymph nodes</td>
<td>3 years</td>
<td>—</td>
</tr>
<tr>
<td>Simkin, et al (9)</td>
<td>yes</td>
<td>Local</td>
<td>5 years</td>
<td>Operative</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sphenoid sinus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rovit and Berry (10)</td>
<td>yes</td>
<td>Adrenal</td>
<td>1 year</td>
<td>Postoperative</td>
</tr>
<tr>
<td>Queiroz, et al (11)</td>
<td>no</td>
<td>Liver</td>
<td>1 year</td>
<td>Postoperative</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gasserian ganglion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kaiser, et al (12)</td>
<td>no</td>
<td>Liver, lung, bones</td>
<td>9 years</td>
<td>Alive</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Zafar, Mellinger, and Chason

Fig. 4
Metastatic implant on surface of medulla. Cytoplasmic granules reveal ACTH. ABC-PAP stain for ACTH. X840.
Cushing's Disease Due to Pituitary Carcinoma

Very high ACTH and cortisol levels associated with increasing skin pigmentation and a rapidly developing clinical disorder suggest either pituitary carcinoma or the more common ectopic ACTH syndrome, but these are not characteristic features of pituitary adenomas.

Function of the pituitary tumor in this patient is not considered to have been influenced by the administration either of dexamethasone or metyrapone. In the original studies, ACTH levels (which exceeded 2000 pg/ml) were unchanged after the administration of dexamethasone or metyrapone. Plasma and urinary cortisol actually seemed to increase with the administration of dexamethasone. In studies performed during clinical remission, plasma ACTH was not inhibited by dexamethasone but seemed to fall paradoxically from 159 to 85 pg/ml the morning after the infusion of metyrapone. During the 8 mg dexamethasone study, ACTH concentration was unchanged, although the plasma and urinary cortisol levels were somewhat reduced. After the administration of metyrapone, plasma desoxycortisol did rise, but the plasma cortisol change was not striking. Moreover, the increase in desoxycortisol concentration was less than is anticipated in Cushing's disease (Table I).

The very high level of ACTH before any treatment is considered a clue to the nature of the pituitary disorder. Kaiser, et al (12) reported a patient who had a cytologically benign pituitary neoplasm which metastasized five years after bilateral total adrenalectomy for Cushing's disease. In this patient, the ACTH value was reported at the remarkable level of 230,000 pg/ml.

In our patient the initial lack of symptoms suggesting intracranial tumor and the negative skull x-ray failed to direct attention to the pituitary gland. Even if CT scan had been performed initially and had disclosed minor enlargement of the pituitary gland, such a finding would not have been considered compatible with an ACTH level approaching 2,500 pg/ml. Selective venography failed to demonstrate an ACTH gradient, although no attempt was made to reach the petrosal sinus. Only the development of impaired visual fields called attention to the rapidly enlarging pituitary tumor (1).

Combined surgical and radiation treatment produced a period of clinical remission. However, during this time the abnormal physiologic relations between the pituitary neoplasm and the adrenal persisted. ACTH levels always remained above normal, even with normal urinary cortisol and plasma cortisol concentration. Possibly, the ACTH derived from the precursor molecule oiomelanocortin had less biologic activity than does ACTH secreted by the normal pituitary. Secretion of corticotropin with altered molecular weight and reduced biologic activity has been demonstrated in vitro for some pituitary and other functioning neoplasms (14). A similar phenomenon in our patient may account for the striking change in ACTH concentration that followed pituitary radiation as well as the observations of reduced cortisol concentration without concomitant changes in ACTH when dexamethasone was administered.

Pituitary carcinoma is an invariably fatal disorder. Of the reported cases, only one is still alive nine years after the diagnosis (12). Response to irradiation with apparent reduction in the rate of tumor growth and temporary clinical remission was observed in our patient as well as in most previously reported cases. During the final relapse, efforts were made to reduce adrenal secretion by pharmacologic means but neither metyrapone nor aminogluthethemide proved effective. Results with mitotane suggested a beneficial effect, but the patient had already entered the terminal phase of his pituitary malignancy.
References


