Review

Pituitary Carcinomas

Wolfgang Saeger, MD and Dorothee Lübke, MD

Abstract

Pituitary carcinomas are defined by their metastatic growth. Most of them also invade into surrounding tissues. They should be classified by the site of their metastases (cerebrospinal, systemic, or combined) and by the presumable cell type of origin, respectively with the hormone being demonstrable by immunohistochemistry (adrenocorticotrophic hormone [ACTH], prolactin [PRL], growth hormone [GH], hormone-negative). Pituitary carcinomas develop from invasive adenomas. Nearly all tumors had been treated by surgery or X-ray before they metastasized. Since 1976, 37 cases demonstrated with modern methods were reported: 23 had metastasized into the brain or meninges, 10 showed extracerebral metastases, and 4 showed both types of metastases. In our collection of pituitary tumors, three carcinomas (0.13%) were identified: two with systemic metastases (one ACTH secreting and one PRL secreting) and one with meningeal dissemination and ACTH production. The diagnosis of pituitary carcinomas should be based on four criteria: a demonstrable metastasis, identification of the primary tumor as a pituitary tumor, similarity between the structure and immunohistological marker expression of metastasis and primary tumor, and exclusion of an alternative primary tumor.

Key Words: Pituitary carcinoma; invasive adenoma.

Introduction

The ability to metastasize and the presence of an invasive growth are the standard indicators of malignant tumors. These attributes also characterize most carcinomas of endocrine glands or the disseminated endocrine cells. On the other hand, encapsulated papillary carcinomas of the thyroid metastasize but do not grow invasively [1], and carcinoids of the stomach, appendix, and colon grow strongly invasively but metastasize very rarely [2].

Invasive Adenomas and Definition of Carcinomas

Pituitary adenomas are said to be absolutely benign tumors, but many of them in surgical collections are invasive by growth into surrounding tissues (capsule, adjacent anterior gland, neurohypophysis, sellar bone). Reports on the frequency on invasion vary greatly. In our material [3], 41.9% of the adenomas were invasive: 7.8% invaded the anterior lobe, 3.8% the posterior lobe, 12.1% the dura, 3.0% the leptomeninges, 15.9% the bone, and 9.1% the mucosa of paranasal sinuses. Other reports record an invasion rate of up to 90% by demonstration of small adenoma foci in the adjacent dura [4].

Why do we not call an invasive adenoma a carcinoma analogous to the situation in other endocrine glands? The clinical significance of invasiveness in most adenomas is low. The recurrence rate correlates more to the size of the tumor and to residual adenoma tissue, which could not be resected during surgery and is the source of the tumor regrowth rather than of the invasiveness. Whereas larger adenomas are

Department of Pathology, Marienkrankenhaus, Hamburg, Germany.

Address correspondence to Dr. Wolfgang Saeger, Department of Pathology, Marienkrankenhaus, Alfredstrasse 9, D-22087, Hamburg, Germany.

Endocrine Pathology, vol. 7, no. 1, 21–35, February 1996

1046–3976/96/7:21–35/$8.75

more frequently invasive, we also find microadenomas with invasive growth. What are the specific factors of invasive growth in the pituitary? The local anatomic factors—especially the sellar bone—may be important, since many adenomas not only compress the bone but also invade the medullary tissue of bone. We do not know whether adenoma cells express lytic enzymes causing invasion or whether the surrounding tissue has a particularly decreased or defective content of adhesion molecules.

Why do invasive pituitary tumors not metastasize? Adenoma growth can reach the liquor space and the cavernous sinus, but metastases are extremely rare. We do not know the reasons for this. Is it a question of disconnection from the tissue arrangement, or is it a matter of nonreceptivity to tumor cells in other organs from the blood or liquor?

Sixty-seven carcinomas have been described in the literature up to now (Tables 1–4, pp. 24–28). They have been defined by their metastases, the only proof of malignancy of pituitary tumors. In our surgical material of pituitary tumors ($N = 2342$) (1970–1994), we have found three carcinomas, which resulted in a proportion of 0.13%.

We have reviewed the published reports of pituitary carcinomas in the literature to find common attributes. The diagnoses of 30 reported carcinomas (Tables 1 and 2), mostly from the years up to 1975, were based on conventional methods without immunohistochemistry. These old case reports cannot fulfill modern criteria for pituitary carcinoma identification, since it is essential to have distinct structural similarities between the primary tumor and the presumable metastasis as well as a comparable marker expression for the diagnosis of pituitary carcinomas. Molecular pathology can offer valuable insights in carcinoma biology. Reports of gene expression, therefore, appear to be relevant.

The diagnosis of a primary pituitary carcinoma must rest basically on the following criteria:

1. The primary tumor has to show structures of pituitary tumors via light and electron microscopy;
2. A metastasis must exist showing a distinct disconnection from the primary tumor;
3. The structure of the metastasis has to be proven identical or very similar to the primary tumor; and
4. An alternative primary tumor has to be excluded.

Classification of pituitary carcinoma has to be carried out in relationship to the site of metastases (cerebrospinal, systemic, or combined) and to the presumable cell type of origin.

Carcinomas with Cerebrospinal Metastases

Thirty-nine tumors have been reported in the literature as primary pituitary carcinomas metastasizing exclusively intracranially/intraspinally into the brain, spinal cord, or meninges. Six cases could not be identified with sophisticated methods and are, therefore, questionable (Table 1). Ten tumors had to be classified as probable pituitary carcinomas since the pituitary tumors appeared to be structurally identical with the metastases, but an alternative primary tumor could not be excluded with certainty (Table 2). Twenty-three tumors were explicit carcinomas (Table 3) because alternative primary tumors were excluded according to the aforementioned criteria and because structure and marker expression of tumor and metastases were similar.

Of the proven carcinomas, 9 (39%) secreted prolactin (PRL) and induced hyperprolactinemia, 4 (17%) were accompanied by acromegaly, 7 (30%) produced adrenocorticotrophic hormone (ACTH) with Cushing' s disease ($n = 3$, 13%) or

Nelson' s syndrome (n = 4, 17%) (Fig. 1, p. 29) and 3 (13%) appeared to be inactive.

Twenty-two carcinomas (96%) were diagnosed as recurrent pituitary tumors. Of the 22 cases, 11 (55%) were operated on twice, 5 (23%) three times, 4 (18%) four times, and 2 (9%) five times. Twenty carcinomas (91%) were pretreated by X-ray. The metastases were localized in the spinal cord (n = 6, 21%), cerebellum (n = 5, 20%), occipital brain (n = 3, 12%), parietal brain (n = 3, 12%), temporal brain (n = 3, 12%), frontal brain (n = 4, 16%), brainstem (n = 6, 24%), and meninges (n = 9, 41%).

Carcinomas with Systemic Metastases

Twenty-four tumors have been published as pituitary carcinomas with exclusively extracerebral metastases. Four tumors in the previous literature appeared unlikely from a modern standpoint (Table 1). Ten were probable pituitary carcinomas which could not be identified with certainty owing to methodical insufficiencies (Table 2) and 10 were certain primary carcinomas of the pituitary (Table 4). Five of these 10 (50%) patients suffered from hyperprolactinemia (Figs. 2 and 3, pp. 29 and 30, respectively), 3 (33%) from Cushing's disease, and 2 (20%) tumors were inactive. All except 1 had been operated on before, 6 patients two times, 1 patient three times. All except 1 had been pretreated by X-ray. Sites of metastases were the liver (n = 5, 50%), lungs (n = 4, 40%), bones (n = 6, 60%), kidney (n = 1, 10%), gluteal muscle (n = 1, 10%), and lymph nodes (n = 3, 30%).

Carcinomas with Cerebrospinal and Systemic Metastases

Five pituitary carcinomas with spinal and systemic metastases have been reported in the literature. Four could be accepted as undoubted carcinomas (Table 5, p. 31), one was a PRL-producing carcinoma, and the other three were inactive carcinomas. The cerebrospinal compartment was restricted to the spinal cord. The systemic metastases were found in the liver (n = 2), lungs (n = 2), lymph nodes (n = 1), heart (n = 1), and peritoneum (n = 1). Two were pretreated by X-ray, and only 1 was operated on previously.

Tumor Development and Molecular Pathology

Pituitary tumorigenesis appears to be a multistep process; hormonal dysregulation may enable the clonal expansion of genetically transformed cells. Probably more than one somatic mutation has to occur for development of pituitary adenoma. *Gsp* oncogenes were discovered in endocrine tumors [67]. In about 40% of growth hormone (GH)-secreting tumors, the α-subunit of the Gs protein may reveal point mutations at amino acid residues 201 and 227, which inhibit GTPase activity so that trophic stimulation of AMP pathway by growth hormone-releasing hormone (GHRH) is bypassed [68]. Other pituitary adenomas are negative.

Ras mutations (in codon 12 of H-*ras* gene) were found only in one highly aggressive prolactinoma [69] and in three metastases of pituitary carcinomas but not in their primary tumors [70]. In a single prolactinoma [71] and a single ACTH-positive adenoma c-*fos* gene amplification was also identified. The c-*myc* gene was also overexpressed in single cases of inactive, ACTH-positive, PRL-positive and GH-positive adenomas [72]. The c-*myb* gene was not overexpressed [72].

In 13 malignant or highly invasive pituitary tumors, a loss of heterozygosity at the retinoblastoma (Rb) susceptibility

Table 1. Uncertain Pituitary Carcinomas (Not Precisely Identified)[a]

No.	Refs.	Yr	Sex	Age, yr	Hyperfunction	Local invasion	Spread	Type	Immuno-histology	Metastases	In/ex	Pretreatments		Duration of symptoms	Remarks
												No. of surgeries	No. of X-ray therapy		
1	[5]	1904	M	35	Acromegaly	Clivus	Supra, para	Chromophobic	—	Spinal cord	In	—	—	NA	Postmortem examination not complete
2	[6]	1904	M	40	Acromegaly	NA	NA	NA	—	Occipital brain	In	—	—	NA	
3	[7]	1909	F	31	—	Os sphen.	Supra	NA	—	Cerebellum	In	—	—	1 yr	
4	[8]	1918	M	38	—	Os sphen.	Para	Chromophobic	—	Tonsil, lymph node	Ex	—	—	NA	
5	[9]	1921	F	27	—	Sin. sphen., sin. cav.	Intra	Undifferentiated	—	Lung, lymph node	Ex	—	—	7 mo	
6	[10]	1930	M	27	—	—	Intra	Eosinopilic	—	Bone	Ex	—	—	6 mo	
7	[11]	1931	F	25	—	NA	Supra	NA	—	Spinal cord	In	—	—	NA	Description not complete
8	[12]	1932	F	55	—	Sin. cav., clivus	Supra	Chromophobic	—	Liver, kidney, lymph node, adrenal, uterus	Ex	—	—	7 wk	
9	[13]	1936	F	24	Acromegaly	Dorsum sellae	Supra	Eosinophilic	—	Cerebellum	In	—	—	7 yr	
10	[14]	1962	M	69	Cushing's disease	Sin. sphen.	NA	Chromophobic	—	Lymph node	Ex	Biopsy	1	3 yr	Postmortem examination not complete

[a]Abbreviations: ex, extracranial; in, intracranial; intra, intrasellar; NA, not available; os sphen., os sphenoidal; para, parasellar; sin. cav., cavernous sinus; sin. sphen., sphenoidal sinus; supra, suprasellar.

Table 2. Probable Pituitary Carcinomas (Uncertain Points in Identification)[a]

No.	Refs.	Yr	Sex	Age, yr	Hyperfunction	Local invasion	Spread	Type	Immuno-histology	Metastases	In/ex	Pretreatments		Duration of symptoms	Remarks
												No. of surgeries	No. of X-ray therapy		
1	[15]	1936	F	50	Cushing's disease	—	Intra	Basophilic	—	Liver	Ex	—	1	6 yr	
2	[16]	1944	M	46	—	Os sphen., sin cav.	NA	Chromophobic	—	Liver	Ex	1	1	2 yr	
3	[17]	1947	F	43	Cushing's disease	Sellar ground	NA	Chromophobic	—	Liver	Ex	Biopsy	—	1.5 yr	Metastasis, eosinophilic
4	[18]	1953	F	32	Cushing's disease	Sin. sphen.	Supra	Chromophobic	—	Frontal brain	In	2 C	6	6 yr	
5	[19]	1954	F	26	Cushing's disease	Sin. sphen., sin. ethm.	Supra	Basophilic	—	Liver	Ex	—	—	2 yr	
6	[20]	1959	M	75	—	Yes	Supra	Chromophobic	—	Heart	Ex	—	—	3 yr	
7	[21]	1959	M	42	Nelson's syndrome	Sin. cav.	Supra	Chromophobic	—	Liver, spinal cord	Ex, In	1 C	2	5 yr	
8	[22]	1962	F	7	—	Sellar ground, sin. sagit.	Supra, para	Chromophobic, eosinophilic	— —	Liver, lung	Ex	1 C	1	7 mo	
9	[23]	1962	F	27	Acromegaly	Sin. cav.	Supra	Chromophobic	—	Hippocampus	In	—	—	3 mo	Exitus post-OP
10	[24]	1963	M	75	—	4th ventricle	Supra	Chromophobic	—	Medulla	In	—	—	NA	
11	[25]	1964	M	29	—	NA	Supra	Chromophobic	—	Spinal cord, lumbal	In	2 C	3	14 yr	
12	[26]	1965	F	23	—	Sin. cav.	Supra, para	Eosinophilic, chromophobic	—	Frontal brain	In	2 C	1	4 mo	
13	[27]	1967	F	56	—	Sin. sphen.	Supra, para	Chromophobic	—	Frontal brain	In	3 C	2	14 yr	
14	[28]	1969	M	74	—	Sin. cav., os sphen.	Supra	Chromophobic	—	Liver, bone	Ex	—	—	9 mo	
15	[29]	1972	M	43	—	Sin. cav., os sphen.	Supra	Chromophobic	—	Pons	In	1 T, 1 C, 1 Lo	—	4 yr	Exitus post-OP
16	[30]	1973	F	24	—	Frontal cerebellum	Supra	Chromophobic	—	Lymph node	Ex	1 C	2	5 yr	
17	[31] Case A	1973	M	54	—	—	Supra	Chromophobic	—	Parietal-brain	In	1 C	1	6 yr	
18	[31] Case B	1973	F	49	Acromegaly	Sin. cav., sin. sphen.	Supra	Eosinophilic	—	CPA	In	1 C	2	7 yr	
19	[32]	1974	M	47	—	—	Supra	Chromophobic	—	Parietal-brain	In	3 C	1	5.5 yr	Patient is living
20	[33]	1975	F	38	Cushing's disease	Sin. cav., sin. sphen.	Supra, para	Chromophobic	—	Liver	Ex	—	—	14 mo	Illness after pregnancy

[a]Abbreviations: C, transcranial; CPA, cerebellopontine ancle; sin. ethm., ethmoid sinus; sin. sagit., sagital sinus; T, transsphenoidal. For other abbreviations, refer to Table 1.

Table 3. Unequivocal Pituitary Carcinomas with Cerebrospinal Metastases[a]

No.	Refs.	Yr	Sex	Age, yr	Hyperfunction	Local invasion	Spread	Type	Immunohistology	Metastases	Pretreatments		Duration of symptoms	Remarks
											No. of surgeries	No. of X-ray therapy		
1	[34]	1981	F	31	Prolactinoma	Sin. cav.	Supra	Densely granulated	PRL	Cerebellum	1 T, 1 C	3	6 yr	Bromocriptine, patient is living
2	[35]	1983	M	70	Prolactinoma	Sin. sphen.	Intra	Chromophobic	PRL	CPA	—	—	4 yr	
3	[36]	1984	M	38	Acromegaly	3rd ventricle brainstem	Supra	Eosinophilic	PRL, GH	Occipital brain	1 T	—	13 yr	
4	[37]	1984	F	32	Nelson's syndrome	Sellar ground	Supra	Low differentiation	ACTH, β-endorphin, α-subunit	Frontal brain, 4th ventricle, brainstem	2 T	1	12 yr	Adrenalectomy
5	[38]	1984	M	56	Cushing's syndrome	3rd ventricle, brainstem	Supra	Basophilic	ACTH	Medulla, pons, spinal cord	1 C	1	4 yr	Metyrapone, mitrotane
6	[39]	1984	M	62	Prolactinoma	Capsule	Intra	Chromophobic	—	Occipital brain	1 C	2	6 yr	Bromocriptine, exitus to emboly metastasis after first irradiation
7	[40]	1984	F	32	Nelson's syndrome	Posterior fossa	Para	Low differentiation	ACTH	4th ventricle brainstem	—	1	NA	Adrenalectomy, Nelson's syndrome, after gestation, exitus after second irradiation
8	[41]	1985	M	28	Prolactinoma	—	Intra	Chromophobic	PRL	Frontal, temporal, parietal, brain	4 C	3	11 yr	Bromocriptine, patient is living
9	[42]	1985	M	28	—	Sellar ground	Intra	Chromophobic low differentiation	PRL	Frontal, temporal, brain	3 C	2	12 yr	Bromocriptine
10	[43]	1985	F	44	Prolactinoma	NA	Supra	"Benign"	PRL	Spinal cord, lumbal	1 C		1 yr	Bromocriptine, patient is living
11	[44]	1986	F	48	Acromegaly	Frontal left	Supra	NA	GH	Occipital brain, CPA, pons, spinal cord	1 TC, 2 C	1	2 yr	Bromocriptine, chemotherapy
12	[45]	1988	F	28	Acromegaly	Sin. cav.	Para	"Benign"	GH	Frontal brain	4 C	2	9 yr	Chemotherapy, patient is living
13	[46]	1988	M	26	Prolactinoma	Sin. cav.	Para	"Benign"	GH	Frontal brain, cerebellum	1 C	1	12 yr	Bromocriptine, patient is living
14	[47]	1990	F	37	—	Sin. cav.	Para	Low differentiation	Negative	Temporal, basal	1 C	1	6 mo	
15	[48]	1991	M	25	Cushing's disease	Sin. cav.	Para	Densely granulated	ACTH	Meninges	1 T	1	3 yr	No postmortem examination

16	[49] Case A	1991	M	47	Prolactinoma	NA	Supra	NA	PRL	Frontal brain	2 C	1	1.5 yr	Bromocriptine
17	[49] Case B	1991	F	56	Prolactinoma	Sin. cav.	Intra	Chromophobic	PRL	Medulla, spinal cord	1 T	1	13 yr	
18	[50]	1992	M	29	Nelson's syndrome	Sin. cav.	Supra	Eosinophilic	ACTH	Cervical, spinal cord	2 T	1	1.5 yr	Adrenalectomy, bromocriptine, patient is living
19	[51]	1992	M	49	Acromegaly	Sin. cav.	Supra, para	Eosinophilic	GH, PRL	Temporal, parietal brain pons, CPA	1 T, 2 C	1	13 yr	Bromocriptine
20	[52]	1992	F	52	Cushing's disease	—	Supra, para	Eosinophilic	Metastasis, NSE ACTH	Frontal brain, cerebellum	1 T	1	3 yr	
21	[53]	1992	M	45	Prolactinoma	Sin. cav.	Supra, para	Chromophobic differentiation	PRL, GH, keratin, S-100 protein, NSE	Spinal cord	1 C	1	13 yr	Chemotherapy
22	[54]	1994	M	40	Inactive	NA	Supra, para	Chromophobic		Dura	1	1		
23	[55]	1995	F	45	Nelson's syndrome	Sin. cav.	NA	Low differentiation	ACTH	Meninges	1 T, 1 C		2 yr	

[a]NSE, neuron-specific enolase. For abbreviations, refer to Tables 1 and 2.

Table 4. Unequivocal Pituitary Carcinomas with Systemic Metastases[a]

No.	Refs.	Yr	Sex	Age, yr	Hyperfunction	Local invasion	Spread	Type	Immunohistology	Metastases	Pretreatments		Duration of symptoms	Remarks
											No. of surgeries	No. of X-ray therapy		
1	[56]	1983	F	27	Cushing's disease	NA	Para	"Benign"	ACTH	Liver, bone, lung	1 T	1	6 yr	Adrenalectomy, chemotherapy
2	[57]	1984	F	56	—	Sin. cav., 3rd ventricle	Supra, para	Chromophobic, undifferentiated	GH	Bone	1 ?	1	6 yr	
3	[58]	1985	F	60	—	Sin. cav. sin. sphen.	Supra, para	Undifferentiated	Negative	Liver, lung, kidney	—	—	2 mo	
4	[59]	1985	F	60	Prolactinoma	Sin. sphen.	Supra, para	Undifferentiated	PRL	Bone	1 C, 2 T	2	5 yr	Bromocriptine, pergolide mesylate
5	[60]	1986	M	58	Cushing's disease	NA	Supra	Chromophobic, eosinophilic	ACTH	Liver, bone lymph node	2 ?	1	5 yr	Adrenalectomy, metyrapone
6	[61] Case A	1993	M	32	Prolactinoma			Chromophobic	PRL	Liver, lung, lymph node	7 T, 1 C	2	5 yr	Bromocriptine, chemotherapy
7	[61] Case B	1993	F	48	Prolactinoma			PRL tumor	PRL	Bone	1 T	1	15 yr	Bromocriptine, chemotherapy
8	[61] Case C	1993	M	49	Prolactinoma			Chromophobic		Lymph node, lung	2 C	2	4 yr	Bromocriptine, octreotide
9	[55]	1995	M	60	Cushing's disease	Sin. sphen.		Sparsely granulated ACTH cell type	ACTH	Bone, gluteal, muscle	2 T	1	13 yr	
10	[62]	1995	M	59	Prolactinoma			Sparsely granulated PRL cell type	PRL, TSH	Liver	2 T	1	2 yr	Bromocriptine, chemotherapy

[a]TSH, thyroid-stimulating hormone. For abbreviations, refer to Tables 1 and 2.

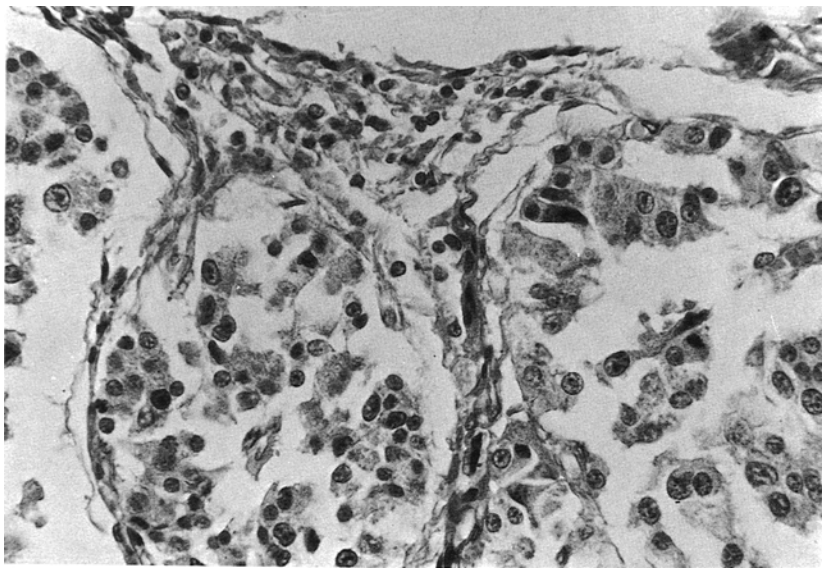

Fig. 1. Case 23 of Table 3. Pituitary carcinoma in Nelson's syndrome: solid tumor cell complexes in meninges (PAS reaction, ×260).

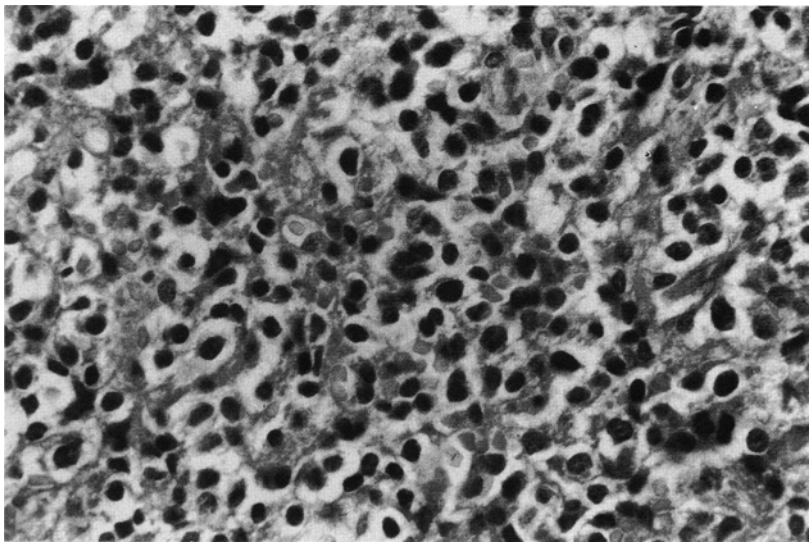

Fig. 2. Case 10 of Table 4. Pituitary carcinoma in hyperprolactinemia: features of an adenoma with moderately pleomorphic cells of medium size (H & E, ×285).

gene on the long arm of chromosome 13 was found [73]. Chromosomal deletions as allele loss in the 11q13 locus were found to be a feature of MEN1 syndrome and were demonstrated in prolactinomas [74] and somatotroph adenomas [75].

Close to the MEN1 locus lies the *hst* gene, a member of the fibroblast growth factor family [76]. The c-*erb* B proto-oncogene encoding a membrane receptor with homology to the epidermal growth factor was not overexpressed in pituitary adenomas [77].

The cytokine interleukin-6 affecting differentiation and growth promotion is expressed in most pituitary adenomas and in normal pituitary cells [78]. Protein kinase C is overexpressed in GH-secreting and nonsecreting adenomas and is higher in invasive than in noninvasive adenomas [79], but it is also demonstrable in lower amounts in other pituitary tumors and normal pituitary cells. The p53 protein as a tumor suppressor gene is not demonstrable by immunohistochemistry in one collection of pituitary adenomas [80], whereas others [81] found p53 in 50% of ACTH-secreting adenomas and in 27% of invasive nonfunctional tumors. Animal experiments revealed immunoreactivity of p53 in nuclei of all pituitary adenomas from AVP/SV 40 transgenic mice [80].

The pituitary-specific transcription factor pit-1 protein can be found in nearly half of pituitary adenomas [82]. It is important for functional differentiation but does not appear to influence cell proliferation. Some numerical chromosome aberrations have been described in one nonsecreting and one PRL-secreting pituitary adenoma [83]. By x-chromosomal inactivation analysis, pituitary adenomas were found to be monoclonal in origin [84,85].

From all the data, we do not find any specific expression of oncogenes or suppressor genes in highly aggressive pituitary adenomas. Pituitary carcinomas have been studied only rarely for overexpression of these factors. In our material [55], we did not find significant differences in overexpression of epidermal growth factor or Cathepsin D, which is used in cancer biology as a marker for increased invasion, and we could not demonstrate p53. From ani-

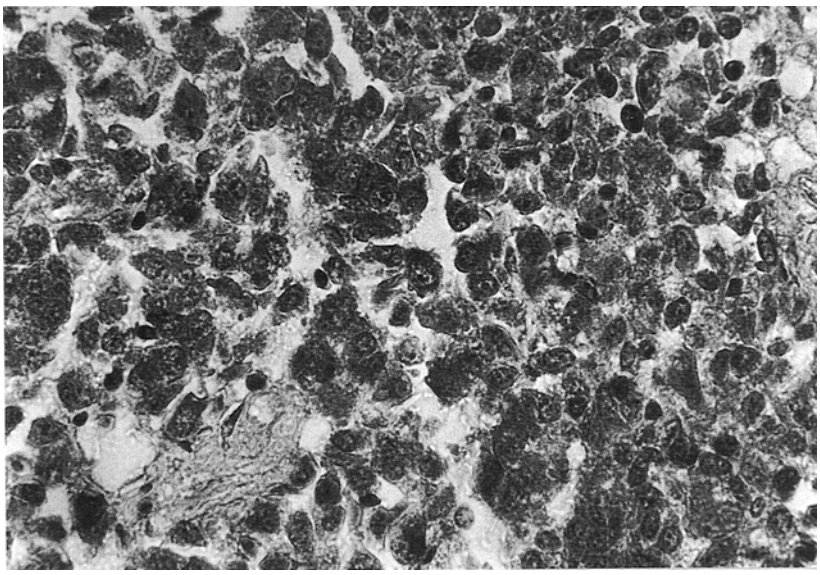

Fig. 3. Case 10 of Table 4. Metastases of pituitary carcinoma in the liver with hyperprolactinemia: similar structures as in Fig. 2 (anti-PRL-alkaline phosphatase-antialkaline phosphatase, ×450).

mal experiments, we know of only one report showing the development of pituitary carcinoma in transgenic mice with one disrupted allele of the Rb gene [86].

Proliferation Markers

Ki-67 is widely used as a marker for tumor cell proliferation. In pituitary adenomas, some reports described a higher rate of Ki-67-positive nuclei in invasive adenoma compared with noninvasive adenoma [87] and more numerous positive nuclei in ACTH adenomas and recurrent tumors [88], whereas others [89] found invasive ACTH adenomas without Ki-67 positivity. In our material, we did not find significantly different proliferation indices but immunostaining for Ki-67 in noninvasive and invasive adenomas, carcinomas, and their metastases [55]. Proliferating cell nuclear antigen was found in significantly more recurrent adenomas [90], whereas other investigators [91] demonstrated different values in different adenoma types: GH- and PRL-producing adenomas and inactive adenomas contained more than 2.5% positive nuclei, whereas ACTH adenomas showed a 0.1–2.2% rate. Our collection of ACTH adenomas revealed a higher rate in the recurrent adenomas compared with the nonrecurrent ones and a higher rate in adenomas pretreated by X-rays. Significant data for carcinomas compared with adenomas were not demonstrable [55].

Conclusion

Pituitary carcinomas are extremely rare. Thirty-seven cases have been reported in the literature since 1976. Our collection (1970–1994) contained three (0.13%) cases, two with ACTH hyperfunction and one with hyperprolactinemia. The diagnosis should fulfill four criteria [92]:

1. A metastasis has to be demonstrable;
2. The primary tumor has to show features of pituitary tumor;
3. The structure and the immunohistological marker expression of primary tumor and metastasis have to be identical or very similar; and
4. An alternative primary tumor must be ruled out.

Consequent on these criteria is the fact that pituitary carcinomas cannot be identified in surgical specimens from the sellar region because in this material a metastatic growth cannot be shown. They are classified, as are the adenomas, by their presumable cell of origin and their type of hyperfunction. They are further classified by the localization of metastases (cerebrospinal, systemic, or combined cerebrospinal/systemic).

Pituitary carcinomas develop from invasive adenomas in different settings. Nearly all had undergone previous treatment by surgery or X-ray. How the pretreatment influences the carcinogenesis

Table 5. Unequivocal Pituitary Carcinomas with Cerebrospinal and Systemic Metastases[a]

No.	Refs.	Yr	Sex	Age, yr	Hyperfunction	Local invasion	Spread	Type	Immunohistology	Metastases	Pretreatments		Duration of symptoms	Remarks
											No. of surgeries	No. of X-ray therapy		
1	[63]	1986	M	28	—	Sin. sphen.	Supra	Basophilic	ACTH, LPHβ	Liver, heart, spinal cord	—	2	4 yr	Glioblastoma
2	[64]	1987	F	64	—	NA	Supra	Undifferentiated	Keratin	Cervical, lymph node, spinal cord	—	—	d	
3	[65]	1991	M	34	Prolactinoma	Sin. sphen.	Supra	Undifferentiated	PRL	Lung, spinal cord	1 C	1	5 yr	Bromocriptine
4	[66]	1993	F	40	—	Sin. cav., sin. sphen., nasopharynx	Para	Undifferentiated	PRL, TSH, α-subunit	Liver, lung, peritoneum, spinal cord	2 T, 1 C	2	10 yr	Bromocriptine, chemotherapy

[a]LPH, lipotropic hormone. For abbreviations, refer to Tables 1 and 2.

from an adenoma is not known. A special oncogene expression or a typical molecular pathology of pituitary has not yet been found but proliferation markers, especially Ki-67, present increased numbers of positive nuclei in comparison with invasive adenomas in some studies.

References

1. Hedinger C, Williams ED, Sobin LH. Histological typing of thyroid tumours. 2nd ed. Berlin: Springer Verlag, 1988; 1–66.
2. Capella C, Heitz Ph, Höfler H, Solcia E. Revised classification of neuroendocrine tumours of the lung, pancreas and gut. Virchows Arch 425:547–560, 1995.
3. Sautner D, Saeger W. Invasiveness of pituitary adenomas. Pathol Res Pract 187:632–636, 1991.
4. Selman WR, Laws ER, Scheithauer BW, Carpenter SM. The occurrence of dural invasion in pituitary adenomas. J Neurosurg 64:402–406, 1986.
5. Cagnetto G. Zur frage der anatomischen beziehung zwischen akromegalie und hypophysentumoren. Virchows Arch. 176:115–169, 1904.
6. Stolpe R. Deutsche gesellschaft für Chirurgie 33. Kongr Dtsch Med Wochenschr 30:696, 1904.
7. Smoler F. Zur operation der hypophysentumoren auf nasalem Wege. Wien Klin Wochenschr 13:1488,1489, 1909.
8. Fahr Th. Beiträge zur pathologie der hypophyse. Dtsch Med Wochenschr 44:206–211, 1918.
9. Budde M. Zur Kenntnis der bösartigen hypophysengeschwülste und hypophysärer kachexie. Fr Z Pathol 25:16–34, 1921.
10. Vasiliu T. Durch ein hypophysenadenom hervorgerufene multiple knochenmetastasen. Virchows Arch 276:141–146, 1930.
11. Cairns H, Russell D. Intracranial and spinal metastases in gliomas of the brain. Brain Liv 377–421, 1931.
12. Gilmour MD. Carcinoma of the pituitary gland with abdominal metastases. J Pathol 35:264–266, 1932.
13. Kontchakova M. Metastasen von tumoren der hypophyse, ihre pathologische anatomie und ihre klinik. Zentralbl Gesamte Neurol 86:572(Abstract), 1936.
14. Scholz DA, Gastineau CF, Harrision EG. Cushing's syndrome with malignant chromophobe tumour of the pituitary and extracranial metastasis: report of case. Am J Med 17:34–41, 1962.
15. Cohan H, Dibble H. Pituitary basophilism associated with a basophil carcinoma of the anterior lobe of the pituitary gland. Brain 59:395–407, 1936.
16. Köhlmeier W. Zur kenntnis der metastasienden hypophysengeschwülste. Virchows Arch 312:26–34, 1944.
17. Forbes W. Carcinoma of the pituitary gland with metastases to the liver in a case of Cushing's syndrome. J Pathol Bacteriol 59:137–144, 1947.
18. Feiring EH, Davidoff LM, Zimmermann HM. Primary carcinoma of the pituitary. J Neuropathol Exp Neurol 12:205–222, 1953.
19. Sheldon WH, Goden A, Bondy PK. Cushing's syndrome produced by a pituitary basophil carcinoma with hepatic metastases. Am J Med 17:134–142, 1954.
20. Moberg A. A case of pituitary chromophobe adenoma with metastases of the heart. Acta Pathol Microbiol 45:243–249, 1959.
21. Salassa RM, Kearns TP, Kernohan JW, Sprague RG, MacCarthy SS. Pituitary tumours in patients with Cushing's syndrome. J Clin Endocrinol Metab 19:1523–1539, 1959.
22. Graf CJ, Blinderman EE, Terplan KL. Pituitary carcinoma in a child with distant metastases. J Neurosurg 19:154–159, 1962.
23. Newton TH, Burhenne HJ, Palubinskas J. Primary carcinoma of the pituitary. Am J Roentgenol 87:110–119, 1962.
24. Madonick MJ, Rubinstein LJ, Dasco MR, Ribner H. Chromophobe adenoma of pituitary gland with subarachnoidal metastases. Neurology 13:836–840, 1963.
25. Epstein JA, Epstein BS, Molho L, Zimmerman HM. Carcinoma of the pituitary gland with metastases to the spinal cord and roots of the cauda equina. J Neurosurg 21:847–853, 1964.
26. Braun W, Tzonos T. Über ein ungewöhnlich rasch wachsendes hypophysencarcinom mit intracerebralen metastasen. Acta Neurochir Wien 12:615–624, 1965.
27. Solitare GB, Jatlow P. Adenohypophysial carcinoma. J Neurosurg 26:624–631, 1967.
28. Geroulanos S. Chromophobes hypophysenadenom mit leber- und knochenmetastasen. Schweiz Med Wochenschr 99: 1817–1824, 1969.

29. Fleischer AS, Reagan T, Ransohoff J. Primary carcinoma of the pituitary with metastasis to the brainstem. J Neurosurg 36:781–784, 1972.
30. D'Abrera VSE, Burke WJ, Bleasel KF, Bader L. Carcinoma of the pituitary gland. J Pathol 109:335–343, 1973.
31. Ogilvy KM, Jakubowski J. Intracranial dissemination of pituitary adenomas. J Neurol Neurosurg Psychiatry 36:199–205, 1973.
32. Ricoy J, Carrillo R, Bravo G. Dissemination of pituitary adenomas. Acta Neurochirurgica 31:123–130, 1974.
33. Queiroz LS de, Facure NO, Facure JJ, Modesro NP, Faria JL. Pituitary carcinoma with liver metastases and Cushing's syndrome. Arch Pathol 99:32–35, 1975.
34. Martin NA, Hales M, Wilson CB. Cerebellar metastasis from a prolactinoma during treatment with bromocriptine. J Neurosurg 55:615–619, 1981.
35. Cohan DL, Diengdoh JV, Thomas DGT, Himsworth RL. An intracranial metastasis from a PRL-secreting pituitary tumour. Clin Endocrinol Oxford 18:259–264, 1983.
36. Duskova J, Chlumska A, Vilikusova E, Marek J, Sprincl L. Pituitary carcinoma with acromegaly. Cesk Pathol 20:170–176, 1984.
37. Gatti G, Limone P. ACTH-producing hypophyseal carcinoma monitored by computed tomography. Diagn Imag Clin Med 53:292–297, 1984.
38. Zafar MS, Mellinger RC, Chason JL. Cushing's disease due to pituitary carcinoma. Henry Ford Hosp Med J 32:61–66, 1984.
39. Hoi Sung U, Johnson C. Metastatic prolactin-secreting pituitary adenoma. Hum Pathol 15:90–96, 1984.
40. Papotti M, Limone P, Riva C, Gatti G, Bussolati G. Malignant evolution of an ACTH-producing tumor treated with intrasellar implantation of 90 Y. Appl Pathol 2:10–21, 1984.
41. Plangger CA, Twerdy K, Grunert V, Weiser G. Subarachnoid metastases from a prolactinoma. Neurochirurgica 28:235–237, 1985.
42. Gasser RW, Finkenstedt G, Skrabel F, Twerdy K, Grundert V, Mayr U, Frommhold H, Nedden D, Feichtinger J, Hofstädter F. Multiple intracranial metastases from a prolactin-secreting pituitary tumour. Clin Endocrinol 22:17–27, 1985.
43. Landgraf R, Rieder G, Schmiedek P, Clados D, Bise K, von Werder K. Hormone—active intradural spinal metastasis of a prolactinoma—a case report. Klin Wochenschr 63:379–384, 1985.
44. Hashimoto N, Handa H, Nishi S. Intracranial and intraspinal dissemination from a growth hormone-secreting pituitary tumor. J Neurosurg 64:140, 1986.
45. Asai A, Matsutani M, Funada N, Takakura K. Malignant growth hormone-secreting pituitary adenoma with hematogenous dural metastasis: case report. Neurosurgery 22: 1091–1094, 1988.
46. Muhr C, Bergström M, Lundberg PO, Hartmann M, Bergström K, Pellettieri L, Langström B. Malignant prolactinoma with multiple intracranial metastases studied with positron emission tomography. Neurosurgery 22:374–379, 1988.
47. Sakamoto T, Itoh Y, Fushimi S, Kowada M, Saito M. Primary pituitary carcinoma with spinal cord metastasis case report. Neurol Med Chir Tokyo 30(10):763–767, 1990.
48. Levesque H, Freger P, Gancel A, Tayot J, Cortois H. Carcinoma primitif de l'hypophyse avec syndrome de Cushing et metastases. A propos d'un cas avec revue à la litterature. Rev Med Interne 12:209–212, 1991.
49. Popvic EA, Vattuone JR, Siu KH, Busmanis I, Pullar MJ, Dowling J. Malignant prolactinomas. Neurosurgery 29:127–130, 1991.
50. Kouhara H, Tatekewa T, Koga M, Hiraga S, Arita N, Mori H, Sato B. Intracranial and intraspinal dissemination of an ACTH-secreting pituitary tumour. Endocrinol Jpn 39:177–184, 1992.
51. Stewart PM, Cary MP, Graham CT, Wright AD. Growth hormone secreting pituitary carcinoma: a case report and literature review. Clin Endocrinol 37:189–195, 1992.
52. Tonner D, Belding P, Moore SA, Schlechte JA. Intracranial dissemination of an ACTH-secreting-pituitary neoplasm—a case report and review of the literature. J Endocrinol Invest 15:387–391, 1992.
53. Kamphorst W, Wolbers JG, Ponssen H, Karim ABMF. Ectopic parasellar pituitary adenoma with subarachnoid seeding. J Neurol Neurosurg Psychiatry 55:73,74, 1992.
54. Taylor WA, Uttley D, Wilkins PR. Multiple dural metastases from a pituitary adenoma—case report. J Neurosurg 81:624–626, 1994.
55. Lübke D, Saeger W, Lüdecke DK. Proliferation markers and EGF in ACTH-secreting adenomas and carcinomas of the pituitary. Endocr Pathol 6:45–55, 1995.

56. Kaiser FE, Orth DN, Mukai K, Oppenheimer HJ. A pituitary parasellar tumour with extracranial metastases and high, partially suppressible levels of adrenocorticopin and related peptides. J Clin Endocrinol Metab 57:649–653, 1983.
57. Myles ST, Johns RD, Curry B. Clinicopathological conference: carcinoma of the pituitary gland with metastases to bone. Can J Neurol Sci 11:310–317, 1984.
58. Nudleman KL, Choi B, Kusske JA. Primary pituitary carcinoma: a clinical pathological study. Neurosurgery 16:379–384, 1985.
59. Scheithauer BW, Randall RV, Laws ER, Kovacs KT, Horvath E, Whitaker MD. Prolactin cell carcinoma of the pituitary. Cancer 55:598–604, 1985.
60. Casson IF, Walker BA, Hipkin LJ, Davis JL, Buxton OH, Jeffreys RV. An intrasellar pituitary tumor producing metastases in liver, bone and lymph glands and demonstration of ACTH in the metastatic deposits. Acta Endocrinol Copenh 111:300–304, 1986.
61. Walker JD, Grossman A, Anderson JV, Ur E, Trainer PJ, Benn J, Lowy C, Sonkson PH, Plowman PN, Lowe DG, Doniach I, Wass JAH, Besser GM. Malignant prolactinoma with extracranial metastases—a report of three cases. Clin Endocrinol 4:411–419, 1993.
62. Saeger W, Bosse U, Pfingst E, Schierke G, Kulinna H, Atkins D, Gullotta F. Prolactin bildendes hypophysencarcinom. Kasuistik eines äußerst seltenen metastasierenden tumors. Pathologe 16:354–358, 1995.
63. Gabrilove JL, Anderson PJ, Halmi NS. Pituitary pro-opiomelanocortin-cell carcinoma occurring in conjunction with a glioblastoma in a patient with Cushing's disease and subsequent Nelson's syndrome. Clin Endocrinol 22:17–27, 1986.
64. Luzi P, Miracco C, Lio R, Malandrni A, Piovani S, Venezia SG, Tosi P. Endocrine inactive pituitary carcinoma metastasizing to cervical lymph nodes: a case report. Hum Pathol 18:90–92, 1987.
65. Atienza DM, Vigersky RJ, Lack EE, Carriaga M, Runwock J, Tsou E, Cerrone F, Kattah JG, Sausville EA. Prolactin-producing pituitary carcinoma with pulmonary metastases. Cancer 68:1605–1610, 1991.
66. Mixson AJ, Friedman TC, Katz DA, Feuerstein IM, Taubenberger JK, Colandrea JM, Doppman JL, Oldfield EH, Weintraub BD. Thyrotropin-secreting pituitary carcinoma. J Clin Endocrinol Metab 87:529–533, 1993.
67. Lyons J, Landis CA, Harsh G, Vallar L, Grunewald K, Feichtiger H, Duh Q, Clark OH, Kawasaki E, Bourne HR, McCormick F. Two G protein oncogenes in human endocrine tumors. Science 249:655–659, 1990.
68. Spada A, Vallar L, Faglia G. G-proteins and hormonal signalling in human pituitary tumors—genetic mutations and functional alternations. Front Neuroendocrinol 14:214–232, 1993.
69. Karga HJ, Alexander JM, Hedley-Whyte ET, Klibanski A, Jameson JL. Ras mutation in human pituitary tumors. Clin Endocrinol Metab 74:914–919, 1992.
70. Pei L, Melmed S, Scheithauter BW, Kovacs K, Prager D. H-ras mutations in human pituitary carcinoma metastases. J Clin Endocrinol Metab 78:842–846, 1994.
71. U HS, Kelley P, Lee, WH. Abnormalities of the human growth hormone gene and protooncogenes in some human pituitary adenomas. Mol Endocrinol 2:85–89, 1988.
72. Woloschak M, Robert JL, Post K. c-myc, c-fos, c-myb gene expression in human pituitary adenomas. J Clin Endocrinol Metab 79:253–257, 1994.
73. Pei L, Melmed S, Scheithauer BW, Kovacs K, Benedict WF, Prager D. Frequent loss of heterozygosity at the retinoblastoma gene (RB) locus in aggressive pituitary tumors: evidence for a chromosome 13 tumor suppressor gene other than RB. Cancer Res 55:1613–1616, 1995.
74. Bystrom C, Larsson C, Blomberg C, Sandelin K, Falkmer E, Skogseid B, Oberg K, Werner S, Nordenskjold M. Localization of the MEN 1 gene to a small region within chromosome 11q13 by deletion mapping in tumors. Proc Natl Acad Sci USA 87:1968–1972, 1990.
75. Thakker RV, Pook MA, Wooding C, Boscaro M, Scanarini M, Clayton RN. Association of somatotropinomas with loss of alleles on chromosome 11 and with gsp mutations. J Clin Invest 91:2815–2821, 1993.
76. Gonsky R, Herman V, Melmed S, Fagin J. Transforming DNA sequences present in human prolactin-secreting pituitary tumors. Mol Endocrinol 5:1687–1695, 1991.
77. Wetherall MRB, Corbett IP, Ince P, James RA, Daniels M, Harris PE, Hendall-Taylor P. Human pituitary adenomas do not overexpress the c-erbB-2 oncoprotein. Endocr Pathol 2:210–213, 1991.

78. Tsagarakis S, Kontogeorgos G, Giannou P, Thalassinos N, Woolley J, Besser GM, Grossman A. Interleukin-6, a growth promoting cytokine, is present in human pituitary adenomas—an immunocytochemical study. Clin Endocrinol 37:163–167, 1992.
79. Alvaro V, Touraine P, Vozari RR, Baigrenier F, Birman P, Joubert D. Protein kinase-C activity and expression in normal and adenomatous human pituitaries. Cancer 50:724–730, 1992.
80. Sumi T, Stefaneanu L, Kovacs K, Asa SL, Rindi G. Immunohistochemical study of p53 protein in human and animal pituitary tumors. Endocr. Pathol. 4:95–99, 1993.
81. Buckley N, Bates AS, Broome JC, Strange RC, Perrett CW, Burke CW, Clayton RN. P53 protein accumulates in Cushing's adenomas and invasive non-functional adenomas. J Clin Endocrinol Metab 80:692, 1995.
82. Inada K, Oda Y, Utsunomiya H, Sanno N, Itoh J, Osamura RY, Voss JW, Rosenfeld MG. Immunohistochemical expression of Pit-1 protein in human pituitary adenomas. Endocr Pathol 4:201–204, 1993.
83. Dietrich CU, Pandis N, Bjerre P, Schroder HD, Heim S. Simple numerical chromosome aberrations in two pituitary adenomas. Cancer Genet Cytogenet 69:118–121, 1993.
84. Herman V, Fragin J, Gonsky R, Kovacs K, Melmed S. Clonal origin of pituitary adenomas. J Clin Endocrinol Metab 71:1427–1433, 1990.
85. Gicquel C, Lebouc Y, Craig J, Luton JP, Girard F, Bertagna X. Pituitary corticotroph adenomas are monoclonal. 73rd Annual Meeting of the Endocrine Society, Washington, DC, 1636 (abstract), 1991.
86. Jacks T, Fazeli A, Schmitt EM, Bronson RT, Goodell MA, Weinberg RA. Effects of an Rb mutation in the mouse. Nature 359: 295–300, 1992.
87. Landolt AM, Shibata T, Kleihues P. Growth rate of human pituitary adenomas. J Neurosurg 67:803–806, 1987.
88. Shibuya M, Saito F, Miwa T, Davis RL, Wilson CB, Hoshino T. Histochemical study of pituitary adenomas with Ki67 and anti-DNA polymerase alpha monoclonal antibodies, bromodeoxy-uridine labeling, and nucleolar organizer region counts. Acta Neuropathol 84:178–183, 1992.
89. Tsanaclis AM, Robert F, Michaud J, Brem S. The cycling pool of cells within human brain tumours: in situ cytokinetics using the monoclonal antibody Ki-67 Can J Neurol Sci 18:12–17, 1991.
90. Hsu DW, Hakim F, Biller BMK, Delamonte S, Zervas NT, Klibanski A, Hedleywhyte ET. Significance of proliferating cell nuclear antigen index in predicting pituitary adenoma recurrence. J Neurosurg 78:753–761, 1993.
91. McNicol AM, Sheperd M, Lane OP. Cell proliferation in pituitary adenomas; correlation with hormonal immunoreactivity. Abstract 14. J Endocrinol Invest 14(Suppl. 1):55, 1991.
92. Pernicone PJ, Scheithauer BW. Invasive pituitary adenomas and pituitary carcinomas. In: Lloyd RV, ed. Surgical pathology of the pituitary gland. Major problems in pathology. vol 27. Philadelphia, PA: Saunders, 1993; 121–136.