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CASE REPORT

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Combined sellar gangliocytoma and pituitary adenoma in acromegaly or Cushing's disease

A report of 3 cases

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Abstract Three cases of a composite sellar tumour composed of a gangliocytoma and an adenoma are presented. Two patients who showed acromegaly and hyperprolactinaemia had a gangliocytoma and a growth hormone (GH)-prolactin cell adenoma in close proximity. The gangliocytoma contained growth hormone-releasing hormone (GHRH) by immunohistochemistry. At the electron microscopical level, the gangliocytoma was characterized by numerous synaptic vesicles. The third patient, a child with Cushing's disease, presented a corticotropin-releasing hormone (CRH)-positive gangliocytoma in close contact with an adrenocorticotropic hormone (ACTH) secreting adenoma, the latter a typical densely granulated ACTH cell adenoma. Ultrastructurally, the gangliocytoma revealed synaptic vesicles and sparse secretory granules. The results suggest that gangliocytomas may promote the development of pituitary adenomas by hypersecretion of releasing hormones. Whereas 20 cases of sellar GHRH producing gangliocytomas in acromegaly are reported in the literature, the combination of a CRH-positive gangliocytoma and an ACTH cell adenoma in Cushing's disease is apparently the first case.

Key words Pituitary adenoma · Sellar gangliocytoma
Immunohistology · Ultrastructure

Dedicated to Prof. Dr. H.-D. Herrmann, Director of the Neurosurgical Department of the University of Hamburg, on the occasion of his 60 th birthday

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Introduction

The pathogenesis of pituitary adenomas is unclear. Local factors of the pituitary cellular level such as irradiation, genetic mutations or viral infections may play a role [11]. Increased secretion of brain peptides from the hypothalamus is thought to promote the development of adenomas [11]. In 6.3% of unselected post mortem pituitaries we found small nodules representing border-line lesions between focal hyperplasia and small adenomas [21]. Factors that promote focal hyperplasia to adenoma can be postulated but have been traced only in very rare cases, in which a "secondary" increase of hypothalamic hormones due to insufficiency or destruction of peripheral endocrine organs, especially of the adrenal and thyroid glands was assumed or demonstrated. In such cases, rare and mostly small ACTH cell adenomas [27] or TSH cell adenomas [28] have been described.

Primary hyperfunction of hypothalamic releasing hormones may be the cause of the development of a pituitary adenoma from the target cell system [25], but reports so far describe 20 cases of a growth hormone-releasing hormone (GHRH) producing sellar tumour in combination with a growth hormone (GH) secreting pituitary adenoma (for review see [17]).

Corticotropin-releasing hormone (CRH) producing sellar tumours are extremely rare. Only three cases of gangliocytomas in Cushing's disease have been reported: a CRH-positive gangliocytoma and an ACTH cell hyperplasia [2], a CRH-negative gangliocytoma in combination with an ACTH cell adenoma [6, 9, 15] (Table 2) and a CRH-positive gangliocytoma without concomitant adenoma [14] (Table 2).

As our files contain three sellar gangliocytomas in combination with active pituitary adenomas (2 in acromegaly, 1 in Cushing's disease) we wish to present their light microscopical and ultrastructural features and the immunohistological data. Some morphological findings of two cases (Cases 2 and 3) have been mentioned in a review [17] and in a case report (Case 3) [16] but many details, especially the ultrastructure of gang-

liocytomas and the morphology of the concomitant adenomas have not been described.

Case reports

Case 1

A 27-year-old woman with acromegaly and elevated GH- and prolactin-plasma levels underwent trans-sphenoidal surgery for a large intra-, para- and suprasellar tumour in another hospital. Post-operatively GH- and prolactin-plasma levels did not normalize. Because her elevated GH- and prolactin-plasma levels responded well to bromocriptine, medical therapy was continued. However, at radiological examination 2 years after the operation, progressive recurrent tumour growth into the left parasellar and retrosellar region and into the sphenoidal sinus was seen. Since the patient felt well at that time, she refused any further therapy. The patient was lost to follow-up.

Case 2

A 28-year-old woman suffering acromegaly for 4 years, was operated on a large intra-, para- and suprasellar tumour. As extremely high GH-plasma levels persisted despite treatment with octreotide, multistage therapy was performed with transcranial resection of the suprasellar tumour (mainly gangliocytoma tissue) resulting in a decline of GH-plasma levels from 170 µg/l to 99 µg/l. Eleven months later trans-sphenoidal resection of the intra-sellar tumour (mainly adenoma tissue) was carried out resulting in a decline of GH-plasma levels from 90 µg/l to 15 µg/l. A further year later radiotherapy resulted in normalization of GH-plasma levels (2.9 µg/l).

Case 3

A 10-year-old girl suffered from Cushing's disease for at least 2 years. An intrasellar and suprasellar tumour measuring 2×2×1 cm and invading the right cavernous sinus was resected trans-sphenoidally. The macroscopical aspect was atypical for an adenoma showing large amounts of fibrous tissue and a greenish colour. Frozen section examination revealed tumour tissue not typical of a pituitary adenoma. Further exploration showed a small invasive intrasellar adenoma. Post-operatively ACTH-hyperfunction ceased. There is no evidence of recurrent disease 9 months after surgery. Substitution of cortisol is still necessary.

Material and methods

For intra-operative tumour diagnosis frozen sections from very small specimens were performed. The remaining parts were fixed in glutaraldehyde, post-fixed in buffered formalin and embedded in paraffin. For electron microscopy (only cases 2 and 3) small pieces of tissue were fixed in glutaraldehyde, post-fixed in osmium tetroxide and embedded in Epon 812. Ultrathin sections were studied with a Zeiss EM 9S2 electron microscope. Immunohistology on paraffin sections was carried out with the following monoclonal (mc) and polyclonal (pc) antibodies: anti-GHRH (pc, gift of Dr. Schulte, Essen and Kiel) [30], anti-CRH (pc, Milab, Malmö, Sweden, 1:50), anti-GH (mc, Biogenex, San Ramon, Calif., USA, prediluted), anti-prolactin (mc, Immunotech, Marseille, France, 1:100), anti- adrenocorticotrophic hormone (ACTH) (pc, Dako, Hamburg, Germany, 1:300), anti- thyroid stimulating hormone (TSH) mc, Immunotech, 1:100) anti-follicle stimulating hormone (FSH) (mc, Immunotech, 1:200), anti-luteinising hormone (LH) (mc, Immunotech, 1:200), anti-α-subunit (mc, Immunotech, 1:500), anti-S100-protein (pc, Dako, 1:800), anti-keratin KL1 (mc, Immunotech), anti-vimentin (mc, Dako, 1:10), anti-neuron specific enolase (NSE) (mc, Dako, 1:200), anti-synaptophysin (mc, Dako, 1:20), anti-glial fibrillary acid protein (GFAP) (mc, Dako, 1:80), anti-neurofilament protein (mc, Dako, 1:200) and anti-chromogranin A (mc, Boehringer, Mannheim, Germany, 1:100).

For the second layer biotinylated anti-IgG and for the third layer the avidin/biotinylated peroxidase complex was used. Chromogen was diaminobenzidine. For the hypothalamic hormones GHRH and CRH normal human hypothalamus from autopsy was used as positive control. The omission of primary antibody served as specificity control.

Results

Case 1

Histology revealed two tumours: a larger tumour with a diffuse pattern composed of medium-sized moderately pleomomorphic cells. Their nuclei appeared to be of medium size. Their chromatin was poorly developed and their nucleoli were medium-large. The cytoplasm was broad, acidophil and partly elongated. Some necrobiotically shrunken cells were intermingled. Connective tissue was sparsely developed around the capillaries. Immunohistologically, there was positivity for GH in about 50% of cells and for prolactin in about 20% of cells. No other pituitary hormones were expressed. Keratin was demonstrable in a globular perinuclear pattern indicating fibrous bodies. This lesion was classified as a mixed GH/prolactin cell adenoma.

The other, smaller tumour was irregularly outlined (Fig. 1) and revealed ganglionic cells of slightly variable size with large oval nuclei, distinct large nucleoli and broad cytoplasm with Nissl's substance. Some harboured two nucleoli. The cells were embedded in an eosinophilic fibrillar matrix with sparse cells of glial type.

Case 2

Histology presented two different relatively sharply demarcated parts. The larger, centrally located, was composed of adenoma tissue with very similar structures to case 1. Immunohistologically (Table 1), 50% of tumour-cells were positive for GH and 20% for prolactin. The other pituitary hormones, S-100-protein, releasing-hormones, GFAP and neurofilament were not immunostained. Keratin was demonstrable in a globular perinuclear pattern indicating fibrous bodies. An electron microscopic analysis was not possible as this tumour part was not included in Epon embedded tissue.

Table 1 Clinicopathological data in sellar gangliocytomas combined with pituitary adenomas

Case	Age/Sex	Hyperfunction	Immunostaining		Adenoma classification
			Gangliocytoma	Pituitary adenoma	
1	27y F	Acromegaly, hyperprolactinemia	Not done	GH+, Prolactin+ other pituitary hormones negative	GH/Prolactin cell adenoma
2	28y F	Acromegaly	GHRH ++, CRH (+) GFAP +[a], –; Neurofilament +, Synaptophysin +, NSE ++, Keratin +, Vimentin[a]	GH ++, Prolactin +, other pituitary hormones negative	GH/Prolactin cell adenoma
3	10y F	Cushing´s disease	CRH +, GFAP –, S100-Protein –, Synaptophysin +, NSE +	ACTH +++, other pituitary hormones negative, Keratin ++, S100-protein neg.	Densely granulated ACTH cell adenoma

[a] Not in tumour cells but in associated glial tissue

Table 2 Hypothalamic-sellar tumours and pituitary lesions in Cushing´s disease

Authors and year	Age and sex	Hypothalamic-sellar tumour (classification and immunostaining)	Pituitary lesion
Asa et al. 1984	58y F	gangliocytoma CRH +, glucagon (+), pituitary hormones neg.	ACTH cell hyperplasia (no adjacent pituitary)
Nawata et al. 1990	53y M	neuronal tumor (?)[a]	metastasizing pituitary carcinoma with distinct cell populations: one CRH +[a], one ACTH +, one CRH and ACTH +
Jakumeit et al. (1974) (case 3) Olivier et al., (1975) (case 4) Li et al., (1989) (case 3)	31y F	Gangliocytoma CRH –, ACTH +, somatostatin +, βLPH + E_{max}	ACTH cell adenoma adjacent pituitary not mentioned
Nishio et al., 1987	58y F	Gangliocytoma CRH +	?
Present case (Table 1)	10y F	Gangliocytoma CRH + pituitary hormones negative	ACTH cell adenoma very sparse compressed adjacent pituitary without ACTH cells

[a] Presumably representing a hypothalamic neuronal tumour

As in case 1, the tumour was classified as a mixed GH/prolactin cell adenoma.

The smaller tumour portion showed ganglionic cells in a fibrillar matrix with sparse glial cells. Within this tumour dense fibrous tissue of collagenous type with granulation tissue was observed and appeared to be connected with previous surgery. Immunostaining (Table 1) showed GHRH in the ganglionic cells and also NSE, synaptophysin, chromogranin A and neurofilament.

The sparse glial elements were partly positive with anti-GFAP and with anti-S100-protein. Pituitary hormones were not demonstrated in this tumour.

Electron microscopically the slightly lobated nuclei revealed condensed chromatin, small partly doubled nucleoli and a dilated nuclear membrane. The rough endoplasmic reticulum was sparsely developed and partly dilated. Secretory granules were sparse, small to medium-sized and partly oval. Mitochondria were numerous, oval or slightly irregular and harboured numerous slightly irregular cristae. Microvesicles as synaptic vesicles were strongly developed. The cellular membranes appeared slightly winding.

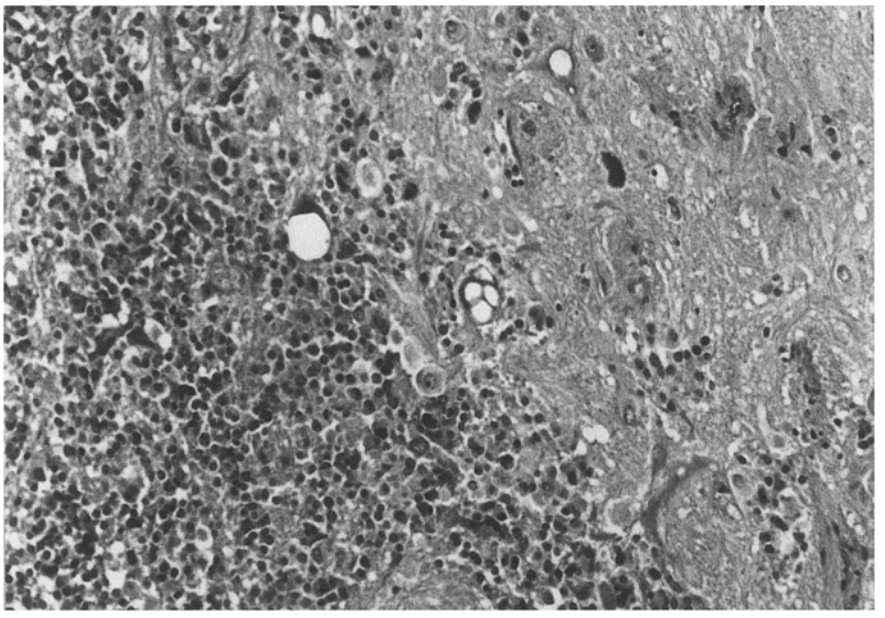

Fig. 1 Gangliocytoma and GH/Prolactin cell adenoma (case 1). Adenoma with relatively small, densely arranged cells (left) and GHRH-gangliocytoma with large cells (right). Haematoxylin-eosin, 160×

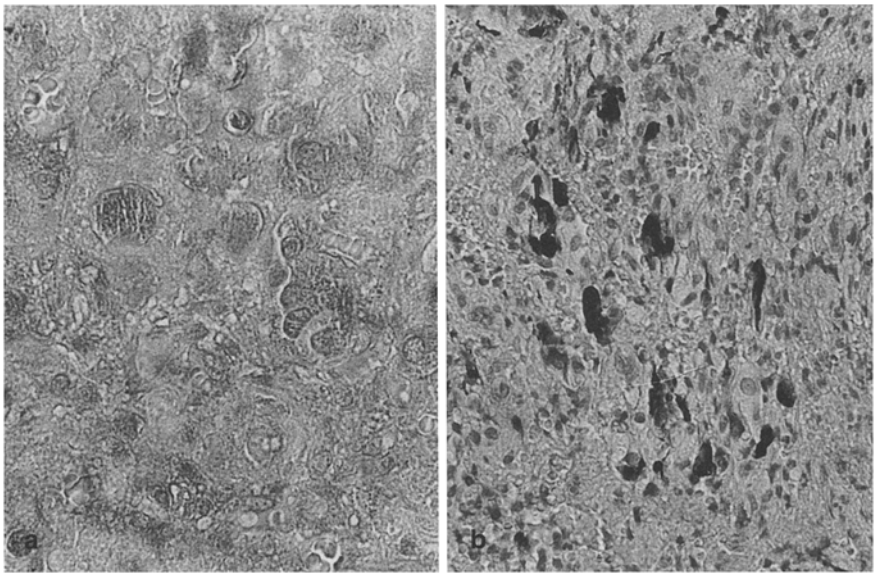

Fig. 2a CRH-gangliocytoma (case 3): large cells of gangliocytic type, positive for CRH. Anti-CRH, 450×. **b** (Case 3) CRH-gangliocytoma: sparse glial cells. Anti-GFAP, 280×

Case 3

Histology revealed a large cell tumour adjacent to a tumour with smaller cells. There was no sharp border between the two lesions (Fig. 3).

The smaller cells corresponded to adenoma cells showing oval nuclei with medium amounts of chromatin and distinct nucleoli and a PAS-positive granular cytoplasm. The larger cells resembled ganglionic cells with medium-sized oval nuclei and distinct nucleoli. The cytoplasm was broad, acidophilic and slightly granular.

Immunostaining (Table 1) revealed CRH- (Fig. 2a), NSE- and synaptophysin-reactivity in the gangliocytic tumour, which was negative for GHRH, S100-protein, keratin and pituitary hormones. Sparse small foci of glial cells expressing GFAP (Fig. 2b) were found at the periphery. The adenoma was positive for ACTH (Fig. 3) and keratin, and negative for the other pituitary hormones, GFAP, S100-Protein and releasing hormones. Electronmicroscopically (Fig. 4), the adenoma cells displayed oval or slightly lobated nuclei with small nucleoli, a moderately developed rough endoplasmic reticulum, medium-sized Golgi complexes, numerous secretory granules of medium size, sparse small lysosomes with much pigment, sparse oval mitochondria and focally densely arranged cytofilaments. The ganglionic cells (Fig. 5) contained slightly lobated nuclei with condensed chromatin at the periphery and medium-sized nucleoli. The rough endoplasmic reticulum was sparsely developed and partly dilated. The Golgi complexes were small and showed partly dilated cisterns. Secretory granules were rare and small. Some larger granules resembled

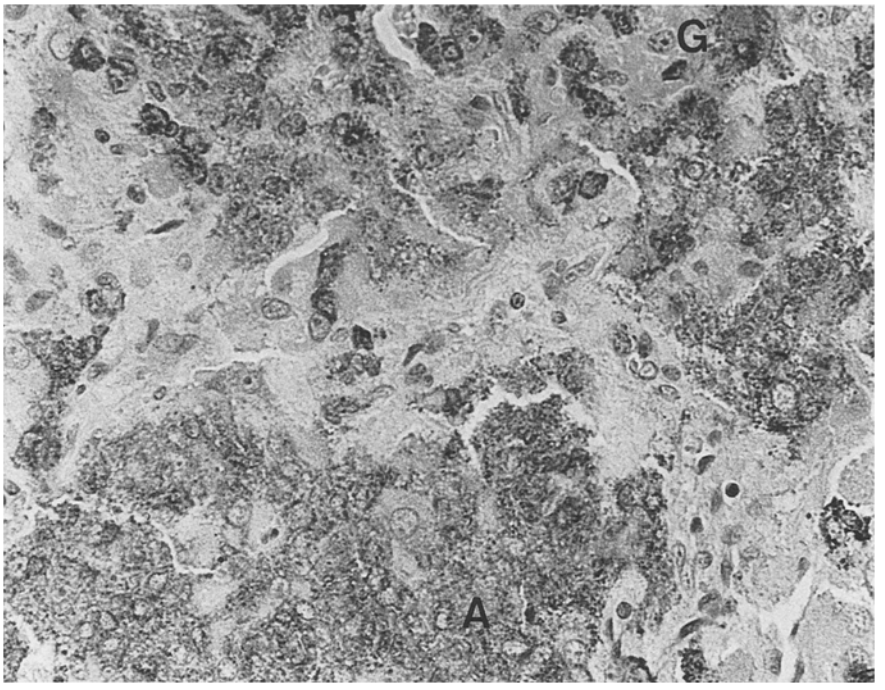

Fig. 3 CRH-gangliocytoma and ACTH-cell adenoma (case 3): CRH-gangliocytoma (upper right and left) (G) and adenoma (A), positive for ACTH, with indistinct border and intermingled adenoma cells (upper part). Anti-ACTH, 400×

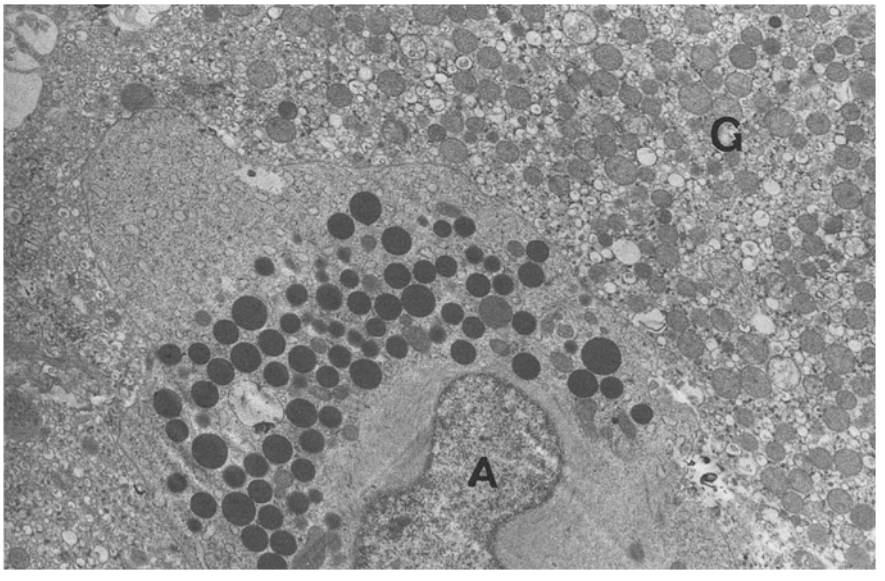

Fig. 4 CRH-gangliocytoma and ACTH cell adenoma (case 3): Adenoma cell (*A*) with many secretory granules and cytofilaments and gangliocytoma cell (*G*) with mitochondria and synaptic vesicles. Uranyl-acetate-lead citrate, 7200×

lysosomes. Mitochondria were numerous, oval or circular and showed tubular cristae. Rarely, they were combined with lamellar bodies of equal size. Also numerous were vesicles of synaptic type (Fig. 5). Some lamellar structures were found which resembled myelin sheaths. The contact zone between both tumours (Fig. 4) was characterized by very narrow intercellular spaces and desmosomal complexes. Typical synapses were not observed.

Discussion

In three patients, two with acromegaly and one with Cushing's disease, we found a composite sellar lesion consisting of a gangliocytoma and a pituitary adenoma. Apart from the neoplastic tissue there were also some rare glial elements in the gangliocytomas of cases 2 and 3 which appeared to be reactive rather than neoplastic proliferations. Therefore we did not use the terms "gangliоglioma" [5], ["hamartoma" [1, 29, 31] or "choristoma" [26, 33], but called the neuronal lesions gangliocytoma [19]. In a first brief communication of our third case in a review [23], the gangliocytic tumour was

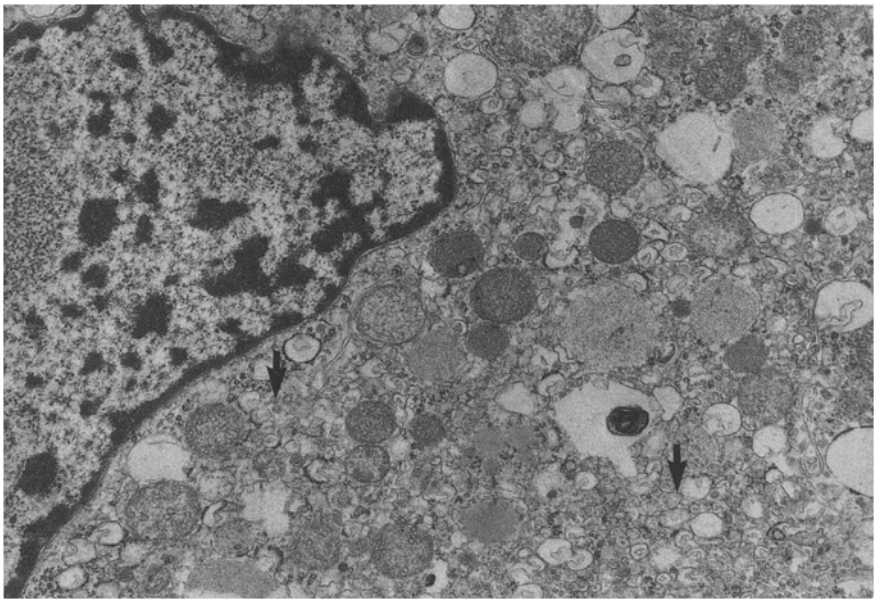

Fig. 5 CRH-gangliocytoma (case 3): gangliocytoma cell with many synaptic vesicles (*arrows*), mitochondria and lysosomes. Uranyl acetate-lead citrate, 14300×

named a choristoma, i.e. a tumour-like growth of heterotopic tissue, according to the definition of Zülch [34]. Such choristomas, some with acromegaly [18, 33] had already previously been published. Our electron microscopic examinations and immunostaining for neuronal and glial markers, however, revealed only sparse glial cells between and particularly around the gangliocytoma cells (Fig. 2b). These cells appeared to be comparable with the S100-protein-positive satellite cells in phaeochromocytomas [8] and the folliculo-stellate cells in pituitary adenomas [10] which are regarded as remnants of normal tissue or as reactive proliferations, but not as another tumour cell type.

In the gangliocytoma we demonstrated GHRH and CRH, respectively, while in the pituitary adenomas GH/prolactin and ACTH, respectively, were found. The distribution of the hormones to the various tumours suggests that the gangliocytomas may have triggered the development of pituitary adenoma via paracrine secretion of the hypothalamic releasing hormones. The resulting pituitary adenomas were then the source of the elevated hormones responsible for the hormonal syndromes.

Only in the second patient, were the gangliocytoma and the adenoma sharply demarcated. In the other two patients the tumours had blurred outlines and appeared to invade each other. This combination of a gangliocytoma and an adenoma is very rare. Only 28 cases have so far been published (for review see [17]). Most cases with acromegaly and a GHRH-positive gangliocytoma revealed similar findings. [17].

Our third case, the patient with Cushing's disease, seems to be unique (Table 2); the case reported by Asa et al. [1] did not show an adenoma but an ACTH cell hyperplasia beside the gangliocytoma; the case of Li et al. [9] – also published by Jakumeit et al. [6] and Olivier et al. [15] – was not immunoreactive for CRH but positive for ACTH in the gangliocytoma part; and the case of Nawata et al. was a CRH- and ACTH-secreting carcinoma of the pituitary.

A few extra-hypothalamic and extra-sellar GHRH-producing tumours, were also reported mainly in the pancreas and lung [12, 22], for review [24]. In these tumours the histology differs from that of the gangliocytomas, showing aspects of a typical neuroendocrine tumour, with some similarities to paragangliomas. Ultrastructurally [22] secretory granules measuring 100–250 nm or about 600 nm, microtubules, microfilaments, Nebenkerne, short or medium-long rough endoplasmic reticulum, oval mitochondria with lamellar cristae in varying numbers and abundant free ribosomes were found. Despite the same product being secreted, GHRH, the structure of the tumours is thus very different. CRH was identified in extra-hypothalamic tumours [3] mainly in small cell carcinomas of the lung and in carcinoids of bronchus or thymus. Again, these tumours failed to show any similarities to CRH producing gangliocytomas. The accompanying adenomas do not differ from those without gangliocytomas. All were reported to be sparsely granulated adenomas harboring GH immunoreactive cells [4, 7].

In cases with extra-sellar GRH-secreting tumours no GH-cell adenomas but GH-cell hyperplasias were identified. It is unclear why oversecretion of the same releasing hormone induces an adenoma if it comes from a sellar gangliocytoma, or only hyperplasia, if originating from extra-sellar sources. It may base on the type of secretion (paracrine versus endocrine) or on the concentration or level of the releasing hormones from the gangliocytoma; or else further agents, especially neurotransmitters or other hormones [20] are expressed in sellar gangliocytomas and responsible for the development of pituitary adenomas.

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References

1. Asa SL, Bilbao JM, Kovacs K, Linfoot JA (1980) Hypothalamic neuronal hamartoma associated with pituitary growth hormone cell adenoma and acromegaly. Acta Neuropathol (Berl) 52:231–234
2. Asa SL, Kovacs K, Tindall GT, Barrow DL, Horvath E, Vecsei P (1984) Cushing's disease associated with an intrasellar gangliocytoma producing corticotrophin-releasing factor. Ann Int Med 101:789-793
3. Asa SL, Kovacs K, Vale W, Petrusz P, Vecsei P (1987) Immunohistologic localization of corticotropin-releasing hormone in human tumors. Am J Clin Pathol 87:327–333
4. Bevan JS, Asa SL, Rossi ML, Esiri MM, Adams CBT, Burke CW (1989) Intrasellar gangliocytoma containing gastrin and growth hormone-releasing hormone associated with a growth hormone-secreting pituitary adenoma. Clin Endocrinol 30: 213–224
5. Courville CB (1930) Ganglioglioma. Tumor of the central nervous system: review of the literature and report of two cases. Arch Neurol Psychiat 24:439–491
6. Jakumeit H-D, Zimmermann V, Guiot G (1974) Intrasellar gangliocytomas. Report of four cases. J Neurosurg 40:626–630
7. Kamel OW, Horoupian DS, Silverberg GD (1989) Mixed gangliocytoma-adenoma: a distinct neuroendocrine tumor of the pituitary fossa. Hum Pathol 20:1198–1203
8. Lauriola L, Maggiano N, Sentinelli S, Michetti F, Coccia D (1985) Satellite cells in the normal human adrenal gland and in pheochromocytomas. An immunohistochemical study. Virchows Arch [B] 49:13–22
9. Li JY, Racadot O, Kujas M, Kouadri M, Peillon F, Racadot J (1989) Immunocytochemistry of four mixed pituitary adenomas and intrasellar gangliocytomas associated with different clinical syndromes: acromegaly, amenorrhea-galactorrhea, Cushing's disease and isolated tumoral syndrome. Acta Neuropathol (Berl) 77:320–328
10. McNicol AM (1991) Folliculostellate cells in pituitary adenomas: studies of hormonal profile and tumor vascularity. Endocr Pathol 2:193–199
11. Melmed S (1992) Etiology of pituitary acromegaly. Endocrinol Metab Clin North Am 21:539–551
12. Melmed S, Ezrin C, Kovacs K, Goodman RS, Frohman LA (1985) Acromegaly due to secretion of growth hormone by an ectopic pancreatic islet-cell tumor. N Engl J Med 312:9–17
13. Nawata H, Higuchi K, Ikuyama S, Kato K-I, Ibayashi H, Mimura K, Sueishi K, Zingami H, Imura H (1990) Corticotropin-releasing hormone- and adrenocorticotropin-producing pituitary carcinoma with metastases to the liver and lung in a patient with Cushing's disease. J Clin Endocrinol Metab 71: 1068–1073
14. Nishio S, Takei Y, Fukui M (1987) Immunoreactivity with "hypothalamic" neuropeptides in neuronal neoplasma of the central nervous system (in Japanese). Neurol Med Chir (Tokyo) 27:105–109
15. Olivier L, Racadot J, Vila-Procile E, Racadot O (1975) Adenomes hypophysaires et ganglioneuromas de la selle turcique. J Microsc Biol Cell 23:66a–67a
16. Puchner MJA, Lüdecke DK, Valdueza JM, Saeger W, Willig RP, Stalla GK, Odink RJ (1993) Cushing's disease in a child caused by a corticotropin-releasing hormone-secreting intrasellar gangliocytoma associated with an adrenocorticotropic hormone-secreting pituitary adenoma. Neurosurgery 33:920–925
17. Puchner MJA, Lüdecke DK, Saeger W, Riedel M, Asa SL (1994) Gangliocytoma of the sellar region – a review. Exp Clin Endocrinol (in press)
18. Rhodes RH, Dusseau JJ, Boyd AS Jr, Knigge KM (1982) Intrasellar neural-adenohypophyseal choristoma: a morphological and immunocytochemical study. J Neuropathol Exp Neurol 41:267–280
19. Russell DS, Rubinstein LJ (1989) Pathology of tumours of the nervous system. 5th edn, Arnold, London
20. Saeger W (1992) Effect of drugs on pituitary ultrastructure. Microsc Res Techn 20:162–176
21. Saeger W, Schmidt W (1979) Vor- und Frühformen der Hypophysenadenome. Histologische und statistische Untersuchungen am unausgewählten Sektionsgut. Verh Dtsch Ges Pathol 63:409–415
22. Saeger W, Schulte HM, Klöppel G (1986) Morphology of a GHRH producing pancreatic islet cell tumour causing acromegaly. Virchows Arch A Path Anat 409:547–554
23. Saeger W, Reincke M, Scholz GH, Lüdecke DK (1993) Ektop ACTH- oder CRH-bildende Tumoren mit Cushing-Syndrom. Zentralbl Pathol 139:157–163
24. Sano T, Asa SL, Kovacs K (1988) Growth hormone-releasing hormone-producing tumors: clinical, biochemical, and morphological manifestations. Endocrinol Rev 9:357–373
25. Scheithauer BW (1991) The hypothalamus and neurohypophysis. In: Kovacs K, Asa SL (eds) Functional endocrine pathology, vol 1: Blackwell, Oxford, pp 170–244
26. Scheithauer BW, Kovacs K, Randall RV, Horvath E, Okazaki H, Laws ER (1983) Hypothalamic neuronal hamartoma and adenohypophyseal neuronal choristoma: their association with growth hormone adenoma of the pituitary gland. J Neuropathol Exper Neurol 42:648–663
27. Scheithauer BW, Kovacs K, Randall RV (1983) The pituitary gland in untreated Addison's disease. A histologic and immunocytologic study of 18 adenohypophyses. Arch Pathol Lab Med 107:484–487
28. Scheithauer BW, Kovacs K, Randall RV, Ryan N (1985) Pituitary gland in hypothyroidism. Histologic and immunocytologic study. Arch Pathol Lab Med 109:499–504
29. Schindler C, Nürnberger F, Schachenmayr W (1993) Invasive pituitary adenoma in a patient with hypothalamic neuronal hamartoma. Clin Neuropathol 12:264
30. Schulte HM, Benker G, Windeck R, Olbricht T, Reinwein D (1985) Failure to respond to growth hormone releasing hormone (GHRH) in acromegaly due to a GHRH secreting pancreatic tumor: dynamics of multiple endocrine testing. J Clin Endocr Metab 61:585–587
31. Slowik F, Fazekas I, Balint K, Gaszo L, Pazstor E, Czirjak S, Lapis K (1990) Intrasellar hamartoma associated with pituitary adenoma. Acta Neuropathol (Berl) 80:328–333
32. Thorner MO, Perryman RL, Cronin MJ, Rogol AD, Draznin M, Johanson A, Vale W, Horvath E, Kovacs K (1982) Somatotroph hyperplasia – successful treatment of acromegaly by removal of a pancreatic islet tumor secreting a growth hormone-releasing factor. J Clin Invest 70:965–977
33. Ule G, Waidelich FW (1976) Neurosecretory nerve-cell choristoma in the anterior pituitary. Acta Neuropathol (Berl) 36:81–84
34. Zülch KJ (1982) Brain tumors: their biology and pathology. 3rd edn. Springer, Berlin Heidelberg New York, pp 292–301, pp 445–447