‘Gangliocytomas’ of the Pituitary
A Heterogeneous Group of Lesions With Differing Histogenesis

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Hamartomatous or neoplastic ganglion cells in the sella turcica are an unusual cause of symptoms. They have been reported in association with a functioning or nonfunctioning pituitary adenoma, with pituitary cell hyperplasia, and occasionally as masses unassociated with an adenoma, again with variable endocrinologic findings. Fewer than 50 cases of intrasellar ganglion cell lesions have been reported in the literature, only six of them associated with Cushing’s syndrome. We describe the clinicopathologic features of another eight patients, three of whom presented with acromegaly, four with apparently nonfunctioning adenohypophyseal masses, and one with Cushing’s syndrome. On histology, six of them were found to have sparsely granulated growth hormone (GH)-producing adenomas with ganglion cell areas, one appeared to have a gangliocytoma not associated with an adenoma, whereas the eighth had a ganglion cell lesion in the posterior pituitary. The morphologic and immunohistochemical findings suggest that the ganglion cell component of seven of these tumors has resulted from neuronal differentiation in a GH-producing adenoma, despite the lack of demonstrable adenoma in one case. A true sellar “gangliocytoma” or hamartoma of ectopic hypothalamic-type neurons appears to be a rarer explanation for the presence of ganglion cells in a pituitary biopsy.

Key Words: Anterior pituitary—Gangliocytoma—Ganglion cell tumor—Growth hormone adenoma—Neurohypophysis.


Although the adenohypophysis and the neurohypophysis do not normally contain neurons, occasional pituitary tumors composed partly or entirely of ganglion cells have been reported. Being uncommon, these tend to be found in the literature as case reports or small series, so that differences between cases, or indeed, similarities, tend not to be evident. The terminology is confusing, and their taxonomy not resolved, although the usual assumption is that they have a uniform histogenesis. Two recent reviews by Puchner et al.19 and Towfighi and coworkers25 have assembled the entities that have been described. Towfighi concluded that a common origin from embryonal pituitary cell rests that have features intermediate between neurons and adenohypophyseal cells was most likely, whereas Puchner favored a common hypothalamic origin. A careful immunocytochemical and ultrastructural study from Horvath et al., ignored by subsequent authors, has suggested that the neuronal component may be the result of neuronal differentiation in sparsely granulated growth hormone cell adenomas. We have studied eight intrasellar ganglion cell lesions, seven of which have histopathologic appearances that would support this as the mechanism of origin; the eighth lesion clearly has a different histogenesis.

METHODS AND CLINICAL DETAILS

All eight biopsies were stained with hematoxylin and eosin (H&E), reticulin, periodic acid Schiff’s (PAS), hematoxylin van Gieson (HVG), and Nissl stains. Immunohistochemistry was performed on all cases, the antibodies used being ACTH (Dako, Denmark; monoclonal, used at a dilution of 1:1000); GH (Dako, polyclonal 1:1200); PrL (Dako, polyclonal 1:800); TSH, FSH, LH (Dako, monoclonal 1:400 [TSH], 1:300 [FSH], 1:600 [LH]); αSU (Biogenesis, polyclonal 1:10000); GFAP (Dako, monoclonal 1:2000); synaptophysin (Dako, monoclonal 1:500); 2F11 (Dako, monoclonal 1:200); and MNF116 (Dako, monoclonal 1:100). Where sufficient tissue remained, staining for GHRH and CRH was also performed (polyclonal antisera raised by the Department of Endocrinology, St. Bartholomew’s Hospital, London, used at a dilution of 1:10000). There was insufficient material in any of the cases for glutaraldehyde fixation; electron microscopy on “lift-off” preparations of two tumors was unsuccessful.
Two control series were used. The first, a collection of 25 assorted ganglion cell and neuroendocrine lesions, was retrieved from the surgical pathology files. These comprised 14 neuroepithelial lesions containing neuronal cells (2 hypothalamic hamartomas, 2 cerebral gangliocytomas, 4 gangliogliomas, 1 medulloblastoma, 2 adrenal ganglioneuromas, and 3 peripheral ganglioneuroblastomas), and 11 neuroendocrine tumors (7 paragangliomas and 4 pheochromocytomas). Sections of each were stained with anti-cytokeratin antisera (MNF116). A second series, comprising six consecutive sparsely granulated GH adenomas taken from the surgical neuropathology files, was stained for cytokeratin and neurofilament (2F11) on serial sections.

Case 1

A 45-year-old man with short stature since childhood presented with sudden onset of headaches, found to be the result of a sellar tumor which showed marked suprasellar extension. It was incompletely resected but no further treatment was given. In the 9-year follow-up period since surgery, the residual tumor has shown no regrowth.

Case 2

A 43-year-old woman presented with a 1-year history of left temporal visual field impairment and thickening of her fingers. Investigations revealed persistently elevated serum GH concentration, and computed tomography (CT) revealed a sellar mass with suprasellar extension causing chiasmal compression. The tumor was completely resected. Postoperatively, mean serum growth hormone levels were in the normal range.

Case 3

A 60-year-old woman presented with a 3-year history of headache. CT and magnetic resonance imaging (MRI) scans revealed a mass in the sella, partially enhancing with contrast, compressing the chiasm. Pituitary function was normal on preoperative endocrine investigation. A 2-cm mass was completely resected.

Case 4

This 38-year-old woman had had features of acromegaly for several years before being referred to an endocrinologist. She was found to have nonsuppressible GH hypersecretion, and MRI showed a large sellar–suprasellar tumor displacing the stalk and extending into the right cavernous sinus. She underwent transsphenoidal hypophysectomy and 6 months later a second operation for residual tumor.

Case 5

A young male presented with acromegaly and gigantism at the age of 18 and was found to have an intrasellar mass lesion. He was initially treated with bromocriptine and radiotherapy but despite treatment, the tumor increased in size. A CT scan performed 4 months later showed that it now involved the left cavernous sinus. The tumor was incompletely resected, but sequential scans over the succeeding 19 years have shown an enhancing residual mass which has not changed significantly in size.

Case 6

A 56-year-old woman presented with persistent headaches and was found on examination to have bitemporal hemianopia. An MRI scan demonstrated a pituitary mass with suprasellar extension compressing the optic chiasm. The mass enhanced with contrast but remained relatively hypointense in comparison to the normal pituitary tissue. The patient’s pituitary function was normal on endocrine assessment, and she was referred for neurosurgery. At operation there was an apparent plane of cleavage between normal pituitary and a firm gray mass situated in the left side of the gland. The patient received radiotherapy to the residual tumor.

Case 7

A 53-year-old woman had observed an increase in the size of her feet and hands over the previous 2 years and deterioration of her vision for 2 months. Investigation demonstrated raised GH and prolactin levels, and CT and MRI showed an intrasellar tumor with suprasellar extension. She underwent a frontotemporal craniotomy and her tumor was partially resected.

Case 8

A 54-year-old man presented with a 12-month history of back pain, weight gain, proximal weakness, and clinical evidence of Cushing’s syndrome. Further investigation demonstrated elevated 24-hour urine free cortisol, symmetric adrenal gland appearances on computerized tomography, grossly raised plasma ACTH, displacement of the infundibulum on MR imaging, and a suggestion of a posterior placed intrasellar tumor on dynamic CT scanning. Further investigation, including inferior petrosal sinus sampling, supported a diagnosis of pituitary-dependent Cushing’s syndrome. A 1-cm lesion was removed trans-sphenoidally. Postoperative serum cortisol concentrations were unrecordable, confirming cure of the Cushing’s, and he remained dependent on hydrocorti-
sone replacement for the next 2 years. Five years postoperatively there is no evidence of disease recurrence.

**HISTOLOGIC FINDINGS**

The principal immunocytochemical findings are given in Table 1.

**Cases 1–6**

The first five cases were all adenomas showing variable, but usually sparse, immunoreactivity for GH, with characteristic globular juxtanuclear positivity for cytokeratins (“fibrous bodies”) in the cytoplasm of tumor cells. In addition, in each case there were large ganglion cell areas intermingled with the adenoma, with variable amounts of connective tissue intersecting the neuropil. Morphologically, the neuronal cells ranged from relatively normal forms with peripheral Nissl substance to large bizarre bi- and trinucleate cells. In cases 2, 3, and 4 there were also several smaller foci of neuropil scattered through the adenoma (Fig. 1), at the edges of which nuclei appeared to be transitional between adenohypophyseal and ganglion cells. Occasional large neuronal cells could be found in otherwise unremarkable adenomatous tissue (Fig. 2).

Case 6 appeared, on routine stains, to be a gangliocytoma with crushed anterior pituitary cells at the periphery. However, on immunocytochemistry these pituitary cells were all GH-positive and all contained fibrous bodies, strongly suggesting that they too derived from a sparsely granulated GH-producing adenoma.

In all six tumors there was cytokeratin positivity in the neuronal areas as well as in fibrous bodies. Some of the ganglion cells displayed diffuse cytoplasmic cytokeratin immunoreactivity (Fig. 3), often extending into dendrites or axons, and also occasional small globular cytoplasmic deposits of positive staining, which resembled fibrous bodies. Other neurons showed no staining for cytokeratin. However, diffuse immunoreactivity for neurofilament was seen in all ganglion cells, although the intensity varied from cell to cell. The overall appearances were of transition from cytokeratin to neurofilament expression in neuronal cells.

There was no pituitary hormone expression in ganglion cells in any of the six cases.

**Case 7**

There was no pituitary adenoma in case 7, the tumor being entirely a ganglion cell lesion, otherwise identical to cases 1 through 6. On immunohistochemistry some of the ganglion cells expressed cytokeratin, both in their cytoplasm and in processes, seen both as diffuse staining and as dense, rounded cytoplasmic collections.

**Case 8**

There was no adenoma or normal anterior pituitary in the material excised. The small biopsy comprised fragments of normal posterior pituitary tissue as well as some which also contained groups of ganglion cells. Some of these cells resembled hypothalamic neurons; most were small and did not have the rather pleomorphic appearances seen in some of the other lesions in this series. Immunostaining revealed intense expression for synaptophysin outlining the neuronal cell borders. In between

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**TABLE 1. Immunohistochemical results on ganglion cell lesions**

<table>
<thead>
<tr>
<th>Case</th>
<th>GH</th>
<th>PrL</th>
<th>ACTH</th>
<th>FSH</th>
<th>LH</th>
<th>TSH</th>
<th>αSU</th>
<th>GHRH</th>
<th>CRH</th>
<th>MNF116</th>
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</thead>
<tbody>
<tr>
<td>Case 1</td>
<td>+</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>n/d</td>
<td>n/d</td>
</tr>
<tr>
<td>Case 2</td>
<td>+</td>
<td>+§</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>n/d</td>
<td>n/d</td>
</tr>
<tr>
<td>Case 3</td>
<td>+</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>n/d</td>
<td>n/d</td>
</tr>
<tr>
<td>Case 4</td>
<td>+</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>n/d</td>
<td>n/d</td>
</tr>
<tr>
<td>Case 5</td>
<td>++</td>
<td>+</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>+o</td>
<td>A;N</td>
</tr>
<tr>
<td>Case 6</td>
<td>+</td>
<td>+§</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>A;N</td>
</tr>
<tr>
<td>Case 7</td>
<td>no adenoma present</td>
<td>N</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Case 8</td>
<td>o</td>
<td>o</td>
<td>+</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>n/d</td>
</tr>
</tbody>
</table>

++, strong staining; +, positive staining; o, no immunoreactivity; n/d, not done (insufficient tissue); A, staining in adenoma; N, staining in neurons and neuropil; §, weak positivity.

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**FIG. 1.** In addition to large ganglion cell areas, several of the adenomas contained multiple small foci of tumor neuropil, highlighted by immunocytochemistry for neurofilament (2F11).
these ganglion cells, there were small groups of PAS-positive anterior pituitary cells with granular eosinophilic cytoplasm, all strongly immunoreactive with anti-ACTH antiserum (Fig. 4). The neurons themselves did not express ACTH or CRH. No other anterior pituitary cells were included in the biopsy. Staining for GFAP was negative. The lesion was interpreted as a gangliocytoma in pars nervosa surrounded by non-neoplastic corticotrophs, possibly from an area of “basophil invasion.”

Examination of the tumor by in situ hybridization was negative for both CRH and AVP mRNA. CRH was not detectable in plasma stored during petrosal sinus sampling, and it was not detected during in vitro culture. No tissue remained for further study.

**Control Series**

**Ganglion Cell and Neuroendocrine Lesions**

No immunoreactivity for cytokeratins was seen in the hypothalamic hamartomas, in any of the central neuroepithelial tumors, or in the peripheral neuroblastic lesions. There was, however, variable expression in the paragangliomas. Two of the cauda equina tumors, which showed extensive ganglionic differentiation, were strongly positive, both in the tumor and in the ganglion cells (Fig. 5), the latter also expressing neurofilament. A paraganglioma of the thymus and two of the pheochromocytomas were the only other tumors to show strong immunoreactivity with anti-cytokeratin antisera. Three other paragangliomas and another pheochromocytoma contained rare cells that were positive.

**Sparsely Granulated GH Adenomas**

All six tumors exhibited cytokeratin-positive fibrous bodies. One tumor in addition showed neurofilament expression in what appeared to be axons in among the adenoma cells, and in rounded cell bodies which may have been neurons.

**DISCUSSION**

Ganglion cell-containing neoplasms in the sella turcica have been infrequently described. A literature re-
view by Towfighi et al. found 42 sellar lesions, whereas Puchner et al. assembled 44. Further reports not included by these authors or published more recently and the eight cases presented here bring the total in the literature to 55. The majority have been mixed gangliocytic and adenohypophyseal tumors; isolated gangliocytic tumors without an adenomatous component are distinctly rare. The lesions have been variously referred to as “choristomas” (a confusing term often also applied to the unrelated granular cell tumors of the posterior pituitary), “ganglioneuromas,” and more recently “gangliocytomas.” In Towfighi’s well-documented series, 28 of the 32 patients in whom an adenoma was found were endocrinologically symptomatic: acromegaly (in a few cases with galactorrhea and amenorrhea) was seen in 19 patients, Cushing’s in five, and three had galactorrhea/amenorrhea alone. One patient also had Zollinger-Ellison syndrome associated with MEN1. In four cases the adenoma was endocrinologically silent. Of the 10 patients with an isolated sellar gangliocytoma, two presented with acromegaly, one with Cushing’s syndrome, one with diabetes insipidus, and one with hypopituitarism. Five had no endocrine symptoms.

Neuronal Differentiation in GH-Producing Adenomas

At first sight, the ganglion cell lesions in our series fall into three neuropathologically distinct groups: (1) admixed with a GH-producing adenoma (cases 1–6), (2) apparently occurring as an isolated tumor (case 7), and (3) as a functioning lesion in the posterior pituitary (case 8). However, we think the first two groups, comprising the majority of our cases, occur as the result of neuronal differentiation in a pituitary adenoma. The histologic appearances of cases 2, 3, and 4 in particular, in which several small foci of neuropil containing mature ganglion cells were seen with considerable intermingling of adenoma and ganglion cells, strongly suggested this possibility, as did the apparent morphologic and immunohistochemical transition between the two cell types. Neuronal differentiation is a well-recognized, if rare, feature of other neuroendocrine tumors, such as the paraganglioma. In 1984, Asa et al., describing four intrasellar gangliocytomas causing acromegaly, noted “an intimate association between neurons and adenomatous GH cells” on electron microscopy. Ten years later, the same workers reviewed 14 cases of this type of pituitary ganglion cell lesion, and noted not only that several cases contained cells transitional between adenoma cells and neurons on ultrastructure, but also that one tumor showed remarkable progression toward a neuronal phenotype with subsequent biopsies. They concluded with the hypothesis that their lesions were the result of neuronal differentiation within sparsely granulated GH cell adenomas. The alternative hypothesis, namely, that the presence of a GHRH-producing gangliocytoma had resulted in hypersecretion and eventual adenomatous transformation of surrounding pituitary, with the adenoma finally overrunning the original ganglion cell lesion, was discounted by these authors. Their view was that morphologic evidence of previous GH cell hyperplasia was lacking, that in three of their cases, like three of ours, there were no clinical manifestations of GH excess. A previous report that also lends support to the hypothesis that some gangliocytic pituitary lesions represent neuronal differentiation in an adenoma is that of Li et al., who detected pituitary hormones in the neuronal element of three pituitary adenomas, two functioning, the hormones in question being prolactin and ACTH.
The immunohistochemical findings in our two control series would also favor such an interpretation. We studied a small unselected group of sparsely granulated GH adenomas with a neurofilament antiserum to see whether expression of neuronal epitopes could be detected in otherwise unremarkable tumors. One of the six did show focal neurofilament expression, both in axons and in rounded cell profiles which looked like neurons, which had not been noticed on routine stains. We also examined a series of 25 neuronal and neuroendocrine tumors to see whether cytokeratin expression was normally present. All the central neuroepithelial and the peripher al neuroblastic tumors were negative, as anticipated, because the characteristic intermediate filament of neuronal cells is neurofilament, not cytokeratin. Six neuroendocrine tumors expressed cytokeratins in varying degrees. Two of them, both cauda equina paragangliomas with extensive ganglionic differentiation, showed staining patterns identical to those seen in our pituitary lesions, with strong globular cytokeratin positivity in paraganglioma cells as well as in the ganglion cells (Fig. 5). Previous workers have documented cytokeratin expression in paragangliomas of the cauda equina, corresponding to fibrillar cytoplasmic inclusions that resemble fibrous bodies; it appears that outside the spinal canal these tumors rarely express cytokeratin.11,15

The staining of adenoma and ganglion cells by MNF116 is remarkable. MNF116 detects keratins 5, 6, 8, 17, and probably 19 (Dako product datasheet). Although cytokeratins are expressed in some pituitary tumors, principally somatotroph and corticotroph adenomas, MNF116 should not be present in ganglion cells. While we cannot prove that MNF116 is detecting the same epitope in both elements of the lesions because we were unable to carry out immunoelectrophoresis, we think this is important evidence of neuronal differentiation in these adenomas.

Finally, the adenohypophysis develops from Rathke’s pouch, which is an ectodermal diverticulum of the stomatodeum. In the embryo, growth hormone is the first of the pituitary hormones that can be detected biochemically and subsequently shown by immunohistochemistry.1 Morphologic studies have shown that the earliest growth hormone-producing cells contain sparse numbers of small granules with a mean diameter of 268 nm and bundles of filaments resembling fibrous bodies. With further maturation these cells decrease in number whereas more densely granulated cells with increasing granule size become predominant.2,24 The morphologic resemblance between these early growth hormone-producing fetal cells and those of sparsely granulated GH adenomas suggest that the latter may represent a more primitive cell line. The common derivation of the adenohypophysis and neural tube from ectoderm may predispose this primitive cell type to differentiate along neuronal pathways.

**Case 7: “Fully Differentiated” Adenoma or Hamartoma?**

Case 7 of the present series, at first sight a different lesion, is probably of similar histogenesis. Although there was no adenoma in the biopsy, the lesion stained in an identical way to the neuronal component of the other six tumors, with many of the neurons expressing both neurofilaments and cytokeratin. We think the most likely explanation for the “gangliocytoma” in this patient is that it represented complete differentiation in what was originally a silent GH-producing adenoma. In the absence of demonstrable adenoma, however, we can do no more than suggest this interpretation; the other possibility is that it was a true mature hamartoma of hypothalamic type.

The boundary between a hamartomatous and a neoplastic ganglion cell lesion is not always clear-cut15, the two belong to a heterogeneous group of malformative entities, some of which show a propensity to enlarge, and which differ principally in the type and number of neurons and the amount of glial cells and connective tissue that they contain, although there are histologic features that may help to discriminate between a hamartoma and a tumor.6 Theoretically, it is also possible that immunocytochemistry for hypothalamic-releasing factors might be useful in this respect.

Central nervous system neuronal hamartomas, although rare, appear to be most frequent in the hypothalamus,23 where they are composed of mature, “normal-looking” neurons and histologically resemble brain tissue, although the cytoarchitecture is not appropriate to their site. The two cases that we included in our control series, first reported by Northfield and Russell in 1967,18 did indeed look like normal, if slightly disorganized, brain. Case 7, on the other hand, was histologically identical to our first six cases, the appearances being more those of a tumor rather than of a neuronal hamartoma; specifically, the chronic inflammatory cell infiltrate, the connective tissue reaction, and the pleomorphism of the ganglion cell element in case 7 would not be expected in a hypothalamic hamartoma.6 Similarly, its immunocytochemical profile was not that of the two hypothalamic hamartomas, but identical to that of cases 1–6. For these reasons we think the suggestion that this was a fully differentiated GH-producing adenoma is most likely, in much the same way as reports of solitary “ganglioneuroma” of the duodenum may well in fact represent a differentiated paraganglioma.14

**Gangliocytic Hamartoma of the Neurohypophysis**

The final case in the series (case 8) was completely different, functionally and neuropathologically. The
patient presented with Cushing’s syndrome, which was cured by surgery, suggesting that the lesion was itself the cause. The morphology was of a collection of relatively normal-appearing small ganglion cells situated in the posterior pituitary with groups of highly granulated corticotrophs interspersed between them. There was no adenoma or anterior pituitary tissue in the material resected, and the lesion appears to have been a hamartoma located in the neurohypophysis. The corticotrophs were presumably part of a population often seen at the edges of the pars nervosa in normal pituitary tissue, the phenomenon termed “basophil invasion.” While we were unable to demonstrate either CRH or AVP mRNA in the tumor, the complete biochemical and clinical remission achieved by surgery strongly supported the hypothesis of paracrine corticotroph stimulation by the lesion.

Few cases of Cushing’s syndrome associated with intrasellar ganglion cell lesions have been described (see reviews by Towfighi and Puchner,22,25), even fewer in which the lesion was found to be the only pathology. In two such cases,5,13 the neuropathologic detail given is insufficient to say whether they could have been sited in posterior pituitary. The earlier case of Asa et al.3 is, however, clearly different from ours, so Cushing’s syndrome caused by ganglion cell lesions may have differing underlying pathology. The neurohypophysis is an exceedingly rare site for ganglion cell tumors; the single case of Robertson and Hetherington,20 two early reports of one case by Benda and Casper (quoted by Robertson and Hetherington), and a recent gangliocytoma reported by Saeger et al.22 are the only examples we can find in the literature.

SUMMARY
We have described a series of sellar lesions composed exclusively or partly of ganglion cells. The majority appear to have resulted from neuronal differentiation in sparsely granulated GH cell adenomas; a single, much rarer lesion which appears to have been a functioning hamartoma causing Cushing’s syndrome is also reported.

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REFERENCES