Endocr Pathol (2008) 19:112–116
DOI 10.1007/s12022-008-9030-6

Ganglioglioma of the Neurohypophysis

B. W. Scheithauer · A. I. Silva · J. E. Parisi · K. Kovacs · E. Horvath

Published online: 22 May 2008

Abstract The normal infundibulum and neurohypophysis consist entirely of neuronal processes, the neuronal cell bodies of which lie within the supraoptic and paraventricular nuclei of the hypothalamus and supportive glial cells or pituicytes. The finding of neurons within the neurohypophysis is exceedingly rare, as are ganglion cell tumors at this site. In this paper, we report a ganglion cell tumor of the neurohypophysis found incidentally at autopsy. Despite chronic hypertension and the finding of some vasopressin immunoreactivity in lesional neurons, the syndrome of inappropriate antidiuretic hormone secretion (SIADH) was excluded on the basis of normal serum sodium levels. The morphologic and immunohistochemical features of the tumor are presented, cytogenetic considerations are discussed, and literature regarding neuronal lesions of the pituitary gland is reviewed.

Keywords ganglion cell tumor · ganglioglioma · pituitary · neurohypophysis · immunohistochemistry

B. W. Scheithauer (✉) · A. I. Silva · J. E. Parisi
Department of Laboratory Medicine and Pathology, Mayo Clinic,
200 First Street, SW,
Rochester, MN 55905, USA
e-mail: scheithauer.bernd@mayo.edu

A. I. Silva
Hospital Sao Marco,
Braga, Portugal

K. Kovacs · E. Horvath
St. Michael's Hospital, University of Toronto,
Toronto, ON, Canada

Introduction

Neurohypophysial lesions are rare. Most consist of inflammatory processes, some related to adenohypophysitis [1]. Neoplasms are rare and consist primarily of glial lesions originating in modified astrocytes of the posterior lobe also termed pituicytes. Such cells presumably give rise to both granular cell tumor [2] and to pituicytoma, a recently characterized tumor [3] distinct from pilocytic astrocytoma, a much more common lesion of the hypothalamus [4]. Neuronal lesions are exceedingly rare. They include one report of neuronal ectopia [5], a lesion less cellular and tumefactive than gangliocytoma, and one example of a symptomatic, vasopressin (antidiuretic hormone)-producing ganglioglioma associated with syndrome of inappropriate antidiuretic hormone secretion (SIADH) [6]. Herein, we report a nonvasopressin-producing neurohypophysial ganglion cell tumor, an incidental autopsy finding. Although associated with hypertension, no evidence of SIADH was apparent on laboratory examination.

Clinical History

The patient was an 89-year-old female with early dementia consistent with Alzheimer's disease, systemic arterial hypertension and an 8-year history of chronic lung disease consistent with usual interstitial pneumonia. She was recently discharged from the hospital for a hip fracture and, shortly thereafter, developed pneumonia. Despite antibiotic and prednisone therapy as well as BiPAP ventilation, she showed no improvement. An echocardiogram revealed severe bi-atrial dilation, aortic valve regurgitation, and left ventricular diastolic dysfunction and hypertrophy. Death was attributed to acute respiratory failure.

Pathology

The 1,260-gram brain showed mild generalized and moderate temporal lobe atrophy corresponding to moderate to marked (Braak & Braak stages IV–V) neurodegenerative changes of Alzheimer type in association with mild-to-moderate amyloid angiopathy. Microsections of the neocortex and mesial temporal lobe structures disclosed moderate diffuse plaques, sparse to moderate neuritic plaques and absent (calcarine) to moderate neurofibrillary tangle and thread formation. Mild cranial arterial atherosclerosis was also noted. Grossly, coronal sections throughout the anteroposterior extent of the hypothalamus appeared normal. Despite lack of gross abnormalities of the pituitary, horizontally cut microsections revealed mild, asymmetric enlargement of the posterior lobe because of a bilobed infiltrate (Fig. 1A), one ill-defined and the other more discrete, consisting of mature neurons and a very minor component of astrocytes. The appearance was that of a ganglion cell tumor (ganglioglioma). The neurons included dysmorphic and occasional binucleate examples (Fig. 1B), some showing marked cytoplasmic neurofibrillary tangle formation (Fig. 1C). No inflammatory infiltrate was noted within the lesion. Basophil invasion, moderate in extent, was partially displaced and partly infiltrated by the tumor, the neurons being intimately associated with the basophils (Fig. 1D). The pituitary stalk and adenohypophysis were normal and uninvolved by tumor. Immunostains (streptavidin–biotin peroxidase complex method) for pituitary hormones showed only normal reactivities within the adenohypophysis, but no staining within the tumor. The accompanying basophil invasion showed staining for adrenocorticotropic hormone (ACTH) and endorphin. Immunostains for chromogranin (Fig. 2A) (Dako, Carpinteria, CA; 1:800, 2F11) were positive in ganglion cells, whereas the vasopressin (Sera, West Sussex; 1:500, AE8

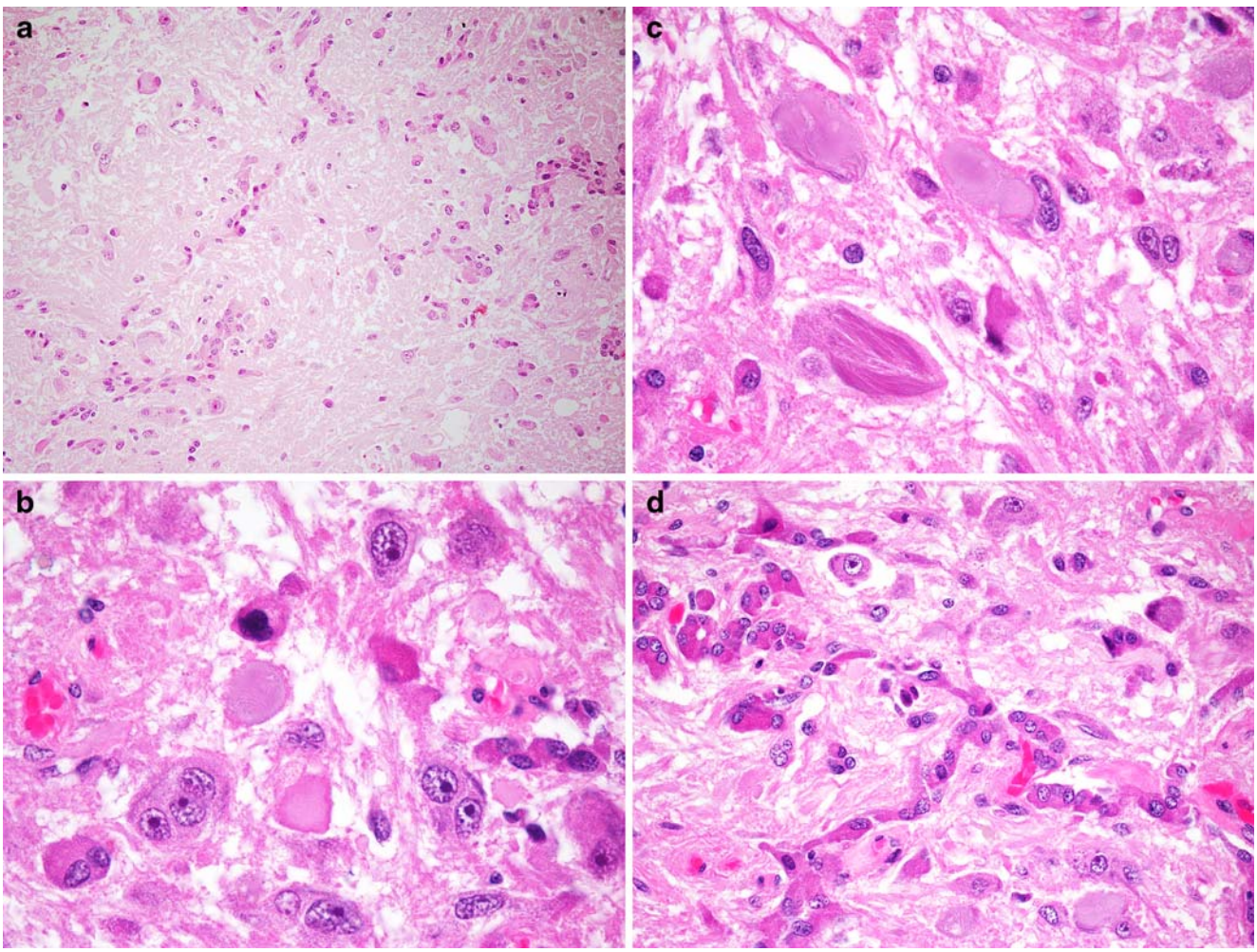

Fig. 1 Microsections of the expanded asymmetric posterior lobe show accumulation of ganglion cells and scant astrocytes (**A**). Ganglion cells are dysmorphic (**B**), and feature neurofibrillary tangles (**C**). Note association of ganglion cells with basophil invasion (**D**)

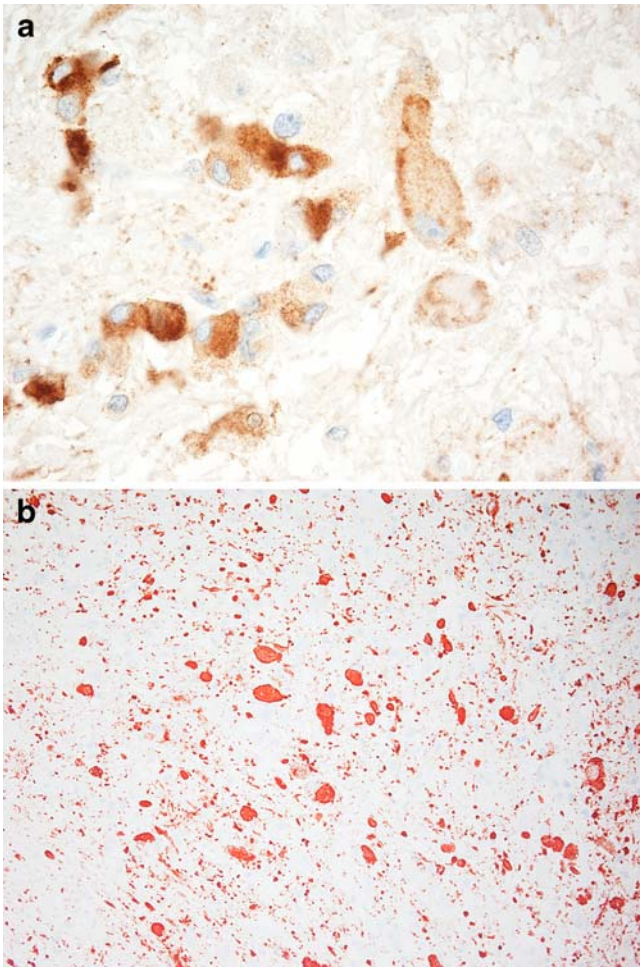

Fig. 2 Immunohistochemical features include reactivity of ganglion cells for chromogranin (**A**) and tau protein (**B**)

321) reaction was negative. Reactivity within residual neurohypophyseal tissue also included neurophysin (Dako, 1:1000, polyclonal). Tau protein immunoreactivity (Endogen, Woburn, MA; 1:3750, AT8) was strong within tangle-bearing neurons (Fig. 2B) and threads. No Pick bodies were noted. Alpha synuclein stains were negative. Microsections through the paraventricular and supraoptic nuclei showed all but one, a markedly gliotic paraventricular nucleus, to be histologically normal.

Discussion

The neurohypophysis consists of: (a) axons of magnocellular neurons comprising the supra-optic and paraventricular nuclei of the hypothalamus, (b) functionally specialized astrocytes termed "pituicytes" [7], and (c) fenestrated capillaries at which the hormones vasopressin and oxytocin as well as their respective neurophysins are released into the circulation. When compared to the adenohypophysis with its high frequency of pituitary adenomas, 20% in one autopsy series [8], neurohypophysial tumors are rare. They include primarily granular cell tumors [2] and the very infrequent pituicytoma [3], both derived from pituicytes, functionally specialized, osmotically reactive astrocytes of the posterior lobe.

A number of pituitary and sellar region lesions are neuronal in nature. These include: (a) hypothalamic neuronal hamartoma, some of which are endocrine-active by way of producing releasing hormone [9], and (b) gangliocytoma of the sella, either in isolation [10, 11] or in association with a pituitary adenoma [10, 12]. Both of the above are rare. Of gangliocytomas of the sella, entirely 65% are adenoma-associated, and 75% are endocrine-active [12]. The genesis of those in which a pituitary adenoma, typically a growth hormone and only rarely an adrenocorticotropin [13–15] or prolactin-producing adenoma [16–18], have invited two very different pathophysiologic explanations. One mechanism, the earliest proposed, suggested that the neuronal lesions, by producing hypothalamic releasing hormones, result in pituitary hyperplasia and promote adenomagenesis [12]. Multiple reports invoked this explanation [11, 13, 19], and the concept still has its adherents [20]. Demonstration of both the releasing hormone in the gangliocytomas and the respective pituitary hormone in the adenoma lends it support. Of particular interest is one case in which a hypothalamic and sellar gangliocytoma-producing enkephalin was associated with a prolactinoma [16]; enkephalin is known to have a stimulating effect on prolactin cells. On the other hand, several observations support an alternative, very different view, which is that adenoma cells undergo neuronal metaplasia, the resultant lesion being termed "pituitary adenoma-neuronal choristoma" (PANCH) [21]. Such transformation has been documented by morphologic, immunohistochemical, and ultrastructural methods [21]. A number of observations lend insight into this mechanism and support its occurrence, including: (a) lack of pituitary hyperplasia as an element of PANCH [21], (b) the almost exclusive GH-producing adenoma subtype involved, (c) transition to adenoma cells being minute and multifocal in some adenomas, and (d) the fact that a subset of pituitary adenomas of acromegaly produce growth hormone-releasing hormone [22], its stimulatory effect apparently being autocrine. In contrast, the posterior pituitary is rarely affected by neuronal lesions; only four cases have been reported in humans [5, 6, 10, 23]. One previous example of ectopic ganglion cells, perhaps an example of a gangliocytoma was reported by Horvath et al [5]. It was an incidental autopsy finding in an 80-year-old female with no evidence of endocrinopathy. The neurons resembled magnocellular hypothalamic neurons, were α-SU and β-endorphin immunoreactive, and were intimately associated with

basophil invasion. No vasopressin staining was noted. Etiologic considerations included: (a) an ectopia, possibly the result of a migration abnormality, (b) maturation of neuroblasts presumed to occur in the embryonic neurohypophysis, and lastly, (c) neuronal "transdifferentiation" from the ACTH-positive cells of basophil invasion. A second published neuronal lesion of the neurohypophysis was a ganglioglioma like our own [6]. Its key feature was its occurrence in association with the syndrome of inappropriate antidiuretic hormone (ADH) secretion and the finding of vasopressin within its neurons. This rare lesion expanded the spectrum of processes underlying this syndrome, which includes vasopressin production by malignant tumors at ectopic sites, as well as head trauma, infection, drugs, and pituitary stalk compression. Yet another posterior lobe ganglion cell lesion has recently been reported [10]. It occurred in a 54-year-old man with Cushing syndrome and positive inferior petrosal sinus sampling for ACTH. The 1-cm lesion was removed transsphenoidally and consisted entirely of posterior pituitary tissue containing normal-appearing, small ganglion cells in association with a basophil invasion. The ganglion cells were immunonegative for ACTH and corticotropin-releasing hormone. After the operation, Cushing syndrome abated. Also of interest is a long-standing neuronal lesion of the sella associated with hyperprolactinemia, but no adenoma [23]. This tumor was termed "differentiating neuroblastoma" due to its partial composition of immature neurons. The tumor adds to the already complex classification of neuronal sellar lesions in that its ultrastructurally biphasic cell composition included: (a) a neuroblastic and gangliocytic element showing some oxytocin and perhaps prolactin immunoreactivity, in addition to (b) cells compatible with adenohypophysial epithelium, and (c) transitional forms. On an interesting note, a gangliocytoma with an immature neuronal component occurring in the pituitary of a rat has also been recently described [24]. The lesion consisted of mature, small immature, and transitional cells and exhibited occasional mitotic figures. Lastly, reference is also made to a "mature ganglioneuroma" in the pituitary of a Fischer rat [25].

Of tangential interest is the finding in our case of conspicuous neurodegenerative changes. These have been described in isolated cases of ganglion cell tumor [26, 27] and were recently the subject of a systematic study of 72 examples involving the brain, including 61 gangliogliomas and 11 gangliocytomas in patients of various ages [28]. Abnormalities related to tau protein (neurofibrillary tangles, neuropil threads, Pick bodies) and granulovacuolar degeneration were noted in approximately 10%, being much more common in older patients but unrelated to the Apo E genotype, a factor predisposing to Alzheimer disease.

References

1. Scheithauer BW. The hypothalamus and neurohypophysis (Chapter 10). In: Kovacs K, Asa SL, eds. Functional endocrine pathology. Malden: Blackwell Science, pp. 171–246, 1998.
2. Fuller GN, Wesseling P. Granular cell tumour of the neurohypophysis. In: Louis DN, Wiestler O, Ohgaki H, eds. World Health Organization classification of tumours: Pathology and genetics—tumours of the nervous system. Lyon: IARC, pp. 241–2, 2007.
3. Wesseling P, Brat DJ, Fuller GN. Pituicytoma. In: Louis DN, Wiestler O, Ohgaki H, et al, eds. World Health Organization classification of tumours: Pathology and genetics—tumours of the nervous system. Lyon: IARC, pp. 243–4, 2007.
4. Scheithauer BW, Hawkins C, Tihan T, Vandenberg SR, Burger PC. Pilocytic astrocytoma. In: Louis DN, Wiestler O, Ohgaki H, et al, eds. World Health Organization classification of tumours: Pathology and genetics—tumours of the nervous system. Lyon: IARC, pp. 14–21, 2007.
5. Horvath E, Kovacs K, Tran A, Scheithauer BW. Ganglion cells in the posterior pituitary: result of ectopia or transdifferentiation? Acta Neuropathol 100(1):106–10, 2000.
6. Fehn M, Lohmann F, Ludecke DK, Rudorff KH, Saeger W. Ganglioglioma of the neurohypophysis with secretion of vasopressin. Exp Clin Endocrinol Diabetes 106(5):425–30, 1998.
7. Scheithauer BW, Horvath E, Kovacs K. Ultrastructure of the neurohypophysis. Microsc Res Tech 20(2):177–86, 1992.
8. Costello RT. Subclinical adenoma of the pituitary gland. Am J Pathol 12:205, 1936.
9. Scheithauer BW, Kovacs K, Randall RV, Horvath E, Okazaki H, Laws ER Jr. Hypothalamic neuronal hamartoma and adenohypophyseal neuronal choristoma: their association with growth hormone adenoma of the pituitary gland. J Neuropathol Exp Neurol 42(6):648–63, 1983.
10. Asa SL, Scheithauer BW, Bilbao JM, Horvath E, Ryan N, Kovacs K, et al. A case for hypothalamic acromegaly: a clinicopathological study of six patients with hypothalamic gangliocytomas producing growth hormone-releasing factor. J Clin Endocrinol Metab 58(5):796–803, 1984.
11. Geddes JF, Jansen GH, Robinson SF, Gomori E, Holton JL, Monson JP. 'Gangliocytomas' of the pituitary: a heterogeneous group of lesions with differing histogenesis. Am J Surg Pathol 24 (4):607–13, 2000.
12. Puchner MJ, Ludecke DK, Saeger W, Riedel M, Asa SL. Gangliocytomas of the sellar region—a review. Exp Clin Endocrinol Diabetes 103(3):129–49, 1995.
13. Asa SL, Kovacs K, Tindall GT, Barrow DL, Horvath E, Vecsei P. Cushing's disease associated with an intrasellar gangliocytoma producing corticotrophin-releasing factor. Ann Intern Med 101 (6):789–93, 1984.
14. Li JY, Racadot O, Kujas M, Kouadri M, Peillon F, Racadot J. 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 77 (3):320–8, 1989.
15. Saeger W, Puchner MJ, Ludecke DK. Combined sellar gangliocytoma and pituitary adenoma in acromegaly or Cushing's disease. A report of 3 cases. Virchows Arch 425(1):93–9, 1994.
16. Bodi I, Martin AJ, Connor SE, Thomas NW, Lantos PL. Mixed pituitary gangliocytoma/adenoma (prolactinoma) with histogenetic implications. Neuropathol Appl Neurobiol 28(3):252–5, 2002.
17. Matsuno A, Nagashima T. Prolactin-secreting gangliocytoma. J Neurosurg 95(1):167–8, 2001.

18. Serri O, Berthelet F, Belair M, Vallette S, Asa SL. An unusual association of a sellar gangliocytoma with a prolactinoma. Pituitary 11:85–7, 2007.
19. Bevan JS, Asa SL, Rossi ML, Esiri MM, Adams CB, Burke CW. Intrasellar gangliocytoma containing gastrin and growth hormone-releasing hormone associated with a growth hormone-secreting pituitary adenoma. Clin Endocrinol (Oxf) 30(3):213–24, 1989.
20. Kurosaki M, Saeger W, Ludecke DK. Intrasellar gangliocytomas associated with acromegaly. Brain Tumor Pathol 19(2):63–7, 2002.
21. Horvath E, Kovacs K, Scheithauer BW, Lloyd RV, Smyth HS. Pituitary adenoma with neuronal choristoma (PANCH): composite lesion or lineage infidelity? Ultrastruct Pathol 18(6):565–74, 1994.
22. Thapar K, Kovacs K, Stefaneanu L, Scheithauer B, Killinger DW, Lioyd RV, et al. Overexpression of the growth-hormone-releasing hormone gene in acromegaly-associated pituitary tumors. An event associated with neoplastic progression and aggressive behavior. Am J Pathol 151(3):769–84, 1997.
23. Lach B, Rippstein P, Benott BG, Staines W. Differentiating neuroblastoma of pituitary gland: neuroblastic transformation of epithelial adenoma cells. Case report. J Neurosurg 85(5): 953–60, 1996.
24. Okazaki Y, Katsuta O, Yokoyama M, Wako Y, Yamagishi Y, Tsuchitani M. Gangliocytoma with immature neuronal cell elements in the pituitary of a rat. J Vet Med Sci 59(9):833–6, 1997.
25. MacKenzie F, Boorman GA. Pituitary gland. In: Boorman GA, Eustis SL, Elwell MR, et al, eds. Pathology of the Fischer rat: reference and atlas. San Diego, CA: Academic Press, pp. 485–500, 1990.
26. Hortobagyi T, Honavar M, Selway R, Al-Sarraj S. Desmoplastic ganglioglioma with meningiomatous and myofibroblastic components presenting with epilepsy. Neuropathol Appl Neurobiol 34:118–23, 2007.
27. Raffo S, Rubio A, Rodenhouse TG, Patel U, Bonfigilo T, Powers JM. September 2001: 51-year-old man with seizures since childhood. Brain Pathol 12(1):137–9, 2002.
28. Brat DJ, Gearing M, Goldthwaite PT, Wainer BH, Burger PC. Tau-associated neuropathology in ganglion cell tumours increases with patient age but appears unrelated to ApoE genotype. Neuropathol Appl Neurobiol 27(3):197–205, 2001.