Hypothalamic Vasopressin-Producing Tumors

Often Inappropriate Diuresis But Occasionally Cushing Disease

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Abstract: Tumors of hypothalamic neurons that produce vasopressin are rare. We retrieved all cases of vasopressin-positive tumors in the sellar region from the database of the Department of Pathology. Five cases fulfilled the selection criteria, representing the first series of such tumors. Clinical, radiologic, and pathologic features were reviewed. Four tumors classified as neurocytomas were identified in 3 females and 1 male patient; the ages at onset of symptoms ranged from 17 to 40 years. All were large sellar masses with suprasellar extension and/or invasion of the parasellar sinuses. Three patients had the syndrome of inappropriate antidiuresis; in one of these, a 6-year history was initially considered to be idiopathic. One patient died of progressive disease; 3 had incomplete resections and are being followed. In contrast to these patients with neurocytoma, a 65-year-old woman had Cushing disease and a 0.8 cm mass that was completely resected at transsphenoidal surgery; this tumor was a gangliocytoma producing vasopressin associated with corticotroph hyperplasia. We postulate that the small amount of vasopressin secreted by this mature gangliocytic tumor was locally bound to corticotrophs, resulting in hyperplasia and Cushing disease, without sufficient overproduction to cause systemic effects of vasopressin excess. Hypothalamic neurocytoma is a tumor that can mimic pituitary neuroendocrine tumors and olfactory neuroblastoma but is distinguished by positivity for neurofilaments, NeuN, and TTF-1 and negative staining for adenohypophysial biomarkers. Our cases illustrate that neurocytoma and gangliocytoma are 2 variants of tumors of hypothalamic neurons that can produce vasopressin. The morphologic and proliferative features of these 2 tumor types represent 2 ends of a spectrum; their function also can result in divergent clinical manifestations, one characterized by reduced urine output and the other by the more insidious features of glucocorticoid excess.

Key Words: vasopressin, hypothalamus, pituitary, tumor, syndrome of inappropriate antidiuresis (SIAD), Cushing disease

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Tumors of the sella turcica include a large number of entities.[1] By far the most common are the epithelial neoplasms of hormone-secreting adenohypophysial cells that can be associated with hormone excess, such as prolactinomas or tumors giving rise to acromegaly or Cushing disease, or clinically nonfunctioning tumors that may produce hormones but do not give rise to clinical or biochemical features of pituitary hormone excess. The latter group can cause headache, visual symptoms, and hypopituitarism.

Other lesions occur in the region of the pituitary. These include cysts, inflammatory lesions and tumors of other cell types, including craniopharyngiomas, pituicytomas, gliomas, germ cell tumors, mesenchymal and hematopoietic proliferations, and metastatic malignancies.[1] The manifestations of these various entities can overlap with hormone-secreting tumors. Through interference with tonic inhibition of prolactin, they cause hyperprolactinemia. Some interfere with neurohypophysial function, giving rise to diabetes insipidus. However, excess production of vasopressin (antidiuretic hormone, ADH) associated with sellar tumors is exceedingly rare.

The syndrome of inappropriate antidiuresis (SIAD), formerly known as syndrome of inappropriate ADH secretion (SIADH), is associated with excess vasopressin production by tumors, usually small cell lung carcinomas[2] but also other ectopic sources.[3] It also may be due to medications; in addition to anticancer therapies, many classes of medications can also lead to SIAD such as nonsteroidal anti-inflammatory drugs, antiseizure medications and some psychotropic agents.[2] It can be attributed to head trauma,[4] and occurs in hospitalized patients due to poorly understood mechanisms.[5] Here, we report a series of 5 patients with sellar lesions producing vasopressin that resulted in 2 distinct manifestations, usually SIAD, but in one case, with Cushing disease. These tumors

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TABLE 1. Clinical and Radiologic Features of Sellar Tumors Producing Vasopressin

Age at Onset (y)	Sex	Presentation	Recurrence	Location	Tumor Pathology
39	F	6 y history of idiopathic SIADH	Unknown	Focally calcified 3 cm sellar mass with suprasellar extension and cavernous sinus invasion	Neurocytoma
34	F	Galactorrhea, amenorrhea, hyponatremia	Multiple recurrences	Sellar mass with erosion of the sellar floor by a contrast-enhancing tumor that also extended (superiorly into the suprasellar cistern	Neurocytoma
17	M	Nausea, vomiting, dysarthria, hyponatremia	Stable residual	Focally calcified sellar mass with cavernous sinus invasion	Neurocytoma
40	F	Sellar mass with visual disturbance and headache	Recurrence requiring reoperation	Sellar mass invading right cavernous sinus and encasing ICA; suprasellar nodule abutting the floor of the third ventricle	Neurocytoma
65	F	Cushing disease	Unknown	Intrasellar 0.8 cm microtumor	Gangliocytoma with corticotroph hyperplasia

F indicates female; M, male.

were all neoplasms of hypothalamic neuronal lineage but showing different degrees of differentiation, distinct proliferative capacities and levels of hormone production and secretion that resulted in markedly distinct clinical manifestations.

MATERIALS AND METHODS

Cases were retrieved from the archives of the Department of Pathology of a tertiary referral center between 2001 and 2017 with the approval of the University Health Network Research Ethics Board. The selection criteria included all cases of vasopressin-positive tumors in the region of the hypothalamus and sella turcica. Five cases were identified as fulfilling the selection criteria. Clinical, radiologic, and pathologic features were reviewed. Consent to publish their case was obtained from 4 patients after full explanation of the purpose and nature of this publication; the details of the fifth patient who could not be reached are abbreviated to ensure confidentiality.

The following immunostains were performed: synaptophysin (27G12; Novocastra), chromogranin A (polyclonal; Dako), neurofilaments (M076229-2, Dako), neuronal nuclear antigen (NeuN; MAB 377(CH), Millipore), S100 protein (polyclonal, Dako), glial fibrillary acidic protein (GFAP; 6F2, Dako), epithelial membrane antigen (EMA; E29, Roche), calretinin (DC8, Thermo-Fisher), CD99 (EPR3097Y, Abcam), thyroid transcription factor-1 (TTF-1; SPT24, Leica), low–molecular-weight keratins (CAM5.2, Becton Dickenson), pankeratins (AE1/AE3 cocktail, Dako), pituitary transcription factor-1 (Pit-1; D7, Santa Cruz), steroidogenic factor-1 (SF-1; n1665, Cedarlane), estrogen receptor alpha (ER; SP1, Ventana), GATA-3 (L50-823; Intermedico), adrenocorticotropin hormone (ACTH; 02A3, Dako), growth hormone (GH; A0570, Dako), prolactin (PRL; B109.1, Immunotech), alpha subunit of glycoprotein hormones (αSU; clone 6E4, Immunotech), α-human chorionic gonadotropin (αhCG; Z007 Biogenex), beta-thyrotropin (βTSH; 0042, Dako), beta follicle–stimulating hormone (βFSH; 300.10.E.14.5, Immunotech), and beta luteinizing hormone (βLH; 430.16, Immunotech), tyrosine hydroxylase (EP1533Y, Abcam), corticotropin-releasing hormone (CRH; T-4037.0050, Peninsula Laboratories), vasopressin (ADH; T-4563, Peninsula), and Ki-67 (MIB-1, Dako). The Ki-67 labeling index (LI) was calculated as the percentage of positive cells over total nuclei based on manual counts of printed images that included at least 500 cells. Not all stains were performed on all cases, as in 2 instances (cases 4 and 5), the material was insufficient for complete analysis.

RESULTS

The 5 tumors occurred in 4 females and 1 male (Table 1). The age range was 17 to 65 years.

Four tumors classified on pathology as neurocytomas were identified in 3 females and 1 male patient whose age at onset of symptoms ranged from 17 to 40 years. Three had clinical features of vasopressin excess with SIAD; the history of the fourth patient is incomplete. The tumors were large and focally calcified sellar masses; all had suprasellar extension and/or invasion of the cavernous and sphenoid sinuses. Three patients have persistent disease and are being followed; one died of progressive disease.

In contrast, 1 patient, a 65-year-old woman, had Cushing disease and a 0.8 cm sellar gangliocytoma producing vasopressin associated with corticotroph hyperplasia; she had no clinical evidence of vasopressin excess. She has had an apparent complete surgical cure.

Clinical, Biochemical, and Radiologic Findings

Case 1

A 39-year-old woman presented with a 5-month history of worsening visual field loss. Brain magnetic resonance imaging (MRI) revealed a 2 cm sellar mass with suprasellar extension to the optic chiasm, causing enlargement of the sella and infiltrating the right cavernous sinus (Figs. 1A, B). The tumor was heterogenous with focal cystic change, consistent with hemorrhage, and focal calcification.

The patient had a 6-year history of what had been diagnosed as idiopathic SIAD after presenting with a first-trimester miscarriage with a serum sodium of 122 mmol/L with a depressed serum osmolality of 262 mmol/kg. Metabolic and hormonal testing had demonstrated no

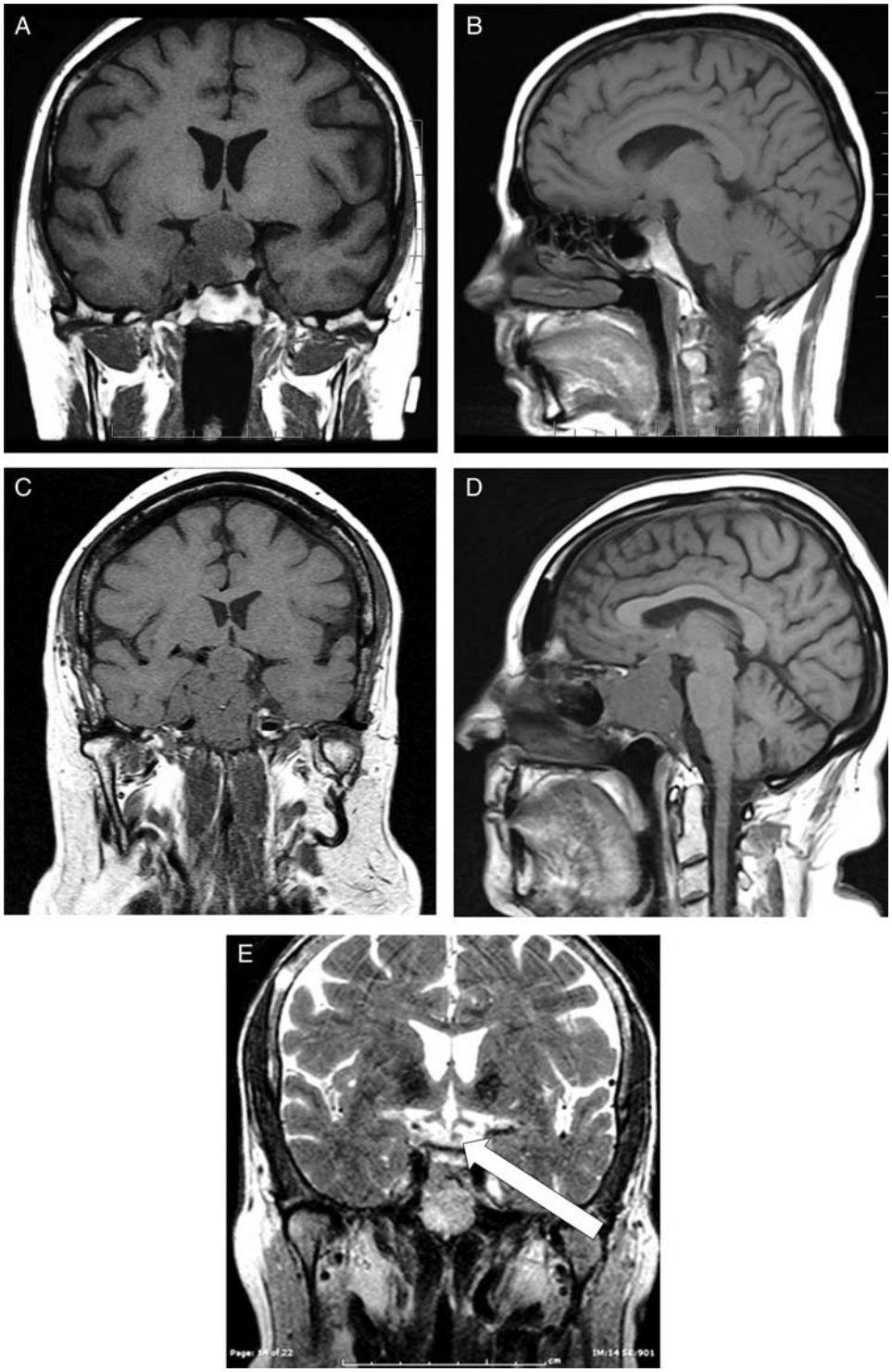

FIGURE 1. Imaging findings in patients with hypothalamic tumors producing vasopressin. Coronal and sagittal images show large invasive hypothalamic neurocytomas of patient 1 (A, B) and patient 2 (C, D) compared with the coronal image of the 0.8 cm intrasellar gangliocytoma (arrow) of patient 5 (E).

abnormalities including: thyroid-stimulating hormone 4.0 mIU/L (0.35 to 5.0 mIU/L), creatinine 72 μmol/L, fasting plasma glucose 5.6 mmol/L. A 250 mcg ACTH stimulation test yielded a 1 hour serum cortisol of 875 nmol/L (normal > 550). Computerized tomographic (CT) imaging of the head and thorax showed no abnormalities. At the time of her initial investigation, serum ADH was 1.9 pmol/L (0.8 to 3.5) despite a relatively low concomitant sodium

of 133 mmol/L. Despite ongoing therapy for SIAD with fluid restriction (1 to 1.5 L/d) and furosemide, she maintained serum sodium levels of 128 to 131 mmol/L with chlorides of 90 to 94 mmol/L.

She underwent endonasal endoscopic resection of the tumor that achieved subtotal mass resection with residual cavernous sinus disease. Postoperatively she had panhypopituitarism requiring replacement with hydrocortisone and thyroxine. Serum ADH was 2.1 pmol/L with concomitant sodium of 129 mmol/L.

Case 2

In 1981, at age 34 years, a woman presented to her gynecologist with an 18-month history of galactorrhea, oligomenorrhea followed by amenorrhea, weight gain, and eye discomfort. Serum prolactin was 83 ug/L (normal < 25 ug/L) and CT scan showed expansion of the sella with erosion of the sellar floor by a contrast-enhancing tumor that extended superiorly into the suprasellar cistern. Transsphenoidal biopsy of the sellar lesion was initially diagnosed as pituitary adenoma. Because of incomplete resection, she was administered external beam radiotherapy. With a provisional diagnosis of prolactinoma, she was treated with bromocriptine 2.5 mg daily that resulted in normalization of prolactin levels and resumption of menses. In 2004, with regrowth of the tumor, her treatment was switched to cabergoline. MRI showed a solid 3.0×3.0×2.3 cm sellar mass with extension into the sphenoid sinuses and suprasellar cistern and laterally to the right displacing the cavernous segment of the right internal carotid artery superiorly, but no chiasmal compression. In 2007, with interval increase in size of the lesion to 4.0×3.0×2.7 cm and pressure on the optic chiasm, she had repeat transsphenoidal surgery with reduction in volume of the sellar mass; however, 17 months later, there was rapid deterioration of her vision due to increase in size of the mass compressing the optic chiasm, invading the floor of the third ventricle, and hypothalamus with extension laterally into the right Meckel's cave and posteroinferiorly into the clivus (Figs. 1C, D). A third transsphenoidal surgery was performed. Her postoperative course was complicated by meningitis and hyponatremia. Her comorbid conditions included type II diabetes managed with metformin, postradiation hypopituitarism requiring adrenal and thyroid hormone replacement, osteoporosis on a bisphosphonate, and dyslipidemia on rosuvastatin. Over the next year, she experienced further clinical progression with symptoms of cavernous sinus invasion. MRI showed tumor extending into the sphenoid sinus, ethmoid air cells, cavernous sinus (right more than left), filling Meckel's cave, protruding into the right foramen ovale and narrowing of the right temporal lobe sulci, abutting the intracranial prechiasmatic segment of the optic nerve as well as the optic chiasm on the right. Because of the proximity of the lesion to the optic chiasm, reradiation was excluded. Given the limited treatment options, and the marked uptake by the mass on octreotide scanning, she underwent peptide receptor radionuclide therapy (PRRT) with ^{177}Lu-[DOTA^{0},Tyr^{3}]octreotate as reported previously.[6] This ameliorated her headaches with limited improvement of her vision and stabilization of her sellar mass. In May 2016, she developed significant hyponatremia with sodium of 123 mmol/L from SIAD which initially responded to treatment with fluid restriction. In August 2016, she had hyponatremia of 114 mmol/L with an elevated serum ADH level of 8 pmol/L (N: 0.8 to 3.5 pmol/L). In October 2016, she developed meningitis complicated by intracranial hemorrhage. She was managed conservatively and died 1 month later.

Case 3

A 17-year-old male presented with nausea, vomiting, and dysarthria. Initial serum sodium was 104 mmol/L, improving to 129 mmol/L following 5 days of intravenous saline. He had a history 3 years previously of an episode of bilious vomiting, fever, hematuria, and a diffuse pruritic rash; at that time he had normal electrolytes (sodium: 142 mmol/L), elevated liver function tests, C-reactive protein and erythrocyte sedimentation rate and a normal complete blood count with a slight shift to the left. Upon admission, hypotonic intravenous dextrose 5% in water was administered, following which SIAD was diagnosed with sodium levels dropping to as low as 126. He was treated with fluid restriction and oral sodium chloride supplementation and was discharged with the diagnosis of resolving renal tubulopathy.

On investigation, brain MRI revealed a 4.5×2.8×2.9 cm sellar and suprasellar mass with optic chiasm compression and clival and bilateral cavernous sinus invasion. Hormonal testing demonstrated a low total testosterone (190 ng/dL), reduced free thyroxine 0.74 (0.77 to 1.37 mg/dL) and inappropriately normal thyroid-stimulating hormone 1.04 (0.43 to 4.20 uIU/mL). He underwent endonasal endoscopic extended skull base approach for near-total tumor removal. Immediate postoperative sodium was 125 mmol/L. Following a single dose of tolvaptan 15 mg, serum sodium rose to 144 mmol/L over 10 hour, reaching 163 mmol/L by 24 hours. Despite intravenous dextrose 5% in water and Desmopressin 0.1 mg×2, he developed altered mental status and seizures. Although his serum sodium level was ultimately normalized, he went on to develop MRI-confirmed pontine and extrapontine myelinolysis. He had a long and complicated postoperative course but ultimately made a good clinical recovery and has since been stable with residual bilateral cavernous sinus tumor for 4 years since surgery.

Case 4

This case was referred and detailed information is not available. No consent was obtained therefore the information is limited. A 40-year old woman presented to the ophthalmologist complaining of visual loss and headache. Examination identified bitemporal hemianopia and follow-up imaging revealed a sellar tumor. Biochemical information was not available. The patient underwent transsphenoidal resection of the pituitary mass. The initial diagnosis was pituitary adenoma. Rapid recurrence was identified on imaging and within less than a year there was a 1.6 cm seller mass invading the cavernous

sinus and encasing the right internal carotid artery, associated with a right suprasellar nodule extending more posteriorly, abutting the floor of the third ventricle. She underwent reoperation and the lesion was described as fibrotic and difficult to dissect.

Case 5

A 65-year-old woman had initially presented at age 45 years with classic symptoms of Cushing syndrome. Investigations at that time identified a nonsuppressed ACTH and a 3 cm right adrenal mass that was surgically resected. Signs and symptoms of Cushing syndrome regressed for almost 20 years, but then recurred. Her serum sodium was normal; her urinary free cortisol was 3 times the upper limits of normal, and her serum cortisol failed to suppress after dexamethasone. Serum ACTH was in the 30 pmol/L range, indicative of ACTH-dependent Cushing syndrome and MRI disclosed an 8 mm intrasellar mass (Fig. 1E). The left adrenal gland was diffusely enlarged consistent with hyperplasia. The diagnosis of Cushing disease was made and she underwent transsphenoidal resection of the pituitary tumor. Postoperatively, she developed symptoms of cortisol withdrawal; her serum cortisol dropped very slowly (over a period of weeks) but never reached subnormal levels. One month after surgery, her 24-hour urinary free cortisol dropped to the lower limits of normal and she was started on corticosteroid replacement due to unrelenting severe symptoms of cortisol withdrawal including nausea, anorexia, and fatigue. The left adrenal was reduced to about 30% of its previous size on imaging. Six months after pituitary surgery, the patient underwent surgical removal of a parathyroid adenoma for primary hyperparathyroidism (serum calcium: 10.4 mg/dL and intact parathyroid hormone: 49 pg/mL, urinary calcium: 247 mg/24 h, and bone density T-score of −3.4 at the radius). Her hypothalamic-pituitary-adrenal axis recovered 12 months after pituitary surgery and she was weaned off corticosteroid replacement. *MEN-1* genetic testing revealed no deletions, duplications or pathogenic variants in exons 2 to 10, or all splice junctions including that of noncoding exon 1. To date, she remains in remission from both Cushing syndrome and primary hyperparathyroidism.

Pathology Findings

The tumors of patients 1 through 4 all had similar morphologic features consistent with a diagnosis of neurocytoma. They were composed of solid nests and sheets of small to medium-sized round cells with monotonous architecture and occasional rosette-like structures within a reticulin-rich vascular stroma composed of abundant fibrillar neuropil (Fig. 2). The tumor cells had granular, pale eosinophilic to chromophobic cytoplasm that merged with neuropil, and there were scattered homogenous acidophilic globules within the neuropil that resembled the Herring bodies of the posterior pituitary. The tumor cell nuclei were round to oval with finely granular chromatin and small or occasionally prominent nucleoli. There were areas of fibrosis and focal calcification. Immunohistochemistry identified strong reactivity for synaptophysin, chromogranin A, and neurofilaments. Tumor cells also expressed variable positivity for S100 protein and CD99. Some tumor cells, often the larger ones, expressed NeuN. Scattered tumor cells also exhibited nuclear positivity for TTF-1 (clone SPT24). Stains for keratins, pituitary transcription factors and hormones as well as GFAP, EMA, GATA-3, and tyrosine hydroxylase were negative. Calretinin was identified in 2 cases and not investigated in the others. In all cases, the tumor cells showed diffuse and strong cytoplasmic reactivity for vasopressin with accentuation in the Herring body structures; CRH was not detected in 3 of the 4 cases where it could be examined. There was no striking vascular proliferation, no necrosis and mitoses were rare (< 1/10 high power fields); the Ki-67 LI ranged from 4% to 12% with variation within individual tumors and at different times of resection. The expression of TTF-1 and vasopressin indicate hypothalamic differentiation of these neurocytomas.

The tumor of patient 5 was a vasopressin-producing gangliocytoma associated with corticotroph hyperplasia (Fig. 3). The tumor was composed of large mature ganglion cells of variable size and shape randomly oriented within a stroma composed of neuropil. The tumor cells had large nuclei with very prominent nucleoli and occasional binucleate forms were identified. Mitoses were not seen. Intermingled adenohypophysial cells were seen within the tumor and in neuropil as well as around the lesion. Corticotrophs were numerous and showed no evidence of Crooke's hyaline change; staining for PAS identified diffuse but relatively weak positivity throughout the cytoplasm of corticotrophs that was punctuated by enigmatic bodies. The neurons stained for synaptophysin as well as the neuronal markers neurofilament and NeuN and TTF-1. Glial elements identified with GFAP were scant. The Ki-67 stain was negative in neurons; a few scattered positive cells represented neutrophils and intravascular lymphocytes, and one or 2 positive nuclei may have represented proliferating corticotrophs. Stains for keratins and pituitary transcription factors and hormones identified the adenohypophysial cells around and within the lesion. The neurons were completely negative for CRH, but stained strongly for vasopressin that also showed intense reactivity on the membranes of corticotrophs with enigmatic bodies.

DISCUSSION

Neurocytoma and gangliocytoma are rare neoplasms of neurons; gangliocytomas are composed of large mature neurons, whereas neurocytomas are composed of small, less well-differentiated cells. We report 5 cases of sellar tumors that display this spectrum of differentiation and expressed both TTF-1 and vasopressin, indicating origin from and/or differentiation as neurons of the paraventricular or supraoptic nuclei of the hypothalamus.[7–9]

The clinical manifestations of these tumors were markedly different. The neurocytomas presented as large sellar and suprasellar masses with manifestations of electrolyte imbalance consistent with the immunoreactivity of the tumor for vasopressin. The gangliocytoma, in contrast, presented with manifestations of Cushing disease; while

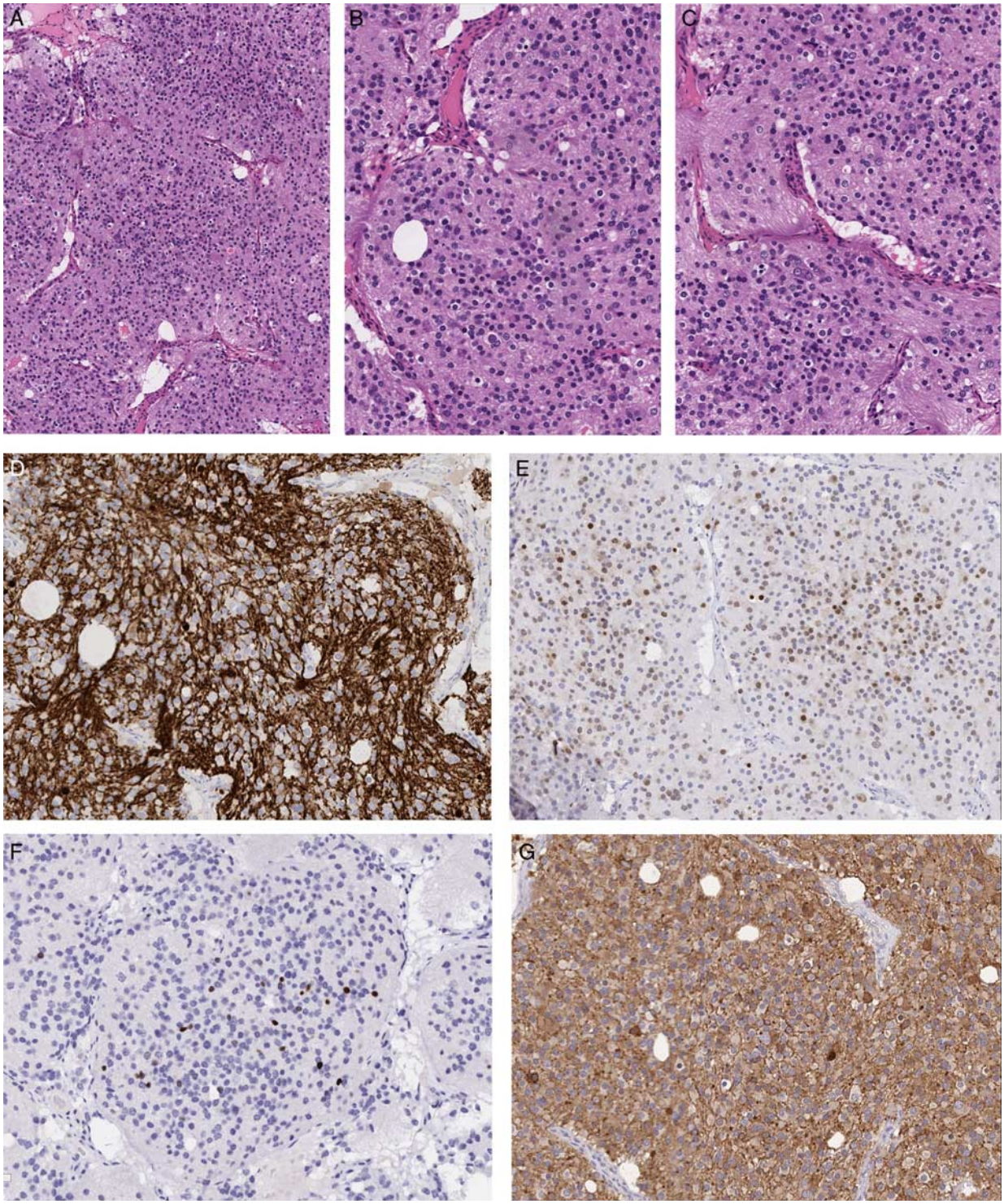

FIGURE 2. Histomorphology of hypothalamic neurocytoma producing vasopressin. The tumor is composed of solid nests of small to medium-sized round cells with monotonous architecture within a vascular stroma composed of abundant fibrillar neuropil (A). The tumor cells have granular, pale eosinophilic to chromophobic cytoplasm and round to oval nuclei with finely granular chromatin and small or occasionally prominent nucleoli; occasional binucleate cells are seen (B). The tumor cell cytoplasm merges with neuropil (C). The tumor exhibits strong positivity for neurofilaments (D) and variable nuclear reactivity for NeuN (E), confirming neuronal differentiation. Scattered cells have nuclear positivity for TTF-1 (F) and there was diffuse cytoplasmic reactivity for vasopressin (G), with scattered homogenous strongly reactive globules that resemble the Herring bodies of the posterior pituitary.

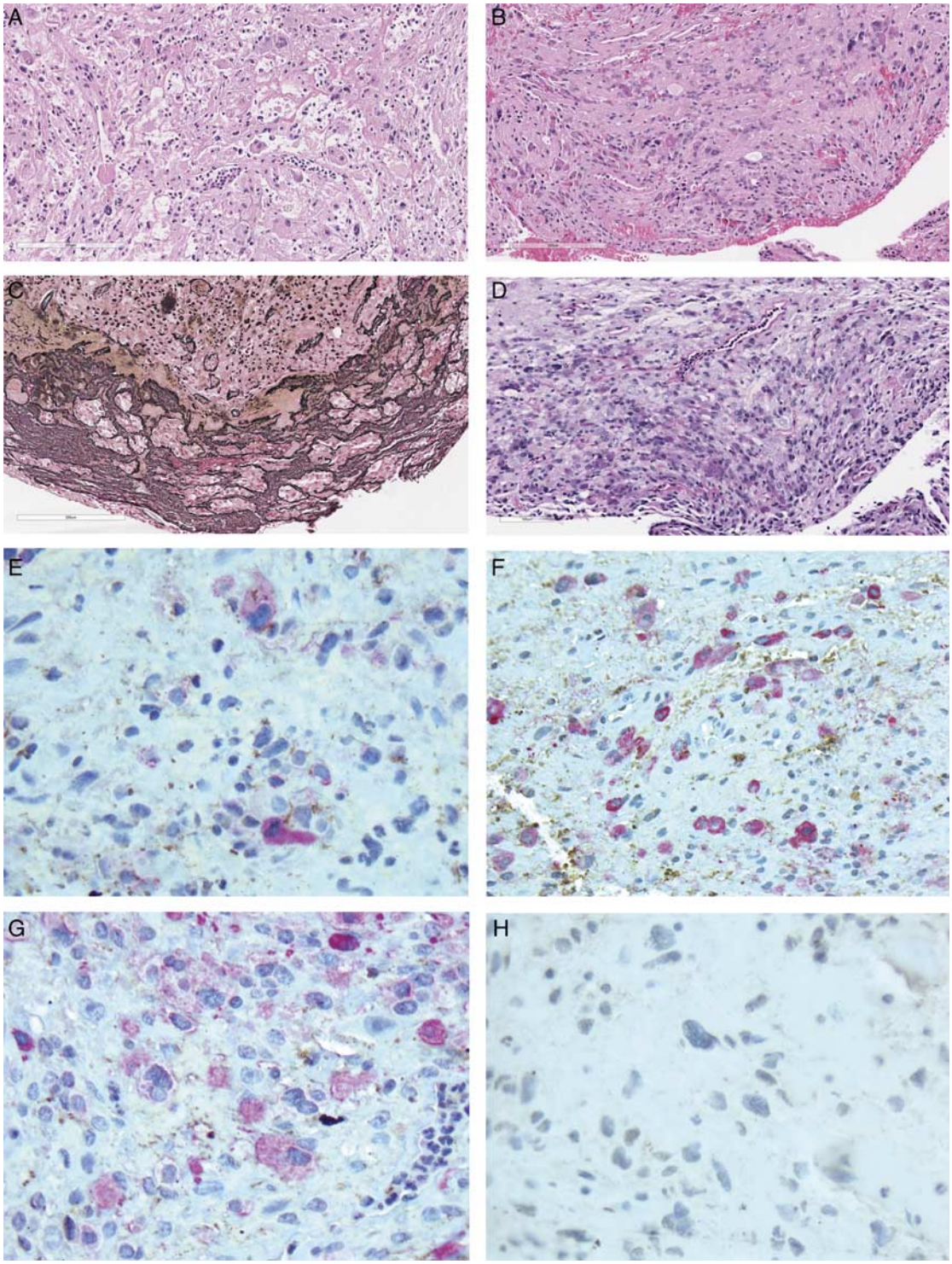

FIGURE 3. Histomorphology of hypothalamic gangliocytoma producing vasopressin associated with adenohypophysial corticotroph hyperplasia. The tumor was composed mainly of mature neurons within a stroma composed of neuropil (A). In the surrounding tissue, there were large clusters of corticotrophs (B) that were identified in enlarged but intact acini identified on the reticulin stain at the periphery of the tumor (C). The corticotrophs exhibit variable positivity with the PAS stain (D). The ganglion cells showed immunoreactivity for vasopressin that was detected using the NovaRed chromogen (E) and positivity was also strong on corticotrophs (F); higher magnification shows that the vasopressin staining on corticotrophs is on the cell membrane (G). The tumor was completely negative for CRH (H) despite the diagnosis of Cushing disease.

this is harder to reconcile, the role of vasopressin in ACTH regulation is well known. Pituitary corticotrophs express vasopressin receptors that, when activated, can play a role in ACTH regulation.[10,11] In our patient with the vasopressin-producing gangliocytoma, the low but persistent vasopressin secretion appeared to be locally bound and active, accounting for corticotroph hyperplasia, and ACTH excess that declined after resection of the gangliocytic tumor. There were no symptoms of SIAD, suggesting that there was insufficient overproduction by this small mature tumor to cause systemic effects of vasopressin excess.

Sellar neurocytoma is a rare tumor that shares histologic features with central neurocytoma and resembles other extraventricular neurocytomas.[12,13] These tumors express synaptophysin and neurofilaments, and may stain for NeuN.[12] The ultrastructural features of sellar neurocytoma have confirmed neuronal differentiation, as the irregularly shaped tumor cells have numerous elongated processes that contain microtubules and resemble nonmyelinated neurites with abundant dense core secretory granules associated with synaptic junctions.[14,15] In central neurocytoma, mitoses are usually inconspicuous and the Ki-67 LI is usually <2%; more aggressive lesions have been classified as "atypical central neurocytoma" when they exhibit vascular proliferation, necrosis, and conspicuous mitoses (>3 mitoses per 10 high power fields), and a Ki-67 proliferation index of >3% has been associated with worse prognosis, in terms of both local control and survival.[15,16] A rare sellar neurocytoma has been associated with acromegaly[17] and a previous report has documented vasopressin excess,[15] consistent with their capacity to produce hypothalamic hormones. The spectrum of proliferation and behavior seems to mimic those of central neurocytoma; our cases have had a Ki-67 ranging from 2% to 12%, the patients have had persistent/recurrent disease, and one of our patients ultimately died of disease despite peptide receptor radiotherapy.[6]

The molecular alterations in neurocytomas are unclear and the management of invasive neurocytomas that cannot be completely resected remains uncertain.[18] Previous studies of extraventricular neurocytomas have shown that isocitrate dehydrogenase enzyme isoform 1 (*IDH1*), alpha-internexin, and p53 are not implicated and no *IDH1 R132* and *IDH2 R172* mutations were identified by direct sequencing.[12] One case showed polysomy of the epidermal growth factor receptor (*EGFR*) gene; O6-methylguanine-DNA methyltransferase (*MGMT*) promoter methylation and 1p/19q co-deletion were not detected.[12] Two cases subjected to array-based comparative genomic hybridization revealed different profiles, with loss and gain of multiple chromosomal loci.[12]

The differential diagnosis of sellar neurocytoma includes pituitary neuroendocrine tumor (formerly known as pituitary adenoma),[19] paraganglioma, and olfactory neuroblastoma. Two of our patients initially received the incorrect diagnosis of pituitary adenoma. The diagnosis of tumors in the sellar region is often incorrect, as these tumors may have variable presentations, including as paranasal masses.[20,21] The value of immunohistochemistry to ensure the correct diagnosis of a pituitary neuroendocrine tumor has been emphasized;[20] these tumors should routinely be stained for keratins, pituitary transcription factors and hormones to ensure the correct diagnosis.[1,22] Also in the differential diagnosis is paraganglioma[1] which can be identified by lack of keratin reactivity, staining for GATA-3[23] and tyrosine hydroxylase.[24] There have been reports of primary sellar olfactory neuroblastomas[17–19] that were almost certainly hypothalamic neurocytomas, and cases of olfactory neuroblastoma associated with SIAD[25] were likely also misdiagnosed hypothalamic neurocytomas. Similar to the distinction of pituicyte-related neoplasms in the sellar region, the recognition of TTF-1 as a biomarker of neurons and glial tissues derived from the basal hypothalamus[7,8] has provided a diagnostic tool to distinguish these lesions that may also produce hypothalamic hormones.

The importance of diagnosing SIAD preoperatively should also be emphasized. One of our patients with hypothalamic neurocytoma causing SIAD developed extrapontine myelinolysis postoperatively due to a very rapid diuresis, diabetes insipidus and acute severe hypernatremia. This acute diabetes insipidus presumably resulted from a near complete tumor removal and consequent rapid drop in chronically elevated vasopressin levels. It is important to remember that although the rise in sodium levels after a single dose of vasopressin receptor antagonists is typically only 1 to 5 mEq/L, rapid correction of sodium in patients with longstanding or severe hyponatremia may be seen. After tumor resection, careful monitoring is required and an abrupt rise in sodium level should precipitate aggressive fluid replacement to match urine output and administration of desmopressin.

Gangliocytomas are also exceptionally rare tumors of hypothalamic neurons that arise in the sellar region and have been reported to produce various hypothalamic peptides.[7,8,26] They may be associated with acromegaly when production of growth hormone–releasing hormone is implicated and some are associated with an adenohypophysial somatotroph tumor; they may also occur in children with precocious puberty, when gonadotropin-releasing hormone is the main product.[27–29] Hypothalamic gangliocytomas have also been reported to express glucagon, somatostatin, vasoactive intestinal peptide, gastrin, galanin, and enkephalin.[30–36] Rare cases have caused Cushing disease as in our patient reported here; production of CRH, ACTH, β-endorphin, β-lipotropin and somatostatin as well as oxytocin have been identified in these tumors previously.[26,37,38] Some gangliocytomas unassociated with clinical evidence of hormone excess show multiple immunoreactivities for peptides such as somatostatin, serotonin, vasoactive intestinal peptide, galanin, and α-subunit.[1,39]

To our knowledge, this is the first report of vasopressin production by a sellar gangliocytoma. While the production of this hypothalamic hormone is not unexpected in this tumor type, the clinical manifestations can be unusual for a sellar mass. Initially, we expected to

identify CRH in the tumor, as previously reported.[37] However, the tumor was completely negative for this hormone. Instead, vasopressin staining was strong and localized to the neuronal cell bodies, neural processes, as well as the membranes of the associated corticotrophs. Vasopressin is known to stimulate pituitary corticotrophs through the arginine vasopressin (Avp) 1b receptor subtype (Avpr1b)[10] that is expressed by corticotrophs and indeed, arginine vasopressin was used clinically to asses pituitary ACTH regulation in the past.[40] It is interesting to speculate on the reasons for the lack of SIAD in this patient; as there was only a small tumor with a small number of vasopressin-producing neurons, it is entirely possible that the effect of the hormone secreted would have been only local, where the vasopressin was bound to corticotrophs that responded with the production of central ACTH-dependent Cushing disease. The chronic stimulation explains the lack of Crooke's hyaline changes in the face of glucocorticoid excess, and the hyperplastic hyperfunctioning corticotrophs would be expected to gradually be released from this state after resection of the tumor, consistent with the delayed recovery of the pituitary-adrenal axis manifested by our patient.

CONCLUSIONS

Neurocytoma and gangliocytoma are 2 variants of tumors of hypothalamic neurons that can produce vasopressin. Hypothalamic neurocytoma is a rare tumor that can mimic pituitary neuroendocrine tumors and olfactory neuroblastoma but is distinguished by positivity for neurofilaments, NeuN, and TTF-1 and negative staining for adenohypophysial biomarkers. The morphologic and proliferative features of neurocytoma and gangliocytoma represent 2 ends of a spectrum; their function when producing vasopressin also can result in 2 different clinical manifestations, one characterized by altered water regulation and the other by the more insidious features of glucocorticoid excess.

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