

Pituitary Ganglioneuroma: Case Report and Literature Review

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Abstract

We present a case of pituitary ganglioneuroma occurring in a 25 year old woman who presented with headache and hemianopsia. The histologic, immunohistochemical, and ultrastructural features of this tumor support the view that these rare hypothalamic-pituitary tumors are independently functioning neurohormonal units. Immunostaining is strongly positive for neuron-specific enolase (NSE) in all tumor cells and cell processes and for synaptophysin in a few cells and fibers. Few cells closely associated with tumor cells are positive for S100 protein. The cell processes are positive for neurofilament antigen. Ultrastructural analysis documents a spectacular neoplasm of neural derivation. The tumor consists of ganglion cells and areas of neuropil. The most typical tumor cells have relatively lucent spherical nucleus with large nucleolus, and abundant cytoplasm harbors compact sacks of RER membranes studded with ribosomes. Particular emphasis is given to the ultrastructural features which strongly support the functional relationship between the tumor components. It should be kept in mind that unusual and rare ganglionic tumors might show a progressive clinical course and needs surgical intervention as the major part of their treatment whereas ontogenetic and pathogenetic mechanisms taking part still need more work to enlighten pituitary neuronal tumorigenesis.

Keywords: Electron microscopy; Ganglioneuroma; Immunohistochemistry; Neuronal tumors; Pituitary neoplasms

Introduction

Primary tumors arising in neural tissue located in the sella turcica are seldom encountered. The pars nervosa of the pituitary gland contains glial cells ('pituicytes'), generally thought to be modified astrocytes, and axons derived from the neurons of the supraoptic and paraventricular nuclei, but are devoid of neurons. An abundance of the reported tumors originating in the neurohypophysis are gliomas. Historically, Scotherne in 1955 [1] described a piloid astrocytoma confined to the posterior lobe of the pituitary gland, and reviewed several similar previously reported cases; since some of these had also involved hypothalamic structures their site of origin was open to question [2].

So far, in the relevant literature the term 'infundibuloma' was recommended for gliomas of the neurohypophysis by Globus [3]. However, Russell and Rubinstein [4] regarded these tumors as identical to pilocytic astrocytomas occurring elsewhere in the brain. Ganglioneuromas of the neurohypophysis appear to be much less common. One example, reported briefly by Benda [5] and subsequently in greater detail by Casper [6], was an incidental finding at necropsy in a 72 year old woman. Histopathological examination revealed numerous large and small neurons, several were binucleated, and axons and glial elements. Moreover, due to the presence of groups of cluster small, dense nuclei, they were interpreted as precursor immature neural elements.

Ganglion cell tumors are a group of unusual neoplasms that disclose in common the presence of ganglion cells with inconsistent amounts of glial elements. By and large, this group includes gangliogliomas, gangliocytomas, ganglioneuromas, neuronal hamartomas, and neuronal choristomas [7-10]. As a rule, these tumors are generally regarded as indolent; a distinguished exception is the ganglioglioma which harbors tumorous glial cells that may reflect a tendency to behave aggressively. Moreover, two separate ganglion cell lesions that occur in

the region of the hypothalamus and pituitary fossa are associated with syndromes that result from the production of neurosecretory products by the ganglion cells. A hypothalamic hamartoma occurs in the young pediatric age group and may present with neurodevelopmental delay with or without accompanied by gelastic (laughing) seizures or, most frequently rapidly progressing sexual precocious puberty [11-15]. The second sellar ganglion cell lesion most commonly involves middle-aged women in association with a pituitary adenoma [8-10,16-20]. For the reasons discussed later, this tumor is probably best referred as a mixed gangliocytoma-adenoma, although it has also been termed ganglioneuroma and hamartoma.

By definition, ganglioneuroma is mainly composed of gangliocytic cells with occasional Schwann cells. Most frequently, it is accompanied by abnormalities of the autonomous and peripheral nervous systems; the exceptions, reported in the central neuraxis, are associated with ectopic peripheral neural tissue or peripheral nerve roots. [21] Ganglioglioma (GG), it has a less common cystic component. This tumor customarily bears pleomorphic and bizarre formed neurons. The hamartomatous or neoplastic nature of this lesion has been inquired [21]. Among sellar lesions, fewer than 50 cases of intrasellar ganglion cell

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lesions have been reported in the literature; 6 of them were associated with Cushing's syndrome [22]. Histologic examination discloses a heterogeneous lesion, with divergent histological cell growth patterns. The cytoarchitectural design of this tumor fluctuates in individual cases or even among the different portions of the same tumor. The reticulin framework assumes an alveolar arrangement harboring a dense capillary network with accompaniment of clustered seemingly mature neuronal cells in the central areas. In our case most of the tumor cells represent ganglion cells although generally smaller than usually observed. Most of the hyperchromatic nuclei may contain inclusions accompanied by prominent nucleoli. The peripheral portion of the abundant cytoplasm may contain basophilic Nissl substance. Areas of connective tissue accumulation small hemorrhagic areas and focal minimal mononuclear cell infiltration are noted. Therefore with these characteristic features, our case was consistent with a ganglioneuroma.

Case Report

Medical history

This 25-year-old G1P1 woman was presented in May 2010 with 7 years of post partum amenorrhea without galactorrhea and recent visual disturbances. MRI disclosed a sellar tumor of 37 mm × 27 mm × 22 mm with suprasellar extension and optic chiasm compression. The lesion had hypointense areas compatible with cystic degeneration or hemorrhage (Figure 1). At clinical examination visual acuity was OS: 20/70, OD: 20/30. Bitemporal hemianopsia was found and no papilledema at fundus examination.

Blood hormone levels were as follows: Growth hormone 0.10 ng/ml (normal <5.0); insulin-like growth factor (IGF-1) 76.2 ng/ml (48-255); prolactin 16.65 ng/ml (0-15); luteinizing hormone (LH) 4.37 mUI/ml (2-12); follicle stimulating hormone (FSH) 8.38 mUI/ml (1-8); thyroid stimulating hormone (TSH) 1.8 mUI/ml (0.5-6.0), free thyroxine (T4) 0.85 ng/dl (0.8-1.8), and cortisol 18.27 mcg/dl [5-25].

She was operated on in August 2, 2010 by transsphenoidal approach. A soft lesion was found and it was resected totally. During operation a complete hemostasis was achieved. At 4 hours after the operation she suffered from right hemiparesis. As an early postoperative complication CT scans revealed subarachnoid hemorrhage and hemorrhage in the sellar area, and CT angiogram showed no aneurysm. She was diagnosed as vasospasm due to subarachnoid hemorrhage and recovered in 2 days. Upon her progressive clinical alleviation she was discharged at 10th post operative day. Five days later, she complained of acute

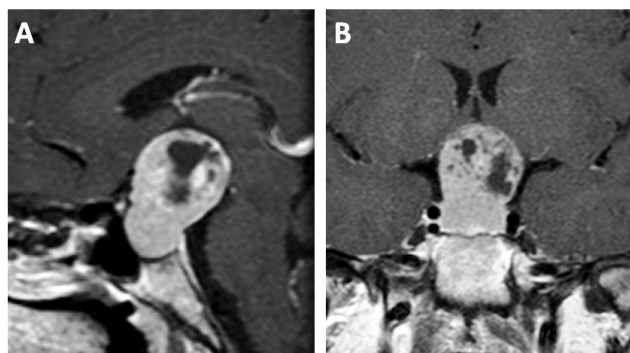


Figure 1: Sagittal (A) and Coronal (B) T1-weighted MRI with gadolinium enhancement show a sellar and suprasellar lesion with intratumoral cystic areas and optic chiasm compression.

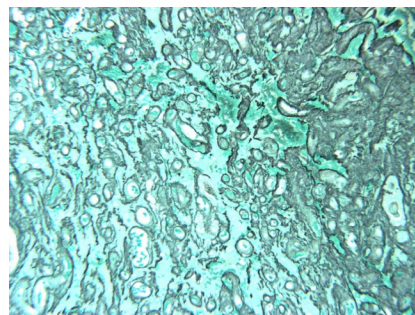


Figure 2: Sliver stain demonstrates irregular network of reticulin fibers. Reticulin staining. Original magnification: 100x.

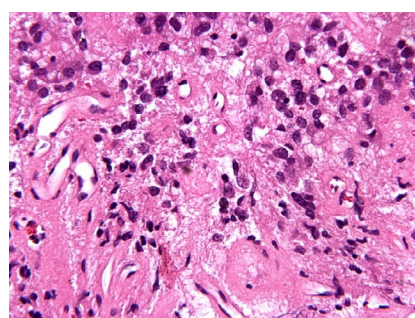


Figure 3: Connective tissue accumulation, hyaline protein droplets and eosinophilic granular bodies are apparent. H&E. Original magnification: 250x.

dyspnea, chest pain and underwent cardiovascular collapse. The most likely explanation for this serious clinical table was interpreted as a pulmonary thromboembolism. Although postmortem study was offered, her family rejected.

Pathology

The histology specimen contains a neoplasm of apparently neural derivation. Nests of slightly acidophilic PAS negative tumor cells are embedded in fibrovascular stroma and neuropil. The Gordon-Sweet technique demonstrates irregular network of reticulin fibers (Figure 2). CD34 immunoreactivity shows a well-vascularized tumor. Focally, connective tissue accumulation, hyaline protein droplets and eosinophilic granular bodies are apparent (Figure 3). Most of the tumor cells represent ganglion cells although generally smaller than usually observed. Nearly all of the hyperchromatic nuclei may contain inclusions accompanied by prominent nucleoli. The peripheral portion of the abundant cytoplasm may contain basophilic Nissl substance. Areas of connective tissue accumulation small hemorrhagic areas and focal minimal mononuclear cell infiltration are being noted. For immunohistochemistry, the streptavidin-biotin peroxidase complex method was used. Immunostainings are conclusively negative for all pituitary hormones (GH, PRL, ACTH, TSH, FSH, LH and alpha subunit) as well as for HU (ganglion cell marker), chromogranin, GFAP, EMA, PLAP, C-KIT, VIP and CK20. Immunostaining is strongly positive for NSE in all tumor cells and cell processes and for synaptophysin in a few tumor cells and fibers (Figure 4). Few cells closely associated with tumor cell are positive for S100 protein. The cell processes are positive for neurofilament antigen. Some tumor cells and several fibers are immunopositive for LMWK and occasional positivity is notes for CK7. Several regular vessels but no tumor cells stain for vimentin.

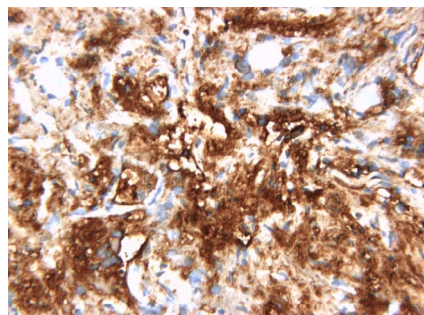


Figure 4: Synaptophysin is immunopositive in a few tumor cells and fibers. Staining for Synaptophysin. Original magnification: 250×.

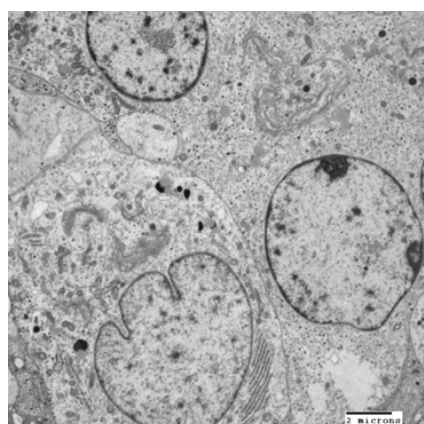


Figure 5: Three neuronal cells are seen. The large cytoplasm contains moderately developed RER and large Golgi. Original magnification: 6000×.

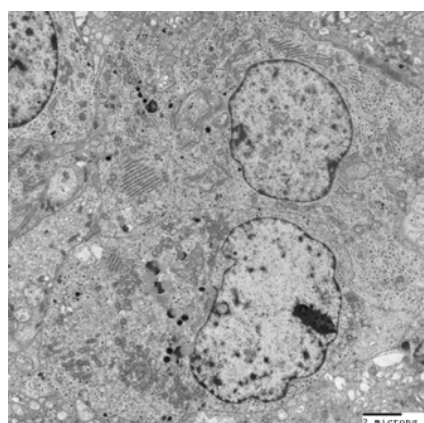


Figure 6: Binucleated neuronal cell located in upper half of image. Well developed RER and Golgi apparatus seen in the cell located in lower half of image. Original magnification: 7000×.

Immunostains for several hormonal peptides (somatostatin, serotonin, pancreatic polypeptide, CRH, and GHRH) appear variably immunopositive for some tumor cells. However, nonspecific background coloration renders these findings inconclusive.

Electron microscopy documents a spectacular neoplasm of neural derivation. The tumor consists of ganglion cells and areas of neuropil. The most typical tumor cell have relatively lucent spherical nucleus with

large nucleolus. The ample cytoplasm harbors compact sacks of RER membranes studded with ribosomes. These units, the EM equivalent of Nissl substance, are often located on the plasmalemma. A large active Golgi apparatus is located perinuclear location. The rest of the cytoplasm incorporates the rod shaped mitochondria, abundant free ribosomes and neurofilaments, a well as numerous mostly peripherally located neurosecretory granules averaging 100 m in diameter. The latter features suggest secretory cell type (Figure 5). A significant percentage of tumor cell are less typical having multiple nuclei (Figure 6). A minority of tumor cell display cytoplasmic vacuolation, shrunken dense pleomorphic nucleus, increased electron density of the entire cytoplasm, heralding cell death.

Discussion

The intrasellar neoplasm described here represents a ganglionic tumor. Such tumors in this location have been called hamartomas, gangliocytomas, and ganglioneuromas. Fischer et al identified 21 reported cases, of which 12 were associated with pituitary hypersecretion, two thirds being acromegaly [9]. More recently, Li et al. in a review of more than 2,000 intrasellar tumors, identified a gangliocytic component in only six cases, and reported on four of these [10]. Although an astrocytic component has been described in these tumors, it seems to be a minor constituent, with the ganglion cell by far being the predominant component. In the present case, astrocytes were not identified by immunohistochemical staining for GFAP and electron microscopy. It seems reasonable, therefore, for these tumors to be termed ganglioneuroma if occurring independently, or mixed gangliocytoma-adenoma if in association with a pituitary adenoma.

The predominant ganglion cell component of these tumors may explain their indolent nature although they may be occasionally locally destructive, as in the case described by Serebrin and Robertson [20]. In their case, the tumor, which was designated as a ganglioneuroma, was surgically removed piecemeal as being composed predominantly of ganglion cells with supporting cells, presumed to be glial. In our case, the presence of dense core neurosecretory granules in the cell bodies and axonal processes of the ganglion cells indicate active neurosecretory activity. Moreover, the structures which appear as spherical, hyaline eosinophilic bodies by light microscopy are shown ultrastructurally to resemble interrupted axons or focal axonal dilatations filled with neurosecretory granules. These structures are reminiscent of Herring bodies, suggesting similarity to that seen in the normal hypothalamic-hypophyseal axis. The terminology of ganglion cell tumors occurring in the region of the hypothalamus and pituitary fossa has been confusing, most likely due to their rarity. Hamartomas occur in the region of the hypothalamus and are associated with a variety of neurologic and neuroendocrine presentations, including sexual precocious puberty [11-15]. These tumors are considered by most investigators to be congenital malformations of ectopic neuronal tissue composed of a mixture of neuronal elements, including ganglion cells, astrocytes, and oligodendroglial cells, often appearing to recapitulate the hypothalamus or tuber cinereum. The term hamartoma seems appropriate given the composition of these tumors, their early presentation, and the lack of evidence for a neoplastic nature. Ultrastructural components of our case lack morphologic evidence of astrocytes and oligodendroglial cells.

The origin of ganglion cells in sellar region is still unclear. The theory of an incidental finding was supported by the hypothesis of abnormal migration of hypothalamic neurons within the adenohypophyseal parenchyma during the early phase of embryogenesis [23]. Another hypothesis suggests the origin of the neuronal component from

neuronal differentiation of a pre-existing pituitary adenoma reporting the presence of transitional cell forms between neurons and adenohypophyseal cells [24]. Vidal et al. [25] supports the assumption of neuronal metaplasia of pituitary adenoma cells describing that somatotrophs exhibit plasticity and under certain conditions they can undergo transdifferentiation. Although this assumption may be challenging, we remain critical, as it is difficult to completely understand the transformation of a neoplastic pituitary cell to a well-differentiated mature neuron with the dominating embryological concepts [26]. Both hypotheses contradict with the findings of our case, since our case was unaccompanied with any diminutive findings of pituitary neoplasia.

Ganglioneuromas have been variously regarded as true neoplasms and as hamartomas. Our case demonstrates that a ganglioneuroma in sellar region may behave as a truly progressive neoplasm with an exceedingly indolent course. Although tumors bearing mature ganglion cells are accepted as hamartomatous in nature, the progressive course of this tumor is difficult to explain. As it has been proposed previously, only the presence of undividable (postmitotic cells) mature ganglion cells does not sufficiently explain progressive course of the tumor. Alternatively, neoplastic transformation of these lesions is well recognized. In general, astrocytic component of tumor progresses, an element that was not identified in our case. Conclusively, although transitional forms of tumors containing primitive neural elements have been demonstrated, no such features were present in our case to suggest dedifferentiation into more primitive neuroblastic elements. In conclusion, one has to keep in mind that these relatively unusual and rare ganglionic tumors might show a progressive clinical course and needs surgical intervention as the major part of their treatment whereas ontogenetic and pathogenetic mechanisms taking part still need more work to enlighten pituitary neuronal tumorigenesis.

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