pituitary neuroendocrine tumor with gangliocytoma

AKA Mixed Gangliocytoma-pituitary neuroendocrine tumor

Gangliocytomas originating in the sellar region are rare; most are tumors composed of gangliocytic and pituitary neuroendocrine tumortous elements, forming the so-called mixed gangliocytoma-pituitary neuroendocrine tumor. The majority of mixed gangliocytoma adenomas are associated with endocrinopathies, mainly acromegaly and less often Cushing disease and hyperprolactinemia.

Differentiating these mixed tumors from conventional pituitary neuroendocrine tumors can be difficult pre-operatively, and careful histological analysis after surgical resection is key to differentiating the two entities. There is little literature addressing the possible mechanisms for the development of mixed pituitary neuroendocrine tumor-gangliocytomas; however, several hypotheses have been proposed. It still remains unclear if these mixed tumors differ from a clinical perspective to pituitary neuroendocrine tumors; however, the additional neural component of the gangliocytoma does not appear to modify the aggressiveness or risk of recurrence after surgical resection. We report a unique case of acromegaly secondary to a mixed GH-secreting pituitary neuroendocrine tumor, co-existing with an intrasellar gangliocytoma.

Acromegaly due to a mixed GH-secreting pituitary neuroendocrine tumor and intrasellar gangliocytoma is rare. These mixed tumors cannot be distinguished easily from ordinary pituitary neuroendocrine tumors on the basis of clinical, endocrine or neuroradiologic findings, and histological analysis is required for a definitive diagnosis. Surgical resection is usually sufficient to provide a cure, without the need for adjuvant therapy. These mixed tumors appear to have a good prognosis although the natural history is not well defined [1)].

Pathogenesis

The pathogenesis of these mixed tumors remains debatable, and ongoing research is required [2)].

Case series

10 cases of mixed gangliocytoma and somatotroph adenomas were evaluated for patterns of cellular differentiation and expression of lineage-specific transcription factors. The tumors were characterized by immunohistochemistry for pituitary hormones, cytokeratins, Pit-1, and the neuronal markers NeuN, neurofilaments (NFP), and MAP2. Double-labeling immunohistochemistry for Pit-1/GH, Pit-1/NFP, Pit-1/MAP2, and NeuN/GH was performed in 9/10 tumors. The data demonstrate that both adenomatous and ganglionic cells express the acidophilic lineage transcription factor Pit-1. Although mixed gangliocytomas and somatotroph adenomas show histologically distinct cellular populations, there is at least a small population of cells that coexpress the Pit-1 transcription factor and neuronal-associated cytoskeletal proteins favoring the theory of transdifferentiation of neuroendocrine cells into neuronal elements of these mixed tumors [3)].

Case reports

Although pituitary macroadenomas often cause mass effects on surrounding structures, it is extremely rare for pituitary lesions to disturb cerebrospinal fluid circulation. Sellar gangliocytoma-pituitary neuroendocrine tumors (SGPAs) (pituitary neuroendocrine tumor with gangliocytoma) are also extremely rare.

Ryder et al., reported the unique case of a man with the unusual combination of acromegaly from an SGPA, who presented with unilateral hydrocephalus. A 60-year-old man presented with rapid neurological deterioration, bitemporal hemianopsia, and acromegalic features. Neuroimaging revealed a large sellar lesion extending superiorly into the left foramen of Monro, causing acute obstructive unilateral hydrocephalus. External ventricular drain placement improved consciousness immediately. The biochemical assessment confirmed acromegaly. Following transsphenoidal debulking, histology revealed a mixed gangliocytoma/sparsely-granulated somatotrophinoma. Despite the residual disease, his vision recovered remarkably, low-dose cabergoline controlled residual excess growth hormone (GH) secretion, and the residual tumour has remained extremely stable over 2 years. Hydrocephalus is an extremely rare complication of pituitary lesions, and unilateral hydrocephalus has never been reported previously. GH secretion in SGPAs is more common than for pituitary neuroendocrine tumors in general, raising questions regarding the aetiology and therapeutic approach to this rare combination tumour [4)].

A 67-year-old woman with a past history of type 2 diabetes mellitus presented with worsening glycemic control. She had some acromegaly symptoms and magnetic resonance imaging demonstrated a pituitary tumor. Endocrinological examination found the resting growth hormone (GH) level within the normal range, but elevated insulin-like growth factor 1 level. A 75 g oral glucose tolerance test showed inadequate suppression of nadir GH levels. Acromegaly due to GH-secreting pituitary tumor was diagnosed. The patient underwent endoscopic transsphenoidal surgery resulting in gross total removal of the tumor and recovered well postoperatively. Histological examination of the tumor showed coexistence of relatively large gangliocytoma cells and pituitary neuroendocrine tumor cells, suggesting mixed gangliocytoma-pituitary neuroendocrine tumor. In addition, colocalization of GH and GH-releasing hormone (GHRH) in pituitary neuroendocrine tumor cells was revealed, so the adenomatous components were more likely to produce GHRH in our mixed gangliocytoma-pituitary neuroendocrine tumor case. Mixed gangliocytoma-pituitary neuroendocrine tumor is very rare, and the present unique case demonstrated only the adenomatous components associated with GHRH production.

Sellar gangliocytoma coexisting with pituitary neuroendocrine tumor is recognized as a mixed gangliocytoma-pituitary neuroendocrine tumor and is very rare. A proposed developmental mechanism of growth hormone (GH)-secreting mixed gangliocytoma-pituitary neuroendocrine tumor involves GH-releasing hormone (GHRH) produced by the gangliocytic components promoting the growth of tumor including GH-secreting adenomatous components. Since the present case indicated that the adenomatous components of mixed gangliocytoma-pituitary neuroendocrine tumor could secrete both GH and GHRH simultaneously, progression of GH-secreting mixed gangliocytoma and pituitary neuroendocrine tumor may involve exposure to spontaneously produced GHRH due to the adenomatous components [5)].

Two 47-year-old females who presented with masses in the sellar region following a general examination and radiological imaging. The two patients underwent sellar region tumor resection via the trans-naso-sphenoid approach. The histopathological examination confirmed the diagnosis of a hormone-free pituitary neuroendocrine tumor with gangliocytoma. The two patients were in good condition and experienced no specific discomfort subsequent to the follow-up after surgery. Gangliocytoma is a slowly growing and non-metastasizing tumor. A biopsy is required to differentiate a gangliocytoma from a malignant neuroblastoma, and excision is usually curative [6].

Three cases of a composite sellar tumor composed of a gangliocytoma and an adenoma are presented. Two patients who showed acromegaly and hyperprolactinemia had a gangliocytoma and a growth hormone (GH)-prolactin cell adenoma in close proximity. The gangliocytoma contained growth hormone-releasing hormone (GHRH) by immunohistochemistry. At the electron microscopical level, the gangliocytoma was characterized by numerous synaptic vesicles. The third patient, a child with Cushing's disease, presented a corticotropin-releasing hormone (CRH)-positive gangliocytoma in close contact with an adrenocorticotropic hormone (ACTH) secreting adenoma, the latter a typical densely granulated ACTH cell adenoma. Ultrastructurally, the gangliocytoma revealed synaptic vesicles and sparse secretory granules. The results suggest that gangliocytomas may promote the development of pituitary neuroendocrine tumors by hypersecretion of releasing hormones. Whereas 20 cases of sellar GHRH producing gangliocytomas in acromegaly are reported in the literature, the combination of a CRH-positive gangliocytoma and an ACTH cell adenoma in Cushing's disease is apparently the first case [7].

1) , 2)
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