Mixed somatotroph adenoma-gangliocytoma: A rare sellar combined tumor

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ABSTRACT

Introduction: Gangliocytomas are rare entities that correspond to less than 1% of the brain tumors, and can be present in the sellar region or more frequently in association with a pituitary adenoma. Hormonal overexpression has also been described in this tumor association leading to endocrine syndromes. Case Report: We report a case of a 23-year-old female diagnosed with a pituitary macroadenoma. The first symptoms were unilateral amaurosis and contralateral reduced visual acuity. On physical examination, she had unilateral amaurosis and galactorrhea, while the laboratory showed hyperprolactinemia and hypogonadotropic hypogonadism. Eight months after starting cabergoline and without any follow-up visit, the patient was subject to an emergency transsphenoidal surgery due to pituitary apoplexy. At this moment, growth hormone (GH) and insulin-like growth factor-1 (IGF-1) previously collected were checked and acromegaly was diagnosed [GH 10.68 µg/dL; IGF-1 2.25 ULN (the upper limit of normality)]. Histopathology revealed a mixed somatotroph adenoma-gangliocytoma with areas of apoplexy. Unfortunately, surgery did not cure acromegaly, and clinical treatment was started but without hormonal control. A new surgery was scheduled. Conclusion: Mixed pituitary adenoma-gangliocytoma is a rare entity. The diagnosis is only possible after surgery and immunohistochemistry of the mass, once radiologically, it is indistinguishable from other sellar masses.

Keywords: Acromegaly, Gangliocytoma, Hyperprolactinemia, Pituitary adenoma

INTRODUCTION

Gangliocytomas are rare and usually benign tumors accounting for less than 1% of brain tumors [1]. They are well-differentiated slow-growing neuroepithelial tumors formed from different types of ganglion cells. Gangliocytomas may occur in the sellar region or more frequently in association with pituitary adenomas [1–3], named as mixed tumors. These mixed tumors are composed of both adenomatous adenohypophysial cells and differentiated ganglion cells [1–5]. In approximately 75% of the cases, gangliocytomas that are located in the sellar region are associated with a functional pituitary adenoma [6].

There are 130 cases of gangliocytomas associated pituitary adenomas reported in the review of Cossu et al. in 2016 [1], and there are more than 19 cases reported afterward [7–13]. The incidence of this association varies from 0.52% to 1.26% in different series [14, 15]. In the
mixed tumors, hormonal overexpression may occur, leading to endocrine syndromes [16]. Therefore, the clinical presentation may be related to hypercortisolism, hyperprolactinemia, and excessive circulating GH levels. The most common finding is the coexistence of neural tissue and GH-secreting pituitary adenoma, while histologically mixed GH-prolactin adenomas are most frequently isolated (43%) [1].

We aimed to report a rare case of a mixed somatotroph adenoma-gangliocytoma. Additionally, we reviewed the rare presence of gangliocytoma in the pituitary gland.

CASE REPORT

A 23-year-old female patient with unilateral amaurosis and contralateral reduced visual acuity was submitted to an ophthalmologic investigation. A pituitary macroadenoma was diagnosed, and the opinion of an endocrinologist was requested during the hospital internment. At that time, she reported galactorrhea for seven years, amenorrhea for two years, and chronic headaches. She denied any other symptoms, including those related to acromegaly. In addition, she had a regular physical exam, except for the presence of unilateral amaurosis and galactorrhea. There was no acromegaly stigma.

Laboratory exams demonstrated serum prolactin of 81.08 ng/mL [normal reference range (RR) 4.79–23.3 ng/mL], normal thyroid function and hypogonadotropic hypogonadism. Serum GH and IGF-1 samples were collected, but results were not yet available. Sella turcica magnetic resonance image (MRI) revealed a voluminous expansive intra and suprasellar lesion, isointense in T1 and T2-weighted images, with hemorrhagic areas and heterogeneous contrast uptake, measuring 3.6 × 2.4 × 2.9 cm; compressive effect on optic chiasm, third ventricle and hypothalamic region, bilateral extension to cavernous sinus and inferior extension to sphenoidal sinus (Figure 1).

Cabergoline was initiated during the hospital internment. On endocrinology follow-up a month later, she reported that her menses had returned and galactorrhea had disappeared, but headaches and visual impairment remained. A surgical intervention was scheduled. The growth hormone and IGF-1 were not ready at this time. After that, the patient abandoned medical follow-up, but continued cabergoline use on her own.

After eight months of treatment with cabergoline, the patient returned with a severe headache and bilateral amaurosis at the emergency room. An MRI exam confirmed a pituitary apoplexy, and the patient was subjected to an emergency transphenoidal surgery. At this moment, GH and IGF-1 results (that samples collected earlier to cabergoline use) were re-checked, and both were increased (GH 10.68 µg/dL and IGF-1 22.5 ULN), leading to acromegaly diagnosis. After surgery, she recovered temporal vision on one side. The histopathology of the resected tumor revealed an eosinophilic fibrillary stroma with low cellularity and similar to neuropil, containing neurons of varying size and shape, eosinophilic cytoplasm, and vesicular nuclei. The immunohistochemistry was positive for GH, prolactin, synaptophysin, and neurofilament on the fibrillary stroma, and negative for glial fibrillary acidic protein (GFAP). Ki-67 was immunostained in 3–5% of the neoplastic cells. These findings were compatible with mixed somatotroph adenoma associated with gangliocytoma with areas of apoplexy (Figure 2).

Six months after surgery, we observed high levels of basal GH and the absence of GH suppression after oral glucose tolerance test on lab tests. A serum IGF-1 of 2.6 ULN, and also hypogonadotropic hypogonadism were present. Magnetic resonance imaging revealed a reminiscent lesion of 2.6 × 2.3 × 2.3 cm on the sella turcica, extending to the cavernous sinus and pituitary stalk, in contact with optic chiasm. Octreotide LAR 20 mg (monthly) and cabergoline (0.5 mg, three times a week) were prescribed to promote tumor shrinkage and a possible reoperation in the near future.

During follow-up, the patient kept high levels of GH and IGF-1 despite the regular use of cabergoline and octreotide LAR. The dosages of both drugs were...
progressively increased (2.0 mg weekly and 40 mg monthly, respectively). Even with our instructions, the patient was not regular on her medical follow-up. She still had unilateral amaurosis and lateral hemianopsia of the contralateral eye. Moreover, she also claimed of forehead enlargement and increased jaw (perceptible at physical examination). An MRI of the sella turcica was performed two years after surgery and showed the same size and characteristics of the tumor. A new transsphenoidal surgery was scheduled.

DISCUSSION

These pituitary tumors have also been called pituitary adenoma-neuronal choristoma (PANCH), pituitary adenoma with neuronal choristoma, and pituitary adenoma with gangliocytic component. The pituitary gangliocytoma is a rare brain tumor, usually associated with an adenoma leading to hypersecretion of pituitary hormones, with an approximate incidence of 149 cases in the literature according to our review [1, 7–13]. Pituitary gangliocytomas consist of ganglion cells with a variably dense fibrillary substrate, frequently associated with the adenomatous proliferation of pituitary cells [14]. The most frequent endocrine syndrome associated with gangliocytoma is acromegaly, followed by hyperprolactinemia, and less frequently, Cushing’s disease [1]. Non-functioning tumors have also been reported to be associated with gangliocytomas [1, 2]. We described a case of a young female patient with a mixed somatotroph adenoma-gangliocytoma, which is most frequently described histological association in the literature [1].

It is well known that the identification of a dual sellar pathology is challenging since most of the cases are presented clinically and radiologically as pituitary adenomas. The definitive diagnosis is determined by the histological and/or immunohistochemistry studies [5]. Most common patients are females, and the most preoperative diagnosis is a GH-producing tumor [5]. In our case, the lack of clinical signs of acromegaly, and no prompt access to serum IGF-1 levels delayed the diagnosis. The prescription of cabergoline was realized in order to recover the hypoestrogenism status and to interrupt galactorrhea.

Our patient proceeded with an emergency surgery due to a pituitary apoplexy, the primary purpose of which was to decompress sellar and suprasellar structures and recover vision. Radical tumor removal or hormonal overproduction cessation were achieved, and long-acting somatostatin analogue was indicated for use. It is essential to point out that suprasellar and/or parasellar extensions were found in 79% of patients with sellar gangliocytomas, which leads to the difficulty of radical tumor resection [4].

The origin of the pituitary gangliocytomas is still controversial, with several hypotheses being proposed. The first one is that the pituitary adenoma formation occurs as a result of endocrine or paracrine stimulation of adenohypophysial cells by the pituitary hormone-releasing hypothalamic hormones, produced by ganglion cells [6, 17]. The second hypothesis suggests that the ganglionic component originates from the neural differentiation of a preexisting pituitary adenoma in a process suggestive of transdifferentiation [18]. The third hypothesis suggests a common origin for both neuronal and adenomatous components from uncommitted stem cells from the adenohypophysis, which is capable of multidirectional differentiation [14]. A common origin for neuronal and pituitary adenoma cells elements in gangliocytomas was suggested by the presence of neurofilament protein (NFP) in the adenoma cells compartment of gangliocytomas [14]. Neurofilament protein indicates neuronal differentiation in adenoma cells. In our patient, the adenoma was immunoreactive for NFP further supporting this theory.

In the study of Shepard et al. [9], 3 out of 4 patients treated with pegvisomant. All 4 patients got clinical improvement, and hormonal remission in a median follow-up of 74 months.
CONCLUSION

In conclusion, we report a rare presentation of somatotroph adenoma associated with gangliocytoma. The diagnosis of these tumors is only possible after surgery and immunohistochemistry evaluation as radiologically they are indistinguishable of sellar/suprasellar masses, independent of associated endocrine syndromes.

REFERENCES


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Acknowledgments

We acknowledge Dr. Ellington Simões and Dr. Felipe Carvalho, neurosurgeons (from Neurosurgery Service, Faculty of Medical Sciences, State University of Rio de Janeiro) who realized the surgical procedure of the patient.

Author Contributions

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Guarantor of Submission
The corresponding author is the guarantor of submission.

Source of Support
None.

Consent Statement
Written informed consent was obtained from the patient for publication of this article.

Conflict of Interest
Authors declare no conflict of interest.

Data Availability
All relevant data are within the paper and its Supporting Information files.

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