Clinical case

Silent GH pituitary tumor: Diagnostic and therapeutic challenges

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Abstract

Silent GH pituitary tumors are characterized by the absence of clinical features of acromegaly, normal to slightly elevated GH and/or IGF-1 levels, as well as immunohistochemical expression of GH. The diagnostic and the therapeutic challenges of these “silent” GH tumors are illustrated in this case report, supported by a literature review. A 20-year-old woman presented with visual disturbances related to an invasive macroadenoma but without clinical and biological signs of GH hypersecretion. After two surgeries, a residual tumor remained in the right cavernous sinus. According to the recent classifications, the histopathological diagnosis was a sparsely GH-PRL atypical adenoma or invasive and proliferative (Ki-67 index: 4%) and p53 positive (1%) grade 2b tumor, with high expression (>75% of the cells) of somatostatin receptors type 2A and 5. From this case and the review of the literature, an invasive macroadenoma in young women requires: the preoperative determination of plasma GH and IGF-1, the immunohistochemical detection in the tumor of GH, PRL, somatostatin receptor expression and the evaluation of the proliferation (mitoses count, Ki-67 and p53 indexes). The suspicion of an aggressive behavior needs a particular follow-up. In the case of tumor remnant, a postoperative treatment such as radiotherapy and/or somatostatin analogs must be considered.

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Résumé

Les adénomes somatotropes silencieux sont des adénomes hypophysaires présentant une expression immunohistochimique de GH mais sans signes cliniques d’acromégalie, et pour lesquels les taux de GH ou d’IGF1 sont généralement normaux ou légèrement augmentés. L’objectif de cet article est d’illustrer les difficultés diagnostiques et les défis thérapeutiques que représentent ce type d’adénome hypophysaire. Pour cela nous décrivons le cas d’une jeune patiente de 20 ans présentant un volumineux adénome invasif, cliniquement et biologiquement non sécrétant, révélé par d’importants troubles visuels. Malgré deux interventions, un résidu tumoral persistait dans le sinus caverneux droit. L’analyse histologique classait cet adénome comme un adénome mixte GH-PRL « atypique » et « invasif et proliférant » [index Ki-67 à 4 % et p53 positif (1 %)] de grade 2b, avec une expression élevée (> 75 % des cellules) des récepteurs de la somatostatine de type 2A et 5. Ce cas et la revue de la littérature soulignent l’importance de l’évaluation préopératoire des concentrations de GH et d’IGF-1, et de l’analyse histopathologique complète comprenant l’analyse de l’expression immunohistochimique de la GH, de la PRL, de l’expression des récepteurs de la somatostatine et de l’évaluation de la prolifération (nombre de mitoses, l’index Ki-67 et l’expression de la p53). Ce type de tumeurs doit être considéré comme « agressif » et nécessite un suivi postopératoire rapproché. La présence d’un résidu tumoral doit faire considérer l’intérêt d’un traitement complémentaire par radiothérapie et/ou analogues de la somatostatine.

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1. Introduction

GH adenomas are defined as pituitary tumors with clinical and biochemical evidence of GH hypersecretion, confirmed by histologic somatotroph differentiation and GH
immunoreactivity [1]. Beside this classical form of GH adenoma, some tumors, without clinical symptoms of acromegaly, exhibit immunohistochemical evidence of GH secretion. In the first cases described in the literature, the GH plasma levels were increased [2,3]. In other cases, biochemical data were normal to slightly elevated and these GH tumors without acromegaly were referred to as “silent GH adenomas” [4]. Some of those so-called silent GH adenomas are diagnosed in women mainly because of the amenorrhea and/or galactorrhea, due to co-secretion of PRL [5].

A recent publication [6] classified GH adenomas into four categories depending on the presence or not of acromegaly and on IGF-1 plasma levels: classic (obvious acromegaly and elevated IGF-1), subtle (subtle acromegaly and elevated IGF-1), clinically silent (no acromegaly, but elevated IGF-1) and silent (no acromegaly and normal IGF-1). The authors underlined that one third of GH adenomas are clinically nonfunctioning and that IGF-1 plasma levels were slightly elevated in almost all of them. They suggest that IGF-1 secretion should be determined for all patients with a pituitary tumor. Very few studies analyzed characteristics of silent GH adenoma with normal GH and IGF-1 plasma levels. However, it seems that compared to tumors associated with acromegaly, silent GH adenomas are larger, more invasive and less differentiated, with histologic and electron microscopy features of sparsely granulated subtype [4,5,7,8]. Some silent GH-PRL tumors are aggressive, with multirecurrent and resistance to temozolomide [9].

In case of acromegaly, response to somatostatin analogs (SA) depends to a large extent on somatostatin receptor (SSTR) expression, especially SSTR2A and SSTR5 [10]. For silent GH tumors, a first therapeutic option is surgery. If the surgical resection is not complete, further therapy is required, including medical treatment or radiotherapy. No data are available to choose the optimal treatment of these tumors. Knowledge of positive immunostaining for GH and SSTR expression level in silent GH adenoma could guide the management for patients with persistent disease after surgery [11].

To illustrate the diagnostic and therapeutic challenges of silent GH tumors, we described the initial management of a 20-year-old woman with a large silent GH-PRL pituitary tumor expressing SSTRs and we did a literature review.

2. Case report

2.1. Clinical data

In 2011, a 20-year-old woman presented with visual disturbances associating loss of visual acuity (3/10 on right eye) and atypical bitemporal hemianopsia. A magnetic resonance imaging (MRI) identified a large pituitary tumor (38 × 27 mm) with suprasellar extension and right cavernous sinus invasion. There were no evident endocrine signs of hypersecretion or pituitary deficit. Menstrual cycles were maintained and clinical examination did not reveal any galactorrhea. As clinically expected, hormonal evaluation were normal: GH 3.2 mUI/L (<1.5 mUI/L), IGF-1 265 μg/L (195–495 μg/L), UFC 132 nmol/day (<180 nmol/day), TSH 0.51 mUI/L (0.4–3.1 mUI/L), T4-free 18.8 pmol/L (11.1–18.8 pmol/L), except for a slight increase of PRL concentration to 29.6 μg/L (<20 μg/L). Given the large size of the pituitary tumor, its polylolobulated appearance and the right lateral extension observed on MRI (Fig. 1A), a transcranial approach was proposed in attempt to insure right optic nerve decompression. Postoperatively, visual acuity was not improved and ophthalmological examinations revealed right optic atrophy. Six months after, a transphenoidal surgery completed the transcranial approach because of the persistence of residual tumor (24 × 26 mm, Fig. 1B). Nevertheless, a complete surgical removal was impossible due to the cavernous sinus invasion (Fig. 1C). The patient underwent stereotactic radiotherapy 6 months after the second surgery. Following the second surgery, cabergoline (Dostinex®; 0.5 mg/d) was initiated in attempt to control tumor growth before radiotherapy efficacy. So far, she has been treated for 9 months without tumor shrinkage but a slight decrease of PRL (from 13 to 3.4 μg/L) and IGF-1 (from 309 to 290 μg/L) concentrations were noted but within the normal values. Genetic studies were negative for AIP and MEN-1 mutations.

2.2. Pathological data

Tumoral tissue removed from both surgeries was fixed in Zinc-formalin fixative and embedded in paraffin. For routine histology, the slides were stained with

Fig. 1. MRI of pituitary tumor: coronal T2-weighted images. A. Before first surgery. B. After first surgery. C. After second surgery.
Hematoxylin-Phloxine-Saffron (HPS) and Herlant’s tetrachrome. Automated immunohistochemistry (IHC) reactions were performed with Benchmark XT, Ventana Medical Systems, Tucson, AZ, USA, using antibodies against hormones (anti-GH, PRL, ACTH, beta-FSH, beta-LH and beta-TSH) and antibodies against Chromogranin A (CgA) and pancytokeratin (KL1). The immunoprofile of all of these antibodies was described in a previous publication [12]. The proliferative rate (mitoses and Ki-67 - Mib1, 1/50, Dako, Glostrup, Denmark) and expression of p53 (clone DO-7, 1/200, Novocastra Laboratories, Newcastle upon Tyne, UK) were evaluated. Immunohistochemical (IHC) expression of SSTR2A and SSTR5 was determined using the new monoclonal antibodies (SSTR2A - clone UMB-1, reference 3582-1, dilution 1/4000 and SSTR5 - clone UMB-4, reference 3619-1, dilution 1/1000, CliniSciences, Nanterre, France) as recently published [13].

3. Results

The tumor had similar histologic appearance and IHC profile (Fig. 2) in all the fragments removed from two surgeries. The tumor showed a diffuse pattern (Fig. 2A), with monomorphic, agranular cells under Herlant’s tetrachrome. The nuclei were large with prominent nucleoli. By IHC, focal and low percentages of GH- and PRL-immunoreactive cells (Fig. 2C–D) were observed (GH = 30% and PRL = 5%, respectively). Chromogranin A was also expressed (Fig. 2B) and detection of pancytokeratine (KL1) was negative. Antibodies against other
pituitary hormones were negative. The tumor had high proliferative index (Ki-67 = 4%, Fig. 2E), few mitoses (1 mitosis/10 high power fields), p53 detection was positive (1%, Fig. 2F). This tumor was diagnosed as silent GH-PRL pituitary adenoma, invasive (right cavernous sinus), with proliferation (Ki-67 > 3%, p53 positive and 1 mitosis), named “atypical adenoma”, according to the WHO classification 2004 [1] and classified grade 2b, according to a recent clinicopathological classification [14]. The IHC expression of SSTR2A and SSTR5 was high. All the cells presented a strong membrane staining (Fig. 3) and the tumor was included in group 3 (> 75% immunoreactive cells) for both SSTRs according to a recent study [13].

4. Discussion

This case highlights several issues related to the clinical and histological characteristics and the management of these rare patients with silent GH adenomas. In most cases, the diagnosis is made in young females, due to the presence of visual signs or to amenorrhea and/or galactorrhea [5,8]. In our young female patient, pituitary adenoma was found in the context of visual disturbances, without presence of amenorrhea and/or galactorrhea. In some cases, hormonal workup can show elevated levels of GH and/or IGF-1, without signs related to acromegaly [2,3,5,7,15,16]. In these cases, the first therapeutic option may be medical therapy with SA or surgery, depending on the clinical context and the patient’s desire. In other cases, hormonal data show normal or slightly elevated levels of GH and/or IGF-1, without presence of acromegaly, as in our case. In this situation, surgery is the first therapeutic option, mainly because these tumors are often large and invasive [4,8]. Moreover, there is no data on the use of SA for the treatment of silent GH pituitary tumors. In most cases, tumor resection is subtotal, especially when cavernous sinus is invaded. Either multiple surgeries are required or complementary therapies are needed such as radiotherapy. Unfortunately, radiotherapy is associated to a risk of side effects. In our case, the patient presented with a rapidly growing macroadenoma. Two surgeries were needed with two different surgical approaches, because of the polylobulated shape and large size of the tumor. However, a residual tumor remained in the right cavernous sinus. In these cases presenting with a postoperative remnant and classified as grade 2b, a recent case-control study [14] underlines the high risk of tumor progression during the follow-up, which leads to the necessity of an additional treatment.

Two options are available: radiotherapy, which is efficient for controlling tumor progression, but associated with a high risk of hypopituitarism [17] and medical treatment. Dopamine agonist treatment could be an option for some GH or GH-PRL secreting tumors [18]. However, to our knowledge, there is no publication studying tumor response of silent GH-PRL or PRL tumors. In our case, despite 9 months of treatment with cabergoline, no tumor shrinkage has been noted. SA, which is the cornerstone of the treatment of GH secreting tumor [10], should be proposed. Indeed, in case of classical GH secreting tumor, the response to SA on GH secretion and tumor shrinkage seems to correlate with SSTR2A expression [19]. However, data are lacking in this specific condition of silent GH secreting tumor. The study of SSTR expression may be useful to identify if the tumor will be susceptible to respond to SA treatment. In our case, both SSTR2A and SSTR5 were highly expressed, indicating that medical treatment could be proposed as an alternative to radiotherapy or in attempt to control tumor growth before radiotherapy efficacy. In our case, radiotherapy has been delayed to limit the risk of optic side effects. According to the results of the GH and PRL immunostaining even in absence of clinical or biochemical abnormalities, both SA and dopamine agonist medical treatments could be proposed but due to the injections and the cost associated with SA, the patient chose cabergoline treatment instead of SA.

Based on IHC reaction with cytokeratin antibodies, GH adenomas are classified into densely (DG) and sparsely granulated (SG). According to Obari’s criteria [20], DG tumors have a predominant perinuclear pattern cells and SG tumors a dot pattern cells. SG type tumors mainly occur in younger women, are invasive macroadenomas and have a lower surgical cure rate compared with DG type [21]. Most reported silent GH adenomas are SG type tumors and GH-PRL with a low GH and PRL immunoreactivity [4,5]. Similarly, our case is a SG adenoma on the agranular aspect by Herlant’s tetrachrome, but is completely negative for cytokeratine with a low percentage of GH and PRL-immunoreactive cells. These features suggested a poorly differentiated tumor associated with high risk of progression.

In conclusion, the presence of a macroadenoma in a young woman, who presented with signs of tumor compression or with amenorrhea and/or galactorrhea, requires the preoperative...
determination of GH and IGF-1 and the IHC detection in the
tumor of GH, PRL expression, the evaluation of the prolifera-
tive rate on the mitosis count, and the Ki-67 and p53 indexes.
The suspicion of an aggressive tumoral behavior needs a partic-
cular clinical follow-up and a postoperative treatment. The SSTR
expression must be systematically studied, but its value to predict
the tumor response to the SA treatment in silent GH adenomas
remains unknown.

Disclosure of interest

The authors declare that they have no conflicts of interest
concerning this article.

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References

pituitary tumors: introduction. In: DeLellis RA, Lloyd RV, Heitz PU, Eng
C, editors. Tumors of the pituitary, chapter 1, Pathology and genetics of
tumours of endocrine organs. World Health Organization Classification of
A, Girod C. Somatotrop adenoma manifested by galactorrhea without
[3] Klihanski A, Zervas NT, Kovacs K, Ridgway EC. Clinically silent hyper-
secretion of growth hormone in patients with pituitary tumors. J Neurosurg
et al. Silent somatotroph adenomas of the human pituitary. A mor-
phologic study of three cases including immunocytochemistry, electron
microscopy, in vitro examination, and in situ hybridization. Am J Pathol
1989;134:345–53.
Clinically silent somatotroph adenomas are common. Eur J Endocrinol
2011;165:39–44.
Endocrine and morphological study of a clinically silent somatotroph ade-
[8] Naritaka H, Kameya T, Sato Y, Furuhata S, Otani M, Kawase T. Morpho-
logical characterization and subtyping of silent somatotroph adenomas.
[9] Batisse M, Raverot G, Maqdasy S, Durando X, Sturm N, Montoriol PF,
et al. Aggressive silent GH pituitary tumor resistant to multiple treatments,
somatostatin analogs in acromegaly. Endocr Rev 2011;32:
247–71.
[11] Cooper O, Melmed S. Subclinical hyperfunctioning pituitary adenoma:
the silent tumors. Best Pract Res Clin Endocrinol Metab 2012;26:
447–60.
Branger D, et al. Pituitary tumors and hyperplasia in multiple endocrine
neoplasia type 1 syndrome (MEN1): a case-control study in a series of
77 patients versus 2509 non-MEN1 patients. Am J Surg Pathol
2008;32:534–43.
las J, et al. Expression of somatostatin receptors, SSTR2A and SSTR5,
in 108 endocrine pituitary tumors using immunohistochemical detection
with new specific monoclonal antibodies. Hum Pathol 2013,
http://dx.doi.org/10.1016/j.humpath.2013.08.007 [in press].
G, et al. A new prognostic clinicopathological classification of pitui-
itary adenomas: a multicentric case-control study of 410 patients with
8 years post-operative follow-up. Acta Neuropathol 2013;126:123–35,
somatotropinomas may be biochemically active. J Clin Endocrinol Metab
without acromegalic features: more quiet than silent: case report. Neu-
surgery 2005;56:E1154 [discussion E1154].
pituitary irradiation is effective in lowering serum growth hormone and
insulin-like growth factor-I in patients with acromegaly. J Clin Endocrinol
Metab 2006;91:1239–45.
[18] Sandret L, Maison P, Chanson P. Place of cabergoline in
acroegaly: a meta-analysis. J Clin Endocrinol Metab 2011;96:
1327–35.
LM, et al. Quantitative analysis of somatostatin receptor subtype (SSTR1-
5) gene expression levels in somatotropinomas and non-functioning
Morphologic characterization of clinically silent somatotroph
Growth hormone-producing pituitary adenomas: correlations between clin-