CUSHING'S DISEASE ARISING FROM A CLINICALLY NON-FUNCTIONING PITUITARY ADENOMA AFTER CRANIAL TRAUMA: A CASE REPORT

Abstract

Introduction. Silent corticotrope adenomas are a subtype of nonfunctioning pituitary adenomas that exceptionally differentiate into functioning adenomas due to multiple causes.

Case report. A 42 years old man was referred to the department of Endocrinology in Hedi Chaker hospital in March 2021 with an incidental finding of pituitary adenoma. He had a history of traumatic brain injury 3 months earlier. Initial biochemical assays showed normal pituitary function. In September 2021, he was readmitted after showing florid Cushing's disease features with severe hypokalemia. Hormonal dosages showed the lack of suppression of cortisol at the suppression tests with high levels of ACTH. The patient underwent pituitary surgery and a recovery was noted.

Conclusion. This is a rare case of silent corticotrope macroadenoma which became hyper secreting after a cranial trauma. Although the nature of the change which occurred in this tumor remains uncertain, it's important to identify and follow closely the patient with such tumors because of the risk of evolution to a functional adenoma.

Key words: Silent corticotrope adenoma; nonfunctioning pituitary adenoma; Cushing's disease; cranial trauma; case report.

Introduction

Adrenocorticotropic hormone (ACTH) adenomas are among invasive subtype of pituitary adenomas (1,2). "These tumors are known to have ability to modify their clinical expression from a silent adenoma to Cushing disease. Silent corticotrope adenoma was first described in 1970 by Kovacs' group as a distinct clinic and pathologic entity with positive immuno-reactivity for adrenocorticotropic hormone without any clinical and biochemical evidence of Cushing's syndrome" (3). The possibility for these tumors to transform into Cushing disease is poorly reported in the literature. A change in the immunophenotype of a tumor is usually seen in malignant tumors and it can be caused by several factors.

We report the clinical course of a Tunisian patient with incidental pituitary adenoma transformed after cranial trauma and began to secrete ACTH that led to severe Cushing syndrome. We discuss putative mechanisms of tumor transformation.

Case report:

A 42-year-old man was referred to the department of Endocrinology in March 2021 with an incidental finding of a pituitary adenoma. He had a traumatic brain injury in January 2021. Brain magnetic resonance imaging (MRI) was performed, confirmed the presence of a macro adenoma with a diameter of 21*26*22 mm with suprasellar extension, hemorrhagic necrosis and compression of the optical chiasm and the optic nerve.

In March 2021, he had no symptoms or signs of Cushing disease or acromegaly. He was 184 cm in tall and weighed 100 Kg (Body mass index of 29 K/m^2). Biochemical assays noted normal pituitary function. Serum cortisol was 204 ng/ml (normal range NR: 70-210 ng/ml). FT4 level was 15,2 pmol/ml and TSH was 1,27 mIU/l. Prolactin level was normal. Evaluation of somatotropic axis showed normal growth hormone (GH) and insulin like growth factor 1(IGF1) levels. By July 2021, his weight increased. He complained from fatigue, weakness and muscular cramps. He reported polyuria and polydipsia since few weeks. In the physical exam. The weight was 114kg (+7kg in six months), the pulse was 107 per minute. He had a severe hypertension. Blood pressure was 180/110 mmHg. Chvostek and Trousseau signs were positive.

We objected erysipelas in the left lower limb. The endocrine evaluation showed a florid Cushingoid features such as facial-truncal obesity, facial reddening, buffalo hump, increased pigmentation of face and hands (fig. 1). These anomalies emerged in the last three weeks. No clinical signs of hypothyroidism neither GH deficiency were noted. Furthermore, the patient reported erectile problems in the last two years. Laboratory investigations revealed a marked hypokalemia at 1.1 mmol/l, metabolic alkalosis, leukocytosis, hyperlipidemia but no hyperglycemia. Results of endocrinological evaluation were remarkable with extremely high ACTH level 2446 pg/ml (NR 10-55 pg/ml). Plasma cortisol concentrations were greatly increased with loss of the circadian rhythm (serum cortisol at 8am: 546 ng/ml, serum cortisol at 4pm: 333.6 ng/ml and serum cortisol at 11 pm: 239 ng/ml). Cortisol level after 4-mg dexamethasone suppression test (DST) was 177 ng/ml. Moreover, after two days treatment with dexamethasone, 2 mg six-hourly, plasma cortisol fell to 45 ng/ml excluding ectopic hypercortisolism. A hypogonadotropic hypogonadism and hypothyroidism were also objected on him (table1). The visual field was normal. MRI was performed to check for tumor bleeding and the result was compatible with pituitary macroadenoma and pituitary hemorrhage (Fig.2). He underwent surgery through a transsphenoidal approach, because of the clinical and endocrinological changes, in October 2021 and the mass was totally resected. Conventional histological examination of the excised material showed a pituitary adenoma with no signs of

malignancy. It was made of small to medium sized rounded or polyhedral monomorphic cells, organized in clusters and nests separated by thin conjunctive-vascular septs. The tumor cells were eosinophilic or with pale cytoplasm, with rounded or ovoid nuclei, non-typical, with a fine chromatin dispersed homogeneously. Immunohistochemical examination showed positive staining for synaptophysin and ACTH up to 40%.

Two weeks following surgery, a post-operative recovery was objected, plasma ACTH level was reduced to 0,35 ng/ml and plasma cortisol to 64 ng/ml. The patient was put on hormone replacement therapy, 15 mg per day of hydrocortisone and 100 µg per day thyroxin. MRI three months later showed no residual tumor. Pituitary function was ameliorated post operatively and hormone replacement therapy was continued.

Discussion

About 7% of pituitary tumors are silent ACTH-producing adenomas (3). Pituitary adenoma that changed phenotype between initial resection and recurrence had been reported in some publications (4). However, metamorphosis of a nonfunctioning pituitary adenoma to Cushing's disease is extremely rare (5).

At first presentation and after review of previous photographs, our patient did not have clinical features of hypercortisolism. He had normal morning serum cortisol levels at that time. Since no other hormonal anomalies were presented, it was a non-functioning or silent pituitary adenoma at presentation. In this case immunocyto-chemical study cannot be contributory because he had not yet undergone surgical resection of the tumor. Vaughan et al. (6) and Cooper et al. (7) were the first to report Cushing disease after transformation of a silent ACTH adenoma. Between 1983 and 2015, 15 cases of non- functioning pituitary adenoma were reported to be transformed to Cushing disease (5,8). Zoli et al. reported that "the transformation from a silent ACTH adenoma to a functioning tumor was noted in 9% of silent ACTH adenoma" (5). "In addition Baldeweg et al. noted this phenomenon in 26% of silent corticotrope cell adenomas" (9).

In case of nonfunctioning pituitary adenoma and negativity for ACTH immunostaining, others suggest that female sex hormones can promote ACTH secretion and contribute to clinical finding of Cushing disease (10).Gamma Knife radiotherapy was proposed as a potential mechanism but it is not yet clear (11). "May be unrecognized genetic factors predispose tumors to phenotypic modification after radiotherapy. It has been proposed also that episodic

hemorrhage and necrosis of cells adenomas causes a cyclical release of cortisol like our case. In case of non-functioning pituitary adenomas (NFPA) and positivity for ACTH immune staining, It can be postulated that a change in the cell membrane lead to exocytosis through it" (12). "In addition, the change in hormonal secretion can be attributable to an alteration in the activity of corticotrophin releasing factor. Alternatively the release of biologically active ACTH could explain the phenotype change (6). Some papers report that an episode of pituitary adenoma hemorrhage could result in stormy release of the hormone leading to Cushing disease" (13).

These changed tumors are usually macroadenomas and sometimes locally invasive. Thus, to control hypercorticism might be more difficult to achieve. Vaughan et al. reported "a case of changed NFPA in a woman, the severity of her Cushing's was of such a degree that it caused a marked hypokalemic alkalosis, normally only associated with very high ACTH levels seen with ectopic ACTH sources. This report is similar to ours but the ACTH level of the reported patient has never been described before. Even so MRI 3 months later confirmed radical tumor removal".

Recently, Righi et al. (14) investigated "the involvement of the prohormone convertase1/3 (PC1/3). This prohormone belongs to the large family of proprotein convertases and is distributed in secretory granules of neural and neuroendocrine tissues (15). It's involved in the post-translational processing of proopiomelanocortin (POMC) into mature and biologically active ACTH". "The PC1/3 expression was analyzed by both immunohistochemistry and quantitative real time-polymerase chain reaction in primary and recurrent tumors. The immunohistochemical PC1/3 expression was negative or weak in the initial phase of NFPA, while a strong expression was observed in the majority of neoplastic cells in tissue specimens obtained from the same patients at the time of recurrence as Cushing disease thus causing the overproduction of bioactive ACTH. This phenomenon is of great interest and remains to be elucidated" (Righi et al. (14)).

Conclusion

In conclusion, although there is still a great deal of work ahead to understand in detail the mechanism(s) responsible for the transformation of phenotype from silent to ACTH secreting adenomas associated with Cushing disease. It was a silent corticotrope macroadenoma which became hyper secreting after a cranial trauma. Although the nature of the change which occurred in this tumor remains uncertain, it's important to identify and follow closely the patient with such tumors because of the risk of evolution to a functional adenoma.

Conflict interest disclaimer:

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

Consent: The patient gave written informed consent for publication

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Table 1 : Hormonal exploration

	3 months after the cranial trauma	**6 months after the cranial trauma**	**1-month post-operative**	**6 months post-operative**
TSH mU/l (0,27-4,2)	1,27	0,8	0,57	0,4
FT4 pmol/l (12-22)	15,2	9,9	15,8	12,1
Cortisol ng/ml (60-184)	204	546	64	42

ACTH pg/ml (10-50)	--------	2446	0,35	42
FSH mU/ml (1,5-12,4)	--------	3,1	--------	5
LH mU/ml (1,7-8,6)	--------	2,6	--------	8,2
Testosterone ng/ml (2,85-8,01)	--------	1,56	--------	4,32
Prolactin ng/ml (4-15)	--------	14	--------	7,2
GH ng/ml (0,119-2,47)	0,3	--------	--------	--------
IGF 1 ng/ml (81-227)	210	106	--------	--------
HCG, FSH, LH, TSH Alpha sub unit IU/l (<0,7)	--------	0,23	--------	--------

(a)2016

(b) March 2107

(c) September 2017

(d) 

Figure 1: patient in 2016(a) and March 2017 (b) before the cranial trauma ; (c,d)patient in September 2017 , 9 months after the cranial trauma , showing florid Cushing's disease features

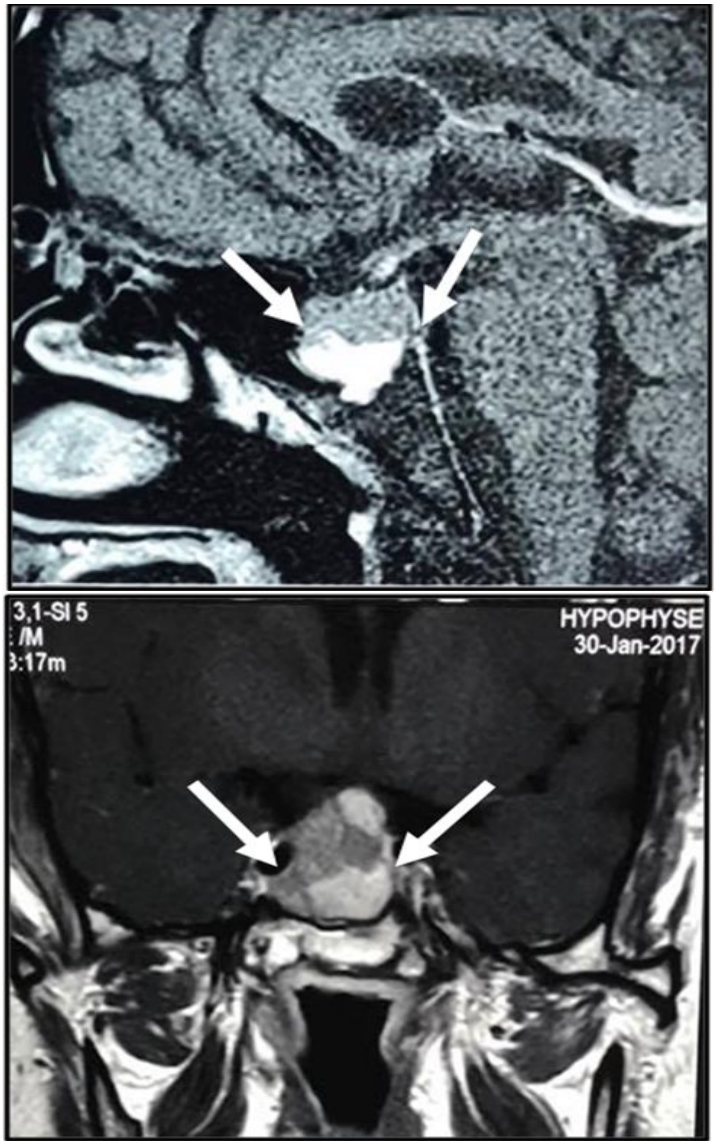

Figure 2: Pituitary MRI (a) sagittal T1 weighed view (b) axial T1 weighed view showing a pituitary macroadenoma measuring 21*26*22 mm with sellar and suprasellar development in hemorrhagic necrosis, pushing back the optic chiasma, compressing its left half as well as the optic nerve