Spontaneous remission of hypercortisolism presumed due to asymptomatic tumor apoplexy in ACTH-producing pituitary macroadenoma

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SUMMARY

Cushing’s disease (CD) is usually caused by secretion of ACTH by a pituitary corticotroph microadenoma. Nevertheless, 7%-20% of patients present with ACTH-secreting macroadenomas. Our aim is to report a 36-year-old female patient with CD due to solid-cystic ACTH-macroadenoma followed up during 34 months. The patient presented spontaneous remission due to presumed asymptomatic tumor apoplexy. She showed typical signs and symptoms of Cushing’s syndrome (CS). Initial tests were consistent with ACTH-dependent CS: elevated urinary free cortisol, abnormal serum cortisol after low dose dexamethasone suppression test, and elevated midnight salivary cortisol, associated with high plasma ACTH levels. Pituitary magnetic resonance imaging (MRI) showed a sellar mass of 1.2 x 0.8 x 0.8 cm of diameter with supra-sellar extension leading to slight chiasmatic impingement, and showing hyperintensity on T2-weighted imaging, suggesting a cystic component. She had no visual impairment. After two months, while waiting for pituitary surgery, she presented spontaneous resolution of CS. Tests were consistent with remission of hypercortisolism: normal 24-h total urinary cortisol and normal midnight salivary cortisol. Pituitary MRI showed shrinkage of the tumor with disappearance of the chiasmatic compression. She has been free from the disease for 28 months (without hypercortisolism or hypopituitarism). The hormonal and imaging data suggested that silent apoplexy of pituitary tumor led to spontaneous remission of CS. However, recurrence of CS was described in cases following pituitary apoplexy. Therefore, careful long-term follow-up is required.

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INTRODUCTION

Cushing’s disease (CD) is generally caused by excessive secretion of ACTH, usually by a pituitary corticotroph microadenoma. However, 7%-20% of cases are due to ACTH-producing macroadenomas (1-3).

Apoplexy is described in pituitary tumors, especially in those macroadenomas of the non-clinically functioning, prolactinomas, and GH-producing adenomas subtypes (4). In CD, these cases are infrequent and associated with macroadenomas (5-11), although there are also descriptions in patients with ACTH-producing microadenomas (12,13). Nevertheless, the majority of CD patients with pituitary apoplexy described were symptomatic at the initial presentation.

The aim of the present study is to report a patient with 34 months of CD evolution harboring a solid-cystic ACTH-macroadenoma, who presented spontaneous remission of hypercortisolism due to presumed asymptomatic tumor apoplexy.

CASE REPORT

A 36 year-old female patient was admitted to our Neuroendocrine Unit in April 2009 for evaluation of CS. She had a 7-month history of weight gain, acne, hirsutism, progressive proximal muscle weakness, arterial hypertension, and secondary amenorrhea. At admission, she showed typical clinical features of CS, BP: 160 x 100 mmHg, 90 kg, BMI: 35 kg/m² (with truncal obesity), and Ferriman-Gallwey score 12. Initial hormonal data were consistent with ACTH-dependent CS: elevated urinary free cortisol (1200/1000/1180 μg/24h, reference 10-90 μg/24h), non-suppressed serum cortisol (Fs) after low-dose dexamethasone suppression test (Fs: 2.56 μg/dL), and elevated plasma ACTH: 89.5 pg/mL (reference < 60 pg/mL). Our lab assessment also confirmed CS diagnosis: 24-h urinary cortisol: 648 μg/24h (reference 30-300 μg/24h), and midnight salivary cortisol: 460 ng/dL (reference < 130 ng/dL) (Table 1). The patient showed no ACTH and cortisol responses after IV administration of desmopressin (10 μg) (ACTH: 42.5 to 49.8 pg/mL, 17.2%; Fs: 26.7 to 27.1 μg/dL, 1.5%). Other hormonal analyses were normal (T3, FT4, TSH, IGF1, estradiol, LH, FSH, prolactin). Pituitary MRI (January 2009) revealed a 1.2 x 0.8 x 0.8 cm sellar mass with supra-sellar extension leading to minor optic chiasmatic compression, with hypointense signal in T1 and partial hyperintense in T2-weighted imaging, suggesting a solid and cystic component (Figure 1A and 1B).

Figure 1. Pituitary magnetic resonance imaging (MRI).
(A) Initial coronal post-gadolinium T1-weighted MRI pituitary scans; (B) Initial coronal T2-weighted; (C) After spontaneous remission coronal post-gadolinium T1-weighted; (D) After spontaneous remission coronal T2-weighted.
She had no visual impairment. Thoracic and abdominal computed tomography were negative for any lesions, and serum tumor markers were in the normal range. After two months, while she was waiting for pituitary surgery without any clinical treatment, she presented spontaneous resolution of CS characterized by loss of weight (6 kg), return of regular periods, improvement of hypertension and hirsutism, and decreased the abdominal obesity. New tests were consistent with remission of hypercortisolism: normal 24-h urinary total cortisol and midnight salivary cortisol (Table 1, Figure 2). Subsequent pituitary MRI (August 2009) showed tumor shrinkage with disappearance of optic chiasmatic compression (Figure 1C and 1D). After 28 months of follow-up, she remains in clinical remission of CS and did not develop hypopituitarism. Up to today, she lost 22 kg (actual weight 68 kg, BMI: 27 kg/m²).

Last imaging analysis (October 2011) was similar to the August 2009 MRI. Hormonal and imaging data suggested that silent apoplexy of pituitary tumor probably occurred, leading to spontaneous remission of CS. The patient remained in clinical remission until October 2011.

The Research Project and Graduate Studies Commission, and the Ethics Commission of our Institution approved the study, and the patient signed an informed consent form.

**Table 1. Hormonal and weight evolution during patient follow-up**

<table>
<thead>
<tr>
<th>Date</th>
<th>UC μg/24h</th>
<th>NSC ng/dL</th>
<th>LDDST F, μg/dL</th>
<th>ACTH pg/mL</th>
<th>Weight kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>December 2008</td>
<td>1200*</td>
<td>-</td>
<td>2.56</td>
<td>89.5</td>
<td>85</td>
</tr>
<tr>
<td></td>
<td>1000*</td>
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<td>-</td>
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<tr>
<td></td>
<td>1180*</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>January 2009</td>
<td>-</td>
<td>2.5**</td>
<td>-</td>
<td>-</td>
<td>90</td>
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<td>April 2009</td>
<td>648</td>
<td>460</td>
<td>1.6</td>
<td>-</td>
<td>84</td>
</tr>
<tr>
<td>June 2009</td>
<td>54</td>
<td>&lt; 100</td>
<td>-</td>
<td>-</td>
<td>58</td>
</tr>
<tr>
<td>August 2009</td>
<td>47</td>
<td>-</td>
<td>24</td>
<td>78</td>
<td></td>
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<tr>
<td>November 2009</td>
<td>49</td>
<td>-</td>
<td>20</td>
<td>70</td>
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<tr>
<td>July 2010</td>
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<td>March 2011</td>
<td>78</td>
<td>30</td>
<td>1.1</td>
<td>34</td>
<td>67</td>
</tr>
<tr>
<td>October 2011</td>
<td>83</td>
<td>70</td>
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<td>35</td>
<td>68</td>
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</table>


Spontaneous remissions in CS and CD are infrequent events that have been already reported more than fifty years ago (14,15). In the subsequent years, some other cases were published and some of them presented recurrence in the follow-up period (7,8,16). However, the cyclic aspect of cortisol secretion that account for 15% of CS patients from several etiologies, mainly CD, are well-described (17). Therefore, these two clinical conditions may overlap, and some of the cases may have been mistakenly described.

Some factors are considered to explain spontaneous remission, principally pituitary apoplexy, an event that has also been enrolled as one of the mechanisms for cyclic CS.

Pituitary apoplexy is more prevalent in other pituitary adenoma subtypes. This event is infrequent in CD, occurring mainly in ACTH-secreting macroadenomas (5-11). However, it may also take place in ACTH-secreting microadenomas (12,13). Pignatta and cols. reported a case of CD that showed a 3-mm microadenoma next to the pituitary stalk that, after short period of ketoconazol use, presented a sudden clinical picture of pituitary apoplexy with remission of CS and concomitant disappearance of pituitary tumor in the follow-up imaging analysis (13). Commonly, pituitary apoplexy in CD patients occurs spontaneously. However, others conditions, such as pituitary radiation therapy (18) or corticotrophin-releasing hormone test (19), were previous correlated with this clinical manifestation.

Pituitary apoplexy occurs as a result of infarction, hemorrhage, or a combination of hemorrhagic infarction in a pituitary tumor tissue. Apoplexy may cause a sudden enlargement of the tumor and frequently results in acute pituitary insufficiency. Patients commonly
experience sudden onset of symptoms that may vary in severity, from headache, with or without endocrine deficiency; visual impairment; ophthalmoplegia; coma; and even death. However, many cases are subclinical or asymptomatic (20), and are suggested by pituitary imaging analysis, during pituitary surgeries or in necropsy studies. In CD patients, the majority of cases described was symptomatic and submitted to pituitary surgery.

The risk for pituitary infarction may be increased by provocative tests for pituitary reserve assessment, anti-coagulation, oral contraceptive agents, and clomiphene. The susceptibility to apoplexy may also be increased by head trauma, non-pituitary surgery, pregnancy, thrombocytopenia, and increased intracranial pressure (21).

The case reported here present non-frequent aspects for CD, such as macroadenoma secreting tumor and spontaneous remission without interventions, probably due to asymptomatic pituitary apoplexy. Other similar case was previous reported by Le Nestour and cols., but in a patient with microadenoma. In the follow-up, pituitary MRI showed spontaneous T1-weighted hiperintensity suggestive of apoplexy, but without any clinical complaints. One year after that, new imaging analysis revealed an empty sella, and the patient achieved spontaneous CS remission (12).

Natural evolution of some pituitary adenomas is known, particularly microprolactinomas. Nevertheless, this aspect is poorly established in ACTH-secreting macroadenomas.

Finally, several cases of CD that showed initial pituitary apoplexy or spontaneous remission presented recurrence in the follow-up up to seven years after remission (7,8,16,22). Alarifi and cols. reported a case of macroadenoma with some two-year periods of spontaneous remission after clinical pituitary apoplexy events (8).

Therefore, careful long-term follow-up is required for patients with CD following remission after pituitary apoplexy, in order to detect hypercortisolism recurrence or the development of hypopituitarism.

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REFERENCES