Fatal factitious Cushing syndrome (Münchhausen’s syndrome) in a patient with macroprolactinoma and silent corticotrophinoma: case report and literature review

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Abstract

Münchhausen’s syndrome (MS) is a chronic factitious disorder characterized by the intentional production of clinical symptoms without external incentive [1]. One type of MS is factitious Cushing syndrome, an extremely rare clinical situation in which the diagnosis is challenging mainly due to interference of the exogenous medication in cortisol immunoassays. We described a 26-year-old woman who was originally diagnosed with a macroprolactinoma and during follow-up developed clinical and laboratorial hypercortisolism. A transsphenoidal surgery was performed and immunohistochemistry revealed positive and diffuse staining for both hormones. Four years later, her hypercortisolism recurred and the confirmation of factitious Cushing syndrome was delayed due to conflicting laboratorial results. There are few cases in the literature of factitious Cushing syndrome, and only one had a fatal outcome. The diagnosis of this condition is complex and includes cyclic Cushing syndrome in the differential diagnosis. These patients have high morbidity and increased mortality risk and are likely to have other psychiatric disorders. Prednisone was identified as the culprit in the majority of the cases.

Keywords: Factitious Cushing’s syndrome, Münchhausen’s syndrome, Cortisol immunoassay

Background

Münchhausen’s syndrome (MS) is a chronic factitious disorder characterized by the intentional production of clinical symptoms without external incentive [1]. One type of MS is factitious Cushing syndrome, an extremely rare clinical situation in which the diagnosis is challenging mainly due to interference of the exogenous medication in cortisol immunoassays [2].

Case presentation

A 26-year-old married female former health professional, who was previously treated for depression, was originally diagnosed with a macroprolactinoma due to secondary amenorrhea and galactorrhea. During follow-up she developed clinical and laboratorial hypercortisolism (Table 1) and a transsphenoidal surgery was performed despite the control of serum prolactin (PRL) levels with high doses of cabergoline (0.5 mg/day). Immunohistochemistry revealed positive and diffuse staining for PRL and ACTH; the pattern of ACTH staining was typical of a corticotrophinoma (diffuse cytoplasmic staining in corticotroph cells), whereas the pattern of PRL staining was atypical (no characteristic Golgi-like pattern of immunoreactivity seen in lactotroph adenomas). There was also no evidence of lactotroph differentiation by ultrastructural analysis. After surgery, PRL levels were controlled without cabergoline, no glucocorticoid replacement was necessary and clinical and hormonal control was obtained.
Four years later, the patient presented with typical, albeit sporadic, signs and symptoms of Cushing syndrome (CS) paralleled by intermittent hypercortisolism, indicating potential cyclic CS. Exogenous intake of glucocorticoids was strongly denied by the patient. A progressive worsening of the clinical features of CS was evident, with the onset of diabetes and hypertension (Table 2). At that time, a chemiluminescence immunoassay (Immulite 2000/Siemens Healthcare Diagnostics) revealed markedly elevated urinary total cortisol levels (UTC = 12,200 μg/24 h reference values = 50–310 μg/24 h), although the morning serum cortisol level was normal (Fs = 12 μg/dL).

The patient's midnight salivary cortisol level was elevated (salivary F = 0.2–2.3 μg/dL – RR < 0.12 μg/dL), as measured using a manual ELISA Millipore kit (Fig. 1), and plasma ACTH measurements were within the reference interval at 14 pg/ml (reference values = 10-46 pg/ml) by chemiluminescence immunoassay (Immulite 2000/Siemens Healthcare Diagnostics). The DHEA-S level was low (208 ng/ml – RR 988–3,400 ng/ml) according to electrochemiluminescence immunoassay (Roche Diagnostics, Sidney, Australia), although the serum PRL levels were normal. Abdominal CT showed normal adrenal glands and pituitary MRI exhibited a cystic lesion similar to the previous tumor tissue, but could also represent an arachnoid cyst (Fig. 2 A).

To further investigate the discordance between UTC and morning serum cortisol, urinary free cortisol (UFC) was measured by high-pressure liquid chromatography tandem mass spectrometry (HPLC/MS). These results revealed a UTC level of 6 μg/24 h (RV = 3–43 μg/24 h) and a suppressed morning serum cortisol level (1.6 μg/dL – normal 7 up to 25 μg/dL), in contrast to the previous results.

The psychiatric evaluation did not identify any mental disorder, although the psychological evaluation identified a complex familial relationship, especially involving her father, who had a history of alcoholism and had left home when she was a teenager. The patient presented a fragile ego, with predominant defense mechanisms of projection, negation, somatization and reactive reactions. Before the result of UFC, bilateral adrenalectomy was suggested to the patient in order to control the hypercortisolism, and the patient agreed to the treatment despite all the risks, showing a desire to get healthy and to be pregnant as soon as possible.

### Table 1 Hormonal profile during the follow-up

| Exam | Mar/2006 Before TS* | Jan/2010 After TS** | Aug/2013 Recurrence | Normal range |
|------|---------------------|---------------------|---------------------|--------------|
| ACTH | 43                  | 27                  | 24                  | <46 pg/mL    |
| Salivary cortisol (midnight) | 0.13                | <0.1                | 2.49               | <0.12 μg/dL  |
| Overnight DST§ | 4.1                 | NA                  | 15.1               | <1.8 μg/dL   |
| 24-h UTC | NA                  | 132                 | 12,200             | 50–310 μg/24 h |
| Serum cortisol (morning) | 19.6               | 11.4                | 33                 | 5–25 μg/dL   |
| DHEA-S | 2,246               | NA                  | 208                | 988–3,400 ng/mL |
| LH | 1.1                 | 0.2                 | 0.9                | 14.0–95.6 IU/L |
| FSH | 1.7                 | <1                  | 2.4                | 4.7–21.5 IU/L |
| E2 | 42.6                | <13                 | <15                | 85.8–498.0 pg/mL |
| Prolactin | 57                  | 13.3                | 27                 | 4.8–23.3 ng/mL |
| TSH | <0.03               | <0.03               | 0.58               | 0.27–4.20 μIU/mL |
| Free T4 | 1.2                 | 0.97                | 0.63               | 0.93–1.70 ng/dL |
| GH | 0.6                 | <0.1                | <0.1               | <4.4 ng/mL   |
| IGF-I | 179                 | 75                  | 26                 | 152.7–396.5 ng/mL |

* Using bromocriptine 5 mg/day; ** Using cabergoline 0.5 mg/day; TS: transsphenoidal surgery; § Dexamethasone suppression test

### Table 2 Biochemical findings during hospitalization

| Exam | Aug/2013 | Normal range |
|------|----------|--------------|
| Sodium | 140      | 135–145 mEq/L |
| Potassium | 4.4      | 3.5–5.0 mEq/L |
| Calcium | 9.1      | 8.60–10.20 mg/dL |
| PTH | 41       | 15–65 pg/mL |
| 25OH vitamin D | 18        | 30–100 ng/mL |
| Urea | 25       | 10–50 mg/dL |
| Creatinine | 0.61     | 0.50–0.90 mg/dL |
| HbA1C | 7.2      | 4.1–6% |
| Glucose | 130      | 70–100 mg/dL |
| HDL-cholesterol | 51       | <65 mg/dL |
| LDL-cholesterol | 129     | <130 mg/dL |
| Cholesterol | 342      | <200 mg/dL |
| Triglycerides | 1,514   | <150 mg/dL |
During hospitalization and despite the multidisciplinary treatment approach, the patient showed persistent hypercortisolism and high levels of triglycerides, amylase and lipase.

Abdominal CT at this time showed bilateral atrophic adrenal glands and severe pancreatitis, and since she had low cortisol laboratory values, a hydrocortisone stress dose was administered. The pancreatitis, however, had a fatal outcome. Additionally, high levels of serum prednisone and prednisolone (7.4 μg/dL and 97 μg/dL, respectively – RR < 0.1 μg/dL - HPLC/MS) were demonstrated and, after her death, her husband found several prednisone tablets at their home.

Discussion

There are few cases in the literature of factitious CS, and only one has reported a case with a fatal outcome [3]. The diagnosis of this condition is complex and includes cyclic CS in the differential diagnosis. The difference between these possible diagnoses is the periodicity of hormone fluctuation, which can take years in the case of cyclic CS but can change dramatically over short periods of time in factitious CS [4–6]. Another clue can be provided by DHEA-S measurements, as ACTH-dependent CS is associated with normal/high levels of this hormone. In our case, variations from 100 to 12,000 μg/24 h in UTC levels could be observed from one day to the next, and DHEA-S levels were suppressed.

Immunoassays for Fs and UTC demonstrated variable cross-reactivity with synthetic corticosteroids and their metabolites; these variations can range from 6 % for prednisone to 62 % for prednisolone, depending on the kit, and can lead to a false elevation of Fs [4,7]. A reliable ACTH assay is crucial for differentiating ACTH-dependent from ACTH-independent Cushing syndrome. However, the performance of ACTH immunoassays has

![Fig. 1](image1.png) Evolution of UTC, salivary F and serum F during follow-up, normalized by the upper limit normal range (ULNR)

![Fig. 2](image2.png) MRI sequences during follow-up. (A) May/2007: coronal view on T 1-weighted MRI of the pituitary gland identified a heterogeneous solid macroadenoma (1.9x1.8 cm of diameter – arrow). (B) August/2013: MRI after four years of transsphenoidal surgery – questionable remnant tumor tissue or arachnoid cyst (arrow)
been questioned recently after several case reports showed unsuppressed ACTH levels in factitious CS, as in our patient [2, 7]. In addition, the intermittent intake of glucocorticoids could lead to fluctuating levels of ACTH [7]. In the few cases of factitious CS in the literature, synthetic glucocorticoids detected in blood and urine by HPLC/MS confirmed the diagnosis since this method can discriminate similar molecules with a different mass to charge ratio [2].

The diagnosis of factitious CS represents a challenge to the physician. These patients have high morbidity and increased mortality risk and are likely to have other psychiatric disorders. Among the patients’ profiles described in the literature (22 cases – Table 3), 80% were female, with a median age of 38 years. The medical history of these cases included drug addiction in 19% and psychiatric disorders in 57%, mainly depression and anxiety, and 42% of patients had personal contact with health professionals. In regard to laboratory tests, 48% of cases showed unsuppressed ACTH levels, and 66% also showed elevated UFC at the same time [1–3, 6–11, 13, 14]. In addition, one-third of patients presented a suspicious pituitary MRI [1,7]. Only three cases in the literature reported DHEA-S measurements, and all of them were suppressed [1, 9]. Half of the reported patients showed normal adrenal glands on abdominal imaging [1–3, 6, 9–12]. Prednisone was identified as the culprit in the majority of the cases [1, 3, 10, 12].

**Conclusions**

The current case reported a patient with chronic factitious CS with a fatal outcome. Factitious CS is an important diagnosis to consider in the evaluation of patients with apparent hypercortisolism; of particular importance is the recognition of discordant hormonal data among urinary and serum cortisol levels, ACTH and DHEA-S associated with atrophic adrenal glands on CT scan. In addition, HPLC/MS analysis of blood and urine steroids is the definitive test for the diagnosis of factitious CS and should be performed when there is a clinical suspicion of glucocorticoid mishandling.

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**Table 3** Clinical and laboratory data from 22 patients with factitious Cushing’s syndrome from review of literature

| Authors       | Age (year) | Gender | 24 h UC | DST   | Serum cortisol | Plasma ACTH | Pituitary MRI | Adrenal CT | Medication          |
|---------------|------------|--------|---------|-------|----------------|-------------|---------------|------------|---------------------|
| Witt, 1981    | 15         | F      | Up      | Suppression | Up | N | Normal | Normal | Prednisone |
| Cook, 1985    | 33         | F      | Lo      | Absent | Up | N | Normal | NA | NA |
| O’Hare, 1986  | 22         | M      | Up      | Suppression | V | N | Normal | Normal | Hydrocortisone |
| Anderson, 1993| 46         | F      | N       | NA    | Lo | NA | Normal | Normal | Prednisolone |
| Anderson, 1993| 23         | F      | Lo      | NA    | N | NA | Normal | Normal | Prednisone |
| O’Shaughnessy, 1995 | 37 | F | Up | Suppression | Up | N | Questionable | Normal | Prednisolone |
| Workman, 1995 | 33         | F      | Up      | Suppression | N | NA | NA | Hydrocortisone |
| Cizza, 1996   | 37         | F      | V       | Paradoxical | Up | Microadenoma | Normal | Prednisolone/Dexamethasone |
| Cizza, 1996   | 31         | M      | Up      | Absent | Up | Lo | Microadenoma | Atrophy | Cortisone |
| Cizza, 1996   | 44         | F      | Up      | NA    | N | N | Questionable | Normal | Unknown |
| Cizza, 1996   | 32         | F      | V       | Suppression | Lo | NA | Questionable | Atrophy | Unknown |
| Cizza, 1996   | 36         | F      | NA      | NA    | Lo | Lo | Normal | Left-sided mass | Prednisolone |
| Cizza, 1996   | 31         | F      | Lo      | NA    | Lo | Lo | Normal | Atrophy | Prednisone |
| Villanueva, 2000 | 37   | F | Lo      | NA    | Lo | NA | NA | Dexamethasone |
| Villanueva, 2000 | 57   | F | V       | NA    | V | Lo | Normal | Normal | Dexamethasone |
| Villanueva, 2000 | 47   | F | NA      | NA    | V | Lo | Normal | Right-sided mass | Unknown |
| Villanueva, 2000 | 54   | F | Lo      | NA    | Lo | Lo | Normal | NA | Dexamethasone |
| Ach, 2005     | 29         | M      | N       | NA    | N | N | NA | Normal | Dexamethasone/Hydrocortisone |
| Ach, 2005     | 60         | M      | N       | NA    | N | NA | NA | NA | Betamethasone |
| Kansagra, 2006*  | 33   | F | Lo      | NA    | Lo | N | Normal | Normal | Prednisone |
| Thynne, 2013  | 54         | F      | Up      | NA    | V | V | Normal | Normal | Prednisolone |

NA: not available; Up: upper; Lo: lower; N: normal; V: variable F (female), M(male), DST (dexamethasone suppression test), UC urinary cortisol *Fatal case
Consent
Written informed consent was obtained from the patient’s husband for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Abbreviations
MS: Münchhausen’s syndrome; PRL: Prolactin; CS: Cushing’s syndrome; UTC: Urinary total cortisol; Fs: Serum cortisol; F: Cortisol; RR: Relative risk; DHEA-S: Dehydroepiandrosterone sulfate; CT: Computed tomography; MRI: Magnetic resonance imaging; UFC: Urinary free cortisol; HPLC/MS: High-Pressure Liquid Chromatography Tandem Mass Spectrometry.

Competing interests
The authors declare that they have no competing interests.

Authors’ contributions
CAM, ALAC and EVAA assisted the patient during hospitalization and drafted the manuscript. LMLL and AG participated in the design of the study. MDB, MCM and MCBVF conceived the study, and participated in its design and coordination and helped to draft the manuscript. All authors read and approved the final manuscript.

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