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CASE REPORT

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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. 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.

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Table 1 Hormonal profile during the follow-up

Exam	Mar/2006	Jan/2010	Aug/2013	Normal range
	Before TS*	After TS**	Recurrence	
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

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

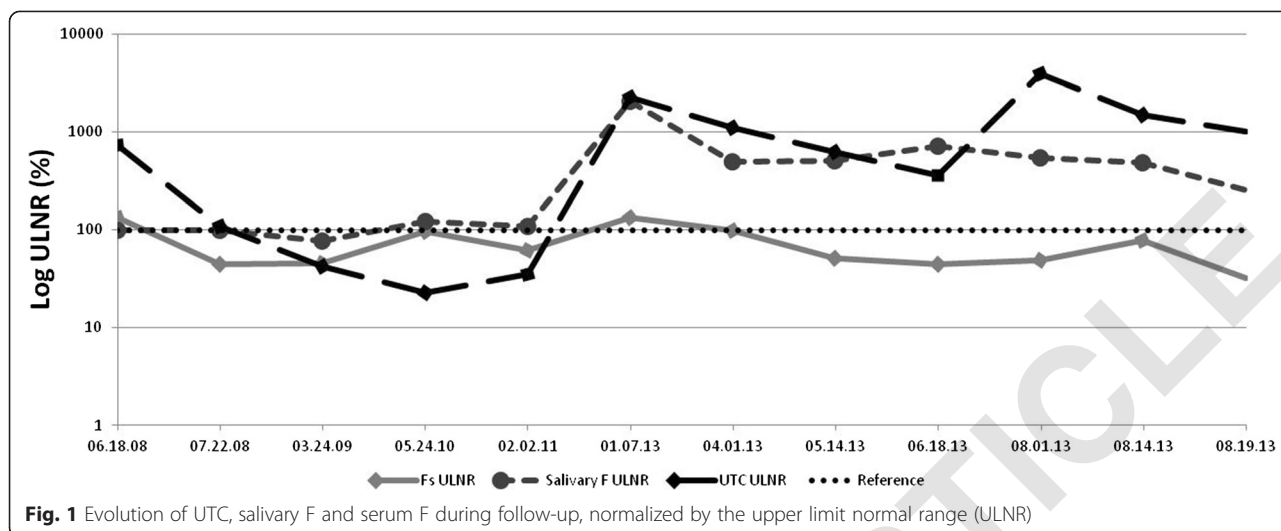
(salivary F = 0.2–2.3 µg/dL – RR < 0.12 µg/dL), as measured using a manual ELISA Millipore kit (Fig. 1), and plasma ACTH measurements were within the reference interval at 14 pg/ml (reference values = 10–46 pg/ml) by chemiluminescence immunoassay (Immulite 2000/Siemens Healthcare Diagnostics). The DHEA-S 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).

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

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.



During hospitalization and despite the multidisciplinary treatment approach, the patient showed persistent hypercortisolism and high levels of triglycerides, amylase and lipase.

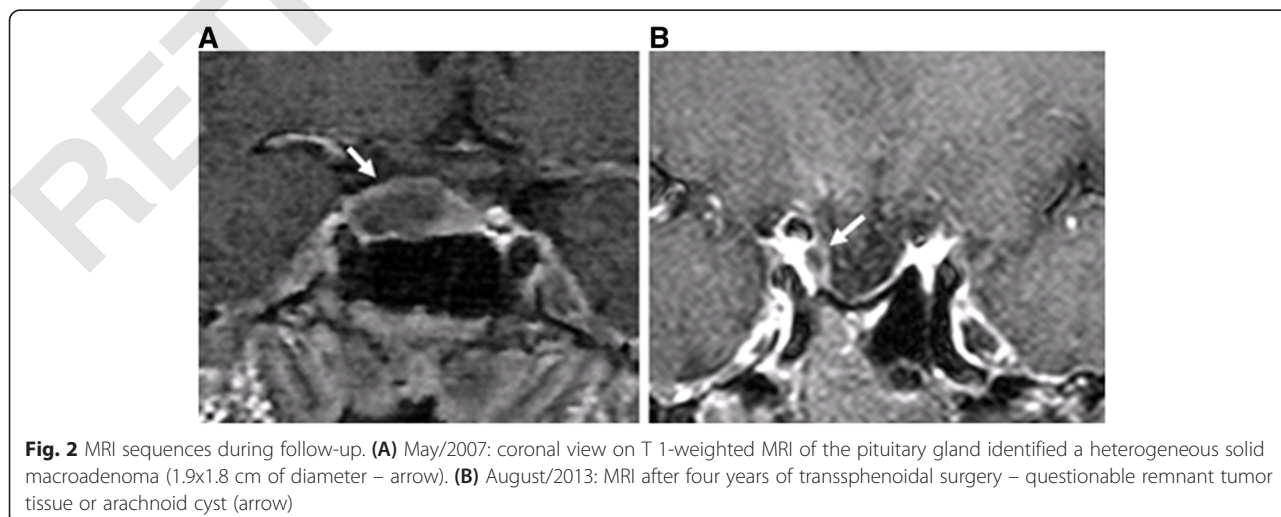
Abdominal CT at this time showed bilateral atrophic adrenal glands and severe pancreatitis, and since she had low cortisol laboratory values, a hydrocortisone stress dose was administered. The pancreatitis, however, had a fatal outcome. Additionally, high levels of serum prednisone and prednisolone (7.4 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



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.

Table 3 Clinical and laboratorial 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 [10]	15	F	Up	Suppression	Up	N	Normal	Normal	Prednisone
Cook, 1985 [14]	33	F	Lo	Absent	Up	N	Normal	NA	NA
O'Hare, 1986 [11]	22	M	Up	Suppression	V	N	Normal	Normal	Hydrocortisone
Anderson, 1993 [12]	46	F	N	NA	Lo	NA	Normal	Normal	Prednisolone
Anderson, 1993 [12]	23	F	Lo	NA	N	NA	NA	Normal	Prednisone
O'Shaughnessy, 1995 [7]	37	F	Up	Suppression	Up	N	Questionable	Normal	Prednisolone
Workman, 1995 [13]	33	F	Up	Suppression	N	N	NA	NA	Hydrocortisone
Cizza, 1996 [1]	37	F	V	Paradoxical	Up	Up	Microadenoma	Normal	Prednisolone/ Dexamethasone
Cizza, 1996 [1]	31	M	Up	Absent	Up	Lo	Microadenoma	Atrophy	Cortisone
Cizza, 1996 [1]	44	F	Up	NA	N	N	Questionable	Normal	Unknown
Cizza, 1996 [1]	32	F	V	Suppression	Lo	NA	Questionable	Atrophy	Unknown
Cizza, 1996 [1]	36	F	NA	NA	Lo	Lo	Normal	Left-sided mass	Prednisolone
Cizza, 1996 [1]	31	F	Lo	NA	Lo	Lo	Normal	Atrophy	Prednisone
Villanueva, 2000 [9]	37	F	Lo	NA	Lo	NA	NA	NA	Dexamethasone
Villanueva, 2000 [9]	57	F	V	NA	V	Lo	Normal	Normal	Dexamethasone
Villanueva, 2000 [9]	47	F	NA	NA	V	Lo	Normal	Right-sided mass	Unknown
Villanueva, 2000 [9]	54	F	Lo	NA	Lo	Lo	Normal	NA	Dexamethasone
Ach, 2005 [6]	29	M	N	NA	N	N	NA	Normal	Dexamethasone/ Hydrocortisone
Ach, 2005 [6]	60	M	N	NA	N	NA	NA	NA	Betamethasone
Kansagara, 2006* [3]	33	F	Lo	NA	Lo	N	Normal	Normal	Prednisone
Thynne, 2013 [2]	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. LPB and BBM carried out the immunoassays. ERUV provided psychological evaluation and follow-up. 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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