



## Case Report

# Factors predicting prolonged glucocorticoid therapy in patients with adrenal insufficiency after laparoscopic adrenalectomy

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## ABSTRACT

**Introduction and importance:** Adrenal insufficiency (AI) is common after adrenalectomy for Primary Adrenal Cushing's syndrome (PACS), due to the inhibition of the Hypothalamic-Pituitary-Adrenal Axis (HPAA) by the functioning adrenal mass. The treatment of post-surgical AI is based mainly on glucocorticoid supplementation therapy. To date, however, there is no known predicting factor of the duration of supplementation therapy in patients treated with laparoscopic adrenalectomy for PACS.

**Case presentation:** We report the case of a 22-year-old Caucasian female who presented with dyspnea, osteoporosis, vertebral collapses and fractures of the pelvis. The diagnosis of ACTH-independent Cushing's syndrome was provided. Abdominal MRI revealed a left adrenal mass suggestive for adrenal adenoma, highly suggestive for PACS. The patient underwent left laparoscopic adrenalectomy. After surgery, glucocorticoid supplementation therapy was started. More than A-year steroid replacement therapy was necessary before the patient completely recovered the function of the HPAA. During this period the patient was strictly followed up in order to adjust pharmacologic treatment, thus allowing to investigate the possible causes of such a slow and hard recover of the contralateral adrenal gland function.

**Conclusion:** AI is common after adrenalectomy for PACS due to HPAA suppression. The duration of steroid replacement therapy may vary depending on patient's characteristics and may be uncommonly long, as in our case. We concluded the not only cortisol and ACTH level, but also radiological findings, such as the size of the mass, its functional activity as well as the hypotrophy or atrophy of the contralateral adrenal gland may be predictive of the duration of the steroid therapy. These factors, if correctly studied before surgery, may be of help in tailoring the postoperative management of the patients after adrenalectomy.

## 1. Introduction

Adrenalectomy is one of the treatment options for Cushing's Syndrome (CS), if symptoms are related to a secreting adrenal mass. In many cases, steroid replacement therapy is needed in the first weeks after surgery, as the glucocorticoids secreted by the adrenal mass inhibit the Hypothalamic-Pituitary-Adrenal Axis (HPAA), thus leading to a functional impairment of the contralateral adrenal gland.

If in the majority of cases steroid replacement is discontinued after a short period, in few cases there is a need for a prolonged replacement therapy. To date, there is no known predictive factor for postulating the

duration of the replacement therapy after adrenalectomy.

We report the case of a 22-year old Caucasian female diagnosed with an adrenal adenoma, who needed a very long steroid replacement therapy after laparoscopic adrenalectomy. We analyzed the patient's characteristics, symptoms and hormonal setting as well as mass characteristics that may have led to a prolonged need for steroid replacement therapy and we discussed any possible preoperative factor may predict an uncommonly long duration of steroid therapy.

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## 2. Presentation of case

A 22-year-old Caucasian female was referred to the endocrinological unit because of hypertension (150 over 100 mmHg), hirsutism, and two-year lasting secondary amenorrhoea.

On presentation, peripheral blood oxygen was 96% in room air and tympanic temperature was 36.6 °C. Heart rate was normal (68 bpm).

Her past history was consistent with osteoporosis with multiple vertebral collapses and a recent fracture of the pelvis. The patient referred previous episodes of dyspnoea. The patient was not on any medications at the time of admission.

The examination of the extremities revealed skin thinning and vascular fragility. Neck and shoulders showed a central obesity (buffalo hump). The abdominal skin presented purple wide striae and hair loss/hair thinning was noticed, also. Laboratory evaluation showed urinary cortisol 1247 µg/24h. ACTH was 3 pg/ml, while catecholamines were within the normal range. Chronic hypokalemia was found on blood test, also.

On echocardiography, global systolic function was not depressed, with an ejection fraction of 55%. Electrocardiogram was normal. She has never been tachycardic.

As these findings suggested an ACTH-independent Cushing's syndrome, the patient was further investigated with an abdominal MRI, showing an adenoma of the left adrenal gland (27 × 22 mm), with clear margins and homogeneous contrast enhancement (Fig. 1).

After discussion within the multidisciplinary team, the patient underwent left laparoscopic adrenalectomy. Before surgery, the patient was pre-treated with alpha- and beta-blockers as well as potassium implementation.

In the post-operative period, intravenous hydrocortisone was administered for 3 days, due to persistent hypokalemia and low blood pressure. As soon as the hypokalemia and blood pressure returned to normal, the patient was started on oral steroid therapy.

The patient was discharged on day 4 after surgery in good condition. Histological examination showed a cortico-adrenal adenoma.

Even if her general conditions improved quickly after surgery, her ACTH level has been persistently low and the patient was continued on a full dose of corticosterone acetate (25 mg OD). After 9 weeks, ACTH was 11 µg/mL, still too low for discontinuing oral steroid therapy. For this reason, the patient was put on a reduced dose of glucocorticoid, which was necessary for other 4 months, when she eventually recovered her HPA axis function completely.

## 3. Discussion

Cushing's syndrome (CS) is a well known condition of cortisol excess

related to the impairment of the hypothalamic-pituitary-adrenal axis (HPAA) or the presence of a functioning adrenal mass. In the last decades, the refinements in the radiologic techniques, such as Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) led to an increased detection of adrenal masses, whose prevalence is reported from 4% to 7% [2,3].

While in some cases the hypothalamic-pituitary-adrenal abnormalities are mild and asymptomatic (6%–30%), which defines the so called Subclinical Cushing's syndrome (SCS), in many other cases the biochemical abnormalities are more evident, thus giving rise to the classical signs and symptoms of the CS [4,5].

Adrenalectomy is a treatment option in patients with primary adrenal Cushing's syndrome (PACS), specially in case of young age at diagnosis. The laparoscopic approach for adrenalectomy has been widely explored and is now considered safe and effective. After the first series described by Gagner et al. [6], the technique underwent many refinements. To date, in experienced hands, laparoscopic adrenalectomy is considered a gold standard even for the treatment of large adrenal masses [7,8] as well as in patients presenting with urgent clinical pictures [9] or requiring bilateral surgical treatment [10–12].

Reportedly, cortisol secreting adenomas inhibit the HPA axis, thus leading to cortisol suppression of the contralateral adrenal gland. After adrenalectomy, this may result in acute adrenal insufficiency (AI), a condition potentially fatal if not treated.

Although some Authors reported that a few number of patients with no alteration of the adrenal function preoperatively have no need for steroid replacement therapy after adrenalectomy, glucocorticoid administration after surgery is still considered a milestone for post-operative management of patients after adrenalectomy [13].

Indeed, a small number of patients with normal adrenal function preoperatively may still present post-surgical hypocortisolism after they underwent unilateral adrenalectomy and there is no known preoperative test or algorithm for predicting the lasting of AI [14].

In our case, there was no suspicion of impaired contralateral adrenal function on the basis of clinical tests. However, our patient needed supplementation therapy for 9 months and a reduced dose of steroid therapy for other 4 months before showing a complete recovery of the HPA axis.

Sugiura M et al., in a series of patients with SCS, postulated that contralateral adrenal gland width may predict the duration of prolonged post-surgical replacement therapy in patients diagnosed with adrenal mass and treated with adrenalectomy. If on one side the Authors found no correlation between cortisol excess or ACTH suppression at the diagnosis and the duration of the supplementation needed after surgery, on the other side they concluded that the contralateral adrenal width was correlated to the duration of steroid replacement therapy [15].



Fig. 1. The small size of right adrenal gland before left laparoscopic adrenalectomy.

In this view, even if we maintain that the results obtained from a series of patients with SCS cannot be extended to CS cases, it may be argued that in both clinical entities long lasting morbidity may induce histopathologic changes in the contralateral adrenal gland, such as hypotrophy and atrophy, thus leading to the long time needed for the HPAA to come to a complete recovery, as reported in our case.

Prete A et al. found a longer need for steroid supplementation in patients with PACS who received ketoconazole before adrenalectomy [16]. As this drug is administered in order to reduce cortisol level and control symptoms through the suppression of the HPAA, in our case it is likely that analogously the high level of activity of the adrenal adenoma caused a huge suppression of the HPAA, which in turn led to the long-lasting inhibition of the contralateral adrenal gland, thus ending in a long-lasting AI after surgery.

In this perspective, the duration of the AI, which is strictly related to the HPAA recovery may ultimately depend on the activity of the adenoma itself. Noteworthy, in our case, Magnetic Resonance Imaging (MRI) showed that contralateral adrenal gland was very small in size (Fig. 1), which supports the role of the adenoma in inhibiting the HPAA, and in turn the contralateral adrenal gland, thus accounting for the duration of the supplementation therapy.

In this regard, we suggest that MRI, which is the gold standard for the detection of adrenal masses and for investigating alteration of adrenal tissue [17,18] may play a role in predicting AI as well as in speculating on the possible duration of steroid replacing therapy after unilateral adrenalectomy, even if it should not be considered an absolute predicting factor in all cases.

Our case corroborates the hypothesis of Di Dalmazi G et al. that both cortisol production and duration of the exposure to hypercortisolism may affect the duration of prolonged supplementation therapy [19]. In this respect, Eller-Vainicher et al. stated that the risk of AI after adrenalectomy is much higher when more than one test to define the function of the HPAA is pathological [14].

Another crucial point is the activity of the functioning mass itself, that may play a role as a determinant of the recovery of the HPAA [16, 19]. We argue that the higher the activity of the adrenal adenoma, the longer the AI and the time to a complete recovery of the contralateral adrenal function.

#### 4. Conclusion

In patients with PACS and treated with adrenalectomy, AI is common due to the suppression of the HPAA. Reportedly, the treatment of AI is glucocorticoid replacement therapy, whose duration depends on a wide range of factors, such as the activity of the adrenal mass and the consequent grade of suppression of the HPAA before surgical removal. In our case, the patient required a very long steroid replacement therapy after adrenalectomy, to the best of our knowledge one of the longer reported in the literature. We speculated on the possible causes of this prolonged need for steroid therapy after adrenalectomy and argued that in similar cases its duration may be predicted by well defined preoperative factors, such as the radiological volume of the mass and the hypotrophy of the contralateral adrenal gland.

For this reason, we concluded that a high quality endocrinological and radiological study before surgery is of the utmost importance not only for planning surgery and managing intra- and post-operative course after adrenalectomy but also for predicting the need to manage mid-to long-term medical treatment after surgery and tailoring follow-up on patient's characteristics.

#### Ethical approval

Not applicable.

#### Sources of funding

None.

#### Author contribution

Francesco Ziglioli, study concept or design, data analysis or interpretation, writing the paper; Simona Cataldo, data analysis or interpretation; Domenico Maria Cavalieri, writing the paper; Davide Campobasso, data collection; Giulio Guarino, data collection; Umberto Maestroni, study concept or design.

#### Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images.

#### Research registration

Not applicable.

#### Guarantor

Francesco Ziglioli.

#### Provenance and peer review

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#### Declaration of competing interest

None.

#### Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.amsu.2022.103390>.

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