Severe Cushing's syndrome from an ectopic adrenocorticotropic hormone-secreting neuroendocrine tumour treated by osilodrostat

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Summary
Severe Cushing's syndrome from an ectopic adrenocorticotropic hormone-producing tumour is rare but often demands rapid diagnostics and treatment of hypercortisolism with its comorbidities. Pharmacotherapy of hypercortisolism by ketoconazole, metyrapone and osilodrostat is currently available. If unsuccessful or insufficient a bilateral adrenalectomy is an option. We present a 28-year-old female with severe Cushing's syndrome caused by a bronchial metastatic neuroendocrine tumour (NET). Hypercortisolism was efficiently treated by osilodrostat with block–replace and then titration regimen. A once-daily dose was finally used with normalised cortisol levels. Androgen levels measured by liquid chromatography–mass spectrometry were slightly elevated during the treatment but without any symptoms. A simple once-daily use of osilodrostat with titration regimen led to normalised cortisol levels in a severe Cushing's syndrome patient with an incurable bronchial NET. Transient hypocortisolism during treatment appeared but was easily treated by hydrocortisone.

Learning points
• Cushing's syndrome from an ectopic adrenocorticotropic hormone-producing tumour is rare.
• Cortisol upregulation is often severe and rapid, though clinical signs are not always fully pronounced.
• Rapid treatment is a key for preventing and reducing complications such as fractures, thromboembolism, bleeding, hyperglycaemia, and arterial hypertension.
• The novel potent steroidogenesis inhibitor osilodrostat can be used as first-line treatment for reducing hypercortisolism.

Background
Cushing's syndrome (CS) is a clinical and biochemical syndrome caused by inappropriately high exposure of tissues to glucocorticoids. Clinical signs include facial plethora, weight gain, easy bruising, proximal muscle myopathy with weakness (especially legs), striae, osteoporosis, impaired wound healing, and decreased growth velocity in children. Laboratory examination and findings consist of decreased or missing diurnal cortisol level variation measured in plasma or saliva, non-suppressibility of cortisol after dexamethasone and increased 24-h urinary free cortisol in at least 2 measurements (1).

Endogenous CS is in approximately 80% of cases adrenocorticotropic hormone (ACTH) dependent,
whereas 20% are ACTH independent (presenting with low and suppressed ACTH levels). Among ACTH-dependent CS about 90% are caused by pituitary hypersecretion, only 10% are represented by an ectopic ACTH secretion from non-pituitary tumours. These are most frequently intrathoracic bronchopulmonary neuroendocrine tumours (NETs), small-cell carcinomas and thymic NETs. Other rarer tumours include pancreatic and gastrointestinal NETs, medullary thyroid carcinoma, pheochromocytoma, lymphomas, sarcomas, and others (2).

Severe Cushing’s syndrome from ectopic ACTH secretion treated by osilodrostat has recently been published by several authors. In most cases a block–replace regimen was used. This report presents so far unpublished titration regimen strategy with finally once-daily osilodrostat dosing offering good control of hypercortisolism.

Additionally, we show concomitant LC-MS/MS measured osilodrostat induced steroid changes during treatment titration.

Case presentation

A 28-year-old female was referred to a tertiary endocrine centre for a suspected CS. She had a history of partial right ovariectomy for cystic tumour 3 years before and a left ovariectomy 2 years prior to admission for suspected CS. Histology of both ovarian cystic tumoural lesions revealed a NET G2 in the right and NET G1 in the left ovarian tumour. Before each of these resections she suffered from CS symptoms, which were repeatedly relieved by a surgery. Both NETs were first considered as of primarily ovarian origin.

Upon admission, she had several CS symptoms: moon face, purple striae, buffalo hump, proximal muscle atrophy with lower limb hematomas, and mild distal oedemas. She has had secondary amenorrhea for 6 months, arterial hypertension with blood pressure 160/120 mmHg on perindopril 10 mg in monotherapy, osteoporosis with a L1 compressive fracture.

Investigation

Hormonal examination revealed high plasma cortisol levels without diurnal variation (Fig. 1A), non-suppressible cortisol levels in 1 mg dexamethasone (DXM) test and elevated urinary free cortisol (UFC) levels in both collections (Table 1).

Irresponsive CRH test (using human CRH, Ferring, 100 µg/mL) and history of ovarian NETs raised suspicion of an ectopic ACTH secretion. Revised histology

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![Figure 1](https://edm.bioscientifica.com/)

(A) Diurnal cortisol rhythm. (B) Morning cortisol levels on treatment by osilodrostat. (C) Urinary free cortisol/24 h on treatment by osilodrostat.
of left ovarian NET was positive for ACTH immunohistochemistry staining. 

Ga-DOTA-TOC PET/CT showed mediastinal lymphadenopathy near right major bronchus with SUV max 3.41. Subsequent bronchoscopic biopsy confirmed bronchial NET. Lanreotide 120 mg every 4 weeks was initiated (first application on day 6 of osilodrostat treatment) by an oncologist.

After a discussion with the patient suffering from ACTH-dependent CS with suspected ectopic ACTH secretion with severe complications, a pharmacological treatment by osilodrostat was preferred against bilateral adrenalectomy.

**Methods**

Measurement of plasma cortisol was performed using Siemens Atellica IM Cortisol kit (intra-assay variation coefficient ≤ 2.3% for plasma, inter-assay variation coefficient ≤ 7.7% for plasma). Reported cross-reactivity with steroid precursors: 11-deoxycortisol ≤ 25%, 21-deoxycortisol ≤ 15%, 17α-hydroxyprogesterone ≤ 2%, pregnenolone ≤ 0.5%, and progesterone ≤ 1%

The 24 h UFC was measured by a Beckmann Coulter Cortisol RIA kit (intra-assay variation coefficient ≤ 8.9% for urine, inter-assay variation coefficient ≤ 13.3% for urine). Blood samples for ACTH measurement were kept on ice, temporarily frozen at −20°C and analysed with a Thermo Scientific BRAHMS ACTH RIA kit (intra-assay variation coefficient 3.5%, inter-assay variation coefficient 4.7%).

Plasma steroids including cortisol were measured by two-dimensional liquid chromatography–tandem mass spectrometry (Agilent technologies 1260 Infinity II, Agilent 6470 triple quadrupole) using pre-mixed sets of steroids and their internal standards (Chromsystems Instruments & Chemicals GmbH) with in-house developed method for a multiplex quantitative analysis of steroid hormones (3).

**Treatment**

First twelve days was osilodrostat titrated in an inpatient, then in outpatient setting. The initial dose of 6 mg daily in two equal doses was progressively up titrated to 45 mg/day divided in higher evening dose and lower morning dose. On the 12th day, when discharged from the hospital, her UFC normalised, and morning plasma cortisol was 420 nmol/L (Fig. 1B and C). She felt better and had no symptoms of adrenal insufficiency. We did not observe any hypokalaemia nor QTc change.

In upcoming weeks in the outpatient setting, she started to have nausea and weaknesses. She was equipped with and educated about hydrocortisone supplementation, which relieved her symptoms. Further on, she has decided to stop her hydrocortisone in block–replace regimen as she did not want to take ‘so many pills’. Therefore, osilodrostat was tapered and as morning cortisol remained low, we stopped completely the osilodrostat treatment on the 52nd day. Till the 85th day without any anticortisolic treatment her cortisol levels were 440 and 457 nmol/L, and she was symptom free. On the 85th day, her morning cortisol increased to 1014 nmol/L, so osilodrostat treatment was reintroduced with 5 mg in the morning and 10 mg in the evening. Four weeks later she reported nausea, with morning cortisol 48 nmol/L, hydrocortisone supplementation was recommended and osilodrostat was reduced to a sole dose of 5 mg in the evening. With this dose reduction morning cortisol levels normalised as well as UFC, which has remained in the normal range for 4 months so far.

Blood pressure levels were repeatedly 150–160/100–120 mmHg before treatment. After the alleviation of hypercortisolism by osilodrostat they decreased to 130/100 mmHg. Antihypertensive treatment by spironolactone was recommended, but the patient refused this therapy as non-essential. Later she agreed on angiotensin-converting-enzyme inhibitor therapy, which lowered the blood pressure to 130/90 mmHg.

Bone densitometry showed Z score −2.0 s.d. in lumbar spine and Z score −2.0 s.d. in femur. MRI revealed

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Initial evaluation.</th>
</tr>
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<tbody>
<tr>
<td>Result</td>
<td>Reference range</td>
</tr>
<tr>
<td>1 mg DXM test, nmol/L</td>
<td>1565</td>
</tr>
<tr>
<td>UFC/24 h, nmol/24 h</td>
<td>2179</td>
</tr>
<tr>
<td>10 × ULN</td>
<td>3394</td>
</tr>
<tr>
<td>CRH test</td>
<td>217</td>
</tr>
<tr>
<td>ACTH, ng/L</td>
<td>265</td>
</tr>
<tr>
<td>−15 min</td>
<td>283</td>
</tr>
<tr>
<td>0 min</td>
<td>264</td>
</tr>
<tr>
<td>15 min</td>
<td>279</td>
</tr>
<tr>
<td>30 min</td>
<td>239</td>
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<tr>
<td>45 min</td>
<td></td>
</tr>
<tr>
<td>60 min</td>
<td></td>
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</tbody>
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L1 compressive fracture. Treatment by calcium and vitamin D was introduced. Due to limited compliance with this treatment and patients decision no further therapy such as bisphosphonate or teriparatide was added. The predominant effect of hypercortisolism on bone is the impairment in bone formation. After the rapid cure of hypercortisolism bone formation recovery was observed. Procollagen type I N-terminal propeptide (PINP) went from 23 \( \mu \text{g/L} \) (normal 15–58) before treatment to 266 \( \mu \text{g/L} \) after 2 months and 331 \( \mu \text{g/L} \) after 7 months of treatment.

Clinical signs of hypercortisolism: moon face, purple striae, buffalo hump, proximal muscle atrophy with lower limb hematomas, and mild distal oedema regressed during the first months of treatment. With gradual ACTH rise her skin pigmentation increased. After 6 months of treatment her menstrual cycle restored (part of the right ovary was not resected).

Repeated 68Ga-DOTA-TOC PET/CT after 6 months on osilodrostat and lanreotide therapy showed stable disease. She had no clinical symptoms of active CS (except for hypertension and hyperpigmentation) limiting her daily life. We did not observe any clinical signs of mild androgen elevation due to blockade of cortisol steroidogenesis.

Discussion

Severe CS defined by random plasma cortisol above 1000 nmol/L and/or four-fold elevation of UFC above the normal levels represents a relatively rare therapeutic emergency in endocrinology (4). Rapid treatment of hypercortisolaemia is an essential therapeutic step in the patient management (5). In this case a choice between pharmacological treatment and bilateral adrenalectomy had to be done. In the light of unknown primary tumour, patient age and opinion we opted for pharmacotherapy. Ketoconazole, metyrapone and osilodrostat are available in the Czech Republic. Due to high CS activity and highest osilodrostat efficacy, we chose osilodrostat as a first-line treatment (6, 7).

The benefit of osilodrostat over metyrapone has been shown in preclinical and clinical studies including more potent reduction in hypercortisolaemia, multiple enzyme inhibition leading to lower levels of troublesome steroid intermediaries such as 11-DOC, and rapid onset of action (6, 8). Another option would be a combination therapy by metyrapone+ketoconazole due to lower metyrapone efficacy in monotherapy or even combination of metyrapone+ketoconazole+mitotane (9).

Possible liver enzyme elevation should be monitored if ketoconazole is administered. Whereas in metyrapone+ketoconazole treatment a total highest dose of 6000 mg metyrapone (24 tablets/day, divided three to four times) and 1200 mg ketoconazole (6 tablets/day) makes up to 30 tablets/day, treatment by osilodrostat is usually administered in two daily doses. The price of the treatment is another significant factor in some countries. Osilodrostat in our conditions has a significantly higher price, but taking into account the high number of metyrapone and ketoconazole tablets per day the final price can be finally comparable. Additionally, a lower number of tablets per day increases patients' compliance.

Osilodrostat has a declared plasma half-life around 4 h with urinary elimination, so the twice daily (e.g. morning and evening) administration is recommended. Some authors tend to imitate physiological diurnal cortisol variation by higher osilodrostat dosing in the evening dose; however, clear data for this approach are lacking (10). In our patient we also believe that nocturnal cortisol dip is beneficial and therefore we increased osilodrostat evening doses. Furthermore, after the episode of hypocortisolism due to osilodrostat treatment, which was fully covered by a temporary hydrocortisone replacement, we introduced a once-daily administration of osilodrostat, which showed good tolerability and promising diurnal cortisol variation (Fig. 1A). To our knowledge, once-a-day dosing is an unpublished modification so far. Although a short 4 h osilodrostat half-life is documented, clinical efficacy seems to be longer as shown in Fig. 1B and already documented in recent works (11).

Recommended starting dose for osilodrostat is 2 mg twice daily. From our previous experience we expected that rapid dose increase will be necessary to control cortisol levels; therefore, we began with 3 mg twice daily and as shown on Fig. 1B and C uptitrated the dose rapidly. Rapid restoration of normal cortisol levels after initiation of osilodrostat could have been partially explained by concomitant introduction of lanreotide. As ACTH levels slightly rose in time and tumour extension on PET scan did not decrease, the effect of lanreotide on cortisol levels seems to be rather low if any.

While osilodrostat was initially developed as an aldosterone synthase (CYP11B2) inhibitor, it was found to have strong 11β-hydroxylase (CYP11B1) inhibition and further clinical studies suggest that the drug also inhibits 17α-hydroxylase and 21-hydroxylase based on measured ratios of precursors/metabolites (12).
Table 2  Changes of steroid hormones (in nmol/L) levels during treatment by osilodrostat.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Day 0</th>
<th>Day 5</th>
<th>Day 10</th>
<th>Day 12</th>
<th>Day 43</th>
<th>Day 195</th>
<th>Reference range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osilodrostat (mg/day)</td>
<td>0</td>
<td>7</td>
<td>26</td>
<td>40</td>
<td>35</td>
<td>5</td>
<td>160–600</td>
</tr>
<tr>
<td>Cortisol</td>
<td>743</td>
<td>833</td>
<td>524</td>
<td>294</td>
<td>45</td>
<td>339</td>
<td></td>
</tr>
<tr>
<td>Progesterone</td>
<td>&lt;0.38</td>
<td>0.45</td>
<td>0.62</td>
<td>0.52</td>
<td>&lt;0.38</td>
<td>0.97</td>
<td></td>
</tr>
<tr>
<td>11-deoxyF</td>
<td>4.24</td>
<td>26.5</td>
<td>&gt;42</td>
<td>39.6</td>
<td>8.98</td>
<td>40.1</td>
<td>0.21–2.62</td>
</tr>
<tr>
<td>21 - deoxyF</td>
<td>1.13</td>
<td>1.26</td>
<td>0.572</td>
<td>0.396</td>
<td>&lt;0.165</td>
<td>0.248</td>
<td>&lt;0.16–0.19</td>
</tr>
<tr>
<td>DHEA</td>
<td>6.5</td>
<td>7.4</td>
<td>11.8</td>
<td>6.5</td>
<td>3.4</td>
<td>&lt;3.2</td>
<td>3.2–38</td>
</tr>
<tr>
<td>DHEAS</td>
<td>2360</td>
<td>2580</td>
<td>3550</td>
<td>2070</td>
<td>865</td>
<td>901</td>
<td>1360–10700</td>
</tr>
<tr>
<td>Androstenedione</td>
<td>6.92</td>
<td>14.5</td>
<td>25.4</td>
<td>19</td>
<td>4.76</td>
<td>18.2</td>
<td>1.45–6.6</td>
</tr>
<tr>
<td>Testosterone</td>
<td>0.8</td>
<td>1.83</td>
<td>3.23</td>
<td>2.74</td>
<td>1.21</td>
<td>4.75</td>
<td></td>
</tr>
<tr>
<td>ACTH (ng/L)</td>
<td>208</td>
<td>225</td>
<td>285</td>
<td>310</td>
<td>503</td>
<td>10–60</td>
<td></td>
</tr>
</tbody>
</table>

Interestingly, when expressed alone, negligible inhibition of these enzymes occurred in vitro (13). The side-chain cleavage enzyme or StAR (steroidogenic acute regulatory protein) partial inhibition was also observed (6, 13).

Isolated 11β-hydroxylase block leads to accumulation of precursors such as 11-deoxycortisol and androgens (androstenedione, testosterone and DHEA/DHEAS). Treatment by osilodrostat showed only mild androgen elevations when compared to metyrapone (12). In this patient DHEA, DHEAS decreased, while androstenedione and testosterone were slightly elevated during the osilodrostat treatment (Table 2). We observed no clinical signs of mild hyperandrogenaemia.

Conclusion

This case report presents a successful treatment of severe CS from ectopic ACTH secreting NET by osilodrostat. Using titration regimen instead of block–replace strategy, we achieved both biochemically and clinically close to physiological cortisol diurnal rhythm with normalized UFC. Pharmacological therapy by osilodrostat offers a comparable alternative to bilateral adrenalectomy in patients with severe Cushing’s syndrome where successful treatment of primary cause of hypercortisolism is impossible.

Declaration of interest

There is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Funding

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Patient consent

The patient has agreed with this publication. A written informed consent for publication of clinical details was obtained from the patient.

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