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Progression of a corticotroph tumour during durable medical therapy with osilodrostat in a patient with persistent Cushing's disease

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Cushing's disease (CD) is a rare but severe endocrine disorder characterized by a pituitary tumour (corticotropinoma) that secretes an excess of adrenocorticotropic hormone (ACTH), which in turn stimulates overproduction of cortisol from the adrenal glands [1]. Sustained hypercortisolism is associated with significant morbidity, including metabolic syndrome (comprising hypertension, obesity, diabetes mellitus, and dyslipidaemia), increased cardiovascular and thromboembolic risk, neurological disorders, infections, and musculoskeletal problems. These complications are associated with significantly impaired quality of life and, if untreated, substantially increased mortality. While the treatment of choice for CD is transsphenoidal pituitary surgery (TSS), some patients require additional treatment, including medical therapy. Treatment with osilodrostat, a potent oral inhibitor of 11 -hydroxylase (CYP11B1), represents a novel and effective approach to control hypercortisolism in adults with Cushing's syndrome [2, 3]. Corticotroph tumour progression (CTP) is a rare clinical complication that classically occurs after bilateral adrenalectomy, but it has also been reported with therapies that decrease cortisol production [4, 5].

A 30-year-old female patient with a 6-year history of CD, following 2 ineffective TSS (01/2014, 09/2018; proliferative index Ki-67 > 3%), was admitted to the Department of Endocrinology with suspicion of CTP. In December 2018, due to incomplete transsphenoidal resection (pituitary tumour remnants 3.5 × 5.5 mm) and persistent hypercortisolism, medical therapy was initiated. Treatment with osilodrostat at a dose of 5 mg *bis in die* (*b.i.d.*) initially resulted in clinical and biochemical control of the disease. After 5 weeks of taking a stable dose of the drug the urinary free cortisol (UFC) and late-night salivary cortisol (LNSC) had dropped to subnormal levels: 25.9 nmol/day (N < 182.4 nmol/day) and 0.8 nmol/L (N < 5.1 nmol/L), respectively, which required dose reduction to 1 mg b.i.d. In July 2020 rapid deterioration was observed. The physical examination was remarkable for weight gain, acne, skin hyperpigmentation, and hypertension. The hormonal evaluation showed UFC as high as 2878.95 nmol/day (21× > upper limit of normal [ULN]) whereas LNSC was elevated to 33.25 nmol/L (6× > ULN) with concomitant rapid increase in plasma ACTH to 182.7 pmol/L (N: 2.0–11.0 pmol/L). Pituitary magnetic resonance imaging (MRI) showed enlargement of the pituitary mass to 14.5 × 5.5 × 8.5 mm with left cavernous sinus invasion (Fig. 1). A subsequent MRI of the pituitary after 6 weeks showed further progression of the tumour. The patient was addressed to TSS and adjunctive radiation therapy, while treatment with osilodrostat was continued in an increased dose (5 mg *b.i.d.*). Histopathological examination revealed high proliferation index (Ki-67 > 10%) suggesting aggressive behaviour of the corticotroph tumour. After such a treatment, the UFC had normalized, increased plasma ACTH at 200.2 pmol/L persisted, and the patient remained on a stable dose of osilodrostat (2 mg *b.i.d.*).

This report documents a case of significant CTP requiring repeated TSS and radiotherapy after medical treat-

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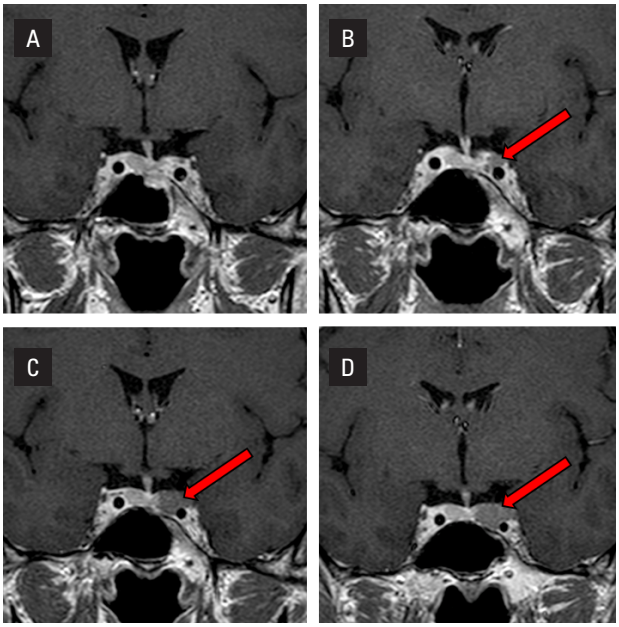

Figure 1. A. *Coronal T1-weighted post-gadolinium pituitary magnetic resonance imaging (MRI) after initial transsphenoidal surgery;* **B.** *Coronal T1-weighted post-gadolinium pituitary MRI after second incomplete transsphenoidal surgery;* **C.** *Coronal T1-weighted post-gadolinium pituitary MRI demonstrates corticotroph tumour progression during long-term treatment with osilodrostat;* **D.** *A subsequent MRI of the pituitary gland after 6 weeks showed further progression of the tumour*

ment with osilodrostat for persistent CD. Clinically significant tumour growth or appearance of a new lesion on pituitary MRI represents the primary criteria to diagnose CTP, while ACTH level and hyperpigmentation are considered secondary criteria [5]. Pharmacotherapy has played a secondary role in the management of patients with CD, but recently, due to significant progress, it has become an important component in the treatment algorithm, especially when surgery is delayed, contraindicated, or unsuccessful (bridging therapy) [3]. Compared to other therapeutic options, medical therapy has the advantages of a durable, stable effect, it is reversible, and the dose can be precisely adjusted. In recent clinical trials, treatment with osilodrostat has been associated with rapid UFC normalization and sustained clinical improvement, and the safety profile was favourable [2, 3]. In the LINC-3 study, osilodrostat did not adversely affect the pituitary tumour volume over 48 weeks of follow-up, with small proportions of patients (mostly with microadenomas) having either a decrease or an increase of ≥ 20% in tumour volume from baseline, which was considered clinically insignificant [3]. CTP has rarely been observed in patients treated with long-term medical therapy. Fontaine-Sylvestre et al. described the first CTP requiring surgical intervention after long-term treatment with osilodrostat [4]. The pathophysiologic mechanism underlying CTP is not fully understood. It remains unclear whether tumour progression is caused by genetic mechanisms implicated in corticotroph tumour development (CTP as a part of the natural history of CD), or whether it is an effect of reduced glucocorticoid negative feedback on tumour cells [1, 4, 5]. Of note, approximately one-third of patients experience persistent or recurrent disease following TSS. The patient described here developed a significant CTP after almost 2 years of therapy with osilodrostat. The case we report demonstrates that rarely CTP is possible even long after osilodrostat administration. One can hypothesize that in the described case the coexistence of aggressive tumour behaviour (Ki-67 > 10%) and adrenal insufficiency following osilodrostat treatment may have contributed to the accelerated corticotroph tumour growth. Taking into consideration that CTP tumours can be aggressive and rapidly invasive, lifelong surveillance for recurrence is essential in clinical practice.

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