

## SCIENTIFIC LETTER

Cushing's syndrome secondary to inhaled fluticasone<sup>☆</sup>

## Síndrome de Cushing secundario a fluticasona inhalada

Antiretroviral therapy (ART) has increased the life expectancy of patients with human immunodeficiency virus (HIV) infection to the point that it is now similar to that of the general population.<sup>1</sup> The increase in age-associated comorbidities and the need to add treatments have rendered drug interactions a challenge in the management of the therapy. Cobicistat is an inhibitor of the isozyme of the hepatic cytochrome P450 3A4 (CYP3A4) usually employed to enhance drugs used in HIV treatment. Concomitant use of drugs metabolised through this pathway promotes the onset of potentially harmful drug-drug interactions.

Below, we report the clinical case of a 49-year-old man with a personal history of active tobacco use, dyslipidaemia, bronchial asthma, ischaemic heart disease and HIV infection known for more than 10 years. The patient has received various treatments to date. He was initially treated with efavirenz, emtricitabine and tenofovir, with virological failure after a few months. He was then switched to darunavir/ritonavir, raltegravir and etravirine, and this treatment was maintained for five years with an undetectable viral load and decreasing CD4 T lymphocytes. This regimen was subsequently simplified to treatment with darunavir/ritonavir plus raltegravir, and a year before our assessment, he was switched to his current combination with darunavir, cobicistat and raltegravir. In addition to ART, he was on oral treatment with omeprazole, bisoprolol, ramipril, acetylsalicylic acid, ezetimibe and rosuvastatin. His inhaled treatment for bronchial asthma consisted of on-demand salbutamol, fluticasone 500 µg and salmeterol 50 µg every 12 h, which had required an increase to a maximum dose around five months earlier due to poor disease control.

The patient was assessed as he exhibited asthenia, worse exercise tolerance and increased abdominal fat with red striae in that location, accompanied by thinning of the limbs and easy bruising for the past month and a half. Physical examination revealed the patient to have a weight of 74.9 kg, a body mass index of 24.73 kg/m<sup>2</sup>, blood pressure of 113/71 mmHg, moon face with increased bilateral supraclavicular fat (Fig. 1A), abdominal obesity with

a periumbilical predominance and red-wine striae around 3 cm thick (Fig. 1B), skin atrophy and thinning of the limbs with healing bruises (Fig. 1C). Complementary tests showed adrenocorticotropic hormone (ACTH) below 2 pg/mL (normal range 10–46 pg/ml) and baseline plasma cortisol 0.4 µg/dl (normal range 7–25 µg/dl), in addition to abnormal baseline blood glucose (114 mg/dl).

Given the clinical findings of Cushing's syndrome and laboratory findings of suppressed ACTH and cortisol, iatrogenic Cushing's syndrome was suspected. After administration of glucocorticoids by other routes was ruled out, only exposure to inhaled fluticasone was observed. Adrenal axis suppression is reported in 20.5% of patients receiving inhaled corticosteroids. Furthermore, some studies have suggested that adrenal axis suppression is subject to individual variability in glucocorticoid action and metabolism, including CYP3A4 activity, which is the main route of inactivation of most prescription glucocorticoids.<sup>2</sup> The drugs the patient was receiving included cobicistat, a powerful inhibitor of this metabolic pathway. As an interaction between fluticasone and cobicistat was suspected, both drugs were suspended, beclometasone was started and the patient's ART was switched to bictegravir, emtricitabine and tenofovir alafenamide. After two months, the Cushingoid appearance described was seen to have virtually resolved (Fig. 1D and E), the patient had lost 8 kg and his blood glucose levels had returned to normal. Hormone testing showed ACTH 52 pg/mL and baseline plasma cortisol 5.6 µg/dl; therefore, a short stimulation test was performed with 250 µg of ACTH, yielding a peak plasma cortisol level of 8.49 µg/dl. The clinical and laboratory changes observed following suspension of both drugs led to the diagnosis of iatrogenic Cushing's syndrome secondary to interaction between fluticasone and cobicistat and subsequent tertiary adrenal insufficiency due to adrenal axis suppression. Replacement therapy was started with Hidroaltesona (hydrocortisone) 30 mg/day, and recommendations on the use of glucocorticoids in the event of surgery or intercurrent disease were provided.

Inhaled corticosteroids, such as budesonide, ciclesonide, flunisolide, fluticasone, mometasone and triamcinolone, are CYP3A4 substrates, and therefore have the potential to interact with inhibitors of this cytochrome such as ritonavir and cobicistat. These interactions result in increased exogenous corticosteroid exposure with a risk of developing Cushing's syndrome and adrenal suppression.<sup>3</sup> Beclometasone, despite also being a CYP3A4 substrate, is mainly hydrolysed by esterases and has low affinity for the glucocorticoid receptor, as well as a short half-life; hence, it should be considered an option in these patients.<sup>4</sup> There are published cases of iatrogenic Cushing's syndrome secondary to interaction between cobicistat and ritonavir with oral and

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**Figure 1** (A and B) Cushing's syndrome at diagnosis. (C) Skin atrophy. (D and E) Resolution of signs and symptoms following suspension of cobicistat and fluticasone.

inhaled corticosteroids.<sup>5,6</sup> A series of 139 cases found that inhaled fluticasone was involved in 20.1% of these cases.<sup>7</sup>

The case reported highlights the importance of drug-drug interactions with the use of CYP3A4 inhibitors. Powerful CYP3A4 substrate steroids, such as fluticasone, budesonide and triamcinolone, should ideally not be prescribed to patients on treatment with inhibitors of this pathway. If this is unavoidable in the case of a patient with HIV, it is advisable to use alternative ART combinations not including cobicistat or ritonavir before introducing steroids. If this is still not possible, the patient should be monitored closely in the two to three subsequent months, given the possibility of the patient developing iatrogenic Cushing's syndrome like that reported, and specific algorithms for its management should be used.<sup>8</sup>

## References

1. Cobos Manuel I, Jackson-Perry D, Courvoisier C, Bluntschli C, Carel S, Muggli E, et al. Stigmatisation et VIH: tous concernés [Stigma and HIV: relevant for everyone]. *Rev Med Suisse*. 2020;16(690):744–8.
2. Woods CP, Argese N, Chapman M, Boot C, Webster R, Dabhi V, et al. Adrenal suppression in patients taking inhaled glucocorticoids is highly prevalent and management can be guided by morning cortisol. *Eur J Endocrinol*. 2015;173(5):633–42.
3. Saberi P, Phengrasamy T, Nguyen DP. Inhaled corticosteroid use in HIV-positive individuals taking protease inhibitors: a review of pharmacokinetics, case reports and clinical management. *HIV Med*. 2013;14(9):519–29.
4. Moore CD, Roberts JK, Orton CR, Murai T, Fidler TP, Reilly CA, et al. Metabolic pathways of inhaled glucocorticoids by the CYP3A enzymes. *Drug Metab Dispos*. 2013;41(2):379–89.
5. Lewis J, Turtle L, Khoo S, Nsutebu EN. A case of iatrogenic adrenal suppression after co-administration of cobicistat and fluticasone nasal drops. *AIDS*. 2014;28(17):2636–7.
6. Monge E, Colombo V, Giacomelli A. Iatrogenic Cushing syndrome due to drug interaction between inhaled fluticasone and cobicistat. *Infez Med*. 2019;27(4):445–8.
7. Peyro-Saint-Paul L, Besnier P, Demessine L, Biour M, Hillaire-Buys D, de Canecaude C, et al. Cushing's syndrome due to interaction between ritonavir or cobicistat and corticosteroids: a case-control study in the French Pharmacovigilance Database. *J Antimicrob Chemother*. 2019;74(11):3291–4.
8. Elliot ER, Theodoraki A, Jain LR, Marshall NJ, Boffito M, Baldeweg SE, et al. Iatrogenic Cushing's syndrome due to drug interaction

between glucocorticoids and the ritonavir or cobicistat containing HIV therapies. *Clin Med (Lond)*. 2016;16(5):412–8.

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## Erdheim–Chester disease: Diagnosis in endocrinology<sup>☆</sup>



### Enfermedad de Erdheim-Chester: diagnóstico en endocrinología

Dear Editor,

Erdheim–Chester disease (ECD) is a rare form of non-Langerhans' cell histiocytosis first reported in 1930. This disease of unknown aetiology manifests in adults around their 40s–60s, predominantly in males. It is a multisystemic disease featuring bone involvement in all cases, with a predilection for the long bones.<sup>1</sup>

Some 50% of cases feature extraskelatal clinical signs with central nervous system involvement, including central diabetes insipidus and orbital, cardiac, pulmonary, pleural, vascular (great vessels), retroperitoneal and cutaneous involvement. The prognosis depends on the extent of organ involvement; cardiovascular and central nervous system involvement are associated with a more serious disease course.<sup>2</sup>

We report a case detected in an endocrinology practice in which ECD was suspected given the existing association between diabetes insipidus and bone involvement (symmetric osteosclerosis of the long bones) previously reported by the patient.<sup>3</sup> Imaging tests and, in particular, bone biopsy were key to arriving at the diagnosis.

The patient was a 50-year-old man in follow-up by rheumatology for migratory arthralgia with bone scintigraphy showing diffuse radioactive tracer deposition in the long bones of the arms and legs, consistent with osteosclerosis. At an appointment in early 2019, the patient reported that he drank around nine litres of water per day due to intense thirst, whereupon he was referred for assessment by endocrinology. The possibility of polydipsia was considered, but ruled out following a dehydration test, with results consistent with central diabetes insipidus and an excellent response to desmopressin.

The test results were:

- Hormone tests: no other pituitary or gonadal deficiencies.

- Imaging tests: (Fig. 1).
- Computed tomography (CT) of the chest, abdomen and pelvis: lung parenchyma featuring a ground-glass pattern with interstitial thickening in the right lower lobe consistent with an inflammatory process, without any other findings of note.
- Magnetic resonance imaging (MRI) of the brain: multiple small signal abnormalities on both sides of the midline of the brain stem and cerebellum. No pathological abnormalities were seen in the pituitary gland.
- Positron emission tomography/computed tomography (PET/CT): diffuse involvement of bone marrow of long bones, with greater uptake in the left proximal tibial metaphysis. Hypermetabolic focus in left pons in relation to active lesion. Increases in hypermetabolic density in right lung consistent with inflammatory signs which, along with the hypermetabolic lymphadenopathy reported in the right paratracheal and subcarinal region, were suggestive of an inflammatory process.
- Bone biopsy of proximal tibial metaphysis: lesions suggestive of histiocytosis. CD68+, CD1a and S100 negative. Positive for BRAF V600E mutation.

With the above findings, the patient was diagnosed with ECD. In this case, the patient was referred to haematology to start treatment as mandated by the central nervous system involvement he exhibited.

In adults, the most common type of non-endocrine involvement in ECD is bone involvement, in the form of metadiaphyseal osteosclerosis of the long bones (80%–95% of patients), which can cause bone pain or be asymptomatic.<sup>4</sup>

Regarding endocrine manifestations,<sup>5</sup> diabetes insipidus develops in a third of patients, often as the first sign.<sup>6,7</sup> Anterior hypopituitarism is found in the vast majority of patients when complete pituitary function is evaluated. The following may appear, in order of frequency: growth hormone (GH) deficiency, hyperprolactinaemia, gonadotropin deficiency,<sup>8</sup> thyrotropin deficiency and corticotropin deficiency. On MRI, infiltration of the pituitary gland with pituitary stalk thickening is found in 24% of patients.

Testicular failure appears in half of patients, with bilateral testicular infiltration on ultrasound. Adrenal infiltration on CT is seen in a third of patients and may manifest as adrenal insufficiency.<sup>9</sup>

Central nervous system involvement occurs in around 30%–50% of cases. It sometimes leads to severe disability and constitutes the main factor in a poor prognosis. Pyramidal and cerebellar syndromes are the earliest and most common neurological signs.

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