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Iatrogenic Cushing syndrome due to drug interaction between inhaled fluticasone and cobicistat

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SUMMARY

In this paper we report a case of iatrogenic Cushing syndrome due to a pharmacological interaction between fluticasone and cobicistat. Inhaled corticosteroids were previously thought to be safe, but increasing numbers of cases of iatrogenic Cushing syndrome are being reported, especially in patients taking cytochrome P450 inhibitors, including cobicistat. Although the drug interaction between cobicistat and fluticasone has been described elsewhere, to our knowledge we present one of the first descriptions of iatrogenic Cushing syndrome due to this pharmacological interaction.

Keywords: HIV, drug interactions, cobicistat, corticosteroid, pharmacokinetics.

INTRODUCTION

Pharmacological interactions are a well-known challenge in the management of HIV infection [1]. Current antiretroviral treatment (ART) has improved life-expectancy and turned HIV infection into a chronic illness. As the HIV population ages, comorbidities have become more and more common and made drug interactions a major concern [2]. Besides Infectious Diseases Physicians, this problem may involve other specialists to whom HIV-infected patients are increasingly referred to for concurrent disorders.

CASE REPORT

A 49-year-old man with a long-standing HIV-1 infection presented for a scheduled visit to our Infectious Disease Clinic reporting a history of progressive muscle weakness leading to walking difficulties, abdominal distension, weight gain, ankle edema and dysthymia. He also complained of worsening back pain that had appeared 2 weeks earlier. His antiretroviral therapy was darunavir/cobicistat and emtricitabine/tenofovir (started one year before), CD4-T lymphocytes were 601/µL and HIV-1 RNA replication was suppressed in plasma. His past medical history was notable for a diagnosis of Hodgkin lymphoma (2013); hypertension (under treatment with perindopril); alcoholic fatty liver disease; dyslipidemia; cigarette smoking; obstructive sleep apnea with continuous-positive-airway-pressure treatment and chronic obstructive pulmonary disease (COPD). Five months earlier, during hospitalization for an exacerbation of COPD, a Pulmonary Specialist prescribed treatment with fluticasone/formoterol combination inhaler.

Clinical examination revealed: abdominal distension with red *striae* (Figure 1), moon *facies* (Figure 2), dorso-cervical fat accumulation, proximal muscle weakness, bilateral ankle edema and skin telangiectasias. Blood test showed: leukocytosis (18,000 WBC/µL with 78% neutrophils) and liver enzymes elevation (AST: 81 IU/L, ALT: 501 IU/L, GGT: 1,391 IU/L). Serum bilirubin and C-reactive protein concentrations were in the normal range. Radiography of the spine evidenced multiple osteoporotic vertebral fractures. Measurement of

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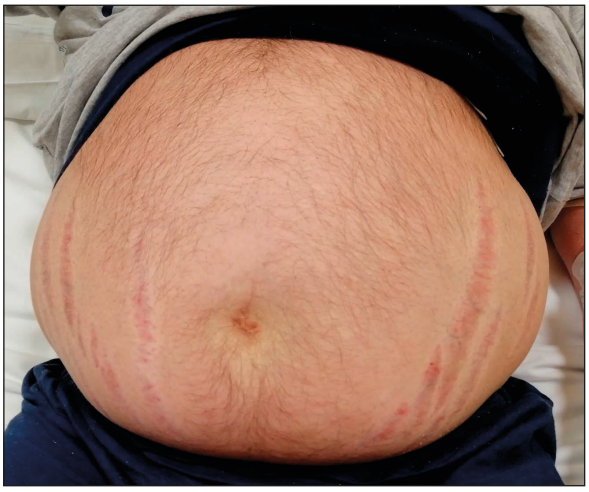

Figure 1 - Abdominal distension with red striae.

hormone concentrations revealed low levels of: serum cortisol (2,7 µg/dL; range: 7-25 µg/dL), ACTH (4 pg/mL; range: 5-60 pg/mL) and 24-hour urinary free cortisol (2,7 µg/24 h; range: 36-127 µg/24 h). Altogether, these findings were consistent with suppression of the hypothalamus-pituitary-adrenal axis and iatrogenic Cushing's syndrome due to a pharmacologic interaction between fluticasone and cobicistat. Cholestatic hepatitis was considered to be a consequence of Cushing's syndrome [3]. Therapeutic management included: darunavir/cobicistat-switch to dolutegravir (an antiretroviral agent that does not inhibit the CYP3A4 isozyme), tapering of the inhaled corticosteroid and cortisone acetate replacement therapy, in order to prevent an adrenal crisis.

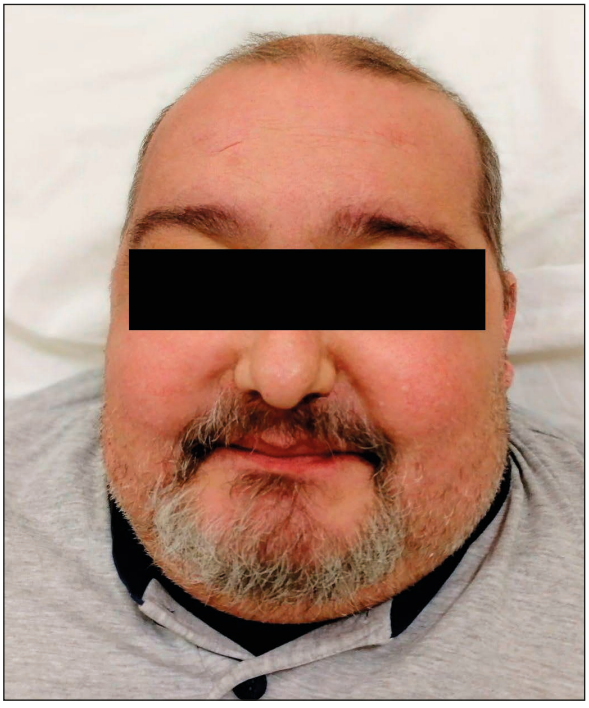

Figure 2 - Moon facies.

Although the appropriate treatment strategy, important consequences were impossible to prevent. In detail, the reduction of bone mineral density due to Cushing's syndrome resulted in multiple vertebral fractures with spinal cord compression requiring surgical intervention. Then, due to the extended hospital stay, the patient developed a bloodstream infection complicated by spondylodiscitis due to methicillin-resistant *Staphylococcus aureus*, which was successfully treated. Afterward, in consideration of paraplegia, the patient was sent to a neuro-rehabilitation clinic and lost to follow-up ever since.

DISCUSSION

Inhaled corticosteroids were previously thought to be safe, but several cases of iatrogenic Cushing's syndrome have been reported in the literature, especially in patients taking drugs that inhibit cytochrome P450 (CYP) [4]. Fluticasone normally has favorable pharmacokinetic properties, but, in the presence of CYP inhibitors, it shows considerable accumulation because of long half-life, high lipophilicity and higher binding affinity for the glucocorticoid receptor [5]. Patients with HIV infection who take regimens containing protease inhibitors (PIs) or pharmacokinetic enhancer (*i.e.* booster) are at risk for exogenous corticosteroid accumulation in serum: among these medications, ritonavir and cobicistat are the strongest CYP3A4 inhibitors. Several cases of Cushing's syndrome due to an interaction between fluticasone and ritonavir have been reported in literature [6-20]. In fewer patients, the inhaled corticosteroid responsible for toxicity, when co-administered with ritonavir, was budesonide [18, 21-23].
Cobicistat is a mechanism-based inhibitor of CYP3A that is used in HIV-1 infection as a "booster"of PIs atazanavir and darunavir and the integrase inhibitor elvitegravir. The drug interaction

between cobicistat and fluticasone is described and expected, but we present herein one of the first descriptions of full-blown, iatrogenic Cushing's syndrome due to this pharmacological interaction [24, 25].

In this report the patient had been taking cobicistat for more than a year. Then, after seven months he started fluticasone inhalation and within two months he complained the first symptoms (muscle weakness, abdominal distension, weight gain and ankle edema).

Every time a patient receiving cobicistat needs treatment with inhaled steroids, clinicians should consider switching to an antiretroviral agent which doesn't inhibit CYP (*i.e.* a non-nucleoside reverse transcriptase inhibitor or an unboosted integrase inhibitor) or using a steroidal medication with less potential drug interactions. Beclomethasone represents a relatively safer option to fluticasone due to its shorter elimination half-life, lower glucocorticoid receptor binding affinity, low lipophilic activity and lower dependence on CYP for its metabolism: when it's co-administered with an enzymatic inhibitor, no drug interaction is expected [26].

In conclusion, meticulous review of pharmacologic interactions, including topical treatments, is warranted before the introduction of any new drug to a complex regimen, in order to avoid serious harm to patients. Moreover, active communication between Infectious Disease Physicians and other specialists can contribute to reducing clinical errors among patients with HIV infection.

Conflict of interest None

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