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CLINICAL VIGNETTE

Iatrogenic Cushing's Masquerading as Lipodystrophy and Adrenal Insufficiency

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A 53-year old man with a greater than 20-year history of HIV positivity complicated by a previous history pneumocystis pneumonia, asthma and atrial fibrillation who was sent for an endocrinology evaluation after he was found to have abnormal adrenal hormone levels. The patient had complained of feeling weak, gaining weight and losing his muscles, particularly his buttock muscles. He also had developed gynecomastia and had been told that he had myopathy and lipodystrophy. He admitted to minimal lightheadedness on standing but had no clear orthostatic symptoms. He denied using alternative medicines or substances and specifically denied using megestrol.

His medications included fluticasone nasal spray, fluticasone HFA, ritonavir (Norvir), atazanavir (Reyataz), and emtricitabine/tenofovir disoproxil (Truvada) (as well as acetaminophen, albuterol, amoxicillin/clavulanic acid, atorvastatin, brimonidine eye drops, eszopiclone, , latanoprost eye drops, loperamide, metoprolol, glucosamine- chondroitin complex, multivitamins, trazodone, and minocycline).

His physical exam revealed a well-developed well-nourished man. Vital signs: Blood pressure and pulse supine - 142/81 and 64; standing - 152/83 and 62. BMI 21.8. There was no clear loss of adiposity. There was no central obesity, dorsocervical-hump or increase in supraclavicular fat pads. There was no acne or striae present. Minimal gynecomastia was present and the exam was otherwise unremarkable.

Laboratory Data: Random cortisol 0.5 mcg/dL and ACTH <2 pg/dL. A cosyntropin stimulation test was performed: Cortisol baseline 0.6 mcg/dL Cortisol at 30 and 60 minutes: 6 mcg/dL and 6 mcg/dL.

The patient was sent to his pulmonologist to change his allergy and asthma medications. He was placed on beclomethasone dipropionate nasal and oral inhalation sprays.

Two months later a cosyntropin stimulation test was again performed. Baseline cortisol 3 mcg/dL Cortisol at 30 and 60 minutes: 13 mcg/dL and 17 mcg/dL.

This patient's presentation raised several interesting clinical problems which were investigated to understand the mechanism of the unexpected biochemical findings.

The initial ACTH and cortisol were performed by the patient's HIV specialist because she suspected that he had become Cushingoid based on his original presentation of fat distribution, muscle weakness and body fat distribution. This is not an uncommon issue for protease inhibitor treated patients. The combination of HIV induced muscle wasting and protease inhibitor induced lipodystrophy can create a clinical picture suspiciously similar to the clinical picture of Cushing's syndrome, and so investigation of the adrenal axis is often excessively delayed because the early signs of Cushing's syndrome are mistaken for lipodystrophy. In this case what was truly surprising was the biochemical evidence from the cosyntropin stimulation test, which indicated severe secondary (i.e. pituitary mediated) adrenal insufficiency, however, the patient did not clinically appear to be adrenally insufficient. How could this discrepancy be explained?

This patient did not appear to have any clinical situation such as hemorrhage, infection, or metastases, which would have accounted for adrenal insufficiency. In addition, he was not taking any medication known to interfere with adrenal biosynthesis (keotconazole, fluconazole, metyrapone, suramin, mitotane) or accelerates glucocorticoid catabolism (phenytoin, barbiturates, mitotane, rifampin). Besides, all of the above would have accounted for a low cortisol level, but should not have suppressed the ACTH. Megestrol, in contrast, is a progestin with intrinsic glucocorticoid activity used to stimulate appetite in AIDS wasting

syndrome. By mimicking glucocorticoid activity, it is capable of causing secondary adrenal insufficiency, but the patient denied having taken it.

The secret to this patient's secondary adrenal dysfunction lies in a medication interaction which has been previously described but is often not recognized. Ritonavir, which is itself a protease inhibitor, is used as a booster for protease inhibitor therapy. It is a powerful CYP3A4 inhibitor. Glucocorticoids are generally deactivated by CYP3A4 enzymes and therefore when ritonavir is given together with glucocorticoids the systemic levels of glucocorticoids increase dramatically. This interaction has been well documented to occur after inhaled^{1,2}, as well as intra-articular^{3,4}, epidural^{3,5}, periradicular⁵, intramuscular⁵ and subacromial³, injection of glucocorticoids. Glucocorticoids, which have been documented to contribute to this problem include triamcinolone^{1,3-6}, budesonide², methylprednisolone⁶, and fluticasone^{1,7-10}.

Attempts have been made to characterize this syndrome further. Schwarze-Zander⁵ et al reviewed the course of 15 patients who had received a triamcinolone injection and showed that symptoms of hypercortisolism could appear as early as 2 weeks after a single injection in ritonavir boosted protease inhibitor treated patients. Symptoms included weight gain, a Cushingoid facial appearance, insomnia, dorsal hump, fatigue, hypertension, hyperlipidemia and hyperglycemia. Avascular necrosis of the femoral head was also seen in one patient. More than half the patients were continued on the same HAART regimen including ritonavir and patients recovered in²⁻⁸ (median 4.9) months after a triamcinolone injection. Foisy et al⁹ reviewed 28 cases of intranasal or orally inhaled fluticasone in patients ranging in age from 1.8 to 66 years who had been treated with both low "boosting doses" (100-200 mg per day) and high (800-1200 mg per day) "treatment doses" of ritonavir. They also found common Cushingoid symptoms including Cushingoid facies, truncal obesity, abdominal striae, dorsocervical hump, acne and hirsutism, hypertension, diabetes and osteoporosis. Symptoms occurred as soon as 2 weeks after initiation of combined therapy with oral inhalation but were somewhat slower to appear with nasal fluticasone.

Our patient recovered substantially after switching his inhaled steroids from fluticasone to beclomethasone. Given that all glucocorticoids are metabolized by the CYP3A4 dependent enzymes in the liver, it is worth asking why our patient was able

to recover his adrenal function simply by making this switch. The answer is multifaceted and lies in the unique pharmacokinetics of beclomethasone. Beclomethasone dipropionate (BDP), unlike most glucocorticoids, is a prodrug, which must be converted before it is biologically active. Normally, esterases in the lung and nasal mucosa act on the BDP and transform it to a number of biologically inactive substances as well as to beclomethasone monophosphate (BMP) which has an affinity for the glucocorticoid receptor which is 25 times that of the parent compound¹¹. After oral and nasal inhalation, essentially none of the unchanged BDP is systemically bioavailable¹² because BDP is largely transformed into BMP. In addition, direct absorption of BMP from the nose is negligible. In a series of elegant experiments using ingestion of activated charcoal prior to inhalation¹³, it was shown that direct absorption from the lung and absorption of swallowed material each contributed significantly to systemic bioavailability of BMP. Once in the circulation, BMP is rapidly cleared by esterases via extensive extra hepatic metabolism and does not accumulate. Therefore, the CYP3A4 enzymes are not critical in its biological inactivation and CYP3A4 inhibitors do not play a substantial role in raising systemic levels of BDP or BMP. In contrast, in a different study, the concentration-time curve (AUC) of fluticasone was increased by a factor of 350 when healthy volunteers were given ritonavir and nasal fluticasone⁹. This explains why our patient simultaneously became Cushingoid and developed secondary adrenal insufficiency from non-systemic exogenous steroids. It also explains why adrenal function was restored with the change of inhaled fluticasone to inhaled beclomethasone.

There are several lessons to be gleaned from review of this case:

- 1) Be careful to distinguish the syndrome of protease inhibitor induced lipodystrophy from Cushing's syndrome since the clinical profiles can be similar.
- 2) Whenever a patient appears to have Cushing's but the tests suggest adrenal insufficiency, look for an exogenous source of steroids.
- 3) Avoid using any glucocorticoid therapy by any route whenever possible in patients on ritonavir boosted protease inhibitor therapy.
- 4) When inhaled steroids are unavoidable in ritonavir treated patients, do not use fluticasone, and in most cases use beclomethasone.

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