



# Acute development of Cushing syndrome in an HIV-infected child on atazanavir/ritonavir based antiretroviral therapy

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## Summary

An 11-year-old male with perinatally acquired human immune deficiency virus (HIV) infection on antiretroviral regimen, which included abacavir plus lamivudine (Epzicom), didanosine, ritonavir and atazanavir presented with bilateral axillary striae, increased appetite, fatigue, facial swelling and acute weight gain. Two months prior to presentation, the patient had received a diagnostic and therapeutic intra-articular triamcinolone injection in the knee for pain relief and subsequently became progressively swollen in the face, developed striae bilaterally at the axillae, experienced increased appetite, fatigue and an 8 pound weight gain. During the endocrine workup, suspicion for adrenal insufficiency prompted 24-h urine collection for free cortisol, which was found to be undetectable (below LLQ of 1.0 µg/L). This prompted further evaluation of the hypothalamic–pituitary axis (HPA) by standard dose adrenocorticotrophic hormone (ACTH) stimulation test. A 250 µg cosyntropin stimulation test was performed and confirmed HPA axis suppression. Baseline cortisol level was <1 µg/dL and stimulated cortisol level at 30 min was 3.8 µg/dL. The patient was diagnosed with iatrogenic Cushing syndrome and suppression of HPA axis secondary to the drug interaction between ritonavir (RTV) and intra-articular triamcinolone injection. Following endocrine evaluation and workup, the patient was admitted for planned orthopaedic procedure including elective left hamstring lengthening, distal femoral osteotomy and patellar tendon advancement. Taking into consideration the diagnosis of iatrogenic Cushing syndrome, at the start of the surgical procedure, 100 mg IV stress dose of hydrocortisone followed by 50 mg hydrocortisone every 8 h for 24 h was administered. Stress dosing was discontinued 24 h after the procedure. Throughout the hospitalization and upon discharge, the patient continued his ART. From initial presentation, patient has remained clinically stable throughout surgery and postoperative period.

## Learning points:

- Drug–drug interaction between ritonavir and triamcinolone can cause Cushing syndrome.
- Although triamcinolone has a half-life of 3 h, an intra-articular injection may be systematically absorbed for 3 weeks after injection, and adrenal suppression may last as long as 30 days.
- Co-administration of ritonavir and corticosteroids may result in an increase of plasma levels of corticosteroids levels, as they are both eliminated by CYP3A metabolism, and this interaction has the potential to prolong the half-life of triamcinolone several fold.
- No specific guidelines are available for the management of iatrogenic Cushing syndrome secondary to ritonavir and corticosteroids.
- One treatment option includes replacing ritonavir with a non-protease inhibitor-based regimen.
- Initiating hydrocortisone replacement therapy to prevent an adrenal crisis is also an alternate option.



## Background

This case describes a child who presented with iatrogenic Cushing syndrome secondary to adverse interaction between ritonavir and intra-articular triamcinolone. Although a few cases have been documented in the literature in adults of developing Cushing syndrome secondary to intra-articular triamcinolone while on a regimen that included ritonavir, this is the first documented case in the literature in a child. The literature has documented development of iatrogenic Cushing syndrome in pediatric patients on ART therapy including ritonavir with administration of inhaled fluticasone and budesonide. In children with no underlying immunodeficiency, Cushing syndrome developed after intra-articular administration of triamcinolone for treatment of hypertrophic scars, keloids and arthritis. Although Cushing syndrome secondary to intra-articular administration of triamcinolone may develop in immunocompetent and immunocompromised patients, the risk is higher in patients being administered medications such as ritonavir that act as potent inhibitors of cytochrome P450 3A enzymes.

## Case presentation

An 11-year-old male with perinatally acquired HIV presented with facial swelling, fatigue and acute weight gain. Two months before presentation, the patient had received an intra-articular triamcinolone injection in the knee for pain relief and subsequently became progressively swollen in the face, developed striae bilaterally at the axillae, experienced increased appetite, fatigue and an eight pound weight gain. He was admitted to the inpatient unit for elective left hamstring lengthening, distal femoral osteotomy and patellar tendon advancement.

## Past medical history

The patient was diagnosed with HIV perinatally. He has a history of ASD repair, osteopenia, spastic diplegia, cerebral palsy and hamstring lengthening. From an HIV perspective, the patient has been doing well on his antiretroviral regimen with good adherence and non-detectable viral loads of less than 20 copies/mL for over 2 years.

## Medications

The patient's current antiretroviral regimen for the last 2 months included abacavir plus lamivudine (Epzicom),

didanosine, ritonavir and atazanavir. Two months prior to presentation, his regimen of over 2 years consisted of abacavir, atazanavir, ritonavir and didanosine. Two weeks after the patient received an intra-articular triamcinolone injection, abacavir was substituted for abacavir plus lamivudine to decrease pill burden as abacavir is administered twice daily and abacavir plus lamivudine is administered once daily. HIV-1 genotyping results, performed 3 years prior, were positive for the M184V mutation and displayed resistance to emtricitabine and lamivudine. Genotype studies have not been repeated as patient's viral load has been suppressed for over 3 years. Upon receiving a 40 mg intra-articular triamcinolone injection in the knee, patient was not administered any medications other than anti-retrovirals.

## Physical examination

The patient's weight on admission to the hospital was greater than the 97th percentile for age, with a weight gain of eight pounds in two months, and length was 79th percentile for his age. Vital signs were normal limits with a blood pressure of 118/57 mmHg (75th–90th percentile for age and height), a pulse of 61 beats per minute, a temperature of 36.6°C and a respiratory rate of 24 breaths per minute. Significant clinical findings included a very full round face, temporal fossae fat deposition (Fig. 1), flesh coloured striae were noted longitudinally along the upper arms by the axillae bilaterally (Fig. 2) and on the flanks of the abdomen. The striae on the flanks were 3–4 mm in diameter, raised and darker than that in the axillae.

## Investigation

From the 2 months earlier when he received the intra-articular injection to presentation, the patient's CD4 T-cell count decreased from 1150 cells/mm<sup>3</sup> (39%) to 796 cell/mm<sup>3</sup> (37%) and the viral load was undetectable. Prior to being administered the intra-articular injection, his CD4 count for the previous 2 years has always been over 1000 and his viral load remained undetectable. The patient's white blood cell count was 10 × 10<sup>3</sup> μL (normal range 4–11 × 10<sup>3</sup> μL) with no bands, 73 percent segmented neutrophils, 13 percent lymphocytes and 0.9 percent eosinophils. Platelet count was 180 × 10<sup>3</sup> μL (normal range 200–370 × 10<sup>3</sup> μL). The 24-h urinary free cortisol was noted to be below reportable range for this study, which is



**Figure 1**  
Round, 'moon' facies, with bitemporal fat deposition 2 months after intra-articular steroid injection.

1.0 µg/L. His liver enzymes, renal function and urinalysis were normal.

### Diagnostic procedure and results

Suspicion for iatrogenic adrenal insufficiency resulting from the undetectable urinary free cortisol measurement prompted evaluation of the HPA by standard dose ACTH stimulation test. A 250 µg cosyntropin stimulation test was performed and confirmed HPA axis suppression. Baseline cortisol level was <1 µg/dL and stimulated cortisol level at 30 min was 3.8 µg/dL.

### Treatment

Following endocrine evaluation, the patient was admitted for a planned orthopaedic procedure including elective



**Figure 2**  
Striae in the left axillae 2 months after intra-articular steroid injection.

left hamstring lengthening, distal femoral osteotomy and patellar tendon advancement. Taking into consideration the diagnosis of iatrogenic Cushing syndrome, at the start of the surgical procedure, 100mg IV stress dose of hydrocortisone followed by 50mg hydrocortisone every 8h for 24h was administered. Stress dosing was discontinued 24h after the procedure.

### Outcome and follow-up

Throughout the hospitalization and upon discharge, the patient continued his ART including ritonavir and was closely monitored for adrenal insufficiency. As no specific guidelines are available for the management of iatrogenic Cushing syndrome secondary to drug–drug interactions between RTV and corticosteroids, following a multidisciplinary meeting and a thorough literature review, it was decided to continue ritonavir. From initial presentation, patient has remained clinically stable throughout surgery and postoperative period. Teaching was performed on recognition of signs and symptoms of adrenal crisis, hydrocortisone stress dosing for illness and intramuscular hydrocortisone administration for emergencies. Following discharge from the hospital, patient was closely followed by endocrinology with frequent clinic follow-ups to assess for symptoms of Cushing's syndrome. Repeat ACTH stimulation testing and medical evaluation performed 12 weeks post initial evaluation in order to assess recovery of the HPA axis were



reassuring as the cortisol levels were near normal, and patient's weight returned to his previous level before the administration of the intra-articular injection.

## Discussion

Clinical symptoms of Cushing's syndrome include weight gain, cushingoid or 'moon' facies, facial plethora, violaceous striae, acne, hirsutism, hypertension, increased truncal adiposity and proximal muscle weakness (1). Although clinical features of HIV-1 lipodystrophy syndrome associated with ART may overlap with Cushing syndrome, key findings that are more likely to indicate Cushing's syndrome are the presence of abdominal striae and facial plethora (2). Cushing syndrome can be caused by endogenous or exogenous exposure to excess glucocorticoids (3). In case of iatrogenic exposure, pituitary production of ACTH suppressed by supra-physiologic levels of exogenous glucocorticoids can result in secondary adrenal insufficiency and adrenal cortex atrophy (4). Laboratory findings consistent with exogenous Cushing syndrome and iatrogenic adrenal insufficiency include low early morning plasma cortisol and ACTH levels, and subnormal response to standard ACTH stimulation test (4). An early morning serum cortisol levels of  $<3\ \mu\text{g/dL}$  strongly suggest adrenal insufficiency, whereas levels of  $>15\ \mu\text{g/dL}$  predict a normal response of serum cortisol to ACTH stimulation (5, 6). Patients with low serum cortisol levels should undergo standard ACTH stimulation test.

Injectable triamcinolone is an exogenous corticosteroid that can be used as adjunctive short-term therapy for acute bursitis, tenosynovitis, epicondylitis, rheumatoid arthritis and osteoarthritis (7). Although it has a half-life of 2–3 h, intra-articular injection may be systematically absorbed for 2–3 weeks after injection, and adrenal suppression may last as long as 30–40 days (7, 8, 9). With the development of triamcinolone-induced Cushing's syndrome, weight gain and cushingoid facial changes are usually the leading symptoms (2). Time to development of symptoms following triamcinolone injection has been reported to range from one week to five months (10).

RTV, a protease inhibitor (PI) used as boosting agent for other protease inhibitors (lopinavir, atazanavir and darunavir), is recommended by the US and WHO pediatric treatment guidelines as a component of first- and second-line ART in children. Ritonavir acts as a potent inhibitor of the cytochrome P450 3A (CYP450

3A) enzymes allowing for the higher plasma exposure of concomitantly administered PIs (11). Co-administration of RTV and corticosteroids may also result in an increased plasma exposure of corticosteroids, which are also metabolized through CYP450 CYP3A pathway (4). This drug–drug interaction has the potential to prolong the half-life of triamcinolone by several folds and can cause long-lasting suppression of the HPA axis (2, 12).

Currently, no specific guidelines are available for the management of iatrogenic Cushing syndrome secondary to drug–drug interactions between RTV and corticosteroids. One option includes replacing RTV with a non-PI-based regimen. Individual case reports have also substituted RTV for an unboosted PI (10), a choice not applicable for pediatric patients or integrase inhibitors such as for raltegravir (2, 13). Hydrocortisone replacement therapy may be initiated while awaiting HPA recovery. Instruction on oral stress dosing for illness and IM hydrocortisone for emergencies should be performed while awaiting recovery of the HPA axis. A complete resolution of the clinical symptoms and a full recovery of the HPA axis are usually achieved after a median time of 4.9 months (range: 2–8 months) (2).

Our case, which is the first documented in the pediatric literature to our knowledge, highlights the importance of the thorough review of the patient medications profile and consideration for drug–drug interactions in HIV-infected patient undergoing concomitant treatment with injectable corticosteroids for orthopaedic co-morbidity. It is important to note as there are no established guidelines in the management of Cushing syndrome secondary to drug–drug interactions between RTV and corticosteroids, that it requires prompt medical evaluation and a multidisciplinary approach between infectious diseases, endocrinology, orthopaedics and rheumatology. Following a single injection exposure to intra-articular triamcinolone, a pediatric patient on RTV-based regimen can develop acute Cushing's syndrome with clinical features and significant ACTH suppression. If an intra-articular injection is administered, medical providers should follow-up patients for symptoms of Cushing syndrome, as timely identification and treatment of the ACTH suppression can potentially prevent significant complications during surgery and recovery.

### Declaration of interest

All authors have no conflicts of interest that could be perceived as prejudicing the impartiality of the case reported.



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#### Patient consent

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#### Author contribution statement

All authors contributed equally to the case.

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