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Cushing Syndrome Following Single Steroid Injection: A Case Report and Review of the Literature

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Abstract Iatrogenic Cushing's syndrome (ICS) is a well-known adverse effect of glucocorticoids. It usually develops after prolonged exposure to excessive amounts of synthetic glucocorticoids. The manifestations of ICS are generally dose and time dependent. We will report on our own case of ICS followed by a review/highlight of published cases of ICS following single steroid injection. The development of ICS after a single and low dose of synthetic glucocorticoid is an exceptional event and only a few patients have been reported to date in the literature. Here we will report on the case of a twenty-one -year-old female patient who developed ICS with striae rubra which appeared fifteen days after irrational use of a single intramuscular injection of betamethasone (Diprofos). Endocrinological evaluation confirmed hypothalamic-pituitary-adrenal axis suppression. Her striae showed gradual fading over the next two months leaving only thin white striae similar to stretch marks. We performed a review of the literature using a computer search in the Science Direct, Google Scholar, and National Library of Medicine from 1950 to January 2016 for ICS following single injection of synthetic glucocorticoids using the terms 'single injection', 'iatrogenic', 'betamethasone', 'triamcinolone', 'hydrocortisone' 'dexamethasone' 'adrenal suppression' 'Cushing case report' and 'Cushing's syndrome'. Nine case reports of ICS were found in both children and adults following a single steroid injection. There are multiple factors affecting the response to steroids that make one develop Cushing's syndrome while the others do not. Governments in developing countries must make more serious efforts to enforce the existing laws that prohibit the irrational use of steroids.

Keywords: *Iatrogenic Cushing's syndrome, Betamethasone, hypothalamic-pituitary-adrenal axis suppression, Diprofos, Cushing case report*

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1. Introduction

Iatrogenic Cushing's syndrome (ICS) is a well-known adverse event of glucocorticoids that develops after prolonged exposure to excessive amounts of synthetic glucocorticoids. The manifestations of which are generally dose and time dependent [1]. The development of ICS after a single and low dose of synthetic glucocorticoid is an exceptional event [2] and only a few patients have been reported to date in the literature. Here we report a twenty-one-year-old female patient who developed ICS with striae rubra fifteen days after a single intramuscular injection of betamethasone *(Diprofos).*

2. Case Report

A twenty-one-year-old unmarried female student was referred to us for the appearance of purple abdominal striae. She was not regularly taking any medications. Three days before her final examination she developed generalized arthralgia and bone aches not responding to non-steroidal-anti-inflammatory drugs. A single betamethasone injection *(Diprofos)* was prescribed by her orthopedic surgeon, after which purple striae started to appear mainly in the abdomen fifteen days later. There were no other associated symptoms, and she had regular menses. On physical examination, her weight was 65 kg, height 157 cm, BMI 26.37 kg/m^2, blood pressure 110/70 mmHg, and pulse 86 bpm. She had no central obesity, acne, hirsutism, moon face, or proximal myopathy. *Purple striae* were seen in both arms just below the axillae and the abdomen mainly at both flanks. Otherwise the rest of the examination was completely normal. Her endocrinal investigations showed *low* levels of 24 h urinary cortisol of 17 ug/24 h (28-213), early morning serum cortisol of 2.2 Ug/dl (2.3-11.9), and ACTH pm of 9 pg/ml (10-52 pg/ml). Other investigations including complete blood picture, liver and kidney function tests, serum electrolytes, random blood sugar and abdominal CT were all normal. After two months, the purple striae faded away leaving white thin striae similar to stretch marks.

3. Materials and Methods

We performed a review of the literature using a computer search of the Science Direct, Google Scholar, and National Library of Medicine from 1950 to January 2016 using the terms 'single injection', 'iatrogenic', 'betamethasone', 'triamcinolone', 'hydrocortisone' 'dexamethasone' 'adrenal suppression' 'Cushing case report' and 'Cushing's syndrome'. All Case reports of ICS following single corticosteroid injection with their reference lists were included. We excluded the articles that were not in English, cases of ICS due to more than single injection, or single injection with accidental over dosage and animal cases of ICS. This article was approved by the local ethical committee of the Mansoura Faculty of Medicine.

4. Results

We found 38 relevant articles through the search criteria, most of which were case reports. Most of the case reports documented the occurrence of ICS following prolonged topical application [3,4], short term intranasal [5], concurrent use of inhaled steroids with agents that inhibit cytochrome p450 [6,7], concurrent use of epidural [8], or intramuscular Triamcinolone with agents that inhibit cytochrome p450 [9] that is involved in **corticosteroid** metabolism resulting in increasing their concentrations and half-life prolongation [10,11]. The development of ICS after a single injection is an unusual event with *only* nine case reports been found in both children and adults. Augspurger and Wettlaufer reported two cases of ICS following single intralesional triamcinolone acetonide injections of urethral strictures in children [12]. Teelucksingh et al. reported ICS in a nine-year-old girl after a single treatment with 40 mg triamcinolone acetonide injected into keloids [13]. Kumar et al. reported ICS after intra-articular and intradermal administration of triamcinolone acetonide in three pediatric patients, two of them following multiple injections and one after single injection [14]. Jansen and Van Roon reported ICS in four cases, two of them due to single injection [11]. Tomé et al. reported a case of ICS after single epidural triamcinolone injection [15], Stephen M. Tuel et al. reported a case of ICS after single epidural methylprednisolone 60mg injection [16]. Finally, Iglesias et al. reported ICS 1 month after a single dose of intramuscular 40 mg triamcinolone acetonide for treatment of acute laryngitis, and these features disappeared completely after eight months [1]. Our patient developed striae rubra which is considered to be the first reported case of ICS following single intramuscular injection of betamethasone 14 mg and also the first to present with striae rubra as the sole clinical manifestation of Cushing's syndrome.

4.1. Clinical Presentation

The clinical manifestations of ICS as a result of single corticosteroid injection use vary greatly. The symptoms may be as subtle as change in weight distribution/weight gain [17]. The severe presentations reported hot flushes, hyperhidrosis, tachycardia, palpitations, nervousness, amenorrhea, facial hirsutism, hypertension, moon face and depression with anxiety [16]. The more severe presentations reported were not associated with single corticosteroid injection alone but with concurrent use of ritonavir (protease inhibitor that inhibit cytochrome p450), glucose intolerance to the point of hyperglycemic hyperosmotic state, metabolic syndrome, and avascular necrosis [17-27]. Other severe presentations reported include steroid induced myopathy and herpes zoster reactivation due to secondary immune deficiency [26]. Our patient had only striae rubra in both arms just below the axilla and the abdomen mainly at both flanks that appeared fifteen days after betamethasone injection and faded away after two months leaving white striae similar to stretch marks.

4.2. Diagnosis

When there is a clinical suspicion of ICS, a patient's adrenal axis needs to be assessed in a systematic manner. An early morning serum cortisol level should be assessed as well as an ACTH level. An ACTH stimulation test can be used to confirm adrenal axis suppression from exogenous steroids [8].

4.3. Management

Most patients in the literature had spontaneous improvement of symptoms with recovery of adrenal axis within months, ranging from two to eight months depending on the dose of the corticosteroid used and the severity of the initial presentation [8]. Similarly, our case recovered spontaneously within two months.

5. Discussion

We performed a review of the literature searching for similar cases, and all case reports of ICS following single corticosteroid injection with their reference lists were included. We exclude the articles that are not in English, cases of ICS due to more than single injection, or single injection with accidental over dosage and animal cases of ICS. We found thirty-eight relevant articles, most of which were case reports. Nine case reports have been found, four children and five adults. The clinical manifestations of the adults vary greatly ranging from mild features as change in weight distribution/weight gain to sever features as steroid induced myopathy with a wide range of symptoms in between. The diagnosis of these cases was dependent on history of single steroid injection followed by appearance of the clinical features with suppression of the adrenal axis. Most of the patients had spontaneous recovery of symptoms with recovery of adrenal axis within months, ranging from two to eight months. Our patient had just striae rubra in both arms just below the axilla and the abdomen mainly at both flanks, these striae appeared fifteen days after single steroid injection and faded away spontaneously after two months later, a condition which cannot be explained except that these striae are due to corticosteroid intake and this was confirmed by the suppressed pituitary-adrenal axis found in the laboratory results.

This case suggests that single use of a potent, long-acting, steroid may cause ICS. There is no published

literature regarding the magnitude of glucocorticoid misuse in the Middle East. Guidelines for preventing this misuse are lacking in the developing countries [28]. The irrational prescriptions of steroids as treatment for common cold are increasing. Kshirsagar et al., found that more than 30% of the prescriptions of the medical practitioners were irrational [29].

Many forms of synthetic steroids are available for local and systemic uses, Betamethasone, one of the synthetic steroids, is available in many forms, betamethasone dipropionate, betamethasone sodium phosphate, betamethasone acetate, betamethasone valerate and betamethasone benzoate.

DIPROFOS: Betamethasone 17α, 21-dipropionate and 21-disodium phosphate. Each ml of *DIPROFOS* Suspension is a combination of soluble, betamethasone dipropionate (BDP), equivalent to 5-mg betamethasone and very slightly soluble, betamethasone sodium phosphate (BSP), equivalent to 2-mg betamethasone in a sterile buffered and preserved vehicle. Prompt therapeutic activity is achieved by the soluble ester, BSP, which is absorbed quickly after injection. Sustained activity is provided by the slightly soluble, BDP, which becomes a depot for slow absorption, thereby controlling symptoms over a prolonged period [30].

Betamethasone shows extreme rapid clearance from the circulation with rapid distribution to the periphery. Elimination rates are slower than cortisol and are dependent upon the return from the periphery probably adipose tissue, unlike other steroids which are affected by their binding and release from the cortisol binding globulin [31].

BSP, is highly ionized in the aqueous solution, it is rapidly absorbed and hydrolyzed by phosphatase to Betamethasone, with peak plasma concentrations at approximately 2.8 h post dose [32]. While, BDP, being highly hydrophobic, needs to dissolve first in the fluids of the intercellular space of muscle fibers before diffusion into the vascular space [33]. BDP hydrolyzes via esterases to betamethasone 17-monopropionate (B17P) which had a long t1/2 (80.8 h), thus creating dissolution rate limiting absorption with sustained-release property after intramuscular injection [34]. In summary, betamethasone i.m. produced rapid onset and sustained action through an initial rapidly-increased plasma concentration of betamethasone and a sustained plasma concentration of B17P [32].

Generally, cushingoid features take weeks or even months to develop depending on the type, dose and modes of delivery of the steroid used. However, it is difficult to predict doses and time courses in which Cushing's syndrome will develop, because various factors like different potencies, different formulations, different modes of delivery of various glucocorticoids and the varying levels of sensitivity of the individual patients to glucocorticoids, will complicate the issue [7].

6. Conclusion

Review of the literature and our case report illustrate how the irrational use of steroids can cause significant morbidity even with single doses. Governments in developing countries must take more serious actions to enforce the existing laws to prevent steroid misuse. There are multiple factors affecting the response to steroids that may make one develop Cushing's syndrome while the others do not. Perhaps there is a future role for assessing markers of individual steroid sensitivity.

Conflict of Interest

The authors declare that they have no conflict of interest.

List of Abbreviations

1. **BDP:** betamethasone dipropionate
2. **B17p:** betamethasone 17-monopropionate
3. **BSP:** betamethasone sodium phosphate
4. **ICS:** Iatrogenic Cushing's syndrome

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