

Iatrogenic Cushing's Syndrome in Patients with Superficial Dermatophytosis

Abstract

Background: The epidemic-like scenario of superficial fungal infections in India has been complicated by the prescription of systemic and topical potent steroids. As a result, alarming number of patients are presenting with exogenous Cushing's syndrome. **Methods:** This cross-sectional study involved 23 patients of superficial dermatophytosis on steroids who presented with clinical features like that of Cushing's syndrome. Their clinical details and laboratory investigations including fungal culture and serum cortisol, were recorded on a pre-designed proforma. **Results:** There were 23 patients (14 males and 9 females) with mean age of 29.47 ± 15.5 years, majority with extensive tinea cruris and corporis. All of them received oral (Betamethasone) or parenteral corticosteroids along with potent topical steroids (clobetasol propionate and betamethasone valerate) for at least two months. In majority (56.5%), treatment was prescribed by unqualified medical practitioners and in the rest by alternative medical practitioners. Striae, buffalo hump, hirsutism were observed in 16 (69.5%), 15 (65.2%), 13 (56.5%) patients, respectively. Serum cortisol estimation revealed low levels and ranged from 0.66 to 6 $\mu\text{g/ml}$ with a mean of 1.53 ± 1.27 $\mu\text{g/ml}$ (normal 7-25 $\mu\text{g/ml}$). **Conclusions:** Corticosteroids are life saving for many dermatological diseases; their injudicious use (topical, oral, and parenteral) for prolonged periods in the treatment of superficial dermatophytosis can lead to Cushing's syndrome.

Keywords: Superficial dermatophytosis, tinea incognito, tinea pseudoimbricata, Cushing's syndrome, serum cortisol

Introduction

Superficial dermatophytosis is one of the most common dermatologic indication for outpatient consultations in India.^[1] Over the last 6–7 years, dermatophytosis has become an ongoing menace and has attained a magnitude of epidemic like situation.^[2] During this period, there has been a sudden rise in the prevalence of dermatophytosis all over India. What was always thought to be an easy to treat entity has undergone a significant clinical and epidemiological change, often with chronic, relapsing and remitting course and unresponsive to the conventional antifungal drug dosing and duration.^[3,4] The lesion morphology too has changed dramatically as increasing number of patients are presenting with large, rapidly spreading multiple lesions of tinea corporis et cruris or one of the two. There is a significant increase in the incidence of tinea faciei and its encroachment to the adjacent scalp in adults, involvement of genitalia, and alarmingly increased incidence in children. The

incidence of tinea with altered morphology like eczematous tinea with activity in the center, "double edged tinea," pustular tinea, tinea pseudoimbricata, highly inflammatory variants and many more has gradually increased over the past few years.^[3,5,6]

Besides the *Trichophyton mentagrophytes* with its relatively newly described novel ITS genotype VIII^[7], the other important incriminating factor for this epidemic like phenomenon is the rampant and unchecked use of the irrational fixed drug combinations (FDCs) that are freely available in the Indian market without the requisite prescription.^[3,8] A majority of these FDCs contain a super-potent or potent topical steroid like clobetasol propionate with antifungal, antibacterial, and antiprotozoal agents like miconazole, clotrimazole, terbinafine, itraconazole, neomycin, gentamycin, and ornidazole which contributes to increased resistance with antifungal therapy. To make matters

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worse, even oral and injectable steroids are being used for treating widespread, chronic dermatophytosis.^[5,9] Side effects of topical or systemic steroids are being seen in large numbers, very often with alarming presentations. Most of these patients belong to poor socioeconomic strata, have low levels of education and awareness and have been treated by neighborhood pharmacists, unqualified practitioners or both. We, hereby, present a cross-sectional study of such patients with the primary diagnosis of superficial dermatophytosis and clinical features of iatrogenic Cushing's syndrome. To the best of our knowledge there is no published study of such a phenomenon in English dermatologic literature.

Study Objective

This study highlights the increasing abuse of long-term topical, oral, and parenteral corticosteroids in patients of superficial dermatophytosis with local as well as systemic adverse reactions. It is a cross-sectional study analyzing the patients of superficial dermatophytosis on steroids (oral/parenteral/topical) with clinical features of Cushing's syndrome, in Dermatology outpatient department of a tertiary care hospital, in Delhi, India, in the past one year.

Materials and Methods

Twenty-three consecutive patients with active superficial dermatophytic infection taking prolonged potent steroids (oral/parenteral/topical) and presenting with following clinical signs and symptoms; moon-facies, buffalo-hump, central obesity, striae, lethargy, easy fatiguability, proximal muscle weakness etc., were recruited from Dermatology outpatient department of a tertiary care hospital, New Delhi. After obtaining informed written consent, details of patient's profile, disease history, treatment history, and laboratory investigations were recorded on a pre-designed proforma. All of them reported history of steroid intake (topical/oral/parenteral) for a minimum of two months. The details of topical steroid (with contents and brand name after seeing the tubes used or from the prescription), systemic (oral and parenteral) with molecule, dose, and frequency of intake were recorded [Table 1]. A detailed clinical examination was performed (weight, heart rate, blood pressure, waist circumference, BMI, dermatological examination). Pre-steroid abuse parameters were not known, although

a detailed medical history was taken including diabetes. All relevant biochemical investigations [morning serum cortisol levels using radio-immunoassay (Cortisol RIA kit, Beckman Coulter, Czech Republic), fasting blood sugar, serum electrolytes and calcium, complete blood count with liver and kidney function tests] were performed. Skin scrapings were performed in all patients for direct microscopic examination in 10% KOH from multiple sites and fungal culture was put up on Saboraud's Dextrose Agar (SDA) with cycloheximide and chloramphenicol.

Results

Twenty-three patients were included in this study. There were 14 males (60.8%) and 9 females (39.2%)



Figure 1: An adult male presenting in erythroderma with two islands of uninvolved skin on the abdomen, note the abdominal protuberance

Table 1: Different corticosteroids used by the patients

Route of administration	Steroid	Dose	Duration
Oral	Betamethasone	0.5-1 mg	Once/ Twice daily (on and off)*
Parenteral (IM/IV)	Inj Dexamethasone	4 mg/ml	Daily to once in 2 weeks (on and off)†
	Inj Triamcinolone acetoneide	10 mg/ml	Daily to once in 2 weeks (on and off)†
Topical	Clobetasol propionate (0.05%)	10-15 g/day	Once/twice daily (on and off)*
	Betamethasone valerate (0.1%)	10-15 g/day	Once/ twice daily (on and off)*

*Maximum off period was 1 week. †Maximum off period was 2 weeks



Figure 2: A child with erythroderma with involvement of face, ears, neck and scalp

with M: F ratio of 1.6:1. The mean age of the patients was 29.48 ± 15.5 years (age range 1 year–65 years). Disease duration of superficial dermatophytosis ranged from 3 to 14 months (mean duration 6.7 ± 2.6 months). A positive family history of superficial dermatophytosis was present in 12 (52.17%), of which 8 (34.7%) had disease in more than one family member. All 23 patients had an involvement of more than three anatomical sites. Eight (34.8%) patients presented with erythrodermic tinea (more than 90% BSA involvement), seven (30.4%) had extensive tinea involving minimum three anatomical sites with body surface area (BSA) of more than 10%, and rest had tinea corporis et cruris. Of the eight patients of erythroderma [Figures 1 and 2], two presented with adrenal crisis in the form of altered sensorium, high blood sugar, low blood pressure, nausea, and vomiting. One patient with erythroderma also had deep dermatophytosis in the form of sub cutaneous abscess, ulceration, and pus discharge. Majority of patients had facial involvement and seven (30.4%) patients had onychomycosis of finger and toenails with proximal onychomycosis seen in three patients. All of them had received oral or parenteral (intramuscular or intravenous) corticosteroids along with topical steroids for a minimum of two months although the frequency of parenteral steroids ranged from daily to once in two weeks. The two most common parenteral steroid molecules used were injection dexamethasone (available as 4 mg/ml vial) and triamcinolone acetonide (available as 10 and 40 mg/ml vial) while the most common oral steroid was tablet betamethasone (available in 0.5 and 1 mg tablet) taken



Figure 3: Broad erythematous atrophic striae on lower abdomen and thighs with multiple depigmented macules following topical and intralesional steroids with. Note tinea pseudoimbricata lesions

once or twice daily. Sixteen patients (69.5%) were receiving injectable steroids, three patients received only oral steroids and four were being prescribed/administered oral as well as parenteral steroids. Exact dosages of the drugs could not be calculated as many patients failed to recall the dosages due to intermittent self-medication. All patients were using topical FDCs, the most common steroid molecules being clobetasol propionate alone or in combination with antibacterial and antifungal agents and betamethasone valerate. In thirteen (56.5%) patients the treatment was prescribed by unqualified medical practitioners, in five (21.7%) by practitioners of alternative medicinal systems and in the rest, it was suggested by neighbors/friends.

Clinical features [Table 2]

All patients complained of fatigue, muscle cramps, had moon like facies, and central obesity. Striae [Figure 3], buffalo hump [Figure 4], acneiform eruptions, and acanthosis nigricans [Figure 5] were observed in 16 (69.5%), 15 (65.2%), 4 (17.3%), and 1 patient, respectively. All patients had a minimum of 1 tinea lesion larger than 10 cm in diameter. Six patients (26.1%) showed pustule formation inside the lesions and four (17.4%) had tinea lesion in concentric rings (pseudoimbricata) [Figure 6].

Table 2: Clinical profile of the patients

Case no	Age (years) & Sex	Disease Duration (in months)	Diagnosis	S. Cortisol (Normal 7-25 µg/ml)	Steroid abuse Injectable (I)/ Oral (O)/Topical (T)	Truncal obesity/Moon face/Striae/Buffalo hump/ Acneiform eruption
1	45 F	9	Extensive Tinea*	1.80	I+T	+/+/+/-
2	50 F	4	Tinea corporis et cruris	6.00	I+T	+/+/+/-
3	24 F	8	Tinea corporis et cruris	0.72	I+T	+/+/+/+
4	2 M	5	Extensive Tinea	1.13	I+T	+/-/-/-
5	65 M	4	Erythroderma (Adrenal crisis)	0.85	I+T + O	+/-/-/-
6	35 M	6	Extensive Tinea	1.66	I+T	+/+/+/-
7	26 M	7	Erythroderma (Deep dermatophytosis)	0.57	I+T + O	+/+/+/-
8	27 M	8	Tinea corporis et cruris	2.54	I+T	+/+/+/+
9	25 M	5	Erythroderma	1.07	I+T + O	+/+/+/-
10	35 M	8	Extensive Tinea	0.75	O+T	+/-/-/-
11	30 M	12	Extensive Tinea	1.45	I+T	+/+/+/-
12	13 M	14	Extensive Tinea	0.79	I+T	+/+/+/-
13	1 M	3	Erythroderma	1.70	I+T	+/-/-/-
14	50 M	8	Erythroderma (Adrenal crisis)	0.66	I+T	+/+/+/-
15	29 M	7	Tinea corporis et cruris	3.50	O+T	+/+/+/-
16	35 F	6	Erythroderma	0.63	I+T + O	+/+/+/-
17	29 F	8	Tinea corporis et cruris	1.43	O+T	+/-/-/-
18	22 F	3	Erythroderma	11.77	I+T	+/-/-/-
19	39 M	5	Erythroderma	1.23	I+T	+/+/+/-
20	18 F	6	Tinea corporis et cruris	10.50	I+T	+/-/-/+
21	12 M	4	Tinea corporis et cruris	8.19	I+T	+/-/-/-
22	16 F	6	Extensive Tinea	17.87	I+T	+/+/+/+
23	50 F	8	Tinea corporis et cruris	0.62	I+T	+/+/+/-

*Extensive tinea: Involving anatomical sites and more than 10% body surface area. '+' means Present, '-' means absent



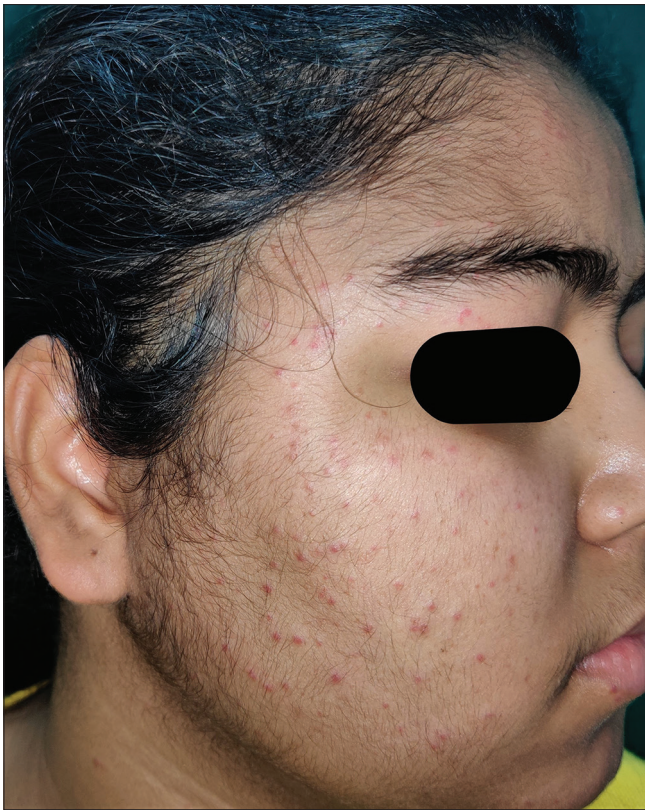
Figures 4: Marked acanthosis nigricans, and buffalo hump on upper back.

Blood pressure was within normal limits except in two patients who presented with adrenal crisis and were in hypovolemic shock. Most patients (91.3%) noticed significant weight gain ranging from 4 to 15 kg, with mean

gain of 8.95 ± 2.75 kg except in two. Hyperglycaemia was observed in 9/23 cases (39.1%).

Morning serum cortisol levels were measured in all patients; 19 (82.6%) had significantly low levels and four had low values just above the lower limit of the normal range (7–25 µg/ml). Serum cortisol levels ranged from 0.66 to 6 µg/ml with a mean of 1.53 ± 1.27 µg/ml. Serum electrolyte levels were available for 14/23 patients and was normal in all except in two, who presented with adrenal crisis. Serum calcium levels, liver, and kidney function tests and complete blood counts were normal in all cases. Hence on the basis of prolonged potent steroid intake, characteristic clinical features of exogenous corticosteroid excess and low morning serum cortisol levels, a diagnosis of exogenous Cushing syndrome was made.

Direct 10% KOH examination was done in all patients from multiple sites and all samples (100%) showed branched and septate hyphae. Fungal culture was positive in 10 patients (43.47%) and grew *Trichophyton mentagrophytes*. KOH and fungal culture and PAS stain was performed in one case with deep dermatophytosis, with isolation of *Trichophyton mentagrophytes*. HIV serology performed in 17 (73.9%) was non-reactive.



Figures 5: Acneiform eruption over face. Also note hypertrichosis and facial puffiness



Figure 6: Multiple tinea pseudoimbricata lesions (ring within ring) over trunk

Discussion

Superficial dermatophytosis has become a disabling disease owing to the accompanying severe itching resulting in intense, uninhibited scratching.^[10] In order to get rid of this intense itch, patients seek help of easily accessible and affordable unqualified and unqualified medical practitioners and local chemists who prescribe and advocate fixed drug combinations (FDCs) containing potent topical steroids and systemic steroids (oral or injectable). As we know, the clearance of fungus mainly depends on cell-mediated immunity CMI (Th1/Th17 immune responses)^[11] that accounts for the initial temporary improvement in the symptoms with use of steroid. However, its prolonged use inhibits the systemic and local immunological responses, resulting in inefficient clearance of the fungus leading to widespread disease.^[9] In extreme cases, extensive dermatophytosis may lead to erythroderma. It has been reported that the topical application of steroids results in profound local immunosuppression as compared to other routes.^[12] As is evident in our study, 8/23 (34.8%) patients presented with erythrodermic tinea and 7/23 (30.4%) with extensive tinea. Other important adverse effect is Lipodystrophy which is characterized by loss of fat with or without redistribution of fat at other sites. In a study conducted by Fardet *et al.*, 80 consecutive patients on long-term (3 months), high dosage (20 mg day) prednisone

were evaluated after 3 months for adverse events. These patients were suffering from different auto-immune disorders among these were giant cell arteritis, connective tissue diseases, systemic sarcoidosis etc., 63% of the patients developed lipodystrophy, 39% had moon-face, 46% had hirsutism, 8.7% had new onset hypertension and 2.5% had acneiform eruption. In contrast, all of our patients had central obesity and moon facies, 65% had buffalo hump, 17% had acneiform eruptions and hirsutism was observed in 56.5% probably due to prolonged potent steroid intake.^[13] However, out of 23 patients 4 (case: 18, 20, 21, and 22) had serum cortisol within normal range. Although, all of them had clinical features suggestive of Cushing's syndrome with clear history of intake of corticosteroids. In such cases ACTH stimulation test can be performed to look for adrenal reserves, but due to its un-availability the test could not be performed. To the best of our knowledge, there is no published English literature pertaining to the development of Cushing's syndrome following use of topical and systemic steroids in the management of superficial dermatophytosis. All patients in the present cross-sectional study, gave history of oral or parenteral steroids that resulted in classical symptoms of Cushing's syndrome in the form of significant weight gain, moon facies, truncal obesity, abdominal, groin, and

axillary striae and metabolic derangements. Steroids were prescribed by non-dermatologist (unqualified medical practitioners, local pharmacists, or alternative medicine practitioners). Most of our patients (18/23 = 78.2%) belonged to lower socio-economic strata. Twelve (52.17%) had positive family history of superficial dermatophytosis, of which 8 (34.7%) had involvement of more than one family member. This finding is in concordance with Ghosh *et al.*^[14] In a study by Mahajan *et al.*, topical steroid antifungal combinations were used by 70.6%^[15] while a study done in a tertiary care center in Kerala, FDCs were used by 63%.^[4] However 100% of our patients used topical FDCs.

Cushing's syndrome is the result of the body being exposed to high levels of cortisol hormone for a long period of time. It can be either endogenous or exogenous. Endogenous Cushing's syndrome happens secondary to increased autonomous production of cortisol from adrenal neoplasms (adenoma or carcinoma, 15%) or hyperplasia or pituitary gland tumors (adenoma or carcinoma, 70%). Estimation of morning ACTH levels is undertaken to know the source of endogenous cortisol production.^[16,17]

Most common cause of exogenous Cushing's syndrome is prolonged intake of oral or parenteral steroids, although few cases have also been reported after the use of megestrol acetate. Exogenous Cushing's syndrome can be easily distinguished from the endogenous variant by the positive history of treatment with high-dose glucocorticoids in the former. The classical stigmata include weight gain usually presenting as central obesity with redistribution of body fat to truncal areas and the appearance of dorsocervical and supraclavicular fat pads and the classic moon face, which was evident in all of our patients. Other signs and symptoms include easy bruising, thin skin, striae, poor wound healing, and increased susceptibility to infections. Exogenous glucocorticoids induce a catabolic state of skeletal muscles, skin, and connective tissue. There is increased protein wasting and proximal muscle atrophy with predominant involvement of the pelvic girdle musculature resulting in proximal muscle weakness.

Dermatological indications of systemic steroids are well known and their judicious use is often lifesaving. This cross-sectional study, however, exemplifies blatantly injudicious use of steroids (dose, mode of administration, and duration), in the treatment of a disease where they are contraindicated and have led to disastrous consequences. This study underscores the alarming laxity in the formation and implementation of drug control laws pertaining to steroids in all conceivable forms, licensing laws related to medical practitioners as well as laws relating to sale and purchase of steroids in all forms.

Limitations

In the current study, three patients had normal cortisol levels and ACTH stimulation test facility was unavailable for further confirmation. This is a limitation of our study.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published, and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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