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A case of hyperpigmentation and acanthosis nigricans by testosterone injections

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Abstract

Drug-related skin disorders may occur in many different ways. Despite pigmentary changes being less important for morbidity, these changes precipitate depressed mood and reduce self-confidence. Testosterone is a steroid hormone from the androgen group and primarily used for the treatment of hypogonadism in males. Testosterone replacement can cause skin problems like acne, hair loss, redness, pain, or infection at the injection site.

The study was conducted on a 49-year-old man with adult onset idiopathic hypogonadotropic hypogonadism, which is an acquired form of isolated gonadotropin-releasing hormone deficiency. He was presented with lack of energy and decreased sexual function 10 years ago and was given an oil-based injectable blend of four esterized testosterone compounds as hormone replacement treatment in a urology polyclinic. He was referred to our polyclinic by endocrinologist because of progressive hyperpigmentation marked on his face and oral mucosa. In the present study, we report the first testosterone therapy-related facial and oral mucosal hyperpigmentation and acanthosis nigricans in the same patient.

Keywords

Drug-induced hyperpigmentation, acanthosis nigricans, testosterone

Introduction

Adverse cutaneous drug reactions are one of the most common reasons of consultation to dermatologists. Drug-induced skin disorders can include exanthems, urticaria, hypersensitivity syndromes, pustular eruptions, erythema multiforme, toxic epidermal necrolysis, cutaneous necrosis, and abnormal pigmentation of the skin and mucosa.[1] Testosterone is a steroid hormone primarily used for the treatment of males with hypogonadism. In this report, hyperpigmentation associated with testosterone therapy in a patient with adult-onset idiopathic hypogonadotropic hypogonadism (IHH) has been firstly described. Acanthosis nigricans can be associated with drugs as well. In this case, we report a patient with co-occurence of two drug-induced skin disorders, hyperpigmentation, and acanthosis nigricans.

Case

A 49-year-old male presented with lack of energy and decreased sexual function for 10 years. He was diagnosed with adult onset IHH and was treated with an oil-based injectable blend of four esterized testosterone compounds (sustanon 250) as hormone-replacement therapy in a urology clinic. He was referred to endocrinology clinic for progressive hyperpigmentation marked on his face and gingival mucosa with suspicion of adrenal insufficiency. His serum basal cortisol and adrenocorticotropic hormone (ACTH) levels and ACTH stimulation test

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results were within normal limits. Then, he was referred to our clinic for hyperpigmentation evaluation.

He was in a depressive mood due to hyperpigmentation of face, dorsal hands, and oral mucosa that progressively worsened over 10 years. He had no history of contacting with any other poisoning metal and chemical poison, such as arsenic, and so on.

The dermatological examination revealed dark brown periorbital pigmentation with a general brown hyperpigmentation in a photo distribution of the face, neck, and dorsal hands (Figure 1(a)). Diffused, macular, blue-gray pigmentation on ventral of the tongue, brown pigmentation on the buccal mucosa (Figure 1(b)), and brown patches on the extensor surface of the cruris (Figure 1(c)) were detected as well. His hair, nails, and other mucosa were normal. Punch biopsies were taken from three different areas, including zygomatic area, oral mucosa, and extensor surface of cruris.

The histopathologic examination of the skin biopsies from zygomatic area and oral mucosa revealed hyperpigmentation of the basal cell layer, pigment incontinence, and accumulation of pigment-laden macrophages within the dermis. The pigment within macrophages was positive for the Fontana-Masson stain, indicating the presence of melanin, confirming the clinical diagnosis of drug-related hyperpigmentation (Figure 2(a) and (b)). The third biopsy from the cruris showed hyperkeratosis, papillomatosis, and acanthosis with minimal dermal lymphocyte infiltrate consisting with acanthosis nigricans (Figure 2(c)).

The results of the laboratory investigations including complete blood cell count, glucose, serum urea nitrogen, creatinine, liver function tests, serum iron studies, basal cortisol levels, and ACTH stimulation test results were within normal limits.

He was diagnosed with testosterone-induced photodistributed cutaneous and oral mucosal hyperpigmentation and acanthosis nigricans. After the diagnosis, the endocrinologist suggested to stop testosterone therapy. Unfortunately, our patient refused to stop testosterone therapy, and therefore, we could not show remission of the skin lesions following the discontinuation of the testosterone therapy.

Discussion

Hypogonadotropic hypogonadism is a form of hypogonadism that is due to a deficiency of the pituitary secretion of follicle-stimulating hormone and luteinizing hormone. In the absence of pituitary or hypothalamic anatomical lesions and anosmia (Kallmann syndrome), hypogonadotropic hypogonadism is defined as IHH. Adult-onset IHH, also known as idiopathic-isolated hypogonadotropic hypogonadism, is a very rare form, occurring in sexually mature men with normal pubertal development.[2]

Our patient was diagnosed with adult-onset IHH, which is an acquired form of isolated gonadotropin-releasing hormone deficiency (GnRH) deficiency.[2] In this group of patients, puberty occurs normally, and it is followed years later by a decrease in libido, sexual function, and fertility. Other pituitary hormones can be accompanied with the diseases. In our patient, local tumors, inflammatory diseases, and traumas were excluded.

Pulsive GnRH or gonadotropins are treatment options for patients who want to be fertile. Testosterone replacement therapy is another option for those who do not demand for spermatogenesis. Acne, oily skin, and hair loss and/or thinning of the hair are well-known adverse effects of testosterone supplementation by dermatologist. However, testosterone-related hyperpigmentation, as in our case, has not been reported in literature before.

Drug-induced pigmentation constitutes 10–20% of all cases of acquired hyperpigmentation. It appears usually slowly, worsens over time, and is frequently located on photo-exposed areas. Oral mucosa, conjunctiva, sclera, and nails may also be involved.[3,4] Nonsteroidal anti-inflammatory drugs, psychotropic agents, tetracyclines, antimalarials, cytotoxic drugs, amiodarone, and heavy metals can cause skin pigmentation as well.[3,4]

The pathogenesis of drug-induced pigmentation show variability according to causative medications: (i) melanin accumulation, which may be due to a nonspecific cutaneous inflammation induced by the medication that worsens by sun exposure, or an increased melanin production by epidermal melanocytes specifically stimulated by the drug, or a lack of melanin clearance due to irreversible binding of the drug to melanin, (ii) accumulation of the triggering drug itself, (iii) synthesis of special pigments like lipofuscin under the direct influence of the drug, and (iv) deposition of iron following drug-induced damage of dermal vessels.[3] Our case is the first report on testosterone-induced pigmentation. The pathogenesis of testosterone-induced pigmentation is still unknown. Based on the histological findings, we postulated that epidermal melanocytes might have been stimulated by testosterone and sun exposure might have increased melanin production.

In differential diagnosis, systemic drugs are one of the major causes of diffused and circumscribed

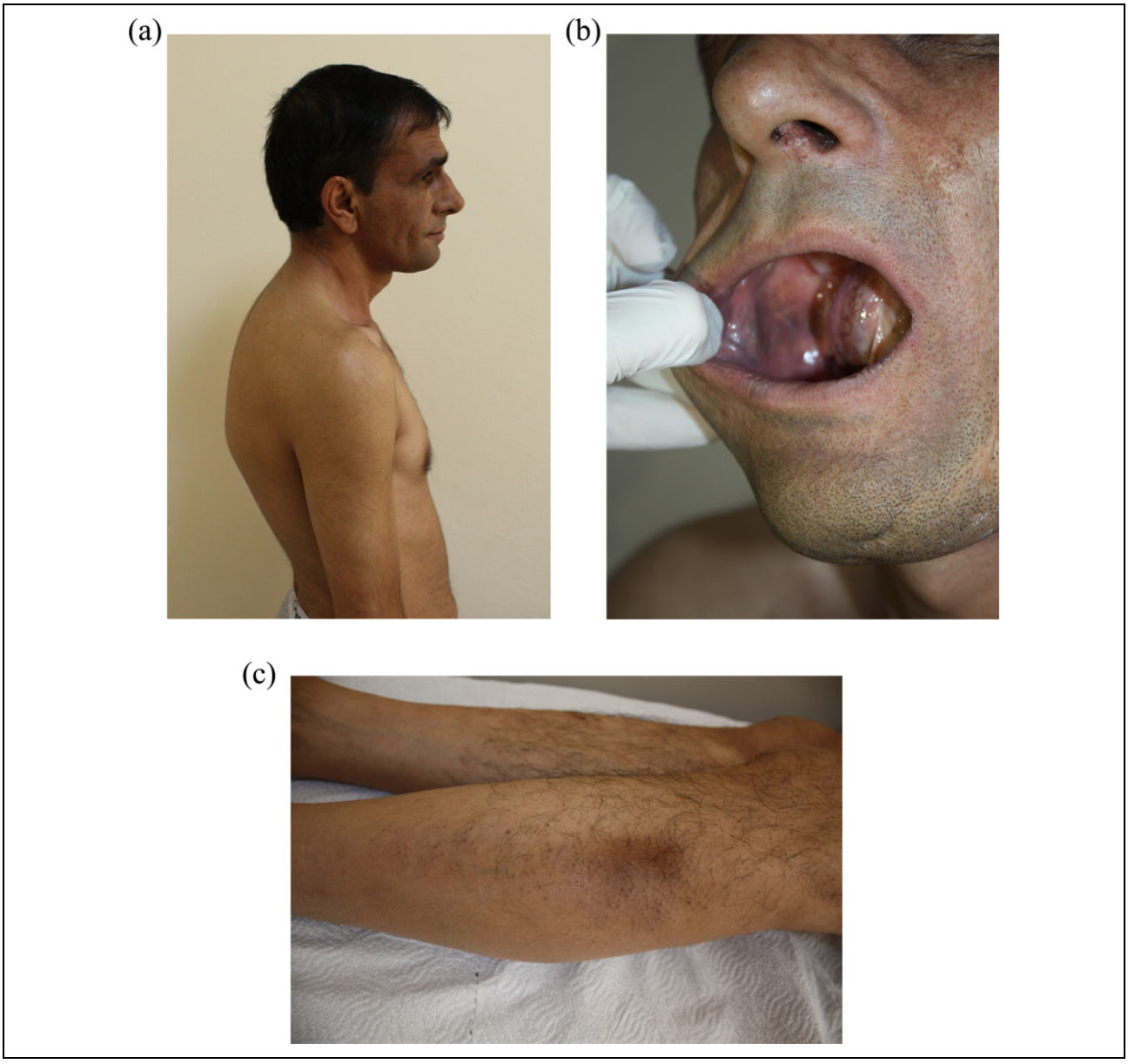

Figure 1. (a) Hyperpigmentation in a photo distribution of the face and neck. (b) Blue-gray pigmentation of the buccal mucosa and brown pigmentation on ventral of the tongue. (c) Brown patches on the extensor surface of the cruris.

hyperpigmentation. In our case, accusing drugs, metabolic and endocrine diseases, sclerodermoid disorders, nutritional deficiencies, post-inflam matory hyperpigmentation, and occasionally HIV infection were excluded.[5] Our patient's hyperpigmentation mimics cutaneous manifestations of Addison's disease with diffused pigmentation of the skin and mucosa. However, our patient had no abnormal serum laboratory test results, including hyponatremia, hyperkalemia, and low serum cortisol levels. The differential diagnosis of hemochromatosis and vitamin B_{12} deficiency were ruled out after finding serum ferritin and vitamin B_{12} level in normal range.

Acanthosis nigricans is a brown-to-black velvety hyperpigmentation of skin that can appear at any locations but most commonly on the intertriginous areas of the axilla, groin, and posterior neck. In our case, the lesions were located on extensor surface of cruris that were very rare location. Endocrine and genetic abnormalities, carcinoma, and drug ingestion are known to be associated with acanthosis nigricans.[6] Our patient had none of the diseases, which are known to be associated with acanthosis nigricans. In the

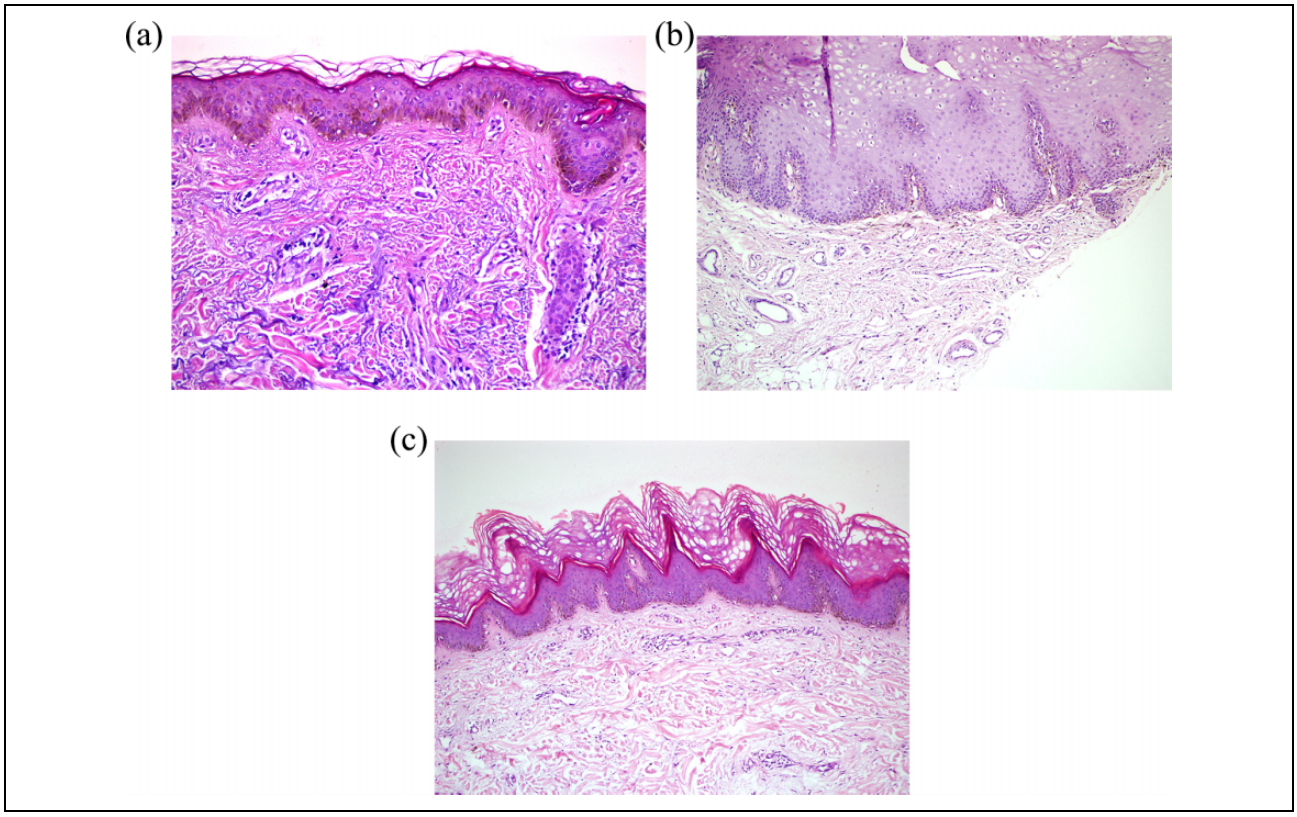

Figure 2. (a) Basketwave keratosis, pigment accumulation on basal layer, sparse melanophages, and elastosis in superficial dermis (H&E; ×20). (b) Hyperplasia of mucosa of epithelium, melanophages under epithelium, and sparse lymphocytes (H&E; ×20). (c) Hyperkeratosis of the epidermis, acanthosis with widening of the epithelial cones, and papillomatosis (H&E; ×20). H&E: hematoxylin and eosin.

differential diagnosis of drug-related pigmentation, acanthosis nigricans should be considered as well. The skin biopsy taken from the crusis was consistent with acanthosis nigricans. Thus, taking skin biopsy from different location is important which is not to be missed during the diagnosis.

Drug-induced type is an uncommon form of acanthosis nigricans. Several medications, including nicotinic acid, insulin, pituitary extract, systemic corticosteroids, and diethylstilbestrol can be associated with drug-induced acanthosis nigricans.[7,8] Therefore, we believe that hyperandrogenism due to exogenous testosterone is responsible for the acanthosis nigricans.

In literature, there was only one report indicating the relationship between methyl testosterone and acanthosis nigricans.[9] Our case is the first report showing that testosterone therapy may be related with hyperpigmentation. Drugs may rarely play a role in the etiology of drug-induced hyperpigmentation and acanthosis nigricans that should be considered in differential diagnosis.

Conflict of interest

The authors declared no conflicts of interest.

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