HAIR-AN Syndrome Associated with Scleroderma

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Abstract: The HAIR-AN syndrome is a rare multisystem disorder in women, that consists of hyperandrogenism (HA), insulin resistance (IR) and acanthosis nigricans (AN). The IR is likely due to a primary defect of the insulin receptor. We report the case of a 25-year-old Caucasian woman with HAIR-AN syndrome, impaired glucose tolerance (IGT), mild hyperlipemia, and hypertension, associated with sclerodermatous skin changes on the extremities and trunk. Though scleroderma may coexist with other autoimmune diseases, its presentation with HAIR-AN syndrome has not yet been described.

Keywords: HAIR-AN, syndrome, scleroderma.

INTRODUCTION

The syndrome of hyperandrogenism, insulin resistance, and acanthosis nigricans, also has been known HAIR-AN syndrome. The primary abnormality in these patients is thought to be insulin resistance with elevated insulin levels. This syndrome is a unique subphenotype of the polycystic ovary syndrome and is seen in almost 5% of all females with hyperandrogenism. Obesity, acne, hirsutism, and acanthosis nigricans usually appear on the afflicted adolescent around puberty [1, 2]. Localized scleroderma is an idiopathic inflammatory disorder that causes sclerotic changes in the skin. Patients present with single or multiple inflammatory or sclerotic plaques. Disease activity typically persists for three to six years, although some patients develop more persistent or recurring episodes of activity [3-5]. It was reported an unusual skin presentation of HAIR-AN syndrome including vitiligo [6]. Herein, we report an unusual skin presentation of HAIR-AN syndrome with concomitant sclerodermatous skin changes in a 25-year-old female adolescent. To our knowledge, this is the first case of this combination.

CASE REPORT

The patient is a 25-year-old female diagnosed with HAIR-AN syndrome 5 years ago. Three year after diagnosis, she developed sclerodermoid skin changes specifically her right upper extremity, anterior abdominal wall and right thighs. Darkly pigmented, velvety areas of the skin (acanthosis nigricans) and also skin tags were positive at neck and axillae. Frontal hair recession was detected (Male pattern alopecia). Pigmented terminal hairs (hirsutismus) on the chest, back, face and lower abdomen were present. She has painless, indurated, discolored, indentations of the skin of right upper extremity, right thigh and lower abdomen. There was no evidence of hand involvement such as thickening and induration of the skin of the dorsum and proximal interphalangeal joints. There was full range of motion in the joints, no flexion contractures, no trigger finger. She had Raynaud's phenomenon. The patient has amenorrhea and signs of virilization including clitoral hypertrophy. The results of routine complete blood cell count, urinanalysis, chemistry group, and thyroid functions test were within normal limits. Dehydroepiandrosteron sulfate (DHEAS), parathhyroid hormone (PTH), estradiol, progesterone, insulin-like growth factor, follicle stimulating hormone, luteinizing hormone and prolactin levels were also normal. LH/FSH ratio was about 1.1. Our patient, free testosteron/total testosterone levels were 0.30/0.12 ng/ml, androstenedione ng/ml level was 0.20 and DHEAS level was 53 µg/dl. Serum FSH, LH, total testosterone, estradiol, progesterone, and DHEAS levels were measured by the chemiluminescent microparticle immunoassay (paramagnetic particle, chemiluminescent immunoassay) using a Unicel DxI 800 System immune-analyzer (Beckman Coulter Ireland Inc., Ireland) with original reagents. Radioimmunoassay (RIA) with commercial kits was employed to assess serum free testosterone (BioSource, Nivelles, Belgium) and androstenedione levels (Radim, Roma, Italy). Complete blood count including MPV was assessed using Roche SYSMEX device.

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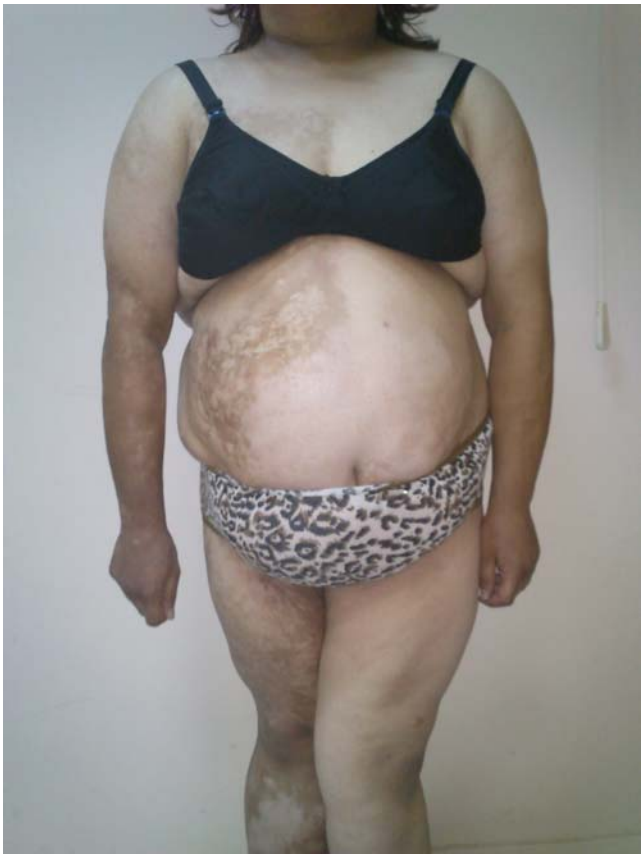

Figure 1: Sclerodermatous skin changes.

The oral glucose tolerance test was consistent with diabetes, as was the fasting blood glucose (139 mg/dl). As the calculated homeostasis model insulin resistance (HOMA-IR), which was 21.6, with a non-gravid adult reference range of <2.0, indicating severe insulin resistance in this patient. Insulin levels ranged from 63 µIU/mL at baseline to 249 µIU/mL at 120 minutes. She has fair diabetes control (HbA_1C 7.8%) and no evidence of nephropathy or retinopathy. ANA (anti-nuclear antibody) test was postive (1/1000 +++). Other laboratory tests included ACA (anti-centromere antibody), Scl-70 and insulin receptor antibodies were negative. A biopsy from the affected areas revealed attenuated epidermis, dermis expanded with fibrous bands, diminution of the adnexal structures. There is perivascular lymphocytic inflammation of dermis. All of the above findings are consistent with the diagnosis of sclerodermal-like skin changes. Mucin stain had been performed on the skin biopsy specimen. The histologic features suggested a "scleroderma-like" disorder. The patient was treated with PUVA (3 times in a week) and topical calsipotriol ointment (twice a day). A recent follow up later after 3 months and again noted to have regression of scleroderma like changes on her abdomen and again there was no hand or joint involvement. No pulmonary, cardiac or gastrointestinal involvement was detected. Our patient did not respond to insuline sensitizer treatments including metformin, rosiglitazone and pioglitazone, also did not respond single anti-androgen treatment. The patient was only treated with flutamide (125 mg orally twice per day), spironolactone (100 mg/d orally) and a combination of ethinyl estradiol and cyproterone acetate (Diane 35, Bayer, Istanbul). She was also advised to follow a reduced calorie intake diet to reduce her body weight, insulin level and the amount of acanthosis nigricans. After 3 months of treatment the patient's hirsutism and acne almost completely resolved. Her menstrual periods became regular.

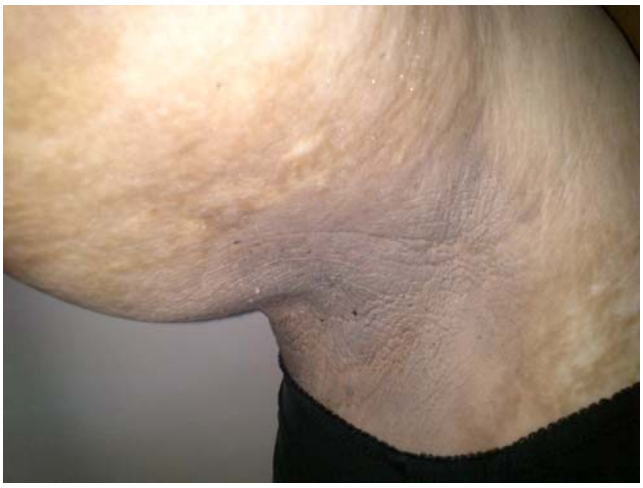

Figure 2: Acanthosis nigricans.

DISCUSSION

Scleroderma is a chronic disease of unknown etiology that affects the microvasculature and loose connective tissue. It is characterized clinically by fibrous deposition and obliteration of vessels in the skin, lungs, gastrointestinal tract, kidneys and heart. Systemic scleroderma is divided into two distinct variant: limited and diffuse [3-5]. Our case is limited type. The primary defect in scleroderma is still unknown. Three pathologies have been identified in scleroderma: endothelial damage, immunologic and inflammatory activation, and dysregulated extracellular matrix production. The basic pathogenic mechanisms are believed to be similar in localised and systemic disease [5].

HAIR-AN syndrome is an acronym for an unusual multisystem disorder in women that consists of hyperandrogenism, insulin resistance and acanthosis nigricans. The precipitating abnormality is thought to be insulin resistance, with a secondary increase in insulin levels and subsequent overproduction of androgens in

the ovaries. Long periods of hyperinsulinism and, some suspect, hyperandrogenism can result in the cutaneous manifestation of acanthosis nigricans, acne, hirsutism, alopecia and soft fibromas. Patients are often concerned about the physical manifestations of this disorder, including virilization and acanthosis nigricans, and may be less aware of systemic problems. Physicians should assess women with these problems for an underlying endocrine abnormality. Although a treatment regimen for the HAIR-AN syndrome has not been established, antiandrogen therapy and weight loss are useful [1, 2]. We used these combinations in our patient.

Syndromes associated with hyperandrojenism and menstrual abnormality, such as Cushing syndrome, and congenital adrenale hyperplasia may be considered in the differential diagnosis of our patient. Major findings of these syndromes were absent in our patient.

The results of previous studies support the hypothesis that nonenzymatic glycosylation may alter the turnover of collagen, thus contributing to the development of a scleroderma-like syndrome with skin, joint, and pulmonary findings in patients with insulin resistance. The scleroderma-like syndrome of diabetes consists of limited joint mobility and digital sclerosis [7, 8]. In our patient has localised linear sclerodermatous changes on the trunk and extremities. Bloise studied a 23-years-old woman with scleroderma and type B insulin resistance. They suggested that the insulin resistance resulted from autoantibodies to the insulin receptor [8]. In our patient, insulin resistance and sclerodermatous changes might result from anti-nuclear antibody and also nonenzymatic glycosylation might alter the turnover of collagen.

Localized scleroderma comprises a spectrum of sclerotic autoimmune diseases primarily affecting the dermis. Various immunsuppressive treatment modalities have been recommended for the management of localized scleroderma. PUVA photochemotherapy is an effective and well-tolerated treatment option for localized scleroderma [9]. Our patient was treated with PUVA and topical calsipotriol ointment.

HAIR-AN syndrome is an unusual multisystem disorders that consist of acne, hirsutism, alopecia, soft fibromas and acanthosis nigricans [1]. Shen *et al.* reported an unusual skin presantation of this syndrome with vitiligo [6]. To our knowledge, HAIR-AN syndrome with scleroderma is an association that has not been reported. Metabolic dysregulation is likely involved in the pathogenesis of scleroderma. We know that metabolic regulation and immune response are highly integrated. It is concluded that patients with HAIR-AN syndrome should be carefully evaluated for the occurrence of sclerodermatous skin changes.

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