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A Case of Generalized Acanthosis Nigricans with Positive Lupus Erythematosus-Related Autoantibodies and Antimicrosomal Antibody: Autoimmune Acanthosis Nigricans?

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Key Words

Acanthosis nigricans · Sjögren's syndrome · Type B insulin resistance · Systemic lupus erythematosus · Chronic thyroiditis · Mucosal papillomatosis · Cyclosporine A

Abstract

Acanthosis nigricans (AN) is a hyperpigmented keratotic skin lesion known to be associated with malignant disease and endocrinopathy. We report a very rare case of generalized AN with Sjögren's syndrome- and systemic lupus erythematosus-like features but without type B insulin resistance. Neither internal malignancy nor other endocrinological disorders, including glucose intolerance, were detected during a 10-year clinical course with benign diffuse papillomatosis extending from the mucosa of the larynx to the esophagogastric junction. The case was complicated with chronic thyroiditis and interstitial pneumonia, which were not treated with any medication. AN skin lesions and mucosal papillomatosis regressed with oral cyclosporine A, accompanied by the lowering of autoantibody titers. This is the first report of generalized AN involving an area from the mucosa of the larynx to the esophagogastric junction accompanied by autoimmune manifestations which responded to systemic immunosuppressive therapy.

Introduction

Acanthosis nigricans (AN) is a disorder characterized by skin hyperpigmentation and thickening, especially in certain regions such as the neck, axillae, and mucosa. AN is well known as a clinical marker of malignancy; however, most cases are related to metabolic or endocrinological diseases such as insulin-resistant diabetes mellitus, hypothyroidism, and obesity [1–5]. In some cases, autoimmune disorders such as systemic lupus erythematosus (SLE) and hypothyroidism complicated with type B insulin resistance were reported to be accompanied by AN [6–12].

Here, we report a first case of generalized AN involving an area from the mucosa of the larynx to the esophagogastric junction, accompanied by autoimmune manifestations but not type B insulin resistance. Our case responded well to systemic immunosuppressive therapy using cyclosporine A (CsA).

Case Report

A 58-year-old Japanese male had noticed a diffuse pigmentation of his face and generalized hypotrichosis 10 years before his first visit to our clinic. He had been diagnosed with AN at the age of 55 years because of mucocutaneous manifestations such as diffuse papillomatosis. No internal malignancy was detected during repeated medical examinations over a 10-year clinical course. He was referred to our outpatient clinic in June 2006. His height was 168.5 cm and his weight 59 kg (body mass index 20.7). He presented with dirty-looking keratosis of the umbilicus, areola, and chest wall, diffuse papillomatosis of the palms and soles in addition to numerous acrochordons of the face, neck, and axilla. Hyperplastic and papillomatous changes of the lips and oral cavity accompanied by impaired taste sensation were also noted (fig. 1a–d). His past medical history showed interstitial pneumonia and chronic thyroiditis. He did not have any familial history of endocrine disorders, including AN. The biopsy specimens taken from skin of the posterior neck and mucosa of the pharynx and larynx revealed slight hyperkeratosis and acanthosis undulating with dermal papillomatosis (fig. 2a, c). Upper endoscopy showed a diffuse papillomatosis extending from the mucosa of the larynx to the esophagogastric junction, where little normal mucosa was left (fig. 2b). No epidermal inclusion bodies were observed and polymerase chain reaction analysis of human papilloma virus DNA in the mucosal region was negative. These findings were compatible with a diagnosis of AN [1, 13–15].

Biochemical and serological examinations yielded the following results: serum immunoglobulin IgG 2,270 mg/dl, antinuclear antibody (ANA) titer 1/1,280 (homogenous pattern), anti-ss/ds DNA antibodies 580/60.8 IU/ml, LE test positive, antimicrosomal antibody titer 1/25,600, and anticardiolipin antibodies 13.0 U/ml. Although anti-SS-A/SS-B antibody and gum and Schirmer's tests showed negative results, lip biopsy and Tc-99m scintigraphy of the salivary gland revealed chronic sialadenitis. Thyroid-stimulating hormone, free thyrotropin3 (F-T3) and F-T4 showed normal levels, and both insulin antibody and insulin receptor antibody were negative. Based on the result of the 75-gram oral glucose tolerance test and HbA1c (6.1%), the patient was classified as borderline diabetes mellitus. HOMA-R, a useful surrogate index of insulin resistance which is calculated by using fasting serum insulin, was in the normal range (normal range <2.5, our case 0.96). For the detection of internal malignancy, we repeatedly performed instrumental and serological examinations. Tumor markers showed a normal range, and a CT scan showed only an interstitial pattern in the bilateral lung. PET scans revealed an uptake of radioisotope from the pharynx to the stomach, but upper endoscopy did not show any carcinomatous changes. Taken together, these findings resulted in a diagnosis of autoimmune AN without type B insulin resistance. Our patient's former treatments included etretinate and vitamin D ointment, with poor clinical response. As we suspected that his AN skin lesions were associated with autoimmune conditions, and as we could confirm that his lesions were not complicated by internal malignancy, administration of oral CsA 150 mg (2.5 mg/kg) was initiated, which gradually resolved the papillomatosis of the lip, keratosis of the umbilicus, papillomatous polyp of the larynx, and generalized hypotrichosis (fig. 3a–d). ANA titers decreased from 1/1,280 to 1/160 and anti-DNA antibody from 60.4 to 24 IU/ml. CsA was discontinued after 8

months because new small nodules in the lung, which could have been malignant, were detected by CT. Later, these lesions were pathologically diagnosed as inflammatory changes. After discontinuation of CsA therapy, the AN skin lesions gradually worsened, followed by the appearance of small nodules in the mesentery, which were pathologically diagnosed as benign.

Discussion

The term AN was originally proposed by Unna, although the first case was described by Pollitzer and Janovsky as early as 1891 [1–3]. Curth classified AN into malignant, benign, and syndromic or pseudo AN [16]. Malignancy-associated AN tends to be extensive and involves mucosal surfaces, mostly in elderly people. The majority of associated malignancies are intra-abdominal adenocarcinomas, most commonly gastric cancer [1, 13, 15]. In our case, the results of repeated examinations over a 10-year clinical course excluded malignancy-associated AN. However, careful examinations for malignancy are needed as the patient may develop malignancy in the future. In 1981, Sturmer et al. [12] reported that some patients with AN who are positive for ANA or show increased immunoglobulin levels might be associated with disordered immunoreactivity not fitting any clinically recognizable syndromes. In our case, SLE and Sjögren's syndrome were strongly suspected from the clinical data; however, he did not meet the criteria of these diseases. CsA was chosen as a treatment of skin and mucosal manifestation in our case. There are no previous reports that describe CsA as a treatment of generalized AN. Based on the speculation that some autoimmune manifestations might have induced the hyperkeratotic and proliferative symptoms, administration of CsA was started. CsA gradually reduced both the papillomatous skin and mucosal lesions of AN in conjunction with a decrease in ANA titers, but reversal occurred, accompanied by a worsening of symptoms, after discontinuation of CsA treatment.

The precise etiology of AN has remained unclear. In general, SLE and related conditions accompanied by AN are, at most, positive for anti-insulin receptor antibodies and often present with severe hyperglycemia and insulin resistance (type B insulin resistance), which might be a cause of AN-associated skin lesions. Insulin-like growth factor 1 receptor (IGFR) is expressed on the surface of human keratinocytes and fibroblasts, while excessive amounts of serum insulin interact with IGFR in peripheral tissues. Binding of insulin to IGFR promotes proliferation of fibroblasts and keratinocytes, which subsequently lead to AN [1]. However, the generalized AN in our case, with Sjögren's syndrome- and SLE-like features, was not associated with type B insulin resistance, and was effectively treated with CsA. We speculate that some unknown autoantibodies other than the insulin-receptor antibody might have similar effects on the generation of AN mucocutaneous lesions. This may be one reason why CsA was effective in treating the AN lesions. In situations where complications of both internal malignancies and diabetes mellitus can be excluded after very careful and intensive examinations, CsA can be expected to be an effective therapy for AN with autoimmune manifestations. Further investigation is needed to determine the pathological aspects that make CsA therapy effective for AN.

Disclosure Statement

No external funding was received for this work. The authors have no conflicts of interest to declare.



Fig. 1. Clinical appearance of the patient at the initial visit in 2006. **a** Diffuse pigmentation of his face and generalized hypotrichosis. **b** Hyperplastic and papillomatous changes of the oral cavity. **c, d** Dirty keratosis of the palms and soles.



Fig. 2. Histological findings. **a, c** Histological features of biopsy specimen from posterior neck (**a**, magnification $\times 40$) and larynx (**c**, magnification $\times 200$). Slight hyperkeratosis and acanthosis were seen undulating with dermal papillomatosis. **b** Upper endoscopy feature. A diffuse papillomatosis extending to the esophagus, where little normal mucosa was left. Carcinomatous changes such as ulcers or nodules were not observed.

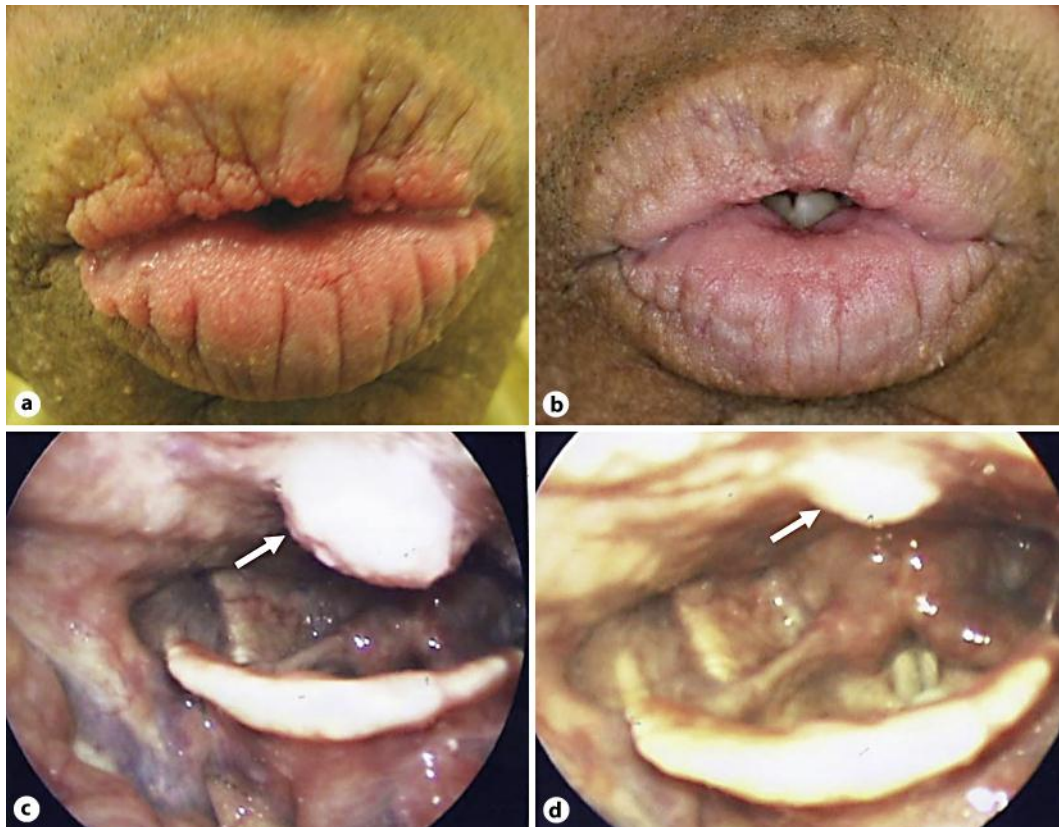


Fig. 3. Papillomatosis of the lip (a, b) and polyp of the larynx (c, d; arrow) before (a, c) and after (b, d) CsA therapy.

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