

Case Report

Epidermodysplasia Verruciformis Associated with Scleroderma

Bilal Bulut¹, MD, Belma Türsen², MD, Prof. Dr. Tamer İrfan Kaya¹, MD, Prof. Dr. Ümit Türsen^{*1}, MD, Rabia Bozdoğan Arpacı³, MD

¹Mersin University, School of Medicine, Department of Dermatology, Mersin, Turkey

²Mersin State Hospital, Department of Dermatology, Mersin, Turkey

³Mersin University, Department of Pathology, Mersin, Turkey

*Corresponding author: Prof. Dr. Ümit Türsen, Mersin University, School of Medicine, Department of Dermatology Mersin, Turkey,

E mail: utursen@mersin.edu.tr

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Abstract

Epidermodysplasia verruciformis (EV) is a rare genodermatosis characterized by flat warts or scaling macules resembling pityriasis versicolor. We describe a 30-year-old man with EV associated with scleroderma. The lesions, persisting for more than 10 years, consisted of widespread planar warts on the backs of the hands and wrists, and reddish-brown macules on the trunk, neck and face. He also presented with sclerodermatous skin changes on the lower extremities last 2 years. There are 2 case reports about autoimmune diseases including vitiligo and autoimmune polyendocrinopathy associated with EV in the literature. Though scleroderma may coexist with other autoimmune diseases, its presentation with EV has not yet been described. It is concluded that patients with EV should be carefully evaluated for the occurrence of sclerodermatous skin changes. The appearance of both diseases in our patient may be a coincidental association but anti-HPV antibodies may also contribute to this co-existence.

Introduction

Epidermodysplasia verruciformis is a rare disease characterized by a unique susceptibility to widespread infection with both common and uncommon human papillomaviruses (HPVs). Onset is usually in childhood, and in many cases an autosomal recessive inheritance pattern has been suggested. Patients have disseminated plane warts that may resemble pityriasis versicolor. Infection with specific HPVs and ultraviolet radiation exposure have been associated with an increased risk of developing squamous cell carcinoma. Abnormal cell-mediated immunity has been demonstrated in many patients with EV, whereas humoral immunity generally remains intact [1-5]. 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 [6-8]. It was reported an unusual skin presentation of EV including vitiligo [5]. Herein, we report a rare skin presentation of EV with concomitant sclerodermatous skin changes in a 30-year-old male adolescent. To our knowledge, this is the first case of this combination.

Case report

A 30-year-old man was referred with persistent, widespread warts and tumoral masses together with brown macules, which had been present for more than 10 years. He had a

negative family history of skin diseases. His parents were nonconsanguineous, and their dermatological examinations were normal. Dermatological examination revealed widespread flat-topped, slightly elevated skin-coloured or reddish papules on the backs of the hands and wrists (Figure 1), and reddish-brown macules similar to those in pityriasis versicolor on the trunk, neck and face (Figure 2). He has painless, indurated, sclerotic, erythematous, desquamative indentations of the skin of both lower extremities (Figure 3). 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. He has no Raynaud's phenomenon. Biopsy of planar warts from the back of the hand and of sclerodermatous skin lesions from the lower extremities respectively confirmed the diagnosis of EV and scleroderma. The samples were fixed in 10% buffered formalin and routine histological examination was performed after paraffin embedding and staining with haematoxylin and eosin. In the first biopsy, affected keratinocytes were swollen and irregularly shaped. They showed abundant, slightly basophilic cytoplasm. The nuclei of the affected keratinocytes appeared large, round and empty. A biopsy from the sclerodermatous areas revealed attenuated epidermis, dermis expanded with fibrous bands, diminish of the adnexial structures. There is perivascular lymphocytic inflammation of dermis. All of the above findings are consistent with the diagnosis of scleroderma-like skin changes. Mucin stained had been performed on the skin biopsy specimen. The histologic features suggest a "scleroderma-like" disorder. Serum levels of immunoglobulins IgG, IgA, IgM and IgE, and complement components C3 and C4 were within normal limits. ANA (anti-nuclear antibody), ACA (anti-centromere antibody), and Scl-70 antibodies were negative. The patient was treated with acitretin (Neotigason®, Roche. Pharm Inc. Germany) at a dose of 0.75 mg/kg/day (50 mg/daily) and topical calcipotriol ointment (Psorcutan® Leo Pharma Inc, Germany) (twice a day) for 3 months. Recent follow up visit after 3 months and again noted to have regressed scleroderma like changes on his extremities and pityriasis versicolor-like skin changes on his chest and still there is no hand and joint involvement. No pulmonary, cardiac and gastrointestinal involvements were detected. We did not detect any arteriovenous insufficiency lower extremities.



Figure 1. Sharply demarcated warty papules on dorsal aspects of both hands.



Figure 2. The anterior aspects of chest exhibit reddish-brown macules.



Figure 3. Sclerodermatous erythematous and scaly skin changes on the anterior aspects of both legs.

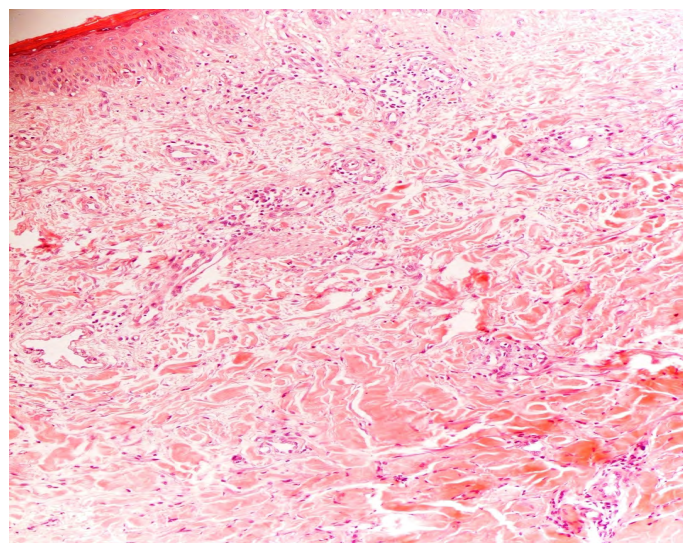


Figure 4. Histological section shows homogenized dermis with acellular fibrosis (arrow) (H-E, x10).

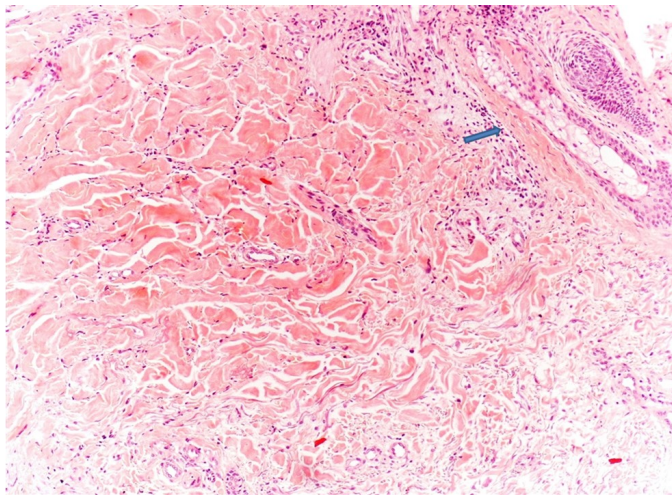


Figure 5. Histological analysis shows diminution of adnexae (arrow) (H-E, x20).

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 variants: limited and diffuse [6-8]. 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 localized and systemic disease [7]. EV is an extremely rare genodermatosis that is associated with widespread and persistent infection by a distinct group of HPV types present in disseminated flat warts and pityriasis versicolor-like lesions. In about half of the patients with EV, the lesions on sun-exposed sites may progress to carcinoma in situ and invasive SCC during the third and fourth decade of life. HPV 5 and HPV 8 are the main oncogenic cutaneous HPV types detected in over 90% of EV-associated SCCs. A lesion of SCC from our patient harbored HPV 15 and HPV 20 DNA, both EV-associated HPV types. HPV 20 has occasionally been reported to be associated with SCC [1-4]. Our case has no SCC or in situ SCC. Besides sex-linked and autosomal dominant inheritance, sporadic cases have also been reported [5]. Our patient may be a sporadic case. In our patient, EV was earlier. It has been shown that patients with the inherited form of EV also exhibit reduced cell-mediated immunity¹. Scleroderma itself, however, also results in reduced cell-mediated immunity secondary to lymphocytopenia and lymphocyte hyporeactivity. Prior reports have noted EV occurring with other diseases such as vitiligo, neurofibromatosis type 1, severe immunodeficiency, lymphoma, disseminated molluscum contagiosum, skin cancers, pulmonary fibrosis associated with autoimmune polyendocrinopathy and isolated IgM deficiency [1-5, 10-12]. There are some other autoimmune ailments like systemic lupus erythematosus accompanied to EV in the literature [13].

This is the first patient, to our knowledge, presenting with EV in association with scleroderma. Although a treatment regimen for the EV has not been established, retinoids and interferon-alpha are useful [4]. We used acitretin treatment in our patient successfully. The lesions slowly regressed within 6 months. We think that the improvement of the sclerodermatous lesions may be due to an immunomodulatory effect of the drug or a decrease in collagen production by dermal fibroblasts due to retinoic acid. Although retinoids do not induce clearing of the EV lesions they may have a role in reducing progression to dysplasia and malignancy as in our case. In our patient, pityriasis versicolor-like skin changes regressed and also we did not observe any carcinoma progression.

Our patient has localized sclerodermatous changes on the lower extremities. Zantour et al reported a case of familial idiopathic pulmonary fibrosis associated with autoimmune polyendocrinopathy and epidermodysplasia verruciformis. This female patient had EV since childhood, with the absence of pubertal development. At the age of 31, she presented diffuse idiopathic pulmonary fibrosis and she has no sclerodermatous skin changes. Endocrine explorations detected hypogonadotropic hypogonadism, primary hypothyroidism and magnetic resonance imaging revealed an empty sella turcica. The authors concluded that the association of familial idiopathic pulmonary fibrosis, autoimmune polyendocrinopathy and genetic dermatosis caused by a cellular immune deficiency supports the hypothesis of an immune dysfunction in the pathogenesis of idiopathic pulmonary fibrosis [9]. Abalians and Talanin also observed EV associated with vitiligo as autoimmune disease [9]. Favre et al found higher anti-HPV antibodies in patients with autoimmune connective tissue disorders and in patients with autoimmune bullous diseases [14]. In our patient, sclerodermatous changes might result from anti-HPV antibodies. To our knowledge, EV with scleroderma is an association that has not been reported. Anti-HPV antibodies are likely involved in the pathogenesis of scleroderma. We know that autoantibody and immune response are highly integrated. It is concluded that patients with EV should be carefully evaluated for the occurrence of sclerodermatous and the other skin changes.

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