CROATIAN MEDICAL JOURNAL

42(1):64-66,2001

CASE REPORT

Sepsis as an Unusual Event in Dyskeratosis Follicularis

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Dyskeratosis follicularis is a genetic disorder characterized by pathogenetic changes of keratinization. We report on a severe case of the disease with an unusual manifestation involving Staphylococcal sepsis. The patient was treated systemically with infusions, oral antibiotics, and retinoids. Antiseptics, keratolytic ointments, and creams were given topically to promote epithelization. His condition improved dramatically after 14 days of treatment. All erosions of the trunk, extremities, neck, and head had epithelized. We suspect that extreme sun exposure and neglect of care on genetically susceptible sites triggered the sepsis.

Key words: *keratolytic agents; keratosis follicularis; retinoids; sepsis; skin diseases, genetic; Staphylococcus aureus; sunburn*

Dyskeratosis follicularis (Darier's disease) is a genetic disorder characterized by the loss of adhesion between epidermal cells (acantholysis) and by abnormal keratinization. Its prevalence has been estimated at 1 in 55,000 (1). The disease was first described by Darier and White in 1889 (2).

Dyskeratosis follicularis is an autosomal dominant disease caused by mutation in the ATP2A2 gene at 12q23-q24.1 (3,4). This gene encodes the sarco/endoplasmic reticulum calcium-pumping ATPase (SERCA2), which is highly expressed in keratinocytes. A variety of missense, nonsense, frameshift, and splicing mutations in ATP2A2 gene have recently been reported in families with dyskeratosis follicularis (5,6). Electron microscopy reveals that the essential abnormality is a defect in the synthesis and organization of the tonofilament-desmosome complex (attachment plaque), as well as perinuclear aggregation of keratin filaments and cytoplasmic vacuolization (3).

Dyskeratosis follicularis clinically manifests as keratotic papules and histologically as dyskeratosis (4). The disease begins very slowly, usually between 8 and 15 years of age, with numerous follicular papules covered with grey-brown crusts erupting on the seborrheic areas, flexural surfaces and sun-exposed areas of the skin (7). Confluent papules enlarge and develop into verrucous or vegetating plaques. Nail changes are also an important sign (8). Systemic manifestations include similar changes in the mucous part of the hypopharynx, larynx, or rectum. Neuropsychiatric features, including mental retardation (in 10% of patients), schizophrenia, bipolar disorder, and epilepsy, have also been reported (9). Some cases demonstrate cystic changes in the bones (2). Basal cell and squamous cell carcinomas (10), renal and testicular agenesis, psoriasis, and multiple *café-au-lait* maculae (1,5,6,11-14) can also be found in patients with dyskeratosis follicularis. Stress, ultraviolet light exposure, heat, sweat, friction, and oral contraceptives may exacerbate the disease symptoms (2). A case complicated by herpes simplex virus has also been reported (15).

Case report

A 28-year-old man from Zagreb, Croatia, was admitted to the Department of Dermatovenerology at the Zagreb University Hospital Center, because of exacerbated dyskeratosis follicularis. That was his second hospitalization due to the disease. Although his skin lesions in the form of keratotic papules first appeared when he was 13 years old, the diagnosis of dyskeratosis follicularis was histologically confirmed not sooner than 1996, on his first admission to the Department. There were no similar changes of the skin in his family members. He was periodically treated with retinoids and regularly with topical keratolytic creams, ointments, and isotretinoin gel as an outpatient at our Department during two years before to his second hospitalization.

On his second visit, he had high fever (41°C) and numerous keratotic papules and erosions of the skin involving the entire trunk and legs. The exacerbation of the disease started five days after an extreme sun exposure that resulted in sunburns (the patient's father stated that the patient fell asleep on a beach). The patient did not use any sun protection creams or after-sun moisturizers. He had numerous follicular keratotic red-brown papules on the classical sites (scalp, retroauricular regions, ears, sternal upper trunk, and axillar and inguinal regions). Some lesions were confluent, with erosions and intertriginous

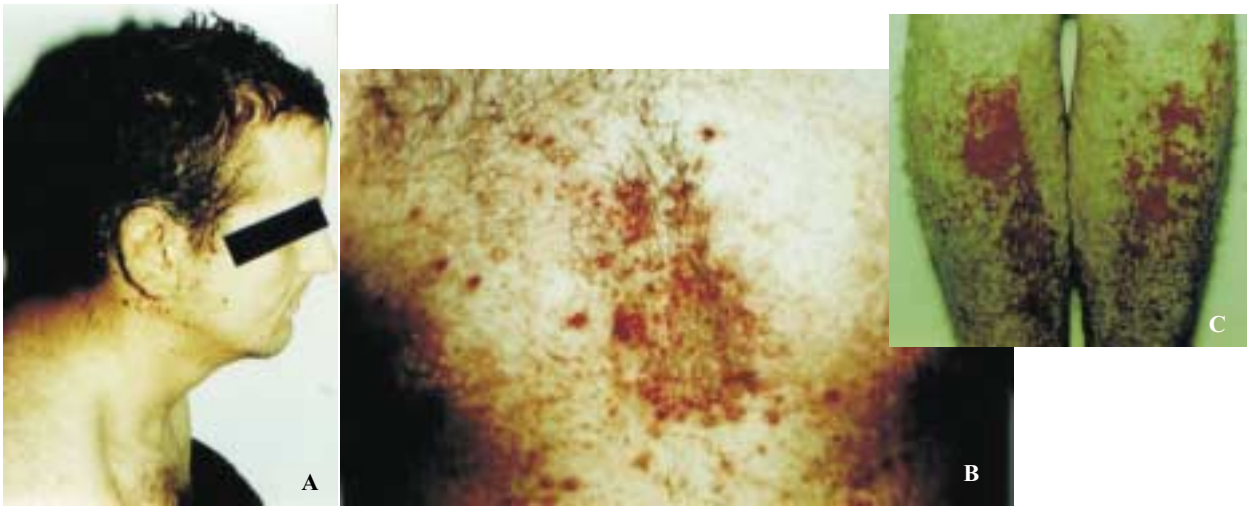

Figure 1. Patient with dyskeratosis follicularis before treatment. **(A)** Crusting papules, simulating seborrhea, on the seborrheic areas of the face, forehead, ears and nasolabial furrows and on the scalp. **(B)** Warty follicular papules widely distributed over the chest, on the seborrheic areas of the trunk. There are skin-colored, greasy, crusted papules of yellow-brown or brown color. **(C)** Punctate keratoses, hemorrhagic macules, papillomatous masses, and vegetating, hypertrophic, and warty masses with pyogenic infections on the lower extremities.

macerations. The toenails were hyperkeratotic and yellowish (Fig. 1).

Staphylococcus aureus was isolated in hemoculture and the culture of skin smears. Sepsis was confirmed by the following laboratory findings: increased erythrocyte sedimentation rate (ESR, 55/74), leucopenia ($2.4x10^9$/L), low total proteins (55.0 g/L), low albumin concentration (23.4 g/L), and proteinuria, albuminuria, microscopic hematuria, and leukocyturia. Urinoculture was also analyzed and 10^3/mL bacterial cells were counted. Herpes simplex, anti-HIV, and purified protein derivative (PPD) tests were negative.

The patient was treated parenterally with saline and glucose infusions, antibiotics (cloxacillin 4x3 g, and aminoglycosides 2x120 mg by intravenous infusion) and systemically with retinoid (acitretin, 40 mg daily administered orally). Nystatin solution (100,000 IU/mL) was given because of the mycosis (*Candida spp.*) confirmed in the throat smear. Antiseptics and keratolytics (ointments, creams) were used for topical treatment to promote epithelization. The recovery, with epithelization of all erosions on the trunk, extremities, neck, and head, followed after 14 days of the treatment (Fig. 2). All keratotic papules were reduced and the patient continued the treatment with oral retinoid in lower doses (the maintenance dose of

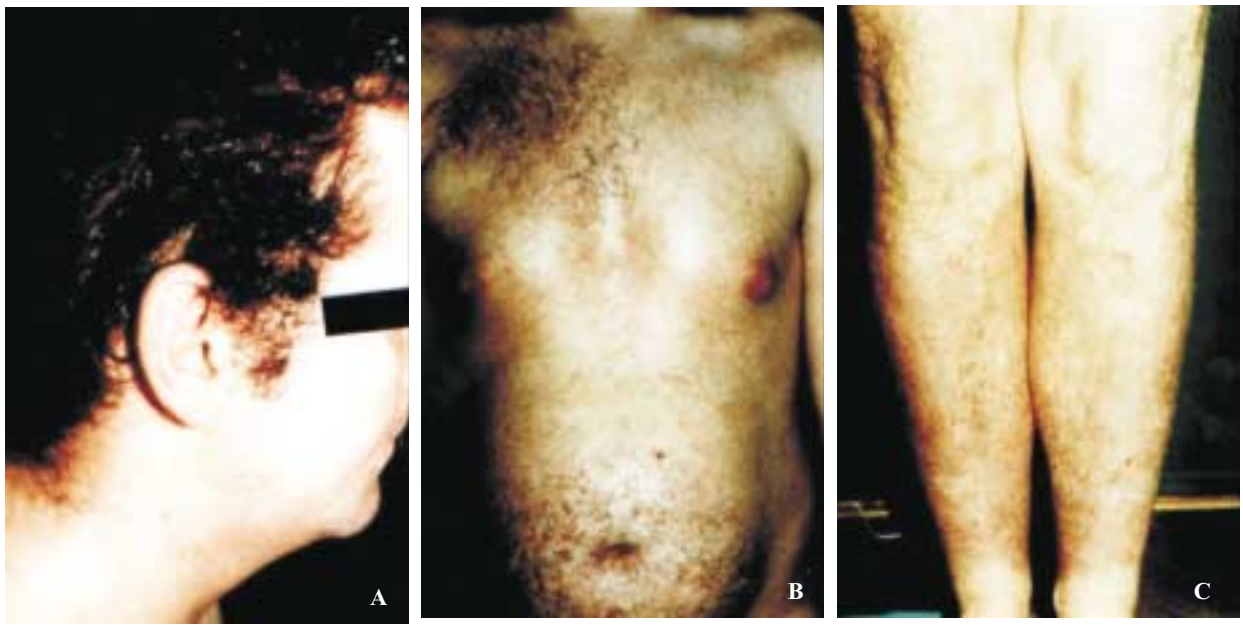

Figure 2. Patient with dyskeratosis follicularis after treatment. **(A)** Very few macules, papules and some residual erythema on the seborrheic areas of the face, forehead, ears, and nasolabial furrows. **(B)** Rare papules on the trunk, with brown or yellow-brown macules. **(C)** Residual macules after the inflammatory reaction of the pyogenic skin changes.

acitretin was 20 mg daily). All laboratory tests were within normal limits at the time of his discharge from the hospital. The patient continued his topical and systemic retinoid maintenance treatment for another year.

Discussion

The case we presented was a severe manifestation of dyskeratosis follicularis with an unusual feature of *Staphylococcal* sepsis, confirmed by blood culture. To the best of our knowledge, sepsis has never been reported in connection to dyskeratosis follicularis. Although the cause of events leading to the sepsis in our patient is still not clear, we suspect that it was triggered by external factors acting upon genetically susceptible background and was most likely due to defective skin barrier. Severe skin damage in our patient was the consequence of sunburns, because he neglected to apply sun protection creams. Skin damage caused by the sun includes changes in skin texture, pigmentation, vascularity, maturation, and production of neoplasms (7). Sun exposure also exacerbates the symptoms of dyskeratosis follicularis but the exact pathophysiological mechanism is not clear (1,5).

One of the possible explanations for the infection progressing to sepsis in our patient could lie in impaired cell-mediated immunity, which may occur in dyskeratosis follicularis patients (15). On the other hand, sepsis may have developed because of a specific genetic profile of our patient. It has been shown by several studies that clinical phenotypes of dyskeratosis follicularis are related to specific genetic mutations (1,3,5). Mutations of the ATP2A2 gene responsible for dyskeratosis follicularis are diverse and probably specific for each patient. The majority of these mutations, however, result in nonsense-mediated RNA decay. The remaining mutations are missense mutations distributed throughout the protein and are significantly associated with atypical clinical features (1,3,5).

These findings suggest that certain mutations may be specifically disruptive to ATP2A2 function, not only in keratinocytes, but also in vascular endothelium cells. Also, the mutant protein could have a secondary effect on the blood vessels.

It would be interesting to search for specific mutations of the ATP2A2 gene in our patient to see whether the development of sepsis was connected with some specific mutation(s).

Acknowledgment

We thank Krka Pharma d.o.o., Zagreb, for the financial support of the reproduction of color photographs in this report.

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Received: June 26, 2000
Accepted: October 20, 2000

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