

# A severe fatal case of Darier-White disease—an extreme phenotype or a new entity?

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## INTRODUCTION

Darier-White disease (DWD) is an autosomal-dominant skin disease characterized by warty keratotic papules and plaques in a primarily seborrheic distribution. Vegetating papules, erosions, or blisters may sometimes be present. Other findings may include varieties of nail abnormalities, “cobblestoning” of the oral mucosa, filiform keratoderma on the palms and soles, and hyperkeratosis verruciformis of Hopf. DWD has an unpredictable clinical course, and patients may present with variable extents of involvement and diverse morphologies at different body areas.<sup>1,2</sup> Neuropsychiatric abnormalities and immunologic aberrations have been reported in association with DWD.<sup>3,4</sup> Clinical subtypes reported to date include hypertrophic,<sup>5</sup> vesicobulbous, hypopigmented, cornifying, zosteriform or linear, and comedonal variants.<sup>6</sup>

DWD has recently been linked to mutations in the SERCA2 gene, which encodes the calcium ATPase pump in the sarcoendoplasmic reticulum. Alterations in calcium signaling cause aberrant keratinocyte differentiation. The result is characteristic dyskeratosis follicularis, demonstrated by the presence of typical dyskeratotic cells, such as, corps ronds and grains.

Treatments may include emollients, topical retinoids, topical steroids, and intermittent courses of oral antibiotics and systemic retinoids.

We present a unique case of DWD showing overlap between several clinical subtypes of the disease with a 20-year course and fatal outcome.

## CASE REPORT

We present a 44-year-old man with a unique severe form of DWD. His medical history was

### Abbreviation used:

DWD: Darier-White disease

otherwise unremarkable, and he had no family member with any remarkable diseases. Symptom onset was during infancy, and the disease was first diagnosed in 1995 when the patient was 27 years old. Data regarding symptoms during infancy were not available, yet according to the patient, mild acne was present in a seborrheic distribution since 6 months of age, with summertime exacerbations. He was treated intermittently with systemic retinoids and from 1995 to 2014 suffered multiple complications including several episodes of sepsis, Kaposi varicelliform eruption, frequent local infection episodes with multiple microorganisms (ie, *Staphylococcus aureus* and *Morganella morganii*), and an atypical *Mycobacterium* cutaneous infection in 2005. All infections were treated successfully with systemic or local antibiotics.

During 2013, the disease reached its peak, manifested by a widespread erythema involving 95% of his body surface area, thousands of hypertrophic warty keratotic papules, and plaques accompanied by multiple cysts and nodules. Numerous giant comedones were observed on his face and trunk. Severe macerations of the skin accompanied by severe fetor were noticed on physical examination in addition to leoninelike facies and diffuse palmo-plantar keratoderma (Figs 1 and 2). Furthermore, extreme cachexia and tachycardia were present (Fig 3). Neuropsychiatric evaluation was normal. An additional skin biopsy obtained from the trunk

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**Fig 1.** Progressive deterioration of 20 years' duration. The patient in 1999, 2005, and 2013.



**Fig 2.** The 2013 DWD episode. Note the filiform keratoderma.

found keratotic plugs, dyskeratosis, corps ronds, grains, and suprabasal clefts (Fig 4); Periodic acid–Schiff staining was negative. Laboratory tests found anemia, leukocytosis, and hypoalbuminemia. Skin cultures were positive for *S aureus*, *M morgani*, and *Streptococcus* group G. Blood cultures were positive for *S aureus*. Fungal infection was excluded by direct smear and cultures, tissue culture, and polymerase chain reaction. HIV serology was negative, and polymerase chain reaction test results for herpes simplex type 1 and 2 and varicella zoster, done in multiple skin lesions, were negative. Blood absorption indexes including blood iron, folic acid, transferrin, and vitamin D were extremely low. Findings on immune function tests, including neutrophil phagocytosis, chemotaxis, and super oxide production, were within normal limits. Flow cytometry test results were unremarkable. The patient refused to undergo any invasive gastrointestinal evaluation, yet computed tomography enterography was normal. Spinal and chest radiographs were

normal, and transthoracic cardiac echo test ruled out endocarditis. Genetic test for the 3-base deletion in exon 2 of leucine (41st residue, N-terminal) reported recently for comedonal DWD was negative.<sup>7</sup>

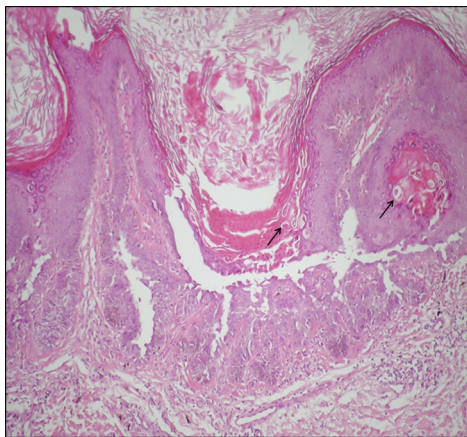
The patient was treated with prolonged intravenous broad-spectrum antibiotics, high-dose oral isotretinoin (Roacutane, Hoffmann-La Roche Ltd, Basel, Switzerland), up to 2 mg/kg at its peak, and topical keratolytic therapy. Although the infections responded well, the cutaneous disease had only partial response to therapy. The patient was discharged from our department. Ten months later, the patient presented to the intensive care unit with severe sepsis accompanied by severe hypoglycemia and widespread erythema and died 2 days after admission.

## DISCUSSION

This case shows several features that establish DWD diagnosis: multiple warty keratotic papules and plaques, obvious seborrheic predilection, and



**Fig 3.** DWD: giant comedons, 2005; cachexia and erythema, 2005; compared with 2013.



**Fig 4.** Skin biopsy photomicrograph shows evidence of keratotic plug, dyskeratosis, and corps ronds (arrows). (H&E stain, original magnification:  $\times 360$ ).

characteristic histopathologic findings such as dyskeratosis, corps ronds, and grains. Nevertheless, this case is unique in its extreme cutaneous manifestations and progressive course. The patient shows the classic complications associated with DWD: multiple local infections, sepsis, and erythroderma. However, no evidence for immunologic or neuropsychiatric aberrations was observed. Clinically, this case exhibits several features that may overlap with the comedonal and hypertrophic variant of DWD, yet genetic analysis for the reported mutation in comedonal DWD was negative. The predominant presence of comedones prompted isotretinoin treatment and, indeed, clinical response while on treatment

during admission was satisfactory, although it was observed to be partial. The progressive fatal deterioration could be explained in this case by either poor adherence, tachyphylaxis to treatment, or malabsorption, as gastrointestinal involvement could not be definitely ruled out.

We present an extremely atypical case of DWD, with overlap between hypertrophic and comedonal subtypes and fatal outcome. Negative genetic findings for the reported mutation in comedonal DWD may suggest the presence of other mutations yet to be discovered.

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