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CASE REPORT

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Undiagnosed Darier's disease comorbid with ambiguous viral infection

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ABSTRACT

Introduction: Darier's disease (DD) is a rare autosomal dominant genodermatosis characterized by hyperkeratotic papules, primarily located on seborrheic areas as well as with palmoplantar, nail or oral mucosa involvement. The course of the disease is chronic with the possible occurrence of coinfection, most commonly with the herpes simplex virus. Each new infection can significantly intensify the symptoms.

Case description: A 42-year-old patient presented with a prolonged history of undiagnosed brownish-grey papules on the limbs and trunk, worsening in the summer was admitted to the dermatology department, to diagnose and treat the one-week history of skin lesions on his arms, chest, and neck, and partially face. Lesions were more intensified on the left side, initially displaying as intense erythema, then covered with multiple papules and grouped vesicles, accompanied by a burning sensation and fever. Laboratory tests showed elevated inflammatory markers. Ultrasonography revealed oedema of the subcutaneous tissue and enlarged cervical lymph nodes on the left side. In the blood culture methicillin-resistant *Staphylococcus Aureus* (MRSA) was detected. Systemic intravenous treatment with antibiotics and acyclovir resulted in slow clinical improvement with normalization in laboratory tests. Histopathological examination in correlation with the clinical data suggested a *Poxviridae* infection along with a typical Darier's disease picture.

Conclusions: Darier's disease, particularly when complicated by cutaneous viral infections, may be misleading, as seen in this case. Eczema herpeticum, eczema vaccinatum, or other pox-zoonoses may explain the severe course observed. The histopathological examination is crucial for accurate diagnosis.

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Keywords: Darier's disease, genodermatosis, viral infection, coinfection, hyperkeratotic papules

CASE DESCRIPTION

The 42-year-old patient with a longstanding history of previously undiagnosed brownish-grey papules and plaques on the limbs and torso, with flares during the summer, presented to the dermatology department due to the exacerbated skin lesions on the arms, chest, neck, and partially on the face, mainly on the left side of the body, persisting for a week. The skin lesions were intense in places particularly exposed to sunlight (Fig. 1). Initially, they appeared as intense erythema, then progressed into numerous vesicles and papules, partially grouped and confluent (Fig. 2), accompanied by a burning sensation and fever. Laboratory test results revealed elevated markers of inflammation: C-reactive protein (CRP) was 67.06 mg/L (norm < 5 mg/L); red blood cells (RBC) was 4.4 × 10^6/µL (norm 4.2–5.4 10^6/µL); white blood cells (WBC) 11.92 × 10^3/µL (norm 4–10 × 10^3/µL); neutrophils (NEU) was 9.13 × 10^3/µL (norm 1.6–7.2 × 10^3/µL). Ultrasonographic examination of the left cheek and neck unveiled subcutaneous tissue swelling without abscess, along with numerous enlarged neck lymph nodes. Blood analysis indicated the presence of methicillin-resistant *Staphylococcus Aureus* (MRSA). The culture from the skin lesion revealed the presence of MRSA and *Pseudomonas putida*. Stool examination did not detect any parasitic presence. Antibodies against HSV-2 were negative, and IgG antibodies against HSV-1 were positive. Histopathological examination of the skin lesion revealed focal necrosis of keratinocytes with abundant, partially purulent inflammatory infiltrate, eosinophil admixture, signs of vascular damage, and erythrocyte extravasation. Within the infiltrate, isolated cells with eosinophilic inclusion bodies in the cytoplasm were present. Focal parakeratosis, dyskeratosis with the presence of occasional round bodies, and mild acantholysis above the basal layer were observed in

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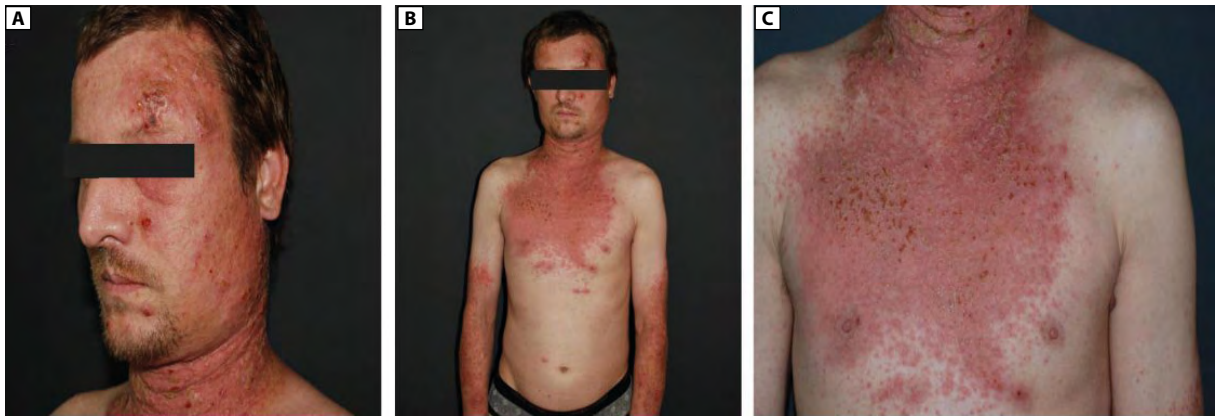

Figure 1A–C. The skin lesions on the day of admission

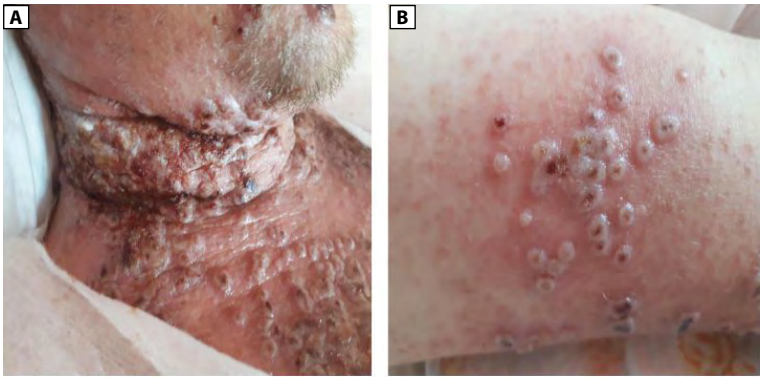

Figure 2A, B. Three days after the admission

the preserved epidermis. This pattern, in correlation with clinical symptoms, suggested Darier's disease with overlapping infection, most likely with a virus from the *Poxviridae* family. Intravenous antibiotic therapy with ceftriaxone (1 g), ciprofloxacin (400 mg twice daily), imipenem with cilastatin (1 g + 1 g three times daily), vancomycin, and intravenous acyclovir treatment (3 times 500 mg) resulted in normalization of laboratory test results and gradual clinical improvement (Fig. 3, 4).

DISCUSSION

Darier's disease, also known as Darier–White disease, follicular keratosis, or follicular dyskeratosis, is a rare genodermatosis inherited in an autosomal dominant manner. It is associated with a mutation in the *ATP2A2* gene, leading to impaired function of the sarcoplasmic/endoplasmic reticulum calcium ATPase 2 (SERCA2) calcium pump in the sarcoplasmic reticulum. This ultimately results in desmosome breakdown and the process of acantholysis. The prevalence in the population ranges from 1:30,000 to 1:100,000, with no gender difference, however, sporadic cases are in 40–50% of cases have been reported [1, 2]. Characteristic is the presence of numerous hyperkeratotic papules, mainly located in seborrheic areas: the head, neck, trunk, and mucous membranes [3]. The skin lesions can range in colour from skin tone to dark brown and typically coalesce to form a confluent larger surface area. They may cause itching and an unpleasant odour associated with the accumulation of dead epidermis. DD is typical during adolescence and tends to be chronic. Symptoms worsen during the summer due to increased exposure to sunlight and heat. Other exacerbating factors may include stress, infections, and friction, thus patients are advised to wear loose, cotton clothing and maintain weight loss [4]. Diagnosis relies primarily on histopathological examination results, where dyskeratosis, premature keratinocyte cornification, and acantholysis can be observed. Changes such as subbasal clefts with dyskeratotic acanthotic cells, grains, and corps may occur in the cornified, granular, and spinous layers and are visualized with haematoxylin and eosin staining [3]. In 2023, an interesting study revealing an alternative to histopathological examination was published. Following the guidelines of the International Dermoscopy Society (IDS), observations were conducted on a patient group, with

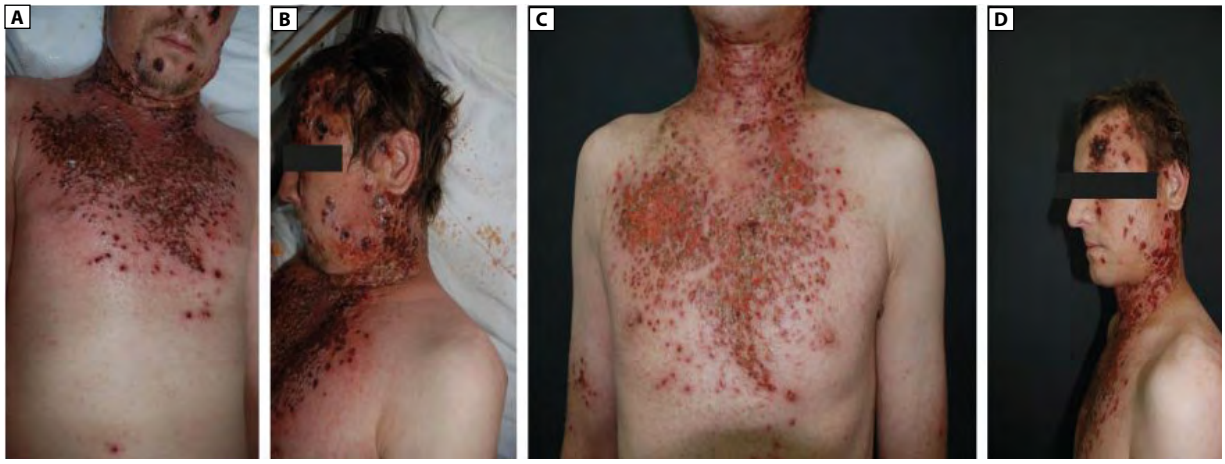

Figure 3A–D. Continuous clinical improvement achieved within the treatment

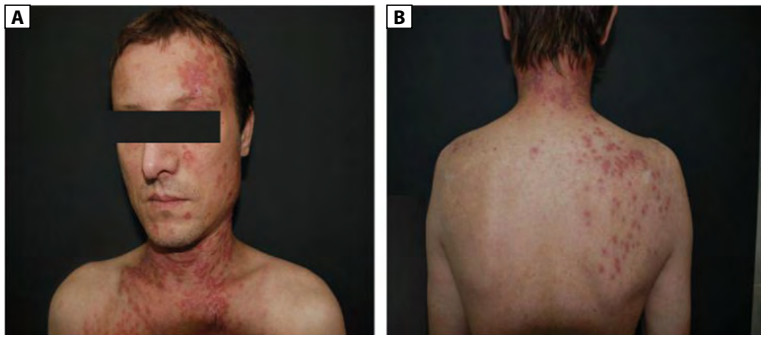

Figure 4A, B. Clinical improvement after 3 weeks, before the discharge

5 individuals with Darier's disease. Dermoscopic examination revealed characteristic features, such as star-shaped or oval yellow areas surrounded by a whitish halo and a pink, homogeneous, structureless background. This resulted in 100% effectiveness in diagnosing DD using dermoscopy, providing hope for future non-invasive diagnostics [5].

Frequently mentioned in the literature as a triggering factor for DD is superinfection with herpes simplex virus (HSV), which induces an increase in interleukin 6 (IL-6) levels in the serum, impacting the exacerbation of DD symptoms by down-regulating the expression of responsible genes [6, 7]. Recently, there has been an increase in reports describing exacerbation of DD during COVID-19. This is due to a cytokine storm characterized by elevated levels of IL-6 and tumor necrosis factor alpha (TNF-α). As a result, besides reducing *ATP2A2* mRNA levels, and decreasing the efficiency of the SERCA2b calcium pump, there is an intensified necroptosis of epidermal keratinocytes, thereby enhancing the processes of acantholysis and apoptosis in the epidermis [6, 7]. To date, two cases of *Poxviridae* infection, specifically *Orthopoxvirus*, during the course of DD have been described [8, 9]. In both cases, it was the cowpox virus transmitted by animals, most commonly by wild cats whose reservoirs are wild rodents [10]. Such superinfections are particularly dangerous for individuals with weakened immunity and patients with extensive skin diseases such as Darier's disease, erythroderma, or atopic dermatitis [8].

In the treatment of DD, retinoids, especially acitretin, have the broadest evidence base. The recommended initial dose is 0.2–0.3 mg/kg body weight (BW), gradually increasing until achieving a therapeutic effect [4]. Publications also suggest the effectiveness of isotretinoin at an initial dose of 0.5 mg/kg BW, prednisolone at the same initial dose, or cyclosporine (3 mg/kg BW per day) [11]. Studies have reported the successful use of 3% sodium diclofenac. It inhibits cyclooxygenase-2, leading to suppression of prostaglandin E2 activity, lowering *ATP2A2* gene levels, and normalizing SERCA2 levels in keratinocytes. Additionally, it is combined with 2.5% hyaluronic acid, improving skin retention and local action [12, 13]. Recent studies report the effectiveness of oral doses of vitamin A and the positive effects of bexarotene [14, 15].

Due to the frequent occurrence of superinfections in the location of DD lesions, accurate diagnosis can be challenging or misleading. Therefore, histopathological examination remains crucial in diagnosis, especially considering that viral infections may contribute to the morbidity and mortality of this condition. To avert disease exacerbation, it is also essential to emphasize preventive measures, including photoprotection. It is important to recognize this manifestation, especially in patients without classic clinical presentation, to implement earlier diagnosis, management, and appropriate counselling to patients and their family members with this genodermatosis.

Article information and declarations

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Author contributions

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Conflict of interest

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Ethics statement

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Supplementary material

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