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Fatal herpes simplex virus infection in Darier disease under corticotherapy

A 67-year-old man is presented with longstanding and severe Darier disease treated by topical antiseptics and potent corticosteroids, in combination with oral glucocorticoids and etretinate. After cardiac bypass surgery in 1997, the patient experienced herpes simplex virus (HSV type-1) infection of the skin that was treated by intravenous aciclovir. In 2003, he presented a widespread atypical exacerbation of his Darier disease, involving the face, trunk, buttocks, intertriginous areas and arms. Initial clinical signs and bacteriological findings suggested a bacterial involvement by multiresistant *Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa*, and *Proteus mirabilis*. Despite antibiotherapy, the clinical presentation progressively worsened. A skin biopsy was performed and immunohistochemical examination identified a type-2 HSV infection. Although intravenous aciclovir was administered, the widespread cutaneous HSV infection was followed by systemic dissemination. A severe acute respiratory distress syndrome (ARDS) developed, leading to a fatal issue. At autopsy, a severe interstitial type-2 HSV pneumonitis with extensive necrotic areas was found, in association with gastro-intestinal involvement. This case represents, to the best of our knowledge, the first case of Darier disease presenting a fatal type-2 HSV infection. It underlines the importance of rapidly recognizing HSV infection in Darier disease and stresses the risk of lethal outcome. The different risk factors for HSV infection in this patient are reviewed.

Key words: acantholytic disease, Darier disease, fatal issue, herpes-induced ARDS, herpes simplex virus

Darier disease is an autosomal dominant disorder with variable penetrance. It is related to mutations in the chromosome 12q23-24 located gene encoding for the endoplasmic reticulum (ER) Ca ATPase ATP2A2. This defect results in impaired intercellular adhesion, causing both dyskeratosic apoptosis and acantholysis [1]. The predominant clinical features consist of small, sometimes profuse, hyperkeratotic papules with a preferential localization on the seborrheic areas of the trunk. Darier disease, either active or in remission, predisposes to some infectious complications, such as herpes simplex virus (HSV) [2-5], varicella-zoster virus (VZV) [6-8], and pox virus infections [9]. The atypical clinical presentations of these viral complications frequently delay their recognition and postpone adequate antiviral treatment [2-5]. Whether this increased susceptibility to cutaneous viral infections is related to impaired cellular and/or humoral immunity in Darier disease or to the disease-associated epidermal alterations remains unsettled [10, 11].

HSV and VZV infections are usually self-limited and self-healing diseases. However, these infections may potentially progress to serious muco-cutaneous and systemic involvement in immunocompetent patients [12, 13]. This condition may prove to be more severe in an immunocompromised background including pregnancy [14, 15], HIV infection [16], and organ transplantation [17]. A fatal outcome is possible [12, 18-20].
To the best of our knowledge, we present the first case of lethal systemic HSV type-2 infection in a patient under corticotherapy for Darier disease. The pathomechanisms leading to the extension of the cutaneous HSV infection and to the systemic dissemination in this patient are reviewed.

Case report

Lifelong, a 67-year-old man had suffered from severe and extensive Darier disease, predominantly involving the back, chest, groin, forearms and arms, face, and intertriginous areas. In addition to the hyperkeratotic papules, he had experienced several episodes of extensive and coalescent crusted plaques and bullous lesions. His medical history also included hypothyroidism and recurrent gastric ulcers. He had been treated by bypass surgery for ischemic cardiopathy. He had no allergy manifestations, and he did not suffer from recurrent oro-labial or genital herpes infections. Over the years, various topical agents, including tretinoin, squamolytic agents and antimicrobial soaps and creams had been used without significant therapeutic responses.

The frequent bacterial colonizations by *Pseudomonas aeruginosa* and *Staphylococcus aureus* had been treated by topical antiseptics, antibiotic creams and oral antibiotics. Due to the disease severity and the therapeutic failures, the patient had been treated since 1978 by retinate (Tigason®, 25-50 mg/d, Roche) and subsequently by etretinate (Neotigason®, 25-50 mg, Roche), supplemented by oral methylprednisolone (Medrol®, 16-32 mg/d).

Rapidly following the cardiac bypass surgery in 1997, the patient developed a circumscribed herpetic infection of his Darier disease on the back. A biopsy revealed a perivascular superficial lympho-monocytic infiltrate with suprabasal acantholysis and dyskeratotic keratinocytes, consistent with Darier disease, but did not reveal any obvious cytological signs of herpes virus infection *(figure 1)*. However, using immunohistochemistry (IHC) [12] with polyclonal anti-HSV type-1 and type-2 antibodies (Dakopatts®, Denmark) a Tzanck smear revealed the presence of type-1 HSV specific antigens *(figure 2)*. VZV antigens were not identified. Intravenous aciclovir (10 mg/kg/8 hours for 7 days) was administered followed by a progressive resolution of the viral infection.

When the patient developed the most recent exacerbation of his skin condition, the daily therapy consisted of dipyridamol 75 mg, L-thyroxin 50 µg, atorvastatine 20 mg, acetylsalicylic acid 100 mg, minocyclin 50 mg, methylprednisolone 32 mg and etretinate 50 mg, as well as topical applications of antiseptics and betamethasone dipropionate. Despite this treatment, the head, neck and trunk were oozing and crusted.

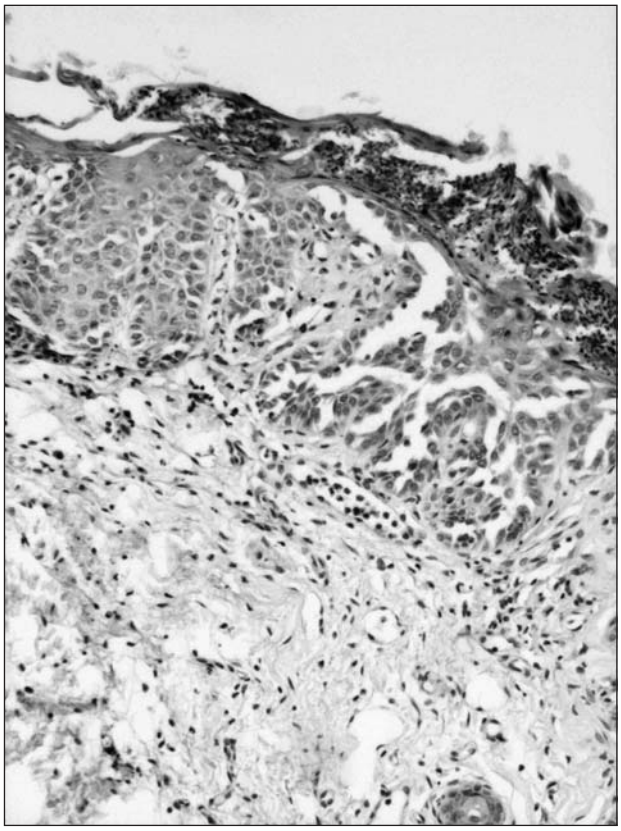

Figure 1. Histology of Darier disease without evidence of HSV infection (H/E 100 ×).

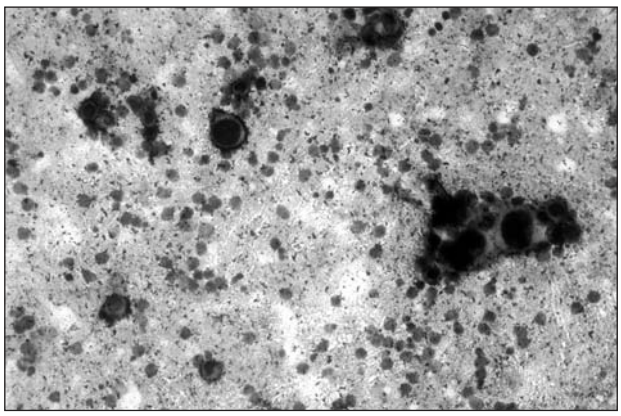

Figure 2. Positive HSV-1 immunostaining on a Tzanck smear (100 ×).

The patient was admitted to the intensive care unit for severe acute respiratory distress syndrome (ARDS), abdominal and dorso-lumbar pains, nausea and vomiting, severe dehydration, and fever. At admission, blood analysis showed corticosteroid-related hyperleukocytosis (24120/mm^3, 87.7% neutrophils), hypercalcemia (2.86 mmol/L), inflammatory syndrome (CRP: 250 mg/L, fibrinogen: 13.12 g/L), increased TSH: 6.99 µUI/L, total CPK: 560 µg/L, CPK/MB: 15.6 µg/L, renal insufficiency (urea: 0.64 g/L, creatinine: 20 mg/L) and hyperglycemia (1.96 g/L). The coagulation parameters were in the normal range. No other biological alterations of the hepatic, pancreatic and cardiac functions were observed. CT scan of the abdomen and pelvis revealed spondylodiscitis of the D12-L1 junction. Thorax X-ray showed a retrocardiac condensation. ECG revealed left a ventricular hypertrophy and tachycardia (113/min). Transthoracic cardiac ultrasound assessment confirmed the presence of a left ventricular hypertrophy, ventricular inferior hypokinesis, without any sign of pericarditis. Numerous and widespread smelly hemorrhagic keratotic papules, and small bullous lesions involved more than 50% of the skin surface, clinically suggested an exacerbation of Darier disease. Furthermore, there were severe neurological alterations caused by dehydration. One week later, after fluid replenishment, the renal function progressively improved and the patient's general condition was stabilized. In an attempt to control the extensive Darier disease, the above-mentioned topical and systemic therapies for his Darier disease were initiated again. The patient was then transferred from the intensive care unit to the rheumatology ward to investigate the D12-L1 spondylodiscitis.

For the next two weeks, numerous painful, smelly, hemorrhaghic, and oozing bullous skin lesions progressively extended, accompanied by increasing fever. Swabs and cultures of several skin lesions revealed the presence of an abnormal biocene composed of multiresistant *Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa*, and *Proteus mirabilis*. Viral cultures revealed no evidence of HSV infection. To eradicate the bacterial load of the Darier disease lesions, intravenous ciprofloxacin 200 mg/mL/d and clindamycin 900 mg/d were administered. In addition, topical applications of fusidic acid (Fucidin® cream) and betamethasone dipropionate (Diprosone® cream) were performed. A 3-day therapy failed to bring any clinical improvement. The skin surface involved was still

expanding over the entire trunk, the genital area, the ears, the lips and the palate. Due to the widespread affected skin surface, the patient was transferred to the burns unit. A skin biopsy was performed revealing a superficial perivascular lymphoid infiltrate with diffuse acantholysis, large keratinocytes and necrotic cells *(figure 3)*. These histological alterations suggested an α-herpesvirus infection of Darier disease. Viral identification by IHC using polyclonal anti-HSV type-1 and type-2 antibodies revealed the presence of type-2 HSV *(figure 4)*. Complementary IHC examinations revealed positivity for the type-2 HSV specific antibody HH2 (Seralab), while the HSV type-1 specific antibody IBD4 (Seralab) remained negative. IHC using the VL8 anti-VZV monoclonal antibody [12] as well as the controls respecting primary antibody omission remained negative. Positive controls consisted of sections from cutaneous HSV infections of other patients. The final diagnosis was a type-2 HSV infection of Darier disease. Intravenous acyclovir (10 mg/kg/8 hours) was administered, beginning on the 5th day of hospitalisation in the burns unit. Serology was consistent with past-HSV infection (IgG+, IgM–), but type-specific HSV identification was not performed. Meanwhile, the pulmonary status of the patient was still worsening with the production of abundant sputum. One day later, oxygen saturation continued to worsen and the patient was placed under assisted ventilation. Thorax radiography revealed bilateral basal condensation with an interstitial syndrome. The next day, severe melena developed, oxygen saturation dramatically fell, and the hemodynamic status deteriorated. Despite intensive medical assistance, ARDS rapidly worsened and the patient passed away a few hours later.

At autopsy, extensive erosions were observed on the trunk and thighs *(figure 5)*. Macroscopic examination revealed a diffusely dense pulmonary parenchyma with numerous white-yellowish abcesses *(figure 6)*. The visceral pleura showed fibrinous deposits. Hypertrophic cardiopathy, vascular atherosclerosis, and myocardal past infarction were evidenced.

Histological examination showed cutaneous erosions covered by a fibrino-leukocytic exsudate. The epidermal architecture was completely disrupted. The bronchioles and alveolar spaces were filled by inflammatory cells, predominantly neutrophils. The pulmonary parenchyma was stud-

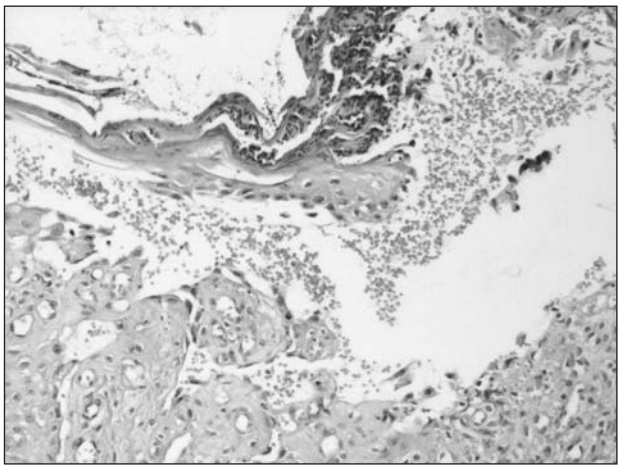

Figure 3. Superficial perivascular lymphoid infiltrate with diffuse acantholysis, large keratinocytes and necrotic cells (H/E).

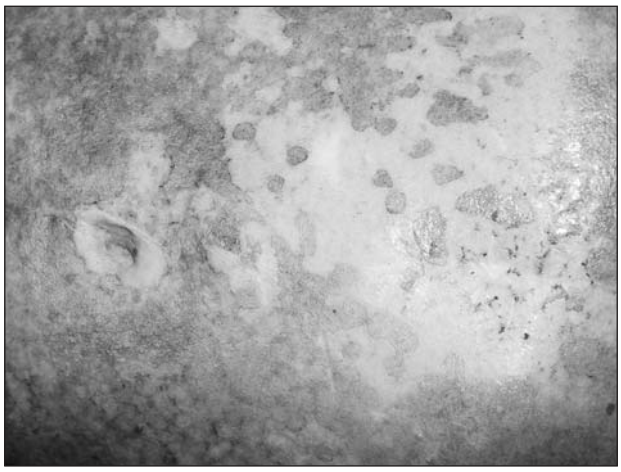

Figure 5. Extensive erosions on the trunk and thighs.

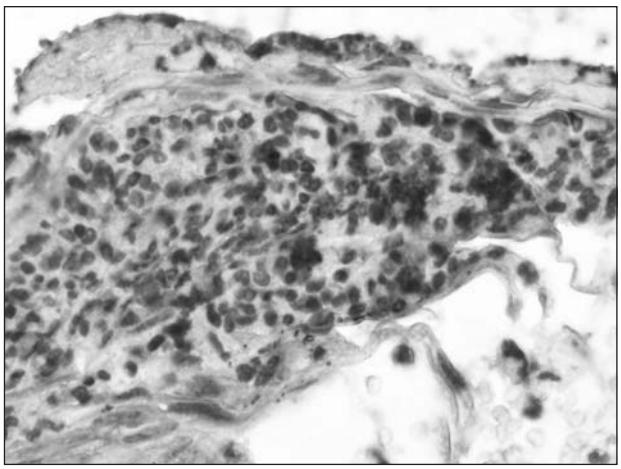

Figure 4. Immunohistochemistry revealed the presence of type-2 HSV in the skin lesions (red signal).

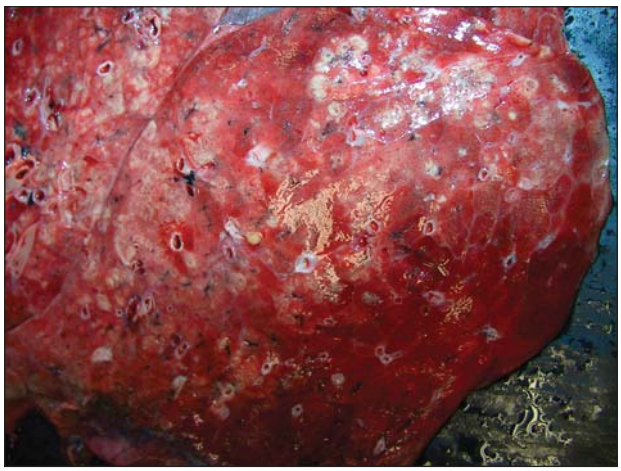

Figure 6. Pulmonary parenchyma with numerous white-yellowish abcesses.

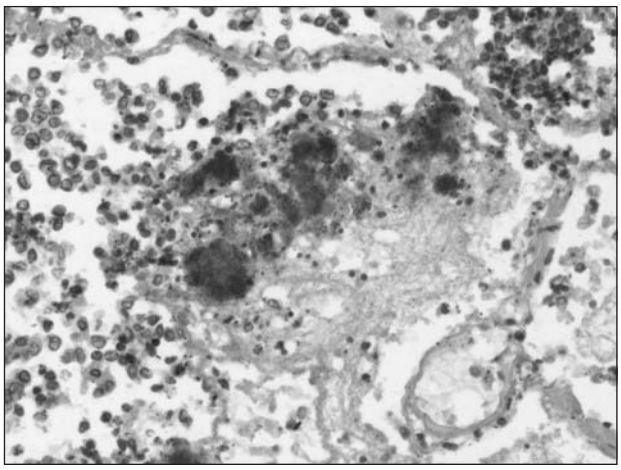

Figure 7. HSV-2 immunostaining in the pulmonary parenchyma.

ded by multiple abscesses. The GI-tract showed congestion of the mucosal layer. A thorough search for HSV type-1, type-2 and VZV antigens was performed by IHC on the autopsy material. Primary antibody omission, and HSV- and VZV- positive control slides were used as negative and positive controls, respectively. Positive type-2 HSV immunostaining was evidenced in keratinocytes showing strong intracellular staining and a more diffuse signal inside the epidermal blisters. Type-2 HSV antigens were evidenced in foci of bronchopneumonia exhibiting a diffuse staining pattern in suppurative areas *(figure 7)*. The mucosal layer of the GI-tract also presented a HSV type 2 immunostaining, in particular in the congested and ulcerated zones. No histological and IHC clues of HSV infection were found in the kidneys, liver, pancreas and spleen.

Discussion

Darier disease, either clinically active or in remission, is prone to HSV skin infections [2-5]. Any unusual disease exacerbations and/or sudden therapeutic failures should prompt to search for a viral complication. The frequently atypical clinical presentations of these viral infections often delay clinical recognition and adequate therapeutic measures [2-5]. This situation occurred in the patient presented here, because the diagnosis of type-2 HSV infection of Darier disease was only reached after histological and IHC examinations. The IHC search for HSV or VZV-specific antigens on Tzanck smears or skin biopsies is currently available for rapid, sensitive and type-specific diagnosis [21]. Diagnosis can also be reached using PCR [22, 23] or viral culture and identification [24]. However, these methods are time-consuming compared to IHC search.

The herpetic infection in 1997 was related to the type-1 HSV, which represents the usual agent of Darier disease-related HSV infection [2-5]. Surprisingly, type-2 HSV antigens were identified in the most recent episode using polyclonal and monoclonal type-2 HSV specific antibodies both in the skin and internal organs. The patient had no history of recurrent genital or oro-labial herpes. Serology was IgG+, IgM– for HSV, but no type-specific serological distinction was performed. Although some patients with widespread herpes infection present recurrent labial HSV infections [2-5], others do not, and it is currently not established whether recurrent oro-labial and genital HSV infections represent a risk factor for developing HSV infection of Darier disease.

The pathomechanisms of the Darier disease-associated susceptibility to herpesvirus infection remain unclear. First, it has been postulated that this event was related to impaired cellular immunity in Darier disease [10, 25]. However, other authors never evidenced any immune impairment associated with this disease [11, 26]. Second, it is unlikely that Darier dyskeratosis is by itself capable of HSV reactivation in the ganglion. It can be postulated that the suprabasal acantholysis provides a favorable environment for HSV disease, by mimicking acantholysis present in cutaneous HSV infection. Third, there may be a deficiency in, or the presence of, non-functional defensins, another non-immune innate host defence line of the skin, displaying antibacterial and antiviral properties [27]. This hypothesis is supported by the variety of different bacterial species colonizing the cutaneous surface of the Darier lesions. Finally, in the present patient, both topical and oral glucocorticoids probably presented an additional risk for HSV cutaneous extension followed by further internal dissemination.

The mechanisms of the skin viral extension and internal dissemination by glucocorticoids are better understood. Experimental evidence showed the reactivation of bovine herpes virus 1 (BHV-1) by means of corticosteroids in an intranasal rabbit model [28]. By contrast, extension of focal HSV encephalitis in a rat model was not increased after administration of systemic glucocorticoids [29]. There is no clinical evidence that HSV is reactivated or induced by the use of topical glucocorticoids. However, inappropriate topical glucocorticoid treatment of HSV skin infection is known to lead to severe expanding infections, often leading to scarring. Through binding to glucocorticoid receptors, the topical corticosteroids may affect about 10-100 genes leading to altered rate of transcription, repressing or inducing mRNA production and protein synthesis. By inhibiting NαB factor, there is a reduction of the inflammatory process including various cytokines, adhesion molecules, inflammatory enzymes and growth factors including TNFα, GM-CSF, IL1, IL2, IL6, IL8, ICAM-1, E-selectin and cyclooxygenase. By inhibiting some of these factors, such as ICAM-1, TNF-α, IL1, IL2, and IL6, the predominant Th1 profile [30-32] of the anti-HSV host defense line is inhibited, allowing extension of the infection. Sudden glucocorticoid withdrawal has also been described as a risk factor for HSV infection [33]. In brief, topical glucocorticoids do not seem to reactivate or induce HSV skin infection. However, once HSV infection is present, they can seriously impair innate as well as adaptive anti-HSV host immune responses, leading to extensive infections.

Although HSV infection of Darier disease is not uncommon, a fatal outcome has, to the best of our knowledge, never been reported. Lethal outcome following extensive cutaneous and internal HSV infection has been documented in an atopic dermatitis patient [19], in burn patients [20] and in 2 cases of pemphigus vulgaris [18]. The cause of death in the present patient was severe ARDS. Type-2 HSV was found in cytolytic areas of the lungs, in keratinocytes of the epidermal blisters and in the congested and ulcerated zones of the GI-tract mucosal layer. The cytopathic effects

associated with the virological findings correlate with the clinical findings of severe ARDS, skin infection and melena. These data confirm earlier findings showing that the HSV disease expression is clearly correlated with histologically recognizable cytopathic effects associated with positive HSV immunostaining [12].

In conclusion, atypical exacerbations and/or sudden therapeutic failure in Darier disease should prompt for a thorough search for herpes viridae infection. Both topical and systemic immunosuppressive therapies of Darier disease represent additional risks. Systemic antiviral therapy should be initiated as soon as possible, limiting the risks of further cutaneous and/ or internal dissemination. ■

References

1. Cooper SM, Burge SM. Darier's disease: epidemiology, pathophysiology, and management. *Am J Clin Dermatol* 2003; 4: 97-105.
2. Hazen PG, Eppes RB. Eczema herpeticum caused by herpesvirus type 2. A case in a patient with Darier disease. *Arch Dermatol* 1977; 113: 1085-6.
3. Toole JW, Hofstader SL, Ramsay CA. Darier's disease and Kaposi's varicelliform eruption. *J Am Acad Dermatol* 1979; 1: 321-4.
4. Hur W, Lee WS, Ahn SK. Acral Darier's disease: report of a case complicated by Kaposi's varicelliform eruption. *J Am Acad Dermatol* 1994; 30: 860-2.
5. Pantazi V, Potouridou I, Katsarou A, Papadogiorgaki TH, Katsambas A. Darier's disease complicated by Kaposi's varicelliform eruption due to herpes simplex virus. *J Eur Acad Dermatol Venereol* 2000; 14: 209-11.
6. Loeffel ED, Meyer JS. Eczema vaccinatum in Darier's disease. *Arch Dermatol* 1970; 102: 451-6.
7. Carney JF, Caroline NL, Nankeivis GA, *et al.* 1973, Eczema vaccinatum and eczema herpeticum in Darier's disease. *Arch Dermatol* 1973; 107: 613-4.
8. Colomb D, Faure M. Frequence des infections virales durant les maladies de Darier et de Hailey-Hailey. *Ann Dermatol Venereol* 1977; 104: 811-5.
9. Claudy AL, Gaudin OG, Granouillet R. Poxvirus infection in Darier's disease. *Clin Exp Dermatol* 1982; 7: 261-5.
10. Jegasothy BV, Humeniuk JM. Darier's disease: a partially immunodeficient state. *J Invest Dermatol* 1981; 76: 129-32.
11. Patrizi A, Ricci G, Neri I, *et al.* Immunological parameters in Darier's disease. *Dermatologica* 1989; 178: 138-40.
12. Nikkels AF, Delvenne P, Sadzot-Delvaux C, Debrus S, Piette J, Rentier B, *et al.* Distribution of varicella zoster virus and herpes simplex virus in disseminated fatal infections. *J Clin Pathol* 1996; 49: 243-8.
13. Sofer S, Pagtakhan RD, Hoogstratten J. Fatal lower respiratory tract infection due to herpes simplex virus in a previously healthy child. *Clin Ped* 1984; 23: 406-9.
14. Peacock Jr. JE, Sarubbi FA. Disseminated Herpes simplex virus infection during pregnancy. *Obstet Gynecol* 1983; 61: 13S-18S.
15. Greenspoon JS, Wilcox JG, McHutchison LB, Rosen DJ. Acyclovir for disseminated herpes simplex virus in pregnancy. A case report. *J Reprod Med* 1994; 39: 311-7.
16. Morgello S, Mahboob R, Yakoushina T, Khan S, Hague K. Autopsy findings in a human immunodeficiency virus-infected population over 2 decades: influences of gender, ethnicity, risk factors, and time. *Arch Pathol Lab Med* 2002; 126: 182-90.
17. De Biase L, Venditti M, Gallo P, Macchiarelli A, Tonelli E, Scibilia G, *et al.* Herpes simplex pneumonia in a heart transplant recipient. *Recenti Prog Med* 1992; 83: 341-3.
18. Zouhair K, el Ouazzani T, Azzouzi S, Sqalli S, Lakhdar H. La surinfection herpétique du pemphigus: 6 cas. *Ann Dermatol Venereol* 1999; 126: 699-702.
19. Sanderson IR, Brueton LA, Savage MO, Harper JI. Eczema herpeticum: a potentially fatal disease. *Br Med J Clin Res* 1987; 294: 693-4.
20. McGill SN, Cartotto RC. Herpes simplex virus infection in a paediatric burn patient: case report and review. *Burns* 2000; 26: 194-9.
21. Nikkels AF, Debrus S, Sadzot-Delvaux C, Piette J, Rentier B, Piérard GE. Immunohistochemical identifiation of varicella zoster virus gene 63-encoded protein (IE63) and late (gE) protein on smears and cutaneous biopsies. *J Med Virol* 1995; 47: 342-7.
22. Schlupen EM, Wollenberg A, Hanel S, Stumpenhausen G, Volkenandt M. Detection of herpes simplex virus in exacerbated pemphigus vulgaris by polymerase chain reaction. *Dermatology* 1996; 192: 312-6.
23. Takahashi I, Kobayashi TK, Suzuki H, Nakamura S, Tezuka F. Coexistence of pemphigus vulgaris and herpes simplex virus infection in oral mucosa diagnosed by cytology, immunohistochemistry, and polymerase chain reaction. *Diagn Cytopathol* 1998; 19: 446-50.
24. Klein Kosann M, Fogelman JP, Stern RL. Kaposi's varicelliform eruption in a patient with Grover's disease. *J Am Acad Dermatol* 2003; 49: 914-5.
25. Marks JG, Thor DE, Lowe RS. Darier's disease: an immunological study. *Arch Dermatol* 1978; 114: 1336-9.
26. Halevy S, Weltfriend S, Pick AI, *et al.* Immunologic studies in Darier's disease. *Int J Dermatol* 1988; 27: 101-5.
27. Yasin B, Pang M, Turner JS, *et al.* Evaluation of the inactivation of infectious herpes simplex virus by host-defense peptides. *Eur J Clin Microbiol Infect Dis* 2000; 19: 187-94.
28. Brown GA, Field HJ. Experimental reactivation of bovine herpesvirus 1 (BHV-1) by means of corticosteroids in an intranasal rabbit model. *Arch Virol* 1990; 112: 81-101.
29. Thompson KA, Blessing WW, Wesselingh SL. Herpes simplex replication and dissemination is not increased by corticosteroid treatment in a rat model of focal Herpes encephalitis. *J Neurovirol* 2000; 6: 25-32.
30. Norval M. Viral infections. In: Bos J, ed. *Skin Immune System*. USA: CRC press Ltd, 1997: 555-70; (2nd Ed.).
31. Memar OM, Arany I, Tyring SK. Skin-associated lymphoid tissue in human immunodeficiency virus 1, human papillomavirus and herpes simplex virus infections. *J Invest Dermatol* 1995; 105: 99S-104S.
32. Nikkels AF, Sadzot-Delvaux C, Piérard GE. Absence of ICAM-1 expression in varicella zoster virus infected keratinocytes during herpes zoster. Another immune evasion strategy? *Am J Dermatopathol* 2004; 26: 27-32.
33. Horiuchi Y. Kaposi's varicelliform eruptions during the course of steroid withdrawal in a senile erythroderma patient: cure of regional erythrodermic lesions following infection. *J Dermatol* 1999; 26: 375-8.