Partial Remission after Continuous Oral Acyclovir in Darier's Disease- Two Sisters in a Family

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Abstract

In addition to bacterial and fungal infection, Darier’s disease may be accompanied by recurrent localized or widespread herpes simplex virus infection. The present paper presents 2 cases with >20-year histories of Darier’s disease in whom specific findings of herpes simplex virus infection were observed by quick Tzanck test with modified preservative Giemsa solution. The test was also performed to follow cytological findings after episodes of herpes simplex virus infection, revealing severe, persistent infection over erosive plaques and in keratotic papules. Continuous therapy with oral acyclovir at 400 mg twice daily was prescribed after a routine 5-day course of acyclovir or valacyclovir. After 3 months of continuous oral acyclovir therapy, itching and pain decreased and normal skin appeared without adverse effects. The quick Tzanck test was thus found to be helpful in detecting the existence of virus-infected cells and monitoring the treatment of Darier’s disease complicated by herpes simplex virus infection.

Introduction

Darier’s disease (DD), also known as Darier-White disease, is a dominantly inherited disease that was described separately by Darier and White in 1889. Since onset at around puberty, the disease continues to progress, fluctuating in severity. Pyogenic, fungal and particularly herpes simplex virus (HSV) infections have been reported to disable patients. The quick Tzanck test enables us to follow the severity of HSV infection. Reappearance of normal skin >20 years after onset was seen during continuous oral acyclovir therapy. Our observations imply the possibility of varying degrees of HSV infection over the erosive and papular lesions in DD. More aggressive treatment with antiviral agents is important not only to achieve better quality of life for patients, but also to decrease and stop virus shedding as a matter of public health.

Abbreviation(s)

1. Darier’s disease (DD)

Case Report

Case 1:
A 33-year-old woman had suffered from itching and follicular keratotic papules along the nasolabial folds, nape of the neck and axillae since she was a teenager. During the 8 years of follow-up in our clinic, oral anti-allergic agents and local steroid ointments were prescribed to relieve severe itching. Valacyclovir was effective for episodic painful vesiculopapules over the plaques after sun exposure. In November 2007, quick Tzanck test from yellowish greasy papules from the nasolabial fold revealed numerous balloon cells and giant cells. In December 2007, neutralizing antibody titer to type 1 HSV was 64 and that to type 2 HSV was 32. The patient had previously been diagnosed with DD based on histopathology using hematoxylin and eosin staining. Findings of the quick Tzanck test, together with serological tests, indicated DD complicated with persistent HSV infection. Continuous therapy with oral acyclovir 400mg twice a day was started in January 2008. A biopsy taken from papules on the left upper chest (Fig. 1) revealed acantholytic cells, suprabasal clefts, corps ronds and grains in the parakeratotic stratum corneum, reconfirming DD (Fig. 2). Quick Tzanck test from vesicles in the same plaques demonstrated that, aside from inflammatory cells infiltrating in the follicular epithelium, two groups of abnormal cells were present. Many balloon cells with large, pale nuclei, scant cytoplasm and thick cell membranes were observed. Some balloon cells had fused to form giant cells. The other type of abnormal cell comprised cells with plump eosinophilic cytoplasm and pyknotic nuclei (Fig. 3). The most evident improvement was a decrease in the itching and pain over several erosive plaques on the scalp that had annoyed the patient for a long time. Greasy and keratotic papules over the face, ears and axillae (Fig. 4) became smaller after expelling pus and greasy plugs through the central pores. Four months later, normal skin appeared and increased (Fig. 5).

Case 2:
A 39-year-old woman (the older sister of Case 1) had been suffering from enlarging red plaques beginning
with itching and burning papules in the nasolabial folds, subclavicular areas, axillae and inframammary regions at the age of 10. After biopsy confirmed DD, long-term administration of local and oral retinoids failed to improve symptoms before the patient visited our clinic in 1997. Despite supportive treatments, she suffered from 3 episodes of painful vesicles over some parts of the diseased skin, which were controlled using a routine 5-day course of either acyclovir or valacyclovir. A biopsy specimen of the papillomatous lesion in the left axilla revealed hyperkeratosis with corsets and suprabasal clefts with acantholytic cells, compatible with DD. No other abnormalities were apparent except an neutralizing antibody titer against type 1 HSV of 32 (February 2008) and an immunoglobulin G level against HSV (enzyme immunoassay) >128 (April 2008). After one 5-day routine course of valacyclovir, quick Tzanck test from the vesicles among crusted papules on the right shoulder revealed numerous balloon cells, together with giant cells. The cytoplasm of these abnormal cells was scant. Some cells displayed eosinophilic inclusion bodies in the pale, large nuclei (Fig. 6). Both histopathological findings (hematoxylin-eosin, quick Tzanck test) and serological studies indicated chronic HSV infection. Continuous therapy with acyclovir at 400 mg twice daily was started in October and monitored by the quick Tzanck test on a weekly basis. The patient achieved relief from the intolerable itching within 8 weeks. Vesicles and pustules dried and desquamated, and papules became smaller. Normal skin appeared in the inframammary area and periphery of lesion areas in the axillae (Fig. 7) as compared with 3 months earlier (Fig. 8).

Discussion

In these cases, recurrence at a primary site and gradual peripheral extension after the onset of disease around puberty rules out the pemphigus group of diseases. Acantholytic cells with various morphology, suprabasal clefts and dyskeratotic cells found in the biopsies of the 2 patients are characteristic histological findings of DD. Genetic studies of DD have localized the autosomal dominant inherited gene to chromosome 12q23-q24.1.1,2 The causative gene in DD has been identified as ATP2A2, which is responsible for calcium transport from the cytosol into the lumen of the endoplasmic reticulum.3 Furthermore, a molecular study has provided evidence that desmosomes are not assembled under low Ca2+ conditions, resulting in defective cell adhesion.4 These latest findings coincide with ultrastructural observations in 19705 and 19776 revealing that the primary fault inducing acantholysis in DD may lie in the formation or maintenance of the intercellular cement layer. It is therefore possible that the persistent HSV infection revealed by the quick Tzanck tests was due to defective cell adhesion that enhanced viral access to keratinocytes. Despite the absence of significant immunological abnormalities, frequent bacterial, fungal and viral infections complicate DD. The chronic, unremitting burden on patients due to these complications was revealed in a clinical review of 163 patients by Burge in 1992.7 The modified preservative Giemsa stain solution used in the quick Tzanck test was devised by Dr. Shino, mixing 2 volumes of Giemsa solution, 1 volume of isopropanol and 1 volume of propylene glycol.8 This mixture can be preserved for half a year. As only 2 min is required to observe the cytology, frequent follow-up of the cytology has become routine in my outpatient clinic. After a regular 5-day course of valacyclovir treatment for HSV infection, quick Tzanck test revealed remnant numbers of infected cells. Reports have described maintenance doses of acyclovir preventing recurrence of herpes-associated erythema multiforme for periods of 10 - 26 months without significant adverse effects,9-11 encouraging us to prolong administration of oral acyclovir. Together with clinical improvement in patients, giant cells and balloon cells with thick cell membranes and large pale nuclei decreased. Conversely, cells with plump eosinophilic cytoplasm and small pyknotic nuclei increased. Immunohistochemical and ultrastructural studies are needed to elucidate the mechanisms causing these changes. These 2 cases demonstrate that DD may be complicated by persistent HSV infection rather than episodic infection as previously described. Furthermore, this persistent infection can be treated using continuous oral acyclovir without adverse effects. Decreased areas of skin lesions may represent decreased shedding of the HSV, which is very important in controlling infectious disease.

References


Illustrations

Illustration 1

Red keratotic papules and yellowish vesicles in brownish plaque over the left upper chest.
Illustration 2

Suprabasal clefts, corps ronds and grains in the parakeratotic stratum corneum (hematoxylin-eosin, original magnification 200).
Illustration 3

Large balloon cells and giant cells. Some cells with plump eosinophilic cytoplasm and pyknotic nuclei are also present (Giemsa stain, original magnification *200).
Illustration 4

Reddish keratotic papules, yellowish greasy papules and some vesicles in the left axilla.
Illustration 5

Papules have decreased in number. Normal skin appeared among flattened plaques in the left axilla about 4 months later.
Illustration 6

Balloon cells with large, pale nuclei. Some cells have fused to form giant cells (Giemsa stain, original magnification ×400).
Illustration 7

Decreased number of papules around the neck. Normal skin has appeared among flattened inframammary plaques and on the periphery of both axillae.
Illustration 8

Reddish papules in plaques over the neck and inframammary areas. Large whitish-gray erosive plaques are seen in both axillae.
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