Herpes Simplex Virus-Associated Dermatitis with Either High or Normal IgE Responded Well to Antiviral Therapy: A Study of 787 Quick-Tzanck-Test-Positive Patients

Peer review status:
No

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Article ID: WMC004846
Article Type: Original Articles
Article URL: http://www.webmedcentral.com/article_view/4846
Subject Categories: DERMATOLOGY
Keywords: herpes simplex virus, quick Tzanck test, erythema multiforme, atopic dermatitis, intrinsic atopic dermatitis
How to cite the article: Hsiao L. Herpes Simplex Virus-Associated Dermatitis with Either High or Normal IgE Responded Well to Antiviral Therapy: A Study of 787 Quick-Tzanck-Test-Positive Patients. WebmedCentral DERMATOLOGY 2015;6(3):WMC004846
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Source(s) of Funding:
None
Competing Interests:
None
Additional Files:
HSVADWMC15
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Abstract

**Background:** The overall age-adjusted seroprevalence of herpes simplex virus (HSV) type 1 is 62.6% and of HSV type 2 is 17%. If a test could diagnose more than HSV immunoglobin G-positive patients, at least these serologically positive patients will benefit from antiviral agents, as do patients with HSV-associated erythema multiforme. Although a high serum immunoglobin E level is an important diagnostic criterion for atopic dermatitis, about 15% of patients have normal serum IgE. Hence, this common and disabling skin disease remains pathophysiologically unclear.

**Methods:** A one-step, two-minute cytologic microscopic Quick Tzanck test (QTT) was used to determine and follow-up mucocutaneous HSV infections. Serum IgE and HSV IgG antibody levels were also evaluated to study the relationship between atopic dermatitis and HSV-associated dermatitis.

**Results:** The QTT showed 787 HSV-positive patients, of whom 578 (73%) were also HSV IgG-positive. HSV antibody levels and mean age were positively correlated. Serum IgE levels were normal in 495 (63%) patients and high in 292 (37%) patients.

**Conclusions:** Patients with normal and high IgE responded well to antiviral agents (valacyclovir and acyclovir) in addition to previous treatment for dermatitis, which suggests that HSV-associated dermatitis may include atopic dermatitis. Moreover, that the QTT diagnosed more than HSV-seropositive patients shows the possibility and importance of a systemic search for HSV-associated lesions in seropositive patients. Early diagnosis and treatment can shorten the clinical course and help attenuate the infection.

**KEY WORDS:** herpes simplex virus, quick Tzanck test, erythema multiforme, atopic dermatitis, intrinsic atopic dermatitis

Abbreviations

1. herpes simplex virus: HSV
2. quick Tzanck test: QTT
3. antibody: Ab
4. herpes simplex virus immunoglobulin G: HSVIgG
5. immunoglobulin E: IgE
6. cell-mediated immunity: CMI
7. enzyme immunoassay: EIA
8. topical corticosteroids: TCS

Introduction

The herpes simplex viruses 1 and 2 (HSV-1 and HSV-2) are among the most common agents that infect humans. People with HSV antibody (Ab) can regularly be shown to harbor a latent virus of either type in an appropriate ganglion, and that the virus may be activated by many dissimilar stimuli, both in vivo\(^1\) and in vitro\(^2\). Erythema multiforme, which appears 1-10 days after recurrent herpes, is the result of cell-mediated immunity (CMI) against viral antigen-positive cells.\(^3,4\) One study\(^5\) reported that children with eczema herpeticum and atopic dermatitis with recurrent HSV infection at multiple skin sites all showed a positive stimulation index to HSV antigens and a high titer of HSV IgG antibody. This study suggests that the immune reaction to HSV may manifest as a type of dermatitis other than erythema multiforme.

A study\(^6\) of 779 women attending a sexually transmitted disease center reported that HSV-2 Ab was the most sensitive way to confirm symptomatic reactivation and to detect asymptomatic genital herpes. The overall age-adjusted seroprevalence of HSV-1 is 62.6%, and that of HSV-2 is 17%.\(^7\) If the serologic test is also useful for detecting HSV mucocutaneous infection in dermatology, many patients will also benefit from the antiviral therapy used for
HSV-associated erythema multiforme. Atopic dermatitis is the most disabling condition among skin diseases, with a lifetime prevalence of 10-20% in children and 1-3% in adults. To study the relationship between atopic dermatitis and patients with cytologically proved HSV infection, the serum levels of IgE and HSV IgG Ab of 787 outpatients were also evaluated.

Materials and Methods

Participants
We retrospectively studied patients that visited our clinic for skin eruptions from 4 January through 28 December 2011. Patients with typical single HSV infections were not included. If the clinical symptoms were considered to be induced by HSV infection, a QTT was done. Patients with a positive QTT were included. The clinical manifestations of the 787 included patients were eczema, vesiculopapular plaque, erythema multiforme, folliculitis, and prurigo.

Quick Tzanck Test
Samples for the QTT were obtained from the vesicles, vesicopapules, pustules, erosions, and scales of the skin lesions. The sample materials, including the epidermal sheet and vesicular content, were removed using a fine tweezers. The sample, spread on a glass slide, was covered with modified Giemsa stain solution (Giemsa stain solution, isopropanol, and propylene glycol in a ratio of 2:1:1) and covered with a cover glass. Excess stain solution was removed with a tissue, and then the sample was observed under a light microscope 2 minutes later.

Examples of positive cytologic findings in QTT
1. Composed mainly of balloon cells, balloon cell nests, and giant cells with scanty inflammatory infiltration.

This 33-year-old woman had many vesiculopapules over her face after one had appeared near her mouth one week previously (Fig. 1a). She had a history of three outbreaks of HSV combined with eczema over her hands. Her HSV enzyme immunoassay (EIA) IgG titer was 65, and her IgE titer was 613 IU/ml. A QTT from a vesicle revealed that cell groups were distributed band-like and were covered by epithelium (Fig. 1b). Under high magnification (X 400), the sizes of the cells varied. All balloon cells had thick cell membranes, swollen nuclei, and nuclear chromatin marginations. They gathered together to form balloon cell nests and giant cells (Fig. 1c).

2. Loss of polarity of the spinous layer; cells with large and irregular nuclei in the overlying epithelium. Scanty balloon cells, balloon cell nests, and giant cells in contrast to severe inflammatory infiltration. Rosette formation.

This 35-year-old patient had irregularly shaped red plaques with erosions and crusts in their centers, and pustules on her back and shoulders for one month (Fig. 1d). A QTT from a pustule surrounded by a rim of erythema revealed that most of the epithelium had been replaced by sheets of cells with large nuclei (Fig. 1e). Balloon cell nests were surrounded by inflammatory infiltration to form rosettes (Fig. 1f). High magnification revealed that the inflammatory infiltration surrounding the balloon cell to form the rosette was composed of many polymorphonuclear leukocytes and some lymphocytes (Fig. 1g).

QTTs of the vesicles, vesicopapules, pustules, erosions, and scales of the skin lesions were evaluated by two dermatologists and diagnosed as positive if the above cytologic findings were found. Serum IgE (normal < 170 IU/ml) and HSV IgG (normal < 2.0) were measured using a fluorescence-enzyme immunoassay and an enzyme immunoassay (EIA), respectively, in the same laboratory.

Treatment of the patients
Anti-allergic agents and topical corticosteroids (TCS) were prescribed to treat the dermatitis. Two antiviral agents, valacyclovir (500 mg) and acyclovir (200 mg), were prescribed based on the result of the QTT.

Results

The QTTs of 787 patients were positive. The clinical manifestations of these cases of HSV-associated dermatitis included eczema, vesiculopapular plaque, folliculitis, erythema multiforme, and prurigo. These patients all complained of itching, and some of itching combined with burning and tingling. Four hundred ninety-five (63%) of the 787 patients had normal levels of serum IgE (< 170 IU/ml) and 292 patients (37%) had abnormal serum IgE (> 170 IU/ml). HSV Ab-positive patients were defined as whose EIA titer of the HSV IgG were over 2.0. Of the patients with normal IgE, 381 (77%) were HSV Ab-positive, as were 197 (67%) of those with abnormal IgE. The overall HSV Ab-positive rate was 73% (Figure 2).

The mean age of the HSV Ab-positive patients was over 50, and that of the HSV Ab-negative patients was under 40 (Table 1a). The mean age of the patients with the same HSV IgG titer (>2.0, 32-64, 64-128, >128) (Table 1b) of the high IgE (> 170 IU/ml) group
was younger than that of the normal IgE (<170 IU/ml) group (Table 1c).

Clinical pictures, cytologic findings, and effect of the antiviral agent

HSV Ab-positive patients with normal serum IgE

This 77-year-old man had itchy erythema on his right inguinal area and a stinging pain on his right scrotum (Fig. 3a). He had been diagnosed with herpes labialis 9 years previously. Because his QTT was positive (Fig. 3b), he was treated with valacyclovir for 5 days, with anti-allergic agents for 8 days, and with low potency TCS. Six days later, there was no more erythema on the inner side of his right inguinal area or right scrotum (Fig. 3c). The patient's pain was also relieved. The EIA titer of his HSVIgG was 65, and serum IgE was 19.5 IU/ml.

This 24-year-old woman was pregnant for 5 months. She had itchy red plaques of various sizes over her trunk, mammary region, and lower abdomen (Fig. 3d). She also had keratosis pilaris with punched-out erosions on her left shin (Fig. 3e). Because the EIA titer of her HSVIgG was 123 and her QTT was positive (Fig. 3f), she was treated with valacyclovir and antihistamine for 5 days and medium potency TCS. This patient had been treated for atopic dermatitis for 10 years until a QTT revealed balloon cells from her palm 2 years ago. She has been treated with valacyclovir three times since. Her serum IgE was 39.4 IU/ml.

HSV Ab-positive patients with abnormal IgE

This 27-year-old man presented with large itchy plaques together with lichenification 2 years ago. He had been treated for atopic dermatitis for 10 years with anti-allergic agents and TCS. Because the QTT from the pustules of a plaque was positive on his first visit, he was given additional medical therapy: 2 tablets of valacyclovir per day for 5 days. Narrow-band ultraviolet B phototherapy was also started. The necessity of the additional valacyclovir treatment (1 tablet a day after dinner) was determined by his once or twice monthly QTT results. Many small papules disseminated between the plaques were seen in the picture taken 6 weeks after his first visit (Fig. 4f). Thirteen weeks after his first visit, the plaques were flatter and not as red, and there were similar eruptions on the dorsum of his hands (Fig. 4g). The size of a large plaque with verrucous nodules above his right ankle (Fig. 4h) decreased as the antiviral therapy continued, and it became flat eleven weeks later (Fig. 4i).

There were no side effects or drug eruptions that led to discontinuing antiviral therapy in any of the 787 patients.

Discussion

The Tzanck test was introduced in 1947.10 Compared with a polymerase chain reaction (PCR), the Tzanck test was confirmed to have a sensitivity of 76.9% and a specificity of 100% in a study of 98 patients (77 patients with recurrent herpes simplex and 21 patients with herpes zoster).11 Its practical use and importance in diagnosing HSV infection, bullous diseases, and epidermal tumors have been recently reconfirmed.15, 16 The advantages of the QTT used in this study are that it is a one-step test, takes only 2 minutes, and involves a microscopic cytological analysis that needs no lengthy procedures such as washing or dipping tissue samples into solutions; thus, nearly all the sample cells, including the epidermis and vesicular cavity of the lesion, are preserved. The ballooned keratinocytes
with margination of nuclei and multinucleated
keratinocytes, which are diagnostic of the early
herpetic infection found in step sections of herpes
incognito,26 are also seen in a positive QTT and are
one criterion for a positive QTT.

Although the QTT does not preserve morphology as
well as does a traditional Giemsa's stain, the QTT makes
it possible to observe nearly all the cells in the
specimen, and it has been used to diagnose typical
and atypical HSV infection in 27 cases28 and in Darier's disease.19 Single, typical HSV infection was
not included in this study. Positive findings from
patients with multiple vesiculopapules reveal many
balloon cells, balloon cell nests, and giant cells.
Scanty inflammatory infiltration indicates active viral
proliferation. On the other hand, the dense
inflammatory infiltration of polymorphonuclear
leukocytes, eosinophils, and lymphocytes accords with
the CMI that targets HSV-infected cells in animal
models.20-22 The QTT enables observation of the in
vivo histopathologic evidence that the immune system
is defending against and reducing the number of
HSV-infected cells through rosette formation-balloon
cells surrounded by inflammatory cells during each
recurrence. The stronger the degree of the CMI in
immunocompetent individuals, the greater the
likelihood that HSV-infected cells will be overwhelmed
by the dense inflammatory infiltration and hinder the
proper diagnosis. Our study includes itchy eczemas,
vesiculopapular plaques, erythema multiforme,
folliculitis, and prurigo, which are the most common
types of dermatitis encountered in skin clinics.
Consequently, these patients may have been treated
as having contact dermatitis, drug eruption, or atopic
dermatitis.

In the group with normal IgE, 381 (77%) patients with
a positive QTT had a positive HSV serologic test; in
the group with high IgE (Abnormal), 197 (67%) had a
positive HSV serologic test. This result is consistent
with the concept that one cannot rule out the
possibility that a patient without HSV IgG Ab does not
have HSV-infected cells.23 The 10- to 15-year higher
mean age of the patients with positive HSV IgG in both
groups may reflect a time delay and individual
differences for seroconversion.23,24

Patient 1 (Fig. 3a) had a history of HS labialis, and
patient 2 (Fig. 3d) had HSV-associated dermatitis on
her hands. Recurrences may be in different and
distant locations because asymptomatic viremia
occurs in primary23,25 and recurrent herpes infections26
in immunocompetent hosts. Detecting HSV in
non-herpetic areas of patients with eczema
herpeticum suggests that they may also be directly
and indirectly spread via the hands and underwear.27
Detecting HSV DNA within the epidermis using PCR in
vivo,28 in cultured keratinocytes,29 and in non-herpetic
areas of patients with eczema herpeticum27 supports
the notion that subclinical HSV infection may spread
during every recurrence. A prospective analysis of
genital specimens by Cone et al,30 which used HSV
cultures and polymerase chain reactions in 100
asymptomatic pregnant women, found that the
frequency of infants exposed to HSV DNA-containing
genital secretions from HSV-seropositive mothers is
about eight times greater than previously reported.
Hence, if a QTT is not done, patients with a recurrent
multiple plaque type of HSV infection may be
diagnosed with and treated for atopic dermatitis, as
patient 2 was. Misdiagnosing HSV-infected pregnant
women may be associated with an increased
frequency of HSV transmission to their infants.

The HSV IgG levels in 11 of 14 patients rose between
the 5th and the 20th days after the patients had been
infected with HSV.31 Our study also showed that HSV
IgG levels were parallel to the mean age.
Consequently, patients more than 50 years old require
special attention for HSV-associated dermatitis.

Atopy is a personal or familial tendency to produce IgE
Ab in response to low doses of allergens, usually
proteins, and to develop typical symptoms such as
asthma, rhinoconjunctivitis, or dermatitis. Because the
allergens are difficult-to-avoid airborne and food
allergens, the treatment for atopic dermatitis is still not
satisfactory.10,32 Patient 3 (Fig. 4a) was treated for
atopic dermatitis for 10 years with anti-allergic agents
and TCS. Antiviral therapy not only cured the itchy
large plaques and lichenification, but also significantly
lowered the IgE level from 17220 IU/ml to 4485 IU/ml
in 33 months. Patient 4 (Fig. 4f) was treated for atopic
dermatitis for 2 years, despite his history of annual
recurrences of herpes simplex labialis for 8 years.
Small papules between the itching plaques over his
left knee provided the clue for the QTT-based
diagnosis of HSV infection. There are many reports
concerning the seroconversion of IgM, IgG, and IgA
following a natural viral infection or immunization with a
virus,20,24,53 yet there is little information about
antivirus IgE Ab. Increased total serum IgE during
acute virus infection,34 during the acute phase of
infectious mononucleosis,35 and in the children of
atopic parents36 was reported around 1980. Ida et al.37
reported a mouse model for the development of IgE
anti-HSV Abs either after immunization with
ultralight-inactivated virus or after natural infection in
1983. That patients with more than five recurrences
per year had IgE serum levels significantly higher than
did patients with few recurrences during the active phase of a single HSV infection was reported in 1986. Moreover, in 2011, patients with atopic dermatitis complicated with eczema herpeticum were reported to have higher IgE than did patients with atopic dermatitis not complicated with eczema herpeticum. Antiviral and antiseptis therapy caused a more dramatic improvement than did anti-inflammatory compounds, which implied that spreading of the HSV worsened atopic dermatitis. Kotani et al. reported in 2012 that the plasma concentrations of LIGHT (homologous to lymphotoxins, exhibits inducible expression, competes with herpes simplex virus glycoprotein D for herpes simplex virus entry mediator (HVEM), and expressed by T lymphocytes) in 29 patients with atopic dermatitis were significantly higher than those in healthy individuals. Its concentrations correlated with IgE and decreased when symptoms improved because of treatment. Several studies have shown that LIGHT-HVEM interaction contribute to CMI toward HSV. HVEM has been proved to be one of the three cell surface receptors responsible for the entry of HSV into cells. All these studies and our data support the notion that patients diagnosed with atopic dermatitis, even those with extremely high serum IgE, such as patient 3, may actually be undergoing an HSV reactivation-induced CMI that manifests as chronic dermatitis.

Four hundred ninety-five (63%) of the 787 QTT-positive patients whose serum IgE levels were normal may correspond to the 15% of patients with atopic dermatitis classified as intrinsic atopic dermatitis due to normal serum IgE. Our study provides a diagnostic method and proposes that the pathophysiology of the patients with normal and high IgE are the same. Treating these patients with antiviral therapy and follow-up using the QTT may change their prognosis, as it has with most of our patients. Because the dermatitis we treated was caused by an immune reaction to HSV infection, early diagnosis and treatment can shorten the clinical course and contribute to decreasing the infection source. Immunosuppressant agents are thus contraindicated, unless the HSV-infected cells is proved to be negative. The number of patients with typical HSV recrudescence is small compared with the overall age-adjusted seroprevalence of HSV type 1 (62.6%) and HSV type 2 (17%) and has been considered due to asymptomatic recurrences. In the present study, the QTT helped to diagnose more than just HSV-seropositive patients. This suggests that a thorough systemic search for atypical HSV-associated lesions is possible and very important. It matters not only to patients, but also for those of us committed to mitigating and controlling this common yet concealed infectious disease. The possible morbidity of HSV infection is greater than 62.6%. The QTT can not only provide an early diagnosis, but it can also allow physicians to follow and monitor the treatment of HSV-associated dermatitis. Consequently, it eventually should be possible to change the prognosis of a large part of the etiologically unknown eczemas such as atopic dermatitis.

References

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Illustrations

Illustration 1

Tables

Table 1a. Correlation between mean age and serum HSVIgG levels.

HSVAb-positive patients were more than 10 years older than HSVAb-negative patients in both the normal (n = 495) and high (n = 292) IgE level groups.

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<th>EIA titer</th>
<th>Men (n)</th>
<th>Mean Age (years)</th>
<th>Women (n)</th>
<th>Mean Age (years)</th>
<th>EIA titer</th>
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(>170 IU/ml).

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Table 1c. Correlation between mean age and titer of HSV IgG in 381 patients with normal IgE

(< 170 IU/ml).

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<tr>
<td>Total</td>
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<td>284</td>
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Illustration 2

Figure 1: Clinical presentation and positive QTT cytologic findings

Fig. 1a. A QTT was done from one of the vesiculopapules on her left cheek (arrow).
Fig 1b: The vesicular content consisted of cell groups distributed band-like and was covered by epithelium (E). (Magnification: x 100.)
Fig. 1c. Balloon cells had thick cell membranes, swollen nuclei, and nuclear chromatin marginations (arrows). They gathered together to form balloon cell nests (circle) and giant cells. (Magnification: x400.)
Fig. 1d. A QTT was done for a pustule surrounded by a rim of erythema (arrow).
Fig. 1e. Normal stratum corneum is whitish (circle). Most of it was replaced by sheets of cells with large and irregular nuclei. (Magnification: ×100.)
**Fig. 1f.** Balloon cell nests (arrows) were surrounded by inflammatory infiltration to form rosettes. (Magnification: x200.)
Fig. 1g. High magnification revealed that the inflammatory infiltration surrounding the balloon cell to form the rosette was composed of many polymorphonuclear leukocytes (circle) and some lymphocytes (arrow). (Magnification: ×400.)
Illustration 3

Figure 2: Distribution regarding to the serum level of IgE and HSV IgG of the 787 QTT positive patients.
Illustration 4

Fig. 3. Clinical presentations and QTT findings of HSV Ab-positive patients with normal serum IgE

Fig 3a: Eczematous type (IgE: 19.5 IU/ml, HSV IgG: 80.6). Irregularly shaped erythema with small vesicles (circle).
Fig. 3b. Balloon degeneration of the follicular epithelium (circle). A giant cell was also observed (arrow). (Magnification: x400.)
Fig. 3c. Six days after treatment, there was no more erythema.
Fig 3d. Multiple plaque type (IgE: 39.4 IU/ml, HSV IgG: 123). Itchy red plaques of various sizes over mammary region and lower abdomen.
Fig. 3c. Keratosis pilaris of the left skin with punch-out erosions (arrows)
Fig. 3f. A QTT done from a red papule on the abdomen revealed loss of polarity and fusion of the balloon cells in the spinous layer (circle). (Magnification: x400.)
Illustration 5

Fig. 4. Clinical presentations and QTT findings of HSV Ab-positive patients with abnormal serum IgE

Fig. 4a. Erythema multiforme type (IgE: 10660 IU/ml, HSV IgG: 87.2). A small erosion in the vermilion border over the upper lip (arrow).
Fig. 4b. Itchy red edematous nodules and plaques of various sizes on his thighs.
Fig. 4c. Two pustules (circle) surrounded by erythema on posterior aspect of his left lower leg. There were also two healed lesions (arrows) on the right side.
Fig. 4d. QTT result of the pustule. Balloon cells with thick cell membranes (arrows) and a giant cell with degenerated nuclei (circle). (Magnification: x400.)
Fig. 4e. Intranuclear inclusion bodies were clearly observed in the nuclei of the balloon cells in a balloon cell nest (circle). X400.
Fig. 4f Prurigo type (IgE: 1272 IU/ml, HS IgG > 128). Large itchy red edematous nodules and plaques with excoriation on his lower extremities with many small papules disseminated between the plaques.
Fig. 4g. Seven weeks later, the plaques were fewer and flatter. There were similar eruptions on the dorsum of his hands.
Fig. 4h. A large plaque with verrucous nodules above his right ankle.
Fig. 4i. Eleven weeks later, the verrucous nodules became flat and the plaque was smaller.