



Clinical characteristics of hypertrophic herpes simplex genitalis and treatment outcomes of imiquimod: a retrospective observational study



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SUMMARY

Objective: Atypical presentations of herpes simplex genitalis are becoming more frequent. The aim of this study was to investigate the atypical clinical manifestations and treatment of this infection.

Methods: The charts of patients with herpes simplex genitalis who attended our clinics between January 2009 and December 2013 were reviewed retrospectively.

Results: Of 294 patients, 147 (50%) were male with a mean (standard deviation, SD) age of 48.3 (16.8) years. An ulcerative lesion was the most common symptom (48.3%), followed by vesicle clusters (36.4%). The mean duration of symptoms at first visit was 6 days. Oral acyclovir was administered to 87.6% of patients. Hypertrophic manifestations were observed in 4.8% (14/294) of patients; 50% (7/294) were male, with a mean age of 44.5 (SD 9) years. All patients with hypertrophic manifestations were infected with HIV. Hypertrophic manifestations had a mean duration of onset of 53.3 days. Acyclovir was prescribed to 11 (78.6%) patients. The mean duration to cure was 40.9 days. Topical imiquimod was given in six resistant cases (42.9%) as adjunctive therapy.

Conclusions: Atypical manifestations of herpes simplex genitalis require careful consideration because their frequency is rising, particularly in patients with HIV infection. Although acyclovir is important in their treatment, imiquimod provides an additional benefit in resistant cases.

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1. Introduction

Herpes simplex genitalis is a sexually transmitted infection (STI), and is one of the most important problematic public health issues worldwide. Globally, the incidence of herpes simplex genitalis is about 23.6 million persons per year, and it has been increasing, especially among patients with HIV infection.¹ Moreover, herpes simplex genitalis is also a marker lesion for new HIV cases and vice versa.^{2,3}

Skin lesions from herpes simplex virus (HSV) infection, particularly those consisting of unusual mucocutaneous wart-like and/or ulcerative types, lasting longer than 1 month, are

among the AIDS-defining illnesses.^{4,5} Many atypical presentations, especially a hypertrophic pattern, most commonly seen in HIV-positive or immunocompromised patients, have been observed increasingly in clinical practice,^{5–7} resulting in difficulties in diagnoses, increased drug resistance, and recurrence. Over the last two decades, several cases of a peculiar clinical appearance – hypertrophic herpes simplex genitalis – have been reported.⁸ However, these clinical manifestations have not been well studied in terms of HIV-infected patients and non-HIV patients. These previous case reports and case series are limited, as they did not compare clinical characteristics between HIV-infected and non-HIV patients.^{5–8}

In Thailand, herpes simplex genitalis is one of the most common STIs.⁹ However, clinical characteristics of herpes simplex genitalis in Thai patients are not well reported, and to our knowledge there has been no published report describing atypical

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HSV manifestations in Thailand.^{5–8} In addition, the unusual clinical presentation increasingly observed in clinical practice has led to the use of novel treatment modalities such as immunomodulatory agents, and in particular, topical imiquimod cream as an adjunctive therapy to the first-line drug, acyclovir, in order to achieve both curative and further preventive outcomes.^{8,10–30} The successful use of topical imiquimod cream for the treatment of atypical, mostly presumed acyclovir-resistant, hypertrophic herpes simplex genitalis often seen in HIV-positive or immunocompromised patients has been reported.^{8,11–20,29,30}

This study aimed to focus on atypical clinical manifestations of herpes simplex genitalis and also to describe demographic data, other clinical presentations, laboratory investigations, treatment, recurrence, and associated complications. To the best of our knowledge, this study is the largest published series of hypertrophic herpes simplex genitalis patients, as well as the largest published series of genital herpes patients receiving imiquimod treatment. Moreover, this study demonstrates the differences in clinical manifestations of herpes simplex genitalis between HIV-infected and non-HIV-infected groups.

2. Methods

2.1. Subjects

This was a retrospective chart review of patients diagnosed with herpes simplex genitalis who attended two sexually transmitted disease clinics, at the Department of Dermatology, Siriraj Hospital and the Bamrasnaradura Infectious Disease Institute, between January 2009 and December 2013. This study was approved by the institutional review boards of the Faculty of Medicine Siriraj Hospital and Bamrasnaradura Infectious Disease Institute and was performed in compliance with the latest version of the Declaration of Helsinki. Because this study involved a retrospective chart review and patients remained anonymous, informed consent was not obtained from the patients included. Diagnoses were based mainly on clinical presentations and physical examination. Laboratory investigations were applied in some atypical cases to support diagnoses. Demographic data, HIV status, clinical manifestations, laboratory investigations, treatment regimens, history of recurrence, and complications were collected. All medical records that fulfilled the diagnostic criteria were collected. Incomplete medical records were excluded. Data were then compared and analyzed between HIV-infected and non-HIV-infected groups.

2.2. Statistical analysis

A Chi-square test was used to compare differences in categorical data and an independent *t*-test was used for continuous variables. A *p*-value of <0.05 was considered statistically significant. The odds ratio (OR) with 95% confidence interval (CI) was also calculated for each relevant variable. All analyses were performed using SPSS for Windows version 18.0 software (SPSS Inc., Chicago, IL, USA).

3. Results

Of 294 patients with herpes simplex genitalis included in this study, diagnosed by clinical presentation and physical examination alone or with additional laboratory investigations, 50% (147/294) were male with a mean (standard deviation, SD) age of 48.3 (16.8) years. The reported sexual risk behaviours were sexual relationship without condom use (66.7%) and multiple sexual partners (47.5%). An ulcerative lesion was the most common presenting symptom (48.3%) and the mean duration of symptoms at first visit was 6 days. Sixty-nine (31.2%) patients presented with a first disease episode and 152 (68.8%) presented with a recurrent episode. Only 33.7% of patients (*n* = 99) underwent a Tzanck smear investigation, of whom 54.5% had a positive result. Of all the patients, 15.6% were also investigated for HSV by direct immunofluorescence antibody testing, with 52.6% yielding a positive result. Two hundred and fifty-eight (87.6%) patients had been treated with oral acyclovir. Complications such as secondary bacterial infection were found in 4.4%, and recurrence in a 5-year follow-up period was 29.3%.

Differences between the groups showed that the HIV-infected group had significantly more male patients. These patients were also younger, had increased hypertrophic-type symptoms, longer durations of symptoms, an increased complication rate, and a higher likelihood of recurrence (*p* < 0.05) (Table 1).

Hypertrophic manifestations were noticed in 14 (4.8%) of the 294 patients, and they were all infected with HIV (Figure 1). Compared with patients infected with typical HSV, patients infected with the hypertrophic type were younger and had a higher incidence of HIV infection, longer duration of symptoms, increased use of imiquimod therapy, and a longer duration to cure (Table 2).

Hypertrophic patients who were non-responsive to acyclovir were treated with imiquimod and this showed promising results. One patient was administered imiquimod for prophylaxis of recurrence.

Table 1
Characteristics of herpes simplex genitalis patients recruited in the study

Characteristics	Total patients (<i>n</i> = 294)	HIV-infected patients (<i>n</i> = 84)	Non-HIV-infected patients (<i>n</i> = 210)	OR (95% CI); <i>p</i> -value
Sex, male	147 (50%)	52 (61.9%)	95 (45.2%)	2.0 (1.2–3.3); 0.010 ^a
Age, years, mean (SD)	48.3 (16.8)	41.9 (9.4)	50.8 (18.4)	<0.001 ^a
Symptoms				
Group of vesicles	107 (36.4%)	12 (14.3%)	95 (45.5%)	66.6 (3.9–1133) ^b
Ulcerative	142 (48.3%)	56 (66.7%)	86 (41.0%)	
Hypertrophic	14 (4.8%)	14 (16.7%)	0 (0.0%)	
Other	31 (10.5%)	2 (2.4%)	29 (13.8%)	
Dysuria	16 (5.4%)	1 (1.2%)	15 (7.1%)	0.046
Inguinal lymph node	4 (1.4%)	3 (3.6%)	1 (0.5%)	-
Duration of symptoms, days, mean (SD)	6 (27.0)	9 (45.9)	5 (9.2)	<0.001 ^a
With complications	13 (4.4%)	7 (8.3%)	6 (2.9%)	4.4 (1.4–13.8) 0.012 ^a
Recurrence	86 (29.3%)	29 (34.5%)	57 (27.2%)	2.6 (1.4–4.9) 0.003 ^a

HIV, human immunodeficiency virus; OR, odds ratio; CI, confidence interval; SD, standard deviation.

^a Statistical significance, *p* ≤ 0.05.

^b *p* < 0.001, hypertrophic vs. group of vesicles.

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