REFRACTORY HYPERTROPHIC HERPES SIMPLEX GENITALIS: A POTENTIAL ROLE FOR PENTOXIFYLLINE AS ADJUNCTIVE TREATMENT AND SUPPRESSIVE THERAPY

Napatra Tovanabutra[1], Mati Chuamanochan[1], Pongsak Mahanupab[2] and Siri Chiewchanvit[1]

[1] Division of Dermatology, Department of Internal Medicine, [2]Department of Pathology, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand

Abstract. Hypertrophic herpes simplex genitalis is a rare disfiguring chronic herpes simplex infection usually seen in patients with human immunodeficiency virus (HIV) infection. These cases are often refractory to oral antiviral treatment leading to the need to use immunomodulating agents. There are no studies of using pentoxifylline, an immunomodulator, as adjunctive treatment for hypertrophic herpes simplex genitalis. In this study, we retrospectively reviewed 9 cases with hypertrophic herpes simplex genitalis in whom oral pentoxifylline was used as adjunctive therapy. Eight of the patients had HIV infection. Each patient had been treated with oral acyclovir for a median of 8 weeks prior to initiation of oral pentoxifylline. Topical imiquimod was also added to the treatment regimen in 6 of these 9 patients. All the patients had significant improvement, the median time to healing was three months. Pentoxifylline was continued as adjunctive suppressive therapy. Five patients were followed up and there were 10 episodes of recurrence, of which 6 episodes occurred after decreasing or discontinuing pentoxifylline. Further studies are needed to determine the role of pentoxifylline for treatment and suppression of herpes simplex virus in patients with hypertrophic herpes simplex genitalis. Further studies are also needed to determine the role of topical imiquimod in this condition.

Keywords: herpes simplex genitalis, refractory disease, hypertrophic type, HIV infection, pentoxifylline

INTRODUCTION

Herpes simplex genitalis is a common sexually transmitted disease. Unusual presentations, such as hypertrophic type, may occur in those with human immunodeficiency virus (HIV) infection or other immunosuppressive disease, (Holmes *et al*, 2007; Mosunjac *et al*, 2009; Leeyaphan *et al*, 2015) causing misdiagnosis and difficulty with treatment. Many cases do not respond well to oral antivirals leading to the use of adjunctive treatments such as immunomodulators. Topical imiquimod cream, oral thalidomide, and other immu-

Correspondence: Dr Siri Chiewchanvit, Division of Dermatology, Department of Internal Medicine, Faculty of Medicine, Chiang Mai University, 110 Intawarorot Road, Sriphum District, Mueang, Chiang Mai 50200, Thailand.
Tel :+66 (0) 53 935482; Fax: +66 (0) 53 935481
Email: drsiri2010@gmail.com

nomodulatory agents have been used to treat hypertrophic herpes simplex genitalis with success (Holmes *et al*, 2007; Cury *et al*, 2010; Sbidian *et al*, 2013; Leeyaphan *et al*, 2015). Pentoxifylline, a methyl xanthine derivative, is an immunomodulator that has been used to treat recurrent aphthous ulcers, Behcet's disease, leprosy reaction, cutaneous leishmaniasis and vasculitis (Çakmak *et al*, 2012). However, there are no published studies of its use in treating hypertrophic herpes simplex genitalis.

In this study we retrospectively evaluated the efficacy of using pentoxifylline as adjunctive therapy in the treatment and suppression of hypertrophic herpes genitalis in HIV infected and other immunocompromised patients.

MATERIALS AND METHODS

We conducted a retrospective review of the charts of patients who met inclusion criteria and presented to the Dermatology Clinic, Division of Dermatology, Department of Internal Medicine, Chiang Mai University, Thailand during January, 2002-January, 2017. Inclusion criteria were: having a diagnosis of hypertrophic herpes simplex genitalis, being aged ≥18 years and having been treated with pentoxifylline. The diagnosis of hypertrophic herpes simplex genitalis was made by clinical examination and confirmed by histopathology. Other data obtained from the chart of each patient included demographic data, duration of disease, history of underlying medical conditions, clinical manifestations, histopathological findings and treatment regimens.

RESULTS

Nine patients were included in this study, 7 women and 2 men, with a median age of 38.7 years (range: 29-55 years). The characteristics of the subjects are summarized in Table 1. Eight subjects had HIV infection and one had adult-onset immunodeficiency (AOID) with interferon (IFN)-γ autoantibodies. Seven of the 8 subjects with HIV were taking highly active antiretroviral therapy (HAART). A CD4 count was available for 6 of the 8 subjects with HIV infection and the CD4 count was ≥500 cells/mm^3 in 4 of the 6 cases. The median duration of the hypertrophic herpes simplex genitalis at the first visit was 12 months (range: 7-60 months). All nine subjects had been treated with oral acyclovir for a median duration of eight weeks (range: 3-36 weeks) without improvement. An ulcerative exophytic mass in the genital area was the most common presentation.

The histopathologic findings in all 9 cases were similar: pseudoepitheliomatous hyperplasia of the epidermis with superficial ulceration; dense dermal and subcutaneous inflammatory cell infiltrates were observed, composed of mostly plasma cells, lymphocytes and few eosinophils (Fig 1). Multinucleated giant cells and cytopathic changes of herpes simplex virus (HSV) infection were observed in 4 of the 9 cases. An atypical lymphocytic infiltrate was seen in one case (Case 5).

Oral acyclovir had been prescribed at dosages of 2,000-4,000 mg/day. Oral pentoxifylline was added to all 9 of the study patients, 800 mg/day in 8 patients and 1,200 mg/day in 1 patient. Six of the 9 patients were also prescribed topical imiquimod three times/week. One case was excluded from the treatment and follow-up period due to having incomplete medical record (Case 1) and one case was excluded because the patient was still undergoing treatment at the time this paper was written (Case 9). Most cases had improvement within two weeks of onset

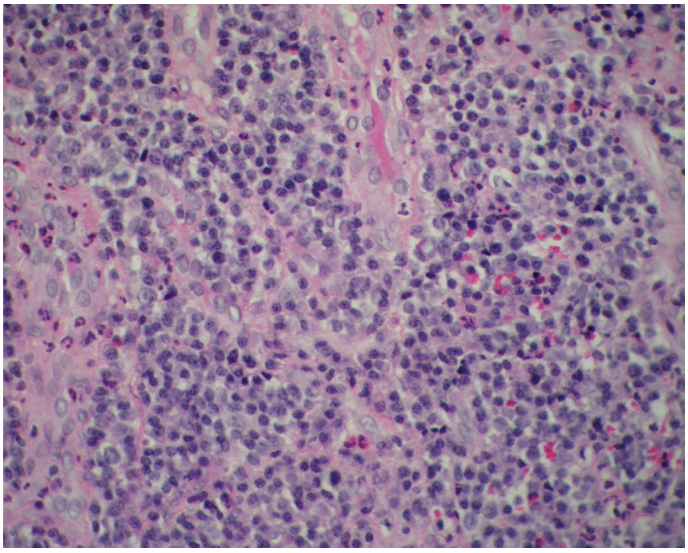

Fig 1 - Dense dermal infiltrates composed of plasma cells and lymphocytes (hematoxylin and eosin stain).

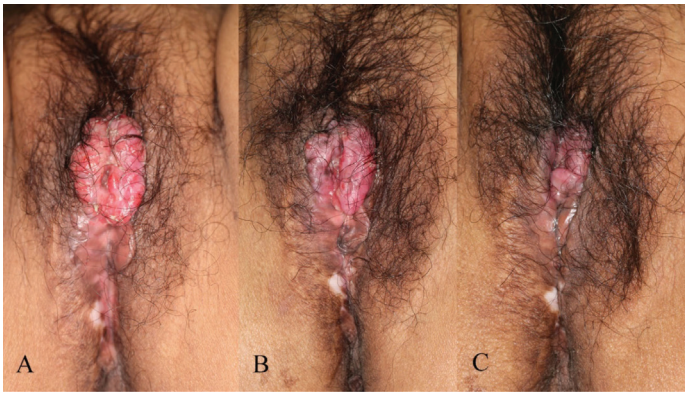

Fig 2 - Ulcerated hyperthophic disease of an HIV-infected woman (Case 9) before treatment (A), after 3 weeks of treatment (B) and after 6 weeks of treatment (C).

of the new regimen and a median healing time of 3 months (range: 1-7 months) (Fig 2). All of the subjects tolerated the pentoxifylline well. After treatment, two patients (cases 7 and 8) did not follow up due to the reasons of inconvenience. For suppressive therapy, acyclovir 800 mg/day and pentoxifylline 800 mg/day were used in 5 patients, of whom 3 patients also used topical imiquimod. The subjects had a median follow-up time of 14 months (range: 2-125 months). Ten recurrences of genital herpes occurred during follow-up among four of those five patients. Four episodes of recurrence occurred after decreasing the dose of pentoxifylline from 800 mg/day to 400 mg/day and two episodes occurred after discontinuing pentoxifylline. Two recurrences occurred after discontinuing acyclovir and one episode developed after discontinuing imiquimod. One episode occurred after discontinuing all suppressive therapy.

DISCUSSION

Hypertrophic herpes simplex genitalis is an uncommon disease mostly presenting with ulcerated or nonulcerated painful exophytic nodules or masses. This atypical presentation is often seen in immunocompromised patients, including HIV infection (Leeyaphan *et al*, 2015). The exact cause of this atypical disease is not fully understood. However, an unusual immune response to HSV secondary to HIV infection may stimulate T-helper 2 immunological pattern and promote epidermal proliferation and fibrosis (Abbo *et al*, 2007). Furthermore, some authors have proposed that hypertrophic lesion is a result of an immune recovery syndrome occurs during HAART (Mosunjac *et al*, 2009).

The hypertrophic disease is often refractory to first-line antiviral agents, including acyclovir, valaciclovir and fam-

ciclovir, leading to treatment failure. The lack of response has been associated with drug-resistance HSV strains that frequently isolated from immunocompromised patients (Ziyaeyan *et al,* 2007). Reduced or absent drug delivery to hypertrophic tissue is the other proposed mechanism (Sbidian *et al,* 2013). Foscarnet and cidofovir have been used as second-line treatment. These agents directly inhibit the pyrophosphate binding site of viral DNA polymerase. Nevertheless, these treatments are expensive and ineffective in some cases (Snoeck *et al*, 1994; Sbidian *et al,* 2013).

Various treatment modalities, including immunomodulators, have been used in refractory cases with variable results. Imiquimod is an imidazoquinoline that stimulates cell-mediated immune response via Toll-like receptor 7. This action leads to the activation of inflammatory cells and production of IFN-γ, tumor necrotic factor (TNF) -α and IL-12, resulting in the resolution of viral lesions (Perkins *et al,* 2011). Several reports revealed the efficacy of topical imiquimod for the treatment of hypertrophic herpes genitalis in HIV patients (Perkins *et al,* 2011; Leeyaphan *et al,* 2015). Thalidomide is another immunomodulating agent which is known to suppress proinflammatory cytokines, and it also has antiangiogenic properties (D'Amato *et al,* 1994; Wu *et al,* 2005). Following the successful treatment of recurrent aphthous ulceration and genital ulcer in HIV-infected patients (Paterson *et al,* 1995; Verberkmoes *et al,* 1996), thalidomide have been used to treat hypertrophic herpes genitalis in HIV-infected patients with impressive results (Holmes *et al,* 2007; Sbidian *et al,* 2013). Sbidian *et al,* (2013) proposed that the efficacy of thalidomide in hypertrophic herpes genitalis resembles the efficacy in B-cell lymphoplasmacytic disorders. However, teratogenicity and peripheral neuropathy are serious side effects that may limit the usage of this agent.

Pentoxifylline is a methyl xanthine derivative with a wide variety of cellular and molecular effects include immune modulation, anti-TNF-α, hemorheological effects, and anti-fibrinolysis (Hassan *et al,* 2014). We used pentoxifylline to treat hypertrophic herpes genitalis due to it has similar immunomodulatory effect to thalidomide. Our patients showed dramatic regression of lesions after starting pentoxifylline with a median healing time of 3 months. Compared to the case series of Leeyaphan *et al* (2015) using imiquimod to treat hypertrophic herpes genitalis in 6 patients, a median healing time was 1.5 months which less than our study. However, other case reports revealed a various healing time ranging from 3 weeks to 4 months (Perkins *et al,* 2011; Strehl *et al,* 2012). The difference of healing time in each case might depend on severity of the diseases, host immune response, drug compliance, and treatment regimen.

Another concern of herpes genitalis is recurrence which is associated with major medical and psychosocial morbidities. Furthermore, recurrent disease tends to be more severe, prolonged and frequent in patients with HIV infection (Severson and Tyring, 1999). Suppressive therapy with oral antiviral agents has been recommended, especially in patient who has frequent and/or severe relapse. Acyclovir, valaciclovir and famciclovir are safe and effective in decreasing recurrent episodes among HIV-infected individuals (Romanowski *et al,* 2000; Conant *et al,* 2002; DeJesus *et al,* 2003). However, these treatments are not effective in some cases and prolonged use of antiviral agent may lead to drug resistance. Im-

Table 1
Demographics and disease data regarding study subjects.

Case	1	2	3	4	5	6	7	8	9
Gender	Female	Female	Female	Female	Female	Female	Male	Male	Female
Age in years	29	34	32	31	49	41	30	47	55
Underlying disease	HIV (HAART)	HIV	HIV (HAART)	HIV (HAART)	AOID	HIV (HAART)	HIV (HAART)	HIV (HAART)	HIV (HAART)
$CD4^+$, cells/mm^3	950	-	500	510	N/A	-	317	260	700
Duration of disease in months	7	12	8	24	2	36	12	12	60
Site	Vulva	Labia majora	Vagina, labia minora and majora, perianal area	Vulva	Mons pubis	Labia minora, vagina	Prepuce, glans penis	Glans penis	Labia majora
Duration of previous acyclovir treatment in weeks	8	8	28	3	12	4	36	10	8
Treatment regimen	ACV, PTX, IMI	ACV, PTX	ACV, PTX, IMI	ACV, PTX, IMI	ACV, PTX, IMI	ACV, PTX, IMI	ACV, PTX, IMI	ACV, PTX	ACV, PTX
Treatment duration in months	Uncertain[a]	3	7	6	1	5	3	2	3
Suppressive therapy regimen	ACV, PTX	ACV, PTX, IMI	ACV, PTX, IMI	ACV, PTX	ACV, PTX	ACV, PTX, IMI	N/A	N/A	N/A
Duration of follow-up in months/ number of recurrences	Uncertain[a]	125/4	12/1	2/No	54/2	14/3	-	-	During treatment

HIV, human immunodeficiency virus; HAART, highly active antiretroviral therapy; AOID, adult-onset immunodeficiency; ACV, acyclovir; PTX, pentoxifylline; IMI, imiquimod; N/A, not applicable.
[a]incomplete medical record.

munotherapy is an alternative treatment mechanism based on increasing immune response to HSV which can decrease the frequency and duration of recurrences. Topical imiquimod has been studied in guinea pigs with recurrent herpes genitalis and revealed that a three-week application can significantly decrease the number of recurrences during and after treatment compared to a placebo (Harrison *et al,* 1994). Although experimental study in humans failed to demonstrate that efficacy (Schacker *et al,* 2002). For our study, the patients received a combination of suppressive therapy, oral acyclovir, oral pentoxifylline and topical imiquimod, with various dosage and duration. In all ten recurrences, two episodes occurred after discontinuing pentoxifylline and four episodes occurred after decreasing the dose of pentoxifylline while these patients were taking oral acyclovir. This finding supports the role of pentoxifylline for suppressive therapy in recurrent herpes simplex infection.

Hypertrophic herpes simplex genitalis is an unusual presentation of HSV infection that is often seen in immunocompromised patients, especially HIV infected individuals. This atypical disease is often refractory to acyclovir. Many studies demonstrated the efficacy of thalidomide and imiquimod for the treatment of stubborn disease. To our knowledge, this is the first study that shows the benefit of pentoxifylline as an adjunctive therapy to acyclovir for the treatment of refractory hypertrophic herpes genitalis. This medication also has a role in suppressive therapy. Prospective studies on large numbers of patient are required to confirm these findings.

ACKNOWLEDGEMENTS

The authors wish to thank Dr M Kevin O Carroll, Professor Emeritus of the University of Mississippi School of Dentistry, USA and Faculty Consultant at Chiang Mai University, Faculty of Dentistry, Thailand, for his assistance in preparation of the manuscript.

REFERENCES

Abbo L, Vincek V, Dickinson G, Shrestha N, Doblecki S, Haslett PA. Selective defect in plasmacyoid dendritic cell function in a patient with AIDS-associated atypical genital herpes simplex vegetans treated with imiquimod. *Clin Infect Dis* 2007; 44: 25-7.

Çakmak SK, Çakmak A, Gönül M, Kiliç A, Gül Ü. Pentoxifylline use in dermatology. *Inflamm Allergy Drug Targets* 2012; 11: 422-32.

Conant MA, Schacker TW, Murphy RL, Gold J, Crutchfield LT, Crooks RJ. Valaciclovir versus aciclovir for herpes simplex virus infection in HIV-infected individuals: two randomized trials. *Int J STD AIDS* 2002; 13: 12-21.

Cury K, Valin N, Gozlan J, *et al.* Bipolar hypertrophic herpes: an unusual presentation of acyclovir-resistant herpes simplex type 2 in a HIV-infected patient. *Sex Transm Dis* 2010; 37: 126-8.

D'Amato RJ, Loughnan MS, Flynn E, Folkman J. Thalidomide is an inhibitor of angiogenesis. *Proc Natl Acad Sci USA* 1994; 91: 4082-5.

DeJesus E, Wald A, Warren T, *et al.* Valacyclovir for the suppression of recurrent genital herpes in human immunodeficiency virus-infected subjects. *J Infect Dis* 2003; 188: 1009-16.

Harrison CJ, Miller RL, Bernstein DI. Post-therapy suppression of genital herpes simplex virus (HSV) recurrences and enhancement of HSV-specific T-cell memory by imiquimod in guinea pigs. *Antimicrob*

Agents Chemother 1994; 38: 2059-64.

Hassan I, Dorjay K, Anwar P. Pentoxifylline and its applications in dermatology. *Indian Dermatol Online J* 2014; 5: 510-6.

Holmes A, McMenamin M, Mulcahy F, Bergin C. Thalidomide therapy for the treatment of hypertrophic herpes simplex virus-related genitalis in HIV-infected individuals. *Clin Infect Dis* 2007; 44: e96-9.

Leeyaphan C, Surawan T M, Chirachanakul P, *et al.* Clinical characteristics of hypertrophic herpes simplex genitalis and treatment outcomes of imiquimod: a retrospective observational study. *Int J Infect Dis* 2015; 33: 165-70.

Mosunjac M, Park J, Wang W, *et al.* Genital and perianal herpes simplex simulating neoplasia in patients with AIDS. *AIDS Patient Care STDS* 2009; 23: 153-8.

Paterson DL, Georghiou PR, Allworth AM, Kemp RJ. Thalidomide as treatment of refractory aphthous ulceration related to human immunodeficiency virus infection. *Clin Infect Dis* 1995; 20: 250-4.

Perkins N, Nisbet M, Thomas M. Topical imiquimod treatment of aciclovir-resistant herpes simplex disease: case series and literature review. *Sex Transm Infect* 2011; 87: 292-5.

Romanowski B, Aoki FY, Martel AY, Lavender EA, Parsons JE, Saltzman RL. Efficacy and safety of famciclovir for treating mucocutaneous herpes simplex infection in HIV-infected individuals. Collaborative Famciclovir HIV Study Group. *AIDS* 2000; 14: 1211-7.

Sbidian E, Battistella M, Legoff J, *et al.* Recalcitrant pseudotumoral anogenital herpes simplex virus type 2 in HIV-infected patients: evidence for predominant B-lymphoplasmocytic infiltration and immunomodulators as effective therapeutic strategy. *Clin Infect Dis* 2013; 57: 1648-55.

Schacker TW, Conant M, Thoming C, Stanczak T, Wang Z, Smith M. Imiquimod 5-percent cream does not alter the natural history of recurrent herpes genitalis: a phase II, randomized, double-blind, placebo-controlled study. *Antimicrob Agents Chemother* 2002; 46: 3243-8.

Severson JL, Tyring SK. Relation between herpes simplex viruses and human immunodeficiency virus infections. *Arch Dermatol* 1999; 135: 1393-7.

Snoeck R, Andrei G, Gerard M, *et al.* Successful treatment of progressive mucocutaneous infection due to acyclovir- and foscarnet-resistant herpes simplex virus with (S)-1-(3-hydroxy-2-phosphonylmethoxypropyl) cytosine (HPMPC). *Clin Infect Dis* 1994; 18: 570-8.

Strehl JD, Mehlhorn G, Koch MC, *et al.* HIV-associated hypertrophic herpes simplex genitalis with concomitant early invasive squamous cell carcinoma mimicking advanced genital cancer: case report and literature review. *Int J Gynecol Pathol* 2012; 31: 286-93.

Verberkmoes A, Boer K, Wertheim PM, Bronkhorst CM, Lange JM. Thalidomide for genital ulcer in HIV-positive woman. *Lancet* 1996; 347: 974.

Wu J J, Huang DB, Pang KR, Hsu S, Tyring SK. Thalidomide: dermatological indications, mechanisms of action and side-effects. *Br J Dermatol* 2005; 153: 254-73.

Ziyaeyan M, Alborzi A, Japoni A, *et al.* Frequency of acyclovir-resistant herpes simplex viruses isolated from the general immunocompetent population and patients with acquired immunodeficiency syndrome. *Int J Dermatol* 2007; 46: 1263-6.