Relevance of Herpes Simplex Virus Infection to Oral Lichen Planus

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Abstract Background: Oral lichen planus (OLP) is a chronic inflammatory disease involving the oral mucosa that induces pain and burning sensations, thus decreasing a patient’s quality of life. Although its etiology has not yet been clearly defined, infection has been suggested to be associated with OLP. We tried to clarify the relevance of herpes simplex virus (HSV) infection in OLP, since HSV infection is the most common infection in the oral mucosa of adults with characteristics of recurrence due to psychological and physical stress. Methods: We enrolled thirty subjects diagnosed with OLP by clinical manifestation and pathologic findings. We tested serum IgG levels against HSV-1 and 2, and performed PCR testing of biopsy specimens for HSV. Additionally, we assessed the treatment effect of an oral anti-viral agent for OLP. Results: Serum HSV-1, 2 IgG levels were markedly elevated in the OLP subjects. HSV DNA was not found in the PCR biopsy specimens. Eight out of thirteen subjects (61.5%) who took oral acyclovir improved in subjective symptoms and objective lesion manifestations. OLP patients treated with conventional treatments showed improvement in 58.8%. Conclusions: Although we did not observe decisive findings, such as a positive HSV-PCR result, to establish a link between HSV and OLP, we did observe an increase in HSV IgG levels and a therapeutic response to oral acyclovir in subjects with OLP.

Keywords Oral Lichen Planus, Herpes Simplex Virus, Acyclovir

1. Background

Lichen planus, first reported by Erasmus Wilson in 1869, is a mucocutaneous disease that involves skin, oral, and genital mucosa, hair follicles of the scalp, and finger nails. Among these, oral lichen planus (OLP) is a chronic inflammatory disease of unknown cause that occurs in the oral mucous. It is a relatively common disease in oral mucosa that appears in approximately 1-2% of the population. OLP affects mostly adults in their 40s and 50s, and occurs twice as often in females. While lichen planus of hairless skin is generally cured spontaneously, OLP is chronic, has a tendency to recur, is mostly not cured spontaneously, and has a possibility of malignant transformation. Various clinical symptoms can arise with OLP: Pain is the most common, and a burning sensation, itching, and irritation may also occur. OLP also precludes patients from consuming hot or spicy food, therefore, further degrading their quality of life.

The precise cause of OLP has not yet been elucidated, but an immune reaction of cytotoxic T cells in keratinocytes is thought to be a main cause. There are various factors that affect such an immune reaction, including allergens, drugs, and viruses. Other hypotheses regarding its pathogenesis include consistent irritation due to dentures or amalgams, drug response, infection, an autoimmune condition, and genetic polymorphism. One prominent hypothesis states that oral infection is involved in initiating OLP. Herpes simplex virus (HSV) infection is the most common infectious disease in the oral mucosa of adults, and frequently recurs due to psychological or physical stress. We performed this research to find out whether HSV infection is relevant to the occurrence of OLP, and if antiviral treatment could be used as an alternative treatment option for OLP.

2. Methods

2.1. Subjects

This study was conducted with 30 adult OLP patients over 30 years of age who visited the Department of Dermatology, Wonju Severance Christian Hospital over a seven-year period (2005 to 2011). The subjects were diagnosed with OLP through characteristic clinical features and histopathological findings. Serum IgG antibodies to HSV-1 and HSV-2 were tested. And the subjects who did not show response to conventional treatment such as topical steroid, intralosomal steroid injection, topical calcineurin inhibitor were treated with oral acyclovir. Control group were treated with conventional treatments (Fig. 1).
2.2. History Taking and Physical Examinations

We obtained information on the subjects’ subjective and objective symptoms, disease duration, medical history, and treatment history by reviewing medical records, and added the clinical manifestations of OLP using photographs.

2.3. Histopathology and HSV-PCR Study

Biopsies were done on the OLP subjects’ lesions. Based on characteristic clinical manifestations and typical histopathology, we confirmed OLP in the subjects. Using the biopsied specimens, polymerase chain reaction (PCR) testing was done to detect HSV DNA. The DNA of HSV-infected cells was used as a positive control. The DNA of normal tonsil tissue or distilled water was used as a negative control. 5' GCG CTT GTC ATT ACC ACC GC 3' and 5' TAC CCG AGC CGA TGA CTT AC 3' were used as primers. We encased the extracted template DNA in a microcentrifuge tube and added 1X PCR buffer. These samples were denatured in a thermal cycler at 94℃ for 5 minutes. We read the 118 base pair PCR band to confirm HSV DNA.

2.4. Evaluation of response to treatment

Oral acyclovir was prescribed to the OLP subjects (400mg daily) who did not show improvement by conventional treatments. All patients were periodically assessed the improvements to the OLP lesions and subjective symptoms.

3. Results

3.1. Epidemiological and Clinical Characteristics of Subjects

Among the OLP subjects, thirteen were female and seventeen were male, and their average age was 57.6 years. The disease duration of OLP varied from several weeks to 10 years, with 19.4 months on average. Among the 30 patients, thirteen had developed OLP in their 50s and six in their 60s, composing more than half the subjects. Most common clinical type was reticular type (61.5% in antiviral treated group, 58.8% in control group) and followed by erosive and atrophic type. In antiviral treated group, erosive and atrophic type was 23.1% and 15.4% respectively. In control group, they were 29.4% and 5.9% (Table 1). All the subjects complained of pain and burning sensations in the oral mucosa and could not eat either spicy or hot food.
Table 1. Clinical types and previous treatment of enrolled patients with oral lichen planus

<table>
<thead>
<tr>
<th></th>
<th>Antiviral treatment group (n=13)</th>
<th>Conventional treatment group (n=17)</th>
</tr>
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<tbody>
<tr>
<td><strong>Age (mean±S.D : years)</strong></td>
<td>55.4±12.0</td>
<td>59.3±12.8</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>5 (38.5%)</td>
<td>12 (70.6%)</td>
</tr>
<tr>
<td>Female</td>
<td>8 (61.5%)</td>
<td>5 (29.4%)</td>
</tr>
<tr>
<td><strong>Duration (mean±S.D : months)</strong></td>
<td>21.2±27.5</td>
<td>17.6±22.9</td>
</tr>
<tr>
<td><strong>Clinical types</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reticular</td>
<td>8 (61.5%)</td>
<td>10 (58.8%)</td>
</tr>
<tr>
<td>Atrophic</td>
<td>2 (15.4%)</td>
<td>2 (11.8%)</td>
</tr>
<tr>
<td>Erosive</td>
<td>3 (23.1%)</td>
<td>5 (29.4%)</td>
</tr>
<tr>
<td><strong>Previous treatments</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Topical steroid</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>Intralosomal steroid injection</td>
<td>4</td>
<td>9</td>
</tr>
<tr>
<td>Topical calcineurin inhibitor</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Cryotherapy</td>
<td>0</td>
<td>8</td>
</tr>
</tbody>
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3.2. Serologic HSV IgG Antibody Test and HSV-PCR Using Biopsy Tissues

We examined the HSV-1 and HSV-2 IgG titers in seventeen patients, the average of HSV-1 and HSV-2 IgG titer was 4209.15 and 1071.61, respectively. These were 10.5-fold higher and 3.5-fold higher than normal range. In the PCR on HSV DNA performed with tissue specimens taken from the 11 OLP subjects, HSV DNA was not found in all subjects.

3.3. Response of OLP to Treatments

All patients underwent with conventional treatment such as topical steroid, intralosomal steroid injection, topical calcineurin inhibitor. We regarded as no response if there was no improvement to more than 3 months of conventional treatments. The patients who did not respond to these therapies were treated with antiviral agent. The intralosomal steroid injection was most commonly used treatment remedy, followed by cryotherapy, treatment with topical steroids. In thirteen subjects, daily acyclovir (400 mg) was prescribed, they took acyclovir for about 4.3 months. In 61.5% of patients who underwent antiviral treatment, the symptoms and lesions were improved and about 23.1% showed marked improvement. In patients who treated with only conventional therapies, the symptoms were improved in 58.8% and 5.9% of patients showed marked improved (Fig. 2) (Table 2).

Table 2. Response of OLP patients to treatment

<table>
<thead>
<tr>
<th></th>
<th>Antiviral treatment group (n=13)</th>
<th>Conventional treatment group (n=17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>5 (38.5%)</td>
<td>7 (41.2%)</td>
</tr>
<tr>
<td>Mild</td>
<td>5 (38.5%)</td>
<td>3 (17.6%)</td>
</tr>
<tr>
<td>Moderate</td>
<td>-</td>
<td>3 (17.6%)</td>
</tr>
<tr>
<td>Much</td>
<td>3 (23.1%)</td>
<td>1 (5.9%)</td>
</tr>
</tbody>
</table>

* No: no response, Mild: improvement < 30%
Moderate: 30% < improvement < 60%, Much: 60% < improvement
4. Discussion

HSV infection is one of the most common oral infectious diseases and recurs depending on a patient’s level of stress and body condition. We have observed that some OLP patients improved after oral antiviral therapy. Although we did not experience the recurrence of typical symptoms of herpetic infections, we intended to study whether HSV infections could play a role in the occurrence of OLP. We evaluated HSV-1 and HSV-2 IgG levels in the blood of 17 OLP subjects, and carried out HSV-PCR testing with biopsy tissues in 11 OLP patients. We also reviewed the response of OLP to antiviral therapy.

The results of HSV-PCR testing came out negative for all tissues. Brice conducted HSV-PCR in lesional tissue to observe the relevance of HSV in erythema multiforme patients. He reported that HSV DNA was found in erythema multiforme tissue16, 17. Therefore, the fact that HSV DNA was not detected in any of the biopsied specimens of OLP with HSV-PCR leads us to infer that HSV infection is not directly related to OLP occurrence.

Serum HSV-1 and HSV-2 IgG antibody testing showed that the HSV-1 IgG titer increased in all of tested OLP subjects and HSV-2 IgG increased in seven (41.2%) OLP subjects. However, normal, healthy individuals also produced IgG antibodies against HSV-1 and HSV-2. Malkin et al. reported that approximately 67% of French adults have IgG antibodies against HSV-1, and 12-13% of them had IgG antibodies against HSV-218. We have noted that an increase in HSV IgG titer of more than 5- to 6-fold over the normal range indicates recurrent infection. Per Juto et al. reported that the IgG titers were higher in recurrent herpetic infections than in primary, in contrast to IgM of which much higher titers were found in primary infections20. We have noted that an increase in HSV IgG titer of more than 5- to 6-fold over the normal range indicates recurrent infection. Per Juto et al. reported that the IgG titers were higher in recurrent herpetic infections than in primary, in contrast to IgM of which much higher titers were found in primary infections20. Our OLP subjects had IgG antibody levels against HSV-1 more than 10-fold the normal titer, and in the case of HSV-2 more than 3-fold.

Exact pathogenesis of OLP is still not known. But, it is reported that the mucosal LP is associated with autoimmune diseases, such as thyroid disease, Sjogren syndrome, multiple sclerosis. A study reported that about 28% of mucosal LP patients had at least one more autoimmune disease and thyroid antibody was significantly higher in OLP patients than healthy control14. There are also some studies examining infectious causes of OLP. Ebrahimi et al. reported that the antibodies against HSV were observed in higher rate than control and patients with significantly higher titers had more oral symptoms and signs than the other patients14. There are some reports linking OLP with chronic hepatitis C21, 22. According to one study, the frequency of CYP2D6*4 allele polymorphism of cytochrome P450 was high, and molecular mimicry existed between CYP2D6*4 WT protein and autoimmune hepatitis type 213. Since the relevance between OLP and HCV has been reported previously, a hypothesis that a sequence homology between CYP2D6*4 WT protein and HCV protein as a pathogenesis of OLP was raised. They argued that CYP2D6*4 WT protein has a similar sequence to HSV type 1, and that HSV infection and CYP2D6*4 polymorphism may be a pathogenesis of OLP13. Based on this argument, they performed genotyping of CYP2D6*4 with collected whole blood of a subject, but polymorphism of the CYP2D6*4 allele was not found (data not shown). We infer that ethnic differences related to CYP2D6*4 allele gene sequences might have affected the result. That is, polymorphism of the CYP2D6*4 allele that was found in Western OLP subjects could not be found in Korean OLP subjects. But, these results could come from the racial difference between Korean and Westerner. Thus, further studies about specific SNP that involved in OLP pathogenesis are needed.

A standard treatment for OLP has not yet been established. Because OLP treatment should primarily focus on preventing symptom aggravation and improving erosive lesions, avoiding aggravating factors such as physical damage or chemical irritation would be a base of treatment. Since smoking is known as one of the major factors that exacerbates OLP, it is crucial to quit smoking3-5. There are various treatments currently being used, and the most common method is to apply a topical corticosteroid that is...
above mid-potency, 3-4 times a day\textsuperscript{1,3,4}. When the lesion is severe, it is possible to try systemic corticosteroid therapy for a short period of time. Topical calcineurin inhibitors (tacrolimus, pimecrolimus) have also been used effectively in cases that do not respond to topical corticosteroids. Topical retinoids could be used as a second choice\textsuperscript{23,24}. Since we have observed that OLP improves after oral antiviral therapy, we prescribed oral acyclovir to OLP subjects with highly elevated HSV IgG levels. As a result, eight out of thirteen subjects showed improvements to subjective symptoms and clinical lesions.

The fact that HSV-PCR tests on the OLP biopsied specimens were negative in all cases, and that HSV-1 and HSV-2 IgG antibodies have been found in a high percentage of healthy adults, did not lead to the conclusion that HSV infection may be a direct cause of OLP\textsuperscript{19,25}. However, subjective symptoms and objective clinical lesions improved in about 61.5% of the OLP subjects who received antiviral therapy and 23.1% showed marked improvement. But, in patients who underwent conventional treatments, the symptoms were improved in 58.8% and only 5.9% of patients showed marked improvement. We assume that the OLP lesions improved due to a mechanism of acyclovir other than its antiviral effect. Actually, there are recent reports of acyclovir having effects other than its antiviral effect. Satoshi et al. reported that acyclovir suppresses airway contraction by controlling the secretion of leukotriene in asthma patients caused by aspirin\textsuperscript{26}. Harrison et al. reported that patients with rheumatoid arthritis showed improved symptoms after using acyclovir\textsuperscript{27}. Based on such research results, it is plausible to suppose that the improvement in OLP symptoms after using acyclovir was a consequence of its anti-inflammatory effect rather than its antiviral effect.

In this study, OLP patients who did not respond to a variety of conventional treatments showed improvement with antiviral treatment. Therefore, we suggested that antiviral treatment would be used as a useful therapeutic option in OLP patients who did not respond to conventional treatments.

5. Conclusions

Although the results of HSV-PCR testing came out negative for all tissues, HSV-1 and HSV-2 IgG titers were elevated in all of OLP patients who examined HSV antibody serologic test. Furthermore, we prescribed the antiviral agent for OLP patients who did not respond to conventional treatments, and the symptoms and lesions were improved in higher rate than the patients who underwent only conventional treatment. Therefore, although we could not find definite evidence of whether HSV infection plays a direct role in OLP, we suggest that oral acyclovir might be used as a possible therapeutic option in treating OLP patients who do not respond to conventional treatments.

Conflict of Interests

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The authors have no conflict of interest to disclose. Prior presentation: none

REFERENCES


