Resistant recurrent aphthous stomatitis in an AIDS patient
～Efficacy and problems of long-term corticosteroid therapy～

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Abstract: Recurrent aphthous stomatitis (RAS) in HIV patients is treated by local application of corticosteroid or oral administration of 40~60 mg/day of prednisone or prednisolone for less than 14 days, as recommended by treatment guidelines. However, when the immune system does not improve, large aphthous stomatitis keeps recurring over a short period of time. We treated an AIDS patient with resistant RAS using long-term prednisolone therapy.

The patient presented with hemophilia B complicated by AIDS. Aphthous stomatitis lesions were 10~15 mm in diameter. Aphthous stomatitis was unresponsive to corticosteroid ointment, but responded to oral administration of prednisolone 40 mg/day for 4~7 days. However, when the immune system became severely compromised, aphthous stomatitis kept recurring over a short period of time.

As a result, 5 mg of prednisolone was administered every other day, and this was successful in suppressing recurrence without adverse effects.

Long-term prednisolone therapy was useful in treating RAS when the immune system was severely compromised. In such treatment, close communication and teamwork is required between the physician and dentist to prevent adverse effects.

Key words: human immunodeficiency virus (HIV), acquired immunodeficiency syndrome (AIDS), aphthous stomatitis, corticosteroid, immunosuppression

Introduction

Recurrent aphthous stomatitis (RAS) is a condition often seen in dentistry, and 10~15% of RAS cases are major aphthae1. In HIV patients, frequency of aphthous stomatitis is about 1.1~3.1%, and when the level of CD4+ lymphocytes drops to < 100/mm³, large lesions of aphthous stomatitis with a diameter ≥ 6 mm typically appear2,3,4,5,6, often causing eating disturbances and weight loss. While corticosteroid ointments and oral medications have been used to treat such lesions2,4,5,6, quality of life can be reduced if aphthous stomatitis recurs frequently over a short period of time. We describe herein a case of RAS in a patient with AIDS that was successfully treated using long-term prednisolone therapy.

Case Report

On February 23, 2001, a 28-year-old male presented to our hospital with eating disturbance due to pain as the chief complaint. The patient displayed hemophilia B (severe type) and HIV infection. Leukocyte count was 4000/mm³, CD4+ lymphocyte count was 21/mm³, and HIV-RNA level was 9000 copies/mL. Stavudine (d4T), lamivudine (3TC) and saquinavir were being administered as highly active antiretroviral therapy (HAART) (Fig. 1). However, this patient was allergic to numerous drugs, and as HAART was discontinued...
on occasion, multidrug-resistant viruses were present. Hence, even when the drug regimen was altered, the patient was not responsive to HAART, and CD4+ lymphocyte count was < 50/mm³ and HIV-RNA level was above the level of detection for more than 4 years. On presentation, a lesion of aphthous stomatitis with a diameter of 5 mm was seen at the gingivobuccal fold for the left maxillary incisor and canine. Triamcinolone acetonide ointment was used for more than 2 weeks, but aphthous stomatitis did not resolve. A physician suspected herpes simplex virus (HSV) infection, so 1000 mg/day of acyclovir was orally administered for 7 days, but no changes were seen. Given the effects of HAART agents and sulfa drugs, no drugs were administered for 1 month, but again no changes were seen.

On April 16, 2001, the patient displayed 5 aphthous lesions: a 15-mm lesion on the left side of the upper lip, and 5- to 8-mm lesions on the sublingual surface (Fig. 2). The physician administered 1000 mg/day of acyclovir intravenously for 7 days and orally for 14 days, and triamcinolone acetonide ointment was used for more than 2 weeks, but again no changes were seen. The patient tested negative to cytomegalovirus (CMV) antigen in blood. Oral prednisolone 40 mg/day was subsequently administered for 7 days, and aphthous lesions disappeared. Prednisolone dose was reduced over time and eventually discontinued.

On June 15, 1 month after the end of prednisolone therapy, the patient visited our department with recurrence of 10-mm aphthous lesions on the left upper lip and right sublingual surface (Fig. 3). Lesions disappeared with oral administration of prednisolone 40 mg/day for 4 days. However, the patient repeatedly visited our hospital on July 5, August 8 and September 3 due to recurrence of aphthous stomatitis. Each time, 40 mg/day of prednisolone was administered for 4 days to clear aphthous stomatitis. The immune system of the patient was further compromised, and in September 2001, CD4+ lymphocyte count was 4/mm³ and HIV-RNA level was 20,000 copies/mL.

As resistance to HAART medication and marked depression of the immune system were responsible for the RAS, improvement of the immune system over such a short period was considered unlikely. 5 mg/day
Recurrent aphthous stomatitis in AIDS

Aphthous stomatitis subsequently resolved. During this procedure, the physician monitored the patient to maintain immune status and avoid the development of corticosteroid-associated adverse effects. Physical conditions and hematological tests were checked at least every 2 weeks. The dentist investigated intraoral condition, to avoid exacerbation of candidiasis or other HIV-associated lesions at the same time. Fortunately, no symptoms of immunosuppression were identified.

In October 2002, zidovudine (AZT), didanosine (ddI) and lopinavir/ritonavir were administered as HAART, and the patient displayed marked improvements in immune status. In November, CD4+ lymphocyte count was 54/mm³ and HIV-RNA level was < 400 copies/mL, and in December, CD4+ lymphocyte count improved to 180/mm³. As the immune system improved and aphthous stomatitis did not recur, prednisolone therapy was discontinued in February 2003. In June 2004, CD4+ lymphocyte count was 381/mm³ and HIV-RNA level was < 50 copies/mL. As of the time of writing, the patient has not displayed any recurrence of aphthous stomatitis.

Discussion

RAS in HIV patients is diagnosed based mainly on clinical symptoms, and HSV infection, CMV infection, deep mycotic infection, lymphoma and pharmacological agents must be excluded as causes⁷,⁸. In the present patient, clinical findings suggested large aphthous stomatitis (diameter, > 6 mm) that persisted for months. The patient did not respond to acyclovir at all, so HSV infection was unlikely. The patient also did not test positive to CMV antigen and had no lymphoma. Furthermore, when use of all drugs was discontinued for 1 month, no changes were seen, thus excluding the possible effects of pharmacotherapy. As a result, RAS was diagnosed. However, since the patient had hemophilia B, no biopsy was conducted. Close collaboration among physicians and dentists is thus necessary for the diagnosis of oral lesions in patients with AIDS.

According to the treatment guidelines for RAS in HIV patients, local application of corticosteroid is selected at the early period and early period of recur-
rence as a first-line therapy, because high-potency topical corticosteroids are the most efficacious and safest option. However, if topical therapy fails to manage the acute ulcer, more aggressive treatment modality is recommended. Friedman et al. reported that weekly intralesional injections of 0.5–1.0 mL of triamcinolone 40 mg/mL were efficacious in HIV-infected patients with major RAS ulcers persisting >2 weeks. However, this method was not adopted in this patient, because he was a hemophiliac and invasive procedures may have led to disastrous hemorrhage.

Oral administration of 40–80 mg/day of prednisone or prednisolone for 3–7 days represents another effective method. A very low prevalence of adverse effects is seen in patients with very low CD4+ counts (<50/mm³). However, Lozada et al. have reported that systemic prednisone administration for >2 weeks significantly increases the onset of complications. The treatment guidelines for RAS in HIV patients thus suggest oral administration of 40–60 mg/day of prednisone for <14 days. However, no reports have provided information on long-term control.

In the present patient, once the immune system was depressed, corticosteroid ointment became ineffective, and prednisolone 40 mg/day was administered orally for 4–7 days. Marked improvements in aphthous stomatitis were seen. However, as the patient was resistant to HAART medication and the immune system did not improve, large aphthous stomatitis kept recurring over a short period of time and caused eating disturbances and weight loss. In the treatment guidelines, use of thalidomide and combination immunosuppressant and topical steroid therapy have been recommended for RAS, but these drugs are not approved for this lesion in Japan. As a result, long-term corticosteroid therapy was considered.

Long-term corticosteroid therapy has been reported for the treatment of recurrent idiopathic esophageal ulcer (IEU) in patients with HIV infection, organ transplant or diseases such as Crohn’s disease or Behcet’s disease. Kotler et al. have reported a comparison of 3 regimens: oral prednisone 40 mg/day for ≥1 month; intravenous hydrocortisone 100–250 mg every 6 h for ≤7 days; and intralesion injection of depomedrol 80–160 mg for management of IEU in HIV-infected patients. A 40% rate of complications such as CMV-associated gastritis, esophagitis and ulcer-associated infection. Pneumocystis pneumonia and tuberculosis was identified. Wilcox et al. reported use of prednisone 40 mg/day for 4 weeks for management of IEU in HIV-infected patients, and a 25% complication rate was suggested with CMV infections. Candida esophagitis, herpes zoster, Pneumocystis pneumonia, progression of Kaposi’s sarcoma and diabetes mellitus. Furthermore, systemic corticosteroid administration can cause complications such as cushingoid faces or thrush. If long-term systemic corticosteroid therapy is indicated, more adverse effects and immunosuppression can thus be observed compared to short-term therapy. The lowest possible therapeutic dosage and shortest duration should be employed with close medical supervision.

As for the dose of corticosteroid therapy, Kotler et al. and Wilcox et al. administered 40 mg/day of prednisone for ≥1 month, but this dose is too high for long-term administration. Use of prednisolone 15 mg/day for 3 months has been reported for the treatment of IEU in Crohn’s disease, while 10 mg/day of prednisolone was administered for 5 months in the treatment of IEU in a renal transplant patient, and 5 mg/day of prednisolone has been administered for IEU in Behcet’s disease.

Since this patient responded well to short-term prednisolone therapy, a minimal dose (5 mg/day) was administered every other day, and this therapy was consequently continued for 17 months until the immune system of the patient improved under a new HAART regimen.

In patients with a severely compromised immune system, long-term corticosteroid therapy can further suppress the immune system and cause other lesions. Close communication and teamwork is thus required between the physician and dentist to prevent adverse effects. In this patient, the physician checked the immune status and other HIV- or corticosteroid-associated physical complications through examination and hematological tests at least every 2 weeks. The dentist also investigated intraoral condition to avoid exacerbation of oral candidiasis or other HIV-associated lesions at the same time. The plan was
made that if either the physician or dentist noticed an abnormal condition, a meeting would be held to determine whether to continue or discontinue therapy. Fortunately, symptoms of further immunosuppression and other abnormal conditions were not identified in this patient.

In this patients, long-term prednisolone therapy was useful in treating RAS when the immune system was severely compromised.

References

AIDS 患者にみられた難治性再発性アフタの 1 例
～長期副腎皮質ホルモン療法の有効性と問題点～

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HIV 感染者における再発性アフタ性口内炎（RAS）は、副腎皮質ホルモン剤軟膏の局所塗布や、プレドニゾロンまたはプレドニゾロン 40～60mg/日を 14 日以内の経口投与により治療される。しかし、免疫状態が改善しない場合は、短期間に大型のアフタ性口内炎の再発をくり返す。われわれは、AIDS 患者に発症した難治性 RAS に対し、長期プレドニゾロン療法を用いて治療した。

患者は血友病 B（重症型）で、AIDS を発症していた。アフタ性病変は、直径 10 ～15mm を呈した。副腎皮質ホルモン剤軟膏の塗布には反応せず、プレドニゾロン 40mg/日を 4 ～7 日の経口投与にて消退した。しかし、免疫能が高度に低下した時期には、短期間にアフタ性口内炎の再発をくり返した。そこで、プレドニゾロン 5mg/隔日投与を行い、副作用なく以後の再発は抑制できた。

免疫能が高度に低下している時期における RAS の治療には、長期プレドニゾロン療法は有効であった。本療法においては、副作用を避けるために、内科医と歯科医の密接な相談やチームワークが必要である。

キーワード：ヒト免疫不全ウイルス、エイズ、アフタ性口内炎、副腎皮質ホルモン、免疫抑制