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Recurrent Aphthous Stomatitis Well-Treated with Inchinkoto: Two Case Reports

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Abstract: *This is the first report of patients with recurrent aphthous stomatitis (RAS) who underwent an effective treatment with inchinkoto, a traditional Kampo (Japanese herbal) medicine. Inchinkoto for the relief of stomatitis is covered by Japanese health insurance, but its effects on RAS have not been established. We treated two RAS patients with inchinkoto (7.5 g/day): 76- and 72-year-old Japanese females. The inchinkoto treatment showed inhibitory effects on RAS and also improved the patients' health-related quality of life (HRQoL) scores on the Short-Form 8 Health Survey and their oral HRQoL scores on the General Oral Health Assessment Index. Significant adverse events did not occur. Inchinkoto may be useful for the treatment of RAS.*

Keywords: *Recurrent aphthous stomatitis, inchinkoto, Kampo, health-related quality of life*

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I. Introduction

Recurrent aphthous stomatitis (RAS) is a common oral mucosal disorder [1-3] and characterized by a round or ovoid ulcer with erythematous haloes and a gray-white pseudomembrane. RAS is classified into three categories: minor RAS, major RAS, and herpetiform ulcers [1,4,5]. However, there is no specific diagnostic examination for RAS. The diagnosis is based on the patients' histories and clinical findings. RAS-like ulceration is known to occur in systemic diseases such as Behçet's disease [1,3,5,6], Sweet's syndrome [3,5,7], cyclic neutropenia [5,6], periodic fever, aphthous stomatitis, pharyngitis, and adenitis (PFAPA) syndrome [5,6], Crohn's disease [1-3,8,9], ulcerative colitis [1-3,8], and immunodeficiencies [10,11]. Therefore, we dentists should take into account the possibility of these systemic diseases in diagnosing RAS. The potential RAS factors are thought to be infections [10,11], food hypersensitivity [9,12], vitamin deficiency [4,7,12,13], microelement deficiency [4,13], hormonal defects, mechanical injuries and stress [4,13,14]; the etiopathogenesis of RAS remains unclear. Numerous topical treatments with tetracyclines [15], corticosteroids [15], anaesthetics [15] and such have been proposed as curative medicines for RAS; the treatment of RAS still remains nonspecific. Kampo medicines, i.e., Japanese or Chinese herbal medicines, are effective for treating stomatitis [16]. In particular, the plant-based Kampo medicine 'inchinkoto' for the relief of stomatitis is covered by Japanese health insurance, but, its effects on RAS have not been established.

We treated two RAS elderly patients with inchinkoto, and their RAS symptoms were ameliorated by this traditional medicine. The treatment procedure was explained to both of the patients in advance of this study, and their informed consent for their cases to be reported was obtained.

II. Case reports

Patient 1

The patient was a 76-year-old Japanese female who visited the Department of Oral Medicine, Tokushima University Hospital because of pain and a burning sensation of the tongue. She was in treatment for chronic gastritis. Intraoral and extraoral examinations, including a blood examination, culture, and salivation test, were performed after her medical history was obtained. There were no apparent abnormalities in these examinations. She had not experienced pathological changes of her tongue, and she was diagnosed with burning mouth syndrome. Powdered processed aconite roots (Aconinsan tablets, Kaken Pharmaceutical Co., Tokyo) was orally administered at 0.5 g daily, and increased gradually to 1.5 g. Aphthae of the lower lip developed frequently during the treatment (Fig. 1). Inchinkoto (TJ-135, Tsumura Co., Tokyo) was orally administered at 7.5 g daily. Forty-one weeks later, inhibitory effects on the patient's RAS were confirmed (Fig. 1). No adverse events including RAS relapse were observed. The patient's RAS was fully controlled with inchinkoto. Her score on a visual analogue scale (VAS) representing stomatalgia was evaluated twice: 0 and 41

weeks after the start of the inchinkoto treatment. We also used a self-administered Japanese version of the Short Form-8 (SF-8) and the Japanese version of General Oral Health Assessment Index (GOHAI), which are designed to measure the respondent's health-related quality of life (HRQoL) [17-20], on the same two occasions, i.e., at baseline and at 41 weeks of treatment. The Japanese SF-8 consists of the following subscales: physical functioning (PF), role limitations due to physical health (RP), bodily pain (BP), general health perceptions (GH), vitality (VT), social functioning (SF), role limitations due to emotional health (RE), mental health (MH). The subscales were scored using a norm-based method (NBM) that standardizes the scores to a mean ± standard deviation (SD) of 50 ± 10 as the Japanese average (2007), with higher scores indicating better health [21]. Regarding the summary score, a physical component summary (PCS) and a mental component summary (MCS) were also calculated by the NBM. The Japanese GOHAI consists of 12 questions regarding physical/psychosocial functioning and the experience of pain/discomfort; the total scores of each question are added to obtain the GOHAI score, with higher scores indicating better health. The patient's VAS score decreased from 58 to 30 (Fig. 2). Her scores on the SF-8 subscales increased as follows: RP, from 27.9 to 47.4; SF, from 29.2 to 37.7; RE, from 31.4 to 42.2; and MH, from 36.3 to 44.9. Her PCS score increased from 40.1 to 43.2 and her MCS score increased from 33.0 to 41.7 (Fig. 2). Her GOHAI score increased from 27 to 29 (Fig. 2).

Patient 2

The patient was a 72-year-old Japanese female who visited our hospital because of gingivalgia and stiff shoulder. She had undergone surgeries for an ileus and goiter, and was in treatment for hypertension. Clinical examinations were performed as described for Patient 1. The blood examination revealed hypochromic anemia. She did not experience pathological changes of her gingiva, but had tenderness of her trapezius muscle on the left side. She was diagnosed with suspected masticatory myofascial pain with gingivalgia. Eperisone hydrochloride (Myonal tablets, Eisai Co., Tokyo) was orally administered at 50 mg daily, and we gradually increased the dose to 100 mg. Aphthae of the lower gingiva developed frequently during the treatment (Fig. 3). Inchinkoto was orally administered at 7.5 g daily and showed inhibitory effects against the patient's RAS 3 weeks later (Fig. 3). No adverse events (including RAS relapse) were observed. The patient's RAS was fully controlled by the inchinkoto treatment, and her VAS score decreased from 23 to 0 (Fig. 4). Her scores on the SF-8 subscales increased as follows: PF, from 47.8 to 53.5; BP, from 38.2 to 46.1; SF, from 45.6 to 55.1; and RE, from 42.2 to 48.0. The patient's PCS score increased from 40.5 to 44.5, and her MCS score increased from 45.0 to 47.7 (Fig. 4). Her GOHAI score increased from 34 to 43 (Fig. 4).

III. Discussion

To our knowledge, this is the first report on RAS patients who underwent an effective treatment with the Japanese traditional medicine, inchinkoto.

Although the etiopathogenesis of RAS remains unclear, stomatitis including RAS is related to the generation of reactive oxygen species (ROS) [22]. It is still not known how Kampo medicines work for RAS; many of these medicines have anti-inflammatory and antioxidant activity [16,22,23]. Inchinkoto contains the following herbal extracts: Artemisia capillaris flower, gardenia fruit, and rhubarb. Artemisia capillaris (the shrub known as capillary wormwood) and gardenia fruit have anti-inflammatory activity [24-26]. More specifically, Artemisia capillaris reduces proinflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin (IL)-6 [26]. TNF-α plays an important role in the development of RAS [9]. Artemisia capillaris flower, gardenia fruit, and rhubarb have antioxidant activity [26-31]. In particular, gardenia fruit induces an expression of nuclear factor (NF)-E2-related factor 2 (Nrf2) mRNA that is followed by an upregulation of antioxidant response element (ARE)-mediated genes such as heme oxygenase-1 (HO-1) [32-35]. Therefore, the curative effects of inchinkoto on RAS were in our two patients are consistent with the previous reports mentioned above. Although our patients had been struggling with RAS for a period of years, no relapse of RAS has occurred in either patient since their treatment with inchinkoto. The effects of inchinkoto on RAS may be not only curative but also preventive.

RAS is not a life-threatening disease, but it often affects the daily lives of RAS patients. RAS is very painful, and its presence can significantly disturb an individual's speaking, eating and swallowing [36], and result in a diminished quality of life [37,38]. Our patients' RAS had a high impact on their oral HRQoL, which is consistent with previous reports [37,40]. The Japanese SF-8 is the Japanese and shortened version of the Medical Outcomes Study (MOS) 36-Item Short-Form Health Survey version 2 (SF-36v2), and it is used as a questionnaire to measure HRQoL in various diseases [18-20]. The Japanese GOHAI is valid oral disease-specifically [39]. The Japanese SF-8 consists of eight questions dealing with a range of physical and psychosocial factors and is summarized with physical and psychosocial score. A VAS is not suitable for dealing with psychosocial issues. Our two RAS patients achieved poorer scores on almost all subscales of the Japanese SF-8; it thus appears that their RAS had negative impacts on their HRQoL. Our results indicate that RAS

patients have a high disease burden both physically and psychosocially; psychosocial supports such as stress relief should thus be considered for their care in addition to physical supports. Inchinkoto showed curative effects on RAS and improved our patients' scores on the subscales of the Japanese SF-8. Thus, the inchinkoto regimen was effective for improving the HRQoL of RAS patients. Inchinkoto not only physically but also psychosocially supported our RAS patients, as indicated by their results on the Japanese SF-8.

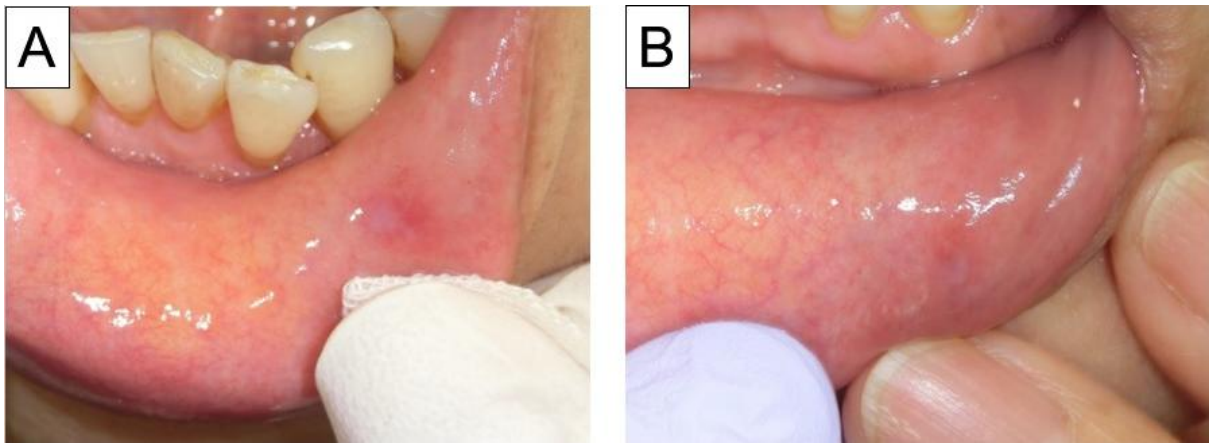

Figure 1 The photograph showing the aphthae of the lower lip in Patient 1. A: Before the start of the inchinkoto treatment. B: At 41 weeks after the initiation of the treatment.

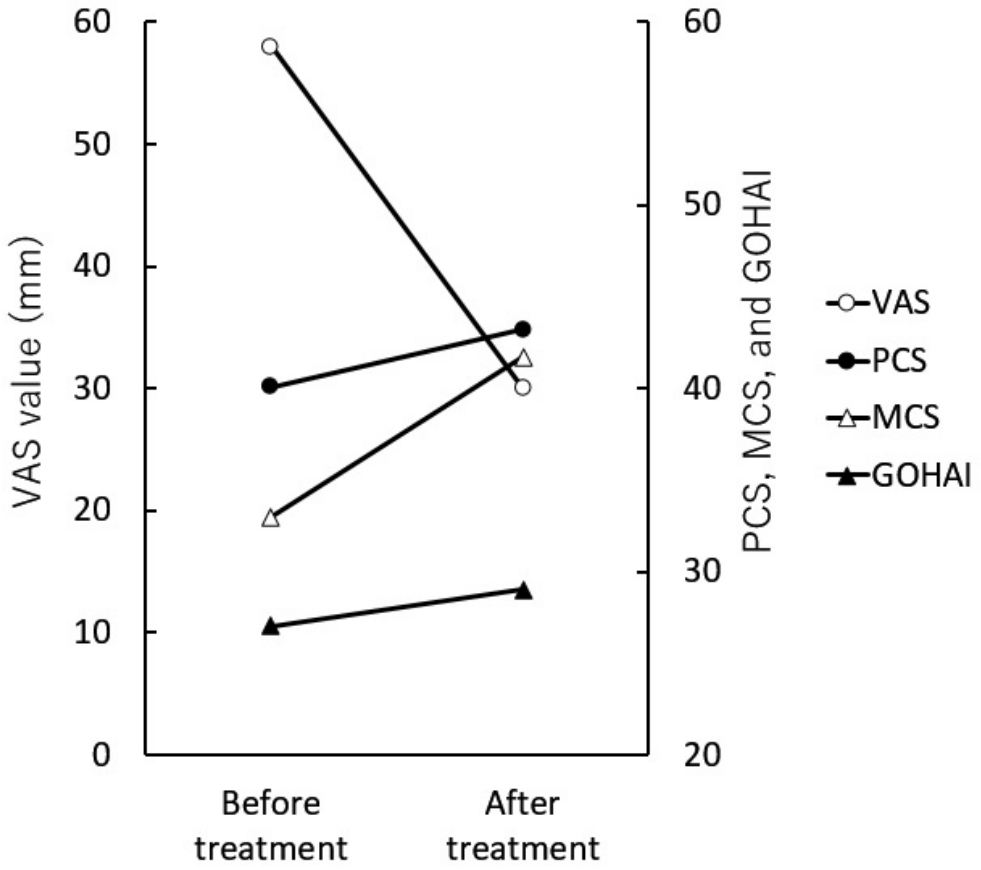

Figure 2 Time course of VAS, PCS, MCS, and GOHAI values during the treatment in Patient 1. VAS, visual analogue scale; PCS, physical component summary; MCS, mental component summary; GOHAI, general oral health assessment index.

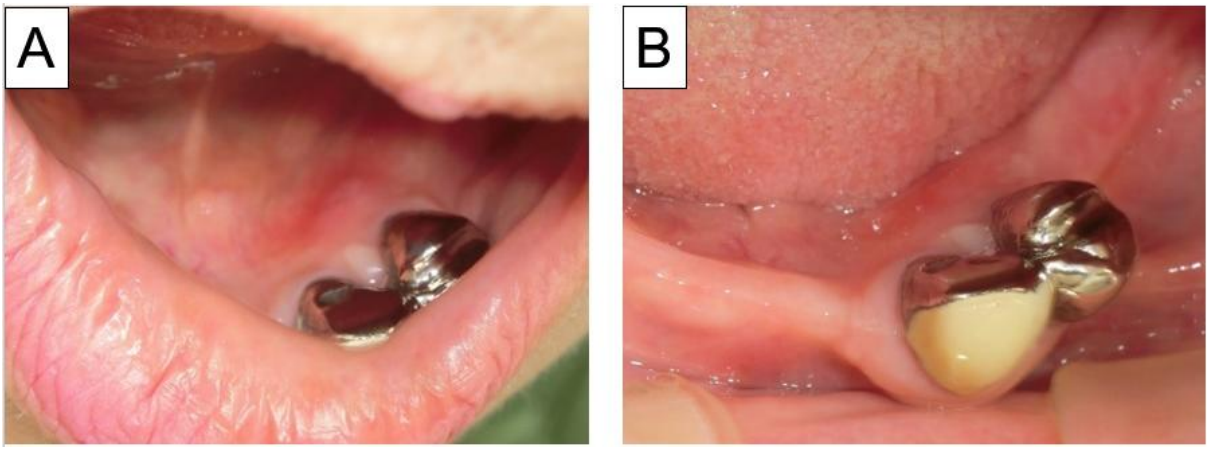

Figure 3 Photograph of Patient 2's aphthae of the lower gingiva. A: Before the start of the inchinkoto treatment. B: At 3 weeks after the initiation of the treatment.

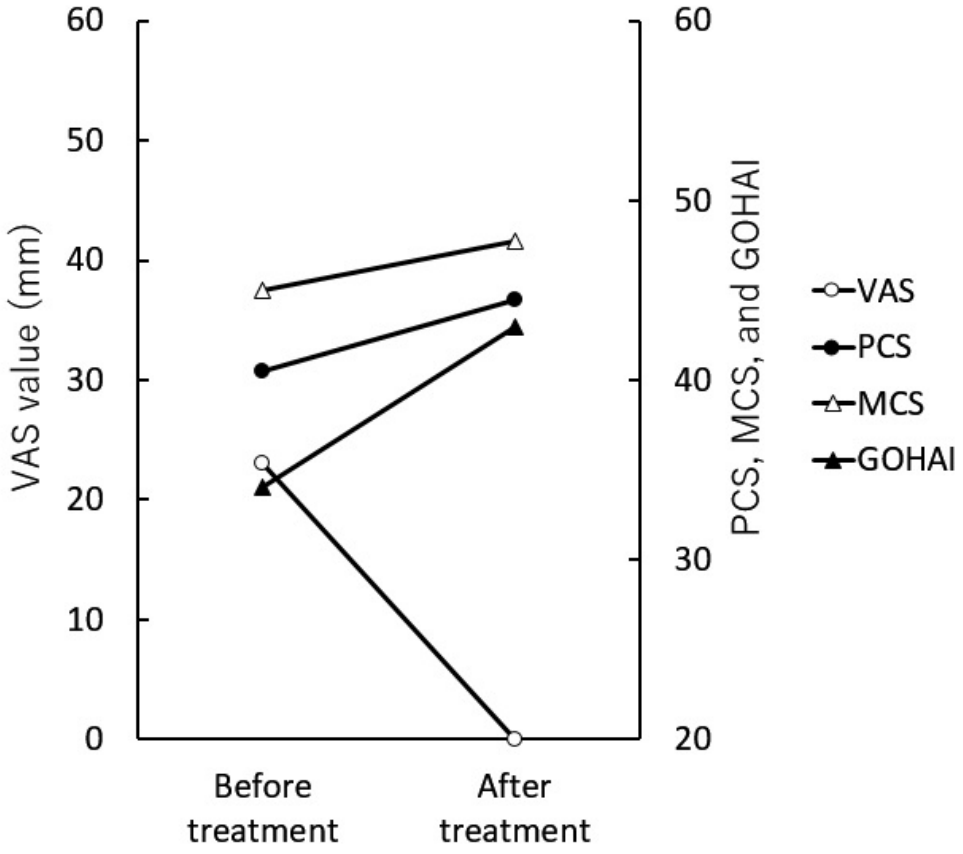

Figure 4 Time course of VAS, PCS, MCS, and GOHAI values during the treatment in Patient 2. VAS, visual analogue scale; PCS, physical component summary; MCS, mental component summary; GOHAI, general oral health assessment index.

IV. Conclusion

Inchinkoto showed curative effects on RAS and was effective for improving the HRQoL of the present two RAS patients. Inchinkoto may thus be useful for the treatment of RAS.

Competing interests

The authors have no conflict of interests to declare regarding this study or the publication of this paper.

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