베체트 증후군 환자에서 과량의 IgK 침착을 동반한 점막하 섬유증
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Abstract
Submucosal Fibrosis with Severe IgK Deposition in Behcet’s Syndrome
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A case of Behcet's syndrome found in a 22 years old male was is reported along with the histological and immunohistochemical studies. The patient had had received prolonged medical therapy of anti-inflammatory agents for the conjunctival ulcer, genital ulcer, oral ulcer, and intestinal ulcers since the first onset of the Behcet's syndrome about approximately 7 years ago. Recently, he felt the thickening of both corners of his lip causing mouth opening difficulty. A plastic reconstructive surgery was performed to enlarge the size of the oral orifice by multiple Z-plasty incisions, and finally resulted in proper enlargement of the circumferential length of the lip. During the operation, a scar-like thick fibrous tissue was obtained and examined pathologically. The microscopic observation revealed the submucosal lesion was to be diffusely fibrosed with the distribution of sclerotic collagen bundles. Particularly, several foci of collagen degeneration were found observed in the deep connective tissue, and the degenerating collagen bundles were gradually lost their fibrillar appearance. In the immunohistochemical observations, the foci of collagen degeneration were strongly positive for IgK, but almost negative for TNF α, lysozyme, and MMP-3. Taken together, it was presumed that the submucosal fibrosis was presumed to have firstly presented in this study was probably induced by the prolonged anti-inflammatory therapy, which may inhibit the removal of sclerosed collagen bundles by the cell-mediated immunity and proteolytic digestion of macrophages, and that it was secondarily aggravated by the deposition of immunoglobulins derived from an autoimmune origin. Therefore, even after the successful plastic surgery of the lip to ameliorate the mouth opening difficulty, the recurrent submucosal fibrosis of lip should be carefully managed in the follow-up treatment.

Key words: Behcet's syndrome, Submucosal fibrosis, Mouth opening difficulty
Introduction

Behcet's syndrome is a multisystem chronic inflammatory disorder characterized by oral and genital ulceration and ocular involvement. Recurrent oral and genital ulcers are the most common symptoms of Behcet's syndrome and occur in more than 80% of patients. The etiopathogenesis of Behcet's syndrome has not yet been identified; but it has generally been accepted that several environmental factors may induce an inflammatory attack in genetically susceptible individuals. However, the multisystemic involvement might be the clue for an autoimmune pathogenesis[1].

The majority of affected individuals do not have life-threatening disease, although mortality can be associated with vascular-thrombotic and neurological manifestations. Currently, treatment of Behcet's syndrome is symptomatic and empirical, and is tailored according to the severity of clinical features[2]. In this study we present a rare phenomenon of severe submucosal fibrosis causing mouth opening difficulty in Behcet's syndrome patients, which was possibly associated with prolonged therapy of anti-inflammatory agents, and also demonstrated an appropriate plastic lip surgery to ameliorate the mouth opening difficulty.

Case Report

A 22 years old male complained of limited mouth opening due to severe fibrosis of both corners of lip. He had received prolonged medical therapy of anti-inflammatory agents (sulfasalazine 500 mg) and immune-suppressants (azathioprine 50 mg) for conjunctival ulcer, genital ulcer, oral ulcer, and intestinal ulcer since the first onset of the Behcet's syndrome about 7 years ago. He had also received a surgical operation for segmental resection of intestine

Fig. 1. (A) Pre-operative view showing limited mouth opening due to severe fibrosis of both corners of lip. (B, C) Continuous multiple Z-plasty incisions were made in the lingual side of whole lip to enlarge the circumferential length of lip. (D) Post-operative care was performed using lip splint in order to retain the enlarged shape of lip.
6 years ago. However, he said that the general symptoms of Behcet's syndrome was uneventful, but he felt the thickening of both corners of his lip and mouth opening difficulty. The laboratory examination of blood chemistry was generally normal but showed only mild elevation of monocyte level in white blood cells, 9.4% (normal range: 2~8%).

In order to treat the chief complain of mouth opening difficulty in the present case, a plastic reconstructive surgery was performed to enlarge the size of oral orifice under general anesthesia. Continuous multiple Z-plasty incisions were made in the lingual side of whole lip to enlarge the circumferential length of lip. Particularly, a scar-like thick fibrous tissue was found in the corners of lip, and examined for pathological diagnosis. Postoperative care was performed using lip splint in order to retain the enlarged shape of lip, and resulted in more increased mouth opening, up to 4.3 cm compared to the preoperative mouth opening, about 3.5 cm (Fig. 1).

The removed specimen was fixed in 10% neutral formalin solution, embedded in paraffin, and sectioned in 4 μm thickness. The serial microsections were stained with hematoxylin and eosin, and followed by immunohistochemical staining using IgK, CD3, CD20, CD68, TNF α lysozyme, and MMP-3. The immunostaining was simultaneously performed with indirect triple sandwich method, background cross reaction was minimized by the negative control staining using no primary antibody in the same immunohistochemical procedures. Each immunoreaction image was taken in the same condition of photogram by digital camera (DP-70, Olympus, Tokyo, Japan). The biopsy specimen used in this study was obtained from the file of the Department of Oral Pathology, Gangneung-Wonju National University Dental Hospital, in the approval of Life Ethics Committee (GWNUDH-IRB2009-1-3).

In the microscopic observation using hematoxylin and eosin stains the submucosal lesion was diffusely fibrosed. Particularly, foci of collagen degeneration were found in the deep connec-tive tissue, and the degenerating collagen bundles were gradually lost their fibrillar appearance and diffusely condensed with their eosinophilic matrix materials. Through-out the specimen examined the thick collagen bundles were found in the juxta-epithelial connective tissue in the replace of skeletal muscle, resulted in no fascicular attachment between orbicularis oris muscle and lip epithelium, And also there appeared almost rare lamina propria zone beneath the lip epithelium (Fig. 2).

In the immunohistochemical observation the area of collagen degeneration was strongly positive for IgK, but almost negative for TNF α, lysozyme, and MMP-3. Many macrophages positive for TNF α and CD68 were diffusely infiltrated into the area of collagen degeneration (Fig. 2).

Discussion

The present case had been already diagnosed Behcet's syndrome through medical examination and therapy exhibiting generalized mucosal ulcerations, including eye ulceration, genital ulceration, oral ulceration, and intestinal ulceration. The intestinal ulceration was severely aggravated and eventually treated by segmental resection of the involved intestine, And the other generalized ulcerations recurred frequently were treated by intensive care using different anti-inflammatory agents and immunosuppressants. However, recently the patient showed no symptomatic lesion of Behcet's syndrome in whole body, but only complained of mouth opening difficulty due to the severely fibrosed corners of lip. The patient could open his mouth only up to 3.5 cm, and was nervous on his facial profile.

The present finding of small mouth orifice caused by severe submucosal fibrosis has been not reported in Behcet's syndrome so far[3-7]. And it is clear that the phenomenon of submucosal sclerosis is different from other syndromes, including dermal sclerosis, amyloidosis, etc. However, the symptom of mouth opening difficulty occurred after the prolonged therapy of Behcet's syndrome for more than 7 years in the present case.

In the operation to enlarge the orifice of mouth the plastic reconstructive surgery via multiple Z-plasty incisions, thick fibrous submucosal tissue was removed from the corner of lip. The removed biopsy specimen was examined pathologically. Otherwise, there was no other pathological abnormality related to the mouth opening difficulty, thereby the postoperative care was uneventful and the patient
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In pathological examination, the submucosal fibrous tissue was abnormal and continuously underwent severe sclerosis. Most of collagen bundles became thickened and slightly denatured in eosin stain, and closely adhered each other without the regenerative reaction via degradation by

Successfully achieved mouth opening up to 4.3 cm.
macrophages and collagenases (MMPs). Particularly, several foci of severe collagen degeneration were found, showing granular degradation of collagen bundles in the lack of inflammatory reaction.

In the immunohistochemistry it was observed that the degenerating collagen bundles were heavily deposited with IgK but negative for lysozyme and MMP-3. The evidence of cellular immunity was assessed by the immunostains of CD3, CD20, CD68, and TNFα, and finally resulted that few T-lymphocyte positive for CD3 and B-lymphocyte positive for CD-20 were present in the submucosal lesion. Only a few macrophages positive for CD68 and TNFα were diffusely distributed in the submucosal lesion. Therefore, it was defined that the submucosal lesion was rarely associated with lymphocyte infiltration, but showed only a few macrophage infiltration around the degenerating collage bundles. And more, there appeared sparse cellularity of fibroblasts in the degenerating fibrous tissue, which was almost negative for lysozyme and MMP-3 antisera. This submucosal fibrosis almost replaced the loose connective tissue, lamina propria zone, beneath the lip epithelium, that might directly interfere the attachment of orbicularis oris muscle to lip epithelium. Therefore, it was presumed that the major pathogenetic evidence of the submucosal lesion was the IgK deposition in the degenerating collagen bundles by immunological origin, and that the sclerotic fibrosis in submucosal area may be occurred secondarily due to the prolonged therapy of anti-inflammatory drugs, which can inhibit the removal of sclerosed collagen bundles via the reduced cell-mediated immunity[2,8-10]. Eventually the submucosal fibrosis could directly affect the mouth opening difficulty.

In the skin samples of 108 Behcet’s syndrome patients (28 perilesional skin, 44 positive pathergy test site, 22 negative pathergy test site, 14 normal skin) highly significant immunoreactants depositions were found in Behcet’s syndrome (deposition rates: IgM 70.3%, IgG 0%, IgA 20.3%, C3 62.9%, F 83.3%) [11]. The significant deposition of immunoreactants in Behcet’s syndrome would be implacable for the autoimmune pathogenesis in Behcet’s syndrome, which was similar findings of the present study.

The treatments of Behcet’s syndrome usually include colchicine, anti-inflammatory agents, corticosteroids, and immunosuppressive drugs in severe cases. Classified among the vasculitides, the clinical spectrum of Behcet’s syndrome ranges from a mild mucocutaneous disease to a life-threatening systemic vasculitis, characterized by remissions and recurrences. The major morbidity is recurrent eye inflammation that may lead to blindness, but severe central nervous system, gastrointestinal, or vascular involvement may occur and might be fatal. The treatment of Behcet’s syndrome is usually symptomatic and palliative. This includes topical steroids for orogenital ulcers, nonsteroidal anti-inflammatory agents for joint involvement, and colchicine as prophylaxis against disease flares (although evidence that colchicine prevents recurrences of oral and genital ulcers is restricted to female patients)[11,12]. Immunosuppressives and cytotoxic agents are used for more severe involvement, and thalidomide and interferon have attracted attention in recent years[13-15]. However, different therapies for Behcet’s syndrome can severely down-regulate the immune reaction to prevent the hypersensitivity against autoimmune antigens, Particularly, the anti-inflammatory agents for Behcet’s syndrome treatment are supposed to inhibit the sclerotic collagen bundles via inflammatory reaction of innate immunity[16,17].

Conclusively, the submucosal fibrosis of lip mucosa in Behcet’s syndrome was firstly reported in the present study. With the histological and immunohistochemical observations in the lip microsections, it was presumed that the submucosa fibrosis of the present case was probably induced by the prolonged anti-inflammatory therapy, which may inhibit the removal of sclerosed collagen bundles by the cell-mediated immunity and proteolytic digestion of macrophages, which was gradually aggravated by the deposition of immunoglobulins derived from autoimmune origin. Therefore, even after the successful plastic surgery of lip to ameliorate the mouth opening, the submucosal sclerotic fibrosis could be recurred and needed to be carefully managed in the follow-up treatment.

References