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Original

IgG4-positive Plasmocytosis of Inflammatory Cell Spreading Pattern Revealed to Differentiation in Classic Oral Lichen Planus

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SUMMARY

Objective : Oral lichen planus (OLP) is a chronic inflammatory oral mucosal disease of unknown etiology. Due to similar histological features of OLP with other oral diseases. IgG4-related disease has been identified, but whether or not there are organ-specific characteristics related to the etiologic factors is still unknown. In the present study, we investigated the significance of IgG4-positive plasma cells as a marker for OLP.

Methods : Biopsy specimens from 63 patients with white papules, erythema and erosive mucosa in the oral cavity were obtained. The lesions were evaluated for inflammatory cell spreading pattern classified as horizontal superficial type and/or expanding type (s), for lymphoid-plasma cell markers (CD3, CD20, CD79a), Immunoglobulin G (IgG, IgG4) immunoreactivity, and for monoclonality.

Results : In the horizontal superficial type with only CD3-positive lymphocytic inflammatory cells were restricted to the epithelial layer of connective tissue without presence of IgG4-positive plasma cells. Lesions were further demonstrated to contain CD3-, CD20- and CD79a-positive lympho-plasma cells with focal cytoplasmic IgG4 expression. However, in IgG4-rich cases, there were no monoclonality. The inflammatory cell spreading pattern differed significantly between the horizontal superficial type with only CD3-positive lymphoid cells and expanding types, and was significantly associated with IgG4-positive plasma cells.

Conclusions : Detection of IgG4-positive plasma cells and inflammatory cell spreading pattern may be useful for differential diagnosis and selection of treatable cases in OLP.

Key Words : IgG4 related disease, oral lichen planus

INTRODUCTION

Lichen planus is a relatively common disorder, and is characterized microscopically by dense subepithelial lympho-histiocytic infiltrate with increased number of intra-epithelial lymphocytes and plasma cells[1)]. The oral mucosa is commonly involved and may be the

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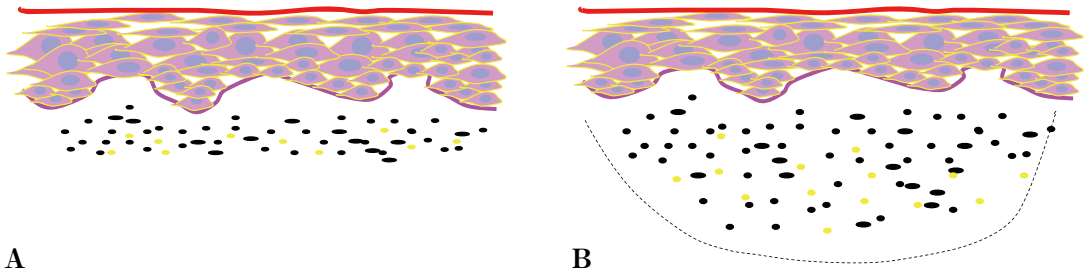

Fig. 1 Scheme of spreading pattern of inflammatory cell in oral lichen planus (OLP).
A：horizontal superficial type. **B**：expanding type.

only site of involvement. OLP affects one to two percent of the general adult population and is the most common noninfectious oral mucosal disease[3]. The management of OLP is still not totally satisfactory in all cases, and there is as yet no definitive treatment that results in long term remission, although advances have been made in the control of this condition[2,3].

On the other hand, IgG4-related diseases have attracted much attention from pathologists and clinicians since Hamano et al reported in 2001 that patients with sclerosing pancreatitis, also called autoimmune pancreatitis, have high serum IgG4 concentrations[4]. Many IgG4-positive plasma cells are present in extra-pancreatic organs in patients with sclerosing pancreatitis, and IgG4-related systemic disorder has been proposed as a distinct disease entity[5]. IgG4-related disease has been identified in various organs, but whether or not there are organ-specific characteristics related to the etiologic factors is still unknown[6~9]. Histologic findings are similar in these diseases, and there is marked lymphoplasmacytic infiltration with IgG4 positive plasma cells and occasional eosinophiles. In addition, there is increasing speculation as to whether IgG4 expression in plasma cells may be applicable as a diagnostic and behavior marker for patients with various lymphoplasmacytotic lesions in IgG4-related disease. However, comparative characterization of the expression of IgG4 positive plasma cells in OLP tissues has not yet been carried out. Consequently, in the present study, we attempted to clarify the significance of IgG4 as a diagnostic marker of OLP, in comparison with the inflammatory cell spreading pattern of IgG4 positive plasma cells.

MATERIAL AND METHODS

Patients and Oral Mucosal Samples

Biopsy specimens were obtained from 63 patients with OLP who were diagnosed with typical macroscopic findings (white papules, erythema and erosive mucosa) in all of cases and histological change of dense subepithelial lymphocytes and plasma cells and treated at Dokkyo Medical University School of Medicine Hospital between 2006 and 2010. This work was carried out in accordance to ethical guidelines of Declaration of Helsinki and was approved by Dokkyo Medical University Surgical Pathology, and informed consent was obtained from all patients. For the ethical procedure, linkable anonymizing method was used to pursue analysis to make even the researcher not be able to identify the individuals. Samples used in this study are materials for biopsy obtained for diagnosis or treatment and not for research. Medical disadvantage or risk of the patients will not increase by participating in this study.

Histological Assessment for Inflammatory Cell Spreading Pattern

Specimens were obtained by mucosal biopsy, fixed in 10% formalin solution, embedded in paraffin, serially sectioned, and stained with haematoxylin and eosin (HE). Each lesion was evaluated for the inflammatory cell spreading pattern, classified as horizontal superficial type (Figure 1 A), and/or expanding type (Figure 1 B). The horizontal superficial type is inflammatory lesion restricted to the epithelial layer, but expanding type is not restricted to epithelial layer and into the deep connective tissue.

A

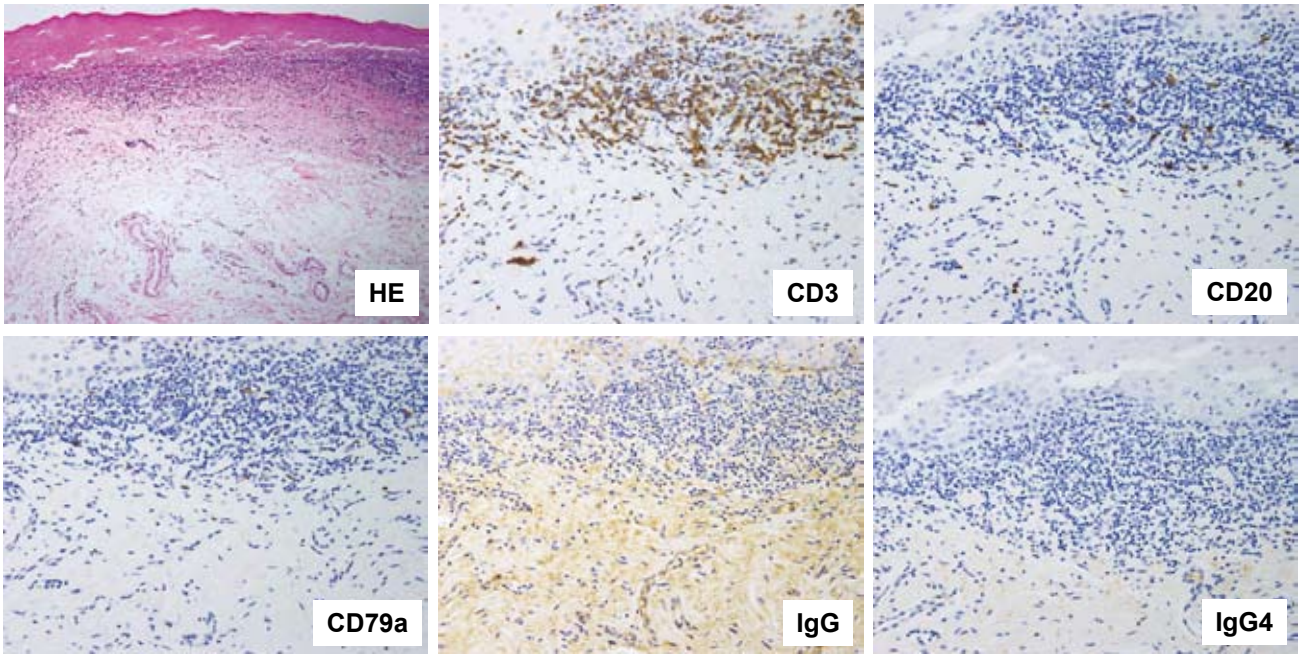

Fig. 2 Spreading pattern of inflammatory cell and its associated lympho-plasmacytic immunohistochemical futures and IgG4 positive plasma cells. HE (low magnification,), CD3, CD20, CD79a, IgG, IgG4 (high magnification).
A : Lympo-plasma cells predominantly expression with T-cell marker of CD3 horizontal superficial type. There is no IgG4 positive cell.

B

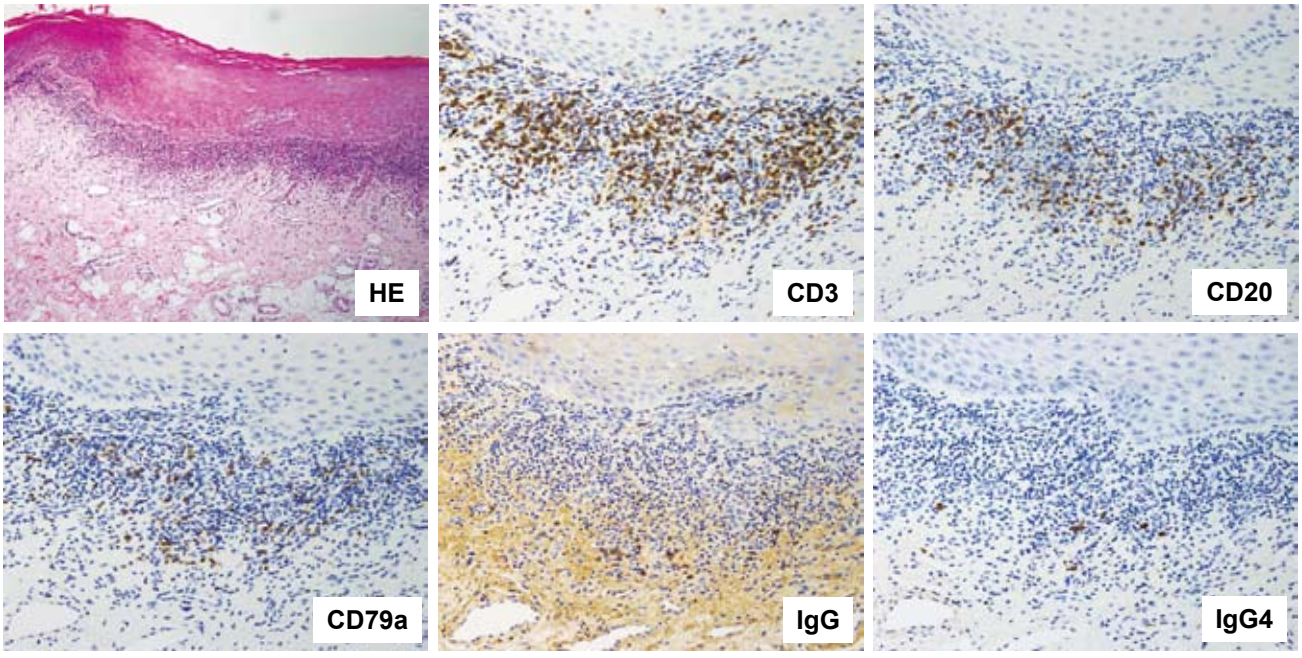

Fig. 2
B : Lympo-plasma cells expression with T-cell marker of CD3 and B-cell marker of CD20 and CD79a in in horizontal superficial type. There are a few number of IgG4 positive cells.

C

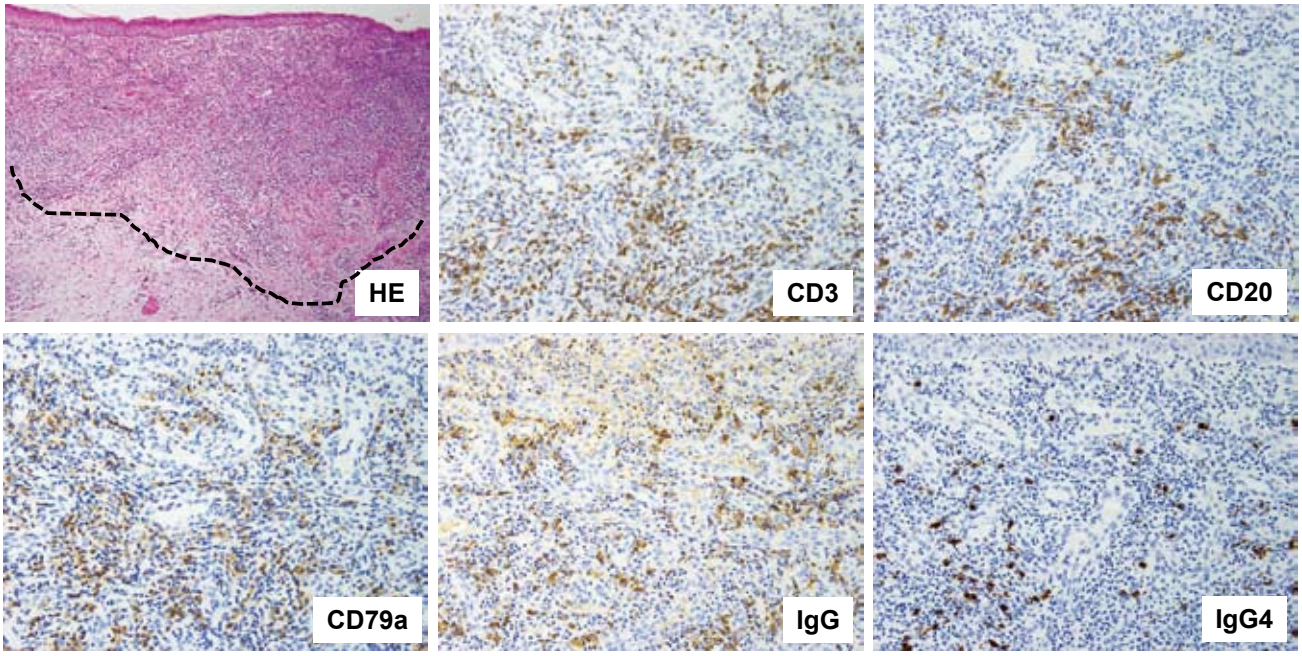

Fig. 2

C : Lympo-plasma cells expression with T-cell marker of CD3 and predominantly B-cell marker of CD20 and CD79a in expanding type. There are a lot of IgG4 positive cells.

Evaluation of Inflammatory Lesion for Immunohistochemical Staining

Immunohistochemical staining for CD3 and CD79a was performed with a LSAB-2 kit (DAKO, Marseille, France) and IgG and IgG4, CD20, kappa, lambda were performed with a ENVISION kit (DAKO, Marseille, France). In brief, the sections (4-μm-thick) placed on silane-coated slides were deparaffinized, rehydrated, and then pretreated with 0.3% H2O2 in methanol for 30 min at room temperature to quench endogenous peroxidase activity. The sections were then placed in 0.01 mol/L citrate buffer (pH 6.0) and treated by microwave heating (MI-77, Azumaya, Tokyo, Japan ; 400 W, 95℃) for 10 min to facilitate antigen retrieval. The sections were incubated with 1% bovine serum albumin in phosphate-buffered saline (PBS) for 30 min, then with anti-IgG (polyclonal, Dako, dilution 1 : 5), anti-IgG4 (clone HP6025. monoclonal, Binding Site, Birmingham, UK, dilution 1 : 2000), anti-CD79a (clone JCB117, Dako, dilution 1 : 50), anti- CD20 (clone L26, histofine, dilution 1 : 1), anti-CD3 (polyclonal, Dako, dilution 1 : 3), anti- kappa (polyclonal, Dako, dilution 1 : 3), and anti- lambda (polyclonal, Dako, dilution 1 : 3) for 1 hour. Thereafter, the sections were incubated with biotinylated secondary antibody for 15 min, washed with PBS, and treated with peroxidase- conjugated streptavidin for 20 min. Finally, the sections were incubated in 3,3'-diaminobenzidine tetrahydrochloride with 0.05% H_2O_2 for 3 min and then counterstained with Mayer's hematoxylin. For immunohistochemical evaluation, we used the areas of each section that had been confirmed to match the area in the specimen the areas from which the final diagnoses had been made. Cases were divided into three groups depending on the extent and pattern of lymphoid-plasma cell marker (CD3, CD20, CD79a) staining as follows : mild (staining restricted to 30% or less of the inflammatory lesion), moderate (staining was 30% to 60% of the inflammatory lesion), and severe (staining was 60% or more in the inflammatory lesion) ; T-cell predominant pattern (CD3-positive cells were more abundant than CD20- and/or CD79a-positive cells) and T-cell with B-cell pattern (CD3-positive cells were equal or less than CD20- and/or CD79a-positive cells), respectively. Tissue sections were examined and scored from each of five random visual fields under microscopy (magnification ×100), results of which were averaged. For light chain immunoglobulin (kap-

Table 1 Clinicopathological features of the patients

Gender	Man	24
	Woman	39
Age at study (mean±SEM)	58.5±1.8	
Location of disease	buccal mucosa	43
	gingival mucosa	7
	lip	6
	tongue	5
	other	2
Complication	Sjögren syndrome	1
	IgG4 related disease (lung)	1
Hepatitis C virus infection	Positive for antibody	2
	Negative for antibody	28
	Not examined	33

pa, lambda) expression, immunoreactivity was evaluated and monoclonal B-cell light chain restriction was considered when overall kappa : lambda ratio>10 : 1 or<10 : 1 was detected. Histopathological findings of IgG4 positive cell infiltration [10 cells/high power field (HPF)] are IgG4 positive case and an IgG4/IgG cytoplasmic expression cell ratio>40% are diagnostic of IgG4-related disease. After staining, the slides were reviewed by the authors using a multiheaded microscope and consensus was reached for all analysis.

DNA Extraction and Analysis of B cell clonality

Formalin-fixed, paraffin-embedded samples were cut serially to a thickness of 10 μm. Using hematoxylin and eosin stained section as a guide, representative areas of the inflammatory lesion was gently taken from three 10 μm tissue section. Genomic DNAs were extracted from the dissected tissue samples using the DNA Isolator PS Kit (Wako, Osaka, Japan) according to the manufacturer's instructions. The immunoglobulin heavy chain CDR3 region was amplified by polymerase chain reaction (PCR) with the following primers : upstream primer (FR3A : 5'-ACA CGG C (C/T) (G/C) TGT ATT ACT GT-3') and downstream primer (LJH : 5'-TGA GGA GAC GGT GAC C-3'). PCR carried out in the thermal cycler (Perkin Elmer 9600 Gene Amp PCR system, USA) using the following amplification profile : one cycle of 94℃ for 5 min followed by 35 cycles of 94℃ for 1 min, 55℃ for 1 min, and 72℃ for 1 min, followed by one cycle of 72℃ for 5 min. The reaction mixture (50 μl) contained 0.3 μg of genomic DNA, 200 μM of dNTP mixture, 2.5 units of Taq polymerase (Amersham Pharmacia Biotec, Chalfront, UK) 10 pmol of a pair of primers. The DNA extracted form diffuse large B-cell lymphoma specimen was used as a positive control, whereas DNA from the reactive lymphoid tissue, was used as negative control. All PCR products were electrophoresed in a 12% Poly-Acrylamide gel and visualized with SYBR Gold Nucleic Acid Gel Stain (Invitrogen, Molecular Probes, Inc. OR, USA) under UV translumination. The determination as monoclonal rearrangement was made only when a single or dominant discrete band was consistently reproduced. A diffuse polyclonal smear was seen in all cases of reactive inflammatory lesion.

Statistical Analysis

StatFlex Ver. 6 statistical software (Artech Co.,Ltd, Osaka, Japan) was used for all analyses. Chi-squared analyses were performed to investigate the relationship among inflammatory grade, lympho-plsma cell marker positivity and spreading pattern of inflammatory cell. All values were expressed as the mean± SEM, and the significance of differences between two groups was assessed using Mann-Whitney U-test. Differences at $P<0.05$ were considered to be significant.

RESULTS

Clinical findings

Of the 63 patients with OLP, 24 were men and 39 women with an age range from 22 to 90 years (mean 58.5±SEM 1.8 years). The distribution of oral mucosal

Table 2 Spreading pattern of inflammatory cell

Lympho-plasma infiltration pattern	Grade			Total
	mild	moderate	severe	
Horizontal superficial type	15	18	10	43
Expanding type	4	7	9	20

mild : restricted to 30% or less of the inflammatory lesion, moderate : 30% to 60% of the inflammatory lesion, and severe : 60% or more in the inflammatory lesion

Table 3 Spreading pattern of inflammatory cell and its associated lympho-plasmacytic immunohistochemical futures and IgG4 positive plasma cells

Lympho-plasma infiltration pattern		IgG4	
		Positive	Negative
Horizontal superficial type	T cell predominat (CD3>CD20/CD79a)	0	5
	T cell with B cell (CD3 : CD20/CD79a)	6	32
Expanding type	T cell predominat (CD3>CD20/CD79a)	0	0
	T cell with Bcell (CD3 : CD20/CD79a)	15	5

T-cell predominant pattern : CD3-positive cells were more abundant than CD20- and/or CD79a-positive cells. T-cell with B-cell pattern : CD3-positive cells were equal or less than CD20- and/or CD79a-positive cells

sites included buccal mucosa (n=43), gingival mucosa (n=7), lip (n=6), tongue (n=5), and other (n=2) (Table 1).

Analyses of Inflammatory Cell Spreading Pattern Immunohistochemical Features of Lymphoplasmatic Cells, and B Cell Clonality.

The relationship between spreading pattern and grade of inflammation is summarized in Table 2. In the present study, inflammatory cells of the horizontal superficial type (Figure 1 (A)) was observed in 43 cases (68.0%), while those of the expanding type (Figure 1 (B)) was detected in 20 cases (32%). The grades of inflammation were quite variable the horizontal superficial type included 15 mild, 18 moderate and 10 severe cases, and the expanding type consisted of 4, 7 and 9 cases, respectively. There was no relationship between inflammatory cell spreading pattern and grade. The lesions classified by type of cell spread was further categorized according to expression of lymphoid-plasma cell markers (CD3, CD20, and CD79a) and IgG4 immunoreactivity (Table 3). Within the horizontal superficial type category, cases with only CD3-positive T-cells (n=5) restricted to the epithelial layer of connective tissue were considered as T-cell predominant pattern. Cases with this pattern did not contain any IgG4 plasma cells. None of the expanding type cases had the T-cell predominant pattern in this series (Figure 2A). Further, the T-cell with B-cell pattern that contained cytoplasmic IgG4 plasma cells were observed in 6 of 38 (15.8%) horizontal superficial type (Figure 2B) and 15 of 20 (75%) expanding type (Figure 2C) cases ($P<0.001$). IgG4-positive plasma cells were more abundant in cases of the expanding type with T-cell with B-cell pattern than those of the horizontal superficial type. However, the plasma cells rich in IgG4 did not contain any light chain restriction and immunoglobulin gene monoclonality (data not shown).

DISCUSSION

IgG4-related disease has attracted much attention from pathologists and clinicians since Hamano et al reported that patients with lymphoplasmacytic sclerosing pancreatitis, also called autoimmune pancreatitis, have high serum IgG4 concentrations and/or abundant IgG4-positive plasma cells in the tissue infiltrate[4,5]. Following reports describing patients with extrapancreatic disease, but with otherwise similar serologic and histologic features, such lesions have been proposed as a manifestation of IgG4-related systemic dis-

eases including orbital[10], pulmonary inflammatory pseudotumor[11], sclerosing sialoadenitis[12], retroperitoneal fibrosis[13], inflammatory aortic aneurysm[14], lymphadenopathy[15], tubulointerstitial nephritis[16], cutaneous plasmacytosis[17], and Hashimoto's thyroiditis[18].

The classic oral lesions of lichen planus can be described as erosive, and planar plaques, Thus, the differential diagnosis of OLP includes squamous cell carcinoma, discoid lupus erythematosus, candidiasis, graft-versus-host disease, and lichenoid lesion, which all similarly present as a whitish lesion[1]. The classic histologic features of OLP consist of predominantly horizontal spreading T-cells and B-cells with plasma cell infiltrate at the interface between the hyperkeratinized epithelium and connective tissue accompanied by apoptotic changes. Non-neoplastic oral mucosa with dense band-like inflammatory cells has been diagnosed as OPL[1,3]. IgG4-related disorders commonly present with abundant IgG4-positive plasma cells in the involved tissues[6~9]. Oral mucosa lesions have not been described in patients with IgG4-related disease.

In this series, no relationship was found between inflammatory cell spreading pattern and grade of inflammation. Specimens of the horizontal superficial type with either the T-cell predominant pattern (5 cases) or the T-cell with B-cell pattern (38 cases) showing dense band-like lesions were considered as classical OLP. None of the expanding type cases showed the T-cell predominant pattern, however, 20 cases of this type demonstrating the T-cell with B-cell pattern showed dense non-band-like lesions and thus, were considered as non-classical or atypical OLP. Moreover, atypical OLP cases included abundant polyclonal non-neoplastic IgG4-positive plasma cells. The case of T cell with B cell pattern, 15.8% (6/38) IgG4 positive is seen in horizontal superficial type, on the other hand, 75% (15/20) in expanding type. These different of IgG4 positive ratio findings reveal that the potential importance of disease progression in the OPL with a predominance of IgG4 positive plasmacytosis. But it has been that OPL is a T-cell mediated chronic inflammatory oral mucosal disease of unknown etiology[3]. Several etiological factors have been reported including genetic status, infection (hepatitis C virus, etc), allergies (food, drug), autoimmune disease and malignancy in OLP. However, the presence of plasma cell infiltration suggests the involvement of chronic inflammation, allergies and autoimmune disease. In the present study, five cases of atypical OLP of the expanding type showed marked IgG4-positive plasma cell infiltration in the oral mucosa, but none of these patients had associated extra-oral cavity IgG4-related disease or hepatitis C virus infection. Two patients each with extra-oral cavity complications (Sjögren syndrome, pulmonary IgG4-related disease) and positivity for hepatitis C virus antibody were classified as classic OPL with the horizontal superficial type. Several studies have suggested that although serum IgG4 may be elevated, plasmacytosis with abundant IgG4 is organ specific and not systemic in IgG4-related disorder tissue[3,8]. The salivary and lacrimal glands have been shown to be involved in an IgG4-related disease, also known as Mickulicz disease, which is defined clinically as symmetrical swelling of these glands. Unfortunately, Mickulicz disease is often confused with Sjögren syndrome[19], a distinct autoimmune disease and histologically represented by lymphoplasmacytic sialadenitis[20]. Our case of OLP accompanied by Sjögren syndrome had presence of anti-SSA and anti-SSB autoantibodies without any infection including Hepatitis C virus. Allergic and autoimmune disease are promoted by activation of IgG4 and IgE, leading to interleukin-6 production and plasmacytosis[21,22]. Many studies have demonstrated a close relationship between type 1 and/or 2 helper T (Th1 and/or Th2) imbalance in allergic and autoimmune disease. Formerly known as the expression pattern of the different cytokines/chemokines, which involved in Th1 and/or Th2 polarization in OLP[23]. Here we present evidence that IgG4 molecules are released from plasma cells in OLP. In expanding type, IgG4 responses can be induced by prolonged or repeated unknown antigen exposures. IgG4 production, like IgE production, is controlled primarily by Th2 cells. Th2 cytokines such as interleukin-4 and interleukin-6 enhance the production of both IgG4 and IgE[24]. This finding is considered to be the theory that production of IgG4 in expanding type of OLP is induced by Th2-cell-dominant immune reaction with the activation of T-cell-mediated immune response. OLP is a chronic inflammatory disorder characterized by a T-cell-mediated immune response with persistent accumulation of lymphoplasmacytes[23]. Although

there is no data of serum IgG4, IgE and Th2 related cytokines including interleukin-6, oral mucosal plasmacytosis could be a chronic allergic reaction in present cases. Moreover, we found the presence of pollinosis (n＝1/0) and slight eosinophilia (n＝6/4) in the expanding type cases (with/without IgG4-positive plasma cells, respectively). Therefore, OLP maybe respond to the steroid-containing agents like a IgG4 related disease[25].

In conclusion, immunohistochemical analysis of IgG4 positive plasma cells and inflammatory cell spreading pattern are useful for differential diagnosis of OLP. Further prospective studies are needed to establish the role of IgG4-positive plasma cells to distinguish between the horizontal superficial and expanding types of inflammatory cell spreading pattern in OLP. Since the pathogenesis of IgG4-positive plasma cells in OLP is unclear, it is necessary to investigate a larger series of patients with OLP.

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