



ORIGINAL ARTICLE

Plasma Cell Cheilitis: A Clinicopathological and Immunohistochemical Study of 13 Cases

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Background: Plasma cell cheilitis is an unusual benign plasma cell proliferative disease of an unknown etiology that typically presents on the lip. **Objective:** The aim of this study was to investigate the clinicopathological characteristics of 13 cases of plasma cell cheilitis. **Methods:** The present study investigated the clinical manifestations, treatment modalities, and outcome of 13 patients diagnosed with plasma cell cheilitis from 2011 to 2016 at Kangdong Sacred Heart Hospital and Hallym University Sacred Heart Hospital. Biopsy specimens of the all cases were evaluated using conventional hematoxylin and eosin staining with kappa and lambda immunoglobulin light chain immunohistochemistry. **Results:** The age of the patients ranged from 39 to 86 years (mean, 64.7 years), with male predominance. Histopathologically, 61.5% and 38.5% of patients showed band-like and peridermal plasmacytic infiltrates, respectively. Eosinophilic infiltration was noted in 69.2% of patients. All cases showed both kappa and lambda immunoglobulin light chain reactivities, and kappa predominance was confirmed in 9 patients (69.2%). A majority of the patients was treated with local therapy, such as intralesional steroid injection with topical tacrolimus. Among the 13 patients, plasma cell cheilitis

completely resolved, partially resolved, and recurred in 3 (23.1%), 5 (38.5%), and 5 patients (38.5%), respectively.

Conclusion: Plasma cell cheilitis presented as erosive edematous circumscribed patches or plaques affecting mainly the lower lip of elderly male patients. The majority of histopathology cases showed characteristic plasma cell aggregation on the upper dermis that was immunopositive for immunoglobulin light chain, with kappa predominance. (Ann Dermatol 29(5) 536~542, 2017)

-Keywords-

Cheilitis, Kappa chain, Lambda chain, Plasma cells

INTRODUCTION

Plasma cell cheilitis (PCC) is a rare, idiopathic, inflammatory disease that occurs on the lip, with histological findings characteristically showing dense infiltration of plasma cells in the papillary dermis of the mucosa¹⁻³. It is also considered as a lower categorical entity that belongs to plasma cell mucositis (PCM), which involves the mucous membrane of the oral cavity and upper aerodigestive tract^{4,5}. PCC clinically presents as minutely prominent erythema or a dark-red or brownish patch or plaque with relatively clear margins, mainly in the lower lip of elderly people^{1,2,6}. This condition can be accompanied by erosion, ulceration, fissures, bleeding, or crusts. Spontaneous resolution of PCC is extremely rare and is known to respond poorly to traditional topical steroid treatment⁷. Besides, systemic steroid ingestion, intralesional steroid injection, systemic griseofulvin administration, and local application of immunomodulatory agents such as tacrolimus and pimecrolimus, are examples

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of various treatments that are being attempted^{6,8-13}.

Most of the cases of PCM have included involvement of the oral cavity and upper aerodigestive tract; therefore, several published studies have been reported in the otolaryngology and oro-maxillofacial surgery literature^{4,5,14}. Otherwise, limited case series on the clinical and histopathological findings of PCC have been reported in the dermatology literature, with only a few showing immunohistochemical analysis^{7,15}. Furthermore, no guidelines were established for the management and clinical outcome prediction of PCC owing to the lack of sufficient case studies. In the present study, we described a case series of PCC, with clinicopathological features and immunohistochemical study along with a literature review.

MATERIALS AND METHODS

A total of 13 cases of patients diagnosed with PCC at Kangdong Sacred Heart Hospital and Hallym University Sacred Heart Hospital were retrospectively reviewed over a 6-year period from 2011 to 2016. The following clinical manifestations, including gender, age, location, presence of erosion or bleeding, smoking habit, accompanying symptoms, habitual behavior, treatment modalities, clinical outcome, and follow-up period were collected from electronic medical record and interview.

Biopsy specimens of all the enrolled patients were retrieved from the Department of Pathology and investigated independently by the three experienced dermatologists. All specimens were formalin fixed, paraffin embedded, and stained; hematoxylin and eosin (H&E) staining and immunohistochemistry analysis of kappa and lambda light



Fig. 1. (A) The lower lip shows a diffuse dark blue-grayish to erythematous patch with several fissures and hemorrhagic crusts (patient 3). (B) Painful ulcerative lesion is noted on the left lower angle of the lip on a patient who used dentures (patient 9). (C) Prominent edematous erosive lower lip mucosa is shown (patient 10). (D) Multiple well-demarcated erythematous patches with crust formation and marked swelling on the lower lip are identified (patient 6).

chains using the Dako Autostainer (Dako, Carpinteria, CA, USA) were used based on the manufacturer and established laboratory protocols. Immunoglobulin (Ig) heavy chain gene rearrangement via polymerase chain reaction analysis was performed only in selected patients to confirm clonality of Ig heavy chain. Each slide was reviewed for the presence or absence of the following histopathological findings: acanthosis, papillary edema, parakeratosis, vacuolar degeneration or melanin incontinence, infiltration of mononuclear inflammatory cells, such as eosinophils or neutrophils, and infiltrative pattern of plasma cells.

The reactivity levels of kappa and lambda light chains based on the starting intensity were graded as follows: – (negative, no positive cells), + (weak positive, $\leq 25\%$ positive cells), ++ (moderately positive, $26\% \sim 50\%$ positive cells), and +++ (strongly positive, $> 50\%$ positive cells).

RESULTS

Clinical characteristics

Majority of the patients were elderly men. Patient ages ranged from 39 to 86 years (mean age, 64.7 ± 13.93 years) with male predominance (male, 9 patients; female, 4 patients). Only one patient was younger than 50 years. Most of the skin lesions in the enrolled patients presented as a well-demarcated dark blue-grayish to erythematous patches (8 patients, 61.5%) and plaques (5 patients, 38.5%) with or without fissures, crusts, and ulcer on the lower lip (Fig. 1A). Accompanying prominent swelling was observed in 9 patients (69.2%). No accompanying lesion of the upper lip and PCC was exclusively located on the lower lip in the present study. The most frequent clinical symptoms were pricking (7 patients, 53.8%), followed by pain (6 patients, 46.2%), pruritus (3 patients, 23.1%), and burning sensation (2 patients, 15.4%). Only one patient reported no symptoms. Three patients complained of discomfort when eating or drinking. Erosion and epidermal detachment were observed in 10 (76.9%) and 2 patients (15.4%) who had ulcerative lesions, respectively (Fig. 1B, C). Bleeding and crusting were identified in 9 patients (69.2%) (Fig. 1D). Almost half of the enrolled patients (53.8%) were current smokers, particularly the men. Three patients (23.1%) used denture in ordinary life, and each patient (7.7%) had the habit of lip biting and chewing gum. The demographic and clinical characteristics are summarized in Table 1.

Histopathological findings

For the histopathological findings, all cases showed similar features; dense, band-like (8 patients, 61.5%) or dif-

Table 1. Demographic and clinical characteristics of patients with plasma cell cheilitis (n=13)

Clinical manifestations	Results
Mean age (yr)	64.7 (39~86)
Sex	
Male	9 (69.2)
Female	4 (30.8)
Location	
Upper lip	0 (0)
Lower lip	13 (100)
Clinical presentation	
Patch	8 (61.5)
Plaque	5 (38.5)
Accompanied by	
Erosion	10 (76.9)
Ulcer	2 (15.4)
Bleeding and crust	9 (69.2)
Swelling or edema	9 (69.2)
Smoking	7 (53.8)
Habitual behavior	
Denture	3 (23.1)
Chewing gum	1 (7.7)
Lip biting	1 (7.7)
Associated symptoms	
Pricking	7 (53.8)
Pain	6 (46.2)
Pruritus	3 (23.1)
Burning	2 (15.4)

Values are presented as number (range) or number (%).

fuse pandermal (5 patients, 38.5%) infiltrates composed mainly of plasma cells in the dermis were the most prominent histological features in PCC (Fig. 2A, B). The remaining cells mainly consisted of lymphocytes and histiocytes. In addition, few eosinophilic infiltrations were noted in 9 patients (69.2%), and neutrophilic infiltrations related with epidermal ulceration were identified in 5 patients (38.5%). The biopsy specimens from 8 (61.5%), 4 (30.8%), and 6 (46.2%) patients showed acanthosis, papillary edema, and parakeratosis, respectively. Vacuolar degeneration in the dermo-epidermal junction with melanin incontinence, suggesting interface dermatitis, was found in 8 patients (61.5%). Mitotic activity, pleomorphism, and cellular atypia were less frequently seen and no granulomas were observed in all specimens.

Kappa predominance was confirmed in 9 of 13 cases (69.2%). Kappa chain was strongly, moderately, and weakly positive in 6 (46.2%), 5 (38.5%), and 2 (15.4%) patients, respectively; in contrast, lambda chain was strongly, moderately, and weakly positive in 1 (7.7%), 4 (30.8%), and 8 (61.5%) patients, respectively (Fig. 2C, D) (Table 2). Ig heavy chain gene rearrangement was performed in 3 patients who showed high cellularity in the

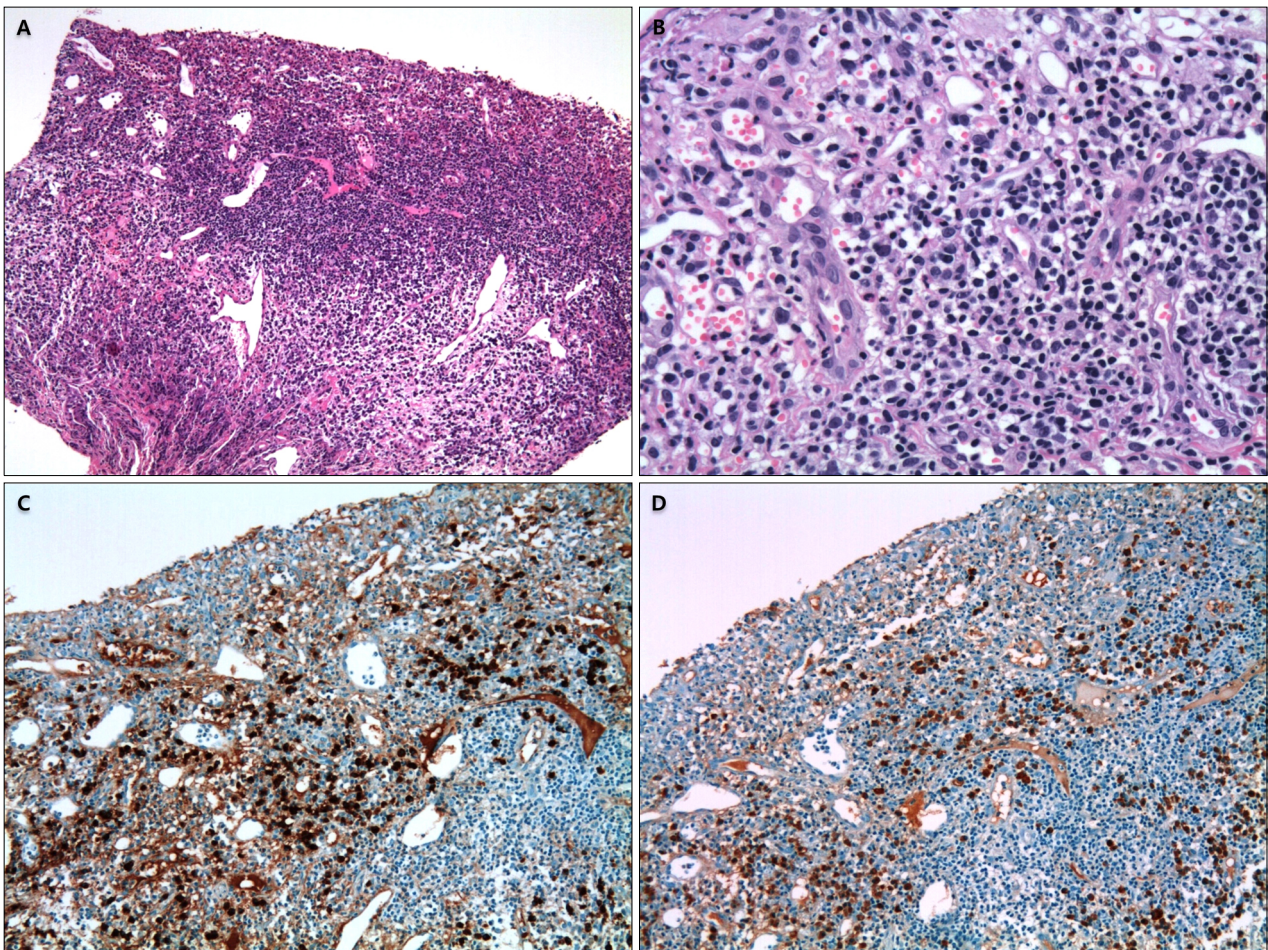


Fig. 2. This specimen from the lip shows an epidermal detachment with a dense, band-like infiltrate of plasma cells in the upper dermis. (A) Eosinophilic infiltration within the dermis is also present (H&E, $\times 100$). (B) A high power view shows a monomorphic population of mature plasma cells without cellular atypia, pleomorphic figures, and mitotic activity (H&E, $\times 400$). (C) A diffuse strong positivity for kappa light chain is noted in the plasma cell infiltrates (kappa chain, $\times 200$). (D) Few plasma cells are positive for lambda light chain restriction (lambda chain, $\times 200$).

specimen, and all results were revealed as having an oligoclonal pattern, which was suggestive of benign reactive proliferative lymphoid lesions.

Treatment and clinical outcome

Most of the patients in the present study were treated with a combination of intralesional steroid injection (triamcinolone) and topical tacrolimus ointment (Protopic[®]). Five patients were prescribed further systemic steroid (methylprednisolone, 0.5~1 mg/kg/day) with local therapy owing to the poor response to topical agents and uncontrolled progressive symptoms. Topical steroid, pimecrolimus, and cryotherapy were also appropriately administered to the patients. Among the 13 patients, PCC spontaneously resolved and partially remitted in 3 (23.1%) and 5 (38.5%) patients, respectively. In contrast, the other five patients (38.5%) had a relapse after complete or partial remission.

The median follow-up period was 11.2 months (range, 3~39 months) (Table 3).

DISCUSSION

PCC is a relatively rare inflammatory disorder of the lip, characterized histologically by dense infiltration of plasma cells in the upper dermis, wherein its pathogenesis remains elusive. It is known as an oral counterpart of plasma cell balanitis (Zoon's balanitis), which was first described by Zoon¹⁶ in 1952 as an inflammatory disorder of the glans penis, showing characteristic band-like infiltrate of plasma cells in the upper dermis. Based on White et al.¹⁷, PCC was observed as a clinically and histopathologically identical disease developing in several orificial surfaces, such as the vulva, buccal mucosa, palate, lip, tongue, epiglottis, and larynx, and collectively known as plasma cell

Table 2. Histopathological characteristics of patients with plasma cell cheilitis (n=13)

Histopathological features	Results
Acanthosis	8 (61.5)
Papillary edema	4 (30.8)
Parakeratosis	6 (46.2)
Vacuolar degeneration	8 (61.5)
Eosinophilic infiltration	9 (69.2)
Neutrophilic infiltration	5 (38.5)
Infiltration pattern of plasma cells	
Band-like	8 (61.5)
Diffuse	5 (38.5)
Kappa chain reactivity*	
+++	6 (46.2)
++	5 (38.5)
+	2 (15.4)
-	0 (0)
Lambda chain reactivity*	
+++	1 (7.7)
++	4 (30.8)
+	8 (61.5)
-	0 (0)
Kappa predominance	9 (69.2)

Values are presented as number (%). *The reactivity levels of kappa and lambda light chains based on the starting intensity were graded as follows: - (negative, no positive cells), + (weak positive, $\leq 25\%$ positive cells), ++ (moderately positive, $26\% \sim 50\%$ positive cells), and +++ (strongly positive, $>50\%$ positive cells).

orificial mucositis. In addition, immunohistochemical analysis of one case in their study showed plasma cell production of both kappa and lambda chains.

Histopathologically, hyperkeratosis, dyskeratosis, intercellular edema, epidermal erosion, and vacuolar or liquefactive degeneration due to inflammatory cell infiltration in the dermo-epidermal junction can be seen in PCC¹⁵. Many plasma cells are infiltrated in a band-like shape in the upper dermis or densely infiltrated throughout the entire dermis¹⁻³. This plasma cell infiltration in the dermis is a characteristic finding of PCC that is rarely seen in common inflammatory dermatosis. Although the pathogenesis for the plasma cell infiltration remains unknown, B-cell growth and differentiation in the mucosa and skin are suggested to be affected by T cells and macrophages^{1,6,7}. In the present study, majority of the cases of infiltrated plasma cells in the dermis showed polyclonality of the kappa and lambda chains in immunohistochemical stains. In accordance with previous literatures, they were also composed of cells primarily the kappa chain instead of the lambda chain^{4,7}. Aiba and Tagami⁷ also demonstrated that plasma cell infiltrates in PCC were composed of IgG- and IgA-producing cells, and those are in accordance with the pattern observed in certain skin diseases, including actinic keratosis, Bowen's disease, squamous cell carcinoma, pemphigus vulgaris, and syringocystadenoma papilliferum. Interestingly, almost 70% of patients in the present study were revealed to have large amounts of admixed eosino-

Table 3. Treatment and outcome of the 13 included patients with plasma cell cheilitis

Patients no.	Sex/age (yr)	Treatment modalities	Outcome	Follow-up period (mo)
1	M/82	Intralesional steroid injection, topical tacrolimus 0.1%	Relapsed	11
2	M/52	Intralesional steroid injection, topical tacrolimus 0.1%	CR	6
3	M/75	Intralesional steroid injection, topical tacrolimus 0.1%	PR	13
4	F/75	Intralesional steroid injection, topical tacrolimus 0.1%, systemic steroid (MPD)	Relapsed	6
5	F/65	Intralesional steroid injection, topical tacrolimus 0.1%, systemic steroid (MPD)	Relapsed	5
6	M/53	Intralesional steroid injection, topical tacrolimus 0.03%	CR	3
7	M/65	Intralesional steroid injection, topical tacrolimus 0.03%	CR	7
8	M/39	Intralesional steroid injection, topical tacrolimus 0.1%	PR	4
9	F/86	Intralesional steroid injection, topical steroid, systemic steroid (MPD)	Relapsed	39
10	M/79	Topical tacrolimus 0.1%, topical steroid	Relapsed	17
11	F/58	Topical tacrolimus 0.1%	PR	9
12	M/55	Topical tacrolimus 0.1%, systemic steroid (MPD), cryotherapy	PR	18
13	M/57	Intralesional steroid injection, topical pimecrolimus, systemic steroid (MPD)	PR	8

M: male, F: female, CR: complete remission, PR: partial remission, MPD: methylprednisolone.

phils with lymphoplasmohistiocytic infiltrates, which is significantly higher than those in the study by Choe et al.¹⁵ who reported only 2 of 8 cases showing mild eosinophilic infiltration.

The etiology and pathogenesis of PCC have not been clarified yet. However, some cases reported until today were believed to be associated with frequent exposures to candy, gum, toothpaste, other foreign substances, and underlying disease, such as hypertension and metabolic abnormalities^{15,18-20}. Other cases were reported to be induced by mechanical irritation or accumulated solar damage. Choe et al.¹⁵ particularly suggested that solar damage accumulating in the lower lip, which is a major exposed area of sunlight, could be considered as the causative agent in all observed cases. All patients in the present study also developed PCC in the lower lip; therefore, solar damage due to chronic sun exposure is speculated as an important cause such as in actinic cheilitis. Moreover, 2 of our patients had habitual behaviors, such as chewing gum and lip biting, and 3 of our elderly patients consistently used dentures, which can play an uncertain mechanical role in the development of PCC.

To date, PCC is regarded as a type of PCM. Solomon et al.⁴ summarized 22 studies of PCM, which encompass the plasma cell-rich condition occurring on all locations of the upper aerodigestive tract, including the lips, mouth, tongue, gingiva, palate, larynx, pharynx, and even the bronchial tree. The mean age of those patients was 56.6 years, which is slightly younger than that of our patients. They also described that majority of PCM cases are associated with a synchronous or metachronous autoimmune or immunologically mediated disease; however, none of our patients were diagnosed with immune disorders. The classic clinical presentation of PCM is known to be various morphologies, such as papillomatous, cobblestone, nodular, or velvety, which are different from PCC, which usually shows patches and plaques with swelling rather than warty or lobulated surface contour. It might result from the different mucosal characteristics located in the inner or outer sites of the body. However, distinct clinical features of PCC as a subordinate disease of PCM should be investigated further.

The clinical course of PCC can be quite prolonged. Moreover epidermal neoplasm, which is composed of plasma cell infiltrates because mononuclear inflammatory cells, may affect the production of factors that induce the peculiar polyclonal plasma cell infiltration⁷. Although PCC is considered a benign disorder with long stability and hardly progresses to malignancy, the treatment is often challenging⁴. Some authors have shown that topical and intralesionally administered steroids and topical im-

munomodulatory agents, such as tacrolimus and pimecrolimus, were effective for the clearing the lesions, whereas others have found that most of the topical therapies were ineffective in their patients and have recommended alternatives, such as surgical excision, radiation therapy, laser therapy, electrocauterization, and cryosurgery^{6,9-13,21,22}. In the present study, majority of the patients were treated by a combination of intralesional steroid injection and topical tacrolimus, with multi-sessions at an interval of 2 weeks. Intralesional steroid injection is known to have an anti-inflammatory property as well as to increase the effects of topical agents by bypassing the epidermal barrier zone¹². Topical tacrolimus preparations, which are being used to treat inflammatory dermatosis, inhibit the signal transduction of the T lymphocytes⁹⁻¹¹. However, some patients in the present study responded poorly to those treatment modalities because of the unclear etiology or resistant factor, such as acanthosis/hyperkeratosis, depth and heaviness of the infiltrates, and accompanying underlying disease. Therefore, well-designed studies on the affecting triggers to manage the clinical course of PCC with long-term follow-up periods are required. Additional investigative analysis to identify accurate functional pathogenesis on the plasma cells should be warranted.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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