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Original Article

Clinicohistological analysis of plasma cell cheilitis: 20 cases

漿細胞口唇炎的臨床組織學分析共二十例

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Background: Plasma cell cheilitis (PCC) is a rare inflammatory disease that occurs on the lip. It is common in elderly people and important a differential diagnosis is actinic cheilitis. ***Objective:*** To analyse the clinical and histopathological features of plasma cell cheilitis. ***Methods:*** PCC patient's characteristics, treatment method and response, histological findings, and clinical course were evaluated. ***Results:*** Of 20 patients, nine (55%) experienced a complete response without relapse and eight (40%) were included in the relapsed group. A band-like infiltration of plasma cells was observed in the dermis of all specimens. ***Conclusion:*** As PCC is likely to relapse, periodic status checks and treatment may be necessary.

背景：漿細胞口唇炎是一種發生在嘴唇上的罕見發炎性疾病。這在老年人中很常見，重要的鑑別診斷是光化性口唇炎。**目的**：分析漿細胞口唇炎的臨床和組織病理學特徵。**方法**：評估漿細胞口唇炎患者的特徵、治療方法和療效，並組織學表現以及臨床病程。**結果**：在二十例患者中，有九例（55％）經歷了完全治愈而沒有復發，另八例（40％）則被歸入復發組中。在所有標本的真皮中均觀察到漿細胞的帶狀浸潤。**結論**：由於漿細胞口唇炎的復發並不罕見，因此有需要定期檢查狀況並治療。

Keywords: Cheilitis, plasma cells, plasma cell cheilitis

關鍵詞：口唇炎、漿細胞、漿細胞口唇炎

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Introduction

Plasma cell cheilitis (PCC) is an uncommon, chronic inflammatory disease that occurs on the lips. It is characterised by well-defined, infiltrated, elevated plaques or patches (Figure 1).[1] Histopathologically, hyperkeratosis, dyskeratosis, vacuolar degeneration in the epidermis and characteristically, plasma cell infiltration can be found in the dermis.[2]

PCC is also classified as plasma cell mucositis because of similar histological findings may occur on other sites of the body, including the oral cavity and upper aerodigestive tract.[1,3] The cause of PCC is often unknown, and is more common on the lower rather than the upper lip.[4,5]

Various treatments for PCC have been tried with variable results. Treatments include systemic and topical corticosteroids, systemic griseofulvin, intralesional steroid injections, and topical calcineurin inhibitors.[6,7]

Differential diagnoses include actinic cheilitis, allergic contact cheilitis, lichen planus, and squamous cell carcinoma. PCC is often difficult to distinguish clinically, so a skin biopsy must be performed to accurately diagnose PCC when it is not evident clinically.[8] PCC tends to be more common in older patients.[7,8]

In this study, we review the characteristics of patients diagnosed with PCC, treatment given and outcomes, histological findings and clinical course. The lips are a prominent facial feature and can affect daily activities such as eating and talking. Therefore, it is necessary to clearly differentiate PCC from other diseases and treat accordingly.

Materials and methods

This study is a retrospective design based on the medical records of patients who were diagnosed with PCC at Chosun University Hospital dermatology from 2012 to 2019. All data were analysed under three main categories: patient characteristics, treatment methods and response, histological findings and clinical course. Patient characteristics included the following: age, sex, duration of symptoms, location (upper lip, lower lip, or both upper and lower lips), associated symptoms (i.e., pain, pruritus, prickling), and accompanying skin disease.

The treatment responses were divided into three groups: (i) Complete response (CR): patients experienced a complete recovery without recurrence until follow up period; (ii) Relapsed group: patients responded to treatment but had relapses. The period without recurrence was based on the medical records indicating when symptoms reappeared and (iii) No response (NR) group: patients did not respond to treatment. If there was no information in the medical record related to CR or relapse, current symptoms and conditions were assessed via patient phone consultation. Treatment response comparisons were analysed in two patient groups: 65 years old or older and under 65 years

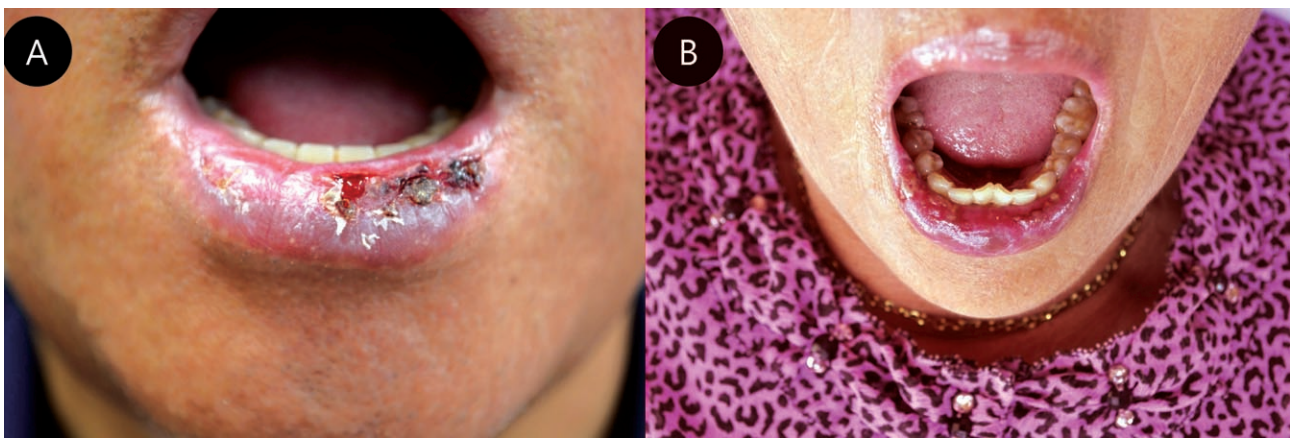

Figure 1. Clinical manifestations of plasma cell cheilitis in a (A) 67-year-old man and a (B) 69-year-old woman.

old. The Chi-square test was used to determine if whether the differences in treatment response between the two groups were statistically significant.

All tissues were prepared with haematoxylin and eosin (H&E) staining and were read by both pathologists and dermatologists. Each slide was classified according to the following findings: acanthosis, intercellular oedema, parakeratosis, vacuolar degeneration, eosinophilic infiltration, neutrophilic infiltration, Russell bodies, dyskeratosis, and other histological findings. Other histological findings included erosion and melanin incontinence. The study was approved by the Institutional Review Board of Chosun University Hospital (No.CHOSUN 2020-02-018).

Results

Patient characteristics

A total of 20 patients were recruited (age range: 51 to 83 years; mean age: 62.65 years). Of the patients, 11 (55%) were 65 years old or older. The male: female sex ratio was 6:4. The disease duration was greater than six months in eleven patients (55%) and under six months in nine patients (45%). The average duration of the disease was approximately 8.15 months. All lesions involved the lower lip with two patients affected on both the upper and lower lips. Sixteen patients (80%) complained of symptoms and four (20%) had lesions but no symptoms. The most common symptom reported was pain (65%) and two patients had complaints of pruritus and prickling. Nine patients (45%) had patch lesions and 11 patients (55%) had plaque lesions. However, in most patients, erosion and crusting were observed as common characteristics of PCC.

Three patients had accompanying skin diseases including actinic keratosis on the face, aphthous ulcers, and oral candidiasis (Table 1).

Treatment method and response

The main treatment method was intralesional injection of triamcinolone acetonide (90%) and topical tacrolimus application (60%). Cryotherapy was attempted in four patients when histologically dysplasia was prominent. One patient was prescribed a systemic steroid (methylprednisolone, 0.1 mg/kg/day). A patient who did not respond to other treatments responded to dapsone (100 mg/day) (Table 2).

Table 1. Patient characteristics

Age	Number of patients	% of sample
65 years old or older	11	55
Under 65 years	9	45
Sex		
Male	12	60
Female	8	40
Duration		
More than 6 months	11	55
Less than 6 months	9	45
Location		
Upper lip	2	10
Lower lip	20	100
Associated symptoms		
Asymptomatic	4	20
Painful	13	65
Pruritic	2	10
Prickling	2	10
Skin findings		
Patch	9	45
Plaque	11	55
Erosion	18	90
Crust	19	95
Accompanying skin disease		
Actinic keratosis	1	5
Aphthous ulcer	1	5
Oral candidiasis	1	5
Pyoderma	1	5

Of the 20 patients, nine (45%) achieved CR, eight (40%) relapsed, and three (15%) did not respond to treatment. Of the 17 patients who responded to treatment, the mean time to achieving significant improvement was 2.3 months. Significant improvement was seen anywhere from two weeks to six months.

In 11 patients over 65, four patients (36.3%) experienced CR without relapse (Figure 2) and six patients (54.5%) that responded to treatment were included in the relapsed group. The remaining patient did not respond to treatment. In nine patients under 65, five (55.6%) experienced CR and two (22.2%) were included in the relapsed group. Two patients (22.2%) did not respond to treatment. There was no statistical significance for the treatment effects between the two groups (P=0.322) (Table 3).

Histological findings

Twenty slides were analysed. First, the band-like infiltration of plasma cells was observed in the dermis on all specimens (Figures 3A & 3B). Intercellular oedema was observed in 11 slides (55%). Parakeratosis and dyskeratosis were also observed in 14 and 15 (70%, 75%) specimens, respectively. Vacuolar degeneration was observed in eight specimens (40%). Lymphocyte infiltration is also a well-known finding in PCC. In this study, 12 specimens showed neutrophilic infiltration (60%) and 11 (55%) eosinophilic infiltration (Figure 3C). In addition, Russell bodies were seen on three specimens (15%) (Figure 3D) (Table 2).

Table 2. Treatment methods

Treatment	Number of patients	% of sample
Intralesional steroid injection	18	90
Topical tacrolimus	12	60
Cryotherapy	4	20
Dapsone	1	5
Systemic steroid	1	5

Clinical course

As we mentioned earlier, of the 20 patients, 8 patients who showed clinical improvement initially experienced relapse. The average time to patient relapse was 10.75 months. Two of eight relapsed patients who were all over 65 had multiple relapses.

Discussion

PCC is a benign and chronic inflammatory skin disease that primarily affects the lips. It is common in men and the elderly. The characteristic clinical features are patches or plaques with ulcerations, erosion, bleeding, and crusting which are usually accompanied by prickling and painful sensations.[7,8] In 1952, Zoon first described balanitis caused by the dermal infiltration of plasma cells.[9] Later studies reported similar findings in other mucosal areas of the body and PCC is considered to be one of them.[10] There are also cases involving the upper aerodigestive tract that includes the buccal mucosa, gums, epiglottis, and larynx. All of these cases are

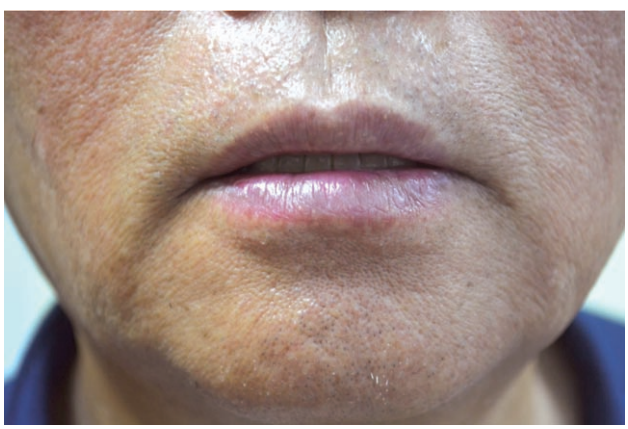

Figure 2. A 67-year-old man who achieved complete response.

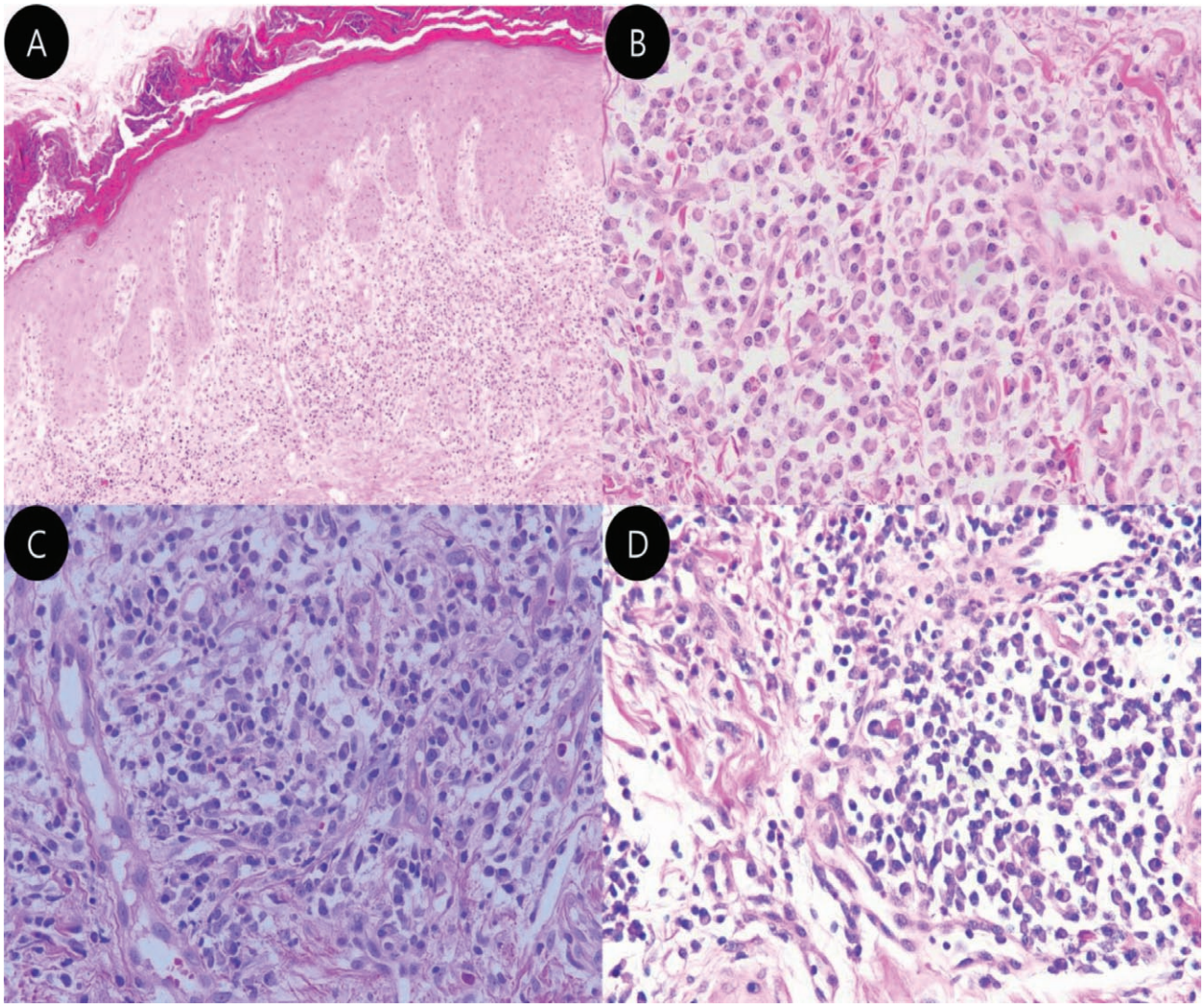

Figure 3. Histological findings. (A) Band-like plasma cell infiltration with dyskeratosis and parakeratosis (H&E, original magnification x 100). (B) Massive plasma cell infiltration (H&E, original magnification x 400). (C) Eosinophilic infiltration with plasma cell (H&E, original magnification x400). (D) Russell body (H&E, original magnification x 400).

Table 3. Treatment response

Group	Complete response	Relapsed	No response	Total
Whole patients	9 (45%)	8 (40%)	3 (17.6%)	20 (100%)
Under 65 years	5 (55.6%)	2 (22.2%)	2 (22.2%)	9 (100%)
65 years old or older	4 (36.3%)	6 (54.5%)	1 (9%)	11 (100%)

referred to as plasma cell mucositis (PCM) (Table 4). PCC can be categorised as PCM and the cause is unknown.[3] Several studies suggest that various risk factors such as chewing gum, toothpaste, smoking, and chronic sun exposure affect disease occurrence.[1,10,11]

The differential diagnosis includes several diseases that may cause cheilitis. There are many criteria for classifying cheilitis; however, the causes include contact, allergy, nutritional deficiency, systemic diseases, trauma, and immunity.[12] Among the classifications, actinic cheilitis (AC) may be the most common differential diagnosis because of its persistence. AC is a precancerous lesion on the lips and is known to be primarily caused by sun exposure. Its clinical features include lip dryness, scaly lesions, atrophy, oedema, and ulcers. One study suggested that dermoscopic findings might help distinguish PCC from AC. On dermoscopy, a regular border with telangiectasia is seen in PCC whereas in AC, irregular, ill-defined borders and ulcers are observed.[13] Although there are differences in dermoscopic findings, a biopsy is still necessary for a definitive diagnosis. The characteristic histological findings for AC are dysplasia, elastosis, and vasodilatation.[14] These histological findings are different from those found in PCC. Considering that both PCC and AC are prevalent in older people and that there are clinical similarities, it is important to differentiate between the two conditions. Another important reason for the differentiation is that squamous cell carcinoma can develop from AC on the lips.

PCC is known to be long-lasting and not very responsive to treatment.[15] Several treatments have been considered and recently, topical calcineurin inhibitors have been reported to be effective. The mechanism is the immunomodulatory effect of calcineurin inhibitors. They inhibit T lymphocyte signal transduction.[16-18] In this study, 0.1% topical tacrolimus ointment was applied twice daily. No side effects such as prickling or heat sensation were reported. This treatment was used in combination with others but was not applied to all patients. In this study, seven of nine patients (77.8%) who achieved CR received topical tacrolimus treatment.

The main treatment for PCC in this study was 0.1~0.5 mL (4.0 mg/mL) intralesional injection of triamcinolone acetonide at two-week intervals. Several studies have reported

Table 4. Histological findings

Histological features	Number of patients	% of sample
Infiltration of plasma cell	20	100
Dyskeratosis	15	75
Parakeratosis	14	70
Neutrophilic infiltration	12	60
Eosinophilic infiltration	11	55
Intracellular oedema	11	55
Vacuolar degeneration	8	40
Russell body	3	15
Acanthosis	2	10
Other histological findings		
Erosion	15	75
Melanin incontinence	2	10

successful therapeutic effects of intralesional steroid injections in PCC. Because injections can penetrate the epidermal barrier, they may be advantageous in terms of drug delivery compared to topical treatments.[15,19] In this regard, study patients were treated with intralesional steroid injections instead of topical steroids.

Also noteworthy was that one patient who did not respond to any treatment was cured by dapsone (100 mg/day for one week). He was treated with an intralesional steroid injection, topical calcineurin inhibitor, and systemic steroid for four months but everything was ineffective. Two weeks after the introduction of the dapsone treatment, a complete response was observed. This complete response suggests that dapsone therapy may be considered for the treatment of PCC especially in patients with treatment-resistant PCC. The anti-inflammatory effect of dapsone may be responsible for alleviating the disease. However, the underlying mechanism of CR is not clear.

Histological findings showed band-like infiltrations in the dermis of all patients. Other histological findings were dyskeratosis, parakeratosis, lymphocyte infiltration, intracellular oedema, vacuolar degeneration, and Russell bodies. Eosinophil and neutrophil infiltration findings were observed in other studies.[1,2] In the present study, the above findings were observed in more than 50% of the patients. The cause of these histological findings is not clear. However, one theory suggests that lymphocytes alter B cell growth and differentiation.[5,8,20] The Russell body, which is occasionally observed in PCC, was also observed in three patients.

PCC is known to be common in older people and is supported by the findings of this study in which patients with a mean age of 62.65 years were more prone to developing it. This study also confirmed that most patients (80%) experience symptoms. Also, the lips are more sensitive to discomfort because they are involved daily activities like eating or talking. In addition, the lips are part of the face, so lip pathology can affect facial appearance and potentially limit social activities. Considering the fact that there were relatively large number of patients (40%) in the relapsed group, regular follow-up and patient education that PCC may relapse despite initial cure are important.

In conclusion, this study reviewed the clinical course and histological findings of PCC. Given that PCC causes adverse symptoms in most patients and affects facial appearance, it may have a negative effect on patient QOL. Therefore, proper diagnosis and treatment are essential. Furthermore, since PCC is likely to relapse, regular follow-up is necessary to determine treatment effects and detect recurrence.

Acknowledgement

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