

Plasma Cell Mucositis: A Clinical Conundrum

Mahnaz Fatahzadeh¹, Joseph Rinaggio¹, Robert A. Schwartz²

¹Rutgers School of Dental Medicine, Newark, United States of America; ²Rutgers New Jersey Medical School, Newark, United States of America

Corresponding author:

Mahnaz Fatahzadeh, DMD, MSD
Rutgers School of Dental Medicine,
110 Bergen Street, Newark,
United States of America
fatahza@sdm.rutgers.edu

Received: August 14, 2023

Accepted: December 6, 2023

ABSTRACT Plasma cell mucositis (PCM) is an unusual disorder most evident in the accessible mucosa and usually reported in the upper aerodigestive tract, although it is named according to its specific anatomical site of involvement such as plasma cell cheilitis, plasma cell gingivitis, plasma cell vulvitis, and Zoon's balanitis. PCM reflects a dense polyclonal rather than a monoclonal plasma cell proliferation of unclear and unknown etiology. This perplexing disorder tends to be treated by avoiding possible triggers and intralesional and/or systemic steroids. In this work, we provide a review and update on PCM, which often represents a clinical conundrum.

KEY WORDS: mucositis, polyclonal, orofacial

INTRODUCTION

Plasma cell mucositis (PCM) is a rare benign chronic inflammatory disorder of the upper aerodigestive tract (UADT) characterized by intensely red mucosa with variable surface alterations. Tissue analysis reveals dense polyclonal plasma cell proliferation. Symptoms can include pain, dysphagia, sore throat, and hoarseness, depending on the anatomical site affected. Similar non-neoplastic proliferations of plasma cells at other body orifices have also been described. Mucosal alterations in PCM are typically diffuse, long-standing, and can involve various sites within the upper aerodigestive tract, including the oral cavity. The etiopathogenesis of plasma cell mucositis remains unknown. Its diagnosis relies on clinicopathologic correlation, with management involving elimination of potential allergens/irritants together with addressing symptoms. Many agents, including steroids, have been tried, with varying outcomes. Monitoring is advisable in order to address potential adverse effects of therapy, progression of disease to other sites, as well as clinical relapse.

ILLUSTRATIVE CASE

A 71-year-old woman presented for evaluation of red swollen oral tissues several months in duration. She reported minimal discomfort but expressed concern about the appearance and texture of her oral tissues. Detailed history failed to identify any precipitating factors such as change in diet, medications, dentifrices, dental work, or cosmetics. She was a non-smoker, did not chew gum or use mints, and was not a mouth breather. Her review of systems was negative for prior or current gastrointestinal problems, dysphonia, dysphagia, dyspnea, or lesions in other mucous membranes including the genitalia. Past medical history was significant for hypertension, anemia, and colonic polyps, for which she was receiving appropriate care. She reported no known drug or environmental allergies. Her family history was non-contributory.

Extra-oral examination revealed perioral erythema and upper lip fullness, but no facial asymmetry or palsy (Figure 1). A non-tender, movable lymph node

of about 3/4 cm could be palpated in the left cheek. Intra-oral, labial, vestibular, and sublingual mucosa were intensely erythematous and swollen, with firm, non-tender proliferations and yellowish exudates within the tissue folds. There was no mucosal ulceration, desquamation, or blisters. The gingiva was enlarged with spongy consistency (maxilla>mandible) and partially covered the crowns of the patient's anterior teeth (Figure 2). The patient's dental/periodontal health was satisfactory. She did not wear an oral prosthesis and had no evidence of mucosal trauma from oral parafunction or physical irritation. The clinical impression included hypersensitivity reaction and local or systemic granulomatous conditions.

The patient was advised to maintain good oral hygiene and use bland oral hygiene products. These measures had no impact on her oral mucosal condition. Microscopic tissue analysis revealed fibrous hyperplasia with leukocytic infiltration, mainly with plasma cells mixed with lymphocytes and neutrophils, spongiosis, superficial microabscesses, and isolated non-caseating granulomas (Figure 3). Polarized microscopy was negative for foreign bodies. PAS and AFB stains were negative for fungal and tuberculosis agents. Immunohistochemistry revealed the polyclonal nature of plasma cells and excluded a neoplastic process (Figure 4). Immunohistochemical staining for IgG subclasses also revealed less than 40% of plasma cells were positive for IgG4 and ruled out IgG4-related disease.

The patient was subsequently evaluated by physicians from various medical disciplines in order to exclude an underlying systemic etiology for buccal lymphadenopathy as well as isolated granulomas noted on microscopic examination. Endoscopy revealed moderate diverticulitis and polyps and excluded inflammatory bowel disease. Serum angiotensin converting enzyme levels and chest radiography were within normal limits and did not support further investigations for sarcoidosis. Rheumatology workup

was also essentially negative, with a few non-specific findings. Extensive allergy testing was only positive for methyl methacrylate, which proved non-contributory, and excluded contact factors.

Extensive work up led to presumptive diagnosis of orofacial granulomatosis, for which the patient was treated with weekly intralesional injections of triamcinolone acetonide 10 mg/mL to address her chief complaint. There was dramatic clinical improvement in the appearance of the lips and oral tissues after 4 weeks. Mild clinical relapse 6 months later prompted further histopathological review, and clinicopathologic correlation led to diagnosis of plasma cell mucositis: a chronic proliferative plasma cell disorder of the oral mucosa. The patient was educated about the benign course of this inflammatory condition, its possible manifestations in other mucous membranes, as well as its potential complications. The relapse gradually resolved without further intervention; the patient's improvement has remained stable to date.

DISCUSSION

Plasma cell mucositis (PCM) is a chronic inflammatory mucosal disorder of the upper aerodigestive tract which shares similar clinical and microscopic attributes with plasma cell balanitis of Zoon, first described in 1952 as affecting the glans penis (13). Similar non-neoplastic proliferations of plasma cells at other body orifices such as the vulva, nares, lips, buccal mucosa, tongue, gingiva, epiglottis, larynx, and trachea have also have been observed (1-4,6,8,11,14-22). Although extremely rare (3), concurrent manifestation of plasmacytosis in the genital and oral or cutaneous tissues has also been documented (11). These manifestations were often named according to the specific anatomical site of involvement (3). Examples include plasma cell cheilitis, plasma cell gingivitis, and plasma cell vulvitis, respectively describing exclusive involvement of the lips, gingiva, and vulva (3,12,20,21,23), as well as plasma cell orificial

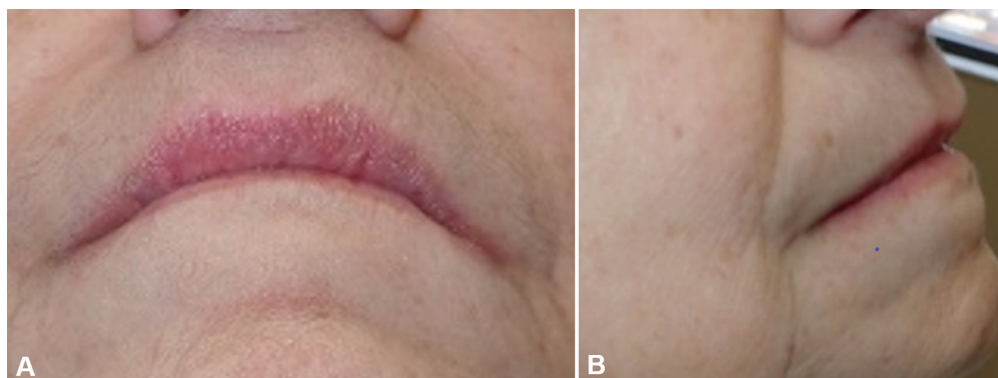


Figure 1. Frontal and profile view of the lips, demonstrating faint perioral erythema and upper lip fullness at the initial visit.



Figure 2. Clinical presentation of the oral mucosa at the initial visit showing intensely red labial, vestibular, and sublingual mucosa with firm, non-tender proliferations and yellowish exudates within the tissue folds. The gingiva was enlarged, with spongy consistency (maxilla>mandible) and partially covered crowns of the patient's upper front teeth.

mucositis or plasmacytosis circumoroficialis, representing reactive plasma cell infiltration at the mucous membranes of body orifices (8,10,13). Because of overlap in the clinical and microscopic features of this distinct entity, many experts collectively refer

to the same inflammatory process as mucous membrane plasmacytosis or PCM, irrespective of the site (3-4,6,12,21). In this article, we also used the same terminology to discuss the oral mucosal condition in our patient.

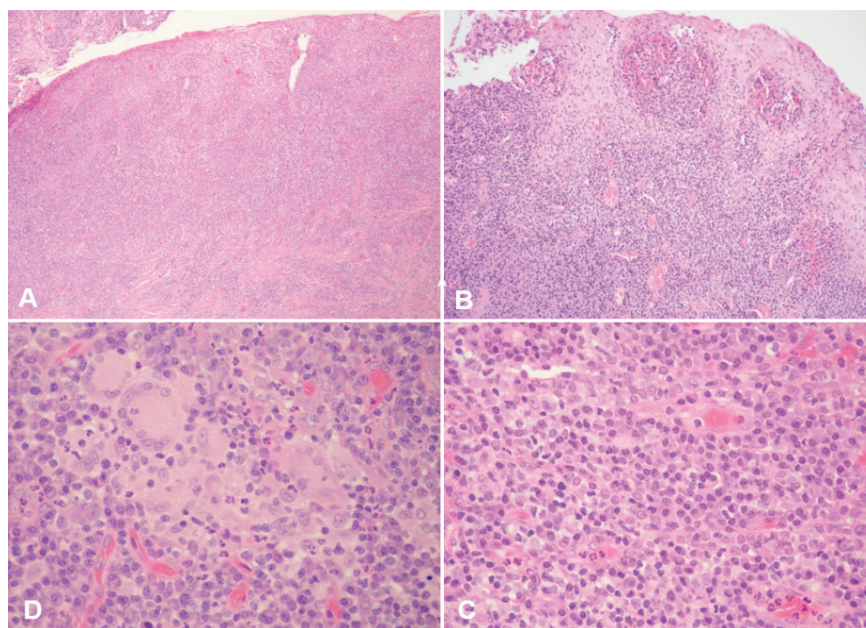


Figure 3. Histology photomicrographs illustrating (A) low, hematoxylin and eosin (H&E) ×40, (B) medium, H&E ×100, and (C) high, H&E ×400 power magnification of segments of the mucosa covered by stratified squamous epithelium and containing diffuse inflammatory cells (predominantly plasma cells mixed with lymphocytes and neutrophils) within hyperplastic connective tissues. Panel (D) shows a high-power magnification micrograph illustrating a non-caseating granuloma with multinucleated giant cells.

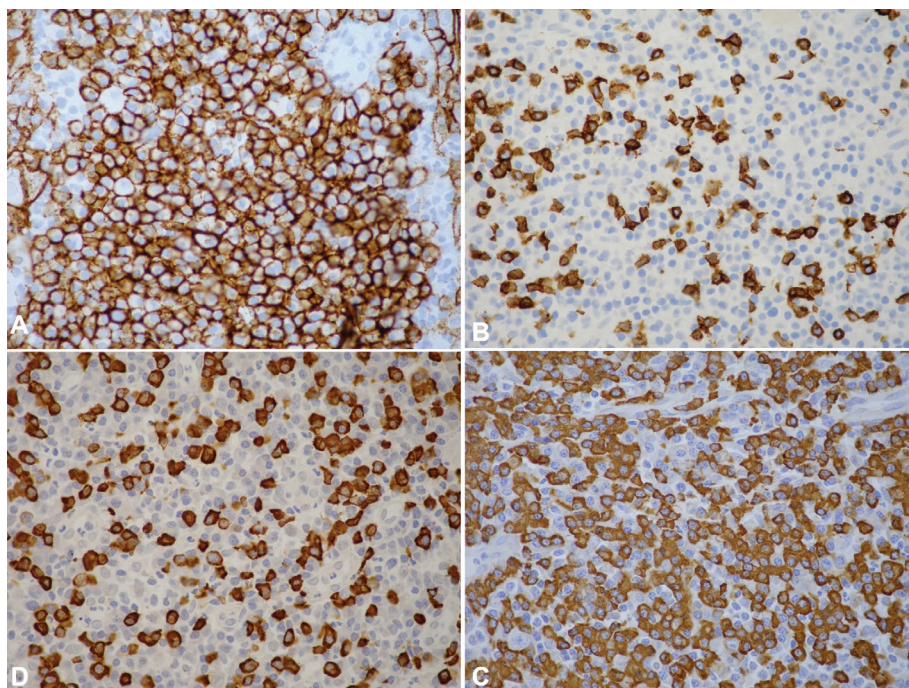


Figure 4. Immunohistochemical photomicrographs demonstrating positive staining of mature plasma cells with (A) CD138, (B) kappa light chain, and (C) lambda light chain, but not for (D) CD20. This immunostaining pattern supports a polyclonal plasma cell population.

Plasma cell mucositis involving the oral cavity, whether alone (1,2) or in association with other sites within UADT, is rare (17). Coppola *et al.* (1) identified 92 studies on 158 patients with oral PCM published until 2022. Mucosal alterations of oral PCM are typically long-standing and may or may not involve the gingiva, although the gingiva is the most commonly affected site within the oral cavity (1,3,21). In spite of limited data because of low incidence, PCM of UADT appears to have a slight predilection for men (1.2:1.0) and older age groups, with the first manifestations often occurring in the forties and fifties (2-3,13,15,19,21). The clinical presentation of PCM is variable, depending on the anatomical site of involvement within the aerodigestive tract (4). When the lips are involved, either exclusively or in conjunction with other mucosal changes within the upper aerodigestive tract, they usually appear diffusely enlarged, fissured, asymmetric, indurated, and non-tender (12,21). Other potential findings include angular cheilitis, papillary hyperplasia, and surface erosions, at times resembling solar cheilosis or even squamous cell carcinoma (3,8,10,14,21,24-28).

Within the oral cavity, the gingiva is the most commonly affected site (29). When the gingiva is involved, whether isolated or as part of a widespread process, the tissue appears diffusely red, friable, spongy, and bleeds easily on contact, manipulation, or even spontaneously (2,3,12,23,24). At times, gingi-

val surface irregularities can resemble those seen in Wegener's granulomatosis (3). The affected oral mucosa appears fiercely red, hyperemic, and edematous, with variable surface alterations described as velvety, plaque-like, lobulated, nodular, papillomatous, ulcerated vegetative growth, and cobblestoning (1-4,9,11,13,15,16,18,19,21,24). Streaks of mucous may be visible within the tissue folds (18). The condition may be asymptomatic or manifest with a broad range of symptoms, depending on the specific site of involvement (1,3,4,13). In the oral cavity, patients may experience swelling, soreness, pruritus or sensitivity, burning sensation on exposure to acidic/spicy foods or flavored oral hygiene products, and inability to fully open the mouth (1-4,15,16,21,24).

This symptomatology can interfere with speech, nutritional intake, and oral hygiene practices, affecting the quality of life in those affected (3,11,13,15). The potential sequela of impaired oral hygiene include plaque accumulation, gingival inflammation, recession, and periodontal disease (3). Although generally considered benign (15), the clinical course of PCM can be aggressive, particularly when involving the nasal, pharyngeal, laryngeal, tracheal, bronchial, and esophageal mucosa (3,6). Functional complications of tissue stricture or obstruction in these anatomical sites include persistent hoarseness, sore throat, stridor, wheezing, dyspnea, dysphonia, sleep apnea, difficulty breathing, choking sensation,

pharyngitis, and dysphagia (1-4,6,8,9,13,15,16,18,19,21). At times, the airway compromise caused by laryngeal lesions can prove life threatening and mandate aggressive interventions, including tracheostomy and intubation (6,17,18,21,25,30).

Although various theories for etiopathogenesis have been postulated, PCM is generally considered idiopathic (1-3,7,9, 13,15,16,17,21). The anatomical proximity of mucosa to the outside environment at body orifices can potentially expose it to a variety of infectious, mechanical, or antigenic stimuli and cause an immune-mediated reaction in those who are predisposed (3,31). Proposed triggers include infectious agents such as candida, herpes simplex virus, or dental plaque bacteria, contact sensitization to an unidentified environmental or dietary antigen such as spices or flavoring agents in chewing gum, foods or oral hygiene products, as well as mechanical irritation, micro trauma, parafunctional habits or actinic damage when the lips are involved (1-3,7,9,11,12,22,23,32-34). A potential role for micro trauma in the pathogenesis of PCM is supported by development of inflammatory plasmacytosis in cutaneous tissues, the axillary region, and the genitalia, which are prone to frictional contact and physical irritation (35). Simultaneous occurrence of plasmacytosis in oral and genital mucous membranes is also consistent with this notion.

An etiologic role for contact hypersensitivity is supported by the documented association between the onset of oral PCM and exposure to contact allergens in food, gum, and oral hygiene products, as well as its resolution following withdrawal of the offending trigger (24,36-39). In practice, however, allergy testing or re-challenge tests for identification of the causative agent often prove inconclusive (3,4,21,33). Frequent development of plasma cell lesions in anatomical sites typically associated with plaque such as the gingiva and periodontium supports a role for bacterial plaque in PCM etiopathogenesis (1). On the other hand, extension of gingival changes beyond the marginal gingiva in PCM and the partial or lack of response to plaque removal suggest additional factors are likely involved (1). Interestingly, there is evidence that many affected patients also have autoimmune or immune-mediated comorbidities such as Sjogren's syndrome, rheumatoid arthritis, psoriasis, polymyositis, Crohn's disease, or diabetes, either at the same time or metachronously (1-3,13,15-17,19,21-23,40), an observation which points to an etiological role for immunity.

The diagnostic work up of PCM affecting the oral cavity should start by excluding potential local causes such as poor oral hygiene, compromised den-

tal/periodontal health, and mouth breathing, which could promote similar mucosal alterations (1). The potential for multifocal manifestations of PCM within the upper aerodigestive tract (UADT) warrants careful consideration and possible evaluation, including by nasoendoscopy as needed (3,34). A thorough evaluation should include identification and elimination of any underlying contact allergy (1,3,10,17). Questions should include patient use of the oral/perioral lipsticks, chewing gums, candies, mints, dentifrices, mouthwashes, and topical medicaments which contain cinnamon, chili pepper, and flavoring agents (1,8,12,23). Attention to the timeline of onset and pattern distribution in the oral cavity (for example, areas of contact with dental prosthesis) is also important and may support or refute the suspicion of contact allergy (4). Patients should be advised to practice gentle, thorough oral hygiene with bland, unflavored, and sodium lauryl sulfate (SLS)-free dentifrices. When indicated, a dietary elimination approach, patch testing, and a biopsy specimen to exclude a local hypersensitivity reaction may be considered (2-4,22,33,34).

Distribution and morphological features of oral mucosal lesions generally guide development of a prioritized list of clinical differentials for plasma cell mucositis (3). Differential diagnoses include a wide variety of disorders such as oral lichen planus, immunobullous disorders, granulomatous conditions, Crohn's disease, infectious diseases, hematologic or epithelial neoplasia, contact reactions, and other entities (1,3,4,9,12,13,15,17,18,21,25,34,41-43). Mucosal erythema in the context of fungal infection, as with erythematous candidiasis, may resemble the patchy and diffuse erythema seen in PCM but can be differentiated from it by exfoliative cytology for KOH preparation, microscopic examination of tissue biopsy for candida hyphae, periodic acid Schiff stain, or by assessing response to empirical antifungal therapy (4,8-9).

Erythroplakia is an ominous mucosal lesion with premalignant potential. This velvety red patch is typically solitary rather than diffuse, as seen in PCM, and can be excluded by tissue sampling and microscopic evaluation. Gingival/mucosal erythema in oral lichen planus (LP) and oral mucous membrane pemphigoid (MMP) resembles PCM. All three conditions typically affect older individuals, but in contrast to PCM primarily affecting men, LP and MMP have a predilection for women (25). The affected oral mucosa in LP and MMP are typically desquamative or ulcerated, compared with PCM in which ulceration is uncommon (25). In addition, LP and MMP do not present with nodular or warty surface features typical of PCM (25). Furthermore, each of these conditions have characteristic

microscopic findings, allowing their differentiation (25): subepithelial lymphocytic band and epithelial basal cell layer degeneration in LP, subepithelial vesiculating mucositis in MMP, and plasmacytic infiltration in PCM.

Indurated swelling and fissuring of the lips or oral tissues in PCM should be differentiated from angioedema as well as granulomatous conditions such as cheilitis granulomatosa, Crohn's disease, sarcoidosis, and orofacial granulomatosis (4,8,10,12,21,22,41,42). Angioedema has an acute onset, is edematous rather than indurated or nodular in texture, and has a transient course. The aforementioned granulomatous conditions are chronic and demonstrate non-caseating granulomas rather than plasma cell infiltration on tissue biopsy (4,8,10,12,22). Evaluation of ACE levels on serology will also be helpful in screening for sarcoidosis (3).

Diagnosis of plasma cell mucositis relies on the histopathological evidence of a dense, subepithelial infiltrate of predominantly plasma cells and pseudoepitheliomatous hyperplasia (i.e. psoriasiform epithelial changes) after exclusion of conditions of neoplastic and infectious etiology which share a similar microscopic appearance (1-4,13,17,25,31). Infiltrating plasma cells are mature without pleomorphism, nucleoli prominence or atypia (1-4,17,25,33). Other less specific histopathological findings reported in PCM include acanthosis, spongiosis, neutrophilic exocytosis, and secondary micro abscesses in the surface epithelium, and occasional presence of Russell bodies (i.e. collection of immunoglobulins within the plasma cell cytoplasm) (1-4,13,22,25,33,34).

The major microscopic differentials for oral mucosa plasmacytosis include reactive conditions such as plasma cell gingivitis and plasma cell granuloma, neoplastic lesions such as extramedullary plasmacytoma (EMP), infectious diseases such as secondary syphilis, and idiopathic PCM (2,8,18,21). Since these conditions differ in both management and prognosis, their differentiation is highly relevant and critical (2). An important diagnostic feature of PCM is the polytypic nature of plasma cell infiltrate (1,18,34). Neoplastic monoclonal plasma cell expansion such as multiple myeloma or plasmacytoma can be excluded by immunohistochemical staining (for CD138 marker) or *in situ* hybridization (for kappa and lambda light chains) of fresh and paraffin-fixed tissue samples (1,3,7,17). Other techniques used in the clinical setting to exclude plasma cell dyscrasias include immunoglobulin serology, serum protein electrophoresis, evaluation of urine for Bence Jones proteins, peripheral flow cytometry, and gene rearrangement studies (2-4,18,21).

Extramedullary mucocutaneous plasmacytoma (EMP) is a soft tissue plasma cell tumor primarily found in older men (aged 50-60) (2,18,44). It is rare (<1-2%), often asymptomatic, and typically starting within the mucosa-associated lymphoid tissue (MALT) in the upper respiratory tracts and more specifically the supraglottic larynx (2,18,21,44). In contrast to PCM, in which plasmacytic infiltration is diffuse and polyclonal, EMP represents a solitary (unifocal) proliferation of monoclonal plasma cells (2,4,17,18). It is rare the oral cavity, were EMP can involve the alveolar tissues and cause pain and tooth mobility (2). It needs to be distinguished from plasma cell predominant B-cell pseudolymphoma (45).

Plasma cell granuloma is an inflammatory pseudotumor comprised of polyclonal plasma cells (46). This benign solitary lesion typically affects the lungs but has also been documented in the oral cavity (46). When involving the gingiva, plasma cell granuloma may be considered a focal variant of plasma cell gingivitis, and chronic antigenic exposure may have a role in its etiopathogenesis (46). For example, local periodontitis, periradicular inflammation, and foreign bodies can promote reactive plasmacytic proliferation (46). The solitary nature of plasma cell granuloma can help differentiate it from the diffuse and multifocal lesions of PCM (25,46).

Patients with secondary syphilis may experience oral manifestations; microscopic examination of the affected tissue can reveal plasma cell infiltration similar to PCM (2,47-50). However, the presence of histopathological findings unique to syphilitic lesions such as unusual epithelial hyperplasia, endarteritis, neuritis, and detection of spirochetes on silver staining of tissue specimen together with serological tests for syphilis can help differentiate it from PCM as the cause of mucosal lesions (2,4).

Diagnosis of PCM can prove challenging; initial misdiagnosis is not uncommon (3,13,21). Arrival at the correct diagnosis often requires multidisciplinary collaboration, exclusion of benign and malignant conditions with overlapping clinical and histopathological features, and clinicopathologic correlation (2-4,13,15,19,21). This illustrative patient was an elderly woman. She was minimally symptomatic and primarily complained of labial fullness and change in the appearance and texture of her upper lip and oral tissues. Orofacial alterations in this patient were diffuse and multifocal, with streaks of mucous within tissue folds. A thorough history and clinical exam did not identify a local allergenic or infectious culprit; allergy testing did not support a hypersensitivity reaction. Although the clinical appearance of mucosal erythema and microscopic presence of neutrophilic abscesses in the

Table 1. A summary of various therapeutic approaches/agents for PCM reported in the literature

Approach	Agent	Efficacy
Withdrawal of suspected allergen/irritant	<ul style="list-style-type: none"> Periodontal/dental intervention (12) Gum chewing (24,36,38) Toothpaste (36-38,57) Qat chewing (9) Dental prosthesis (8,58) Food ingredients (39,59) 	<ul style="list-style-type: none"> ✓ ✓ ✓ ✓ ✓ ✓
Corticosteroids	<ul style="list-style-type: none"> Systemic steroids (2,11,13,16,19,21,38,58,60) Systemic and topical steroids (4,17) Topical steroids (17,18,61,62) Intralesional steroids (63,64) Intralesional & topical steroids (12,33) 	<ul style="list-style-type: none"> ✓ ✓ ✓ ✓ ✓
Topical or systemic immunosuppressive/modulating agents	<ul style="list-style-type: none"> Topical tacrolimus (52,53) Cyclosporine (11) Mycophenolate mofetil (13,19) Methotrexate (13) Hydroxychloroquine (60) Dapsone (11,13,60) Oral steroids plus mycophenolate mofetil and dapsone (19) 	<ul style="list-style-type: none"> ✓ ✓ ✓ ✓
Debulking procedures	<ul style="list-style-type: none"> Excision (10,51) Tracheostomy (25,30) Plasma coagulation & debridement (6) Electrocoagulation (65) Co2 laser (25, 66) Cryotherapy (67) Low dose radiotherapy (30) 	<ul style="list-style-type: none"> ✓ ✓ ✓ ✓ ✓ ✓ ✓
Miscellaneous	<ul style="list-style-type: none"> Antifungals (38) Topical 2% fusidic acid (54,55) Oral griseofulvin (14) Colchicine (13,60) Adalimumab, a monoclonal antibody (13) 	<ul style="list-style-type: none"> ✓ ✓ ✓ ✓

superficial epithelium appeared to suggest chronic candidiasis (22), there were no fungal hyphae on histology or PAS staining. Tissue analysis uncovered massive subepithelial inflammation primarily composed of normal-appearing plasma cells. Immunohistochemistry excluded plasma cell dyscrasia and IgG4-related disease. Presence of isolated granulomas on tissue analysis led to additional evaluation and ruled out a foreign body reaction, tuberculosis, sarcoidosis, and inflammatory bowel disease. The patient was initially thought to have orofacial granulomatosis and responded to intralesional steroids. However, a mild clinical relapse six months later led to re-examination of histopathology, centered on the massive subepithelial plasmacytic infiltration rather than isolated granulomas. Clinicopathologic correlation ultimately led to the diagnosis of idiopathic PCM.

Plasma cell mucositis is generally a benign condition. There is no evidence for its progression to a plas-

ma cell malignancy (1-4,13,15,16,21). Management of PCM is primarily directed at symptoms and often results in stabilization rather than cure (1,3,6,15,16,21). Slow resolution of PCM without intervention has also been documented in the literature (7,13,51). In our patient, clinical relapse resolved in 2 weeks without additional treatment and has remained stable for 6 months. The speed of her recovery does not match the protracted course documented in the literature. In our opinion, the accelerated remission may be related to the initial therapeutic intervention (14). Since remissions and exacerbations can occur during the natural course of PCM, the patient's overall management also involves regular monitoring (3).

There is no consensus on best practices for PCM; a variety of approaches has been utilized, with variable success (1-4,6,13,19). The first step is investigation and elimination of any potential infectious, allergenic, or physical irritant (1). The clinician should

address possible dental/periodontal contributors (12), particularly when gingival lesions are present, and evaluate tissue for a positive response or lack thereof. This concept should be considered even if other treatments are provided because the presence of plaque perpetuates an inflammatory state, which interferes with resolution (1).

Administration of corticosteroids in topical, intralesional, or systemic form is often the initial therapeutic intervention and has proven beneficial in some cases when continued (15,17,18,21,33). Topical steroids are generally preferable to systemic counterparts, which carry dose-related adverse effects. However, the efficacy of topical agents is not consistent and is a function of epithelial barrier thickness and density of plasma cell infiltration (1). Three topical agents found to be effective for some patients with oral PCM are tacrolimus (52,53), cyclosporine (11), and fusidic acid (54,55). These agents are thought to inhibit production of inflammatory cytokines implicated in the onset of plasma cell mucositis (1,54-56). A rare but serious complication of PCM involving UADT is obstruction and stridor (1,18). To that end, systemic cytotoxic agents, low-dose radiation, and debulking procedures are typically reserved for severe and or life-threatening airway compromise (6,25,30). Table 1 provides a summary of strategies/agents for management of PCM and their efficacy in the studies cited.

Long-term use of systemic steroids can lead to significant complications such as osteoporosis, hypertension, chemical diabetes, and hyperacidity (2). These complications are even more concerning in the elderly, a group more likely to have pre-existing comorbidities and considered at a higher risk of PCM (2). Prolonged immunosuppressive therapy can also predispose patients to opportunistic infections or increase risk of malignancy (19). Pepper *et al.* (66) documented squamous cell carcinoma of the lower lip in a patient with pre-existing plasmacytosis treated with multiple immunosuppressive agents and pointed out the possible role of ongoing inflammation and prolonged immunosuppression in carcinogenesis. Given the benign nature of PCM, the non-curative purpose of interventions (15,17,18), and the potential for its spontaneous regression, it is warranted for clinicians to weigh the risks and benefits of long-term immunosuppression when deciding on a therapeutic approach (2,7,66). Close monitoring is also advisable for timely recognition and management of therapeutic adverse effects or clinical relapse (3,13). Focused review of systems during follow-up visits facilitates the identification of possible disease progression to other body sites based on symptomatology and deciding on appropriate referrals (3,17).

CONCLUSION

The chronic and idiopathic nature of PCM can be distressing, and its symptomatology, when present, may diminish quality of life for patients. Although PCM is a rare condition, it should be included in the differential diagnosis of mucosal swelling and abnormalities affecting the oral cavity. Clinicians should be familiar with the spectrum of clinical presentations, evaluation algorithm, and appropriate referrals guided by the patient's review of systems. Microscopic tissue analysis, clinicopathologic correlation, and interdisciplinary collaboration are paramount to establish a correct diagnosis. There is no universally-accepted therapeutic strategy for PCM. However, the benign nature of the condition warrants tailoring its management to the symptomatology and monitoring patients appropriately for potential relapse. Aggressive interventions are reserved for PCM with a severe and/or fatal clinical course.

References:

1. Coppola N, Cantile T, Canfora F, Adamo D, Bucci P, Mignogna MD, *et al.* Pitfalls and Challenges in Oral Plasma Cell Mucositis: A Systematic Review. *J Clin Med.* 2022;11:6550.
2. Gupta SR, Gupta R, Saran RK, Krishnan S. Plasma cell mucositis with gingival enlargement and severe periodontitis. *J Indian Soc Periodontol.* 2014;18:379-84.
3. Martin-Hendrie R, Hadleigh C. Plasma cell mucositis. *Derm Net NZ.* 2022. Available at: <https://dermnetnz.org/topics/plasma-cell-mucositis>
4. Bhatia R, Smith DR. Mucous membrane plasmacytosis: A case report and review of the literature. *Dermatol Online J.* 2003 Dec;9:15.
5. Zoon JJ. Balanoposthite chronique circonscrite benign a plasmocytes (contra erythroplasie de Queyrat). *Dermatologica.* 1952;105:1-7.
6. Lucarelli MR, Allen JN, Magro CM. Plasma cell mucositis of distal airways. *Thorax.* 2005;60:171-3.
7. Madhavarajan S, Tighe J. Orofacial plasmacytosis: A management conundrum. *Br J Oral Maxillofac Surg.* 2015;53:399-402.
8. White JW Jr, Olsen KD, Banks PM. Plasma cell orificial mucositis. Report of a case and review of the literature. *Arch Dermatol.* 1986;122:1321-4.
9. Al-Ak'hali MS, Al-haddad KA, Al-Hebshi NN. Oral plasma cell mucositis exacerbated by qat chewing-A case series. *Saudi J Dental Res.* 2015;6:60-6.
10. Noorily AD. Plasma cell orificial mucositis. *Otolaryngol Head Neck Surg.* 1997;116:416-7.

11. Heinemann C, Fischer T, Barta U, Michaelids A, El-sner P. Plasma cell mucositis with oral and genital involvement-successful treatment with topical cyclosporine. *JEADV*. 2006;20:740.
12. Kaur C, Thami GP, Sarkar R, Kanwar AJ. Plasma cell mucositis. *J Eur Acad Dermatol Venereol*. 2001;15:566-7.
13. Galvin S, Bowe C, Regan EM, Conlon N, Flint SR, Healy CM. Circumferential plasmacytosis/ plasma cell orificial mucositis: a case series and a review of the literature. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 2016;122:e77-e81.
14. Tamaki K, Osada A, Tsukamoto K, Ohtake N, Furue M. Treatment of plasma cell cheilitis with griseofulvin. *J Am Acad Dermatol*. 1994;30:789-90.
15. Antonelli A, Averta F, Diodati F, Muraca D, Brancaccio Y, Mignogna C, *et al.* An uncommon case of plasma cell mucositis of the tongue in a young man. *Case Rep Dent*. 2020;2020:3429632.
16. Antonelli A, Averta F, Diodati F, Muraca D, Brancaccio Y, Mignogna C, *et al.* Plasma cell mucositis: A case report of an uncommon benign disease. *Proceedings*. 2019;35:46.
17. Timms MS, Sloan P. Association of supraglottic and gingival idiopathic plasmacytosis. *Oral Surg Oral Med Oral Pathol*. 1991;71:451-3.
18. Khan NA, McKerrow WS, Palmer TJ. Mucous membrane plasmacytosis of the upper aerodigestive tract. A case report with effective treatment. *J Laryngol Otol*. 1997;111:293-5.
19. Shanahan D, Shipley D, Staines K. Plasma cell mucositis. *Ear Nose Throat J*. 2020 Jul;99:NP64-NP65.
20. Bharatia PR, Pradhan AM, Zawar VP. Plasma cell vulvitis. *Indian J Sex Transm Dis AIDS*. 2015;36:185-7.
21. Solomon L, Wein RO, Rosenwald I, Laver N. Plasma cell mucositis of the oral cavity: report of a case and review of the literature. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 2008;106:853-60.
22. Grattan CEH, Gentle TA, Basu MK. Oral papillary plasmacytosis resembling candidosis without demonstrable fungus in lesional tissue. *Clin Exp Dermatol*. 1992;17:112-6.
23. Sollecito TP, Greenberg MS. Plasma cell gingivitis. *Oral Surg Oral Med Oral Pathol*. 1992;73:690-3.
24. Kerr DA, McClatchey KD, Regezi JA. Idiopathic gingivostomatitis. Cheilitis, glossitis, gingivitis syndrome; atypical gingivostomatitis, plasma-cell gingivitis, plasmacytosis of gingiva. *Oral Surg Oral Med Oral Pathol*. 1971;32:402-23.
25. Ferreira JA, Egorshin EV, Olsen KD, Banks PM, Weiland LH. Mucous membrane plasmacytosis of the upper aerodigestive tract. A clinic pathologic study. *Am J Surg Pathol*. 1994;18:1048-53.
26. Jadotte YT, Schwartz RA. Solar cheilosis: an ominous precursor: part I. Diagnostic insights. *J Am Acad Dermatol*. 2012;66:173-84.
27. Jadotte YT, Schwartz RA. Solar cheilosis: an ominous precursor: part I. Therapeutic perspectives. *J Am Acad Dermatol*. 2012 Feb;66:187-98.
28. Gopal A, Singh M, Singh I, Mandal S. Plasma cell mucositis masquerading as squamous cell carcinoma surgical dilemma: a rare report and review of literature. *Int J Otorhinolary Head Neck Surg*. 2022;8:1012-6.
29. Leuci S, Coppola N, Adamo N, Bizzoca ME, Russo D, Spagnuolo N, *et al.* J Clin Med. Clinico-Pathological Profile and Outcomes of 45 Cases of Plasma Cell Gingivitis. *J Clin Med*. 2021;10:830.
30. Fogarty G, Turner H, Corry J. plasma-cell infiltration of the upper aerodigestive tract treated with radiation therapy. *J Laryngol Otol*. 2001;115:928-30.
31. Moutsopoulos NM, Konkel JE. Tissue-Specific Immunity at the Oral Mucosal Barrier. *Trends Immunol*. 2018 Apr;39:276-87.
32. Owings JR Jr. An atypical gingivostomatitis: a report of four cases. *J Periodontol*. 1969;40:538-42.
33. Baughman RD, Berger P, Pringle WM. Plasma cell cheilitis. *Arch Dermatol*. 1974;110:725-6.
34. Smith ME, Crighton AJ, Chisholm DM, Mountain RE. Plasma cell mucositis. A review and case report. *J Oral Pathol Med*. 1979;28:183-6.
35. Senol M, Ozcan A, Aydin NE, Hazneci E, Turan N. Intertriginous plasmacytosis with plasmocarcinoma: Report of a typical case and review of the literature. *Int J Dermatol*. 2008;47:265-8.
36. Perry HO, Deffner NF, Sheridan PJ. Atypical gingivostomatitis. *ArchDermatol*. 1973;107:872-7.
37. Tong DC, Leaper MR, Colquhoun AN, Rich AM. An unusual presentation of oropharyngeal mucosal plasmacytosis related to toothpaste. *J of Laryngology & Otology*. 2008;122:1112-4.
38. Silverman S, Lozada F. An epilogue to plasma cell gingivostomatitis (allergic gingivostomatitis). *Oral Surg*. 1977;43:211-7.
39. Serio FG, Siegel MA, Slade BF. Plasma cell gingivitis of unusual origin. *J Periodontol*. 1991;62:390-3.
40. Fatahzadeh M, Schwartz RA. Oral Psoriasis: An Overlooked Enigma. *Dermatology*. 2016;232:319-25.

41. Fatahzadeh M, Schwartz RA, Kapila R, Rochford C. Orofacial Crohn's disease: an oral enigma. *Acta Dermatovenereol Croat*. 2009;17:289-300.
42. Randhawa KS, Lee BW, Micali G, Benson BE, Schwartz RA. Cutaneous sarcoidosis: Lupus pernio and more. *Ital J Dermatol Venerol*. 2022;157:220-7.
43. Sharma A, Białynicki-Birula R, Schwartz RA, Janniger CK. Lichen planus: an update and review. *Cutis*. 2012;90:17-23.
44. Horney HP, Kaiserling E. Involvement of the larynx by hemopoietic neoplasms. An investigation of autopsy cases and review of the literature. *Pathol Res Pract*. 1995;191:130-8.
45. Nervi SJ, Schwartz RA. Plasma cell predominant B cell pseudolymphoma. *Dermatol Online J*. 2008;14:12.
46. Peacock ME, Hokett SD, Hellstein JW, Herold RW, Matzenbacher SA, Scales DK, *et al*. Plasma cell granuloma. *J Perio*. 2001;72:1287-90.
47. Emanuel P. Syphilitic pathology. *DermNet*. 2013. Available at: <https://dermnetnz.org/topics/syphilis-pathology>
48. Karanfilian KM, Almohssen AA, Kapila R, Schwartz RA. Malignant syphilis: a new and revised definition. *Int J Dermatol*. 2023;62:369-75.
49. Bhate C, Tajirian AL, Kapila R, Lambert WC, Schwartz RA. Secondary syphilis resembling erythema multiforme. *Int J Dermatol*. 2010;49:1321-4.
50. Rubins S, Morete A, Rubins A, Janniger CK, Schwartz RA. Interdigital syphilis: a rare form of secondary syphilis. *Int J STD AIDS*. 2019;30:1440-2.
51. Puvanendran M, Lieder A, Issing W. Plasma Cell Mucositis of Oro- and Hypopharynx: A Case Report. *Case Reports in Otolaryngology*. 2012;304136.
52. Jin SP, Cho KH, Huh GH. Plasma cell cheilitis, successfully treated with topical 0.03% tacrolimus ointment. *J Dermatol*. 2010;21:130-2.
53. Hanami Y, Yoshikazu M, Toshiyuki Y. Successful treatment of plasma cell cheilitis with topical tacrolimus: report of two cases. *Dermatol online J*. 2011 Feb 15;17:6.
54. Saruya K, Fukuda H, Saito R, Urushibata O, Mukai H. Plasmacytosis circumorificialis successfully treated with topical fusidic acid ointment. *J Dermatol*. 2009;36:232-6.
55. Mahler V, Hornstein OP, Kiesewetter F. Plasma cell gingivitis. Treatment with 2% fusidic acid. *J Am Acad Dermatol*. 1996;34:145-6.
56. Bendtzen K, Diamant M, Faber V. Fusidic acid, an immunosuppressive drug with functions similar to cyclosporin A. *Cytokine*. 1990;2:423-9.
57. Lamdari N, Pradhan S. Plasma cell gingivitis—a case report. *Indian J Public Health Res Dev*. 2019;10:1658-61.
58. Błażewicz I, Baranska-Rybak W, Stawczyk-Macieja M, Petranyuk A, Nowicki R. Plasma cell mucositis—a rare differential diagnosis for ulceration of oral mucosa. *Dermatol Rev*. 2015;6:520-3.
59. Panpradit N, Lapthanasupkul P. Plasma cell gingivitis associated with dry flower buds of clove: A case report. *Dent J*. 2017;37:155-62.
60. Liu F, Chen CB, Kuo TT, Chung WH. Idiopathic lymphoplasmacellular mucositis of the lips: a case report and review of the literature. *J Cut Pat-hol*. 2017;44:776-80.
61. Jones SK, Kennedy CT. Response of plasma cell orificial mucositis to topically applied steroids. *Arch Dermatol*. 1988;124:1871-72.
62. Rocha N, Mota F, Horta M, Lima O, Massa A, Sanches M. Plasma cell cheilitis. *J Eur Acad Dermatol Venereol*. 2004;18:96-8.
63. Tseng JT, Cheng CJ, Lee WR, Wang KH. Plasma-cell cheilitis: Successful treatment with intralesional injections of corticosteroids. *Clin Exp Dermatol*. 2009;34:174-7.
64. Yang JH, Lee UH, Jang SJ, Choi JC. Plasma cell cheilitis treated with intralesional injection of corticosteroids. *J Dermatol*. 2005;32:987-90.
65. Curto CR, Chaves MY, Morán AG, Asensio PG, López G. Plasma cell gingivitis. *Cutis* 2002;69:41-5.
66. Pepper T, Shekar K, Singh M, Brennan PA. Squamous cell carcinoma arising in mucosal plasmacytosis. *Br J Oral Maxillofac Surg*. 2010;48:208-10.
67. Najarian GDJ, Rao BK, Pappert AS. A case of mucous membrane plasmacytosis successfully treated with cryotherapy. *Dermatol online J*. 2008 Feb 28;14:6.

