Case Report

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# Challenges in managing plasma cell gingivitis associated with copper sulphate: A case report

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Plasma cell gingivitis (PCG) is an infrequent, benign inflammatory condition of the gingiva, marked by diffuse, sub-epithelial plasma cell inflammatory infiltration into the connective tissue. Clinically, it is characterized by sharply demarcated erythematous and edematous gingival conditions, often extending to the mucogingival junction. Although the aetiology of the condition is not properly understood, it may be related to specific allergens, neoplasia, or maybe of unknown origin. Therefore, plaque control and conventional periodontal therapy alone will not treat the condition. Here, we present a 15-year-old lady with PCG, brought on by copper sulphate. The condition is diagnosed based on comprehensive history taking, clinical examination, and laboratory tests, managed by conventional periodontal therapy with adjunctive dexamethasone paste.

**Keywords:** Dexamethasone, gingivitis, plasma cells.

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## Introduction

Plasma cell gingivitis (PCG) is a rare gingival condition categorized under non-dental plaque-induced gingival disease based on the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions [1]. It is characterized by diffuse and massive infiltration of non-neoplastic plasma cells into the sub-epithelial gingival tissue [2]. Clinically, it manifests as diffuse erythematous and edematous gingivae extending up to the mucogingival junction, usually at the labial aspect of the anterior region of the maxillary gingivae. A propensity for gingival bleeding upon tissue manipulation is invariably present in all cases [3]. Gingival ulcerations are infrequent, albeit some individuals may complain of pruritus, burning, or pain sensations [4].

Several incidences of mucosal hypersensitivity and cheilitis related to chewing gum use were documented in the 1940s and 1950s [5]. In addition, PCG is a disorder similar to balanitis plasmacellularis, which Zoon reported in 1950 [6].

Over the years, different terminologies were used for PCG, including allergic gingivitis, atypical gingivitis, plasmacytosis of the gingiva, and plasma cell gingivostomatitis [7]. Almost two decades ago, a classification scheme was proposed in 1995 by Garguilo, based on three etiologies: as an immunological reaction to allergens, neoplasia, and unknown origin [8]. However, it is generally regarded as a hypersensitivity reaction to allergens found in chewing gum, dentifrices, chilli pepper, and some dietary agents [2,9].

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The importance of diagnosing PCG is that the appearance of the gingiva can resemble some other aggressive and more serious conditions. The gingival lesions may be clinically similar to leukemia, discoid lupus erythematosus, erosive lichen planus, desquamative gingivitis, or cicatricial pemphigoid. The aggressive nature of this gingivitis that can be seen in HIV-positive patients must also be differentiated from PCG [5]. Hence, differentiating PCG from others is a prerequisite. Once the histologic diagnosis of PCG is made, it is still imperative to identify the antigenic source of the inflammation.

We are reporting a case of PCG presented with redness and swollen gingivae at both maxillary and mandibular anterior gingivae in an otherwise healthy patient related to copper sulphate. This paper aims to highlight its rare occurrence and challenges in managing the condition.

## Case report

A 15-year-old Chinese female was presented to the Periodontology Specialist Clinic, Gunung Rapat, in September 2014 with a chief complaint of redness and swollen gingivae at both maxillary and mandibular anterior gingivae 3 years ago. She noticed the swelling of the gingivae had increased in size gradually throughout the past 3 years. The patient did not report any bleeding while brushing or eating, nor any soreness or discomfort from the affected gingival area. The patient's medical history was non-contributory. She was not taking any regular medications and had no known drug or food allergy.

Extra-oral examination revealed a symmetrical face without skin lesions. There was no palpable lymph node at the head and neck region. Intra-orally, the patient presented with fiery red, soft, and edematous gingival tissue involving the free gingival margin to the mucogingival junction in both maxillary and mandibular anterior segment [Figure 1(a) and (b)], in which the maxillary anterior sextant showed more severe appearance. Moreover, the gingivae at the maxillary anterior segment had a strawberry-like and granular appearance, while the gingivae at the mandibular anterior segment had a smooth and shiny appearance. Moderate deposits of plaque with little calculus were evident. In addition, there was no evidence of gingiva ulceration, desquamation and vesicles noted. Pseudo pockets

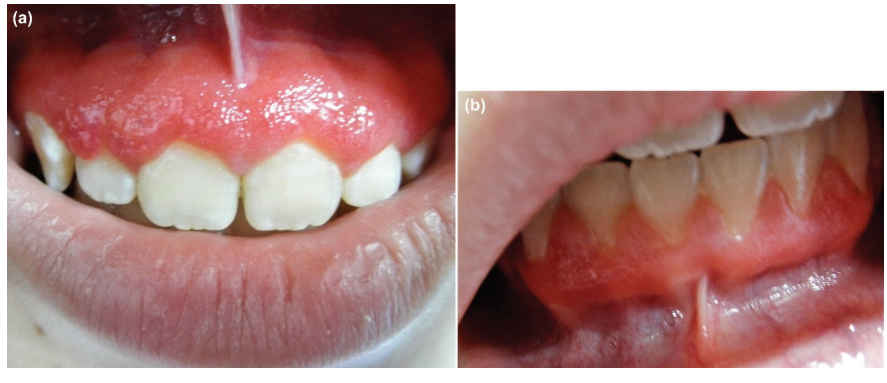


Figure 1 Clinical appearance upon initial presentation. (a) Strawberry-like, granular, erythematous, and oedematous lesion affecting the free and attached gingivae of the maxillary anterior segment. No vesicle or ulceration was seen. (b) Gingival tissue at the lower anterior segment with less severe appearance.

could be appreciated at the maxillary and mandibular right canine, with probing pocket depths of 7 - 10 mm, while other sites recorded 1 - 5 mm. Periapical radiographs of teeth 13 (maxillary right canine) to 23 (maxillary left canine) and 33 (mandibular left canine) to 43 (mandibular right canine) showed crestal bone levels at or close to the cemento-enamel junction with sufficient interdental distance and no other pathologies evident [Figures 2(a), (b), (c), (d) and (e)]. Differential diagnoses of atypical gingivitis, contact dermatitis, and erosive lichen planus were made.

Initial therapy included oral hygiene instructions, which recommended using an ultra-soft bristled toothbrush, flossing, supra- and sub-gingival scaling, and polishing. However, at the one-month review, the gingival condition showed no improvement and was obstinate to conventional therapy. Inflammation of the gingivae was disproportionate to the amount of plaque and calculus present.

Since there was no improvement in the appearance of the gingivae after removing the local etiological factors, a decision was made to biopsy the affected tissue for histopathological evaluation. An incisional biopsy specimen was made at the interdental papillae and the gingival margin of tooth 11 (maxillary right central incisor) and 21 (maxillary left central incisor). At the same time, blood investigations were ordered to rule out haematological malignancies and Anti-Neutrophil Cytoplasmic Antibodies (ANCA)-associated vasculitis. The results of the patient's full blood count and renal function test were unremarkable. Her erythrocyte sedimentation rate was elevated at 42 mm/hour, whereas anti-nuclear antibody (ANA), perinuclear ANCA (P-ANCA), and cytoplasmic ANCA (C-ANCA) were negative.

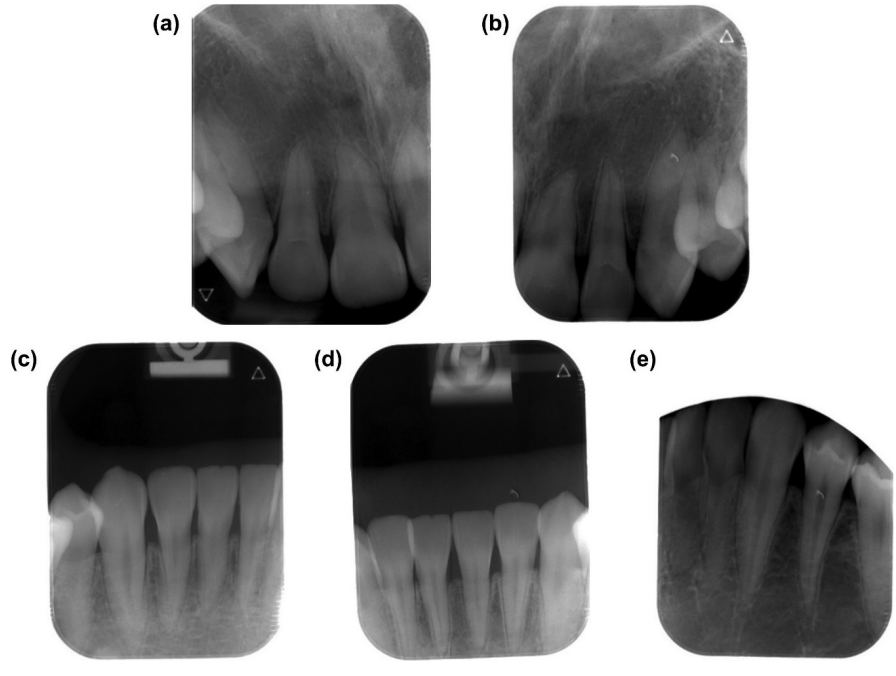


Figure 2 Radiographic images at initial presentation. Intraoral radiographs were taken at (a) right maxillary anterior teeth region, (b) left maxillary anterior teeth region, (c) right mandibular anterior teeth region, (d, e) left mandibular anterior teeth region.

The histopathological report showed hyperplastic parakeratinized stratified squamous epithelium overlying fibrous connective tissue. The underlying fibrous connective tissue was infiltrated by dense chronic inflammatory cells with a predominance of plasma cells [Figures 3(a) and (b)]. Apart from that, no evidence of granuloma or multinucleated giant cells was seen in the section examined. Kappa-lambda immunohistochemical (IHC) analysis showed polyclonal proliferation of plasma cells [Figures 4(a) and (b)]. In order to determine the cause of the condition, the patient was referred to a dermatologist for a skin patch test and was found to have a contact allergy to copper sulphate from local and dental series.

Based on the clinical features, blood investigations, and histopathological findings, a diagnosis of plasma cell gingivitis (PCG) was confirmed. The patient was counseled to refrain from copper sulphate-containing substances and maintain proper oral hygiene. Correspondingly, gingival inflammation became more discernible after the patient switched to an allergen-containing toothpaste. She was treated with prednisolone mouthwash and was recommended to use Oral 7 moisturizing toothpaste (Oral 7, Singapore).

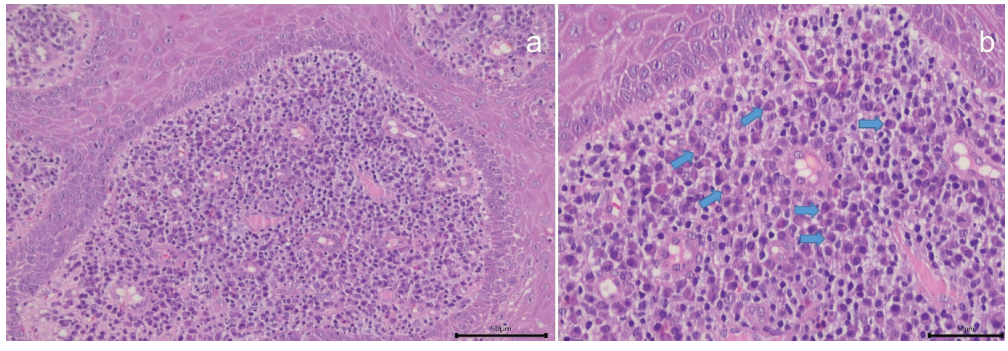


Figure 3 (a) The section shows hyperplastic parakeratinised stratified squamous epithelium overlying fibrous connective tissue. The underlying fibrous connective tissue is infiltrated by dense chronic inflammatory cells with a predominance of plasma cells (H&E, magnification 200) (b) The section shows fibrous connective tissue infiltrated by dense chronic inflammatory cells with a predominance of plasma cells (blue arrow) (H&E, magnification 400)

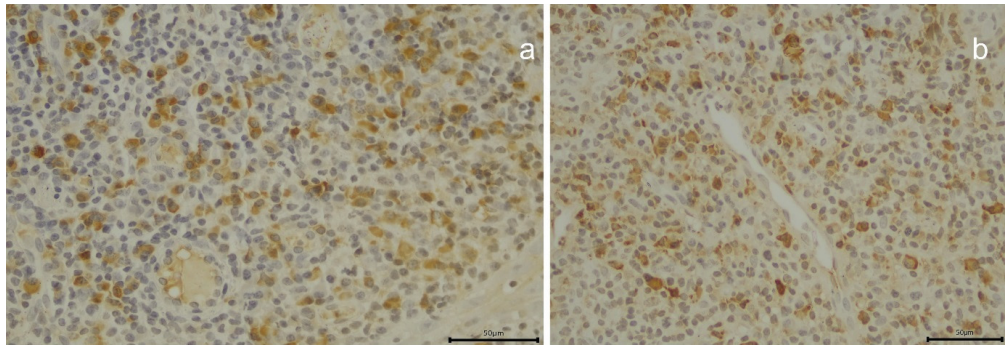


Figure 4 Immunohistochemistry, Kappa-lambda stains. (a) Kappa immunostain, magnification 400, and (b) Lambda immunostain, magnification 400 show polyclonal proliferation of plasma cells.

Nevertheless, there was only limited improvement in the appearance of the gingivae, presumably because the patient dined out frequently. The gingivae at the maxillary anterior segment were still somewhat reddened and granular, extending from the free gingival margin to the mucogingival junction whereas gingivae at the mandibular anterior segment are still soft and shiny, although less severe in intensity.

A year later, prednisolone mouthwash was discontinued to observe the progress of the gingival condition. However, the appearance of the upper and lower gingivae was exacerbated. The presentation of the gingivae intensified further after the patient defaulted to using the prednisolone mouthwash for a couple of months. This further suggested continuation of prednisolone mouthwash as part of the treatment modalities.

Subsequently, the patient was advised to switch to dexamethasone 1 mg/g paste twice daily. The patient reported a significant reduction of erythema of the gingivae compared to when she was treated with prednisolone 5 mg/10mL mouthwash. The upper and lower anterior gingivae appeared less erythematous. Nonetheless, it was still friable and granular in appearance [Figure 5].

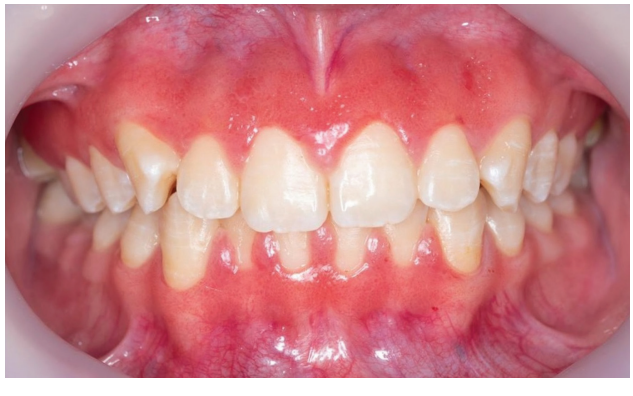

Figure 5 Gingival appearance one month after switching to dexamethasone 1mg/g paste. Note markedly reduced erythema at the upper and lower anterior gingival area.

The patient reported that there was no adverse effect. She is currently being treated with dexamethasone 1 mg/g paste twice daily and is instructed to continue using Oral 7 moisturizing toothpaste (Oral 7, Singapore) regularly.

The patient is subjected to follow-up monthly, and the oral lesions remain unresolved.

## Discussion

Plasma cell gingivitis (PCG) is primarily a diagnosis of exclusion. Thus, comprehensive history taking, hematological screening, and careful histopathological analysis are necessary to arrive at the definitive diagnosis of the gingival condition to exclude leukaemia and other local manifestations of systemic diseases. Due to its rare occurrence, to the best knowledge of the authors, there was no reliable epidemiological data to describe it. However, some reported an occurrence among children up to the geriatric age group with slight male predominance [10,11]. A recent report showed the contrary, whereby female predominance was noted with a mean age of 60 [12]. A dense and massive infiltration of mature plasma cells in the lamina propria disrupting the basement membrane, followed by the capillaries dilatation, is the typical histopathological feature [7,13].

Following periodontal initial therapy on the patient, inflammation of the free gingiva and attached gingiva was found refractory to local treatment. These findings were consistent with earlier reports [14,15]. Still, they were contradictory to a case series study of paediatric PCG conducted by Arduino PG *et al.*, which reported that non-surgical periodontal therapy efficiently reduces clinical gingival inflammation and the extent and severity of PCG lesions [10]. There was no strong evidence in management strategies and it was based on

published case series and reports. However, its management mainly focused on avoiding the antigenic substances and symptom control [11,13] in addition to the non-surgical periodontal therapy to control the gingival inflammation synergistically [10]. The first line of pharmacological intervention for this condition is usually corticosteroid such as prednisolone, clobetasol, or dexamethasone to control the immune-mediated responses, which can be given as mouthwash, topical application, or systemic depending on its severity [12]. Supportive periodontal therapy after active periodontal treatments is essential for the sustenance of the treatment. Nonetheless, a marked reduction in erythema of the gingivae after switching to dexamethasone paste may be resulted from increased time of contact of medication with the lesion, compared to the usage of prednisolone mouthwash. Other than that, prednisolone was chosen as the first treatment choice in this case due to its potency and availability as a mouthwash in our clinical setting. Other highly potent corticosteroids, such as clobetasol, may potentially cause more side effects. Oral 7 moisturizing toothpaste was also recommended to the patient since it does not contain the antigenic substance.

Oral signs could be manifested at an early phase in systemic disease. In the present case, the lack of skin lesions and a negative Nikolsky sign eliminated most cutaneous disorders from consideration. Acute leukemia is frequently accompanied by oral and periodontal symptoms, which include infiltration of gingivae by leukemic cells resulting in gingival overgrowth [16]. A normal full blood count and differential removed leukemia from the differential diagnosis. Strawberry-like gingivitis is an almost pathognomonic oral manifestation of granulomatosis with polyangiitis [17]. Oral lupus was typically presented as an area of well-demarcated erythema or erosion with central white papules surrounded by white radiating striae, most commonly at the hard palate. However, it could also occur on the gingiva, labial mucosa, buccal mucosa, and vermillion border [18]. A negative anti-nuclear antibody (ANA), perinuclear ANCA (P-ANCA), and cytoplasmic ANCA (C-ANCA) result excluded the patient from having systemic autoimmune disorder and vasculitis, including systemic lupus erythematosus and Wegener granulomatosis. The patient also did not have any risk factors associated with HIV infection. The absence of multinucleated giant cells on histopathologic examination ruled out granulomatous gingivitis or systemic condition, such as Crohn's disease. IHC showing polyclonal expression with kappa and lambda chain restrictions confirmed the diagnosis of PCG. Apart from that, Kappa and Lambda chains acted as a marker for plasma cell activation. The monoclonal proliferation of plasma cells was noticed in neoplasms such as multiple myeloma [11].

PCG had been related to the use of strong spices and some herbs such as chilli, pepper, cardamom, and chewing of khat [5,19]. In 1971, Kerr *et al*. [3] reported a case resulting from an allergic reaction to one of the constituents of chewing gum, in which the signs and symptoms resolved once the allergen was removed. Flavouring agents such as cinnamon aldehyde and cinnamon in chewing gum and dentifrices have been associated with the development of PCG. On the other hand, Macleod and Ellis [2] described a case of PCG related to the use of herbal toothpaste, whereas Miller *et al.* [20] detailed 14 cases of cinnamon-induced stomatitis.

In the case depicted here, copper sulphate acted as an allergen, causing PCG. Copper sulphate is a chemical compound used as a fungicide, herbicide, and pesticide. It is used in aquariums for parasitic infections as well as in agriculture to control fungus on grapes, melons,

and other berries. Apart from that, it is used in hair dyes and in processing leather and textiles. Due to the wide range of applications of this specific compound in daily products, complete elimination of the offending causative agent is arduous. This resulted in persistent erythematous and edematous gingival conditions in our patient after unknown exposure to this antigenic agent; unlike in some other cases [3,19], the clinical symptoms disappeared after the implicated agents were eliminated. Furthermore, relapses were reported when an attempt was made to halt or taper the steroid dosage; hence, a change of pharmacological strategies may be required [12]. To date, inadequacies of evidence lead to a lack of a definitive standard of care for PCG [13]. Therefore, the management of PCG is mainly targeted at symptomatic relief [11] and is directed towards the elimination of exposure to the antigenic agent, if any.

In conclusion, PCG is a rare inflammatory lesion of the oral mucosa, and the diagnosis is highly challenging. Considerable attention to the history, physical examination, and histopathological analysis are essential to attain a timely diagnosis and begin appropriate therapy.

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## Declaration of patient consent

The authors clarify that all the appropriate consent was obtained prior to the publication of clinical information and photos in this article. The patient acknowledges that she remained unnamed in this report, but complete anonymity cannot be guaranteed.

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