Letter

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Granulomatosis with polyangiitis in gingiva: A rare case of isolated presentation

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SUMMARY Granulomatosis with polyangiitis (GPA) is a rare autoimmune disease characterized by necrotising granulomatous inflammation of upper and lower respiratory tract, vasculitis and glomerulonephritis. This ailment may present with cough, haemoptysis, sinusitis, nasal deformity, skin lesions, malaise, fever, anorexia, and weight loss. Oral manifestation includes strawberry gingivitis, which is a pathognomonic clinical presentation. Here, we present a case of GPA in gingiva as the first manifestation. Clinical examination of the oral cavity revealed granular, erythematous gingival enlargement in the lower anterior teeth region involving papilla, marginal and attached gingiva with shiny and pebbled surface. Histopathological examination showed pseudoepitheliomatous hyperplasia with vasculitis and inflammation in the connective tissue, neutrophilic infiltration and abscess formation with haemorrhage were noted. Laboratory investigations revealed Proteinase 3 (PR3) antigen and Glomerular basement membrane (GBM) antigen were positive. Clinical, histopathological and laboratory investigations enabled the diagnosis of Granulomatosis with Polyangiitis. We present this rare case report of GPA with primary manifestation in gingiva.

Keywords granulomatosis with polyangiitis, Wegener's granulomatosis, strawberry gingivitis

Wegener's granulomatosis, currently known as Granulomatosis with Polyangiitis was initially described by the German pathologist Friedrick Wegener in 1936 (*1*). This is a rare, systemic disease characterised by necrotising granulomatous inflammation of the upper and lower respiratory tract, vasculitis and glomerulonephritis (*2*). Despite years of research, the aetiology of this disease remains unknown (*2*).

The disease can present in either localised or generalised form. Localised form can involve predominantly upper respiratory tract without any vital organ involvement (*3*). In around 6-13% of cases, lesions in the oral cavity are reported. It is noteworthy that, oral cavity as initial site of presentation was noted only in 2% of the cases (*1*) Clinical manifestations vary from patient to patient, thus forming a challenge in prompt diagnosis and treatment. Rapid progression with multi-organ involvement can be potentially fatal (*4*).

Here, we present an extremely rare case of granulomatosis with polyangiitis of gingiva as the first site of occurrence without any systemic involvement.

A 32-year-old male patient reported to the Department of Periodontology, Krishnadevaraya College of Dental Sciences and Hospital, Bengaluru with a complaint of painful gingival swelling with intermittent bleeding for the past 2-3-months. The patient had visited a general dental practitioner and underwent scaling & root planning followed by administration of medication (Clotrimazole oral paint, Chlorhexidine mouthwash, Analgesics – Aceclofenac (325 mg) + Paracetamol (100 mg), Antibiotic - Amoxicillin 500 mg for 5 days). Respiratory tract infections were elicited and found to be negative. Similarly, there were no abnormalities detected in relation to eyes and kidney. Patient had the habit of smoking cigarettes (0.9 pack years), however, he reports to have quit the habit for the last 2 years. Patient also reported habit of pan chewing with tobacco for 6 years and has quit in the past 2 months. Oral examination revealed a purplish red, irregular, diffuse erythematous enlargement involving interdental papilla, marginal and attached gingiva (Bokenhamp Grade 3 gingival enlargement) with granular, shiny and strawberry like surface, in the lower anterior teeth region (#33-#43). The lesion was tender, soft and oedematous in consistency, immobile in attached gingival region and mobile in the papillary and marginal gingiva with sessile attachment

to underlying tissues and presented with irregular edges. Bleeding was present on probing the involved region. Mobility of teeth was absent and alteration of colour and surface texture was noted in papilla of upper canine region. No discharge and alteration of taste was seen (Figure 1A). Radiographic evaluation (orthopantmography and Chest X-ray) showed no abnormalities (Figure 1B). Routine blood investigation showed increased levels of Erythrocyte Sedimentation Rate (ESR) – 55mm/hr. C-Reactive protein was normal. The anti-neutrophil cytoplasmic antibody (ANCA) analysis revealed, myeloperoxidase (MPO, p-ANCA) as negative and Proteinase 3 (PR3) antigen (c-ANCA) and Glomerular basement membrane (GBM) antigen as positive. Informed and written consent was obtained from the patient.

An incisional biopsy was performed, and histologic examination demonstrated predominantly parakeratinised stratified squamous epithelium exhibiting pseudoepitheliomatus hyperplasia, spongiosis, acanthosis and formation of neutrophilic abscess (Monroe's abscess) within the epithelium. The underlying connective tissue was oedematous and consisted of dense mixed inflammatory cell infiltrate consisting of neutrophils, eosinophils, lymphocytes, plasma cells, macrophages, and mast cells. Proliferating dilated blood vessels, a few congested blood capillaries, areas of haemorrhage, and extravasated red blood cells were evident (Figures 2). Considering the clinical, radiographic, histological and laboratory findings, a diagnosis of GPA was made. The patient was referred to a centre for immunotherapeutics for further management (Supplemental Table S1, *http://www.irdrjournal.com/action/getSupplementalData.php?ID=97*).

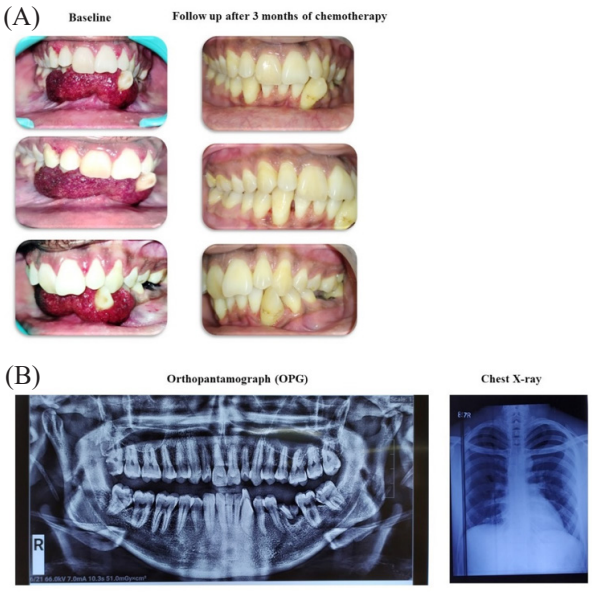

Figure 1. (A) Clinical photographs at baseline and 6-month follow up; (B) Orthopantamograph (OPG) and chest x-ray showing no abnormalities.

The etiology of GPA remains unclear, while various environmental factors like exposure to cadmium, silica, mercury, sand dust, and volatile hydrocarbons have been studied as possible causative agents (5). Furthermore, bacterial and viral agents like Staphylococcus aureus, hepatitis C virus, Epstein-Barr virus, and cytomegalovirus have also been implicated in modulating the clinical phenotype of the disease. Besides, certain medications – phenytoin, hydralazine, anti-thyroid medications, sulfasalazine and allopurinol have been noted in previous reports (*6*). Lately, Fiona *et al*. provided insight into former smoking being associated with development of GPA with an odds ratio of 1.5, when compared with never smokers (*7*). Similarly, McDermott *et al*. have reported association between ANCA associated vasculitis (AAV) and cigarette smoking, suggesting a possible mechanism between respiratory exposure and development of AAV (*8*). A notable fact is that, the patient presented in this case was a former smoker for 6 years (0.9 pack years). Cigarette smoking is a modifiable risk factor which should be given due importance.

GPA affects lower and upper respiratory tracts, thus patients complain of sinus congestion, nasal obstruction, epistaxis, otitis media, or dyspnoea. None of these symptoms were reported by the patient in this case. Oral manifestations of GPA include ulcers of the palate, tongue or other areas of oral mucosa which show delayed healing, oro-nasal fistulas, mobility, loss of teeth and nodules, and swelling of lips. Very rarely parotitis (inflammation of the sublingual salivary gland),

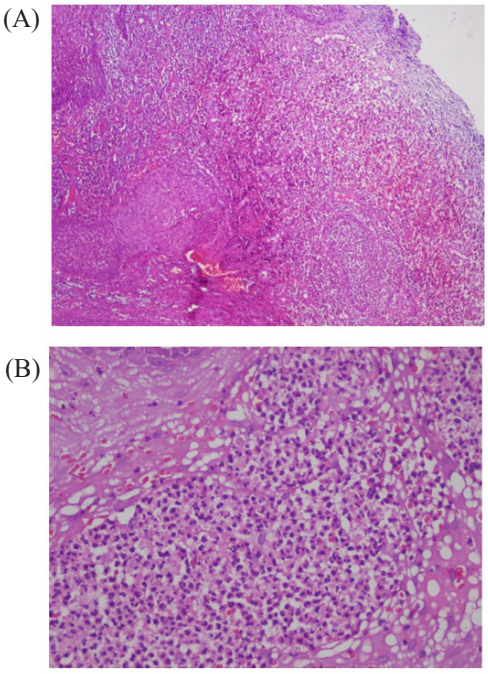

Figure 2. (A) Hematoxylin and eosin (H&E) section showing pseudoepitheliomatous hyperplasia with vasculitis and inflammation in the connective tissue (20×); (B) Hematoxylin and eosin (H&E) section showing neutrophilic infiltration and abscess formation with haemorrhage (40×).

which is painful, is also reported. In the present case, manifestation was restricted only to gingiva, showing the classical picture of "strawberry gingiva" (*9*).

When GPA is suspected due to history and clinical examination of patient, measurement of complete blood count, erythrocyte sedimentation rate, C-reactive protein, proteinuria, urine analysis, serum creatinine, and blood urea nitrogen levels is recommended (*10*). In the current case, only ESR was elevated; the C-reactive protein (CRP) and urine analysis showed no significant deviations. The current recommendations on ANCA testing requires screening of two main patterns of ANCA: cytoplasmic pattern (c-ANCA) and perinuclear pattern (p-ANCA). Studies have shown that c-ANCA is 80-100% specific for GPA (*4*). In the present case, c-ANCA along with glomerular basement membrane antigen were found to be positive. The clinical picture of hyperplastic erythematous gingival tissue may give rise to differential diagnoses like drug induced gingival enlargement, plasma cell gingivitis, sarcoidosis, leukemic enlargement, and chronic inflammatory enlargement. However, the classic clinical presentation and further serological tests helped in ruling out the differentials and confirming the diagnosis to GPA. Sometimes even histopathological findings alone maybe inconclusive, hence it is mandatory to correlate with clinical and systemic findings to arrive at a diagnosis. Special staining to rule out bacterial or fungal etiology is also recommended.

Various treatment protocols have been reported, which include cyclophosphamide and azothiopurine as the main drug of choice. Also, Glucocorticoids with methotrexate are used to induce remission of GPA. A study conducted at National Institute of Health, a regimen of cyclophosphamide (2 mg/kg body weight per day) with prednisone (1 mg/kg body weight), showed complete remission in 93% of the patients (*3*). Currently, Rituximab (monoclonal antibody against CD20) has also been approved as a therapy. In the reported case, a combination of mycophenolate (500 mg, 1-0-2), methotrexate (15 mg, 1/week), hydroxychloroquine (200 mg, 1-0-1), and prednisone (30 mg – 20 mg – 10 mg for 2 weeks and 30 mg – 20 mg for further weeks) was given in first phase up to 3 months. At the end of 3 months, complete resolution of oral lesion and strawberry gingiva was noted. Following this, the dosage was tapered. When prompt diagnosis and correct therapeutic decisions are made, resolution of lesions occurs within a few weeks. However, with tapering of immunosuppressive therapy there are chances of relapse of the disease.

When oral manifestation of GPA is present, albeit very rare, it is imperative for a dental practitioner to critically analyze the clinical, systemic, hematological, and histopathological manifestations to enable an early and accurate diagnosis and appropriate referral for medical management. There may be an isolated clinical presentation of GPA in gingiva as in the current case, which affirms that health professionals should be acquainted with oral manifestations of diseases.

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References

1. Fonseca FP, Benites BM, Ferrari A, Sachetto Z, de Campos GV, de Almeida OP, Fregnani ER. Gingival granulomatosis with polyangiitis (Wegener's granulomatosis) as a primary manifestation of the disease. Aust Dent J. 2017; 62:102-106
2. Hanisch M, Fröhlich LF, Kleinheinz J. Gingival hyperplasia as first sign of recurrence of granulomatosis with polyangiitis (Wegener's granulomatosis): case report and review of the literature. BMC Oral Health. 2016; 17:33.
3. Dhalkari CD, Patil SC, Indurkar MS. Strawberry gingivitis - First sign of Wegener's granulomatosis. J Oral Maxillofac Pathol. 2020; 24:172-175.
4. Lourenço SV, Nico MM. Strawberry gingivitis: an isolated manifestation of Wegener's granulomatosis? Acta Derm Venereol. 2006; 86:90-91.
5. Ponniah I, Shaheen A, Shankar KA, Kumaran MG. Wegener's granulomatosis: the current understanding. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2005; 100:265-270.
6. Weeda LW Jr, Coffey SA. Wegener's granulomatosis. Oral Maxillofac Surg Clin North Am. 2008; 20:643-649.
7. Pearce FA, Lanyon PC, Watts RA, Grainge MJ, Abhishek A, Hubbard RB. Novel insights into the aetiology of granulomatosis with polyangiitis-a case-control study using the Clinical Practice Research Datalink. Rheumatology (Oxford). 2018; 57:1002-1010.
8. McDermott G, Fu X, Stone JH, Wallwork R, Zhang Y, Choi HK, Wallace ZS. Association of Cigarette Smoking With Antineutrophil Cytoplasmic Antibody-Associated Vasculitis. JAMA Intern Med. 2020; 180:870-876.
9. Msallem B, Bassetti S, Matter MS, Thieringer FM. Strawberry gingivitis: Challenges in the diagnosis of granulomatosis with polyangiitis on gingival specimens. Oral Surg Oral Med Oral Pathol Oral Radiol. 2019; 128:e202-e207.
10. Sung IY, Kim YM, Cho YC, Son JH. Role of gingival manifestation in diagnosis of granulomatosis with polyangiitis (Wegener's granulomatosis). J Periodontal Implant Sci. 2015; 45:247-251.

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