CASE REPORT

Wegener's Granulomatosis: Strawberry Gums of the Oral Cavity

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ABSTRACT

Wegener's Granulomatosis is a rare and potentially life-threatening vasculitic disease of unknown origin. The diagnosis of Wegener's Granulomatosis is made on the basis of clinical presentation, positivity for serum c-ANCA and histologic examination of the lesions. This report details a case of limited Wegener's Granulomatosis with hyperplastic gingivitis lesions presenting as an initial manifestation of Wegener's Granulomatosis. The resemblance of the affected gums to over-ripe strawberries is pathognomonic of this condition and is thus highlighted. Because of the rarity of Wegener's Granulomatosis presenting initially in the oral cavity, clinicians should be alerted to the characteristic appearance of "strawberry gingivitis".

Keywords: Necrotising vasculitis, Strawberry gingivitis, Wegener's granulomatosis

INTRODUCTION

Background and Historical Perspective

Wegener's Granulomatosis (WG) is a rare form of systemic vasculitis that can affect the upper respiratory tract, lungs, kidneys and other organs[1]. The head and neck region is usually not spared of the disease either. Peter McBride, a Scottish otolaryngologist, first described the condition in a paper entitled "Photographs of a case of rapid destruction of the nose and face"[2] in 1897. An earlier name for the disease was pathergic granulomatosis[3]. Although it was Heinz Klinger[4] who first described the disease in two patients who succumbed to widespread sepsis in 1931 in the German literature, the disease is named after Dr. Friedrich Wegener[5], who described a similar clinical presentation in three patients in 1936. Wegener reported a triad of signs that consisted of necrotising granulomatous inflammation of the upper or lower respiratory tract, systemic necrotising vasculitis of small arteries and veins, and rapid necrotising glomerulonephritis leading to renal failure. Other clinical signs and symptoms that can accompany the triad of pathological changes include intractable sinusitis and rhinitis, cough, haemoptysis and terminal uraemia[6].

Etiology and Epidemiology

The cause of Wegener's Granulomatosis remains unknown although many investigators believe an immunologic pathology is likely[7]. It has been suggested that the disease onset occurs in genetically-susceptible individuals coupled with an environmental trigger[8]. *Staphylococcus aureus* has been implicated in the initiation and recurrence of WG by changing the immune tolerance, leading to increased vessel inflammation[9,10]. It has also been reported that occupational exposure to silica was found to be related with chronic renal failure or vasculitis similar to that found in WG[11]. The incidence of WG is three cases per million per year[12] and in the USA, it affected three in every 100,000 people in the 1990s[13]. It mainly occurs in the middle-aged, with the highest incidence between 40 to 50 years[14]. It has also been reported in much younger[15] and older patients. Fifteen percent of cases occur in individuals below 20 years old and the disease is extremely rare in children[16].

Clinical Features

The initial signs of WG are extremely variable, but most patients generally present with rhinitis[17]. Diagnosis can be severely delayed due to the non-

Table 1. Some clinical symptoms of Wegener's granulomatosis in the respective organs that may be affected by the disease.

Nose: pain, stuffiness, nosebleeds, rhinitis, crusting, saddle-nose deformity due to a perforated septum
Trachea: Subglottal stenosis
Lungs: Pulmonary nodules (referred to as "coin lesions"), infiltrates (often interpreted as pneumonia), cavitary lesions, pulmonary hemorrhage causing hemoptysis, and rarely bronchial stenosis
Kidneys: Rapidly progressive glomerulonephritis (75%), leading to chronic renal failure
Eyes: Pseudotumours, scleritis, conjunctivitis, uveitis, episcleritis
Ears: Conductive hearing loss due to auditory tube dysfunction, sensorineural hearing loss
Oral cavity: 'Strawberry gingivitis', underlying bone destruction with loosening of teeth, non-specific ulcerations
Joints: Pain or swelling (60%), often initially diagnosed as rheumatoid arthritis
Skin: Nodules on the elbow, purpura
Nervous system: Occasionally sensory neuropathy (10%) and rarely mononeuritis multiplex
Heart, gastrointestinal tract, brain, other organs: Rarely affected

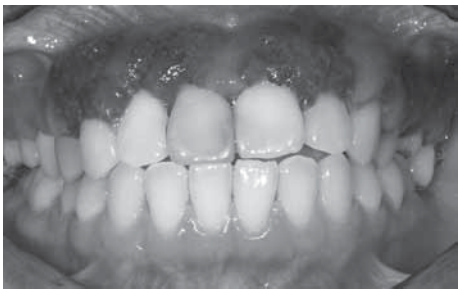
specific nature of the symptoms. The presenting clinical manifestations of WG involving the upper and lower respiratory system, kidney, eyes, ears, oral cavity, joints, skin and nervous system are briefly outlined in Table 1. The heart, gastrointestinal tract, brain and other organs are rarely affected.

As low as 10% of patients with WG have oral manisfestations[18]. Although WG does occur in the oral cavity, oral lesions that present as an initial manifestation of WG are rare[19]. In the oral cavity, WG may present as hyperplastic granular-appearing gingival overgrowth(s) speckled by petechiae and these lesions are associated with pain and bleeding[20-25]. The inflammatory process begins in the interdental papilla and then progresses very quickly to the surrounding gingiva and the supporting periodontium[26]. The appearance of the reddish to purplish-looking hyperplastic gingivae with the numerous petechiae have led them to be called "strawberry gingivitis". "Strawberry gingivitis" when present, is considered to pathognomonic of WG[26-30]. Other oral presentations include palatal mucosal ulceration and the failure of tooth socket(s) to heal[31]. Evidence of teeth mobility as well as alveolar bone loss is also present most of the time[32].

The following is a case report of WG that only involved the head and neck area. The initial presenting feature of WG was that of "strawberry gingivitis".

CASE HISTORY

A 42-year-old Chinese Singaporean woman was referred to the National Dental Centre (NDC) on 12th May 2008 for periodontal treatment. The patient had no relevant medical history and no known drug allergy. The patient complained of profuse gingival bleeding whenever she brushed or flossed her teeth since early May 2008. A full mouth periodontal examination was carried out and probing depths of between 4 to 6mm was detected on every maxillary tooth site. Conversely, all the mandibular teeth except the lower right second molar showed normal probing levels of between 1 to 3mm. The lower right second molar had only two localised pockets of 4 mm and 6 mm at its proximal sites. The upper teeth exhibited increased mobility whereas the lower teeth were within physiological limits. The orthopantomogram and the right and left bite-wing radiographs showed normal horizontal bone levels. Bone loss due to periodontal disease was not detected radiographically. The clinical diagnosis was generalised chronic moderate periodontitis



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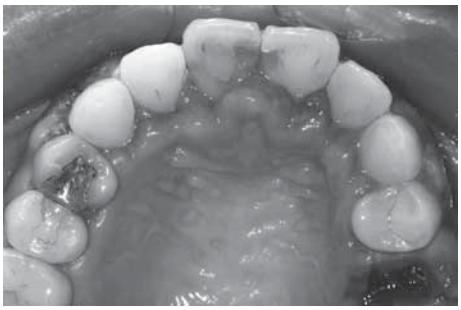


(B)

Fig. 1 (A) Maxillary buccal gingiva at initial presentation. (B) Palatal mucosa and socket of upper left 2nd premolar at initial presentation.

and the treatment plan was for mechanical debridement of the periodontal pockets of her upper teeth and the lower right second molar.

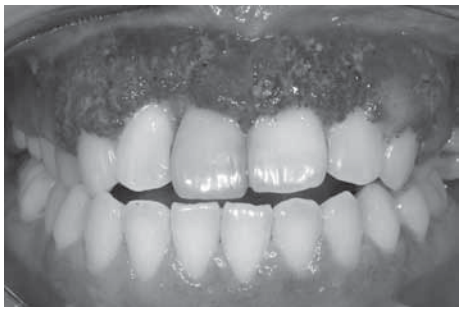
The patient returned to NDC on 27th May with complaint of pain at her upper left second premolar and she was diagnosed to have irreversible pulpitis and was advised root canal treatment for the tooth. However, she opted to have her periodontal treatment and endodontic therapy of her upper right central incisor at a private clinic.

On 19th June 2008, the patient complained again of pain at her upper left second premolar. The patient also claimed that her upper gums had started to swell about three weeks before. On examination, it was noted that the mobility of the tooth of complaint had increased from Grade 1 to Grade 3 mobility. Her upper teeth also exhibited unusual buccal gingival enlargement and the lesion was painful (Fig. 1A). The colour of the hyperplastic gums was dark red to purple and the surface was granular and spongy in appearance. The hard and soft palate did not show any ulceration (Fig. 1B). All the lower teeth demonstrated healthy-looking pink gingiva. The painful upper left second premolar tooth spontaneously exfoliated during this visit. Examination of the upper left second premolar socket showed loss of buccal and palatal cortical bone plate.

The patient was reviewed a week later and at this visit, the patient reported that she developed swelling on the left side of her face on 23rd June 2008. This was associated with tenderness and she also gave a history of epistaxis from her left nostril. She had seen a medical doctor and was prescribed Augmentin. She was noted to have left paranasal swelling. The gingival lesions had become bigger, were dark red to purple in colour, had a more obvious granular appearance and the lesional surface was flecked with numerous petechiae, and the lesion resembled over-ripe strawberries. The gingivae of the lower anterior teeth were red and erythematous at the buccal keratinised tissue. Ulcers ranging from 5 to 7mm in diameter were present at the right palatal mucosa. The upper teeth showed more increased mobility. A joint consultation was made with the oral and maxillo-facial surgeon, and based on the patient's clinical picture, differential diagnoses included Wegener's Granulomatosis, Churg-Strauss Syndrome and Kaposi Sarcoma. A full blood count was ordered and the results were within normal limits except for raised platelet levels (600 x 10^9L). The patient was scheduled for incisional biopsy of her oral lesions on 1st July 2008.

On the 28th June 2008, the patient attended the Department of Emergency Medicine in Singapore General Hospital and was seen by the dental officer on duty. She complained of low-grade fever, blocked nose, gum swelling, ulcers at her palatal mucosa, pain at her left ear when swallowing and severe pain at the gums of her lower teeth when she rinsed or consumed drinks. She also reported bilateral bloody nasal discharge. The patient also experienced non-throbbing pain behind her left eye but had no visual problems. The patient claimed that her pain and discomfort had caused her to be unable to eat or sleep. The dental officer prescribed topical anaesthetic gel for the painful ulcers/swollen gingivae and analgesics for her complaint of facial pain.

On 30th June 2008, the patient requested for an



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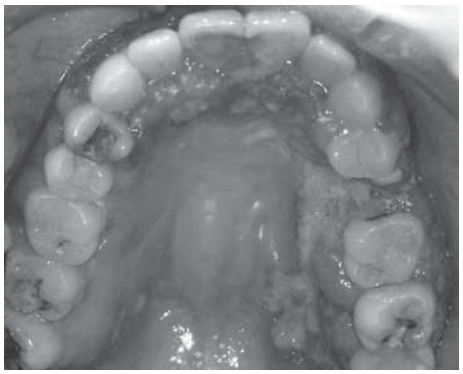


(B)

Fig. 2 (A) Extent of the 'Strawberry gingivitis' lesion at 2-weeks presentation. (B) Extent of the palatal ulceration and non-healing socket of the upper left 2nd premolar.

earlier biopsy. There was facial swelling at the left paranasal region and intra-orally, the hyperplastic gingiva on her upper teeth (Fig. 2A) and the palatal ulceration had increased in extent (Fig. 2B). The patient was referred to an oral and maxillo-facial surgeon and underwent an incisional biopsy on the same day. Biopsies were taken of the palatal mucosa of her upper incisors and the region of the left upper wisdom tooth. Additional investigations included urinalysis, serological assay for antinuclear antibodies, anti-neutrophil cytoplasmic antibodies (ANCA), ANCA-enzyme immunoassay profile, serum C-reactive protein level, erythrocyte sedimentation rate and a chest x-ray. A cone beam CT scan taken showed no nasal bone destruction and the sinuses were clear. However, there was buccal and palatal bone destruction at the upper posterior teeth region.

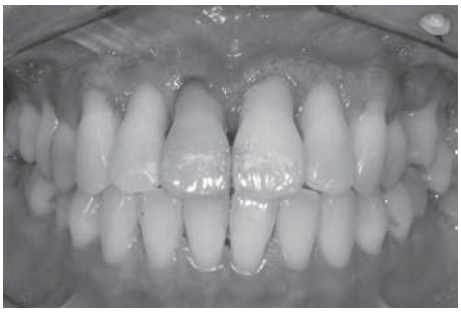
On 4th July 2008, the patient reported that it was getting harder to breathe. Intra-orally, the palatal ulceration had increased considerably to 2cm in size. A 5mm ulcer had developed at the right palatal mucosa. All her upper teeth were mobile and the strawberry gingivitis had enlarged. Necrotic bone fragments were seen at the upper left premolar socket. Serum C-reactive protein and erythrocyte sedimentation rate were raised at 57.6 (norm 0.2-8.8 mg/L) and 71 (norm 3-15 mm/hr), respectively. The nuclear antibody and the neutrophil cytoplasmic antibody were negative. In terms of the ANCA-EIA profile, the anti-myeloperoxidase (MPO) was negative but the anti-proteinase 3 (PR3) was positive. The chest x-ray radiology did not show any lesions in the lungs suggestive of any pulmonary involvement of Wegener's Granulomatosis.

Histopathology findings of the biopsied oral mucosal specimens reported that the covering stratified squamous epithelium was extensively ulcerated and the epithelium was hyperplastic and hyperkeratinised. The connective tissue contained diffuse infiltrates of mixed acute and chronic inflammatory cells with abundant histiocytes. There were numbers of granuloma at the periphery which had abundant foreign body and Langhan's type giant cells. Vasculitis was evident and special stains failed to disclose presence of fungal hyphae or acid-fast bacilli. Immunohistochemical studies were carried out on the specimen taken from the upper left posterior palatal mucosa area. It was found that large numbers of CD68+ macrophages were present within the lesion but only small numbers of CD3+ and CD5+ cells were demonstrable. The specimen also did not show any reactivity for CD56+ or T1A1+ cells.

A provisional diagnosis of Wegener's Granulomatosis was made based on the clinical presentation, histopathological and positive PR-3 findings, and the patient was referred to a rheumatologist for management of her condition. She was started on prednisolone and methotrexate.

At review on 14th July 2008, the patient reported feeling better. Her nose swelling had decreased and the gingival hyperplasia had reduced in size (Fig. 3A). The bilateral palatal ulcers were also noted to be healing (Fig. 3B).

By 22nd August 2008, her prednisolone was tapered to 45mg daily whereas her methotrexate was 20mg per day. The upper left second premolar edentulous ridge showed exposed buccal and palatal bone.



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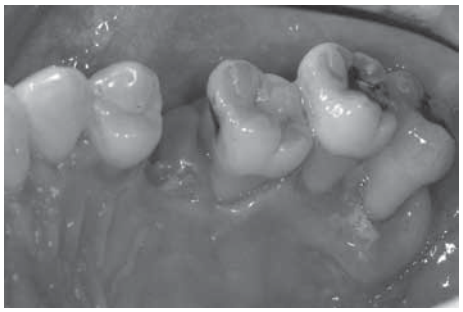

(B)

Fig. 3 (A) Soft tissue resolution after 1 month of immunosuppressants. (B) Ulcers healed at the upper left 2nd premolar site and the palatal molar region.

The upper teeth mobility had reduced to Grade 1 but there was complete loss of the keratinised tissue of her upper buccal gingiva (Fig. 3A).

On 15th October 2008, the patient was referred to NDC by her rheumatologist. She was warded for the flare-up of her Wegener's Granulomatosis associated with severe pain on the left side of her face. This followed an episode of left ear infection at the end of September 2008. Antibiotics prescribed did not help, and drainage of her left infected ear canal was performed by the ENT specialist. It was during this period that her prednisolone dosage was decreased to 20mg per day to help the infection to resolve. However, the lowered prednisolone caused her to have a flare-up. Extra-orally, the patient had developed some weakness of her facial muscles. Intra-orally, there were still necrotic bony spicules coming off the upper left premolar edentulous ridge and gingival inflammation was seen at the palatal of her upper molar teeth. Her lower anterior teeth and lower right first premolar also showed some gingival redness with petechiae spots on the buccal keratinised mucosa. Her oral lesions and facial palsy improved with use of azathioprine and increased dose of prednisolone.

In March 2009, the patient was seen for another flare-up of WG following sinus surgery to treat her left maxillary sinusitis. She still had facial palsy and sustained loss of hearing on her left side. She was prescribed cyclophosphamide by her physician.

DISCUSSION

WG is a necrotising vasculitis and granulomatosis of unknown cause and it can occur in a generalised form involving respiratory, pulmonary and renal lesions or it can occur in limited forms which affect the oral or nasal cavities and the lungs[33,34]. Diagnosis of WG may be delayed when involvement is limited and thus the identification of a distinct feature would be of clinical significance in early diagnosis leading to prompt management[35]. The initial presenting symptoms in 73% of patients diagnosed with WG occur in the head and neck area[1]. Lesions in WG can affect the scalp, skin of the forehead, ears, eyes, nose, sinuses, oral cavity, larynx and trachea as well as the lungs and kidneys. Oral involvement in WG is relatively uncommon, reportedly occurring in 6 to 13% of patients. Oral manifestations of WG as the initial presenting feature is seen in only two percent of cases[18].

Although oral lesions in early WG is uncommon, the strawberry gingivitis is one of the distinctive signs of WG[29,30,35]. When present, this is pathognomonic of the disease[28]. Other oral lesions include painful mucosal ulcerations/ulcers of the hard and soft palate as well as the tongue. Cobblestone-like lesions may occur in the palate[24]. Other less common oro-facial complaints/features include toothache, facial pain associated with sinusitis, temporomandibular joint pain due to arthralgia, non-healing extraction sockets, oro-antral fistulae, enlargement of the salivary glands, facial palsy and skin ulcers[19,27].

A very significant diagnostic feature in WG is the presence of anti-neutrophil cytoplasmic antibodies (ANCA) to the cytoplasmic antigens of neutrophil granulocytes[27]. This is a specific serological marker for WG and it forms the basis of the ANCA test[36]. Anti-neutrophil cytoplasmic antibodies (ANCA) against enzymes in the primary

granules of neutrophils such as proteinase-3 (PR-3) or myeloperoxidase and a classic clinical triad of upper respiratory, lower respiratory and renal involvement are hallmarks of WG[24]. Studies have shown that the c-ANCA/anti PR-3 antibodies are about 90% sensitive and 97% specific for WG[37,38]. The ANCA levels also play an important role in the monitoring of patients' response to treatment[37]. The nuclear antibody and neutrophil cytoplasmic antibody levels in this case report were negative but the ANCA-PR3 profile was positive. A negative result of ANCA does not exclude WG and this is often the case in the early stages of WG, only to become positive in later stages of the disease[19]. A search of the literature by Parsons E et al[27] has failed to find any association between gingival lesions and ANCA levels in WG patients.

An elevated erythrocyte sedimentation rate is present in almost all cases and is a helpful but non-specific test[29]. Biopsy of affected sites is an important diagnostic tool. Current histopathological criteria for a diagnosis of WG are stringent and they include granulomata, necrosis and vasculitis[39]. Other reported histopathological features include pseudoepitheliomatous hyperplasia, polymorph microabscesses and giant cells in the gingival biopsy[40]. In this case report, there was evidence of granuloma and vasculitis in the biopsied specimens and this helped in the diagnosis of WG for the patient.

The mainstay of treatment is to administer corticosteroids and cytotoxic drugs such as cyclophosphamide[8]. A regimen of steroids and cyclophosphamide which sustained disease remission and prolonged survival was reported by Fauci and Wolff[41] in the early 1970s. Treatment usually commences with a high dose of prednisolone and is maintained until all the manifestations of active disease have resolved in approximately a month's duration[23]. The corticosteroids are then gradually tapered over the next few months. Oral cyclophosphamide treatment is often started at about 2mg/kg/day which is usually continued for up to a year after complete remission[18]. For limited forms of WG, methotrexate have been used instead of cyclophosphamide to induce remission[1]. It has been shown in a large randomised trial that the use of methotrexate in patients with limited WG demonstrated comparable remission-induction rates to those on cyclophosphamide[42]. The patient in this case report had quick resolution of her oral lesions after prednisolone and methotrexate were given but she suffered a relapse of oro-facial involvement of WG when her prednisolone dosage was decreased in the management of her ear and sinus problems. Besides methotrexate, azathioprine is used for remission-maintenance treatment[1].

This case report exemplifies the significant contribution that dental clinicians can make in the early recognition of WG and hence the prompt referral for appropriate treatment. This is of significance as without treatment, patients have only a mean survival period of five months whereas treated patients have sustained disease remission[26]. Thus, clinicians should be alerted to the characteristic appearance of strawberry gingivitis pathognomonic of this condition, especially in cases where the oral manifestations of WG precede or accompany pulmonary and renal involvement[29].

CONCLUSION

The clinical picture of "strawberry gingivitis" should alert the dentist to the diagnosis of WG, and patient(s) can be referred without delay for medical evaluation and management.

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