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Gingival granulomatosis with polyangiitis (Wegener's granulomatosis) as a primary manifestation of the disease

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ABSTRACT

Granulomatosis with polyangiitis (GPA) is a potentially lethal disease characterized by systemic necrotizing vasculitis, which affects small- and medium-sized blood vessels and is often associated with serum cytoplasmic antineutrophil cytoplasmic antibody. The upper and lower respiratory tract and kidney are the most involved sites, but oral lesions can be identified in 6–13% of the cases, whereas in only 2% of the cases, oral manifestations represent the first signal of the disease usually as gingival swellings or unspecific ulcerations. Without treatment, the mainstay of which is the combination of immunosuppressants and systemic corticosteroids, GPA may run a fatal course. In this report we describe an original case of GPA affecting a 75-year-old female patient referred to our service due to a gingival swelling with 3-month duration. Although the patient was correctly diagnosed and promptly treated, she died 3 months after the initial diagnosis.

Keywords: ANCA, granulomatosis with polyangiitis, necrotizing vasculitis, oral cavity, Wegener's granulomatosis.

Abbreviations and acronyms: ANCA = antineutrophil cytoplasmic antibody; CT = computed tomography; GPA = granulomatosis with polyangiitis; HE = haematoxylin–eosin; WG = Wegener's granulomatosis.

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INTRODUCTION

Granulomatosis with polyangiitis (GPA), formerly known as Wegener's granulomatosis (WG), is an autoimmune small vessel vasculitis highly associated with antineutrophil cytoplasmic antibodies (ANCA). It was originally described by the German pathologist Friedrick Wegener in 1937 with an incidence ranging 7–12 new cases/million inhabitants per year.[1–3] The aetiology is unknown, but it may originate from infectious (*Staphylococcus aureus*), environmental, chemical, toxic or pharmacological triggers in genetically predisposed patients.[3]

Granulomatosis with polyangiitis is characterized by systemic necrotizing vasculitis, granulomatous inflammation and pauci-immune glomerulonephritis, more frequently affecting the upper and lower airway tracts and the kidneys, although many different organs can be involved.[4] GPA is diagnosed based on clinical manifestations of systemic vasculitis and histological evidence of necrotising vasculitis or granulomatous inflammation.[1] Limited forms of GPA predominantly affect the upper respiratory tract, whereas generalized forms of GPA include renal manifestations and/or alveolar haemorrhage and/or vital organ involvement with an altered general condition.

Oral cavity manifestation is present in 6–13% of the patients during the disease course, but oral involvement as the first sign of the disease is found in only 2% of the cases, representing an important diagnostic pitfall for diagnosticians.[2–5] Hence, in this report we describe a rare case of oral mucosa GPA as the primary signal of the disease in a female patient.

CASE REPORT

A 75-year-old female patient was referred to our department due to a slightly painful gingival swelling with 3-month history that could not be controlled by her private dentist using conventional periodontal treatment. Medical history of the patient included osteoporosis, arthrosis and hypothyroidism that were

currently under control. Palpable lymph nodes were not found during regional physical evaluation. Oral examination revealed an erythematous hyperplasia with a granular surface in the lower gingiva, predominantly affecting the interpapillary areas of anterior teeth, extending from the right second premolar to the left second premolar (Fig. 1). Bleeding was frequent in the involved areas, but the patient denied taste alteration and discharge from the affected sites. Tooth mobility was not found and the upper gingiva was free of lesions. Radiographic evaluation showed no bone alterations and blood tests were within normal limits.

An incisional biopsy was performed and microscopic features revealed a pseudoepitheliomatous proliferation of the surface epithelium with the underlying connective tissue demonstrating an intense mixed inflammatory infiltrate with multinucleated giant cells, microabscess, eosinophils and extensive red blood extravasation (Fig. 2). To better characterize the inflammatory infiltrate, immunohistochemical reactions were performed, revealing the presence of B and T lymphocytes, whereas myeloperoxidase illustrated the presence of neutrophils forming microabscess foci. CD68-positive macrophages and multinucleated giant cells were also diffusely present, although well-formed granulomas were not found, and reactions against CD138 demonstrated the predominance of plasma cells in the lesion (Fig. 3). Additional histochemical reactions of periodic acid-Schiff, Ziehl–Neelsen and Grocott stains were negative, and a descriptive histological diagnosis consistent with GPA was made.

Laboratory examinations were performed and indirect immunofluorescence reaction against cytoplasmic ANCA was positive, as well as the enzyme-linked immunoassay test to proteinase 3 ANCA. Renal tests were normal, but chest radiography and computed tomography (CT) showed diffuse areas of opacification in both lungs (Fig. 4) and the biopsy confirmed the presence of a granulomatous reaction. Taken together, the clinical, microscopic, radiographic and laboratorial findings were consistent with the diagnosis of GPA.

Two weeks after the oral biopsy, the patient demonstrated constitutional complications including dyspnoea, fever, diarrhoea, vomiting and a significant weight loss. Palpable submandibular lymph nodes were found and the patient also developed sepsis that was controlled with broad-spectrum antibiotics. Methylprednisolone 40 mg/day and azathioprine 50 mg/12 h were used to control the inflammatory disease, but the patient subsequently developed a cytomegalovirus infection (laboratorial confirmation with presence of cytomegalovirus antigen) that was controlled with interruption of the immunosuppressive therapy and antiviral medication. Treatment with methylprednisolone and azathioprine was restarted, but the patient developed chronic anaemia, cardiac insufficiency, lung hypertension and further uncontrolled systemic infections, dying 3 months after the diagnosis.

DISCUSSION

Granulomatosis with polyangiitis is a potentially lethal disease characterized by aseptic, necrotizing granulomatous vasculitis of small- and medium-sized vessels, the aetiology of which is associated with the production of ANCA.[6] Its aetiology and pathogenesis are unknown, although various theories have been postulated, such as the autoimmune theory, the hypersensitivity theory and the theory of infection as a precipitating factor.[7] The disease has a predilection for the upper airways, lungs and kidney, but any other organ including the oral cavity can be involved.[8]

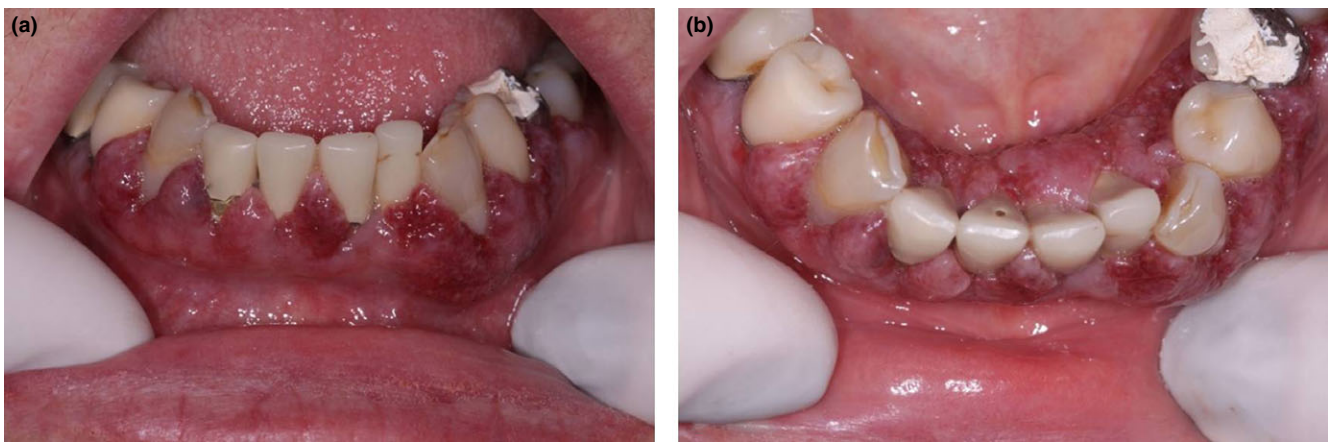

Fig. 1 Clinical presentation of the lesion. (A) Frontal view of a diffuse reddish swelling affecting lower gingiva predominantly located in the interpapillary region and with granulomatous surface. (B) On occlusal view, the lesion demonstrated both vestibular and lingual overgrowth.

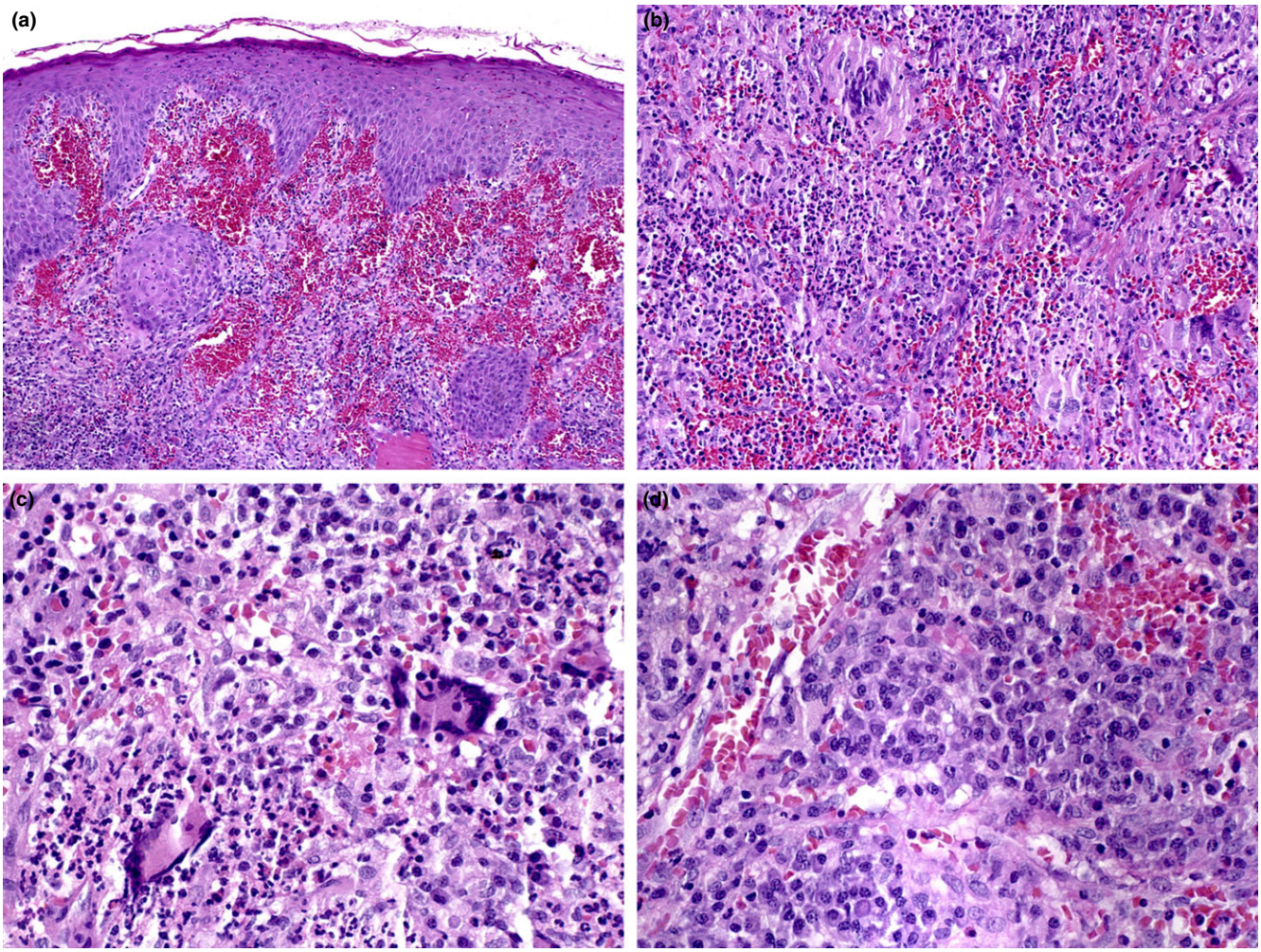

Fig. 2 Histological aspect of the gingival lesion. (A) Small foci of pseudoepitheliomatous proliferation were found (haematoxylin–eosin (HE), original magnification ×100). (B) The lesion demonstrated a mixed inflammatory infiltrate with lymphocytes, macrophages and multinucleated giant cells that were randomly distributed without well-organized granulomas (HE, ×200). (C) Higher magnification with multinucleated giant cells, plasma cells and a small neutrophilic abscess (HE, ×400). (D) Plasma cells predominated in some areas (HE, ×400).

Granulomatosis with polyangiitis has been simultaneously diagnosed in patients affected by other autoimmune diseases[6] and although Hemminki *et al.*[9] demonstrated a slightly increased risk for GPA in patients affected by rheumatoid arthritis, further studies are necessary to validate the presence of other autoimmune conditions as risk factors for GPA. However, it is advisable for clinicians to be vigilant about GPA when unusual gingival and mucosal presentations are seen in patients diagnosed with autoimmune diseases.

Granulomatosis with polyangiitis is more frequently diagnosed in adult patients with a mean age ranging 40–55 years, but cases affecting children are also described. There is no gender predilection and the disease can be classified as either localized or generalized depending on the extension of the process and the involvement of vital organs.[3,5] Constitutional symptoms such as general malaise, myalgia, arthralgia, anorexia, weight loss and pyrexia can be observed as shown in our case and haematological examinations may reveal unspecific alterations like lymphopenia, eosinophilia and hyperimmunoglobulinemia E. As exemplified in this case, anaemia is also a possible finding.[1]

Current diagnostic criteria for GPA include the identification of at least two of the following features: nasal or oral inflammation; presence of abnormal chest radiograph; abnormal urinary sediment; and presence of granulomatous inflammation in a biopsy.[2,3,8] In the current case, the gingival erythematous hyperplastic lesion with areas of granulomatous surface with the so-called 'strawberry-like lesion' was consistent with this diagnosis.[2,8,10] Moreover, the oral biopsy demonstrated an intense inflammatory infiltrate containing both macrophages and multinucleated giant cells, and although small vessel vasculitis and well-formed granulomas were not seen, it is known that these features are usually not found in mucosal specimens.[5,10] The radiograph, CT examinations and lung biopsy demonstrated lung involvement by the

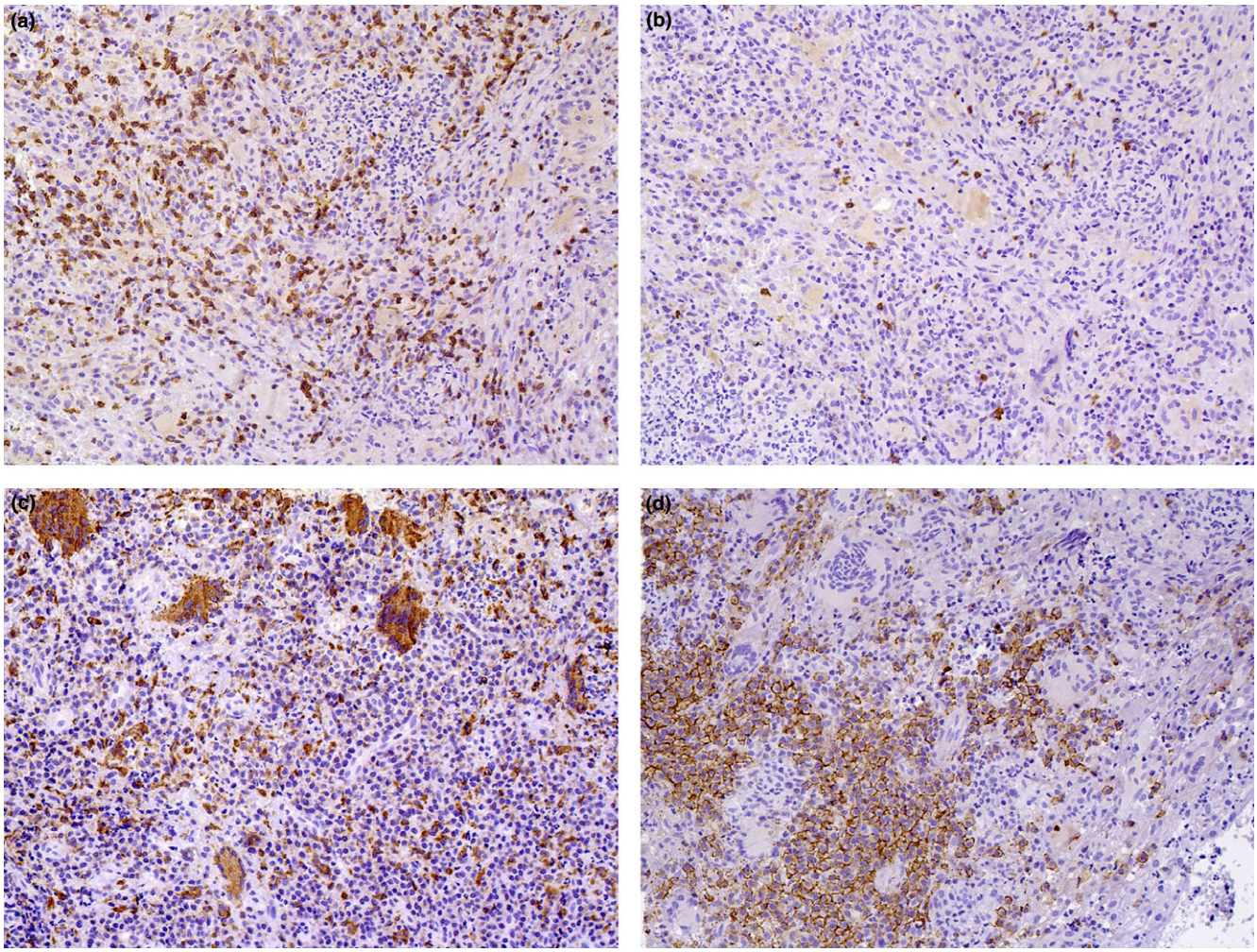

Fig. 3 Immunohistochemical reactions (streptavidin–biotin–3,3′-diaminobenzidine-tetrachloride, original magnification ×200). (A) CD3 demonstrated that T lymphocytes predominated and (B) B lymphocytes that were evidenced with CD20 reaction (×200). (C) Macrophages and multinucleated giant cells were identified using CD68 reactions but no well-formed granuloma could be found (×200). (D) Plasma cells were demonstrated using CD138 reactivity (×200).

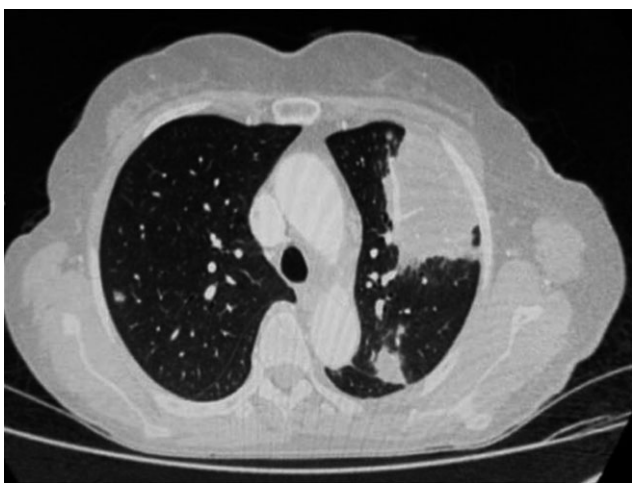

Fig. 4 Chest computed tomography demonstrated the presence of diffuse areas of opacification in both lungs.

disease and the serum test for cytoplasmic ANCA was also positive. Interestingly, our patient did not present renal involvement during the disease evolution.

Strawberry-like gingivitis is the characteristic sign of GPA, manifesting as enlarged, erythematous interdental papillae with red to purple gingival tissue containing petechiae and a granular appearance with yellow punctate foci.[4] In this case, the patient did not present systemic complaints and oral lesions were the first clinical manifestation of the disease, which is very rare for GPA, accounting for less than 2% of the cases. Moreover, hyperplastic erythematous gingival tissue may give rise to a broad number of differential diagnoses ranging from reactive hyperplasia, to infectious diseases to malignant neoplasms, and a careful clinical and microscopic examination is necessary to achieve the appropriate diagnosis. In the present case, we have considered paracoccidioidomycosis, GPA and a leukaemic infiltration as the main differentials. Other lesions such as drug-induced gingival overgrowth, non-neoplastic proliferative lesions, Langerhans cell histiocytosis, Kaposi's sarcoma and metastasis were also considered, but less likely.

Microscopically, GPA reveals leucocytoclastic vasculitis of small vessels that may demonstrate fibrinotic necrosis in their walls, ill-defined granulomas with the presence of multinucleated giant cells, macrophages, lymphocytes and plasma cells, and extensive areas of geographical necrosis.[6] However, these findings are more frequently found in lung biopsies, whereas oral lesions typically demonstrate an intense mixed inflammation with presence of microabscesses, multinucleated giant cells and pseudoepitheliomatous hyperplasia.[2] These non-specific aspects were evident in our case and together with the clinical characteristics helped to confirm the diagnosis. In addition, the typical granulomatous appearance of the disease was seen in the lung biopsy of our patient.

Patients with GPA demand prompt management and current therapeutic protocols aim to achieve disease remission (induction phase), followed by a maintenance approach. Oral or pulsed i.v. cyclophosphamide and corticosteroid combination remains the gold standard therapy.[1,3,11] More recently, rituximab (a monoclonal antibody against CD20) has also been approved for GPA therapy. Maintenance protocol is started after completion of induction therapy, and azathioprine, methotrexate and rituximab are current drug options.[1] In the current case, a combination of azathioprine with corticosteroid (methylprednisolone) was decided upon because of the poor general health status of the patient that would not tolerate the more toxic cyclophosphamide therapy.

Despite significant improvements with immunosuppressive therapy, toxicity of the available protocols represents the main adversity. As previously described and also shown in our case, secondary infections are the main cause of morbidity and death of these patients.[12]

CONCLUSIONS

Although rare, oral lesions as the primary manifestation of GPA may be found and diagnosticians must consider this condition when dealing with erythematous hyperplastic gingival swellings. Moreover, when gingival lesions do not respond to routine periodontal treatment, referral for an opinion and/or a biopsy is essential.

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