Strawberry gingivitis: Challenges in the diagnosis of granulomatosis with polyangiitis on gingival specimens

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Strawberry gingivitis is a rare oral manifestation of granulomatosis with polyangiitis (GPA, formerly known as *Wegener's granulomatosis*). It manifests as a red-purple hyperplastic gingivitis that frequently goes unrecognized as a disease-specific symptom, especially if it is the primary and only manifestation of the disease. GPA is a systemic necrotizing granulomatous vasculitis that takes a fatal course without treatment. Oral health care providers, who are among the first to examine the oral cavity, should be familiar with its typical appearance, clinical course, diagnostic parameters, and management.

This article highlights the challenges to early-stage diagnosis of initial multiple gingival enlargements because histologic biopsies are often nonspecific and histology alone may not be sufficient to make a correct diagnosis of GPA from gingival specimens. Because strawberry gingivitis may be the first manifestation of GPA, awareness of it should be increased so that it can be diagnosed by its unique clinical appearance and additional related diagnostic parameters even if the histologic gingival findings are nonspecific. (Oral Surg Oral Med Oral Pathol Oral Radiol 2019;128:e202–e207)

Lesions of the gingiva are a very common clinical finding and have a broad differential diagnosis. Localized and generalized gingival enlargements may be of developmental, reactive/inflammatory fibromatous, hamartomatous, idiopathic, or neoplastic origin.[1] Granulomatosis with polyangiitis (GPA) is an idiopathic antineutrophil cytoplasmic antibody (ANCA)-associated necrotizing granulomatous vasculitis that affects small-sized vessels of the upper and lower respiratory tract and also frequently causes necrotizing glomerulonephritis. Diagnosis of GPA is often delayed because patients commonly present with prodromal symptoms (e.g., fever, malaise, anorexia, weight loss) lasting for weeks or months, and nonspecific symptoms (e.g., rhinosinusitis) are easily overlooked at first sight. One characteristic clinical feature of GPA is the so-called strawberry gingivitis, which presents as an erythematous enlargement of the gingiva. Its histologic analysis often shows a nonspecific inflammation that lacks the characteristic features of GPA, such as necrotizing granulomas, giant cells, and prominent angiocentric leukocytic vasculitis. Therefore, diagnosis of GPA can be a challenge even for pathologists. Consequently, oral health care providers should be acquainted with the oral manifestations of systemic diseases with nondistinct histology to ensure prompt referral to specialists, thus supporting early-stage diagnosis.

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FINDINGS

A 70-year-old Caucasian male was referred by his dentist to the Clinic of Oral and Cranio-Maxillofacial Surgery of the University Hospital Basel in Switzerland for exclusion of malignancy. The main complaint was a rapidly growing hyperplastic gingival swelling in the upper and lower jaws; the patient had first noticed the swelling 2 months earlier. The patient was in good general condition, well-nourished and was not on any significant medication. Intraoral examination revealed several exophytic enlargements in the attached gingiva in the maxilla and the mandible. The surface appeared reddish with granular aspects, including undefined margins and petechial bleeding upon examination (Figure 1A). To exclude a malignant neoplasm, an incisional biopsy of the most prominent gingival masses was performed for histologic examination. Histology showed nonspecific chronic and acute erosive inflammation, with a prominent hyperplastic epithelium displaying parakeratosis, but no signs of malignancy (Figure 2A). Furthermore, foreign material (arrowhead) was found next to giant cells, which were subsequently classified as foreign body giant cells (Figure 2B). In contrast, no signs of granuloma, necrosis, or vasculitis were detected. Full-mouth disinfection and a systemic antibiotic treatment failed to reduce the gingival enlargements. Therefore, a second incisional biopsy, including all gingival enlargements in the maxilla and the mandible, as well as a carbon dioxide (CO_2) laser ablation was performed. Histology results were similar to those of the previous biopsy specimens and remained inconclusive. After CO_2 laser treatment, the oral lesions healed well. Later, the patient returned with grade 3 tooth mobility (Grace & Smales Mobility Index) of teeth #19 and #20. A panoramic radiography revealed extensive bone loss (Figures 3A and 3B), most probably caused by chronic inflammation, and

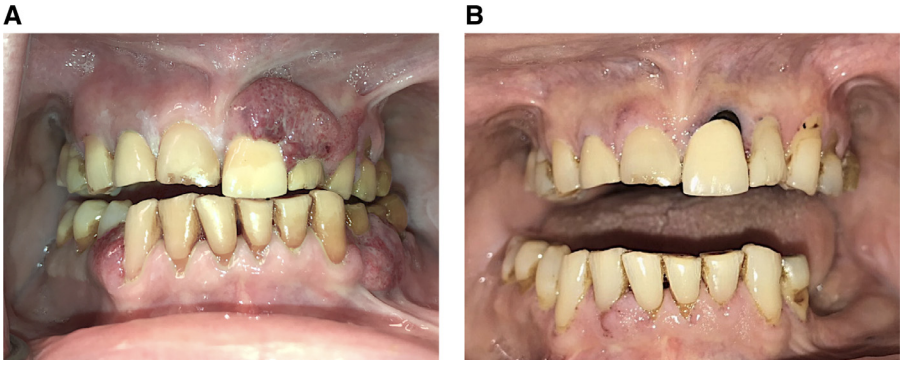

Fig. 1. Intraoral image: Initial manifestation of strawberry gingivitis as an exophytic mass with undefined margins and granular as well as hemorrhagic aspects **(A)**; after carbon dioxide laser treatment as well as extraction of teeth #19 and #20 **(B)**.

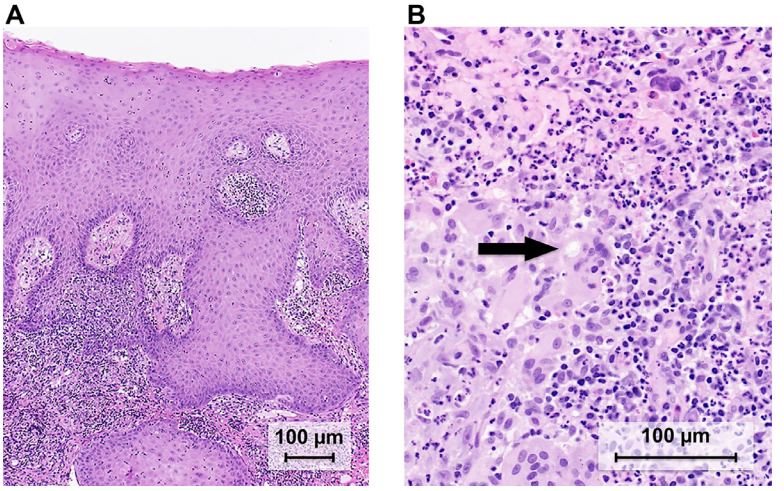

Fig. 2. Histologic image (hematoxylin and eosin [H&E] staining): Pseudoepitheliomatous hyperplasia **(A)**; foreign material *(arrowhead)* and multinucleated giant cells **(B)** (scale bar = 100 μm).

the 2 teeth had to be removed. At the follow-up examinations, the oral mucosa showed no renewed growth of gingival enlargements (Figure 1B), and the patient was transferred back to the referring dentist in good general condition.

The patient was hospitalized approximately one 1 month later in reduced general condition having suffered abdominal pain with persistent diarrhea and intermittent fever for the past 11 days. He reported some constitutional symptoms such as fatigue, weight loss and holocranial headaches. When asked specifically, he confirmed that he had slightly bloody nasal discharge. The oral examination showed no gingival lesions. The laboratory results revealed an elevated level of C-reactive protein (CRP) of 210.2 mg/Ll (reference range < 10 mg/Ll), a normal white blood cell count of 9.97x10^9/Ll (reference range 3.50 to− 10.00x10^9/Ll) and a normal creatinine of 85 μmol/Ll (reference range 49 −to 97 μmol/Ll). Urine analysis showed a slight glomerular microhematuria of 2 to− 8 red blood cells per high-power field (RBC/HPF). The

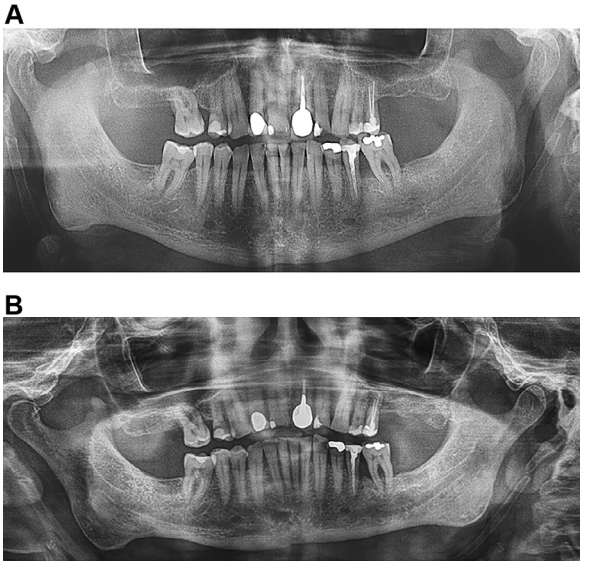

Fig. 3. Radiologic image: Panoramic radiography from the referring dentist **(A)**; after 2 months with increasing loss of periodontal attachment of teeth #19 and #20 **(B)**.

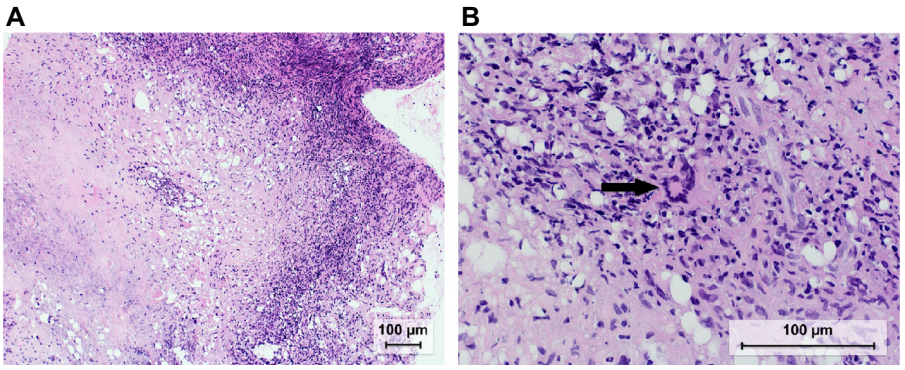

Fig. 4. Histologic image (hematoxylin and eosin [H&E] staining): Geographic necrosis **(A)**; multinucleated giant cells *(arrowhead)* and mixed inflammatory infiltrate **(B)** (scale bar = 100 μm).

chest computed tomography (CT) displayed multiple pulmonary nodules in almost all segments. Magnetic resonance imaging (MRI) of the head revealed pansinusitis and an enlargement of the submandibular salivary gland. A nasal biopsy failed to be diagnostic, but a biopsy from the submandibular mass showed mixed inflammatory infiltrate, geographic necrosis, necrotizing granulomata and multinucleated giant cells, all of which are characteristic of GPA (Figure 4A and B).

Levels of ANCA titer 1:640 and ANCA directed against proteinase-3 (PR3-ANCA) of 119 U/mL (reference range < 3 U/mL) were elevated. ANCA directed against myeloperoxidase (MPO-ANCA) were negative. A diagnosis of GPA with strawberry gingivitis, sinusitis, bloody nasal discharge, pulmonary nodules, glomerular microhematuria, and positive PR3-ANCA was reached. The treatment protocol included glucocorticoids and cyclophosphamide and was later switched to azathioprine. The patient was started on an immunosuppressive treatment with oral prednisolone (100 mg/day) and intravenous cyclophosphamide (800 mg every 2 weeks), resulting in rapid defervescence. Fever is a very common initial symptom that has been observed in 23% of patients with GPA, with the rate rising to 50% during the course of the disease.[2] The prednisolone was then gradually reduced. After 5 months, the cyclophosphamide was switched to oral azathioprine (50 mg twice a day). Approximately 18 months after the primary oral manifestation, the patient was in complete remission. He was in good general health and showed no signs of active disease. The laboratorial parameters showed recovery with good renal function. There was just a slightly abnormal urine sediment with 5 to 10 isomorphic RBC/HPF, equivalent to the values in nonglomerular hematuria. Despite having achieved complete remission, minor anomalies, such as abnormalities of urine sediment or stable scarring in the lungs caused by previous irreversible tissue damage, may persist.[2]

DISCUSSION

Granulomatosis with polyangiitis, eosinophilic granulomatosis with polyangiitis, and microscopic polyangiitis are among the other small-vessel vasculitides generally referred to as *ANCA-associated vasculitides*. As early as the 1990s, the American College of Rheumatology established the following criteria for the diagnosis of GPA and to distinguish GPA from other vasculitides: nephritic urinary sediment (RBC casts or greater than 5 RBC/HPF), abnormal chest radiograph (nodules, cavities, infiltrates), oral ulcers or nasal discharge, and granulomatous inflammation on biopsy analysis.[3] This study showed an 88.2% sensitivity and a 92% specificity if 2 or more of these criteria were present. However, these criteria were developed before major advances in the field of ANCA testing had emerged. Although the American College of Rheumatology classification criteria are used to diagnose vasculitis, some authors advise that they are not adequate for the accurate diagnosis of specific vasculitis and should no longer be used to diagnose vasculitis.[4] The International Chapel Hill Consensus Conference on the Nomenclature of Vasculitides, revised in 2012, defines GPA as necrotizing granulomatous inflammation usually involving the upper and lower airways, and necrotizing vasculitis, predominantly affecting small- to medium-sized vessels (e.g., capillaries, venules, arterioles, arteries, and veins) commonly causing necrotizing glomerulonephritis.[5] It is not a classification or a diagnostic system but, rather, a nomenclature system. The etiopathogenesis of GPA is still unknown and assumed to be of autoimmune origin or caused by environmental influences or genetic susceptibility. Recent studies suggest an association with bacterial infections, but the underlying mechanism is still not clearly understood.[6] The risk of GPA in close relatives is low, but genetic factors may play an important role because increased familial occurrence has been observed in some cases.[7] The incidence is about 6 to 12 cases per million, with median age at first diagnosis

being approximately 60 years and the period between the onset of the first symptoms and diagnosis being approximately 3 months.[8]

The features of GPA are extremely variable, and multiple organ systems are affected. Generic clinical manifestations include malaise, myalgia, arthralgia, and weight loss; sinonasal manifestations include nasal discharge, epistaxis, crusting, mucosal ulceration, nasal bridge collapse, nasal granulomatous lesions, and parasinus and sinus inflammation; upper and lower airway manifestations include tracheal stenosis, cough, pulmonary nodules, cavitating lung lesions, and pleuritis; and renal manifestations include necrotizing glomerulonephritis, hematuria, proteinuria, and chronic kidney disease or end-stage renal failure.[9] Typically, the upper and lower respiratory tract and, in the later stages, the kidneys are affected. In most patients, the airway is initially affected and should always be thoroughly examined even in the absence of symptoms.[2,10] Within the first 2 years of disease onset, glomerulonephritis develops in approximately 77% of patients.[2] Orofacial manifestations may include labial mucosal nodules, gingival enlargements, granulomatous lesions, oral ulcerations, extraction sockets that fail to heal, oroantral fistulae, arthralgia of the temporomandibular joint, and jaw claudication.[9,11-13] Palatal ulcers can be a sign of chronic destructive processes in the nasal cavity, sometimes causing septum destruction that leads to saddle nose or even progressing to the orbit.[14] Facial nerve palsy may also manifest in GPA.[15]

Diagnosis of GPA remains difficult, and patients exhibit increased health-seeking behaviors, consulting various practitioners before they obtain a diagnosis.[16] This emphasizes the need for greater awareness and earlier diagnosis. Although the appearance of hyperplastic gingivitis has been retrospectively described in several reports, the diagnose is generally established after manifestation of additional symptoms.[17] Extensive examination should always start with a detailed anamnestic evaluation, blood tests, urine tests, radiologic imaging, and rapid referral to specialists.[18] ANCA is detected in nearly all severe cases of GPA; however, a small proportion can be ANCA negative, particularly in limited disease.[19] Cytoplasmic ANCA (c-ANCA) is specifically directed against proteinase-3 (PR3) and perinuclear ANCA (p-ANCA) interacts with myeloperoxidase (MPO). GPA is associated with PR3-ANCA in approximately 65% of patients, but it is not specific, and 20% of cases can also be linked to MPO-ANCA.[20] Chest CT is the imaging method of choice for the investigation of thoracic involvement because it detects pulmonary nodules, masses, ground-glass opacity, and consolidation.[21] The most common pulmonary manifestations seen on chest CT scans are nodules and masses.[22]

The differential diagnosis of GPA includes other ANCA-associated vasculitides (eosinophilic granulomatosis with polyangiitis, microscopic polyangiitis), drug-induced gingival changes, granulomatous infections (fungal infections, tuberculosis), granulomatous diseases (sarcoidosis, Crohn disease), orofacial granulomatosis, and blood dyscrasias (leukemia).[23] ANCA-associated vasculitides have overlapping features and should be distinguished on the basis of systemic manifestations with respect to the results of blood tests and histologic examinations. Drug-induced gingival hyperplasia presents a clinical picture of normal-colored mass that is firm and has a smooth, granular or lobulated surface, and histologic examination often shows excessive collagen production.[23] A detailed anamnestic examination frequently reveals exposure to phenytoin, cyclosporine-A, calcium channel blockers, or oral contraceptives.[24] Granulomatous infections, such as deep fungal infections, can be excluded through simple histochemical staining.[25] Tuberculosis can lead to gingival enlargements without regional lymph node involvement. Although the typical tuberculin skin test does not confirm active disease, making diagnosis difficult, the identification of bacilli with special staining can yield a tentative diagnosis.[26] Granulomatous diseases, such as sarcoidosis, manifest in the oral cavity as irregular, firm, submucosal swellings attached to the periosteum.[27] The lesions can vary from papules to submucosal nodules, with superficial ulceration occurring most commonly in the buccal mucosa, followed by gingiva, lips, tongue, and, finally, the palate.[28] The diagnosis is made on the basis of the clinical picture, including histologic proof of noncaseating granuloma, aberrations seen on chest radiographs, tuberculin anergy, a positive result on the Kveim-Siltzbach skin test, elevated serum angiotensin-converting enzyme, and elevated 24-hour urine calcium level.[27] Orofacial granulomatosis is a rare disease that is limited to the oral and perioral regions. After exclusion of sarcoidosis and Crohn disease, clinical presentation is the most important diagnostic factor. Possible manifestations include recurrent swelling that may persist, angular cheilitis, mucosal ulcerations, vertical fissures of the lips, mucosal tags, lingua plicata, craniofacial neurologic disorders, peripheral facial paralysis and histologic proof of noncaseating granuloma.[29] Gingival leukemic infiltrates are present in both acute and chronic forms of all types of leukemia but are more frequent in the acute phase; gingival infiltration is shown by the presence of atypical immature leukocytes that correspond to the type of leukemia.[23] Additional blood testing will help establish the diagnosis.

Immunosuppressive therapy for remission induction in GPA and other ANCA-associated vasculitides includes glucocorticoids in combination with cyclophosphamide or

rituximab.[30] The literature reports treatment protocols with daily cyclophosphamide and glucocorticoids, with a partial remission achieved in 91% of cases and complete remission in 75%.[2] For severe organ-threatening ANCA-associated vasculitis, a single rituximab-based regimen, in combination with glucocorticoids, is considered to be as effective as 18 months of a conventional cyclophosphamide-based regimen with glucocorticoids followed by maintenance with azathioprine.[31]

In about 5% to 6% of cases, the main presenting oral manifestation of GPA is gingivitis or oral ulcers.[10,32] An initial oral manifestation of strawberry gingivitis in the absence of other symptoms is very rare.[17] About 10% of patients experience oral symptoms during the course of the disease, and thus, strawberry gingivitis, if recognized, can be considered characteristic of GPA.[32] Suspicion should be maintained despite biopsy results that indicate only inflammation.[17] Inflammation can affect the periodontium and lead to alveolar resorption and tooth mobility. An extravasation of RBCs caused by weakened vessel walls is typical of small-vessel vasculitides often causing purpura, although this typical feature was not particularly present in our specimens. The classic histologic criteria of GPA comprise vasculitis, granulomata, mixed inflammatory infiltrate, multinucleated giant cells, and geographic necrosis. A retrospective analysis of biopsy specimens from various tissues (except kidneys) of patients with GPA showed that histology was nonspecific in 54.8% of cases.[33] This finding correlated well with those of earlier studies, which reported that characteristic features of GPA, including vasculitis, geographic necrosis, and granuloma formation, are often absent. In contrast, pseudoepitheliomatous hyperplasia, multinucleated giant cells, and microabscesses of the gingiva are more commonly observed.[25] Therefore, many researchers have turned to individual characteristics that are generally considered nonspecific but, together, form a symptom complex that points to a particular diagnosis. The clinicopathologic complex associated with such features as pseudoepitheliomatous hyperplasia, intraepithelial abscess penetrating into the surface epithelium, microabscesses in connective tissue stroma, and multinucleated giant cells are considered to be highly suggestive of GPA.[34] However, taken separately, these common aspects also are associated with many other factors, such as infections, trauma, drugs, foreign material, mechanical irritation, and neoplasia. Microscopic description and diagnosis based on histologic findings should be carefully correlated with the clinical appearance of patients showing oral enlargements, and despite nonspecific histopathologic findings, a diagnosis of GPA should not be excluded. The first gingival biopsy specimen in our case contained not only multinucleated giant cells but also foreign material (Figure 2B, *arrowhead*), probably related to the post and core crown of tooth #9 and, as a result, was interpreted as foreign body giant cells. Consequently, the histologic changes were found to be nonspecific and did not point to the diagnosis of GPA. It was only the biopsy specimen obtained from a submandibular mass that revealed the characteristic changes of GPA. Furthermore, involvement of salivary glands is rare but, if it occurs, diagnosis can often be made solely on the basis of biopsy of the salivary gland.[35]

CONCLUSION

The reported case highlights the fact that histologic analysis of gingival specimens alone may not always be sufficient to make the correct diagnosis of GPA. This means that it is essential to consider clinical manifestations, such as strawberry gingivitis, and other findings, if present (e.g., ANCA, abnormalities of urine sediment, pulmonary symptoms). Nevertheless, strawberry gingivitis may be the first and only characteristic of GPA and can be identified by its characteristic appearance. In summary, there is a need to raise awareness of the oral manifestations of GPA, of which strawberry gingivitis is the most characteristic.

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