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STRAWBERRY GINGIVITIS AS THE INITIAL MANIFESTATION OF GRANULOMATOSIS WITH POLYANGIITIS IN A PATIENT WITH ALPHA-1 ANTITRYPSIN DEFICIENCY

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ABSTRACT

Background: Granulomatosis with polyangiitis (GPA) is a systemic necrotizing vasculitis, associated with anti-neutrophil cytoplasmic antibody (ANCA) that typically affects small- to medium-sized vessels in the upper and lower respiratory tracts and kidneys. While oral involvement is uncommon, the pathognomonic finding of "strawberry gingivitis" can be an initial manifestation in rare cases. The gingivitis presents as a friable, hyperplastic, erythematous gingival lesion. Recognizing this manifestation is critical, as it may precede systemic involvement and facilitate early diagnosis and intervention.

Case presentation: We report a case of a 56-year-old male with a history of chronic epistaxis, alpha-1 antitrypsin deficiency, and recent new onset joint pain who presented with a two-month history of painful gums refractory to antibiotic treatment. Histopathology of the lesion as well as - a positive proteinase 3 titre – and a cytoplasmic ANCA staining pattern confirmed GPA and C-reactive protein was elevated. With this diagnosis, he was treated with prednisone and methotrexate and later switched to azathioprine due to potential toxicity, leading to symptom resolution and normalization of inflammatory markers. At 1-year follow-up, he remained clinically stable on azathioprine 100 mg daily.

Conclusion: Our case highlights the importance of recognizing strawberry gingivitis as a rare but pathognomonic early manifestation of GPA. It underscores the need for prompt biopsy and serologic testing for accurate diagnosis and suggests that alpha-1 antitrypsin deficiency should raise clinical suspicion for GPA. Early initiation of immunosuppressive therapy is crucial to prevent progression to severe systemic disease.

KEYWORDS

Granulomatosis with polyangiitis, strawberry gingivitis, ANCA-associated vasculitis, alpha-1 antitrypsin deficiency

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LEARNING POINTS

- Strawberry gingivitis, albeit uncommon, is a pathognomonic oral manifestation of granulomatosis with polyangiitis (GPA) and may be the first clinical indication in the absence of systemic signs.
- Prompt recognition and biopsy of atypical oral lesions can aid in the early detection of GPA and avert potentially deadly consequences.
- Alpha-1 antitrypsin deficiency, which is frequently ignored, may contribute to GPA development and should be evaluated during the diagnostic workup, especially in patients with a family history or pulmonary susceptibility.

INTRODUCTION

Granulomatosis with polyangiitis (GPA), formerly known as Wegener's granulomatosis, is a rare systemic small to medium vessel vasculitis typically affecting the upper and lower respiratory tract and kidneys[1]. GPA is thought to develop from the interplay of genetic predispositions (e.g., HLA-DP and *SERPINA1* variants), environmental factors (e.g., silica dust, hydrocarbons, chronic *Staphylococcus aureus* carrier state), and dysregulated immune responses[1].

GPA is histologically characterized by necrotizing granulomatous inflammation, vasculitis with fibrinoid necrosis, and the presence of multinucleated giant cells[1,2]. Its pathogenesis is linked to anti-neutrophil cytoplasmic antibodies (ANCAs), predominantly cytoplasmic-ANCA (c-ANCA) targeting proteinase-3 (PR3). Neutrophils play a substantial role in the development of GPA since they express the PR3 autoantigen and have aberrant regulation of their function in affected individuals[3]. In GPA, the immune system produces these autoantibodies against PR3 found on neutrophils[3]. While neutrophils are often attracted to infection sites to fight off infections, in GPA, they can contribute to tissue destruction[3]. One major concern is the production of PR3 on the surface of apoptotic and active neutrophils, which inhibits macrophage clearance and prolongs inflammation[3]. The immune system perceives continuous immunological activity as a danger rather than a resolution[3]. As a result, macrophages and plasmacytoid dendritic cells function erroneously inhibiting the production of CD4+ regulatory T cells and instead encouraging helper T cell responses with a Th2/Th9 phenotype[3]. This dysregulated immune activation exacerbates the autoimmune process found in GPA.

Oral cavity involvement has been identified in approximately 6-13% of GPA cases[4]. The oral cavity is the initial presentation site in only 2% of cases[4]. Oral manifestations of GPA are often nonspecific, most commonly presenting as oropharyngeal and buccal mucosa ulcerations[3,4]. Less frequently, oral-antral fistulae, palatal osteonecrosis, and labial mucosal nodules have been reported[3,4]. Although rare, strawberry gingivitis is a particular oral manifestation and can serve as an important diagnostic indicator when present[4]. This appears as a friable, hyperplastic, erythematous gingival lesion due to vascular inflammation, capillary proliferation, and leukocyte infiltration resembling strawberries[3,4]. Given the relapsing and remitting course of GPA, these subtle yet characteristic lesions can lead to significant morbidity and mortality if left undiagnosed and untreated[1]. Thus, early recognition and awareness of this manifestation are crucial to reducing systemic complications.

Alpha-1 antitrypsin deficiency (AATD) is a genetic disorder caused by mutations in the *SERPINA1* gene on chromosome 14[5]. This gene encodes alpha-1 antitrypsin (AAT), a glycoprotein enzyme inhibitor predominantly found in the liver[5]. AAT's primary function is to protect lung tissue from enzymatic damage by neutralizing proteases such as neutrophil elastase, cathepsin G, and proteinase 3, which are generated during inflammatory or viral responses[6]. In the absence or failure of AAT, these enzymes destroy important structural proteins like elastin and collagen in the lungs, causing tissue damage[5]. AAT also functions as an acute-phase reactant, with levels increasing during systemic inflammation. Mutations in *SERPINA1* can induce misfolded AAT to accumulate in hepatocytes, resulting in cellular stress and liver damage[5]. In the lungs, a mismatch between proteases and inhibitors causes chronic inflammation and gradual respiratory injury[5]. Additionally, neutrophil extracellular traps have been linked to exacerbating pulmonary damage[5]. The typical AAT genotype is PI*MM, which ensures proper protein levels[5]. The most common disease-related variations are PI*Z and PI*S[5]. Individuals with the PI*ZZ genotype are more likely to have serious lung and liver issues, although individuals with PI*MZ or PI*SZ genotypes may experience lesser symptoms or be at a higher risk under certain situations[5]. Less common variations, such as PI*F (which creates defective protein), PI*I (which causes mild deficiency), and null alleles (which produce no AAT at all), are also associated with varied levels of disease severity[5].

AATD is exceedingly uncommon among Asians, particularly the Japanese population, in contrast to its higher prevalence in Caucasians. According to genetic surveys in Japan, just one AATD patient is born out of every 1.37 million births, highlighting the condition's rarity in this community[6]. The typical pathogenic variations found in Europe and North America (PI*Z and PI*S) are almost non-existent in Japan, where a unique variant known as Siyama is more frequently seen among the few recorded cases[6]. Nationwide epidemiological surveys have discovered only a tiny number of AATD cases in Japan, the majority of which involve the Siiyama mutation, with overall diagnoses remaining

exceedingly low[6]. Broader reviews confirm that AATD is uncommon or almost nonexistent in Asian populations, with a substantially greater incidence in Northern and Western Europe (1 in 2,000-5,000) and significantly lower rates in Asia and Africa[7,8]. Despite its rarity, AATD may go undiagnosed in these populations due to a lack of awareness, however the overall prevalence remains very low when compared to Western populations[6-8].

We present a rare case of GPA presenting with strawberry gingivitis as the initial manifestation, highlighting the diagnostic significance of this atypical presentation.

CASE DESCRIPTION

A 56-year-old Caucasian male presented to the Bronson Rheumatology Specialists (Kalamazoo, MI, USA) with the complaint of gum swelling associated with pain and bleeding. He had a 1-month history of diffuse gum swelling and severe oral pain that impaired chewing and tooth brushing. It was the first occurrence of such symptoms. He denied having upper respiratory tract symptoms. After evaluation by his primary care physician, he was prescribed amoxicillin 875 mg two times a day for 7 days, which resulted in a slight improvement in his symptoms. No abnormalities were detected in association with his eyes and kidneys. The lack of response to initial treatment warranted further investigation; thus, he was referred to a dentist who further referred him to a periodontist. The periodontist performed a lower anterior gingiva biopsy. The histology of biopsy revealed oral mucosa exhibiting heavily inflamed fibrous connective tissue and granulation tissue; throughout the connective tissue, a prominent vascular component was observed along with extravasated erythrocytes, and inflammatory cells, including eosinophils, histiocytes, lymphocytes, granulomatous inflammation and multinucleated giant cells. While classic necrotizing vasculitis was not seen, the constellation of features supported a diagnosis of GPA.

A rheumatology referral was made. The patient denied symptoms of nasal sinuses or prior lung, heart, or kidney disease but had a family history of autoimmune conditions, including celiac disease and AATD in his father. He had the AAT mutation without complications. He reported chronic minimal nosebleeds, most recently one month ago, and a two-day history of bilateral knee pain with morning stiffness lasting two hours. He denied smoking tobacco, drinking alcohol, or illicit drug use. On examination, he was afebrile and in no acute distress, with a blood pressure of 128/82 (checked on his left arm while sitting), respiratory rate of 16, height of 1.829 m, weight of 80.7 kg, and body mass index of 24.14 kg/m^2. Physical examination revealed strawberry lesions surrounding the gums with significant swelling, bleeding, and tenderness to palpation; nasal mucosa was diffusely erythematous, the right ear was obstructed by wax, while the left ear had a transparent and normal tympanic membrane.

The complete blood count and comprehensive metabolic panel were within normal limits. C-reactive protein was elevated to 122.4, and the antinuclear antibody titre was 1:160 with a speckled pattern. ANCA analysis revealed a positive result for PR3 (a titre of 1.2 and a c-ANCA staining pattern), while myeloperoxidase was negative (no perinuclear ANCA [p-ANCA] staining pattern). Additionally, testing for anti-glomerular basement membrane antibodies was negative. The erythrocyte sedimentation rate was normal. An X-ray of the paranasal sinuses revealed enlargement of middle and inferior nasal turbinate. The QuantiFERON TB test was negative. Chest X-ray revealed scoliosis and pectus excavatum deformity with no active disease. A computed tomography (CT) scan of the chest revealed dependent ground glass opacities, a 3 mm nodule in the right middle lobe, and a few small, calcified granulomas in the upper lobes. CT sinus revealed small mucous retention polyps in the inferior maxillary sinuses measuring 11 mm on the right and 4 mm on the left, with mild mucosal thickening of the maxillary ostium.

The differential for granulomatous oral lesions includes Crohn's disease, sarcoidosis, and infections. Our patient lacked gastrointestinal symptoms, perianal disease, or diarrhoea, making Crohn's disease unlikely. Sarcoidosis was ruled out due to absence of hypercalcemia, hilar lymphadenopathy, or systemic involvement. Infectious causes were considered but excluded based on a negative QuantiFERON-TB test, lack of immunosuppression, and histology. The presence of PR3-ANCA and granulomatous inflammation with multinucleated giant cells on biopsy strongly supported GPA. Together, these findings fulfilled the American College of Rheumatology/European Alliance of Associations for Rheumatology (ACR/EULAR) classification criteria and excluded other mimics.

The patient was started on methotrexate (10 mg weekly) and high-dose prednisone (60 mg daily). Prednisone was tapered in 4 months, and methotrexate was continued. After 6 months, he was switched from methotrexate to azathioprine (150 mg daily) to avoid potential liver and lung toxicity secondary to methotrexate in the setting of a history of AATD. His symptoms, including gum bleeding and oral pain, significantly improved with these medications. He developed leukopenia; therefore, his azathioprine dose had to be decreased to 100 mg daily. His symptoms remained controlled on the decreased dose. A referral to otolaryngology was made for evaluation of sinusitis. Nasal endoscopy revealed a posterior septal spur on the left that was contacting the middle turbinate, and there was a 2+ rightward septal deviation. Fluticasone propionate nasal spray was prescribed.

At present, he is being treated with azathioprine 100 mg daily and has remained clinically stable at the 1-year follow-up.

DISCUSSION

First described in 1936 by Friedrich Wegener, GPA is a systemic vasculitis affecting small and medium vessels, causing necrotizing disease in the upper and lower

respiratory tract and kidneys. GPA presents in two forms: diffuse, primarily affecting the kidneys and lungs, and localized, confined to the upper respiratory tract. Transitions between localized and diffuse forms can occur. According to the 2022 ACR/EULAR classification criteria for GPA, a cumulative scoring system is used to aid diagnosis. Specific clinical, laboratory, imaging, and histopathological findings are assigned points as follows: bloody nasal discharge, nasal crusting, or sino-nasal congestion (+3); cartilaginous involvement (+2); conductive or sensorineural hearing loss (+1); cytoplasmic ANCA (c-ANCA) or anti PR3 ANCA positivity (+5); pulmonary nodules, mass, or cavitation on chest imaging (+2); presence of granulomas or multinucleated giant cells on biopsy (+2); inflammation or consolidation of the nasal/paranasal sinuses on imaging (+1); pauci-immune glomerulonephritis (+1); p-ANCA or MPO ANCA positivity (−1); and eosinophil count ≥1 $\times 10^9$/l (−4). After excluding mimics of vasculitis, a diagnosis of GPA can be made if the total score is five or more. GPA follows a chronic and unpredictable phase of remission and relapse[1]. In our case, the patient has diffused erythematous nasal mucosa and septal defect. Our patient's biopsy results were notable for multinucleated giant cells on biopsy (+2) and anti–proteinase 3 (PR3) ANCA was positive. These criteria do not include oral manifestations, possibly due to limited awareness or their relatively low frequency.

The aetiology of GPA involves a combination of genetic predisposition and environmental factors[1]. Notable triggers include exposure to silica, cadmium, hydrocarbons, and infections such as *Staphylococcus aureus* and cytomegalovirus[2,4]. In addition, previous reports have noted certain medications, including phenytoin, hydralazine, anti-thyroid drugs, sulfasalazine, and allopurinol[9]. Smoking exacerbates the disease risk by impairing immune defence mechanisms in the respiratory system[4]. In our case, the patient had no notable risk factor; however, our patient had AATD. The allelic isoforms were not worked up because the patient did not have clinical symptoms to warrant further evaluation.

AAT is an acute-phase protein from the serine protease inhibitor family, known for its ability to inactivate several proteases, including PR3, a key autoantigen in GPA[5]. AATD, a common genetic disorder, results from pathogenic variants of the Pi gene and leads to reduced serum AAT levels. This deficiency compromises lung protection and may contribute to conditions like emphysema and inflammatory damage seen in GPA[10]. According to the American Thoracic Society/European Respiratory Society, the pre pathological AAT allele testing is not routinely performed in systemic vasculitis cases. However, its relevance in GPA may be underestimated. Given its clinical significance, AAT deficiency should be considered when evaluating GPA patients. The valence of the PI*Z allele among GPA patients in Europe ranges from 9 to 17.6%[5].

Various treatment protocols for GPA include cyclophosphamide and azathioprine as primary options, with glucocorticoids combined with methotrexate commonly used to induce remission. The 2021 ACR guidelines recommend methotrexate plus glucocorticoids over azathioprine or mycophenolate mofetil with glucocorticoids for active, non-severe GPA[10]. Since our patient had organ-limited disease, we opted for a combination of steroids and methotrexate (MTX), to which he responded well.

Untreated GPA is often fatal, with up to 82% of patients dying within 1 year, primarily due to kidney failure from prior renal damage[1]. Immunosuppressive therapy has improved outcomes, increasing 5-year survival to 70–80%, though complete remission occurs in only 75% of cases[1]. Both localized and generalized forms can relapse, frequently linked to granuloma formation. Early diagnosis and appropriate treatment typically lead to lesion resolution within weeks, but relapse may occur during immunosuppressive tapering; therefore, close follow-up is necessary.

CONCLUSION

Strawberry gingivitis is a rare but pathognomonic manifestation of GPA that clinicians should recognize as a potential early sign of systemic vasculitis. Prompt biopsy, serologic evaluation, and initiation of immunosuppressive therapy are key to preventing progression to severe systemic disease. AATD may be underrecognized in disease pathogenesis and should be considered during evaluation. Our case underscores the importance of considering GPA among the top differentials for patients presenting with atypical oral lesions, such as strawberry gingivitis, to enable timely diagnosis and intervention.

REFERENCES

1. Apoita-Sanz M, Blanco-Jauset P, Polis-Yanes C, Penin-Mosquera RM, Montserrat-Gomá G, Pozuelo-Arquimbau L, et al. Granulomatosis with poliangeitis (Wegener's granulomatosis): orofacial manifestations. Systematic review and case report. *Oral Health Prev Dent* 2020;**18**:929-943. doi: 10.3290/j.ohpd.a45433
2. Stewart C, Cohen D, Bhattacharyya I, Scheitler L, Riley S, Calamia K, et al. Oral manifestations of Wegener's granulomatosis: a report of three cases and a literature review. *J Am Dent Assoc* 2007;**138**:338–348. doi: 10.14219/jada.archive.2007.0166
3. Puéchal X. Granulomatosis with polyangiitis (Wegener's). *Joint Bone Spine* 2020;**87**:572–578. doi: 10.1016/j.jbspin.2020.06.005
4. Thompson G, Benwell N, Hollingsworth P, McLean-Tooke A. Two cases of granulomatosis polyangiitis presenting with strawberry gingivitis and a review of the literature. *Semin Arthritis Rheum* 2018;**47**:520–523. doi: 10.1016/j.semarthrit.2017.06.003
5. Kościelecki K, Kalisz A, Okońska A, Kozakiewicz J, Skorulska I, Długozima P, et al. Alpha-1 antitrypsin deficiency pathophysiology, symptoms, diagnosis, treatment. *Qual Sport* 2025;**2025**:59389. doi: 10.12775/QS.2025.40.59389
6. Pervakova MY, Emanuel VL, Titova ON, Lapin SV, Mazurov VI, Belyaeva IB, et al. The diagnostic value of alpha-1-antitrypsin phenotype in patients with granulomatosis with polyangiitis. *Int J Rheumatol* 2016;**2016**:7831410. doi: 10.1155/2016/7831410
7. Seyama K, Hirai T, Mishima M, Tatsumi K, Nishimura M. A nationwide epidemiological survey of alpha1-antitrypsin deficiency in Japan. *Respir Investig* 2016;**54**:201–206. doi: 10.1016/j.resinv.2015.12.002
8. Serres F, Blanco I. Role of alpha-1 antitrypsin in human health and disease. *J Intern Med* 2014;**276**:311–335. doi: 10.1111/joim.12239
9. Chung SA, Langford CA, Maz M, Abril A, Gorelik M, Guyatt G, et al. 2021 American College of Rheumatology/Vasculitis Foundation guideline for the management of antineutrophil cytoplasmic antibody–associated vasculitis. *Arthritis Rheumatol* 2021;**73**:1366–1383. doi: 10.1002/art.41773
10. Serres F. Alpha-1 antitrypsin deficiency is not a rare disease but a disease that is rarely diagnosed. *Environ Health Perspect* 2003;**111**:1851–1854. doi: 10.1289/ehp.6511