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Case Report

# Granulomatosis with Polyangiitis And Its Impact on Dental Conditions: A Case Report

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## Abstract

Granulomatosis with Polyangiitis (GPA), previously known as Wegener's disease, is a Antineutrophil Cytoplasmic Antibody (ANCA) associated vasculitis disorder affecting the blood vessels of different organs including upper respiratory system, kidneys, lungs, and oral cavity. Oral lesions including gingival inflammation/enlargement, ulcers of the tongue, buccal mucosa, and hard palate and in rare cases dental decay and root resorption have been reported. Thus, dentists may be the first to identify the disease early on and make a referral. Limited research has been undertaken on its oral impacts, thus emphasizing the need for medical-dental collaboration to manage GPA patients. This article reviews a unique case of a patient with GPA and their dental health.

## Introduction

Granulomatosis with Polyangiitis (GPA) was originally named Wegener's disease. GPA is a systemic autoimmune vasculitis of the small and medium-sized blood vessels involved with Anti-Neutrophil Cytoplasmic Antibodies (ANCA) [1,2]. GPA develops from an interaction of genetic predispositions and external influences, initiating the formation of autoantibodies and immune responses against the body's tissues. This leads to inflammation, mainly affecting the respiratory system, lungs, and kidneys. Dental professionals have especially noted an association between GPA and certain oral health issues in 6-13% of patients and may be the first to help identify the disease early on [3,4]. Oral lesions include gingival inflammation and

enlargement (referred to as strawberry gingivitis) hypertrophy of the tongue papillae, petechiae of the oral mucosa, deep ulcers on the tongue, buccal mucosa, floor of the mouth, hard palate, pharynx and tonsils [1,4-7]. Additionally, dental caries and root resorption have been reported [1,4]. Other features include oral antral fistulae, nodule on the lips, and osteonecrosis [3,8]. The disease predominantly affects individuals between 45 and 60 years of age, with both genders being equally affected. Given the aging trend of the American population and advancements in diagnostic techniques, the disease's morbidity has increased in the past 15 years [1]. The exact processes behind root resorption in GPA are still unclear, but it is suspected to originate from autoimmune-driven inflammation in the gingiva and surrounding

tissues. Typically, inflammation in affected individuals starts in the respiratory tract blood vessels, leading to symptoms like nasal blockages, recurrent nosebleeds, breathing difficulties, or coughing [9].

Dentists and physicians treating GPA patients should be aware of these oral health issues and ensure early intervention. This proactive approach improves patient experiences and their overall wellbeing. Further research must be undertaken to thoroughly understand the underlying disease processes and to establish the best care regimen for patients with GPA and their associated dental problems.

**Pathogenesis:** GPA usually progresses in two distinct stages: The preliminary stage manifests primarily in the ear, nose, and throat areas, showing symptoms such as persistent sinusitis, otitis, oral and pharyngeal ulcers, and lung nodules. The more aggressive generalized stage is characterized by rapidly developing glomerulonephritis, lung bleeding, and joint inflammation. During this stage, Anti-Neutrophil Cytoplasm Antibodies (ANCA), which target the enzymes proteinase 3 and myeloperoxidase in neutrophils, can be detected in approximately 90% of the patients. Given that the body's antibody response mainly targets these neutrophil antigens, it is known that neutrophils are essential in GPA, functioning both as the focus and agents of the disease [10]. The multifaceted origins of GPA encompass genetic factors, adverse drug reactions, and infections. Despite gaps in understanding its exact etiology, there is a consensus that a mix of infections, environmental influences, epigenetic shifts, and genetic susceptibilities are involved in the disease process [11,12]. However, GPA's genetic origins remain unclear. Possessing a specific variant of the HLA-DPB1 gene is the most significant genetic vulnerability for the condition. However, many other known and not-yet-discovered also play roles. While the genesis of GPA is still being studied, certain genes such as CTLA4, PTPN22, COL11A2, SERPINA1, and the MHC class II gene cluster have been linked to the disease through various research methods [13]. It is possible that genetic and environmental elements play a part in the onset of GPA. Flawed immune responses to external triggers, such as infections or self-antigens, result in heightened Th1 and Th17 cytokine production (including interleukin 17, tumour necrosis factor, and interferon-gamma). These responses can subsequently trigger the formation of inflammatory vascular granulomas. The ANCA in GPA interacts with proteinase 3, a dominant enzyme in neutrophils, activating these cells. This activation promotes adherence to the endothelium and prompts degranulation, damaging endothelial cells in the process [12,13].

Infectious agents play dual roles in GPA, potentially initiating and exacerbating the vasculitis process, while also influencing the disease's clinical presentation [14]. The presence of *Staphylococcus aureus* is proposed to be a trigger for the inflammation evident in GPA [15]. Links have been established between the disease and various viruses, including cytomegalovirus, hepatitis C,

parvovirus and Epstein-Barr [2]. Additionally, drugs including hydralazine, sulfasalazine, antithyroid drugs, phenytoin and allopurinol are also associated with the condition [16].

## Diagnostic Criteria

Various clinical guidelines have been used to diagnose GPA and differentiate it from other vasculitides. Classification is based on the 2022 American College of Rheumatology/European Alliance of Associations for Rheumatology [17]. Tissue biopsy remains the gold standard for diagnosing various types of vasculitis, especially the small- to medium-vessel vasculitis such as GPA [18]. Inflammatory lesions in GPA typically include necrosis, granulomatous changes, and features of vasculitis. Even though vasculitis and granuloma formation can occur in the same lesion, it is rare to see both in the same biopsy sample [19]. Evaluating a patient with possible GPA involves a comprehensive examination including: clinical, blood tests, radiographs and histopathological testing [17]. A systematic clinical evaluation to evaluate the site and scope of involvement is essential when evaluating a patient with GPA. Although laboratory tests may be relatively nonspecific, they should still be done. Laboratory tests include a complete blood count, renal function panel, electrolytes, Erythrocyte Sedimentation Rate (ESR), urinalysis, titres of PR3-ANCA and MPO-ANCA and C-Reactive Protein (CRP). Radiologic evaluation of the lungs, sinuses, orbits, and trachea should be completed to evaluate the sites and degree of involvement. A chest X-ray and Computed Tomography (CT) scan of the lungs can be performed to identify lung lesions and haemorrhaging [20].

## Treatment

Treatment depends on the extent of the disease and is grouped into the induction phase and the maintenance phase. Drugs prescribed in the induction phase include cyclophosphamide, glucocorticoids, rituximab, azathioprine, and methotrexate. Plasmapheresis may be indicated. Localized mild disease does not require aggressive treatment and is usually managed with methotrexate and glucocorticoids. The more severe, life and organ threatening disease warrants using cyclophosphamide combined with glucocorticoids [21]. According to the Rituximab In ANCA-Associated Vasculitis (RAVE) trial, it was determined that rituximab was not substandard to cyclophosphamide taken daily for induction or first phase of remission and may be better in relapsing disease [22]. In patients that do not have severe disease and are methotrexate would be used in combination with glucocorticoids. Plasmapheresis is indicated if a patient has declining kidney function, anti-glomerular basement membrane antibodies, or pulmonary bleeding with respiratory insufficiency that is not responsive to intravenous glucocorticoids [2].

Maintenance therapy is started after remission is attained, which is typically within 3-6 months. Maintenance therapy is important to avoid relapses and includes the use of methotrexate, azathioprine, and rituximab. depending on whether the patient had been recently diagnosed or had more than one relapse. The

percentage of relapse occurs between 47% and 60% of cases which affects the mortality rate (30.4% with relapse and 7.7% without the relapse) [23]. The duration of maintenance therapy is usually 12-36 months after remission has been induced. Maintenance therapy is continued indefinitely for patients at high risk of relapse. Other drugs used for the induction and/or maintaining remission include intravenous immunoglobulin, mycophenolate mofetil, and cyclosporine. Trimethoprim-sulfamethoxazole can be prescribed if there is no renal disease. These immunosuppressive drugs used in treating GPA have substantial adverse side effects that can result in severe complications [22]. Patients diagnosed with granulomatosis with polyangiitis often lead a difficult life, experiencing tiredness, pain, problems related to the disease, adverse side effects from medications, and emotional distress, which can affect both work and personal relationships. Different health care professionals may be involved in patient care, and it is important to follow up with them as recommended [22].

## Case Report

The principles outlined in the Declaration of Helsinki (ethical approval) were followed. Informed consent to publish the clinical and laboratory data was obtained from this patient. A 50-year-old female patient presented to our private dental clinic in October 2017 with a chief complaint of “my upper right back tooth is hurting.” The patient reports the pain began several months ago and occurs when eating. The patient’s medical history was significant for hypertension, lung disease, breathing difficulties (easily winded), frequent cough, kidney problems, tendency to bruise easily, fainting spells, dizziness, pain in the jaw and joints, shingles, and allergic reactions presenting as hives and rash. The patient had undergone anti-allergen shots and had documented allergic reactions to multiple substances, including lidocaine.

## Clinical Examination



Figure 1: Gingival inflammation



Figure 2: Tooth #10 shows no signs of external root resorption in 2017

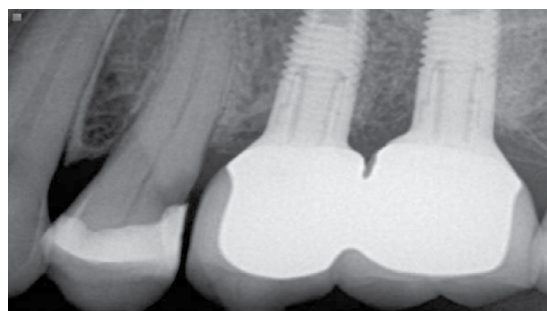


Figure 3: Tooth # 12 before NSRCT (nonsurgical root canal therapy)



Figure 4: Tooth # 2 NSRCT partially calcified canals

Extraoral and intraoral clinical examination was performed by provider N.E. No extraoral pathology was evident. Intraoral examination was significant for generalized moderate to severe gingival erythema, a coated tongue and petechiae on the hard palate. (Figure 1), pain on percussion but not on palpation for tooth #2, which was an abutment for a Fixed Partial Denture (FPD). Radiologically, periapical pathology was noted on the palatal root of tooth #2.

## Treatment timeline

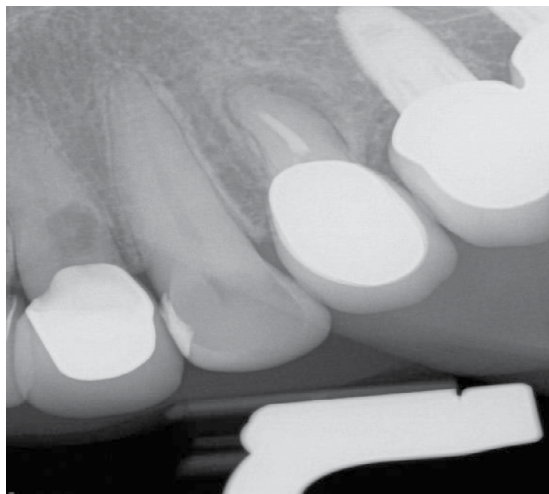


Figure 5: Tooth #2 showing external root 2022

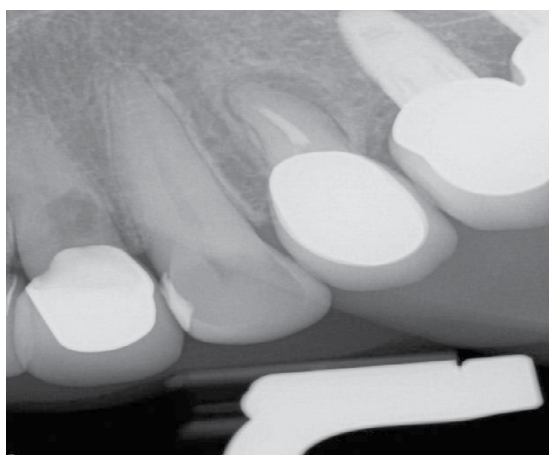


Figure 6: Tooth #10 showing external root resorption in resorption in 2022

2017: The patient was referred for Non-Surgical Root Canal Therapy (NSRCT) for tooth #2 due to pulpal necrosis with symptomatic apical periodontitis. Tooth #10 did not show signs of external root resorption (ERR) at this time (Figure 2).

2018: The patient visited the endodontist in August for tooth #2, but subsequently had several cancelled appointments, primarily due to her medical conditions and allergic events. In October 2018, she presented with a new complaint: "My upper left tooth hurts." She was then referred to an endodontist for NSRCT on tooth #12 due to symptomatic irreversible pulpitis with normal apical tissue (Figure 2). Reports from the endodontist indicated partial calcification of all root canals of teeth # 2 and 12 (Figures 3, 4). After completion of the RCTs, post and core build-ups were performed, and crowns were fabricated and inserted for both teeth #2 and #12. 2022: The patient had multiple skin lesions present and was referred to her physician. Together with her physician, immunologist, pulmonologist, and rheumatologist

a diagnosis of GPA was made based on a skin biopsy, blood work and chest scan. The following were the results of all tests performed on the patient: urine test-negative for blood; C-reactive protein 3.7 mg/dl; ANCA 18 U/ml; erythrocyte sedimentation rate: 82 mm/hour; normochromic, normocytic anaemia [20]. The skin lesion biopsy was typical for GPA (necrosis, inflammation) and chest scan showing left lung in the periphery with multiple dense nodules with some cavitation.

Five years post initial treatment, tooth #2 required extraction due to external root resorption, and a similar pathology was diagnosed for tooth #10, which in 2017 did not show ERR (Figures 5, 6). That same year, the patient was diagnosed with Coxsackie virus, followed by a diagnosis of GPA. Methotrexate was prescribed for the latter. Approximately six months post-initiation of methotrexate, the patient presented with decay on her lower anterior teeth, which were then treated with composite restorations.

### Discussion

Epidemiological studies that included more than 50 cases showed the incidence of GPA of 10.0 per 100,000 in people 50 years and older, with the greatest occurrence in Scandinavia followed by North and South America, and Europe [24]. The delayed diagnosis of GPA is typical due to its overlapping presentation with other autoimmune diseases [25]. The management of this disease is complex, including its effects on the tissues of the oral cavity which complicates dental interventions. Patients on methotrexate often present with dental issues, such as recurrent decay and root resorption, due to the drug's side effects [26]. Additionally, the challenge in dental management for such patients is the difficulty of keeping appointments owing to their fluctuating medical conditions. For patients allergic to lidocaine, alternatives such as articaine, can be considered, as the literature has suggested its efficacy [27].

Hypothetically, correlations between GPA, External Root Resorption (ERR)/external cervical resorption (ECR), and recurrent decay may include:

1) Viral involvement and GPA: While the exact etiology of GPA is not completely understood, no strong evidence has directly linked it to viral infections causing ERR; however, viral infections can sometimes act as triggers for autoimmune reactions [28]. Possibly a viral episode might aggravate both conditions in a susceptible individual; and 2) Autoimmune disease and ERR: Some autoimmune diseases including scleroderma have been associated with ERR [29,30]. Since GPA is also an autoimmune disorder, it is theoretically possible that there may be a connection; however, direct evidence linking GPA and ERR due to autoimmune activity has not been established [30]. We propose a mechanism for the connection between GPA and ERR that is based on the excessive synthesis of pro-inflammatory cytokines, including Tumour Necrosis Factor (TNF)-alpha and Interferon (IFN)-gamma, due to dysregulated or impairment of interleukin-12

(IL-12) which is secreted by T cells and monocytes. Studies have shown that both inactive and active GPA patients produce increased amounts of IL-12, which promotes the overproduction of IFN-gamma and TNF-alpha by peripheral blood mononuclear cells and CD4+ T cells. This cytokine dysregulation suggests that targeting these interleukins may have therapeutic effects in GPA due to its ability to inhibit IFN-gamma production. An increase in the M1 macrophages (pro-inflammatory), associated with higher levels of IFN-gamma and TNF-alpha, correlates with enhanced breakdown of osteoclasts (osteoclast genesis) and root resorption. On the other hand, removing external stimuli increases the M2 macrophages (anti-inflammatory), reducing inflammation and inhibiting root resorption [31-33].

The connection between GPA and ERR/ECR resorption lies in the similar cytokine and inflammatory mechanisms. In GPA, the overproduction of TNF-alpha and IFN-gamma due to dysregulated IL-12 secretion reflects the inflammatory cytokine environment seen in ECR. Both conditions involve an upregulation (increased response) of TNF-alpha and IFN-gamma, contributing to tissue damage and bone loss. Thus, systemic inflammatory responses in GPA could potentially influence or exacerbate local inflammatory conditions such as ECR through similar pathways of cytokine-mediated osteoclast genesis [31,32]. Granulomatosis with vasculitis is a multifaceted autoimmune condition. Its early signs are often evident as oral symptoms including gingival inflammation which can resemble a strawberry-type of gingivitis, but not necessarily [1,5-7,34]. Patient enlightenment and consistent check-ups are crucial for effective disease handling.

GPA, being relatively uncommon, lacks extensive research, especially concerning its oral health implications. This analysis sheds light on the intricate interplay between GPA, recurring caries, and root resorption [35]. Dental professionals, physicians, and specialists must be proactive in identifying and dealing with oral health issues for those with GPA. This not only enhances patient outcomes but also their quality of life. Existing studies emphasize the necessity for dental and medical practitioners to collaborate when treating individuals with GPA. Further studies are essential to fully understand the underlying causes and to devise the best treatment plans for those affected by both GPA and its oral complications. While GPA might not have a direct, well-established connection with External Root Resorption (ERR) due to viral or autoimmune causes, there are intricate interplays between autoimmune conditions, oral health, and associated symptoms or treatments that can affect the oral environment. It is crucial for patients with autoimmune diseases to have regular dental check-ups and adhere to oral care recommendations to prevent complications like ERR or recurrent decay.

## Conclusion

Granulomatosis with Polyangiitis (GPA) presents a complex challenge for both patients and healthcare professionals. This autoimmune disorder, while rare, can manifest with oral health

issues such as gingival inflammation, intraoral ulcers, and dental caries. External root resorption as seen in patients with scleroderma, an autoimmune disease, has been reported in the literature. This article is the first citation of reporting ERR in patients with GPA also an autoimmune disease. As we delve deeper into the intricate connections between GPA, oral health, and systemic effects, it becomes evident that a multidisciplinary approach is essential for effective disease management. Patients must be educated about their condition and the importance of regular dental check-ups to prevent complications. GPA is a disease that impacts multiple systems, necessitating a multidisciplinary team to address the varied organ effects. Rheumatologists, pulmonologists, otolaryngologists, pathologists, radiologists, pharmacists, cardiologists, nephrologists, and dentists all have significant roles to play. Effective communication within the team is crucial. Further research is needed to fully understand the underlying causes and establish optimal treatment strategies for GPA and its associated dental problems. By working together clinicians can improve the results of treatment and enhance the quality of life of the patient. In summary, while GPA previously has not been shown to have a causative connection with ERR due to viral or autoimmune causes, there are intricate interplays between autoimmune conditions, oral health, and associated symptoms or treatments that can affect the oral environment. Since this is the first report of a possible connection between ERR and GPA, more research is needed to clarify and elucidate the mechanism. It is crucial for patients with autoimmune diseases to have regular dental check-ups and adhere to oral care recommendations to prevent complications including ERR or recurrent decay.

## Conflicts of interest

None

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