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Case Report

Dentistry Section

# Granulomatosis with Polyangitis: Rare Cause of Oral Ulcer in Paediatric Patient

PRATHIMA SREENIVASAN[1], VIJAY SYLVESTER[2], JANISHA VENGALATH[3], DIMLA DENNY CHERUVATHOOR[4], TANIYA THOMAS[5]



## ABSTRACT

Granulomatosis with Polyangiitis (GPA), formerly known as Wegener's granulomatosis, is part of a vast spectrum of diseases entitled Anti-Neutrophil Cytoplasmic Antibodies (ANCA)-associated vasculitides. It predominantly presents in adults and is associated with necrotising vasculitis, primarily affecting small to medium vessels. An oral ulcer is one among the myriad clinical presentations of GPA. A long-standing solitary oral ulcer of the oral mucosa can also be the clinical presentation of many different diseases and always poses a significant diagnostic challenge. Appropriate clinical and investigative work-up is required to reach the correct diagnosis. Timely intervention and management are also important in reducing the morbidity and mortality associated with such conditions. Hereby, the authors presents a case of a 13-year-old female patient who complained of a solitary ulcer in the mouth. Additionally, she had a history of recurrent nasal ulcers and epistaxis but did not report any other symptoms. Clinical examination showed nasal ulcers, a solitary ulceroproliferative lesion in the maxillary region and strawberry gingivitis. A systematic investigative work-up was conducted to reach the correct diagnosis and the condition was well-managed with appropriate immunosuppressive therapy.

**Keywords:** Antineutrophil cytoplasmic antibody, Necrotising vasculitis, Strawberry gingivitis, Wegener's granulomatosis

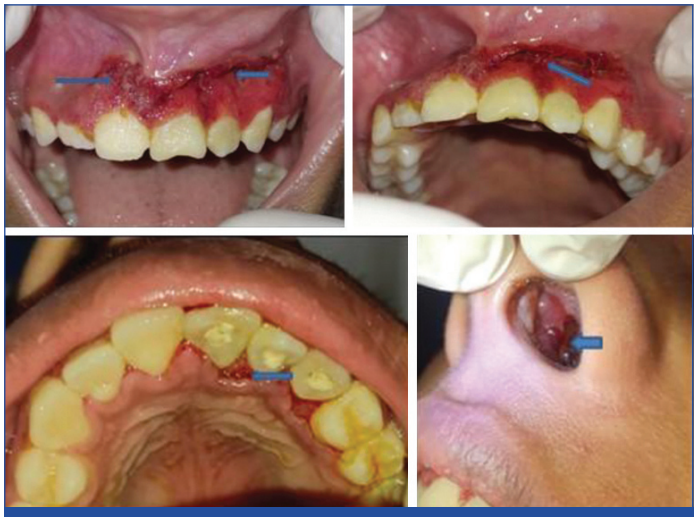
## CASE REPORT

A 13-year-old female patient presented with complaints of an ulceroproliferative lesion in the gums of the upper front teeth region for the past three weeks. She initially noticed a small ulcer, which progressively increased in size with observable growth around the margins. There was bleeding associated with the growth and she experienced moderate to intermittent pain. History revealed trauma and a fracture of the upper front tooth due to a fall four years ago. An endodontic procedure was initiated but was not completed on the fractured tooth. The patient also reported a history of recurrent nasal ulcerations and epistaxis for one year, for which she had consulted an Ear, Nose and Throat (ENT) specialist who prescribed topical antibiotics. The ulcers healed but recurred once the medication was stopped.

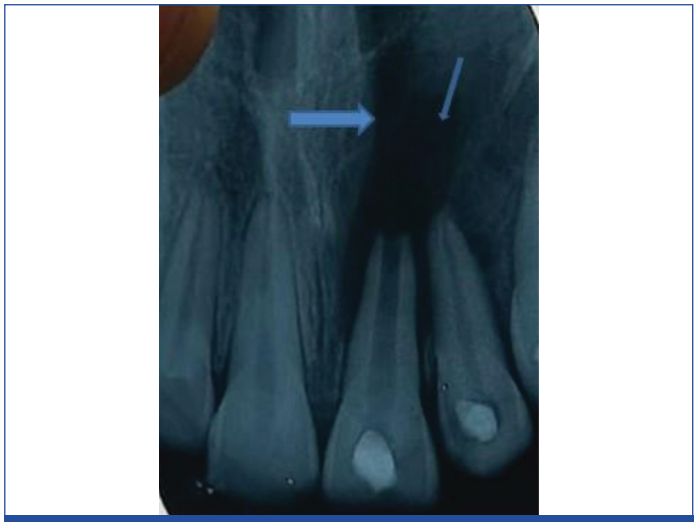
On general examination, she appeared to be well-nourished, moderately built, within the normal height range and had normal vital signs. On extraoral examination, a single ulcer with crusting was noted in the left nasal mucosa. Multiple left submandibular lymph nodes were palpable, which were non tender and firm in consistency.

On intraoral examination, a solitary ulceroproliferative lesion measuring 2×1.5 cm was observed, involving the gingivobuccal sulcus, alveolar mucosa and gingiva in relation to teeth 11, 21 and 22. The floor of the ulcer was shallow and the margins were undermined. The gingiva around the ulcer was enlarged, erythematous and contained reddish-brown petechiae, with no evident discharge or bleeding. The surface had a granular, pebbled appearance, resembling strawberry gingivitis [Table/Fig-1]. It was non tender and friable on palpation. There was also the presence of an Ellis class II fracture concerning tooth 21, with Grade 2 mobility and tenderness on percussion of teeth 21 and 22. Based on the history and clinical features, differential diagnoses, including Tuberculosis (TB), Granulomatosis with polyangitis (GPA) and Mucormycosis, were considered.

The Intraoral Periapical Radiograph (IOPA) radiograph of the 21, 22 region shows a fracture of tooth 21 with a blunderbuss apex and a unilocular periapical radiolucency in relation to teeth 21 and 22 [Table/Fig-2]. Routine blood investigations revealed a

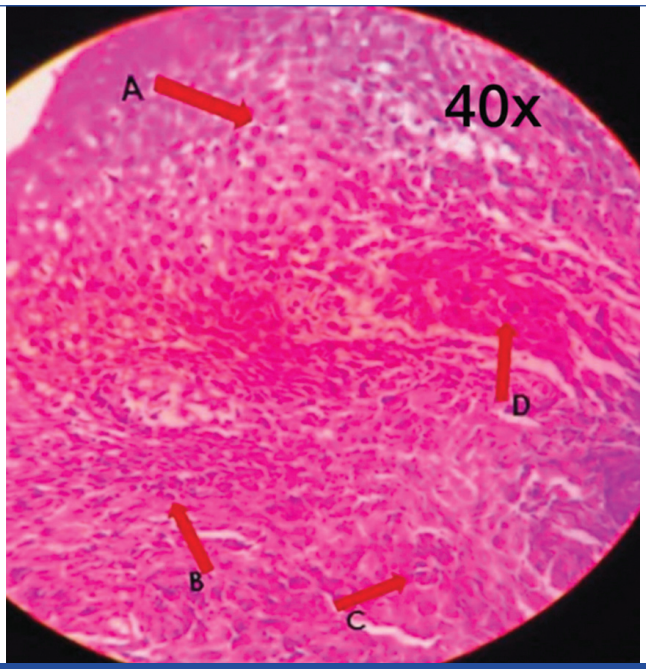


**[Table/Fig-1]:** Pretreatment picture showing ulceroproliferative lesion with strawberry gingivitis of maxillary anterior gingiva and nasal ulceration.

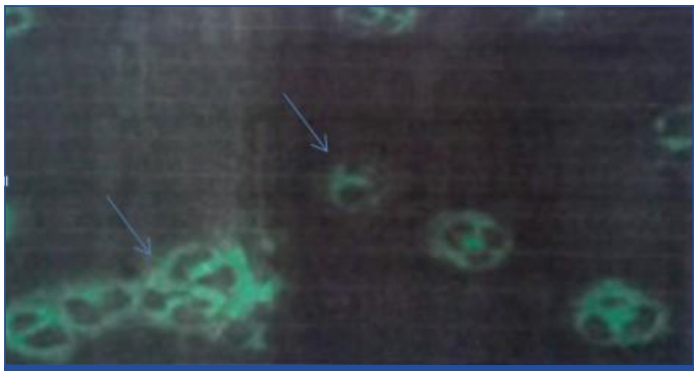


**[Table/Fig-2]:** Pretreatment IOPA radiograph showing periapical radiolucency in relation to 21,22.

decreased haemoglobin count of 8.2 mg/dL and the peripheral smear was suggestive of microcytic hypochromic anaemia. An incisional biopsy was performed and the samples were sent for histopathology and Polymerase Chain Reaction (PCR) testing to check for Mycobacterium tuberculosis. Histopathology reports indicated a dense subepithelial collection of neutrophils, plasma cells, histiocytes, along with ill-formed multinucleated Langhans-type giant cells and focal areas of necrosis and haemorrhage. These features were suggestive of a chronic granulomatous inflammatory lesion [Table/Fig-3]. The PCR test was negative for Mycobacterium tuberculosis. Serum c-ANCA was detected in immunofluorescence tests at a titre of 1:20 [Table/Fig-4]. Correlating the clinical and laboratory findings, the condition was finally diagnosed as GPA.



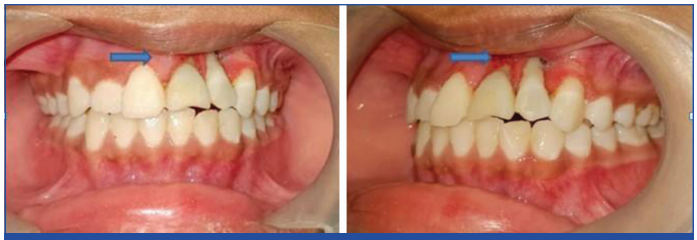

**[Table/Fig-3]:** Subepithelial collection of inflammatory cells predominantly plasma cells (a); neutrophils (b); histiocytes with ill-formed multinucleated Langhans type giant cells and focal areas of necrosis and haemorrhage (c, d) (H&E, 40X).



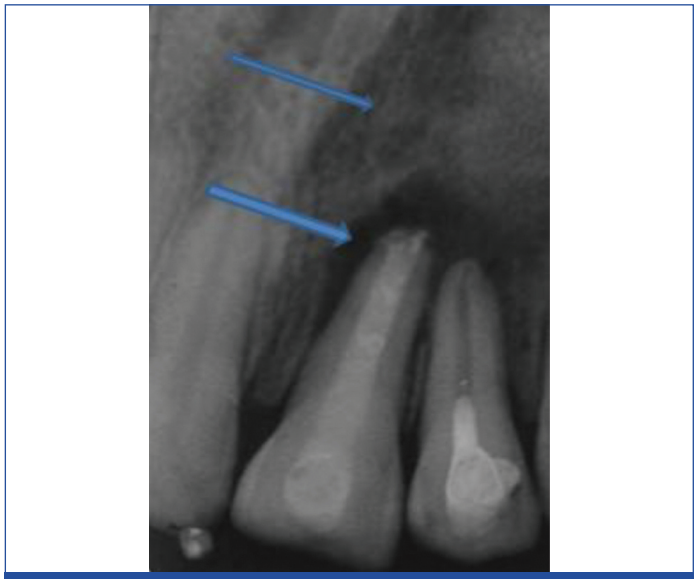
**[Table/Fig-4]:** Immunofluorescence test showing positive c-ANCA.

The patient was referred to a rheumatologist and chemotherapy was initiated with Prednisone at a dose of 1 mg/kg/day, Methotrexate 15 mg once a week and Folic acid 5 mg once daily. Prednisone was slowly tapered and continued until remission of the lesion was achieved. A maintenance dose of Prednisone 2.5 mg/day was given for one year. Endodontic treatment of tooth 21 was also reinitiated and obturation was performed with Mineral Trioxide Aggregate (MTA, brand Angelus).

At one year of follow-up, gingival inflammation had resolved and the ulcer had healed; however, there was a persistent gingival defect in relation to tooth 22 [Table/Fig-5]. The mobility of teeth 21 and 22 had reduced. Follow-up radiographs showed partial resolution of the radiolucency associated with teeth 21 and 22 [Table/Fig-6]. Surgical correction of the gingival defect was advised. The patient is otherwise healthy and is currently attending school regularly.



**[Table/Fig-5]:** Post-treatment clinical picture showing healed lesion in maxillary anterior gingiva.



**[Table/Fig-6]:** Post-treatment, one year follow-up IOPA radiograph showing partial resolution of periapical radiolucency in relation to 21, 22.

## DISCUSSION

GPA, formerly known as Wegener's granulomatosis, is part of a vast spectrum of diseases known as ANCA-associated vasculitides [1]. According to the 2012 International Chapel Hill Consensus Conference on the Nomenclature of Vasculitides, it is defined as a necrotising granulomatous inflammation that typically involves the upper and lower respiratory tracts, accompanied by necrotising vasculitis affecting predominantly small to medium vessels [1,2]. The prevalence and incidence of this systemic disease vary greatly across different ethnic groups, with a higher occurrence reported in the Caucasian population [3].

One of the largest studies, analysing 5,562 cases of GPA in the United States over a nine-year period, reported an incidence rate of 12.8 per million persons per year and a prevalence rate of 30.5 per million person-years among adults. A substantially lower incidence rate of 1.8 per million person-years and a prevalence rate of 3.4 per million person-years were noted in the paediatric age group [4]. A retrospective study focused on an international cohort of patients with childhood GPA recorded only 56 patients [5]. Another study, which analysed data over 21 years at a single tertiary referral centre, identified only 25 paediatric patients with GPA [6]. These data emphasise that the incidence of GPA in children is rare.

A higher prevalence is noted in females, with the mean age of presentation reported as 50 years [3,4,7]. There is a paucity of epidemiological data in the Indian population, as studies on Indian cohorts are few and limited to very small samples. The mean age of presentation is reported to be between 44.5 and 48.5 years, with a female gender predilection noted in these studies [8,9]. In the paediatric population, the disease is predominantly seen in females, with a median age of presentation found to be 11.7 years [5,6]. However, the present case report presents a 13-year-old female patient with GPA.

GPA has an insidious onset, is chronic and progressive in nature and is characterised by a multisystem inflammatory disease. In the classic form, a triad of upper respiratory, lower respiratory and

renal involvement is observed. In some cases, evidence of systemic vasculitis may be lacking, with only limited granulomatous lesions present. Upper respiratory involvement is characterised by rhinitis, nasal ulcerations and crusting, epistaxis and nasal discharge [10]. Oral involvement is reported in 6% to 13% of patients, with oral lesions being the first sign in only 2% of cases. The characteristic oral lesion in GPA is strawberry-like gingivitis, presenting as enlarged, erythematous interdental papillae containing red to purple petechiae with a granular appearance and the most commonly affected area is the maxillary gingiva [3,11]. Advanced disease can result in alveolar bone loss, tooth mobility and palatal destruction [7].

Among paediatric patients, epistaxis, nasal ulcers and oral ulcers are the most common initial presenting symptoms [5,6]. In the present reported case, the patient presented with symptoms of nasal ulcers, epistaxis, an oral ulcer and strawberry gingivitis, which were suggestive of upper respiratory and oral involvement. No signs of involvement of other systems were noted.

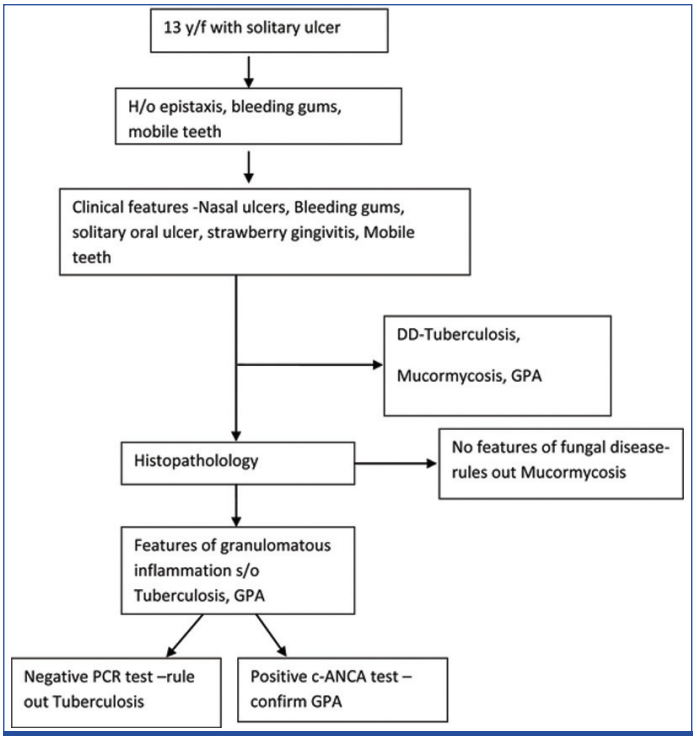
Histopathology is an essential investigation for the diagnosis of GPA. The quintessential histopathological features include necrosis, granulomatous inflammation and the presence of multinucleated Langhans-type giant cells [11]. An immunofluorescence test for the presence of c-ANCA is an important investigation to confirm GPA, with PR3 antibody positivity noted in 85% to 95% of cases [12].

The clinical presentation of GPA can mimic several other conditions due to its systemic and granulomatous features. Tuberculosis (TB) is a chronic granulomatous infection with pulmonary and extrapulmonary involvement and it can present similarly to GPA [13]. Sarcoidosis is a rare granulomatous disease with pulmonary involvement that can also resemble GPA [13]. Deep-seated fungal infections such as Aspergillosis and Mucormycosis may also mimic GPA [14]. Other conditions that could be considered in the differential diagnosis include systemic lupus erythematosus, lymphoma and metastatic cancer [15]. In this patient, the absence of features of systemic involvement helped to exclude these other conditions. The differential diagnosis could be narrowed down to TB and Mucormycosis for the following reasons: TB is a common condition in the paediatric age group and can present with overlapping clinical symptoms, such as a solitary oral ulcer [12,13]. Mucormycosis primarily involves the rhinomaxillary region and can present with similar sinonasal symptoms [14].

The differentials considered in the present case were ruled out based on the following investigatory findings. The absence of fungal elements such as broad non septate hyphae, as well as the lack of necrosis and angioinvasion on histopathological examination, ruled out Mucormycosis. Features of chronic granulomatous inflammation were noted on histopathological examination; however, this is a non specific feature shared by both GPA and TB [11]. The PCR test for Mycobacterium tuberculosis was negative, effectively ruling out active TB as the underlying cause.

According to the American College of Rheumatology (ACR), for a proper diagnosis of GPA, the findings must meet at least two of the following criteria: 1) ulcerative lesions in the oral mucosa or nasal bleeding or swelling; 2) nodules, infiltrates, or cavities on chest radiographs; 3) abnormal urinary sediment; and 4) granulomatous inflammation on biopsy [2]. The presence of clinical symptoms including epistaxis, nasal and oral ulcers, alongside the characteristic features of granulomatous inflammation noted in the histopathology report, satisfied two of the four ACR criteria for the diagnosis of GPA. Furthermore, a positive c-ANCA test at a titre of 1:20 confirmed the diagnosis of GPA in this patient [Table/Fig-7].

Delayed presentation is commonly noted in patients with GPA and poses a significant impediment to the successful management of the disease. In a study involving a cohort of 701 patients with GPA, only 22% of patients were diagnosed within the first month of illness, while 46% were diagnosed between one and six months




**[Table/Fig-7]:** Flowchart showing summary of the diagnostic path.

after the onset of their initial symptoms [7]. When oral lesions are the initial presentation, there can be an average delay of up to 6.4 months before diagnosis, resulting in patients presenting with advanced disease [15].

In the present case, the patient had initial symptoms of epistaxis and nasal ulcerations but did not receive adequate treatment. A delay of almost one year after the onset of initial symptoms allowed the disease to progress to an advanced stage; at the time of presentation, the patient exhibited symptoms of advanced disease, including extensive palatal bone loss. Given the advanced state of the condition, it was crucial to initiate an appropriate treatment protocol promptly to halt further tissue damage and prevent systemic complications.

Immunosuppressive therapy with glucocorticoids as induction agents, along with other cytotoxic drugs, is the treatment of choice [Table/Fig-8] [15]. Glucocorticoids are preferred induction agents due to their minimal side-effects. Cyclophosphamide has also been successfully used as an induction agent, but it is associated with severe side-effects. Therapy with Methotrexate and Azathioprine has been reported in patients without severe disease, with moderate success. Rituximab has been found to be effective in severe cases and provides sustained remission; it is also useful in cases of relapsing disease [7,16]. To achieve adequate remission, the drug dose should be tailored to appropriately treat the manifestations of GPA in each individual while minimising long-term toxicities.

| Drug | Phase | Adverse effects |
|---|---|---|
| Prednisolone | Induction/ maintenance | Weight gain, increased risk of infection, Hyperglycaemia, cushing's syndrome |
| Rituximab | Induction/ maintenance | Neutropenia, increased risk of infection, reactivation of latent viral infection, development of other autoimmune conditions |
| Cyclophosphamide | Induction | Nausea,vomitimg, cytopenia, hairloss, increased risk of malignancies |
| Methotrexate | Maintenance | Nausea, diarhhoea, hairloss, oral mucositis |
| Azathioprine | Maintenance | Nausea, vomiting, diaorrhea, mouthulcers, liver dysfunction |

**[Table/Fig-8]:** Drugs in management of GPA [15].

The prognosis is determined by the type and stage of the disease at presentation, as well as the presence of other co-morbidities.

The mean survival of patients with disseminated disease is poor, with a survival rate of less than a year for 80% of patients; however, the prognosis is better for limited forms of the disease [7,15]. Appropriate therapy and adherence to the treatment protocol can improve the five-year survival rate to between 70% and 80% [11]. Relapses can occur in approximately 50% of patients with systemic disease, but for those with limited oral lesions, the relapse rate is noted to be less than 0.5%. The timeline for recurrence may range from 18 months to 15 years following initial remission [15].

Despite presenting with an advanced lesion, the absence of systemic involvement and co-morbidities supported a favourable prognosis for the patient. Prompt initiation of immunosuppressive therapy, consistent compliance and regular follow-up care ensured a positive outcome with sustained disease remission.

## CONCLUSION(S)

GPA is a rapidly progressive disease characterised by multiorgan involvement and an unpredictable course. The common age of presentation is in the fifth decade of life, although it can rarely present in the paediatric age group. Oral lesions may be the initial manifestation of GPA, making it critical for oral health care professionals to recognise this condition even when it occurs in children. The present case underscores the importance of early recognition and accurate diagnosis and it also emphasises the potential for excellent outcomes in GPA when managed appropriately.

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**PARTICULARS OF CONTRIBUTORS:**

1. Professor and Head, Department of Oral Medicine and Radiology, Kannur Dental College, Kannur, Kerala, India.
2. Professor, Department of Oral Medicine and Radiology, Kannur Dental College, Kannur, Kerala, India.
3. Reader, Department of Oral Medicine and Radiology, Kannur Dental College, Kannur, Kerala, India.
4. Senior Lecturer, Department of Oral Medicine and Radiology, Kannur Dental College, Kannur, Kerala, India.
5. Senior Lecturer, Department of Oral Medicine and Radiology, Kannur Dental College, Kannur, Kerala, India.

**NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:**

Dr. Prathima Sreenivasan,
Professor and Head, Department of Oral Medicine and Radiology, Kannur Dental College, Anjarakkandy Post, Kannur-670612, Kerala, India.
E-mail: prathimasumal@gmail.com



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