

Granulomatosis with polyangiitis with salivary glands involvement: presenting a case and describing its clinical, pathophysiological, and therapeutic aspects

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INTRODUCTION

Granulomatosis with polyangiitis (GPA) is a rare form of small vessel vasculitis characterized by multisystem necrotizing granulomatous lesions with different organs involvements such as the central nervous system, urinary tract, gastrointestinal tract, skin, and even eye (1-3). The main pathological characteristic of GPA is the positivity of autoantibodies against cytoplasmic components of neutrophil cells or C-ANCA as well as proteinase-3 (PR3) over-activation (4). Due to the multisystem involvement nature, the diagnosis of GPA is difficult. Additionally, GPA may overlap with other clinicopathological conditions such as infections, autoimmune-inflammatory disorders, connective tissue diseases, and even neoplasms (5,6). In this regard, the involvement of salivary glands is a very rare phenomenon. Herein, we described a case of GPA with submandibular salivary gland involvement followed by reviewing the literature on similar cases.

CASE PRESENTATION

The case was a 31-years old man, a known case of seronegative peripheral arthritis with involvement of knees, hand wrists, and metacarpophalangeal joints from five years ago that was treated with methotrexate and prednisolone. During the years of illness, the patient had no evidence of skin nodules, exertional dyspnea, sinusitis, or kidney insufficiency, but evidence of scleritis was found during the course of the disease that improved with a gradual increase in the dose of the drug. About 6 months before the last visit, the patient voluntarily stopped his medication regimen, and after that, about two months before, he developed bilateral enlargement of the parotid and submandibular glands. At the time of the visit, the swelling of the mentioned areas was evident in the form of a thundering mass without erythema on the surface of the glands. On examination, the left mandibular margin was not well palpable. The patient did not complain of dry mouth, but he complained of dry eyes without any evidence of visual impairment, pain, or eye inflammation. Also, there was no evidence of purulent or bloody discharge from the nose. Also, there were no signs of fever or shortness of breath. In initial laboratory assessment, cell count, serum biochemistry, thyroid test, and 24-hour urine analysis were found to be normal, however, raised inflammatory indices including C-reactive protein and erythrocyte sedimentation rate were evident. The purified protein derivative (PPD) skin test was also negative. In sonography assessment, a cystic mass with internal echogenic foci measuring 20 x 27 mm was seen in the distal part of the left submandibular gland. For this reason, the patient was a candidate for MRI with contrast indicating a cystic-like lesion with fluid-fluid level and peripheral enhancement in parotid and submandibular glands bilaterally suggestive of hematoma (Figure 1). Pulmonary nodules were also evident in the patient's CT scan (Figure 2). There was also a severe enlargement of bilateral parotid and submandibular glands probably due to vasculitis. Based on the aforementioned findings, the patient underwent fine needle aspiration (FNA) under ultrasound guidance, which indicated the presence

of degenerated squamoid cells, giant cells, and inflammatory cells with a priority of neutrophils in the submandibular gland, as well as the presence of a cyst containing fluid without evidence of malignancy in the parotid gland. The differential diagnosis proposed for the patients included Sjogren's syndrome, sarcoidosis, IgG4-related disease, and Wegener's granulomatosis (GPA). As additional evaluations, an ultrasound of the abdomen and pelvis was requested, the only positive finding of which was grade 1 fatty liver. CT scan of the sinuses was also normal. In the CT scan of the lung, a lung nodule with a diameter of 14 mm was seen in the medial apical segment of the lung, which was not seen in the CT scan of the patient four years ago. The echocardiography of the patient also showed a normal ventricular functional state with normal pulmonary artery pressure and mild MR. In cytological assessment, raised serum levels of immunoglobulin-G4 (IgG4) along with positivity for the C-ANCA marker without any positivity for other rheumatologic markers were revealed. Also, the viral markers of hepatitis and HIV were found to be negative. Due to the size of the submandibular gland containing necrosis, the presence of pulmonary nodules, and positive markers, the diagnosis of GPA was finally made for the patient. He was treated with methotrexate, prednisolone, and rituximab which led to a gradual reduction in the size of the glands and the improvement of the patient's clinical symptoms within one month after the treatment (Figure 3).

DISCUSSION

Wegener granulomatosis or GPA is one of the rare components of a wide spectrum of diseases named ANCA-associated vasculitides. This disease was first described by Heinz Klinger and colleagues in 1931 those five years later; Friedrich Wegener described a series of affected patients and introduced it as a distinct form of vasculitis (7). From an etiological point of view, the exact etiologies of GPA remain unknown, however, the relationship between the pathophysiological changes of the disease and ANCA has been fully confirmed. Now, it seems that a variety of genetic and microbial factors involve in triggering disease and its severity. It is now presumed that the inflammatory basis of GPA is referred to as ANCA positivity (8). In pathological assessments, it has been shown that immune response to some environmental insults may result in hypersecretion of some cytokines such as tumor necrosis factor, interleukin 17, and interferon-gamma leading ultimately to the development of granulomatous vascular lesions (9). Also, via interaction between ANCA and proteinase-3 enzyme, the adhesion of neutrophils to vascular endothelium can be triggered which leads to damage to endothelial cells (10). Moreover, the over-expression of some genes has been also described to be associated with GPA such as the CTLA-4 gene (involved in T-cells activation), PRTN-3 (involved in activation of proteinase-3), and HLA-DP gene (involved in activation of neutrophils and monocytes) (11). Regarding the etiologic role of infections, some evidence is available in the flaring role of hepatitis C virus, Epstein-Barr virus, cytomegalovirus, parvovirus, and Covid-19 infections and the appearance of GPA (12,13). Also, it is now suggested a close link between the likelihood of GPA and some medications such as phenytoin, hydralazine, allopurinol, and anti-thyroid drugs with unclear etiological roles (14,15). Epidemiologically, the annual incidence of GPA is estimated at 10 to 20 cases per one million directly dependent on geographical characteristics, with a higher incidence in colder areas. The disease is more prominent in older adults than in children whose age peaks at 64 to 75 years old but with no gender predilection (16).

GPA is known as a multisystem syndrome with evidence of inflammatory reactions in different organs such as the upper respiratory tract (as rhinitis, sinusitis, otitis, or mastoiditis), vascular bed (as small vessels damages, vasculitis), kidney system (as glomerulonephritis) and respiratory system (as alveolar hemorrhage and lung nodules). In this regard, appearing generalized systemic symptoms, especially non-specific symptoms are expected in relation to GPA. Upper respiratory involvement is predictable in more than 90% of patients, lower respiratory tract involvement (as pulmonary infiltrations, pleural effusion, and nodules) in about 15 to 50% of patients, renal involvement in 10 to 20% of patients, eye defects (commonly as scleritis) in about 50%, skin defects (as purpura, nodules, ulcers, and granulomas) in 50 to 60%, nervous system (commonly as peripheral neuropathies) in 30 to 40%, musculoskeletal system (as myalgia and/or arthralgia) in 70%, and even cardiovascular system (as valvular lesions or pericarditis) in less than 10% of patients (17-20).

To evaluate patients suspected of GPA, all clinical and paraclinical assessments should be considered including minute physical examination, tracking laboratory parameters including blood count, electrolytes,

inflammatory markers, imaging, and titrating specific markers of PR3-ANCA and histological assessments if required (21). Radiological assessment according to the involved organs should be also proposed. Such management can help to differentiate GPA from other misleading conditions. With respect to therapeutic approaches, the treatment of such patients is based on the combination of immunosuppressive drugs such as glucocorticoids, cyclophosphamide, methotrexate, and rituximab (22). In more severe cases, plasmapheresis may be also indicated. In life-threatening conditions, a combination of glucocorticoids and cyclophosphamide was found to be a very effective regimen (23). The efficacy and safety of rituximab and according to the RAVE trial, it has demonstrated the similarity of effectiveness and safety of this drug compared to cyclophosphamide (24). In GPA with a milder state, glucocorticoids combined with methotrexate are preferred. In those with renal dysfunction or pulmonary hemorrhage complicated by respiratory compromise, plasmapheresis should be considered (25).

GPA with salivary glands involvement has been reported rarely. In the present case, despite the previous evidence of arthritis, the occurrence of swelling and involvement of the parotid and submandibular glands along with the observation of the pulmonary nodule raised the suspicion of the occurrence of other autoimmune disorders. Based on this, the general and specific evaluations indicated the positivity of the ANCA marker in this patient, which, along with pulmonary nodular involvement, strongly suggested GPA. Thus, the treatment with a combination of methotrexate, prednisolone, and rituximab was selected leading to improvement of clinical condition. In a similar study by Ryota Kikuchi et al (26), the case described was an old man manifesting with low-grade fever and painful enlargement of the right submandibular gland that led to the definitive diagnosis of GPA based on the presence of multiple organs involvement along with histopathologic evidence in a skin biopsy sample of necrotizing granulomatous inflammation with vasculitis. He was successfully treated with methylprednisone and cyclophosphamide with gradual improvements in symptoms and radiologic findings. Alper Ceylan et al (27) described a young woman with parotid gland swelling along with cough, arthralgia, epistaxis, nasal obstruction, weight loss, and resistance to antibiotic therapy. The prominent findings, in this case, were to reveal diffuse enlargement and cutaneous fistulas on the

bilateral parotid glands and also positivity for c-ANCA that the diagnosis was strongly in favor of the disease. In general, it should be kept in mind that one of the diagnoses in case of symptoms of inflammatory reaction in salivary glands along with involvement in other vital organs such as lung nodular involvement should be this disease and its treatment management should be based on the treatment protocols as soon as possible.

Ethics approval and consent to participate

Approval was not needed by the local Clinical Research Ethics Committee for case reports.

Consent for publication

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Conflict of interests

The authors declare that they have no competing interests.

Data availability statement

Data is available if requested

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Authors' contributions

AA conceived the idea to report the case. DM was responsible for data collection. FF and NB drafted the manuscript. SB and AA commented on the manuscript. All authors read and approved the final manuscript.

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REFERENCES

1. Maqbool A, Maqbool A, Qadeer A, Mehmood MF, Loon M. An atypical presentation of granulomatosis with polyangiitis: A case report. *Maqbool U, Radiol Case Rep.* 2023 Apr 14;18(6):2245-2248.
2. Sahinturk H, Kandemir E, Yeşiler Fİ, Şerifoğlu İ, Şahin Dalgıç G, Erol Ç, Sayin CB, Tezcaner T, Çiloğlu E, Gedik E, Zeyneloğlu P, Kayhan Z. A rare case of granulomatosis with polyangiitis with involvement of the gastrointestinal system. *Ulus Travma Acil Cerrahi Derg.* 2023 Mar;29(3):435-439.
3. Ringwald M, Chevalley D, Bongard C, Kissling S, Rotman S, Von Garnier C, Ribi C, Comte D. Granulomatosis with polyangiitis: what's new?. *Rev Med Suisse.* 2023 Apr 5;19(821):674-679.
4. D'Aquila ML, John VJ. Granulomatosis With Polyangiitis Presenting as Occlusive Retinal Vasculitis. *J Vitreoretin Dis.* 2022 May 5;6(6):467-469.
5. Sowida M. Granulomatosis polyangiitis. *BMJ Case Rep.* 2019 Jul 8;12(7):e228693.
6. Guneyli S, Ceylan N, Bayraktaroglu S, Gucenmez S, Aksu K, Kocacelebi K, Acar T, Savas R, Alper H. Imaging findings of pulmonary granulomatosis with polyangiitis (Wegener's granulomatosis): lesions invading the pulmonary fissure, pleura or diaphragm mimicking malignancy. *Wien Klin Wochenschr.* 2016 Nov;128(21-22):809-815.
7. Lakhani DA, Balar AB, Adelanwa A, Gross A, Mohamed R, Smith KT, Kim C. Granulomatosis with polyangiitis: A case report and brief review of literature. *Radiol Case Rep.* 2021 Sep 5;16(11):3445-3450.
8. Kyurkchiev D, Yoneva T, Yordanova A, Kurteva E, Vasilev G, Zdravkova Y, Sheytanov I, Rashkov R, Ivanova-Todorova E. Alterations of serum levels of plasminogen, TNF- α , and IDO in granulomatosis with polyangiitis patients. *Vascular.* 2021 Dec;29(6):874-882.
9. Kozu Y, Gon Y, Takano Y, Noguchi T, Hayashi S, Kumasawa F, Mizumura K, Maruoka S, Hashimoto S. Time-course of Serum Pro-inflammatory Cytokines and Chemokines Levels Observed in Granulomatosis with Polyangiitis: A Case Report. *Sarcoidosis Vasc Diffuse Lung Dis.* 2016 Dec 23;33(4):407-412.
10. Park J, Lee EB, Song YW. Decreased tumour necrosis factor- α production by monocytes of granulomatosis with polyangiitis. *Scand J Rheumatol.* 2014;43(5):403-8.
11. Banerjee P, Kumar U, Khetarpal P, Senapati S. Meta-analysis confirmed genetic susceptibility conferred by multiple risk variants from CTLA4 and SERPINA1 in granulomatosis with polyangiitis. *Int J Rheum Dis.* 2022 Jul;25(7):811-819.
12. Nakamura Y, Okumura F, Nihei M, Chubachi K, Sakamoto H, Ishioka Y, Makiguchi T, Tanaka H, Taima K, Yajima N, Kurose A, Tasaka S. Granulomatosis with Polyangiitis following COVID-19 in an Adolescent. *Intern Med.* 2023;62(4):589-593.
13. C M Gaffey, B Chun, J C Harvey, H J Manz. Phenytoin-induced systemic granulomatous vasculitis. *Arch Pathol Lab Med.* 1986 Feb;110(2):131-5.
14. Warren K, Vu K, Shergill K, Watson B, Faris M. Rare complication of a commonly used antihypertensive agent: A case of hydralazine-induced ANCA-associated vasculitis presenting as rapidly progressive glomerulonephritis. *Clin Case Rep.* 2022 Feb 7;10(2):e05411.
15. Aeddula NR, Pathireddy S, Ansari A, Juran PJ. Hydralazine-associated antineutrophil cytoplasmic antibody vasculitis with pulmonary-renal syndrome. *BMJ Case Rep.* 2018 Nov 8;2018:bcr2018227161.

16. Sirada Panupattanapong 1, Dustin L Stwalley 1, Andrew J White 1, Margaret A Olsen 1, Anthony R French 1, Mary E Hartman 1. Epidemiology and Outcomes of Granulomatosis With Polyangiitis in Pediatric and Working-Age Adult Populations In the United States: Analysis of a Large National Claims Database. *Arthritis Rheumatol.* 2018 Dec;70(12):2067-2076. doi: 10.1002/art.40577.
17. Koritala T, Mene-Afejuku TO, Schaefer M, Dondapati L, Pleshkova Y, Yasmin F, Mushtaq HA, Khedr A, Adhikari R, Al Mutair A, Alhumaid S, Rabaan AA, Al-Tawfiq JA, Jain NK, Khan SA, Kashyap R, Surani S. Granulomatous Polyangiitis With Renal Involvement: A Case Report and Review of Literature. *Cureus.* 2021 Nov 22;13(11):e19814.
18. Shelton A, Parikh S, Mims C, Quintero-Del-Rio A. A challenging case of granulomatosis with polyangiitis with cardiac involvement: a rare case report. *AME Case Rep.* 2022 Nov 21;7:8.
19. Mei L, Wang L, Yan H. Updates of ocular involvement in granulomatosis with polyangiitis. *Graefes Arch Clin Exp Ophthalmol.* 2022 Dec 7. doi: 10.1007/s00417-022-05918-w.
20. Gaafar Ragab 1, Mohamed Tharwat Hegazy 1, Mohamed Ali 2, Mona R E Abdel-Halim 3, Xavier Puéchal 4. Three Patterns of Cutaneous Involvement in Granulomatosis with Polyangiitis. *J Adv Res.* 2020 May 7;24:311-315. doi: 10.1016/j.jare.2020.05.009. eCollection 2020 Jul.
21. Marius G Pakalniskis 1, Aaron D Berg 1, Bruno A Policeni 1, Lindell R Gentry 2, Yutaka Sato 1, Toshio Moritani 1, Wendy R K Smoker 1. The Many Faces of Granulomatosis With Polyangiitis: A Review of the Head and Neck Imaging Manifestations. *AJR Am J Roentgenol.* 2015 Dec;205(6):W619-29. doi: 10.2214/AJR.14.13864.
22. Mohanan-Earatt A, Biswas J. Clinical profile and management of granulomatosis with polyangiitis-associated scleritis from a tertiary care hospital in South India. *Indian J Ophthalmol.* 2023 Jan;71(1):146-152. doi: 10.4103/ijo.IJO_1411_22.
23. Bellos I, Boletis I, Lionaki S. A Meta-Analysis of the Safety and Efficacy of Maintenance Therapies for Antineutrophil Cytoplasmic Antibody Small-Vessel Vasculitis. *Kidney Int Rep.* 2022 Mar 2;7(5):1074-1083.
24. Valor-Méndez L, Kleyer A, Rech J, Manger B, Schett G. Sustained clinical remission under infliximab/rituximab combination therapy in a patient with granulomatosis with polyangiitis. *Auto Immun Highlights.* 2021 Mar 6;12(1):5. doi: 10.1186/s13317-020-00147-9.
25. Da Silva RC, Adhikari P. Granulomatosis With Polyangiitis Presenting With Diffuse Alveolar Hemorrhage: A Systematic Review. *Cureus.* 2022 Oct 4;14(10):e29909.
26. Ryota Kikuchi 1, Kazutetsu Aoshiba 1, Hiroyuki Nakamura 1. Salivary Gland Enlargement as an Unusual Imaging Manifestation of Granulomatosis With Polyangiitis Involving the Head and Neck Region. *AJR Am J Roentgenol.* 2016 Jun;206(6):W94. doi: 10.2214/AJR.16.16042. Epub 2016 Mar 21.
27. Alper Ceylan 1, Korhan Asal, Fatih Çelenk, Ahmet Köybaşıoğlu. Parotid gland involvement as a presenting feature of Wegener's granulomatosis. *Singapore Med J.* 2013 Sep;54(9):e196-8. doi: 10.11622/smedj.2013183.

Figure legends

Figure: MRI view of parotid and submandibular glands

Figure 2: A feature of pulmonary nodules in CT scanning

Figure 3: The improvement of the patient's clinical symptoms within one month after the treatment



