Granulomatosis with Polyangiitis Masquerading as Lung Cancer

Asma Qasim[1], Sarah Al Qassimi[1], Muriel Ghosn[2], Lara Memisoglu[1], Ahmad Alduaij[3] and Rajaie Namas[1]*

[1]Cleveland Clinic Abu Dhabi, Division of rheumatology, Department of internal Medicine, Cleveland clinic Abu Dhabi, Abu Dhabi, UAE

[2]Cleveland Clinic Abu Dhabi, Division of Nephrology, Department of internal Medicine, Cleveland clinic Abu Dhabi, Abu Dhabi, UAE

[3]Cleveland Clinic Abu Dhabi, Pathology & Laboratory Institute, Cleveland clinic Abu Dhabi, Abu Dhabi, UAE

Received: 5 September 2023

Accepted: 9 January 2024

***Corresponding author:** NamasR@ClevelandClinicAbuDhabi.ae

DOI 10.5001/omj.2026.16

Abstract

Granulomatosis with polyangiitis (GPA) is a necrotizing vasculitis affecting both arterioles and venules. The disease classically presents with a triad involving acute inflammation of the upper airways and lower airways along with renal involvement. We are presenting a case of a 37-year-old male who initially presented with bilateral otitis media complicated by right sided facial palsy. On further investigations and imaging, he was found to have a lung mass highly suggestive of lung cancer, biopsy of which resulted negative for malignant cells. During this time, he also was found to have progressive worsening of renal function and hematuria, for which he underwent a renal biopsy that confirmed granulomatosis with polyangiitis.

Keywords: Granulomatosis with polyangiitis. Lung mass. Facial palsy. Otitis media.

Introduction

Granulomatosis with polyangiitis (GPA) is a necrotizing vasculitis affecting both arterioles and venules. From an immunological standpoint, TGF-β1[1] and interleukin-10 (IL-10) are key regulators of immune homeostasis.[2] IL-10 in particular is noted to be significantly increased in GPA.[3] PD-L1 is responsible for T cell activation, proliferation, and cytotoxic secretion.[4] Programmed death 1 (PD-1) immune checkpoints are negative regulators of T-cell immune function[5] and reduced PD-L1 is demonstrated in neutrophils of anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) patients.[6] Toll like receptors (TLRs) play a considerable role in the host defense against microorganism.[7] TLR2 and TLR9 ligands act as priming agents may be of particular relevance in GPA, as this may play a role in triggering disease activity in the presence of infection.[8]

The disease classically presents with a triad involving acute inflammation of the upper airways and lower airways along with renal involvement. However, it is known that GPA can affect other organs. ENT manifestation including nasal crusting, sinus pain, chronic rhinosinusitis, nasal obstruction, smell disturbances, purulent/bloody nasal discharge, excessive tearing (ie, epiphora), formation of sinus mucoceles (benign, epithelium-lined cysts filled with mucus) and conductive and/or sensorineural hearing loss are common in patient with GPA with estimated frequency of 90%.[9] Facial paralysis may be present in the course of the disease but rarely are the first to appear.[10] It is notable that eosinophilic granulomatosis with polyangiitis (EGPA) should be concurrently ruled out in patients with suspected GPA due to the risk of thromboses and the presence of activated eosinophils in various organs, especially within hepatic veins,[11] which is the most common pattern of vascular involvement in Budd-Chiari syndrome.[12]

Case Report

A 37-year-old male presented with recurrent bilateral otitis media since April 2022 requiring a myringotomy in May 2022 but developed right-sided 7th nerve facial palsy as a result in less than one month. On ENT examination, he was found to have bilateral dull tympanic membranes with purulent discharge bilaterally. He was admitted and given a course of intravenous (IV) antibiotics and IV corticosteroids that was weaned off over a period of eighteen days then discharged to home.

After being weaned off corticosteroids, the patient began experiencing constitutional symptoms including generalized fatigability, recurrent fevers, and unintentional weight loss and during subsequent follow up with which speciality he was found to have an elevated erythrocyte sedimentation rate (ESR) 114 mm/hr and rheumatoid factor (RA) 20 IU/mL with concern of a possible underlying primary malignancy. Although there was improvement in his 7th nerve facial palsy during this time, he began having right-sided hearing loss and ear pain in the interim.

Computerized tomography (CT) of the chest in July 2022 revealed moderate-sized soft tissue mass of the anterior segment of the right upper lobe with an aggressive appearance extending along the margin of the pleura with pleural retraction and parasitization of the adjacent vasculature with multiple other metastatic lesions involving the anterior segment of the right middle lobe, and small nodules of the right lateral segment of the upper lobe, and medial right lower lobe [Figure 1 A-B]. Positron emission tomography (PET) scan was done and was suspicious for lung malignancy [Figure 1 C-D]. Additionally, he underwent magnetic resonance imaging (MRI) of the brain for hearing loss that showed changes of bilateral otomastoiditis with right-sided changes being predominant.

He was admitted to our facility and neurological examination positive for muscle weakness and facial deviation to the left. Bronchoalveolar lavage but returned negative for malignant cells. Lung biopsy was negative for malignant cells but revealed changes suspicious for capillaritis.

Lab investigations includes rapidly worsening creatinine of 213 (45 - 84 micromol/L) with a baseline of 55 micromol/L, urine was positive for red blood cells but no proteinuria, autoimmune workup was positive for proteinase 3 antibodies of >8 AI (0.0 - 0.9 AI), negative cytoplasmic-antineutrophil cytoplasmic antibodies (c-ANCA) and anti-myeloperoxidase (anti-MPO) in addition to significant elevation in ESR to 114 (2 - 28 mm/hr), positive RA 20 (<=13 IU/mL), low C4 11(14 - 44 mg/dL), elevated Ferritin 761.8 (30.0 - 400.0 mcg/L) and protein/creatinine ratio 71 (0 - 14 mg/mmol) negative tuberculosis (TB) QuantiFERON, negative immunoflorescence anti-nuclear antibody (IF-ANA), normal SPEP and normal IFE.

With the clinical suspicion of small vessel vasculitis, likely ANCA-associated vasculitis affecting upper and lower respiratory tracts and the kidneys, he was started on IV methylprednisolone pulse therapy, and underwent a tissue biopsy obtained from the right kidney on July 12, 2022, which showed necrotizing crescentic glomerulonephritis with acute, severe and patchy tubulointerstitial inflammation with minimal tubulointerstitial scarring, consistent with ANCA vasculitis [Figure 2 A-B]. Methylprednisolone was switched to oral prednisone with tapering dose and he received four doses of rituximab afterwards.

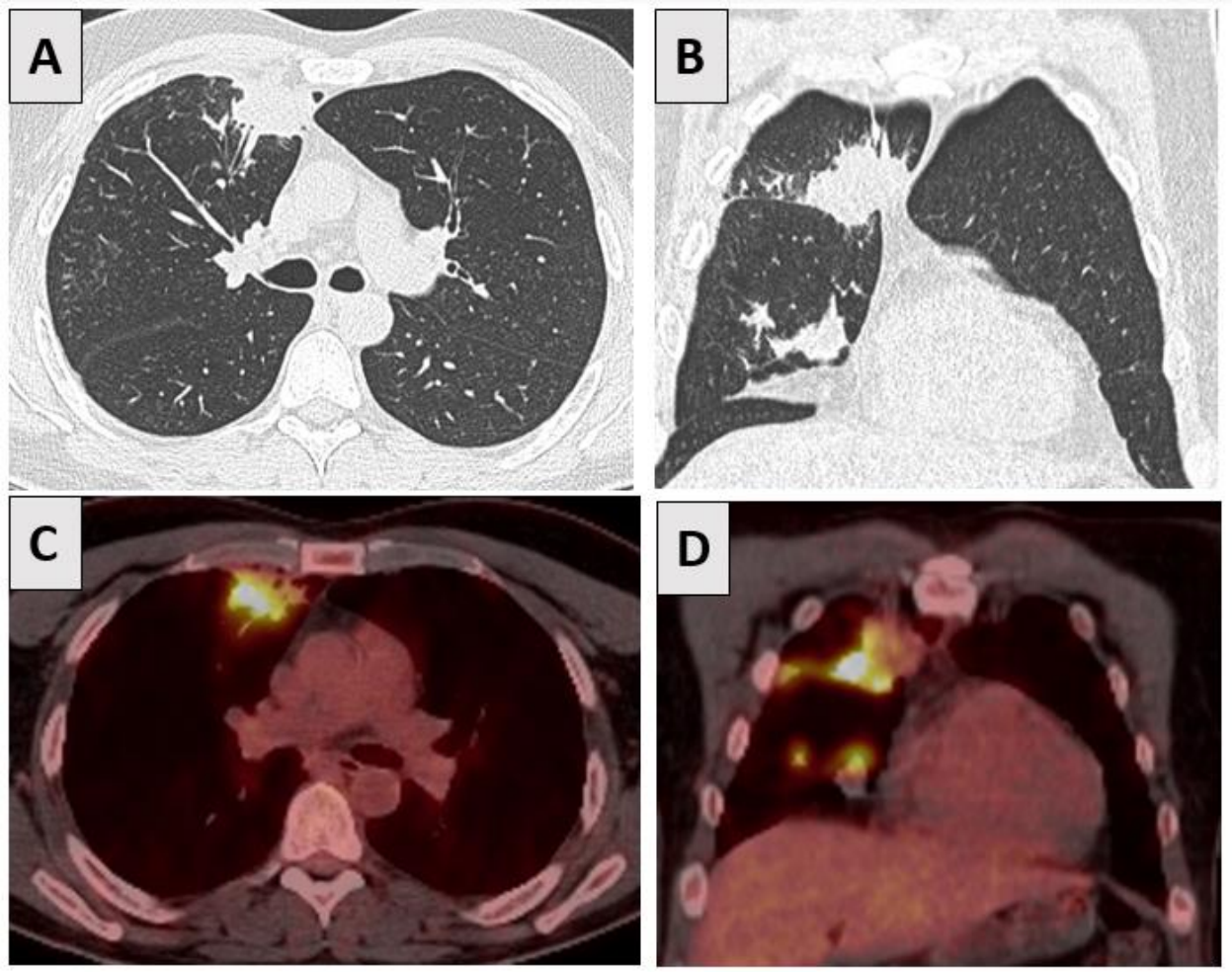

Figure 1: **(A)** axial and **(B)** coronal conventional chest CT images show right upper lung spiculated mass with multiple ipsilateral satellite lesions. **(C)** axial and **(D)** conventional PET-CT images demonstrate increased metabolic activity in each lesion.

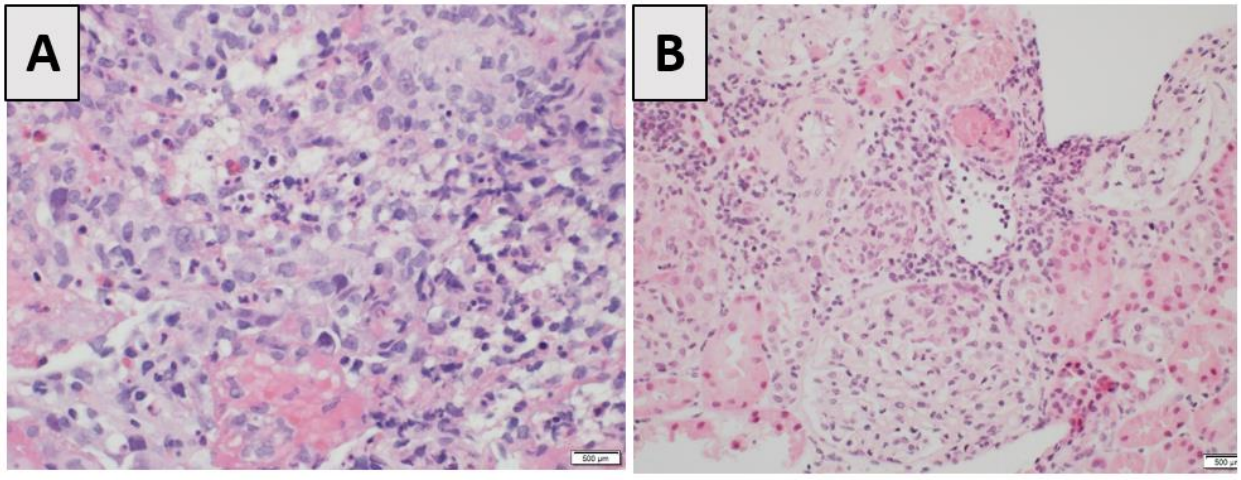

Figure 2: **(A)**Original magnification x400, hematoxylin and eosin (H&E) staining of lung tissue biopsy consisting of fragments of alveolated lung parenchyma. In one fragment, several histiocytes and a few neutrophils replace the alveolar septa, and the adjacent airspaces are filled with blood and a fibrinous exudate containing karyorrhectic nuclear debris. **(B)** Original magnification x400, hematoxylin and eosin (H&E) staining of kidney tissue biopsy consisting of glomeruli display segmental necrotizing lesions and cellular crescents.

There is patchy interstitial inflammation associated with focal tubulitis. Occasional tubules show dysmorphic red blood cells within tubular lumina. Arteries and arterioles are histologically unremarkable.

Clinically, his hearing and facial palsy were improving every time he presents to the infusion center to receive rituximab dose as an outpatient with no reports of cough, hemoptysis, shortness of breath or joint pain. Repeated laboratory investigations were showing improvement in kidney function and ESR.

Discussion

GPA is known to be a rare diagnosis with an annual incidence of 5 to 10 cases per year,[13] its diagnosis is further compounded by the fact it exhibits a wide array of presentations across all systems. Typically, upper and lower respiratory tracts and the kidneys are involved. The most common radiographic presentation is pulmonary masses and nodules.[14] Our patient's diagnosis of GPA was complicated by an initial diagnosis of lung cancer, which required a referral to our oncology services, and affected his wellbeing to the point of depression. In terms of head and neck involvement, the prevalence of ear disorders ranges from 19% to 70% of cases[15] and are rarely the presenting symptoms of GPA.[16] Another report revealed that in 14% of patients with GPA, hearing loss preceded the eventual diagnosis.[17] Amongst the most common otologic disorders in GPA are middle ear lesions including unilateral otitis media, bilateral otitis media and chronic otitis media.[18] Our patient's diagnosis of GPA was preceded by recurrent episodes of bilateral otitis media that was treated initially with myringotomy but eventually progressed with bilateral mastoid and cochlear involvement, more prominently on the right side, as well as facial nerve palsy. It is thought that unilateral or bilateral middle ear disease occurs secondary to formation of granulation tissue in nasopharynx.[18] Destructive granulomas can erode the ossicles, resulting in effusion, mastoiditis or facial palsies, the latter of which occurs in 8%-10% of cases.[18]

Although diagnostic investigations are guided by the patient's presentation, one simple but promising investigation is the complete blood count. Neutrophil-to lymphocyte (NLR) is considered reliable and surrogate marker for PMNL.[19] The NLR may have a significant role in the pathogenesis, diagnosing and evaluating of GPA.[20] RDW is an immediately available inflammatory biomarker[21] and predicts vasculitis activity in GPA. An RDW ≥15.4% at diagnosis may increase the risk of severe GPA at diagnosis and predict refractory diseases during follow-up.[22] As previously mentioned, EGPA carries a risk of thrombosis and was ruled out in the absence of an allergic prodrome, normal eosinophil level and characteristic histological findings on biopsy.

Treatment of GPA with head and neck involvement remains similar to typical GPA, which includes immunosuppressants and corticosteroids. Our patient responded excellently to methylprednisolone followed by rituximab and his course afterwards yielded remission 6 months after his initial presentation.

Conclusion

GPA is a challenging diagnosis that warrants clinical vigilance due to its heterogenous nature and presentations can include head and neck symptoms without initial typical findings of GPA.

References

1. Abdel Hammed MR, Ahmed YA, Adam EN, et al. sVCAM-1, and TGFβ1 in chronic phase, chronic myeloid leukemia patients treated with tyrosine kinase inhibitors. Egypt J Immunol. 2022. Oct;29(4):163-173. PMID: 36208045.

2. Mohammed D, Khallaf S, El-Naggar M, et al. Interleukin-10: A Potential Prognostic Marker in Patients with Newly Diagnosed Multiple Myeloma. Resum Oncol 2021;17(1):38-41. .

3. Wilde B, Thewissen M, Damoiseaux J, Hilhorst M, van Paassen P, Witzke O, et al. Th17 expansion in granulomatosis with polyangiitis (Wegener's): the role of disease activity, immune regulation and therapy. Arthritis Res Ther 2012 Oct;14(5):R227.

4. Abdel Hafeez LA, Mansor SG, Zahran AM, et al. Expression of programmed death ligand-1 (PDL-1) in Acute Myeloid Leukemia Patients and its relation to post induction Response. SECI Oncology Journal 2021;9(2):106-111. .

5. Buchbinder, Elizabeth I. MD; Desai, Anupam MD. CTLA-4 and PD-1 Pathways: Similarities, Differences, and Implications of Their Inhibition. (2016) American Journal of Clinical Oncology. 2016 Feburary; 39(1):p 98-106.

6. Singh J, Minz RW, Saikia B, Nada R, Sharma A, Jha S, et al. Diminished PD-L1 regulation along with dysregulated T lymphocyte subsets and chemokine in ANCA-associated vasculitis. Clin Exp Med 2023 Sep;23(5):1801-1813. .

7. Abdel Hammed MR, Elgendy SG, El-Mokhtar MA, Sayed D, Mansour SM, Darwish AM. T-lymphocytes Expression of Toll-like Receptors 2 and 4 in Acute Myeloid Leukemia Patients with Invasive Fungal Infections. Mediterr J Hematol Infect Dis 2022 Mar;14(1):e2022022. .

8. Holle JU, Windmöller M, Lange C, Gross WL, Herlyn K, Csernok E. Toll-like receptor TLR2 and TLR9 ligation triggers neutrophil activation in granulomatosis with polyangiitis. Rheumatology (Oxford) 2013 Jul;52(7):1183-1189. .

9. Hoffman GS, Kerr GS, Leavitt RY, Hallahan CW, Lebovics RS, Travis WD, et al. Wegener granulomatosis: an analysis of 158 patients. Ann Intern Med 1992 Mar;116(6):488-498. .

10. Preuss SF, Stenner M, Beutner D, Laudes M, Klussmann JP. Fatal course of Wegener's granulomatosis with bilateral otomastoiditis and bilateral facial nerve palsy. Otolaryngol Head Neck Surg 2008 Jun;138(6):799-800.

11. Li D, Shi C, Ding Z, Li X. Budd-Chiari syndrome as a complication of eosinophilic granulomatosis with polyangiitis in a young Chinese man: a case report. J Int Med Res 2020 Oct;48(10):300060520964352. .

12. Abdel Hameed MR, Elbeih EA, Abd El-Aziz HM, Afifi OA, Khalaf LM, Ali Abu Rahma MZ, et al. Epidemiological Characteristics and Etiology of Budd-Chiari Syndrome in Upper Egypt. J Blood Med 2020 Dec;11:515-524. .

13. Mohammad AJ, Jacobsson LT, Westman KW, Sturfelt G, Segelmark M. Incidence and survival rates in Wegener's granulomatosis, microscopic polyangiitis, Churg-Strauss syndrome and polyarteritis nodosa. Rheumatology (Oxford) 2009 Dec;48(12):1560-1565.

14. Han M, Pan C. A case of granulomatosis with polyangiitis mimicking lung malignancy. Respirol Case Rep 2021 Aug;9(9):e0824.

15. McCaffrey TV, McDonald TJ, Facer GW, DeRemee RA. Otologic manifestations of Wegener's granulomatosis. Otolaryngol Head Neck Surg (1979) 1980;88(5):586-593.

16. Gottschlich S, Ambrosch P, Kramkowski D, Laudien M, Buchelt T, Gross WL, et al. Head and neck manifestations of Wegener's granulomatosis. Rhinology 2006 Dec;44(4):227-233.

17. Bakthavachalam S, Driver MS, Cox C, Spiegel JH, Grundfast KM, Merkel PA. Hearing loss in Wegener's granulomatosis. Otol Neurotol 2004 Sep;25(5):833-837.

18. Ferri E, Armato E, Capuzzo P, Cavaleri S, Ianniello F. Early diagnosis of Wegener's granulomatosis presenting with bilateral facial paralysis and bilateral serous otitis media. Auris Nasus Larynx 2007 Sep;34(3):379-382.

19. Abdel Hammed MR, El-Amien HA, Asham MN, Elgendy SG. Can platelets indices and blood neutrophil to lymphocyte ratio be used as predictors for diagnosis of spontaneous bacterial peritonitis in decompensated post hepatitis liver cirrhosis? Egypt J Immunol 2022 Oct;29(4):12-24.

20. Abaza NM, El-Latif EM, Gheita TA. Clinical Significance of Neutrophil/lymphocyte Ratio in Patients with Granulomatosis with Polyangiitis. Reumatol Clin (Engl Ed). 2019 Nov-Dec;15(6):363-367. English, Spanish. . Epub 2017 Dec 21. PMID: 29274703.

21. Abdel Hammed MR, Tohamy MA, Boshra SZ, Taha SM, Saleh MF. Red cell distribution width is an inflammatory predictor marker of contrast induced nephropathy in patients undergoing percutaneous coronary intervention. Egypt J Immunol 2023 Jul;30(3):1-12.

22. Kim HJ, Yoo J, Jung SM, Song JJ, Park YB, Lee SW. Red Blood Cell Distribution Width Can Predict Vasculitis Activity and Poor Prognosis in Granulomatosis with Polyangiitis. Yonsei Med J 2018 Mar;59(2):294-302. .