

Case Report

Granulomatosis with Polyangiitis Manifesting as Refractory Otitis Media and Mastoiditis

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Granulomatosis with polyangiitis (GPA) is a rare rheumatologic disease characterized by small to medium vessel vasculitis and inflammation within multiple organ systems. Majority of cases involve both upper and lower respiratory tracts but other organs including brain, kidneys, joints and skin can also be involved. Patients who have recurrent otitis media and sinusitis often initially present to internists and then to ear nose and throat (ENT) physicians and may be treated with multiple courses of antibiotics without having proper workup for GPA. We present a middle-aged white male who exemplifies this unique presentation with new onset recurrent otitis media and mastoiditis, which did not respond to repeated courses of antibiotics requiring mastoidectomy and myringotomy tube placement. On chest x-ray, he was found to have multiple lung nodules that was followed by a computed tomography (CT) scan of his chest and CT guided biopsy which revealed granulomatous inflammation and necrosis, consistent with GPA. Autoimmune laboratory work-up was also suggestive of GPA. The patient had complete resolution of symptoms with steroid therapy. This case reinforces the concept of high index of suspicion of GPA for patients with recurrent and resistant otitis media or mastoiditis not responding to optimal duration and doses of antibiotics. Appropriate work-up for GPA may allow for earlier diagnosis of this devastating vasculitic disease which can help prevent multi-organ dysfunction.

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Introduction

Granulomatosis with polyangiitis (GPA) is a type of ANCA associated vasculitis (AAV) with multisystem presentation.¹ Majority of cases involve both upper and lower respiratory tracts but other organs including brain, kidneys, joints and skin can also be involved.^{2,3} Patients who have recurrent otitis media and sinusitis often initially present to internists and then to ear nose and throat (ENT) physicians and may be treated with multiple courses of antibiotics without having proper workup for GPA.⁴ GPA should be suspected and investigated in adult patients presenting with new onset and recurrent otitis media, sinusitis or mastoiditis to reduce morbidity.^{2,4,5} We report a case of otitis media in an adult patient in which diagnosis of GPA was made after proper workup was performed, starting with a chest X-ray that showed multiple lung masses in a patient with a history of recurrent of otitis media not responding to antibiotics.

Case Report

A 50-year-old white male with history of diabetes, psoriasis, hypertension, and deviated nasal septum repair presented to the emergency department with complaints

of right ear discharge and pain. After initial evaluation he was discharged from the ER with a course of oral amoxicillin and ciprofloxacin ear drops. He was followed as an outpatient with his otolaryngologist, who performed a right myringotomy, sent cultures of the purulent fluid and started the patient on oral ciprofloxacin and gentamicin ear drops. The cultures of purulent drainage grew methicillin sensitive *Staphylococcus aureus* and *Pseudomonas aeruginosa* that were both sensitive to ciprofloxacin and gentamicin. Despite being treated with appropriate antibiotics, he presented once more to the emergency department due to worsening ear pain and discharge. On physical examination, his vital signs, including temperature, were within normal limits. Head and neck examination revealed erythematous, tender, non-fluctuant edema of the soft tissues around the right ear and right mastoid process with anterior cervical and submandibular lymphadenopathy on the right side. Otoscope examination revealed inflamed auditory canal with greenish-yellow purulent drainage. Tympanic membrane was erythematous, bulging with fluid line. There was tenderness on manipulation of the pinna as well as significant hearing loss on the right side. The patient was placed on intravenous piperacillin-tazobactam

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and oral pain medication. Laboratory data revealed white blood cells of 8.5 k/uL (4.5–11), hemoglobin 12.2 gm/dL (13.2–17.5), euvolemic hyponatremia with sodium of 126 mmol/L (136–145), random blood glucose of 289 gm/dl (<140 gm/dL) with otherwise normal complete blood count and comprehensive metabolic profile (Table 1). Computed tomography (CT) of mastoids with contrast showed fluid in middle ear surrounding the ossicles and in the right mastoid air cells confirming severe right otitis media and right sided mastoiditis. Right myringotomy tube placement with right mastoidectomy was performed by the otolaryngologist. Biopsy of mastoid tissue revealed granulation tissue with marked acute and chronic inflammation consistent with acute and chronic mastoiditis. The patient's symptoms appeared to improve; however, not to the degree that would be expected after appropriate medical and surgical management, prompting further investigation. Chest x-ray showed multiple large bilateral lung masses that mandated CT scan of the chest with contrast for further evaluation. Three large heterogeneous masses measuring about 2 cm, 3 cm, and 5 cm over bilateral lung fields were seen, suspicious of metastatic lung malignancy versus a vasculitic process (Figure 1). CAT scan of the abdomen and pelvis with contrast was performed and showed no

evidence of metastatic disease. CT guided right mid lung biopsy was done. Concurrently, autoimmune work-up was ordered considering patient's history of frequent and resistant otitis media with lung nodules on imaging. Autoimmune work-up revealed positive anti-neutrophil cytoplasmic antibody (c-ANCA) 1:40 (<1:20), positive Protease 3 antibody (PR-3) 285 AU/mL (0–19 AU/mL), negative Anti-nuclear antibody (ANA) 0.4 (<0.90), negative myeloperoxidase IgG 5 AU/mL (0–19), negative Rheumatoid factor and significantly elevated ESR and c-reactive protein suggesting the diagnosis of GPA (Table 1). Lung biopsy confirmed granulomatous inflammation and necrosis, with no evidence of malignancy, which was consistent with the diagnosis of GPA (Figure 2). A rheumatologist was consulted to review the case and the patient was started on high dose steroid, which improved his symptoms significantly with resolution of pain. The patient was continued on tapered dose oral steroids and was discharged with advice to follow-up with his rheumatologist as an outpatient.

Table 1. Summary of Laboratory Data

Laboratory Data	Values (Normal Range)
Comprehensive metabolic panel	
Sodium (Na)	126 (136–145 mmol/L)
Chloride (Cl)	91 (96–100 mmol/L)
Potassium (K)	4.1 (3.5–5.2 mmol/L)
Bicarbonate (HCO ₃)	25 (24–31 mmol/L)
BUN	12 (5–25 mg/dL)
Cr	0.72 (0.61–1.24 mg/dL)
eGFR	>60 (>90 mL/min)
Complete blood count	
Hb	12.2 (13.2–17.5 gm/dL)
Ht	36.5 (40–53%)
MCV	86.1 (80–100 fl)
WBC	8.5 (4.5–11.0 k/uL)
Pt count	358 (140–450 k/uL)
ESR	98(0–20 mm/h)
CRP	18.55(0–0.744 mg/dL)
ANA	0.40(<0.9)
Serine PR-3	285 (0–19 AU/mL)
MPO antibody	5(0–19 AU/mL)
Neutrophilic cytoplasmic antibody (ANCA)	1;40(<1;20), (c-ANCA pattern)

Abbreviations: Cr, Creatinine; BUN, Blood urea nitrogen; EGFR, estimated glomerular filtration rate; Hb, hemoglobin; Ht, hematocrit; MCV, mean corpuscular volume; WBC, white blood count; Pt, platelet; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; ANA, antinuclear antibody; PR-3, protease-3; MPO, myeloperoxidase.

Discussion

GPA is a rare rheumatologic disease characterized by small to medium vessel vasculitis and inflammation within multiple organ systems.¹ It is estimated that prevalence of GPA in the United States is three per 100 000 with about a 1:1 ratio of males to females.⁶ As in our patient, the disease predominately affects the Caucasian population who make up about 80–97% of cases.⁷ There are documented cases involving all age groups with a wide age range of 8–99 years.^{2,7} Nose and paranasal sinuses are affected in 60%–90% of otolaryngologic presentation in GPA as seen in our patient.^{8,9}

Otitis media has been reported in relation to GPA and has been underestimated. Many cases of GPA have been reported with otitis media without systemic involvement as the sole presentation. Hearing loss with facial palsy has also been reported more often as compared to headache

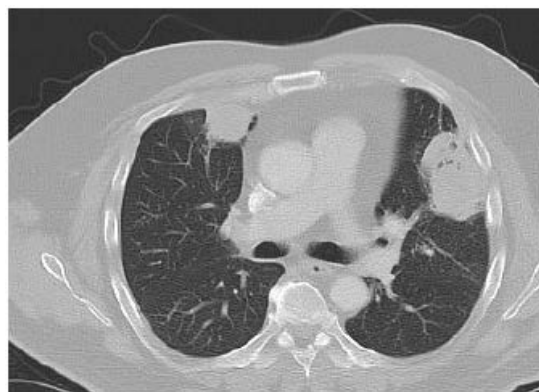


Figure 1. Large heterogeneous masses (5.3 × 4.2 cm) in the Left Upper lobe that extends to the Pleural Surface. Mass (2.2 × 2.5 cm) in the right mid lung anteromedially near the minor fissure.

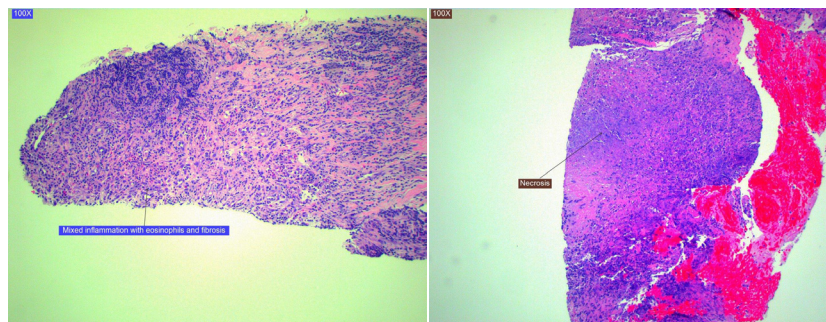


Figure 2. Lung Mass Biopsy Showing Granulomatosis Inflammation and Necrosis.

and ear discharge in the context of otolaryngologic manifestations of GPA.^{10,11} In our patient, ear discharge and otalgia were predominant aspects of his presentation. Although granulomas were discovered in his lungs, the patient reported no respiratory symptoms. Hearing loss is usually reversible and can improve completely after steroid treatment.¹² Otitis media in GPA is mostly unilateral but can be bilateral in 33% of cases.¹³ Presence of granulation tissue is often found in the middle ear and mastoid of patients with chronic otitis media that corresponds to 24 % of cases.¹⁴ Mastoiditis occurs due to the spread of destructive granulomatous masses to the petrous part of temporal bone and usually does not respond well to surgery.^{10,15} Our patient underwent right sided mastoidectomy without appropriate improvement of symptoms, prompting investigation of alternative etiologies of mastoiditis, especially in the context of preoperative imaging that showed multiple lung masses. Felicetti et al¹⁶ studied the outcome of GPA patients between 1996 and 2016 and found that the most common ENT presentation was sinus disease followed by otitis media and mastoiditis. Fortunately, those patients with isolated otitis media had favorable prognosis at 5 years.¹⁶ However, due to its subtle presentation, many cases of GPA may go undiagnosed and not respond to usual medical treatment of otitis media.⁴

GPA is unique in the number of organ systems involved and the variety of presenting complaints.¹ There are several models designed to help diagnose and classify GPA versus other rheumatologic, inflammatory, and vasculitic conditions. American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) hope to solve this issue by developing criteria for Diagnosis and Classification of Vasculitis Study (DCVAS).^{17,18} Miloslavsky et al¹⁹ showed that out of 365 patients analyzed, 273 (75%) had PR3-ANCA-positive GPA, 33 (9%) had MPO-ANCA-positive GPA, 15 (4%) had ANCA-negative GPA, and 44 (12%) had MPO-ANCA-positive MPA. MPO-ANCA-positive GPA patients were younger at diagnosis compared to MPO-ANCA-positive MPA patients (53 versus 61 years; $P = 0.02$). There are no unified criteria for diagnosis of GPA; however, these systems usually involve certain clinical features for making the diagnosis; (1) Laboratory data, such as

elevated inflammatory markers, presence of C-ANCA, Protease-3, and hematuria. (2) Evidence of disease process with inflammation and vasculitis involving classical organ systems including the sinuses (i.e. ulceration), lungs (i.e. X-ray findings), and kidneys (i.e. glomerulonephritis). (3) Pathological tissue samples with evidence of granulomatous processes.²⁰ These signs and symptoms have been described in our patient, uniquely, without evidence of renal involvement. It has been documented that over 90% of patients with GPA seek medical attention for upper and/or lower airways symptoms.¹⁸ Most are benign, however, the disease may progress to produce life threatening respiratory issues.²¹

Typical biopsy findings of GPA are not present in 50% of cases.⁹ Due to the small amount of tissue obtained in the mastoid process biopsy, nonspecific granulomatous tissue can be present on histopathology of sample, as was the case for our patient. However, the biopsy of the lung mass showed granulomatous inflammation and necrosis consistent with GPA. Biopsy results along with positive c-ANCA, positive Protease 3, and clinical symptoms combine to form a compelling argument for the diagnosis of GPA.^{19,22}

Sharma et al³ demonstrated that out of 105 patients with GPA studied, lungs (67.62%) and kidneys (51.43%) were most commonly involved, while ear involvement was present in 18.1%; 9 patients died despite being treated with appropriate antibiotics.³ This shows that GPA has high mortality even with optimal treatment. It was found that up to 82% of patients who were not treated died within the first year and up to 90% within 2 years, especially when there is a late multi-organ involvement.⁴ Although there is no curative treatment, there are several interventions available to manage symptoms and sequelae of disease. Steroids and immunosuppressive agents including Rituximab or cyclophosphamide play a role in optimal treatment and improve prognosis.²³ In cases involving otolaryngologic manifestations of GPA, studies show that patients treated with rituximab were significantly less likely to have active ENT disease compared with those not receiving rituximab.²³

In conclusion, diverse manifestations of GPA are important to be identified as each case may present with

a unique or otherwise innocuous complaint. Therefore, a high index of suspicion by internists and primary care physicians is warranted in refractory “infections” that are not responding to sensitivity directed antibiotic treatment as in our case. Fastidious work-up should be performed to diagnose GPA and look for other organ involvement such as lungs as in our patient. Early referrals to rheumatology can be done to improve prognosis of this disease.

Authors' Contribution

HQ and AK researched and analyzed the literature. In addition, were major contributors to writing and reviewing the article. MS contributed to writing the article. AC contributed to writing and reviewing the article. XT contributed by reviewing the literature and drafts of the article.

Conflict of Interest Disclosures

The authors of this paper have no conflicts of interests or disclosures.

Ethical Statement

Informed consent form was obtained from the patient for publishing this case report.

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