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A unique Presentation of Granulomatosis with Polyangiitis in a Patient of African-Caribbean Descent

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Abstract Herein, we present a case of limited granulomatosis with polyangiitis (GPA) with ocular/aural involvement and sparing of the visceral organs. This atypical constellation of symptoms was initially thought to have an infectious cause prior to repeat imaging and testing of immunological markers. The patient was of African-Caribbean descent, a population where the incidence of granulomatosis with polyangiitis is exceedingly uncommon. This case highlights a unique variant of GPA and emphasizes the importance of early clinical detection and treatment to prevent associated morbidity and mortality.

Keywords: *granulomatosis, polyangiitis, vasculitis, GPA, ocular, aural, ANCA*

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1. Introduction

Granulomatosis with polyangiitis (GPA, formerly known as Wegener's Granulomatosis) is an ANCA-associated vasculitis that affects small vessels and results in the formation of necrotizing granulomas. If this condition is not quickly recognized and treated with systemic immunosuppression, progression will result in death within 5 months on average [1]. The annual incidence is between 10-20 cases per one million people in European populations [2].

Classically, GPA targets primarily the sinuses, lungs and kidneys. We present a case of limited GPA with ocular/aural involvement and sparing of the visceral organs. Furthermore, the patient described in this report lacked classic sinus symptoms such as purulent nasal discharge and epistaxis. The patient was also of African-Caribbean descent, an ethnicity comprising roughly 3% of GPA cases [3].

2. Case Report

A 76 year old female presented to hospital with acute bilateral hearing loss, left sided vision loss and difficulties maintaining her balance. She communicated that her condition had initially started with unilateral hearing loss four days prior to admission, which was associated with both tinnitus and forehead pain. The patient had been assessed by a physician in the community and was treated with a cephalosporin for possible otitis media. After two days, her condition progressed to profound bilateral hearing loss with left-sided ocular symptoms. She experienced unilateral vision loss, ptosis and scleral erythema (Figure 1). One day prior to admission, she developed vertigo and difficulty maintaining her balance. The patient did not have cough, fever or rhinorrhea. Jaw pain associated with mastication consistent with temporal arteritis was not present. Although the patient endorsed a one week history of decreased appetite, she denied experiencing nausea or vomiting, significant weight loss or any other abdominal symptoms. She had not recently travelled.

Her medical history was significant for hypertension and ulcerative colitis, which was clinically quiescent with no recent flares. Her family history was non-contributory and she denied alcohol consumption, smoking or illicit drug use. She was of African-Caribbean descent over 30 years ago. Medications included amlodipine, atenolol, perindopril and 5-ASA. There were no known drug allergies.

In the emergency department, the patient's vital signs were normal. She was alert and oriented. Physical examination revealed left sided ptosis, mild protptosis and conjunctival erythema. There was mild peri-orbital tenderness. Neurological examination revealed limited extra-ocular movements of the left eye in all directions, alongside profound bilateral hearing loss. The remainder of her neurological examination was normal, revealing normal muscle bulk, tone, sensation, coordination, and symmetrical reflexes throughout. On speculum examination of the right ear, the tympanic membrane was perforated and pus was visible. Her tongue was coated in a white film and there were no other oral lesions. We noted the absence of temporal artery beading or forehead tenderness. Cardiovascular examination was normal. In addition, respiratory examination was normal with normal breath sounds bilaterally. The abdomen was non-distended, but she did have mild epigastric tenderness. No skin lesions were identified.

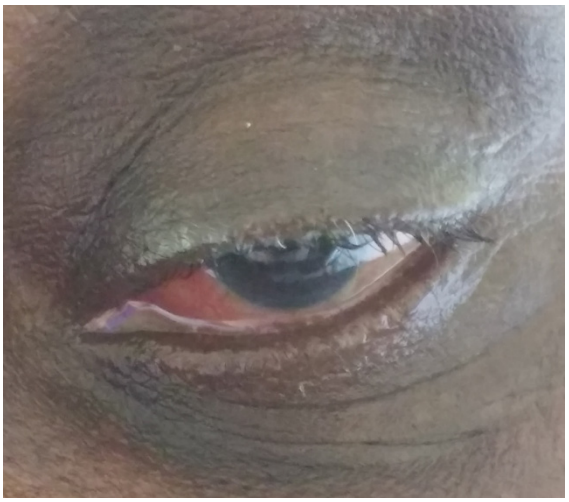

Figure 1. Appearance of the patient's ocular disease involvement after 2 days of high-dose immunosuppressive therapy

Laboratory tests revealed a leukocytosis with total leukocytes of 21.3 x $10e^9$/L, predominantly due to an elevation in neutrophils (16.19 x $10e^9$/L) alongside a monocytosis (1.7 x $10e^9$/L). No eosinophils were detected. Blood and urine cultures were negative for infection. There was an absence of protein on urinalysis and her creatinine was normal at 66 µmol/L. There was transaminase elevation with AST 83 IU/ml), ALT (53 IU/ml), ALP (267 IU/ml) and GGT (298 IU/ml). Bilirubin remained within normal limits.

The patient was treated initially with broad antibiotic coverage including piperacillin/tazobactam as well as vancomycin on suspicion of a severe sinusitis.

The patient's initial imaging helped characterize her unique presentation. Computed tomography of the brain and skull showed enlargement of the left inferior and medial rectus muscles with mild proptosis and inflammatory changes. Possible inflammatory changes were seen in the adjacent ethmoid air cells. Subsequent magnetic resonance imaging of the Head/Orbits showed left orbital scleritis with other findings suggestive of myositis of the rectus muscles within both orbits. Non-specific findings suggestive of inflammation were noted around the skull base. A CT of the thorax did not reveal any cavitary lesions or other pulmonary abnormalities. An abdominal ultrasound did not show any focal hepatic lesions to explain her liver enzyme elevation.

Initially, her CRP was found to be highly elevated at 416 mg/L while her ESR was 119 mm/hr. She had an elevated IgG level of 17.7g/L, which was predominantly found to be of the IgG1 subclass (12.1g/L). Serum ACE was undetectable. The patient was ANA-positive. Finally, she was found to have anti-PR3 (c-ANCA surrogate) of > 8.0 AI units, while her anti-MPO (p-ANCA surrogate) was negative at <0.2 AI units. Her positivity for c-ANCA, combined with her hearing loss, episcleritis, and sinus syndrome essentially confirmed the diagnosis of granulomatosis with polyangiitis. The patient was treated with high dose methylprednisolone (1000mg/day) for three days. She was then placed on a tapering course of prednisone and cyclophosphamide. Her left ocular symptoms improved markedly within the first week. In addition, she also experienced notable improvements in her ability to maintain her balance. Audiology testing revealed that the patient had profound conductive and sensorineural hearing loss. Her bilateral hearing loss did not show signs of improvement despite various efforts including intra-tympanic dexamethasone injections. The patient's laboratory parameters demonstrated resolution with a drop in her CRP, leukocyte count and liver enzyme elevation. An MRCP was performed and there were no signs of primary sclerosing cholangitis given her history of ulcerative colitis.

3. Discussion

We present a case of limited granulomatosis with polyangiitis. Its clinical presentation highlights the variable nature of this disease, which can present a diagnostic challenge. This patient was initially treated with antibiotics for a possible infectious cause due to her elevated white count, tympanic pus and apparent signs of inflammation within the sinuses and basal skull. However, the distribution and timing of her disease made an autoimmune cause a serious consideration. She had initially experienced unilateral hearing loss, progression to bilateral hearing loss as well as ocular involvement with alternating laterality between the two demonstrative imaging studies (computed tomography and magnetic resonance separated by several days). Therefore, a purely infectious cause was unlikely. Her diagnosis was essentially confirmed by c-ANCA positivity, which is 91% sensitive and 99% specific in patients presenting with active disease [4]. Clinical manifestations and ANCA serology diminish the need for a biopsy under the 2017 ACR/EMA Revised Criteria for Early Diagnosis of Granulomatosis with Polyangiitis as seen in Table 1 [5].

Table 1. The 2017 ACR/EMA Revised Criteria For Early Diagnosis of GPA and Scoring System

Clinical Parameters:	Test Result Parameters:
Nasal polyps: – 4	c-ANCA- or PR3-antibody positive: 5
Hearing loss/reduction: 1	Eosinophil count ≥1x109/L: – 3
Cartilagenous involvement: 2	Nodules, mass or cavitation on chest imaging: 2
Red or painful eyes: 1	Granuloma on biopsy: 3
Bloody nasal discharge, ulcers, crusting or sino-nasal congestion: 3	
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*Score of 5 or greater needed to diagnose GPA.

Previous cases of GPA causing otitis media, bilateral hearing loss and dizziness have been described, however these patients were often found to have underlying lung involvement [6,7,8]. Some evidence of ophthalmic involvement is also seen in over half of cases [9]. We noted that the patient had an elevation of all tested liver enzymes at the time of presentation with no hepatic abnormalities on imaging. Although AST elevation can be caused by myositis, her persistently elevated GGT was unexplained. Her liver synthetic function remained unchanged. A liver biopsy was considered but not undertaken. A study by Willeke et al., has shown that elevated liver enzymes are actually seen in 49% of GPA cases [10]. The authors found that high GGT levels in particular are associated with a longer time to remission.

GPA is an uncommon disease that primarily affects people from Northern Europe and is exceedingly rare in patients of African descent [3]. Genetic analysis has supported the theory that GPA has an underlying heritable component. African-Americans positive for c-ANCA had 73.3-fold higher odds of having a specific HLA-DRB1*15 allele compared to community-based controls. The possibility of familial genetic analysis for those affected by GPA is an emerging field.

Our case outlined management of ANCA-vasculitis with both corticosteroids and cyclophosphamide due to the rapidly progressive course. The patient was also initiated on trimethoprim/sulfamethoxazole several days into her course as prophylaxis against *Pneumocystis* infection. Coincidently, trimethoprim/sulfamethoxazole has also been trialed as a direct therapy for GPA in a variety of case reports [9,11,12,13]. Randomized-controlled trials have also shown that trimethoprim/sulfamethoxazole can prevent disease relapse [11,14,15]. Although the patient did experience significant resolution of her ocular symptoms, her hearing loss did not show any signs of improvement. However, we note that there have been previous cases of recovery of complete sensorineural hearing loss after several months of treatment [16]. In conclusion, it is our hope that this case may help illustrate an atypical presentation of GPA and aid clinicians in the future when considering this unusual constellation of symptoms.

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Statement of Interest

The authors do not have competing interests to declare.

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