CASE REPORT

Granulomatous with Polyangiitis (GPA) Presenting with Mononeuritis Multiplex: A Case-based Review.

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Abstract
Granulomatosis with polyangiitis (GPA), formerly known as Wegener's granulomatosis (WG), is a rare rheumatological disease that can affect individuals of any age. ANCA associated vasculitis (AAV) with granulomatous with polyangiitis proteinase 3 (GPA-PR3) is present in approximately 85-90% of cases. We report a 52-year-old Indian female with positive cytoplasmic-antineutrophil cytoplasmic antibody (c-ANCA) presented with chronic sinusitis, orbital cellulitis, and mononeuritis multiplex of the right foot and possible sensorineural defect hearing impairment.

Keywords: *c-ANCA, Granulomatosis with polyangiitis, Mononeuritis multiplex.*

Introduction

GPA is a type of vasculitis that falls under the category AAV. AAV is characterized by a loss of tolerance to neutrophil primary granule proteins, such as leukocyte proteinase 3 (PR3) or myeloperoxidase (MPO), leading to the production of autoantibodies [1]. These autoantibodies cause severe inflammation in small blood vessels, resulting in endothelial injury and tissue damage. There are three types of AAV classified according to 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides (CHCC): granulomatosis with polyangiitis (GPA), formerly known as Wegener's granulomatosis; microscopic polyangiitis (MPA); and eosinophilic granulomatosis with polyangiitis (EGPA), formerly known as Churg-Strauss syndrome [2,3]. A study in Asia found that the mean age for GPA diagnosis among Indians is 40 years, with most cases being PR3-positive, a higher prevalence compared to countries like China, Korea, and Japan [4]. As far as our literature search, we found that this is the first case of GPA with mononeuritis multiplex encountered in Malaysia.

Case report

A 52-year-old Indian female with a history of hypothyroidism (post-total thyroidectomy in 2006), and recurrent chronic sinusitis (underwent Functional Endoscopic Sinus Surgery in 2024 (FESS) and multiple sinus washouts) presented with a one-month history of numbness, paresthesia, and asymmetric distal weakness in her right foot, without any bladder or bowel involvement. She remains ambulatory with the aid of a walking aid, and her upper limbs are unaffected. Additionally, she has experienced a reduced appetite and a five-kilogram weight loss over the past three months, along with recent loose stools for two weeks. She has an intermittent fever without chills or rigor, and a productive cough with yellowish sputum for one week. Otherwise, there are no associated symptoms such as runny nose, sore throat, allergy, asthma, tinnitus, epistaxis, anosmia, hyposmia, foul-smelling nasal discharge, facial pain, hemoptysis, chest pain, palpitations, dyspnea, abdominal pain, rectal bleeding, headache, seizures, dysuria, hematuria, oral ulcers, or malar rash.

The patient has also had a hearing impairment, predominantly on the left side, since January 2024. In February 2024, she developed bilateral eye weakness lasting for one week, accompanied by minimal eye discharge, left facial pain, and headache. A Computer Tomography (CT) scan of the orbit and paranasal sinuses revealed left orbital cellulitis with a subperiosteal abscess secondary to chronic sinusitis. She was treated with intravenous (IV) ceftazidime 1g three times a day for one week and was referred for surgical drainage and a lacrimal gland biopsy. Unfortunately, we were unable to retrieve her biopsy results.

Neurological examination revealed a right-sided foot drop with dorsiflexion and plantar flexion power of 3/5 following the Medical Research Council's scale (MRCS). There was decreased sensation up to knee (L4, L5) to touch, pain, and temperature in the right foot. The left foot had normal power, tone, and sensation. However, other systemic examinations were unremarkable.

Laboratory investigations revealed progressive microcytic hypochromic anemia (Hb range from 7.2 to 7.8 g/dL, MCV 74.5, MCH 13.1), elevated white cell count (17.1 x 10^9/L) with a normal eosinophil count (0.01 x 10^9/L) and normal platelet levels (409 x 10^9/L). Renal and liver function tests were normal, except for low albumin (19 mg/dL). C-reactive protein (CRP) was elevated, 346.9 mg/dL (normal < 5mg/dL). c-ANCA (PR3-ANCA) was strongly positive, 317.4 CU (normal <20 CU), while MPO was negative, 9.1 CU (normal <20 CU). The other serologic tests were negative for antinuclear

antibody (ANA), anti-double stranded DNA (anti-dsDNA), extractable nuclear antigen (ENA) and complement factors. Septic workups were negative except for sputum culture, which yielded *Pseudomonas aeruginosa*. Urine tests showed traces of leukocytes, protein, and blood, with urine red blood cell casts being negative. The electrocardiogram (ECG) and echocardiogram were normal. Plain chest radiograph was normal, and computed tomography (CT) of the abdomen and pelvis showed no significant findings. However, nerve conduction studies were not available.

Based on her clinical presentation and investigations, she was diagnosed with mononeuritis multiplex secondary to positive PR3-ANCA GPA. Due to the element of a concurrent respiratory infection, she was commenced on intravenous tazocin and hydrocortisone 8 hourly for a week. Once the infection was under control, she subsequently underwent induction therapy with intravenous methylprednisolone (MP) 500mg daily for five days and pulse IV cyclophosphamide (CYC) 750 mg/m^2 monthly (planned for 6 months) after completing IV tazosin 4.5g daily for one week. She was also prescribed with oral mecobalamin 500 mg 8 hourly and oral gabapentin 300 mg twice daily. She showed improvement in her right foot drop symptoms after 2 months of IV CYC.

Discussion

Granulomatous with polyangiitis (formerly known as Wegener's granulomatosis) is a rare vasculitis characterized by necrotizing small-to-medium size vessels and classified into three spectrums of AAV phenotypes i.e., GPA, MPA, EGPA [2]. GPA-PR3 positive is present in approximately 85-90% of the cases and typically presents in individuals aged 45-65, with no significant gender difference [5]. GPA primarily affects the upper respiratory tract, pulmonary and renal. It can be classified by granulomatous manifestations (involving the ear, nose, throat, lung, orbital, and pachymeningitis) that tend to relapse, or vasculitic manifestations (granulomatosis, alveolar hemorrhage, scleritis or mononeuritis multiplex), which are associated with higher mortality rates [4]. Table 1 shows types of AAV with a vast spectrum of clinical manifestations reported in Malaysia to date [6-15].

Although in general, neurologic involvement in GPA is uncommon, the peripheral nervous system (sensorimotor polyneuropathy or mononeuritis multiplex) is commonly affected compared to central nervous system [18,19]. Mononeuritis multiplex often involves nerves such as the peroneal, tibial, ulnar, and median nerves, due to inflammation of the vasa nervorum, which leads to ischemia and subsequent axonal degeneration. Mononeuritis multiplex has been reported commonly in EGPA patients, in contrast to our patient with GPA [6,7,9,10,11].

In 90% of cases, patients present with ear, nose, and throat symptoms due to granuloma infiltration from the paranasal sinus. For nasal and paranasal regions, chronic rhinosinusitis occurs in approximately 50% of cases, often accompanied by crust formation, serosanguinous discharge, septal perforation, and saddle nose deformity [17]. This patient had similar symptoms of chronic recurrent sinusitis and underwent FESS and multiple washouts within a year, eventually leading to orbital cellulitis.

Orbital symptoms occur in 45% of GPA patients and typically manifest as episcleritis, orbital cellulitis, and orbital pseudotumor due to granuloma infiltration, though visual loss from nerve compression is rare [18]. Additionally, the lacrimal gland may be affected, often unilaterally, leading to orbital symptoms such as orbital pain, eyelid swelling, proptosis, dacryocystitis, and limited extraocular movement [20]. This patient also presented with orbital pain and minimal eye discharge and was treated for left orbital cellulitis

with a subperiosteal abscess, which was resolved after administration of IV ceftazidime.

Ear involvement occurs in 20-25% of GPA cases and is often secondary to nasal involvement. Patients may present with otitis media, conductive, sensorineural, or mixed hearing loss, as well as vertigo or facial nerve palsy. Conductive hearing loss is more common, typically resulting from granuloma formation that damages the middle ear, whereas sensorineural hearing loss is due to vasculitis [20]. This otologic involvement mirrors our patient's condition, as she has experienced hearing loss on the left side for approximately eight months, though no audiology assessment has been conducted yet.

Throat involvement in GPA is rare compared to ear and nose symptoms, but patients can still present with conditions such as strawberry gingival hyperplasia, ulcerative stomatitis, labial mucosa nodules, or parotid gland enlargement, making the diagnosis challenging [18]. Lung manifestations occur in approximately 90% of cases, with symptoms including cough, dyspnea, and chest pain, and are often seen on chest radiographs as pulmonary nodules or cavitations [18]. Cardiac involvement is also uncommon, occurring in 6-30% of cases, with potential presentations including pericarditis, pericardial effusion, non-infectious endocarditis, myocardial ischemia, and cardiomyopathy [16]. Necrotizing glomerulonephritis is associated with a poor prognosis in GPA patients, presenting with hematuria, proteinuria, edema, decreased urine output, and rapid progressive renal deterioration [16]. However, this patient did not show manifestations in any of the aforementioned systems.

This patient's constitutional symptoms, i.e., loss of appetite, weight loss, and loose stools, may suggest either GPA-related gastrointestinal involvement or another condition. Gastrointestinal manifestations in GPA are typically less specific and can include abdominal pain, diarrhea, and ulceration that mimic inflammatory bowel disease or polyarteritis nodosa (PAN), along with hemorrhage and bowel ischemia secondary to mesenteric vasculitis.[16] These specific symptoms were not observed in this case, although anaemia was noted.

Other non-specific symptoms like fever, anorexia, malaise, weight loss, and muscle pain, which persist for weeks and months, may be mistaken for infections, malignancies, or inflammatory joint diseases if specific organ involvement is not evident. However, if the patient ANCA is positive and involves specific organ systems, GPA should be suspected [19].

Currently, there is no standardized treatment protocol for GPA; however, most institutions utilize immunosuppressive therapies, which have demonstrated a 5-year survival rate of 70-80% [1]. Management of GPA generally involves two phases: the remission induction phase, lasting 3–6 months, typically involves glucocorticoids combined with either cyclophosphamide or rituximab. This is followed by the maintenance phase, which lasts 2–3 years and aims to prevent disease relapse with low-dose glucocorticoids and either rituximab, azathioprine, methotrexate, or mycophenolate mofetil [21,22]. Neuropathic pain management options include tricyclic antidepressants (such as amitriptyline and nortriptyline), serotonin and norepinephrine reuptake inhibitors (SNRIs) like duloxetine and venlafaxine, or antiepileptics (such as gabapentin and pregabalin) [5].

Conclusion

GPA, a subtype of AAV, typically affects the ear, nose, throat, lung, and kidney (ELK) systems and rarely involves neurological manifestations such as mononeuritis multiplex. It should be suspected if these symptoms are present in patients with bronchial asthma and chronic sinusitis with or without other manifestations. The diagnosis of GPA in this patient is probably anticipated earlier

when sinus washout and biopsy were done where histopathological findings may prognosticate the condition. Induction treatment with high dose corticosteroids in combination with pulse CYC may induce remission of GPA followed by maintenance low-dose corticosteroid and longer duration of treatment for 18-24 months may prevent or reduce relapse [23].

Conflict of interest and financial disclosures
None.

Informed Consent
Written informed consent was obtained from the patient for the publication of this report.

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Authors contribution
NAS: data collection, and manuscript writing; WS: Ideas and review of the manuscript.

Table 1. Cases on various types of AAV reported in Malaysia.

Study	Age;sex	Type of AAV	Clinical features	Immune markers and other lab results	Treatment	outcome
Loke *et al*, 1998 [6]	35;F	GPA (WA)	Rt eye uveitis, nasal discharge, LOW, cough, haematuria, dysphagia, hoarseness of voice. (Lt X and XI cranial nerves palsies.) Nasal septum Bx: chronic inflammation with necrotizing vasculitis. Cavitating lung lesion	ANCA – NA	CYC, P	NA
Tan *et al*, 2010 [7]	40;F	EGPA (CSS)	BA, leukocytoclastic vasculitis (skin Bx), Non-healing ulcer Mononeuritis multiplex (NCS)	p-ANCA +ve; Leukocytosis with raised Eos	MP, P, CYC	Residual sensory and motor neuropathy
Tang *et al*, 2010 [8]	39;F	GPA (WA)	multiple non healing ulcers - left face, Rt thigh and both shins and nasal septum; mixed hearing loss, otitis media and chronic sinusitis skin Bx: granuloma with multinucleated giant cells and inflammatory cells	c-ANCA +ve	Declined treatment	Died (pulmonary hemorrhage)
Abdullah *et al*, 2014 [9]	45;M	EGPA	Bronchial asthma; Recurrent Mononeuritis multiplex – both feet and Lt hand (Lt foot drop); Lung: upper zones fibrosis	ANCA -ve; Leukocytosis with predominant Eos.	P, AZA CYC	Remission (with CYC)
Sulaiman *et al*, 2014 [10]	50;M	EGPA	Late onset BA, cough, allergic rhinitis, vasculitis ACS, peripheral neuropathy/mononeuritis multiplex (foot drops) COROS: normal Skin Bx: leukocytoclastic vasculitis with eosinophilic infiltration	ANCA -ve; Raised CKMB and LDH Leukocytosis with raised Eos.	MP, AZA, CYC	Remission
Mohammad *et al*, 2017 [11]	28;F	EGPA	BA, polyarthritis, fever, Mononeuritis multiplex (bilateral wrist drops) NCS: axonal polyneuropathy	p-ANCA+ve, MPO+ve; raised Eos	CYC, P,MTX SABA for BA	Remission
Ang *et al*, 2018 [12]	49;F	GPA	ESRF, epistaxis, hemoptysis, protopsis	p-ANCA +ve	AZA, P CYC (planned)	NA
Anthony *et al*, 2019 [13]	62;F	GPA	Cough, LOW. Lung Bx: necrotizing granulomatous inflammation	c-ANCA+ve, anti-PR3+v3	MTX, P	Remission within 3 months
Sulaiman *et al*, 2019 [14]	15;M	EGPA	Cutaneous vasculitis (skin Bx); no systemic symptoms or signs	ANCA -ve, leukocytosis with raised Eos.; IgE elevated	P, AZA	Remission
Sulaiman *et al*, 2021 [15]	81;F	MPA	Lower limbs weakness; purpuric vesicular lesions on lower limbs; multiple and extensive perforated ischemic bowels. Skin Bx: bullous vasculitis	p-ANCA +ve, MPO+ve, ANA+ve homogenous, anti-dsDNA +ve, low C3,C4	MP, CYC, laparotomy	Died
This case	52;F	MPA	Fever, Chronic sinusitis, mononeuritis multiplex (Rt foot drop), hearing impairment, orbital cellulitis	c-ANCA +ve, MPO +ve	MP, P	Foot drop improving

AAV, ANCA associated vasculitis; F, female; M, male;+ve, positive; -ve, negative; ESRF, end stage renal failure; p-, perinuclear; c-cytoplasmic; GPA, granulomatous polyangiitis; WA, Wegener's granulomatosis; EGPA, eosinophilic granulomatous polyangiitis; CSS, Churg-Strauss syndrome; MPA, microscopic polyangiitis; P, prednisolone; AZA, azathioprine; CYC, cyclophosphamide; MP, methylprednisolone; MTX, methotrexate; BA, bronchial asthma; NCS, nerve conduction study; MPO, myeloperoxidase; SABA, short active bronchodilator agent; ACS, acute coronary syndrome; COROS, coronary angiography; LOW, loss of weight; Bx, biopsy; Eos, eosinophils; Rt, right; Lt, left; NA, not available.

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