



Systemic Clinical Manifestations and Treatment of Granulomatosis with Polyangiitis: A Case Report

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ABSTRACT

Granulomatosis with polyangiitis (GPA) is a granulomatous disorder linked with systemic necrotizing vasculitis with varied initial manifestations. We describe a case of a 49-year-old Malay female patient who gradually developed more symptoms of GPA over the past 14 years. This case emphasizes early detection and optimal treatment to minimize any further complications of GPA.

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Introduction

Granulomatosis with polyangiitis (GPA), formerly known as Wegener's granulomatosis (WG), is an uncommon systemic autoimmune inflammatory disorder characterized by a classic Wegener's triad of ELK (ear, nose, and throat; lung; kidney) manifestations (1,2).

WG was named after Dr Friedrich Wegener, a German pathologist. Later, professional bodies have replaced WG with a descriptive name, which is GPA. However, the term WG is still extensively used in literature, interchangeably with GPA (1). As the name suggests, GPA is a type of ANCA-associated vasculitis (AAV) in which the manifestation of the disease involves inflammation of arteries and veins that limits the flow to vital organs, hence causing damages (2). The disease is uncommon (0.4 per 100,000 people globally) but is slightly more

common among Caucasians (3 per 100,000 people in the United States) (3). In Malaysia, GPA is extremely rare and there is no local literature except a case report in 1998 (2). A case of 13 years of undiagnosed GPA with severe systemic clinical manifestations and acute treatment of GPA are presented.

Case presentation

A 49-year-old Malay female patient, with known cases of hypertension and near end-stage renal failure (ESRF), was admitted to our female medical ward from rheumatology clinic. She was presented with bilateral pitting edema of the lower limbs up to the knees. She had repeated epistaxis and hemoptysis in the past four months and intermittently for the past seven years.

Thirteen years ago, she had a right eye proptosis. A biopsy was conducted and it showed non-malignancy. Both computed tomography (CT) and magnetic resonance imaging (MRI) orbit two years ago showed superolateral orbital lesion with calcification in the right eye. A repeated

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biopsy of conjunctival tissue eight months ago showed chronic inflammation in which our ophthalmologist suspected quiescent GPA. Her perinuclear anti-neutrophil cytoplasmic antibody (p-ANCA) was positive ten months ago.

She was on azathioprine 50mg/d and prednisolone 20mg/d for her GPA prior admission. She was also on felodipine 10mg od, metoprolol 100mg/bd, prazosin 1mg tds for her hypertension, calcium carbonate 500mg/bd, calcitriol 0.25mcg/d, pantoprazole 40mg/d in addition to ferrous fumarate 200mg/d, vitamin B complex I/I/d and folic acid 5mg/d as hematinics. On admission, she had a blood pressure of 160/99 mmHg. Otherwise, her other vital signs were normal. Her current admission diagnosis was the active disease state of GPA with renal and hematological involvements. She had anemia and thrombocytopenia (Table 1). Hence, azathioprine was discontinued in view of thrombocytopenia. However, her platelet count continued to drop: two pints of packed cell and platelets were given daily. Her oral prednisolone dose was increased to 25mg/d for two weeks for the treatment of GPA. Her urine full examination (FEME) showed 3+ red blood cells (RBC), a high urea and serum creatinine (SCr) (Table 1). Hence, renal replacement therapy (RRT) orientation had been conducted and she opted for continuous ambulatory peritoneal dialysis (CAPD).

She was given intravenous (IV) amoxicillin/clavulanic acid 1.2g bd for 11 days and oral azithromycin 500mg/d for the first three days of admission as an empirical treatment for community-acquired pneumonia (CAP) since her chest X-ray showed right lower zone consolidation. She was on syrup nyastatin 500,000IU qid for esophageal candidiasis. The patient was administered IV furosemide 40mg/d for the treatment of lower limb edema and oral calcium polystyrene sulfonate 10mg tds for the treatment of hyperkalemia for the first five days of admission (Table 1). IV pantoprazole 40mg/d was given for the treatment of multiple nodular erosions on the oesophagus. She continued her regular antihypertensive in this admission. On day 15 of admission, she was discharged with her regular antihypertensive, hematinic, pantoprazole, calcium carbonate and calcitriol. Her prednisolone dose was tapered down to 20mg/d for two weeks. She was planned for cyclophosphamide if there was no evidence of ongoing infection in the next nephrology clinic visit.

Discussion

Despite the classical Wegener's triad, ocular manifestations may be the initial presentation in 8–16% of GPA patients. The diagnosis is often difficult as the presentation overlaps with other ocular inflammatory diseases. The mean age at diagnosis is around 40 years old (3). Our patient showed signs and clinical manifestations at the age of 35 but was only diagnosed at the age of 48.

For GPA, ocular involvement may be the sole clinical presentation prior to systemic symptoms (4). Common ocular presentations of proptosis and orbital pseudotumor are believed to be the result of the contiguous spread of long-standing granulomatous sinusitis (4). Inflammatory eye involvement over the entire course of GPA occurs in 30–60% of cases (2,4).

Untreated GPA carries a dismal prognosis, with up to 90% of patients dying within two years, usually of respiratory or renal failure. Even a non-renal GPA carries a mortality rate of up to 40% (1). A positive p-ANCA result only suggests 15–25% sensitivity of diagnosing GPA (1). The diagnosis is still manifestation-dependent based on Wegener's triad (1,3): for otorhinolaryngology manifestation, epistaxis has 11% sensitivity of diagnosing GPA.; for pulmonary manifestation, she suffered episodes of hemoptysis, which has an 18% sensitivity of diagnosing GPA; for renal manifestation, crescentic necrotizing glomerulonephritis characterized by urinary sediment with more than five RBCs per high power field (HPF) or erythrocyte casts suggesting a high sensitivity of diagnosing GPA. Her urine phase contrast two months ago showed the presence of 0-2 dysmorphic RBC per HPF. Renal disease is present in 17% of patients with the initial diagnosis and is usually asymptomatic. Renal failure occurs in 11% of patients at presentation (4).

The American College of Rheumatology (ACR) had developed four classification criteria for GPA which had a sensitivity of 88% and a specificity of 92% (5). The first criterion is the development of oral ulcers, epistaxis or purulent nasal discharge, which she had oral ulcers in this admission and episodes of epistaxis in previous years. The second criterion is for chest radiograph to show nodules, fixed infiltrates or cavities. From high resolution computed tomography (HRCT) of the thorax in a month prior current admission, there was a cavitating lesion at the right upper lobe measuring at 11cm. The third criterion is for urine analysis to show microscopic haematuria or red cell casts, which the patient fulfilled as mentioned in her renal manifestations. The fourth criterion is for histological examination to show granulomatous inflammation in the wall of an artery or in the perivascular area (characteristically necrotizing), but was not conducted in this patient. The patient hit three out of four of the main criteria set by ACR to be diagnosed as GPA (5).

The first-line induction regime for GPA is cyclophosphamide and prednisolone. This is supported by the European Vasculitis Study Group (EUVAS) in the two landmark studies: pulse vs. daily oral cyclophosphamide in ANCA-associated vasculitis (CYCLOPS) (6) and cyclophosphamide vs azathioprine for early remission phase of vasculitis (CYCAZAREM) (7). For induction regimen based on CYCLOPS study, remission is defined as the absence of new or worse signs of disease activity

on Birmingham Vasculitis Activity Score (BVAS) and no more than one item indicating persistent disease activity (BVAS \leq 1). Oral corticosteroid of 1 mg/kg/day and IV cyclophosphamide of 15 mg/kg are initiated two-weekly for three cycles, and then IV cyclophosphamide 15mg/kg pulse three-weekly or 2mg/kg/d daily orally until remission. This regimen is continued for three more months after remission (consolidation phase) (6). On the next clinic visit, our patient would be started on cyclophosphamide since she had a relapse of GPA.

For maintenance regimen based on CYCAZAREM study, azathioprine was used as maintenance of remission with fewer side effects (7). Azathioprine should start at 2mg/kg/d for 18 months (reduced to 1.5mg/kg/d at 1 year from the time of initiation of continuous cyclophosphamide induction therapy). Prednisolone is given at 10mg/d until one year, then 7.5mg/d until month 18. Methotrexate (EUVAS-NORAM & French Vasculitis Study Group (FVSG)–WEGENT could be used as an alternative to azathioprine (8, 9).

The advent of cytotoxic treatment has transformed GPA from a commonly fatal disease to a manageable chronic relapsing-remitting disease. Although there has been a marked improvement in the prognosis, drug-related toxicity and disease recurrence are still prevalent in GPA (10). Monoclonal antibodies targeting B cells such as rituximab has been widely used in treating AAV but it is not widely available in the Ministry of Health Malaysia facilities. Two randomized clinical trials (11, 12) have shown that rituximab is not inferior to cyclophosphamide for the induction of remission, and is superior to cyclophosphamide in relapsed patients in severe GPA. However, the use of rituximab in severely ill patients, especially those with renal impairment and on dialysis requires further study (10).

Granulomatosis with polyangiitis (GPA) is a multisystem disease that requires a multidisciplinary approach in treating the patients, which involves rheumatologists, pulmonologists, ophthalmologists, otolaryngologists, nephrologists (depending on the first clinical manifestation), nurses and pharmacists. Early diagnosis and treatment, including immunosuppression,

antimicrobial therapy, normalization of hematological and renal parameters, are important in managing the patient successfully.

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