

## Eosinophilic Granulomatosis with Polyangitis (EGPA) with unilateral foot drop

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### Abstract

Eosinophilic Granulomatosis with Polyangitis (EGPA), previously known as Churg-Strauss Syndrome (CSS), is rare vasculitis affecting small to medium sized vessels characterized by granulomatous inflammation with eosinophilia. We report a case of a 45 year old lady with background of late onset uncontrolled bronchial asthma, who presented with isolated left foot drop and subsequently developed purpuric rashes and was diagnosed with EGPA. She was started on immunosuppressive therapy and attained full clinical remission. This case highlights the importance of considering EGPA as part of differential diagnosis, among adult patients presenting with unexplained mono or polyneuropathy.

### Keywords

Eosinophilic granulomatosis with polyangitis; foot drop; bronchial asthma; mononeuritis multiplex; churg-strauss; anca; vasculitis

### Introduction

Eosinophilic Granulomatosis with Polyangitis (EGPA), previously known as Churg Strauss syndrome is an Antineutrophil Cytoplasmic Antibody (ANCA) associated vasculitis affecting small to medium sized vessels. It has a predilection to affect blood vessels of the lungs, gastrointestinal system, heart, skin, kidney and peripheral nerves. Here we describe a patient presenting with isolated left foot drop, initially attributed to prolapsed intervertebral disc with nerve root compression. She subsequently developed purpuric rashes prompting a differential diagnosis of vasculitis and was diagnosed as EGPA. She attained full neurological recovery with immunosuppressive therapy.

### Case report

A 45 year-old lady of Malay descent, presented to the emergency department with acute onset of

left lower limb numbness and weakness of 1 week duration and was admitted under orthopaedics. She had no history of back pain, trauma or radicular pain. No history of fever or constitutional symptoms. She had underlying late onset uncontrolled bronchial asthma for the past 11 years, with history of recurrent hospitalization and frequent exacerbations. She also had allergic rhinitis and sinusitis under ENT follow up.

On clinical examination, she had lower motor neuron type of left lower limb distal weakness, evidenced by hypotonia, proximal power left hip 5/5, left knee extension (0/5), knee flexion (0/5), dorsi flexion (0/5), plantar flexion (0/5) and toes (0/5). Knee and ankle reflexes were normal 2+. Sensation was reduced 1/2 over left L4, L5, S1 dermatomes with babinski flexor plantar response. Proprioception was normal. Straight leg raising test was negative. Right lower limb examination and bilateral upper limbs examination were normal. She had no spinal tenderness or deformity. Cranial nerves were normal, with no cerebellar signs and no sphincter disturbances. An initial impression of acute prolapsed intervertebral disc with L5/S1 compression and radiculopathy was made, leading to her admission under orthopaedics. MRI lumbosacral spine was done, which revealed lumbar spondylosis with diffuse disc bulge over L3/L4 and L5/S1 levels, however there was no spinal canal stenosis and both neural foramina and exiting nerve roots were preserved. Patient was able to ambulate with walking aid and she was subsequently discharged home with outpatient physiotherapy and a scheduled follow up visit in orthopaedics clinic.

However, she presented 1 week later to the emergency department with complaints of nonspecific diffuse abdominal pain, nausea, multiple episodes vomiting and non-bloody diarrhoea of 4 days duration. There was no history suggestive of food poisoning. No prior history of prolonged fever, weight loss, night sweats, arthritis, oral ulcers, skin lesion or other connective tissue disease symptoms. Vital signs on admission BP 115/73mmHg, pulse rate 90 beats per minute, respiratory rate 16 breaths per minute, oxygen saturation 96% on room air and temperature 37.1oC. The neurological examination findings remained the same as her previous admission. Her abdomen was soft, non tender, no hepatosplenomegaly with normal bowel sounds. Other examination findings were unremarkable. She was admitted to medical department with preliminary diagnosis of acute gastroenteritis. On day 2 of admission she developed new multiple erythematous papulo purpuric skin lesions over palms, extensor surface of elbows, trunk, upper and lower limbs (Figure 1).





Blood investigations revealed leukocytosis (WBC  $13.7 \times 10^9 /L$ ) with predominant eosinophilia (35%), elevated erythrocyte sedimentation rate (ESR) 76mm/hr and elevated C-reactive protein (CRP) 71.96 mg/L with positive cytoplasmic antineutrophil cytoplasmic antibodies (p-ANCA). Our laboratory assay did not include specificity of p-ANCA for MPO.

Additional laboratory results included Haemoglobin 12.0 g/dl, platelets  $451 \times 10^9/L$ , renal and liver function tests were normal. HIV, Hepatitis B and C serology, antinuclear antibody (ANA), Rheumatoid Factor (RF) and c-ANCA were all negative. Urinalysis revealed no protein or hematuria. Chest radiograph showed clear lung fields. The electrocardiograph showed normal sinus rhythm, with no ischaemic changes.

Skin biopsy done revealed oedematous dermis with neutrophilic infiltrate, karyorrhectic debris within the vessels wall and features consistent with leucocytoclastic vasculitis.

The possibility of left lower limb distal mixed sensory motor deficits occurring due to mononeuritis multiplex was considered. Nerve conduction study was done which confirmed multiple mononeuropathy with sensorimotor axonal loss without demyelination suggestive of mononeuritis multiplex pattern.

In view of presence of vasculitic rash, peripheral eosinophilia, underlying uncontrolled bronchial asthma with p-ANCA positivity, a clinical diagnosis of EGPA with mononeuritis multiplex was made. Her gastrointestinal symptoms of vomiting, diarrhoea and abdominal pain was presumed to be due to eosinophilic gastroenteritis which is seen in EGPA. Her stool culture, ova and cyst were negative.

Patient was pulsed with intravenous methylprednisolone 500mg daily for 3 days, and subsequently put on 1mg/kg of oral prednisolone. She was given 6 cycles of intravenous cyclophosphamide 15mg/kg at 2 weekly intervals for the first 3 cycles, and then at 3 weekly intervals for the remaining 3 cycles, in accordance to EUVAS protocol. Her vasculitic rashes subsided within a month, during follow up clinic review. At the end of 3rd month of therapy, patient regained full neurological function of left lower limb, motor first followed by sensory last. Oral Azathioprine 100mg daily (2mg/kg) was added as remission maintenance agent and prednisolone was gradually tapered. She remained asymptomatic during subsequent follow ups, BVAS score of 0, with no recurrence of symptoms over the next 12 months. Her eosinophil counts and inflammatory markers normalized within 3 month of cyclophosphamide therapy and remained suppressed throughout her follow up.

## Discussion

The worldwide incidence of EGPA is estimated to be 2.5 cases per 100,000 adults per year [1]. The exact incidence is unknown in Malaysia. Most patients are between the ages of 40-60 years. Major clinical features include nervous system (60-70%) mononeuritis multiplex, rarely cranial nerves and central nervous system involvement; skin (50%) subcutaneous nodules, petechiae, purpura; joints (50%) arthralgia, arthritis; lungs, asthma transient migratory pulmonary infiltrates, interstitial lung disease, pulmonary haemorrhage; gastrointestinal, eosinophilic gastroenteritis; paranasal sinus, rhinitis, sinusitis and miscellaneous, cardiac and renal failure.

EGPA typically has three clinical phases with varying intervals ranging months to years, however may also appear simultaneously. The prodromal phase consists of allergic manifestations commonly asthma and rhinitis. This is followed by peripheral eosinophilia or tissue infiltration phase and finally the systemic vasculitis phase. The diagnosis of EGPA relies on a high index of clinical suspicion, when a patient with previous history of allergy or asthma, presents with peripheral eosinophilia and evidence of systemic vasculitis.

In 1990, the American College of Rheumatology (ACR) proposed the following 6 criteria for the diagnosis of EGPA [3]

- Asthma (wheezing, expiratory rhonchi)
- Eosinophilia > 10% in peripheral blood
- Paranasal sinusitis
- Pulmonary infiltrates (may be transient)
- Histological proof of vasculitis with extravascular eosinophils
- Mononeuritis multiplex or polyneuropathy

The presence of 4 or more criteria yields a sensitivity of 85% and a specificity of 99.7%. This patient fulfilled 5 out of the 6 criteria.

Our patient had underlying late onset bronchial asthma since age 34 for 11 years. She had no family history of atopy or bronchial asthma. Her asthma was uncontrolled with frequent exacerbations and multiple hospitalizations, up to 4 times per year. No prior history of intubation or intensive care admission. She was on regular Symbicort turbuhaler (budesonide and formoterol) and also under ENT follow up for her recurrent sinusitis. Although patients with EGPA may have transient non-fixed pulmonary infiltrates, our patient's serial chest radiographs had no parenchymal changes.

Vasculitic neuropathy results from inflammation involving the vasa nervorum and should be suspected when a patient presents with acute onset of pain, paraesthesia or weakness involving one or

more peripheral nerves distribution, in the absence of trauma. The best known pattern of presentation of vasculitic neuropathy is mononeuritis multiplex; which is defined as sensory loss, weakness or both in two or more separate peripheral nerves distribution. Most common systemic vasculitis associated with vasculitic neuropathy are polyarteritis nodosa, microscopic polyangiitis, EGPA, granulomatous with polyangiitis and mixed cryoglobulinaemia.

The diagnosis of vasculitic neuropathy was almost missed in our patient as her foot drop was initially attributed to prolapsed intervertebral disc and radiculopathy, despite patient did not have any history of back pain and the presence of disc bulge at L3/L4 and L5/S1 levels were probably a red herring. This case highlights the importance of further investigation to seek the etiology in patients presenting with unexplained polyneuropathy, especially in the absence of trauma or back pain.

Occasionally sciatic nerve vasculitic neuropathy can produce radicular pain with positive straight leg raising test. Other causes for foot drop include anterior horn cell disease like motor neuron disease, poliomyelitis; nerve root lesions due to disc herniation usually at L4-L5 or L5-S1, meningeal carcinomatosis; cauda equina/lumbar plexus lesion due to metastasis and peroneal nerve lesion due to trauma, diabetes and leprosy.

It is highly likely that our patient also had eosinophilic gastroenteritis as part of her disease manifestation with symptoms of abdominal pain, vomiting and non bloody diarrhoea. Vasculitis affecting gastrointestinal tract may also cause abdominal pain due to mesenteric arteritis, and may be complicated with gastrointestinal ischaemia, infarction, ulceration, perforation and haemorrhage.

Purpuric rashes are an important clue in the suspicion of small vessel vasculitis. The presence of leucocytoclastic vasculitis based on biopsy, was cornerstone in making our diagnosis. Some patients with EGPA can also have subcutaneous nodules, also known as cutaneous extravascular necrotizing granulomas.

Cardiac involvement has been reported in 15% to 52% of patients with EGPA. Fortunately our patient did not have any evidence of cardiac involvement. It may present as eosinophilic myocarditis, myocardial infarction due to vasculitis of coronary arteries, arrhythmias, pericarditis, pericardial effusion or valvular defects. ECG changes can be nonspecific.

Less than 25% of EGPA cases have renal involvement, which ranges from isolated urinary abnormalities to rapidly progressive glomerulonephritis. Our patient did not have any evidence of renal involvement with normal renal function and urinalysis.

It is important to note that the presence of p-ANCA in our patient would not have altered our diagnosis. This is because EGPA has lower tendency to have ANCA positivity as compared to GPA and MPA. The incidence of p-ANCA in EGPA is only about 30-40%. Hence, it is worth remembering that a negative ANCA does not exclude the diagnosis of vasculitis. The presence of ANCA positivity in EGPA may be associated with higher risk to develop renal disease, alveolar haemorrhage, mononeuritis multiplex and purpura.

The principle of management of EGPA and as well as other ANCA associated vasculitis revolves around induction of remission and remission maintenance. Choice of remission induction agents are cyclophosphamide or rituximab, combined with glucocorticoids. Plasmapheresis may be considered as an adjunct in refractory or life threatening cases, especially in the setting of diffuse alveolar haemorrhage or renal failure with creatinine > 500micromol/L.

Remission maintenance agents include methotrexate, azathioprine and mycophenolate mofetil. Average duration of maintenance therapy, in general, would be 3 years for EGPA once patient is in clinical remission. Glucocorticoids may be tapered off after 1 year of remission. In refractory cases, rituximab should be considered. Our patient was given 6 cycles of intravenous cyclophosphamide with glucocorticoids and put on Azathioprine as maintenance agent and had no recurrence of symptoms throughout 12 months follow up.

## Conclusion

There is no single specific presentation for systemic vasculitis. The diagnosis revolves around high index of clinical suspicion and thorough exclusion of other causes. Patients presenting with unexplained mono or polyneuropathy need to be evaluated for possible vasculitic neuropathy. EGPA must be considered in any patient with peripheral eosinophilia and underlying asthma or sinusitis presenting with clinical suspicion of vasculitic neuropathy.

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