CASE REPORT

Eosinophilic granulomatosis with polyangiitis and mononeuritis multiplex responded to induction cyclophosphamide

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SUMMARY

We report a case of 28-year-old Malay woman who initially presented with multiple joints pain with underlying poorly controlled asthma since her childhood. She was treated as seronegative arthritis. However, the involvement of joints, asthma and high-eosinophil counts raised suspicion of Churg-Strauss syndrome. This disease is undoubtedly rare in Malaysians or even in Asian populations. After appropriate therapy was delivered for the correct diagnosis her clinical condition improved. She is currently receiving maintenance treatment.

BACKGROUND

Churg-Strauss syndrome (CSS) is a small vessel vasculitis which may affect many organs and unvaryingly it occurs in people with underlying asthma. This condition is invariably characterised by high blood and tissue eosinophil counts. CSS has now been termed eosinophilic granulomatosis with polyangiitis (EGPA).

Chapel Hill consensus have defined EGPA which was published in 2013.¹ EGPA has the lowest prevalence among the three antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAVs) which include GPA and microscopic polyangiitis. If glomerulonephritis is present it is more likely to be associated with ANCA. The estimated annual incidence of EGPA is around 1–3 cases/million.² Glucocorticosteroid monotherapy has been the mainstay of treatment.³ Severe disease with life or organ threatening should be treated with a regimen combining glucocorticosteroids with another immunosuppressant, for example, cyclophosphamide to induce remission.⁴

Nevertheless the use of adjuvant immunosuppressive therapy is debatable and unlike other AAV, no randomised controlled trial results are available to support this recommendation so far. This case reflects the successful use of cyclophosphamide regime as remission inducer in a severe disease with nervous system involvement.

CASE PRESENTATION

A 28-year-old woman was diagnosed with bronchitis at four and bronchial asthma at 23 years of age, respectively. She has had frequent exacerbations requiring many admissions in a year, including history of endotracheal intubations in 2009 and 2012.

She had multiple visits to A&E department for asthma exacerbations requiring nebulised bronchodilator therapy. She was started on oral prednisolone 30 mg daily in 2009 tapering over 1 year for the difficult-to-control asthma. There was no specific triggers for her asthma exacerbations.

In early 2010, she had multiple joints pain involving bilateral metacarpals, proximal interphalangeal, both wrists and ankles joints. She also had myalgia with persistent low-grade fever. She became bedbound for 1 month. Clinically, there was evidence of bilateral wrist and metacarpal synovitis. Both metacarpophalangeal and metatarsophalangeal squeeze test were positive. She was diagnosed as seronegative rheumatoid arthritis. She was started on hydroxychloroquine 200 mg daily and sulfasalazine 500 mg two times per day. The arthritis resolved for almost 3 years and she was able to walk again.

She was reviewed again in May 2013 and at that time, she had significant weight loss and required wheel chair for ambulation. She had generalised myalgia with flares of her joints pain. She was also dyspnoeic on exertion. She was started on methotrexate and short-term oral prednisolone. However, there was no improvement of the joint pain despite her asthma was stable. She needed regular celecoxib for arthritis.

On examination, she had bilateral wrist drop which was consistent with mononeuritis multiplex.

The diagnosis of EGPA was considered. The blood film revealed normal total white cell counts but hypereosinophilia (59%). Ultimately, there was elevated perinuclear ANCAs (p-ANCAs) and myeloperoxidase antibody, confirming the diagnosis of EGPA.

Due to the presence of Five-Factor Score (FFS), which was the nervous system involvement, we decided to give her intravenous cyclophosphamide 15 mg/kg every 3 weeks for six cycles. A high-dose prednisolone was given and tapered down over 3 months.

INVESTIGATIONS

Initial blood investigation showed normal full blood counts. However, the cell differentials showed high-eosinophil counts of more than 50%. Her erythrocyte sedimentation rate (ESR) was elevated (70 mm/h) and c-reactive protein (CRP) was negative. Urinalysis was normal. Connective

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tissue disease screening including antinuclear antibody, rheumatoid factor were all negative except for elevated p-ANCA and myeloperoxidase antibody. Hepatitis C and B, HIV and syphilis screening were all negative. Blood and urine cultures were negative.

Nerve conduction study proved abnormalities of decreased amplitude in the presence of axonal polyneuropathy. CT scan thorax revealed increased interstitial markings with alveolar opacity in the middle and lower zones of bilateral lungs.

Echocardiogram was normal with good ejection fraction.

DIFFERENTIAL DIAGNOSIS

- ▶ Seronegative rheumatoid arthritis with pulmonary fibrosis
- ▶ Paraneoplastic syndrome
- ▶ Hypersensitivity pneumonitis
- ▶ Allergic bronchopulmonary aspergillosis
- ▶ Eosinophilic pneumonia
- ▶ Parasitic infections
- ▶ Drug reactions
- ▶ Myeloproliferative disorders
- ▶ Idiopathic hypereosinophilic syndrome.

TREATMENT

She was initially started on hydroxychloroquine 200mg daily and sulfasalazine 500mg two times per day for 3 years and later changed to methotrexate and short-term oral prednisolone.

She was then commenced on intravenous cyclophosphamide 15 mg/kg every 3 weeks for six cycles and a high dose of prednisolone which was tapered down over 3 months. Subsequently, she was commenced on methotrexate as maintenance.

OUTCOME AND FOLLOW-UP

Arthritis resolved with tapering down prednisolone. She was able to walk without assistance. Her asthma control remains good with only the use of short-acting bronchodilator (SABA) as needed only. Clinically, she improved with medications as well as ongoing physiotherapy. Maintenance methotrexate and low-dose prednisolone are continued until next follow-up.

DISCUSSION

EGPA manifests itself into a unique sequence of phases. Asthma, allergic rhinitis or atopic disease may occur in the second and third decade of life, which is called prodromal phase. Subsequently, patients develop eosinophilic phase. This is characterised by increased peripheral blood eosinophilia, eosinophilic infiltration to any organs. Lungs are the most commonly involved. Patient can have a life-threatening condition as they develop vasculitic phase which is heralded by constitutional symptoms. These symptoms were present in our patient. However, the incidence of EGPA is rare in our setting making the index of suspicion low. Other organs infiltrations may be seen in the myocardial tissue, skin, gastrointestinal (GI) and nervous system.

Glucocorticoid therapy has been reported to increase the 5-year survival to more than 50%⁵ The survival is poor without treatment. Up to 50% mortality occurs within 3 months after the onset of vasculitis. The leading cause of death is due to coronary vasculitis en route to myocarditis and myocardial infarction. Clinically, EGPA is difficult to discriminate from other types of vasculitis. History of asthma with blood eosinophilia and multi-organ involvement are the important clues to suspect EGPA.

EGPA Consensus Task Force in 2015 recommended that adjunctive cytotoxic drugs should be given to high-risk EGPA

patients. The FFS is a prognostic tool that consists of five parameters. Four of which are associated with poor prognoses and considered high risk if FFS ≥ 1 . These factors are age more than 65 years, heart and GI involvement, stabilised peak serum creatinine more than 150 $\mu\text{mol/L}$. Presence of each factor is scored +1 point. The fifth parameter is ENT (ear, nose and throat) manifestation and its absence is scored +1 point.⁶ The latter is associated with better outcomes. Our patient received multiple courses of high dose and prolonged course of prednisolone, particularly for her uncontrolled asthma and later for the arthritis. The prolonged courses of steroids might explained the delay in the nervous system manifestations or full-blown vasculitis. Despite that the underlying EGPA progressed that later she developed mononeuritis multiplex. She responded very well to intravenous cyclophosphamide regimes for six cycles.

Overall survival without maintenance therapy in high-risk EGPA patients reached 97% and 92% at 5 and 8 years, respectively. This is evident in a prospective study assessing the benefits of steroids and cyclophosphamide induction.⁷ Nonetheless, relapse rates were also high with 73.8% or 85.7%, respectively, depending on whether patients had received 6 or 12 cyclophosphamide pulses.⁷ These observations proposed that likewise other AAV, EGPA patients would also benefit from maintenance therapy to prevent relapses. It also allows reductions in glucocorticoids dose.

Rituximab is an alternative option for the induction and remission in patients with severe disease. Primary results of the Rituximab in ANCA-Associated Vasculitis (RAVE) trial⁸ showed that rituximab was as effective as cyclophosphamide for the induction of remission in patients with severe disease. The rituximab-based regimen was also superior in patients who had relapsing disease at 6 months. RAVE trial concluded that rituximab combined with glucocorticoids is not inferior to glucocorticoids and cyclophosphamide followed by maintenance therapy with azathioprine. The induction using conventional regimen is given for 18 months. Our patient had a good response to conventional cyclophosphamide and glucocorticoids. Rituximab should be considered if she relapses in the future.

We report a case of EGPA due to its rarity especially in Asian population. It is an example of case in a Malay patient that may guide treating physicians with similar patients. The differential diagnosis of AAV may be considered in such instances. We also would like to highlight the effect using intravenous cyclophosphamide in a positive FFS score more or equal to 1, particularly mononeuritis multiplex in our case. She is currently on oral methotrexate maintenance with no sign of relapse after 3 years postinduction.

Learning points

- ▶ Eosinophilic granulomatosis with polyangiitis (EGPA) is a rare disease in Malaysia but not negligible.
- ▶ Suspicion of EGPA in a patient with uncontrolled asthma is important especially when there are accompanying symptoms.
- ▶ Highlight the successful use of cyclophosphamide induction in EGPA with mononeuritis multiplex.
- ▶ It is pertinent to realise this disease has a risk for relapse hence close follow-ups are required.

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Contributors NM wrote the case report. WSWG managed the case and contributed the discussion aspect.

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