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Severe mononeuritis multiplex in a patient with eosinophilic granulomatosis with polyangiitis

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Abstract

Eosinophilic granulomatosis with polyangiitis (EGPA) is a systemic vasculitis characterised by bronchial asthma, hypereosinophilia, and systemic vasculitis. History of asthma with blood eosinophilia and multiorgan involvement are the important clues to suspect EGPA. In the original paper by Churg and Strauss cardiac, gastrointestinal tract, renal, and neurological involvement were noted more frequently. The pattern of neurological involvement may be mononeuritis multiplex, and symmetrical and asymmetrical polyneuropathy. Mononeuritis multiplex was present in 78.1% while cranial nerves were involved in only 4.1% of cases. Glucocorticosteroids and immunosuppressants, especially cyclophosphamide, have considerably improved the prognosis and overall survival rates in patients with systemic vasculitis, including eosinophilic granulomatosis with polyangiitis. The authors present a clinical case of eosinophilic granulomatosis with polyangiitis with severe mononeuritis multiplex. The case reflects the successful application of a cyclophosphamide regime as a remission inducer.

Key words: eosinophilic granulomatosis with polyangiitis, vasculitis, mononeuritis multiplex, granulomatosis process.

Introduction

Eosinophilic granulomatosis with polyangiitis (EGPA) is a systemic vasculitis characterised by bronchial asthma, hypereosinophilia, and systemic vasculitis [1]. Chapel Hill Consensus have defined EGPA, as published in 2013. Eosinophilic granulomatosis with polyangiitis has the lowest prevalence among the three antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAVs), which include GPA and microscopic polyangiitis (MPA) [2]. The prevalence of this disorder is estimated at 10.7 to 13 cases per million [3]. The histopathological features include necrotising vasculitis in both veins and arteries with eosinophilic infiltration in the vessels and the surrounding tissues [4].

Glucocorticosteroid (GC) monotherapy has been the mainstay of treatment [5]. Severe disease with life or organ threatening should be treated with a regimen combining GCs with another immunosuppressant, for example cyclophosphamide, to achieve remission. Nevertheless, the use of adjuvant immunosuppressive therapy is debatable, and, unlike other AAVs, no randomised controlled trial results are available to support this recommendation so far [6].

In this article the clinical case of EGPA with severe nervous system involvement is presented. The case reflects the successful application of cyclophosphamide regime as remission inducer.

Case report

A 62-year-old male patient presented to the otolaryngologist with complaints of fever, headache, and pain in the left maxillary sinus. A computed tomography of the head was performed revealing pansinusitis. Antibiotic therapy was started – amoxicillin/clavulanic acid 2 × 1.2 g daily. Some days later, despite this treatment, the patient reported double vision, paraesthesias and

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weakness of both hands and feet, unstable gait, and falling of the upper right eyelid.

The patient suffered from intermittent asthmatic attacks and had to use inhalations with beclomethasone and formoterol during the previous year. He had a history of sinusitis in the past and underwent sinus surgery intervention a year earlier.

The weakness in the extremities had an ascendant, progressive course. He had difficulty in holding objects with the hands and difficulty in walking. The patient was admitted to the Department of Neurology because of the neurological nature of the symptoms. The primary neurological examination showed:

- polyneuritic syndrome (sensorimotor polyneuropathy),
- weakness in the distal muscle groups of both hands and feet,
- bilateral wrist and ankle drop,
- distal hypesthesia of hands and feet,
- ptosis of the upper right eyelid.

Laboratory studies revealed increased non-specific inflammatory markers (erythrocyte sedimentation rate, C-reactive protein). Other investigations showed hemoglobin 11.8 g/dl, total leukocyte count 27.8 × 10^9/l, and thrombocytes 317 × 10^9/l. The cell differentials showed high-eosinophilic counts 76.6%, neutrophils 14.4%, lymphocytes 6.6%, and basophils 0.7%; renal function tests were normal. Liver enzymes were mildly increased – ASPAT 140 U/l, ALAT 88 U/l. Urine test results were normal. The screening for infections such as: hepatitis B and C, HIV, and syphilis were negative. A lumbar puncture with cerebrospinal fluid (CSF) collection was performed. In cerebrospinal fluid normal total protein 0.35 g/l (reference level 0.15–0.45 g/l), normal cell count, and normal glucose level were found. Blood and urine cultures were negative.

Electroneuromyography showed confluent sensory motor axonal mononeuropathy multiplex.

The patient had a consultation with a rheumatologist because of a diagnosis of possible ANCA-associated vasculitis: EGPA. He presented to the Clinic of Rheumatology. Laboratory testing confirmed previous findings such as: increasing levels of non-specific markers of inflammation, peripheral eosinophilia, and normal serum creatinine level and urine test. The specified immunological tests: anti-neutrophil cytoplasmic antibodies on indirect immunofluorescence ANCA were positive p-ANCA 1 : 160 (normal < 1 : 20) as well as anti-myeloperoxidase antibodies (anti-MPO antibodies) 61.3 U/ml (normal < 5 U/ml).

Echocardiography showed all chambers with normal size and normal left ventricular ejection fraction. Computed tomography of the lung and abdomen did not demonstrate any pathological findings. Sural nerve biopsy showed mononuclear cell infiltration especially around the vasa vasorum. There was reversible airway obstructive abnormality on spirometry: FEV1 was 60% of predicted value, which increased to 85% of predicted FEV1 after bronchodilator testing.

On the basis of clinical features, including history of sinusitis and bronchial asthma, peripheral eosinophilia, and mononeuropathy multiplex, a diagnosis of EGPA was made. Skin involvement was not present in this clinical case. Pulse therapy with methylprednisolone 1000 mg and intravenous cyclophosphamide 15 mg/kg was started every month for six cycles because of rapid neurological deterioration. The methylprednisolone dosage between the pulses was 60 mg/day. Maintenance therapy to a tapering dose of GCs as azathioprine was started.

Discussion

Eosinophilic granulomatosis with polyangiitis is a small vessel vasculitis that can affect many organs, and it occurs in people with underlying asthma [7]. Asthma/allergic rhinitis may occur in the second and third decade of life, known as the prodromal phase. Subsequently, patients develop the eosinophilic phase, which is characterised by increased peripheral blood eosinophilia and eosinophilic infiltration to any organs. Patient can have a life-threatening condition as they develop the vasculitic phase and manifestations of different organs – cardiac, skin, gastrointestinal (GI), and nervous [7].

In the original paper by Churg and Strauss [8] cardiac, GI tract, renal, and neurological involvement were noted more frequently. Glomerular involvement is rare. Focal segmental glomerular proliferation is the major pattern observed, but extracapillary proliferation with necrotising vasculitis and renal insufficiency have also been described. Cardiac involvement is not equally represented in the various populations described; the frequency ranges from 16.6% to 92.3% – cardiomyopathy has been associated with a poor clinical outcome. The GI tract involvement is secondary to mesenteric ischaemia due to mesenteric vessel vasculitis [9]. The pattern of neurological involvement may be mononeuritis multiplex, or symmetrical or asymmetrical polyneuropathy. Mononeuritis multiplex was present in 78.1% of cases while cranial nerves were involved in only 4.1% [10].

Clinically, EGPA is difficult to discriminate from other types of vasculitis [7]. History of asthma with blood eosinophilia and multiorgan involvement are the important clues to suspect EGPA. The patient satisfied the diagnostic criteria of EGPA with asthma, eosinophilia, sinusitis, vasculitis involving the peripheral nerves, and positive p-ANCA. The diagnosis of EGPA was made based on ACR 1990 criteria for the classification [1].

The criteria include asthma, eosinophilia > 10%, neuropathy, non-fixed pulmonary infiltrates, paranasal sinus abnormalities, and extravascular eosinophils. For classification purposes, the diagnosis of EGPA is made if at least four of these six criteria are positive [1]. The presence of any four or more of the six criteria yields a sensitivity of 85% and a specificity of 99.7% [1]. A history of asthma and sinusitis precedes the appearance of EGPA; the median time between the onset of asthma and diagnosis of vasculitis was four years [11]. In this case asthma was present one year before the vasculitis.

Antineutrophil cytoplasmic antibodies can be detected in 38% to 50% of the patients. There are some hypotheses about the existence of two types of EGPA based on the presence or absence of ANCAs [12]. Renal involvement, neuropathy, alveolar hemorrhage, and vasculitis with purpura are predominant manifestations in ANCA-positive patients, while cardiac and pulmonary involvements are the predominant complaints in ANCA-negative patients [13]. Our clinical case supports this relation because p-ANCA and anti-MPO antibodies were positive.

Therefore, the combination therapy of GCs and CF was started. Glucocorticosteroids and immunosuppressants, especially CF, have considerably improved the prognosis and overall survival rates in patients with systemic vasculitis. Therapy with GC has been reported to increase the five-year survival to more than 50% [9]. Without treatment, up to 50% mortality occurs within three months of the onset of vasculitis [7]. The EGPA Consensus Task Force in 2015 recommended that adjunctive cytotoxic drugs should be given to high-risk EGPA patients with Five-Factor Score (FFS) > 1. The FFS is a prognostic tool for predicting sequelae and determining treatment for vasculitis. These factors are as follows: age more than 65 years, heart and GI involvement, serum creatinine more than 150 µmol/l, and ENT manifestations (ear, nose, throat) [14]. Peripheral nervous involvement is not included in FFS. In our case the patient developed a serious neurological manifestation: mononeuritis multiplex, and this was an indication for intravenous cyclophosphamide regimes.

Rituximab is an alternative option for induction of remission in patients with severe disease. Primary results of rituximab in AAVs (RAVE) showed that rituximab was as effective as cyclophosphamide for the induction of remission in patients with severe disease [15, 16]. In our case the patient had a good response to conventional cyclophosphamide and GCs. Rituximab should be considered if he relapses in the future.

Interleukin 5 (IL-5) regulates eosinophilic proliferation, maturation, and differentiation in patients with EGPA, and the neutralisation of IL-5 offers a potential therapeutic option for patients with EGPA. Considering the similarities between EGPA and severe eosinophilic asthma pathogenesis, mepolizumab has been introduced as an add-on therapeutic agent in refractory or relapsing EGPA, with promising preliminary results. However, it is still not clear whether the efficacy of mepolizumab in the treatment of EGPA is due mainly to its ability to control asthma symptoms or whether it also plays a role in systemic vasculitis manifestations [17].

For patients who fail to achieve remission and have persistent low activity, adjunctive therapy with intravenous immunoglobulin (IVIG) may help achieve remission. Prior to therapy the serum immunoglobulin level must be measured because patients with selective IgA deficiency may develop an anaphylactic reaction on receiving IVIG or a pre-existing hyperglobulinaemia may become aggravated leading to a hyperviscosity state [18].

The authors declare no conflict of interest.

References

1. Masi AT, Hunder GG, Lie JT, et al. The American College of Rheumatology 1990 criteria for the classification of Churg-Strauss syndrome (allergic granulomatosis and angiitis). Arthritis Rheum 1990; 33: 1094-1100.
2. Jennette JC, Falk RJ, Bacon PA, et al. 2012 revised International Chapel Hill Consensus Conference of vasculitides. Arthritis Rheum 2013; 65: 1-11.
3. Mouthon L, Dunogué B, Guillevin L. Diagnosis and classification of eosinophilic granulomatosis with polyangiitis (formerly named Churg-Strauss syndrome). J Autoimmun 2014; 48-49: 99-103.
4. Franco DL, Ruff K, Mertz L, et al. Eosinophilic granulomatosis with polyangiitis and diffuse gastrointestinal involvement. Case Rep Gastroenterol 2014; 8: 329-336.
5. Groh M, Pagnoux C, Baldini C, et al. Eosinophilic granulomatosis with polyangiitis (Churg-Strauss) (EGPA) Consensus Task Force recommendations for evaluation and management. Eur J Intern Med 2015; 26: 545-553.
6. Churg A. Recent advances in the diagnosis of Churg-Strauss syndrome. Mod Pathol 2001; 14: 1284-1293.
7. Mohammad N, Wan Ghazali WS. Eosinophilic granulomatosis with polyangiitis and mononeuritis multiplex responded to induction cyclophosphamide. BMJ Case Reports 2017; 2017: bcr-2016-218252.
8. Churg J, Strauss L. Allergic granulomatosis, allergic angiitis and polyarteritis nodosa. Am J Pathol 1951; 27: 277-301.
9. Guillevin L, Cohen P, Gayraud M, et al. Churg-Strauss syndrome. Clinical study and long-term follow-up of 96 patients. Medicine (Baltimore) 1999; 78: 26-37.
10. Kararizou E, Davaki P, Spengos K, et al. Churg-Strauss syndrome complicated by neuropathy: a clinicopathological study of nine cases. Clin Neuropathol 2011; 30: 11-17.
11. Jeong YJ, Kim KI, Seo IJ, et al. Eosinophilic lung disease: a clinical radiologic and pathologic overview. Radiographics 2007; 27: 617-637.

12. Francescutti V, Ellis AK, Bourgeois JM, Ward C. Acute acalculous cholecystitis: An usual presenting feature of Churg-Strauss vasculitis. Can J Surg 2008; 51: E129-130.
13. Sinico RA, Di Toma L, Maggiore M, et al. Prevalence and clinical significance of antineutrophilic cytoplasmic antibodies in Churg-Strauss syndrome. Arthritis Rheum 2005; 52: 2926-2935.
14. Cohen P, Pagnoux C, Mahr A, et al. Churg-Strauss syndrome with poor-prognosis factors: A prospective multicenter trial comparing glucocorticosteroids and six or twelve cyclophosphamide pulses in forty-eight patients. Arthritis Rheum 2007; 57: 686-693.
15. Specks U, Merkel PA, Seo P, et al. Efficacy of remission-induction regimens for ANCA-associated vasculitis. N Engl J Med 2013; 369: 417-427.
16. Bosch X, Guilabert A, Espinosa G, Mirapeix E. Treatment of antineutrophil cytoplasmic antibody associated vasculitis: a systematic review. JAMA 2007; 298: 655-669.
17. Guillevin L. Vasculitis: Mepolizumab for eosinophilic granulomatosis with polyangiitis. Nat Rev Rheumatol 2017; 13: 518-529.
18. Yates M, Watts RA, Bajema IM, et al. EULAR/ERA-EDTA recommendations for the management of ANCA-associated vasculitis. Ann Rheum Dis 2016; 75: 1583-1596.