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Eosinophilic Granulomatosis with Polyangiitis

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Abstract

Aim

Eosinophilic granulomatosis with polyangiitis (EGPA) is a rare, small-to-medium vessel vasculitis presenting most commonly with upper and lower airway symptoms and a peripheral blood eosinophilia (PBE)1. EGPA is highly variable in clinical expression and can be diagnostically challenging as the syndrome slowly evolves over time.

Methods

The aim of this study was to determine the American College of Rheumatology diagnostic (ACR) criteria score[2] in a cohort of patients with EGPA and to describe their treatment and clinical outcomes.

Results

The mean age at diagnosis was 53 ± 12.2 years with an average time in clinic of 1.1 years prior to diagnosis. All patients had ≥4 ACR criteria. All 15 had sinusitis and 14 (93%) lung infiltrates, asthma and >10% PBE. 7 patients (47%) had mono/polyneuropathy and two (13%) had a positive biopsy. One patient had a stroke. 9 patients (60%) remained in remission with a prednisolone/ methotrexate combination, two (13%) prednisolone alone, two patients (13%) with azathioprine, one patient required prednisolone and mepolizumab to attain control and one unstable patient on prednisolone /methotrexate due to start mepolizumab repatriated to eastern Europe.

Conclusion

Clinicians should be aware of the possibility of EGPA in a patient with unstable adult-onset asthma and sinusitis and significant PBE.

Introduction

In 1951, Churg and Strauss first described a syndrome of asthma, 'fever and eosinophilia' with co-existing 'cardiac failure, renal damage and peripheral neuropathy[1]. This syndrome later became known as Eosinophilic granulomatosis with polyangiitis (EGPA) in 2012, in keeping with new nomenclature.
EGPA is a multisystem disorder characterised by necrotizing small and medium vessel vasculitis[1]. Its annual incidence is low with 0.5 – 4.2 cases per million[3] and usually arises in people aged 40 to 60 years with a mean age of 49 years at diagnosis[4] with no sex preponderance.

EGPA presents most commonly as a trilogy of asthma, chronic rhinosinusitis and prominent peripheral blood eosinophilia (PBE)[5] where there are > 10% eosinophils in the total white cell count. Skin, lung, and peripheral nerve involvement can also be seen. Organs, such as the heart, gastrointestinal tract, and kidneys can be affected in severe disease, and this is associated with higher mortality rates[6].

A genome-wide association study in 676 EGPA cases and 6809 controls, stratifying patients by antineutrophil cytoplasmic antibody (ANCA) status revealed EGPA comprises two genetically and clinically distinct syndromes. Myeloperoxidase-positive (MPO+) ANCA EGPA is an eosinophilic autoimmune disease sharing certain clinical features, and an HLA-DQ association, with MPO+ ANCA-associated vasculitides, while ANCA-negative EGPA may instead have a mucosal/barrier dysfunction origin[7]. Approximately 30-40% of patients are ANCA positive[4].

No single diagnostic criteria for EGPA has been universally agreed. One commonly used diagnostic approach for EGPA is the American College of Rheumatology (ACR) criteria[2] (Table 1). This was developed in 1990 and outlines 6 criteria which, if there is ≥4 criteria present, has a diagnostic sensitivity for EGPA of 85% and a specificity of 99.7%[2].

The diagnosis of EGPA can be very difficult to make as the disease often evolves very slowly over years. The features that trigger the diagnosis would be a persistently high PBE, severe persistent rhinosinusitis and lung infiltrates. These patients should have a bronchoscopy and lavage to exclude infection and also to send for a differential cell count (pulmonary eosinophils are normally <2% of the normal lavage cell count; >25% is definite pulmonary eosinophilia)[8].

The aim of this study is to determine the diagnostic ACR score[2] in a cohort of patients with EGPA, their treatment and clinical outcomes. Additionally, each patient's five factor score (FFS), which aims to evaluate prognosis at diagnosis, was calculated[6].

Methods

We performed a retrospective case review of individuals with a diagnosis of EGPA attending our respiratory clinic in Galway University Hospitals between January 2009 and September 2019. These patients were identified from electronic patient records using the search terms "Churg-Strauss" and "eosinophilic granulomatosis" and "granulomatosis with polyangiitis".

Information surrounding their diagnosis, ACR score, previous radiological and biochemical investigations, current treatment regime and clinical outcomes was obtained using Evolve, an electronic database.

Results

We identified 15 paients, 8 (53%) females. Table 2 outlines basic patient demographics and Figure 1 the ACR diagnostic criteria. One patient had a stroke with a full recovery. All patients had ≥4 criteria present and were initially commenced on prednisolone 40-60mg as monotherapy to induce remission. Two patients (13%) stayed in remission with prednisolone alone. 9 patients (60%) went into remission and remain so on a combination of prednisolone and methotrexate therapy (7.5 mg - 20mg daily). One patient developed mild anaphylaxis with the 1st dose of methotrexate and was switched to azathioprine and remains in remission in combination with prednisolone. One patient achieved remission with prednisolone and azathioprine combination and was then slowly weaned off prednislone. Two patients were not stable on prednisolone and methotrexate. One was switched to mepolizumab 300mg/4 weeks 10 months ago and since then has had excellent control. The other patient repatriated to Eastern Europe before starting mepolizumab. 10 patients had a five factor score of zero, with five of our patients scoring one at diagnosis. All were alive at 4.7 years (range 1.4 years - 8.7 years) follow-up.
For our cohort, 66% had an FFS score of 0 when calculated; only 5 patients had a score of 1 and no patient had a score of $\underline{>}$ 2.

Table 1: Criteria for the American College of Rheumatology classification of EGPA by Masi et al. [2]

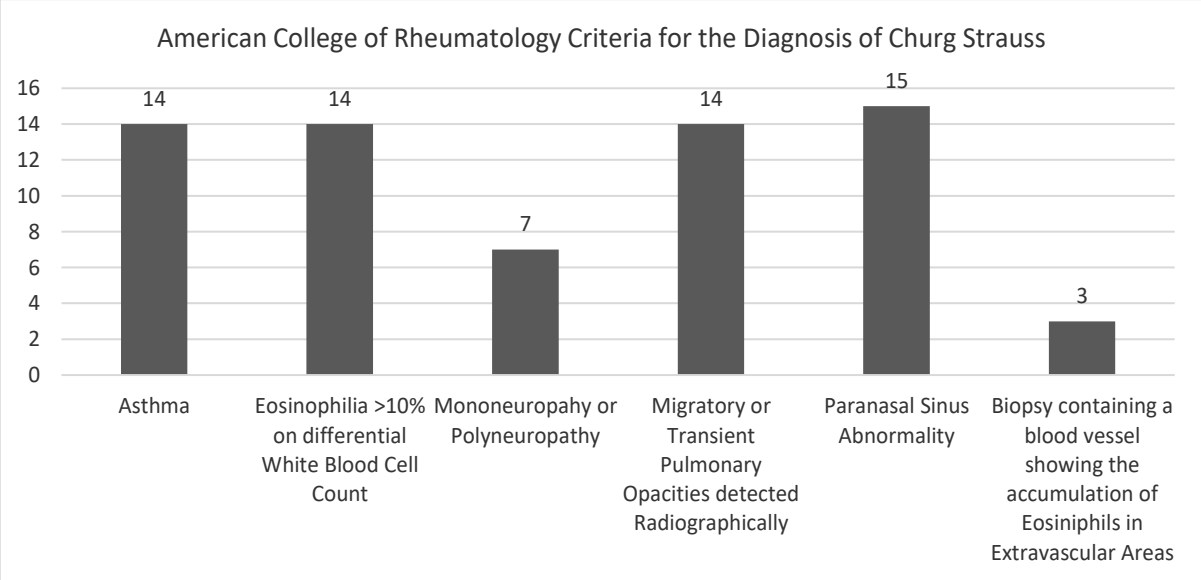
Criterion	Defintion
Asthma	History of wheezing or diffuse high pitched rales on expiration
History of allergy	Eosinophils > 10% on peripheral White Cell Count
Mono/polyneuropathy	Development of mononeuropathy, multiple mononeuropathy or polyneuropathy
Pulmonary infiltrates, non-fixed	Migratory of transitory pulmonary infiltrates on radiographs (not including fixed infiltrates)
Paranasal sinus abnormality	History of actue or chronic paranasal sinus pain or tenderness or radiographic opacification of the paranasal sinuses
Extra-vascular eosinophils	Biopsy including artery, arteriole or venule showing accumulation of eosinophils in extra-vascular areas

Table 2: Basic data of Patients with EGPA

Characteristic	N = 15
Sex, women, n	7
Age (year) ± SD	55.8 years ± 11.2
Age (year) at diagnosis ± SD	53 ± 12.2
Mean time in Clinic pre-diagnosis (year) ± SD	1.1 years ± 1.5
Race/ Ethnicity	14 Irish 1 Eastern European
Mean FEV1 ± SD	2.4 Litres ± 0.8
Mean FEV1/ FVC ratio ± SD	63.5% ± 9.3%
ANCA -positivity	4 (26.7%)

Abbreviation: SD, standard deviation; FEV1, forced expiratory volume in the first second; FVC, forced vital capacity; ANCA, anti-neutrophil cytoplasm antibodies.[1]

Figure 1: ACR criteria present in our population.



Discussion

All patients in this study satisfied the ACR criteria[2] for diagnosis of EGPA. The prevalence of EGPA in this single centre study suggests a national prevalence higher than that reported in the international literature. EGPA may take a long time to evolve, many organs may or may not be affected and a clear diagnosis may be difficult to achieve. Given its heterogenous presentation, and our lack of clear understanding of the interplay between the eosinophilic and vasculitic processes, significant controversy surrounding its diagnosis exists. Therefore, the ACR criteria developed as a diagnostic tool in 1990, are still widely employed which has a high estimated sensitivity (85%) and specificity (99.7%)[2]. In 1994, the Chapel Hill Consensus Conference (CHCC) proposed names and definitions of common vasculitides including EGPA[9]. Between 2009 and 2013 a EGPA European Consensus Task Force was established to produce recommendations for the definition, diagnosis, investigations and management of EGPA[10]. In 2012, the CHCC revised their 1994 definitions and EGPA was defined as a sub-group of ANCA-associated vasculitis although 60% of patients with EPGA are ANCA negative[4].

Most commonly, EGPA initially develops as asthma, of varying severity, and rhinosinusitis. This is known as the 'prodromal allergic phase'. Asthma is found in approximately 95% of individuals with EGPA, does not show typical variation with seasons, and may precede the systemic disease manifestations for many years or decades. Several of our patients, however, appeared to have an abbreviated allergic/ eosinophilic phase of only 2-3 months. Chronic rhinosinusitis and nasal polyposis affect approximately 50% of EGPA patients and commonly recurs following surgical intervention, if not on active systemic treatment.

The 'eosinophilic phase' follows the allergic phase and is characterised by the PBE with organ involvement, including lung (66%), heart and gastrointestinal involvement. Cardiac and gastrointestinal involvement can lead to significant morbidity and mortality. Cardiac involvement is a documented adverse prognostic factor and can lead to impaired systolic function from eosinophilic infiltration of the endocardium, pericardium or valvular dysfunction. Rarely patients may get a mural thrombus[11]. Gastrointestinal involvement most frequently affects the small bowel causing unexplained abdominal pain, and in rare cases upper gastrointestinal haemorrhage[5].

As per the ACR criteria, PBE >10% is considered significant[2]. The degree of eosinophilia correlates with disease activity and high blood values are suggestive of higher disease activity. The 2 main differential diagnoses are asthma and allergic bronchopulmonary aspergillosis (ABPA). In ABPA the PBE can be in the same range as EGPA and similar lung infiltrates (ground glass opacities and bronchiolitis) may be found, which is eosinophilic on lavage[12]. However, ABPA is partially an Immunoglobulin (Ig) E driven process with massive activation of IgE (typically > 1000 u/L[12]) and there are elevated aspergillus IgE and IgG antibodies. In advanced ABPA, high resolution computed tomographic imaging reveals a typical upper and middle lobe proximal bronchiectasis[12].

The vasculitic phase occurs with clinical manifestations directly related to small-vessel vasculitis. Constitutional symptoms such as fever, weight loss and fatigue are often the first symptoms[5].

Peripheral neuropathy, either mononeuropathy or polyneuropathy, is a cardinal feature of this phase and is seen in 70% of individuals[5], as the delicate vasa vasorum are very susceptible to ischaemic injury. This may present as asymmetric foot or wrist drop, sensory disturbance or neuropathic pain. The mononeuropathy may progress and become a symmetric or asymmetric polyneuropathy[5]. Renal vasculitis is seen in approximately one quarter of patients. Severity ranges from microscopic haematuria or proteinuria to rapidly progressive glomerulonephritis[13]. Vasculitic rashes can occur during this phase and primarily affects the lower limbs[13] as the inflamed small vessels rupture under the force of gravity.

EGPA usually responds to moderate doses of glucocorticoid therapy leading to remission. None of the patients in our cohort required high-dose intravenous methylprednisolone to induce remission. A study in the 1970's showed the 5-year-survival had increased to 62% when compared to the pre-corticosteroid era, prior to the 1950's, when EGPA was invariably fatal[14]. Patients with EGPA who are older at presentation or have evidence of cardiac, GI, CNS or renal involvement, or absence of ENT manifestations have a poorer prognosis and often benefit from initial adjunctive Cyclophosphamide therapy[19,20] although IL-5 inhibitors are often now used with good effect in this setting[15–18]

There is no current consensus regarding the remission-inducing and maintenance therapies in EGPA[5]. Combinations of glucocorticoids and immunosuppressant agents including methotrexate, azathioprine and cyclophosphamide are typically required in most cases to maintain remission[19]. In a randomised trial of Methotrexate versus Cyclophosphamide for remission maintenance, the efficacy in preventing relapses of the two study drugs was comparable, and both treatments led to improved outcomes and overall survival[20]. Interleukin 5 (IL-5) promotes the maturation, proliferation and survival of eosinophils in the bone marrow[21]. Up-regulation of IL-5 in EGPA[22] suggests a role for anti-IL 5 therapy in treatment. In the largest trial to date, the anti- IL-5 antibody, Mepolizumab, has demonstrated efficacy in remission-induction and maintenance in patients with refractory or relapsing EGPA[23]. Additionally, withdrawal of mepolizumab has led to flares of EGPA[24].

In a randomised trial of patients without poor prognostic factors, the 5-year survival rates was between 97% and 100%[25]. The Five-Factor Score (FFS), is a tool to assess prognosis of EGPA at diagnosis[6]. Four factors are significantly associated with higher 5-year mortality, namely age >65 years, cardiac symptoms, gastrointestinal involvement, and renal insufficiency (creatinine >150 mmol/L) whereas rhinosinusitis/nasal polyps are associated with a better prognosis[6]. Based on the FFS, 5-year mortality rates are 9% for those with a score of 0, 21% for those with a score of 1 and 40% for those with a score of $\geq$2[6].

Despite improved mortality rate with treatments, a significant degree of morbidity is associated with this condition. Disease-related organ damage including heart failure, chronic neuropathy and renal impairment, can hugely impact on quality of life. Immunosuppressive treatments can also contribute to morbidity as they are associated with side effects, an overall increased risk of severe infections and with the development of malignancies[5].

The prevalence of EGPA appears to be high in Ireland compared to the international literature. The ACR criteria appear to be a good guide for diagnosis in patients affected. In patients with asthma, persistent rhinosinusitis and PBE, with or without lung infiltrates one has to have index of suspicion for the disease. In our cohort, moderate doses of corticosteroid were adequate to induce remission and, in the majority, we have achieved stable remission employing methotrexate or an IL-5 inhibitor.

Declaration of Conflicts of Interest:
There are no conflicts of interest to declare.

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