

## Eosinophilic Granulomatosis with Polyangiitis (EGPA): An Update for the Churg-Strauss Syndrome

M Myrtha Gregoire-Bottex<sup>1\*</sup>, Donald E Greydanus<sup>2</sup> and Kevin W Cates<sup>3</sup>

<sup>1</sup>Associate Professor of Pediatrics, Pediatric Pulmonology, Director, Cystic Fibrosis Center, Department of Pediatrics and Adolescent Medicine, Western Michigan University Homer Stryker M.D. School of Medicine, Kalamazoo, Michigan, USA

<sup>2</sup>Founding Chair and Professor, Department of Pediatric and Adolescent Medicine, Western Michigan University Homer Stryker M.D. School of Medicine, Kalamazoo, Michigan, USA

<sup>3</sup>Western Michigan University, Homer Stryker M.D. School of Medicine, Kalamazoo, Michigan, USA

**\*Corresponding Author:** M Myrtha Gregoire-Bottex, Associate Professor of Pediatrics, Pediatric Pulmonology, Director, Cystic Fibrosis Center, Department of Pediatrics and Adolescent Medicine, Western Michigan University Homer Stryker M.D. School of Medicine, Kalamazoo, Michigan, USA.

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### Introduction

The first observation of periarteritis nodosa is attributed to the renowned Bohemian polymath, Carl von Roikansky (1804 - 1878) (pathologist, physician, philosopher and politician) in 1852 and the initial pathological description was presented by Kussmaul and Maier in 1866 [1-4]. By 1917 there were 52 cases that had been reported in the literature [3]. In 1925 GB Gruber offered the opinion in the German literature that periarteritis nodosa (PAN) is an infection-induced hyper-allergic reaction [5]. In 1936 Cohen, Kline and Young suggested a link between severe asthma and PAN [6] while, in 1945, Wilson as well as Alexander reported that asthma was found in 18% of 300 cases of PAN [7].

In 1951 NY Mount Sinai Hospital pathologists, Jacob Churg and Lotte Strauss, provided initial data for the subsequent symptom complex, Churg-Strauss syndrome; they published their classic paper on "Allergic granulomatosis, allergic angiitis and periarteritis" that was first presented in 1949 at the American Association of Pathologists and Bacteriologists in Boston, Massachusetts [8]. Jacob Churg continued his research linking allergic granulomatosis and granulomatous-vascular syndromes with another classic article in 1963 [9].

Debate on this potential syndrome as a separate entity from PAN continued throughout the rest of the 20<sup>th</sup> century [10-13]. As the third decade of the 21<sup>st</sup> century rapidly approaches the name, Churg-Strauss syndrome, has been modernized to the label "Eosinophilic granulomatosis with polyangiitis" and it is linked as a differential diagnosis of hypereosinophilic syndromes [14].

This complex condition contains various non-pulmonologic features such as cardiomyopathy (myocarditis, myocardial infarction), peripheral nerve involvement (polyneuropathy, mono-neuritis multiplex), gastrointestinal involvement, skin manifestations (purpura, nodules), renal features (i.e., rapidly worsening glomerulonephritis) and others [13-21].

### Pulmonary features

Churg-Strauss syndrome (CSS) is a rare disorder with asthma, vasculitis and hypereosinophilia; various organs can be involved including the lung [22]. A key part of CSS is the presence of asthma typically starting in adulthood along with atopy, sinusitis and nasal polyposis [23]. Though usually diagnosed in adults, it rarely can be found in the pediatric population as well [24].

In one study asthma was severe from the initial diagnosis in 68.5% and poorly controlled in most; the development of vasculitis symptoms with a diagnosis of CSS was seen with significant eosinophilia [23]. Patients with CSS can also have and/or present with alveolar hemorrhage which can be diffuse, hemoptysis and/or bilateral alveolar infiltrates on chest radiographs [25-27].

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### Laboratory features

Laboratory features include eosinophilia ( $> 1,000/\text{mm}^3$ ), anti-MPO (anti-myeloperoxidase) pANCA (ANCA with a perinuclear fluorescence pattern) in 40%, enhanced Th2 responses (with up-regulation of IL-4, IL-13 and IL-5), and dysregulation of humoral immunity (with increased IgG4 and IgE responses [28,29]. Depending on the organs involved, other laboratory features may be found such as abnormal chest radiographs with lung involvement and with nervous system involvement (i.e., abnormal electromyogram as well as abnormal muscle and peripheral nerve biopsies) [27,30].

Bronchoalveolar lavage and/or biopsy can identify respiratory eosinophilia and rule out pulmonary infection or malignancy [31]. Serum ANCA levels can positively be associated with disease activity reflective of central nervous system involvement [32]. Anti-neutrophil cytoplasmic autoantibodies, mostly involving myeloperoxidase, are reflective of CSS patients with glomerulonephritis and small-vessel vasculitis [33].

### Pathogenesis

A complex, autoimmune, multifactorial process is identified with the pathogenesis of CSS that is now called eosinophilic granulomatosis with polyangiitis (EGPA) [29,34]. The development of autoantibodies can be linked to chronic inflammation and eventual pulmonary vascular changes [34]. Necrotizing vasculitis can be linked with the presence of myeloperoxidase-antineutrophil cytoplasmic autoantibodies [33]. EGPA is considered as a Th2-mediated disorder in which ANCAs are directly involved in the pathogenesis of antineutrophil cytoplasmic antibodies and subsequent small-vessel vasculitis [35]. B cells and the humoral response are also involved in this pathogenesis [35].

Other potential stimulants have been seen with the development of CSS (EGPA). For example, the literature does contain a case report of CSS that developed in a 55-year old female after receiving the H1N1 influenza A [36]. Even more intriguing is the potential role of medications used to manage severe and/or persistent asthma-leukotriene receptor antagonists (LTRAs: montelukast, zafirlukast, and pranlukast) in the rare development of CSS [37-46].

Whether LTRA can cause CSS in rare situations or is simply seen in a patient with severe asthma who already has CSS is not clear at this time [40,43]. Worsening asthma can be an early sign of CSS though LTRA should be stopped in a patient with asthma who is taking this medication and is diagnosed with CSS [40]. Rare relapse of CSS has been reported after starting montelukast [46] and CSS may rarely develop in an adult with asthma after steroid withdrawal that may unmask CSS [45].

### Differential Diagnosis

The definition and classification of CSS continues to evolve since the 1951 identification by Churg and Strauss [8]. In 1990 the American College of Rheumatology provided its CSS criteria that defined CSS in a patient with 4 or more of 6 findings: asthma, eosinophilia (eosinophils  $> 10\%$  of a differential white blood count), polyneuropathy (or mono-neuropathy), unfixated pulmonary infiltrates, identified paranasal sinus abnormalities, and/or histological findings of extravascular eosinophils [47].

In 2012 CSS was renamed eosinophilic granulomatosis with polyangiitis (Churg-Strauss) or EGPA and further revision in 2013 placed this condition in a subset of ANCA-associated vasculitides [48]. EGPA should be differentiated from other eosinophilic pneumonias, idiopathic hypereosinophilic syndrome, Wegener's granulomatosis and microscopic polyangiitis [14,27,48,49]. Polyangiitis overlap syndrome has been reported in which a patient can have both EGPA and granulomatosis with polyangiitis (Wegener's granulomatosis) [50]. Pulmonary involvement is less common in other systemic vasculitis disorders such as Goodpasture's syndrome, Behçet's disease, Takayasu's disease, Kawasaki's disease, Henoch-Schönlein purpura, and cryoglobulinemic vasculitis [27,51].

In pediatrics the term, pediatric eosinophilic pneumonias, is used to refer to conditions in which there is significant infiltration of alveolar space and lung interstitium by eosinophils [52]. Eosinophilic pneumonias can be primary or secondary. Primary eosinophilic

pneumonias include EPGA, hypereosinophilic syndrome, idiopathic chronic eosinophilic pneumonia, and idiopathic acute eosinophilic pneumonia [52]. Secondary eosinophilic pneumonias include those seen in allergic bronchopulmonary aspergillosis, adverse medication/drug effects and various parasitic infections [52].

### **Treatment**

Management of EGPA is based on use of high-dose corticosteroids (i.e., prednisolone), other immunosuppressive agents, removal of potential precipitating factors, and treatment of any co-existent infection [28,29,31,35,49,50,53-58]. A proper diagnosis is needed in order to institute immunosuppressant medication [50]. Side effects of steroids and other immunosuppressive agents must be appreciated and managed [52]. Even with remission severe asthma often persists and antibiotics will typically not help the vasculitis [14,56].

The gold standard of management is steroids (prolonged) and cyclophosphamide [35,54,55]. Induction can occur with cyclophosphamide and then maintenance with azathioprine for those with a less favorable prognosis [28,35,53,55]. Biological agents can also be used such as rituximab (B-cell-depleting agent) or mepolizumab (anti-IL5 antibody agent) [29,35,48]. Also being used is omalizumab which is a recombinant humanized anti-IgE antibody agent [58].

EGPA patients are a heterogeneous group and further research will divide them into sub-groups for more individualized management [48,53]. However current management options lead to complete remission in nearly 90% and the 10-year survival is 79.4%; relapses occur in 25% [28,53,57].

The French Vasculitis Study Group developed a five-point system (Five-factor score) that predicts death in these patients. These factors include reduced renal function (creatinine > 1.58 mg/dl or 140 µmol/l), proteinuria (>1 g/24 hours), cardiomyopathy, central nervous system involvement and gastrointestinal manifestations (i.e., GI hemorrhage, GI infarction, or pancreatitis) [35,55,59]. Mild disease is seen without any of these factors (five-year mortality rate of 11.9%) while the presence of one suggests severe disease (5-year mortality of 26%); two findings or more reflects very severe disease with a mortality rate of 46% in 5 years [59].

### **Conclusions**

Various revisions for definition and classification of CSS have occurred since 1951 when Churg and Strauss proposed a complex disorder characterized by asthma, vasculitis and hypereosinophilia [8]. The Churg-Strauss syndrome is now called eosinophilic granulomatosis with polyangiitis (EGPA) and is classified as a small-vessel vasculitis in association with antineutrophil cytoplasmic antibodies (ANCA) and various hypereosinophilic syndromes [14,35].

The development of EGPA involves an initial (prodromic) phase (with asthma and sinusitis), a second phase (eosinophilia and organ disease) and a third phase (vasculitis phase) with the development of small-vessel vasculitis [35]. Anti-MPO (anti-myeloperoxidase) pANCA (ANCA with a perinuclear fluorescence pattern) occurs in 40% [28,29]. Pulmonary findings may include non-segmental pulmonary consolidation (often bilateral), pulmonary nodules, areas of alveolar hemorrhage (which can be diffuse), hemoptysis and/or bilateral alveolar infiltrates on chest radiographs [14,25-27].

The EGPA Consensus Task Force has recently provided a variety of recommendations regarding evaluation and management [60]. Treatment includes the use of steroids and other immunosuppressive agents that includes cyclophosphamide and azathioprine. Biologic agents (i.e., rituximab, mepolizumab, and omalizumab) are used for refractory situations [29,35,48,58]. Patients with EGPA have a complex pathogenesis with overlap disorders and an ever evolving list of differential diagnoses; further studies are reclassifying them into various sub-groups for more individualized management protocols [48,53,61].

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