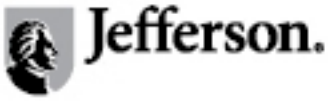

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Head and Neck Manifestations of Eosinophilic Granulomatosis with Polyangiitis: A Systematic Review.

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Abstract

Objective: To conduct the first and only systematic review of the existing literature on head and neck manifestations of Eosinophilic Granulomatosis with Polyangiitis in order to guide clinical decision making for the otolaryngologist.

Data Sources: PubMed, Cochrane Library, Scopus and LILACS. *Review Methods*: A systematic review of the aforementioned sources was conducted per PRISMA guidelines. *Results*: From an initial 574 studies, 28 trials and reports accounting for a total of 1,175 Eosinophilic Granulomatosis with Polyangiitis patients were included. Amongst clinical and cohort studies, 48.0% to 96.0% of all included patients presented with head and neck manifestations. In a distinct group of patients detailed in case reports describing patients presenting with head and neck manifestations on average fulfilled 4.6 American College of Rheumatology diagnostic criteria. Further, 95.8% of reported cases were responsive to steroids and 60% required additional therapy. *Conclusion*: Otolaryngologists are in a unique position for the early diagnosis and prevention of late complications of Eosinophilic Granulomatosis with Polyangiitis. The American College of Rheumatology criteria should be relied upon in the diagnostic work-up. Close surveillance of these patients in a multidisciplinary fashion and with baselines CBCs, chest radiographs and autoimmune labs is often necessary. Such patients with head and neck manifestations of the disease are nearly always responsive to steroids and often require additional immunosuppressive therapy or surgical intervention in cases of cranial neuropathies, temporal bone involvement and refractory symptoms.

Introduction

Eosinophilic Granulomatosis with Polyangiitis (EGPA), also known as Churg-Strauss Syndrome, is a rare systemic vasculitis affecting small and medium-sized vessels of the paranasal sinuses, lungs and nervous system. Initial presentations of EGPA often present with clinical profiles referable to otolaryngology departments. Otolaryngologists are consequently in a unique position to diagnose the disease early and prevent late complications. Due to the potential for extensive head and neck involvement, it is crucial for otolaryngologists to recognize EGPA's characteristic presentation and play a chief role in the interdisciplinary approach to management. To date there have been limited reviews of the literature highlighting generalized patient experiences and rare presentations of EGPA with an otolaryngologic focus.

EGPA clinically manifests in three delineated stages. The disease classically will first present in a prodromal stage which is characterized by asthmatic episodes, allergic rhinitis, rhinosinusitis and occasional nasal polyps.[1] EGPA's second phase will present with peripheral eosinophilia and eosinophilic infiltration of tissues.[2] Lastly, EGPA's third phase will manifest with polyneuropathies secondary to systemic vasculitis.[2] Late debilitating and fatal manifestations of EGPA include: myocarditis, sudden cardiac death, cerebral hemorrhages, ischemic strokes and bowel perforations.[2] As this disease course may persist or recur for several years, an otolaryngologist is afford a large window of time to monitor symptoms and make the diagnosis of EGPA. However this diagnosis may be difficult due to its variable presentation and lack of definitive objective tests to rule the disease in or out.

Historically multiple organizations have defined EGPA differently; however, the American College of Rheumatology's (ACR's) classification criteria has been widely accepted since the 1990's. According to the ACR, in order to be classified as EGPA an individual must present with at least four of six distinct findings: 1) a medical history of asthma, 2) eosinophilia of greater than 10%, 3) mono- or polyneuropathy, 4) non-fixed pulmonary infiltrates, 5) paranasal sinus abnormalities, or 6) biopsy including an artery, arteriole or venule documenting accumulated eosinophils in extravascular tissue.[3]

The objective of this systematic review is to review the current literature on EGPA and its otolaryngologic manifestations as well as investigating the role of the otolaryngologist to assist in early detection of disease. To the authors' knowledge this is the first and only systematic review of EGPA with a focus on head and neck manifestations.

Methods

Search strategy and selection

We conducted a focused literature review targeting the otolaryngological clinical presentations, diagnosis, treatments and outcomes of patients with EGPA. The systematic review was conducted per the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines.[4] Studies were evaluated by four independent reviewers in order to minimize appraisal bias.

Study eligibility and selection criteria were predefined to include: large study groups of general EGPA patients or case reports of EGPA patients with head and neck presentations. For the purposes of this review, diagnosis of EGPA was dependent upon meeting the ACR definition of the disease.

Only those clinical trial and cohort reviews that included a generalized EGPA population in which those patients with specific head and neck manifestations were identified and distinguished were to be included. Case series and reports of interest would include head and neck manifestations meeting the above inclusion criteria.

In March 2016 a search was initiated via PubMed, Cochrane Library, Scopus and LILACS databases. Key terms and their derivatives included: otolaryngology, ear, nose, throat, laryngology, rhinology, otology, cranial nerves, parotid, submandibular gland, sublingual gland, mastoid, paranasal sinuses, neck, churg-strauss syndrome, and eosinophilic granulomatosis with polyangiitis.

Search catalogs were collected and imported into RefWorks software. Exact and close duplicates were detected and manually reviewed for accuracy before deletion of repeated studies. Concerns and discrepancies regarding study relevancy between reviewers were discussed amongst all authors to reach a consensus if necessary.

Titles and abstracts of all search results were thoroughly reviewed for relevance and eligibility. Studies were screened and excluded based upon being: non-head and neck presentations, non-

English without available translation or non-EGPA specific studies. Studies in question were reviewed in full-text for clarity and excluded based on: overlapping patient populations, insufficient data, unavailable English full text, or failing to fulfill ACR criteria.

Data collection

Due to the rarity of head and neck manifestations of EGPA data was collected and organized into two distinct subsets: clinical trials or cohort studies and case report experiences. When available the following patient information was independently extracted from the relevant clinical trial and cohort studies: means of selection, population size, mean age, gender, head and neck manifestations, nasal and paranasal sinus histology, ANCA status, treatment and outcome.

Case series and reports meeting inclusion criteria were reviewed for and had the following data extracted: age, gender, ACR criteria met, non-paranasal head and neck manifestations, ANCA status, treatment and outcome. When available the source of extravascular eosinophilia and histology was noted. Treatment methods were further divided to steroidal and non-steroidal interventions. Outcomes were recorded with a focus on response to given therapy.

Included studies were evaluated in terms of study design, level of evidence and risk of bias. Level of evidence was determined by the Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence.[5] Risk of bias were assessed using the Cochrane Collaboration's tool for assessing risk of bias for a grading of low, high or unclear risk of bias.[6]

Results

Study Results

In our search we collected a total of 574 articles through the above named databases along with additional articles identified through references of seed studies used in introductory background research. Ultimately the results of 1 clinical trial, 6 retrospective cohort studies, 2 prospective cohort studies, 2 case series and 17 case reports accounting for a total of 1,175 EGPA patients were included for systematic review.[7-34]

Figure 1. PRISMA flow diagram for study inclusion

Table 1. Included study designs, levels of evidence and biases

As seen in table 1, of the 28 studies meeting our inclusion criteria levels of evidence ranged from 2 to 4. Risk of bias was either low or unclear in all studies. Unclear risk of bias presented as attrition bias due to insufficiently addressed incomplete outcome data in 3 studies. Reporting bias was unclear in 2 studies that provided insufficient clinical selection criteria.

Clinical trial and cohort study results

Table 2. Clinical trial and cohort study designs, demographics and symptoms

As seen in table 2, individual study patient population sizes ranged from 28 to 383 with a median of 101 patients. The mean age of patient populations ranged from 49.1 to 51.9. Male to female

ratio ranged from 58:43 to 39:54. Of these patients, documented head and neck manifestations included: various rhinologic conditions including sinusitis, nasal polyps, rhinitis nasal crusting and nasal obstruction along with otitis media, sensorineural hearing loss and facial nerve palsies. Of the total number of patients included in each individual study, 48.0% to 96.0% of patients presented with some head and neck involvement.

Table 3. Clinical trial and cohort study diagnostic findings, treatments and outcomes

As highlighted in table 3, patients with documented nasal or paranasal sinus biopsies demonstrated eosinophilic infiltration in 35% to 100% of samples. None of said biopsies had evidence of necrotizing vasculitis or eosinophilic granulomas. In these studies, the presence or absence of a blood vessel was not noted. Additionally the site of the biopsy collected was not specified beyond the general categories of "nasal cavity and paranasal sinuses" or "sinus or nasal mucosa".[9,10]

All patients in each population received some form of steroids. Cyclophosphamide was the second most common offered therapy and received in 49.5% to 71% of cases in which documentation was available. Additional common therapies included: azathioprine, methotrexate, rituximab, mycophenolate mofetil, intravenous immunoglobulin, leflunomide, anti-TNF alpha and plasma exchange. Insufficient data was available to be extracted regarding medication choice or dosage to correlate therapy with clinical presentation and outcome.

Case series and reports results

Nineteen publications accounted for 25 total patients with unique head and neck manifestations. Included patients had a mean age of 52.16 and male to female ratio of 2:5. Patients presented meeting an average of 4.6 ACR criteria. All but 1 patient presented with evidence of asthma and 90% of patients presented with extravascular eosinophilia on histology. Paranasal sinus abnormalities, eosinophilia, neuropathy and non-fixed pulmonary infiltrates presented in 88.%, 88.0%, 56.0%, and 48.0% of patients respectively. Of patients identified, 17 had known ANCA status of which 64.7% were ANCA positive.

Head and neck manifestations varied greatly and involved all systems. Such presentations included: recurrent laryngeal polyposis, anosmia, mastoiditis, intracranial abscesses and a diversity of cranial neuropathies. In the evaluation of these patients, extravascular eosinophilic histology was demonstrated in a diversity of head and neck specific biopsy sites as described by the case reports and series authors such as: laryngeal polyps, the ethmoid sinus, salivary glands and the mastoid.[28, 17, 25] In meeting ACR criteria, mastoid biopsies revealed eosinophilic granulomatous tissue while histology was limited to only eosinophilic infiltration or necrosis in all other above noted head and neck sites.

All but one (96.0%) of included patients with sufficient data received steroids and were found to be responsive in 95.8% of cases. Prednisone was the most commonly offered steroid (56.0%) followed by methylprednisolone (24.0%). The most common inducing dose of prednisone was 60 mg daily and tapered dosages ranged from 4 mg to 10 mg daily. Inducing dosages were administered from 5 days to 6 weeks. Additional medical or surgical therapy was offered in 56.0% of cases. Additional immunosuppressant therapy including cyclophosphamide, azathioprine and methotrexate were provided in 28.0% of cases. All included patients had either stabilization or

resolution of presenting symptoms. Of the 5 patients receiving cyclophosphamide 3 had resolution of symptoms, 1 experienced partial resolution of symptoms and 1 died of secondary pulmonary infection. Of the 3 patients receiving azathioprine, 2 achieved remission and 1 experienced partial resolution of symptoms. The 1 patient treated with methotrexate had resolution of symptoms at 1 year.

Discussion

From its seemingly indolent initial presentations to its debilitating advanced cardiac, neurological and gastrointestinal manifestations, the diagnosis and treatment of EGPA poses a clinical challenge to otolaryngologists. Through reviewing the existing literature we were able to construct a clinical profile of EGPA patients presenting with head and neck manifestations both common and rare. Data was extracted through 28 studies of varied designs including: clinical trials, prospective and retrospective cohort studies along with cases series and reports. Levels of data ranged from 2 to 4 with varying degrees of bias risk. Our review was potentially limited by the inherent quality of included studies. Many of the studies in the field were observational and pooled from various patient databases. Patient populations may be influenced by level of disease severity as well as the subsidiary medical departments being referred to at each medical center.

Patient group populations were consistent in age and gender ratios to one-another and previous reports.[35] Study samples had large variations in proportion of patients with head and neck manifestations. Differences may be attributed to the varied departments referred to within each group

or the definitions of head and neck manifestations by each study. Further, ANCA positive status varied. A majority of studies failed to demonstrate an association between patients with head and neck manifestations and ANCA status compared to the general EGPA population. This suggests that while a positive ANCA status may be helpful in the work-up of EGPA, it is often negative, not required in establishing a diagnosis of EGPA and has an unclear role in the head and neck phenotype of EGPA patients.

Case reports described varying degrees of severity and unique presentations of EGPA. These patients on average exceeded the minimum diagnostic criteria per the ACR guidelines suggesting that a CBC, PFT, EMG, tissue biopsy and full head and neck physical exam are all potentially necessary in the diagnosis of EGPA.

In all studies reviewed, no nasal or paranasal sinus biopsies revealed any eosinophilic granulomas and only one demonstrated evidence of necrotizing vasculitis. It is important to note that while EGPA is regarded as a vasculitis, biopsies are often marked by a non-destructive eosinophilic vessel wall infiltration.[36] While many did demonstrate an eosinophilic infiltration, this is a common histologic finding of upper airway tissue in atopic disease processes.

In understanding the questionable significance of biopsy findings, otolaryngologists would benefit from more objectively defined diagnostic guidelines. Although it is stated in the ACR guidelines that a blood vessel is necessary to be included in a biopsy, further elaboration would assist in diagnosing EGPA. For instance a minimum eosinophil concentration, an eosinophil to neutrophil ratio, a maximum eosinophil proximity to the vessel and a defined eosinophil pattern in relationship to the vessel would assist in determining the context of a sample. These descriptions would

also help define the significance of "eosinophilic infiltration" and "extravascular eosinophils" which are not currently objectively defined in guidelines.

In the setting of equivocal histopathologic findings, an otolaryngologist should also look for concomitant eosinophilia, a longstanding history of refractory or adult onset asthma and sinusitis along with any neuropathies. Moreover, even if nasal or paranasal sinus biopsy demonstrates extravascular eosinophilic histology, one should consider further biopsies when additional body system involvement is suspected to further substantiate the nasal and paranasal sinus findings. Of note, some authors have broadened the diagnostic threshold by proposing the limited form of EGPA. Such cases highlight presentations which fail to fulfill the clinical and histopathological characteristics of EGPA.[37] Although this concept is applied to earlier diagnostic criteria, it is important to recognize EGPA defined by the ACR criteria as a disease which exists on a continuum. Moreover, as otolaryngologists often encounter patients in the earlier prodromal stages of EGPA, neuropathies and eosinophilia may not yet be present.

Given our finding that eosinophilia and pulmonary infiltrates are common manifestations which follow asthma and polyposis, we recommend evaluation with a pre-operative or outpatient CBC with differential as well as a chest radiograph in the presence of any pulmonary symptoms to provide a baseline for patients with a high index of suspicion. Additionally we recommend basic autoimmune labs including ANA and ANCA in such patient. Although not a component of the ACR criteria or directly associated with head and neck manifestation severity, autoimmune findings are effective in ruling out other vasculitides and narrowing a diagnosis of EGPA. We also recommend when such patients undergo FESS for nasal polyposis, close communication with pathology is necessary to ensure the inclusion of blood vessels, to closely evaluate for eosinophilic

patterns and to rule out infection or malignancy. Due to the prevalence of chronic rhinosinusitis with polyposis in many otolaryngology practices, a multidisciplinary approach is often necessary prior to such a work-up. A benefit risk assessment is a strong area for future study given the constraints of the existing data.

In the treatment of patients with head and neck manifestations we see that nearly all were responsive to steroids and often required additional immunotherapy or surgical interventions. Ninety six percent of patients received some form of steroid. Patients on steroids alone had resolution of both clinical symptoms and laboratory abnormalities in 14 of 16 (87.5%) of cases. A common recommendation involved initial inducing dosages of 1 mg/kg of prednisone daily for 1 to 6 months then tapered to 4 to 10 mg of prednisone daily.

Patients with refractory symptoms, neuropathies and those with temporal bone involvement often required additional immunosuppressive therapy. The most common additional therapy offered with cyclophosphamide, often received in 6 to 12 pulses. Other immunosuppressants included azathioprine, methotrexate, rituximab and mycophenolate mofetil. Those receiving additional immunotherapy had resolution in 5 of 8 (62.5%) cases.

Ultimately, despite medical management trends, inadequate dosing and response information exists in drawing definitive recommendations for both steroid and immunosuppressive therapies. Additionally, future studies would benefit from objectively defining response to therapy and with consideration to biologic markers

Conclusion

Given the diagnostic challenge of EGPA, an otolaryngologist must maintain a high index of suspicion for the disease given its characteristic constellation of laboratory values, histologic findings and clinical manifestations which in isolation are often seemingly ubiquitous. Early diagnosis and treatment through multidisciplinary collaboration amongst otolaryngologists on the front line of treatment along with pulmonologists, allergists, immunologists, pathologists and rheumatologists is key in preventing widespread neuropathies and multi-system involvement.

Based on our review of previous otolaryngologists' experiences with EGPA, we recommend that patients presenting with both nasal polyposis and asthma undergo further investigation. Increased suspicion should be given to those patients with adult-onset asthma, poorly controlled asthmatic symptoms and those with recurrent nasal polyposis despite corticosteroid or surgical interventions.

Given our finding that eosinophilia and pulmonary infiltrates are common manifestations which follow asthma and polyposis, we recommend evaluation with a pre-operative or outpatient CBC with differential as well as a chest radiograph in the presence of any pulmonary symptoms to provide a baseline for the patient. Additionally we recommend basic autoimmune labs including ANA and ANCA in such patients with a high suspicion for EGPA. Although not a component of the ACR criteria or directly associated with head and neck manifestation severity, autoimmune findings are effective in ruling out other vasculitides and narrowing a diagnosis of EGPA. We also recommend when such patients undergo FESS for nasal polyposis, close communication with pathology is necessary to ensure the inclusion of blood vessels, to closely evaluate for eosinophilic patterns and to rule out infection or malignancy.

Ultimately EGPA is a rare process and little data exists in specifically guiding the otolaryngologic management of this disease. This is the first only systematic review of the existing literature with a head and neck focus. Due to a paucity of existing data for meta-analysis a treatment algorithm or dosage recommendations for corticosteroid and antimetabolite treatment cannot be reached at this time and is a fertile area for future study.

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Table 1. Included study designs, levels of evidence and biases

	Study Type	Level of Evidence	Risk of Bias
Al-Ammar (2009)	Case report	4	Low
Anar (2011)	Case report	4	Low
Bacciu (2006)	Retrospective cohort study	3	Low
Bili (1999)	Case series	4	Unclear reporting bias
Boin (2006)	Case report	4	Low
Comarmond (2013)	Retrospective cohort study	3	Unclear attrition bias
Durel (2015)	Retrospective cohort study	3	Low
Fernandes (2014)	Case report	4	Low
Healy (2012)	Retrospective cohort study	3	Unclear attrition bias
Ishiyama (2001)	Case series	4	Low
Martinez Del Pero (2008)	Case report	4	Low
Moor (2002)	Case report	4	Low
Moosig (2013)	Retrospective cohort study	3	Low
Ovidia (2009)	Case report	4	Low
Park (2015)	Case report	4	Low
Ribi (2008)	Clinical trial	2	Unclear reporting bias
Sablé-Fourtassou (2005)	Prospective cohort study	3	Unclear attrition bias
Saka (2007)	Case report	4	Low
Samson (2013)	Prospective cohort study	3	Low
Sinico (2005)	Retrospective cohort study	3	Low
Tallab (2014)	Case report	4	Low
Trovoli (2013)	Case report	4	Low
Visentin (2012)	Case report	4	Low
Ozaki (2012)	Case report	4	Low
Plaza (2001)	Case report	4	Low

Sale (1981)	Case report	4	Low
Byun (2014)	Case report	4	Low
Mazzantini (1997)	Case report	4	Low

Table 2. Clinical trial and cohort study designs, demographics and symptoms

	Selection	Patients (n)	Mean age	Gender male/ female	ENT Involvement no. (%)	ENT Manifestations
Bacciu (2006)	Retrospective review of all CSS patients in single study group from 1997 to 2004.	28	51.3	11/10	21 (75%)	Allergic rhinitis, sinusitis, nasal polyps, otitis media, SNHL, facial nerve palsy
Comarmond (2013)	Retrospective review of patients in a single cohort from 1957 to June 2009	383	50.3	199/184	184 (48.0%)	Sinusitis, rhinitis, nasal polyps
Durel (2015)	Retrospective review of patients identified in 3 tertiary centers databases for from 1990 to 2011	101	49.2	58/43	97 (96.0%)	Sinusitis, rhinitis, nasal polyps, nasal obstruction
Healy (2012)	Retrospective review of cases reported to FDA from 1997 to 2003	93	-	-	59 (63.4%)	Sinusitis
Moosig (2013)	Retrospective cohort study of cases documented at a single referral center from 1990 to 2009	150	49.1	76/74	140 (93.3%)	Sinusitis, nasal mucosa inflammation, nasal polyps, middle ear infection

Ribi (2008)	Multicenter screening of patients diagnosed with CSS from 1994 to 2005.	72	51.7	38/34	50 (69.4%)	Sinusitis
Sablé-Fourtassou (2005)	Multi-center cohort study of French Vasculitis Study Group and European Vasculitis Study Group patients enrolled in prospective trials from 1995 to 2002.	112	52	55/57	83 (74.1%(	Sinusitis, rhinitis, nasal polyps, nasal obstruction
Samson (2013)	Clinical reports of patients enrolled in 2 prospective, randomized open label clinical trials from 1994 to 2005)	118	51.9	64/54	88 (74.6%)	Sinusitis, crusting, otitis
Sinico (2005)	Retrospective review of ANCA tested patients identified among internal medicine departments in 4 general hospitals from 1989 to 2004.	93	51.6	39/54	72 (77.4%)	Sinusitis

Table 3. Clinical trial and cohort study diagnostic findings, treatments and outcomes

	ANCA+: No. All (%) No. ENT (%)	Nasal and paranasal sinus biopsies	Treatment	Outcome
Bacciu (2006)	- 10 (47.6%)	5: 100% eosinophilic polyposis or infiltrates.	-CS and nonspecified immunosuppressive treatment in all cases	-No head and neck manifestation relapses; no mortalities.
Comarmond (2013)	108 (28.2%) 64 (34.8%)	23: 35% granuloma, necrotizing vasculitis or eosinophilic infiltration.	-383 CS, 217 CYP; 98 AZA; 26 MTX; 3 rituximab.	-Vasculitis relapse in 97; asthma flares, sinusitis or increased eosinophilia in 72; 236 required maintenance CS
Durel (2015)	43 (42.5%) 41 (42.3%)	-	-101 CS; 45 CYP. -Maintenance therapy: 29 CS alone; 24 AZA; 22 rituximab; 15 mycophenolate mofetil; 1 MTX;1 IVIg	-74 with complete remission.
Healy (2012)	15 (16.1%) 9 (15.3%)	-	-	-
Moosig (2013)	45 (30%) 41 (29.3%)	-	-150 CS; 107 CYP; 105 MTX; 49 AZA; 32 leflunomide; 17 interferon alpha; 10 anti-TNF alpha; 1 rituximab; 5 IVIg.	-70 in remission.

Ribi (2008)	29 (40.3%) - (-%)	13: 9 eosinophilic infiltration.	-72 CS; 10 AZA; 9 CYP.	-77 on CS; 5 on AZA and 7 on CYP with remission.
Sablé-Fourtassou (2005)	43 (38.4%) 36 (43.4%)	-	-Mild disease: CS alone -Severe disease received steroids along with 6 to 12 pulses of CYP therapy.	-102 in remission.
Samson (2013)	48 (40.7%) - (-%)	-	-Mild disease CS alone -Severe disease CS with 6 to 12 pulses of CYP.	-34 in remission. Overall survival of 90% at 7 years.
Sinico (2005)	35 (37.6%) 27 (37.5%)	-	-93 CS; 42 CYP; 5 MTX, 1 AZA, 1 IVIg; 4 and plasma exchange.	- 5 year survival rate of 95.1%
Abbreviations: ANCA+, Anti-neutrophil cytoplasmic antibody positive; AZA, Azathioprine; CS, corticosteroids; CYP, cyclophosphamide; IVIg, intravenous immunoglobulin; MTX, methotrexate				

Figure legend

Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram for study inclusion and exclusion.