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# Ear Nose and Throat (ENT) Manifestations in Granulomatosis with Polyangiitis in Patients from Saudi Arabia

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**Abstract:** Granulomatosis with polyangiitis (GPA) frequently affects ear, nose and throat (ENT) at disease onset. Our aim was to report on our experience with the ENT manifestations in GPA patients, therapy and outcome. A retrospective study of GPA patients was performed who followed up in Rheumatology clinics at King Khalid University hospital, Riyadh during the period 1990-2016. Demographics, different ENT manifestations, laboratory and diagnostic features, therapy and outcome of GPA patients were retrieved from their medical charts. ENT involvement was observed in 15 (65.2%) of the 23 GPA cases identified. Otologic symptoms were noted in 3 (13.0%), nose and sinus symptoms in 13 (56.5%) and throat symptoms in 3 (13.0%) GPA patients. Epistaxis (39.1%) was the most prevalent nose and sinus symptom followed by sinusitis (30.4%), otitis media and hearing loss were the frequent otologic symptoms, oral ulcers and hoarseness of voice constituted frequent throat symptoms in GPA patients. Of the 15 ENT-GPA patients, 9 were males and 6 were females (male: female; 1.5: 1). Their mean age at disease onset was 33.8 ± 18.3 (range 11-57) years and mean duration of disease was 10.1 ± 5.9 (range 1-20) years. ANCA was positive in 93.3% ENT-GPA patients, 73.3% had c-ANCA and 20.0% had p-ANCA. Infections were noted in 33.3% ENT-GPA patients that included pneumonia, septicemia, esophageal candidiasis, bacterial meningitis and herpes zoster. All patients received oral prednisolone, 60.0% received intravenous cyclophosphamide, 20.0% refractory cases received rituximab doses, and the disease outcome was good. Comparison of ENT- GPA with non- ENT GPA cohort showed that 26.7% ENT-GPA patients had renal involvement compared to 87.5% non ENT-GPA patients ($p = 0.009$). Our study showed that the frequency of ENT symptoms in our GPA patients was less compared to other studies, and the disease outcome was good. Renal involvement was significantly less frequent in ENT-GPA cohort compared to non ENT-GPA cohort.

**Keywords:** Granulomatosis with Polyangiitis, ENT Manifestations, Sinonasal Involvement, Otologic Involvement

## 1. Introduction

Granulomatosis with polyangiitis (GPA) is a rare autoimmune multi-systemic disease characterized by necrosis, granulomatous inflammation and vasculitis of small vessels mainly involving upper and lower respiratory tracts and kidneys [1-3]. Antineutrophil cytoplasmic antibodies (ANCA) are found in almost 90% of GPA patients [4]. Ear, nose and throat (ENT) region is frequently affected and is often the initial manifestation of GPA [5-7]. Otologic involvement occurs in 19-61%, sinonasal involvement 85% and oral involvement in 6-13% of GPA patients [8-11].

We intended to study the ENT manifestations in GPA patients from our region, disease course, therapy and the outcome.

## 2. Materials and Methods

We performed a retrospective chart review of GPA patients diagnosed and followed up in Rheumatology clinics at King Khalid University hospital, King Saud University, Riyadh, during the period 1990-2016. GPA was diagnosed as per Chapel Hill Consensus Conference (CHCC) definition of

GPA [12]. The study was approved by Institutional Review Board of College of Medicine, King Saud University, Riyadh. We retrieved demographic data including, patient's age, age at onset of disease, gender, duration of disease, interval between onset of symptoms and diagnosis and duration of follow up. Clinical, hematological and immunological data were also collected. ANCA were detected by indirect immunofluorescence (for detecting c-ANCA and p-ANCA) and enzyme-linked immunosorbent assay (ELISA; for detecting PR3- and /or MPO-ANCA). ENT assessment was done by clinical evaluation, nasal endoscopy, audiometry, tympanometry, endoscopic laryngoscopy and also by X ray, C T, MRI and biopsy of ear, sinus, nasopharyngeal, subglottic and buccal regions. Therapy received by the patients, disease course and outcome were retrieved. ENT-GPA and non ENT-GPA groups were compared.

*Statistical Analysis*: Statistical analysis of the data was performed using IBM SPSS statistics for Windows Version 19.0. (Armonk, NY: IBM Corp) and presented as percentages and means. ENT-GPA and non ENT-GPA groups were compared using chi-square and t-tests and a p-value $< 0.05$ was considered statistically significant.

# 3. Results

We found 23 cases of GPA during the study period. ENT involvement was observed in 15 (65.2%) patients (ENT-GPA) and the remaining 8 patients did not show ENT symptoms (non ENT-GPA). Otologic symptoms were noted in 3 (13.0%), nose and sinus symptoms in all 13 (56.5%) and oral symptoms in 3 (13.0%) GPA patients. Epistaxis (39.1%) was the most prevalent nose and sinus symptom followed by sinusitis (30.4%), frequent otologic manifestations included otitis media and hearing loss and oral ulcers and hoarseness of voice were the frequent oral symptoms in GPA patients (Table 1).

***Table 1.*** *ENT symptoms in 23 GPA patients.*

| Symptoms | n (%) |
|---|---|
| Ear | 3 (13.0) |
| Tinnitus | 1 (4.3) |
| Vertigo | 1 (4.3) |
| Hearing loss | 2 (8.7) |
| Ear pain | 1 (4.3) |
| Otitis media | 1 (4.3) |
| Ear discharge | 2 (8.7) |
| Bilateral mastoiditis | 1 (4.3) |
| Nose and sinus | 13 (56.5) |
| Allergic rhinitis | 2 (8.7) |
| Rhinorrhea | 3 (13.0) |
| Epistaxis | 9 (39.1) |
| Nasal inflammation | 7 (30.4) |
| Nasal ulcers | 2 (8.7) |
| Nasal polyps | 3 (13.0) |
| Nasal septum deviation causing obstruction in nasal cavity | 3 (13.0) |
| Sinusitis | 7 (30.4) |
| Oral | 3 (13.0) |
| Oral ulcers | 2 (8.7) |
| Oral pain | 2 (8.7) |
| Hoarseness of voice | 2 (8.7) |
| Parotid swelling | 1 (4.3) |
| Laryngeal mass with vocal cord invasion | 1 (4.3) |

Of the 15 ENT-GPA patients, 9 (60.0%) were males and 6 (40.0%) were females (male: female; 1.5: 1). Mean present age (± SD) of ENT-GPA group was 44.4 ± 15.0 (range 24-62) years, mean age at onset of disease was 33.8 ± 18.3 (range 11-57) years, mean interval between onset of symptoms and diagnosis was 7.3 ± 11.3 (range 0-30) months and mean duration of disease was 10.1 ± 5.9 (range 1-20) years.

Constitutional symptoms occurred in 7 of 15 ENT-GPA (46.7%) patients which consisted of fatigue in 3 (20.0%), fever in 7 (46.7%), anorexia in 4 (26.7%) and weight loss in 7 (46.7%) patients. Ophthalmic involvement was observed in 7 (46.7%), arthritis in 2 (13.3%), skin rash in 2 (13.3%) comprising of palpable purpuric lesions, pulmonary involvement in 9 (60.0%), renal involvement in 4 (26.7%), end stage renal disease in 2 (13.3%) and neurological involvement in 1 patient (6.7%). Two patients were admitted to intensive care unit. None had lymphadenopathy.

Laboratory findings in 15 ENT-GPA patients are summarized in Table 2. ANCA was found positive in 14 (93.3%) patients and 1 patient was ANCA negative. Of the 14 ANCA positive patients, 11 (73.3%) were c-ANCA positive and 3 (20.0%) patients were p-ANCA positive. PR3 ANCA was tested in 10 patients and it was positive in all while MPO tested in 10 patients was negative in all of them.

***Table 2.*** *Laboratory parameters in 15 ENT-GPA patients.*

| Parameters | n (%) |
|---|---|
| Leukocytosis | 6 (40.0) |
| Anemia | 8 (53.3) |
| Thrombocytopenia | 0 (0.0) |
| Elevated ESR | 10 (66.7) |
| Elevated serum creatinine | 2 (13.3) |
| Abnormal creatinine clearance | 2 (13.3) |
| ANCA Pos | 14 (93.3) |
| ANCA Neg | 1 (6.7) |
| c ANCA Pos | 11 (73.3) |
| p ANCA Pos | 3 (20.0) |
| PR3 Pos (n=10) (not done=4) | 10 (100.0) |
| PR3 Neg (n=10) (not done=4) | 0 (0.0) |
| MPO Pos (n=10) (not done =4) | 0 (0.0) |
| MPO Neg (n=10) (not done =4) | 10 (100.0) |

Diagnostic tests, biopsies and the results are presented in Table 3. Nasal biopsy showed necrotizing granulomatous vasculitis of nasal mucosa, suggestive of GPA in 4 patients. Sinus X ray showed bilateral chronic maxillary sinusitis and maxillary sinus opacity. Sinus CT showed mucosal thickening, maxillary sinusitis, polypoidal mucosal thickening in maxillary antrum with curved nasal septum. Sinus MRI showed otomastoiditis and maxillary sinus opacification, large turbinates nasal cavity with obstruction. A large mass was seen in subglottic region invading vocal cords by laryngoscopy. Renal biopsy was consistent with GPA in 3 (23.1%) patients.

***Table 3.*** *Radiologic tests and biopsies results in 15 ENT GPA patients.*

| Diagnostic tests and results | no |
|---|---|
| *Nasal biopsy* | |
| Necrotizing granulomatous vasculitis of nasal mucosa, Consistent with GPA | 4 |
| Necrotic granuloma tissue with multiple abscesses, nasopharyngeal mass with infection | 1 |
| *Sinus X ray* | |
| Bilateral chronic maxillary sinusitis | 1 |
| Maxillary sinus opacity | 1 |
| *Sinus CT* | |
| Mucosal thickening | 4 |
| Maxillary sinusitis | 4 |
| Polypoidal mucosal thickening in maxillary antrum with curved nasal septum | 1 |
| Ethmoidal sinus opacification | 1 |
| Multiple sinus polyps | 1 |
| Nasal septum deviation | 1 |
| *Sinus MRI* | |
| Otomastoiditis and maxillary sinus opacification, large turbinates nasal cavity with obstruction | 1 |
| *Laryngoscopy* | |
| Large mass in subglottic region with vocal cord invasion | 1 |
| *Telescopic laryngotroboscopy and chip tip laryngoscopy* | |
| Bleeding subglottic mass by both procedures | 1 |
| *Subglottic biopsy* | |
| Large mass, necrotic granuloma tissue with multiple abscesses and infection | 1 |
| *CT buccal region* | |
| Inflammatory changes in pharynx and larynx | 1 |

***Table 4.*** *Therapy in 15 ENT-GPA patients.*

| Therapy | n (%) |
|---|---|
| Prednisolone | 15 (100.0) |
| Methyl Prednisolone | 8 (53.3) |
| Oral Cyclophosphamide | 6 (40.0) |
| Intravenous Cyclophosphamide | 9 (60.0) |
| Azathioprine | 6 (40.0) |
| Cell cept | 3 (20.0) |
| Methotrexate | 3 (20.0) |
| Infliximab | 1 (6.7) |
| Rituximab | 3 (20.0) |

ENT-GPA patients were admitted to hospital for various reasons including oral ulcers, hearing loss, myringotomy, mastoidectomy, intravenous cyclophosphamide (IV CYC) infusion and rituximab administration. Infections were noted in 5 (33.3%) patients which included pneumonia in 2, septicemia in 1, esophageal candidiasis and bacterial meningitis in 1 and herpes zoster in 1 patient. Two patients were admitted to intensive care unit for renal and pulmonary symptoms flare up. Regarding therapy, it was noted that all patients received oral prednisolone (PSL), 9 (60.0%) received IV CYC and 3 (20.0%) patients received rituximab doses (Table 4). One patient developed diabetes mellitus as a side effect of oral PSL, IV CYC had to be discontinued in one patient due to alopecia, oral CYC caused alopecia and hypopigmentation on hands and feet in one patient. All patients were in remission on treatment at the time of follow up. There were no deaths.

The results of comparison of ENT-GPA cohort with non ENT-GPA cohort are summarized in Table 5. We found older age at disease onset, elevated serum creatinine, cutaneous and renal involvement significantly associated with non ENT-GPA cohort but not with ENT-GPA ($p < 0.05$). Renal involvement was less frequent in ENT-GPA cohort (26.7%) compared to non ENT-GPA cohort (87.5%) ($p = 0.009$). Other parameters compared were non-significant.

***Table 5.*** *Comparison of ENT-GPA and non ENT-GPA patients.*

| Characteristic | ENT GPA (n=15) | Non-ENT GPA (n=8) | p value |
|---|---|---|---|
| Age at disease onset (years) Mean ±SD | 33.9 ± 18.3 | 46.2 ± 11.6 | 0.033* |
| Range | 11-57 | 30-63 | |
| | **no (%)** | **no (%)** | **p value** |
| Females | 6 (40.0) | 3 (37.5) | 0.633 |
| M: F ratio | 1.5: 1 | 1.7: 1 | |
| Eye involvement | 7 (46.7) | 2 (25.0) | 0.400 |
| Cutaneous involvement | 2 (13.3) | 5 (62.5) | 0.026* |
| Pulmonary involvement | 9 (60.0) | 6 (75.0) | 0.657 |
| Renal involvement | 4 (26.7) | 7 (87.5) | 0.009* |
| Neurological involvement | 1 (6.7) | 1 (12.5) | 0.585 |
| Elevated Serum creatinine | 2 (13.3) | 5 (62.5) | 0.026* |
| ANCA positive | 14 (93.3) | 7 (87.5) | 0.585 |
| c-ANCA positive | 11 (73.3) | 6 (75.0) | 0.593 |
| p-ANCA positive | 3 (20.0) | 1 (12.5) | 0.593 |

*p value significant.

# 4. Discussion

ENT involvement is often the first manifestation of GPA [6]. ENT involvement was found in 65.2% of our GPA patients, which is less than what is found in previous studies reporting 72%-99% [1, 5, 13-16]. A study from Tunisia has reported initial ENT involvement of 56% and 83% at follow up [17]. Nose and sinus are reported to be affected by GPA in 55-90% of patients, which is comparable to our finding of 56.5% [8, 9, 16, 18]. Nasal crusting and obstruction, rhinorrhea, nasal discharge, epistaxis, sinusitis, nasal septum deviation and perforation, edema of nasal mucosa and turbinates, and saddle nose deformity are frequently reported sino nasal symptoms [19, 20]. Among our GPA patients, epistaxis, nasal inflammation and sinusitis were very frequent however, we did not find nasal septal perforation nor saddle nose deformity. Sinusitis and nasal inflammation were found in 30.4% of our patients. These figures are lower than those reported elsewhere [10, 15, 16]. Likewise all other sino nasal symptoms occurred less frequently in our patients compared to other studies [15, 16].

Overall, otologic manifestations are reported to constitute 36.4% of all cases while it was 13% in our GPA patients [21]. Otological manifestations namely otitis media and hearing loss can be the initial presentations of GPA [22-24]. It is reported that otitis media occurs in 25% of GPA patients and hearing loss in 6% while in our patients, otitis media was observed in 4.3% and hearing loss in 8.7% patients [22].

Thirteen percent of our patients had oral involvement, similar to previous reports indicating occurrence in 6-13% GPA patients [10]. Vocal cord involvement with resulting hoarseness of voice was seen in 8.7% of our patients which is similar to reported rate of 10% [25].

Sininasal biopsies usually show nonspecific inflammation but could be the initial manifestation of GPA [16]. Para nasal sinus and nose biopsies are shown to be highly diagnostic of GPA [22, 24]. In accordance with this sinonasal biopsies aided diagnosis in our GPA patients. Some studies have shown that sinus imaging with CT and MRI reveals a spectrum of non-specific findings [26, 27]. Radiographic sinonasal pathological features including mucosal thickening is seen in 87.7%, bony destruction in 59.9% and nasal septal erosion in 59.4% patients [26]. Maxillary sinuses were found to be the most frequently affected paranasal sinuses by CT imaging [27].

Our patients with refractory disease responded to rituximab therapy. It has been reported that rituximab is an effective treatment for ENT manifestations of GPA and patients treated with rituximab were 11 times less likely to have active ENT disease than patients treated with other therapies [28].

Comparison of our ENT-GPA cohort with non-ENT-GPA cohort showed that ENT-GPA patients were younger and had low risk of renal involvement compared to non ENT-GPA patients which is similar to previous studies [16, 29]. It is suggested that ENT GPA is a milder disease subset with lower renal involvement and could predict a lower mortality rate compared to non-ENT GPA [16].

# 5. Conclusion

This study is the first study of ENT-GPA patients from our region. It showed that the frequency of ENT symptoms in our GPA patients is less (65.2%) compared to other studies (72%-99%). Otologic symptoms were noted in 13.0%, nose and sinus symptoms in 56.5% and throat symptoms in 13.0%. ANCA was positive in 93.3% patients, 73.3% were c-ANCA and 20.0% patients were p-ANCA positive. Patients responded to IV CYC and rituximab treatment. The disease outcome was good. Renal involvement was seen significantly less frequent in our ENT-GPA cohort compared to non ENT-GPA cohort which is in accordance to a previous report suggesting that ENT GPA may be a milder disease with lower renal involvement compared to non-ENT GPA. ENT manifestations can be the initial symptoms in GPA patients and carry a probability of misdiagnosis. GPA should be suspected in patients who do not respond to primary ENT treatment. Early diagnosis and treatment can improve the prognosis of these patients.

# Conflict of Interest

The authors declare that they have no competing interests.

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