Ocular Manifestations in Granulomatosis with Polyangiitis Patients from Saudi Arabia

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Abstract

Eye and/or orbit involvement occurs in Granulomatosis with polyangiitis (GPA) patients frequently. The aim of our study was to describe the clinical manifestations, therapy and outcome of ocular involvement in our GPA patients. A retrospective study was conducted including patients with GPA who followed up in Rheumatology clinics during 1990-2016 at King Khalid University Hospital, Riyadh. Information relating to demographics, ocular manifestations, laboratory findings, therapy and outcome of GPA patients were noted. Ocular involvement was detected in 9 (39.1%) of the 23 GPA cases identified. The mean age of ocular GPA patients was 51.8 (range 27 - 62) years, the mean age at onset of disease was 39.6 (range 11 - 57) years and the mean duration of disease was 9.0 (range 2 - 19) years. Concomitant ear, nose, throat and sino-nasal manifestations occurred with ocular symptoms in 77.8% GPA patients. The most frequent manifestations were, eye pain (66.7%), scleritis/episcleritis (55.6%), eye redness and itching (55.6% each). Antineutrophil cytoplasmic antibodies (ANCA) were positive in 88.9% patients, 55.6% had c-ANCA and 33.3% had p-ANCA. Infections were observed in 22.2% of patients, which included pneumonia in one patient and esophageal candidiasis and bacterial meningitis in another. All patients received oral prednisolone, 44.4% received intravenous cyclophosphamide, 22.2% refractory cases received rituximab doses and the disease outcome was good. Comparison of ocular GPA with non-ocular GPA patients showed that 77.8% of ocular GPA patients had concomitant sino-nasal symptoms compared to 42.9% in non-ocular GPA patients and 22.2% of the ocular GPA patients had renal involvement compared to 64.3% in non-ocular GPA patients (p = 0.049). We found that the frequency of ocular manifestations in our GPA patients was similar to reports elsewhere, and the most frequent symptom was eye pain and scleritis/episcleritis.
Keywords

Granulomatosis with Polyangiitis, Ocular Manifestations, Orbital Involvement, Lacrimal Gland Involvement

1. Introduction

Granulomatosis with polyangiitis (GPA) is an autoimmune granulomatous inflammatory disease that affects multiple organs and is characterized by small vessel necrotizing vasculitis. It predominantly affects upper and lower respiratory tracts and kidneys [1] [2]. Ophthalmic involvement of eye and/or orbit occurs in up to 60% of GPA patients and is the initial manifestation in 8% - 16% [3] [4] [5] [6]. The eye is considered an immune-privileged site, with a high predisposition to develop anti-inflammatory and immunosuppressive mechanisms to prevent the consequences of inflammation [7]. The most common clinical findings are proptosis, scleritis, episcleritis, retinal, and optic nerve vasculitis, nasolacrimal duct obstruction, uveitis, and dacryocystitis [3] [8]. Permanent blindness may occur in 8% of the patients [1] [4]. GPA is the most common rheumatic disease to affect the orbit [9]. Orbital lesions are reported in 5% - 31% GPA patients, which can be bilateral in 14% - 58% while the lacrimal gland may be involved initially [1] [4] [10]-[15].

Our aim was to study the ocular manifestations in GPA patients from our region, its disease course, therapy and the outcome.

2. Materials and Methods

The medical charts of all GPA patients diagnosed and followed up in Rheumatology clinics at King Khalid University Hospital, King Saud University, Riyadh, during the period 1990-2016 were reviewed retrospectively. GPA was diagnosed as per Chapel Hill Consensus Conference (CHCC) definition [16]. Study approval was obtained from Institutional Review Board of College of Medicine, King Saud University, Riyadh. GPA patients who underwent ophthalmic evaluation for ocular symptoms and were diagnosed to have ocular manifestations of GPA were included in the present study. We recorded the demographic data including, patient’s age, age at disease onset, gender, duration of disease, interval between onset of symptoms and diagnosis and duration of follow up. Clinical, hematological and immunological data were also retrieved. Eye and orbital/lacrimal gland computed tomography (CT) and biopsy findings were noted. Antineutrophil cytoplasmic antibodies (ANCA) were detected by indirect immunofluorescence (for detecting c-ANCA and p-ANCA) and enzyme-linked immunosorbent assay (ELISA) for detecting proteinase 3 (PR3) and/or myeloperoxidase (MPO) ANCA). Treatment given to the patients, disease course and its outcome were also recorded.

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. We compared ocular GPA with non-ocular GPA groups using chi-square and t-tests and a p-value < 0.05 was considered statistically significant.

3. Results

Twenty-three cases of GPA were included in this study. Eye was involved in nine (39.1%) patients (ocular-GPA) and the remaining 14 patients did not show eye symptoms (non-ocular GPA). Of the nine ocular-GPA patients, seven (77.8%) were males and two (22.2%) were females (male: female; 3.5:1). Mean present age (±SD) was 51.8 ± 12.6 (range 27 - 62) years, mean age at onset of disease was 39.6 ± 17.2 (range 11 - 57) years, mean interval between onset of symptoms and diagnosis was 7.3 ± 11.2 (range 0 - 30) months, mean duration of disease was 9.0 ± 5.3 (range 2 - 19) years and mean duration of follow up was 5.5 ± 3.96 (range 0.8 - 10.8) years.

Constitutional symptoms occurred in three (33.3%) patients including fatigue in one (11.1%), fever in three (33.3%), anorexia in one (11.1%) and weight loss in two (22.2%) patients. Arthralgia was the presenting symptom in four (44.4%) patients and none had lymphadenopathy. Other systems involved were; ENT in seven (77.7%), skin in two (22.2%), pulmonary in six (66.7%), renal in two (22.2%), neurological in one (11.1%) and gastrointestinal in one (11.1%) patient. Skin involvement was in the form of palpable purpuric lesions. Various eye manifestations are summarized in Table 1. Eye pain (66.7%) and scleritis/episcleritis

Table 1. Eye symptoms in 9 ocular-GPA patients.

| Eye symptoms                                      | No. (%) |
|---------------------------------------------------|---------|
| Eye pain                                          | 6 (66.7) |
| Eyelid swelling                                   | 3 (33.3) |
| Eye redness                                       | 5 (55.6) |
| Eye itching                                       | 5 (55.6) |
| Eye discharge                                     | 1 (11.1) |
| Conjunctivitis                                    | 4 (44.4) |
| Blurred vision                                    | 1 (11.1) |
| Cataract                                          | 1 (11.1) |
| Orbital and lacrimal gland swelling               | 1 (11.1) |
| Scleritis                                         | 1 (11.1) |
| Nodular scleritis                                 | 2 (22.2) |
| Episcleritis                                      | 2 (22.2) |
| Uveitis                                           | 1 (11.1) |
| Bilateral myopic degeneration                     | 1 (11.1) |
| Peripheral corneal infiltrates                    | 2 (22.2) |
| Retinal detachment                                | 1 (11.1) |
(55.6%) constituted the most frequent eye symptoms followed by conjunctivitis (44.4%). One patient had recurrent episcleritis with bilateral myopic degeneration and one patient had corneal infiltrates with retinal detachment and vasculitis.

Laboratory findings in nine ocular-GPA patients are summarized in Table 2. ANCA was positive in eight (88.9%) patients and negative in one patient. Among the eight ANCA positive patients, c-ANCA was positive in five (55.6%) and p-ANCA was positive in three (33.3%) patients. PR3 ANCA was positive in all four patients tested and MPO was negative.

Eye CT showed granuloma. Upper eyelid and lacrimal gland biopsy showed non-necrotizing granulomatous vasculitis. One patient had lacrimal gland drainage and another patient had surgery performed for nodular scleritis.

Patients were admitted to hospital for intravenous cyclophosphamide (IV CYC) infusion, rituximab administration, disease flares and infections. Two patients (22.2%) had infections which included pneumonia in one and esophageal candidiasis and bacterial meningitis in the other patient. They were on corticosteroids and IV CYC treatment. One patient was admitted to intensive care unit for evaluation of pulmonary symptoms flare up, bilateral pleural effusion and pulmonary lesion. All patients were given oral prednisolone (PSL), four (44.4%) patients received IV CYC and two (22.2%) patients received rituximab doses (Table 3). There were no deaths and all patients were in remission on treatment at the time of follow up.

The results of comparison of ocular GPA with non-ocular GPA group of patients are presented in Table 4. There were more males compared to females (7:2) in ocular GPA group while equal number of males and females were affected in non-ocular GPA (7:7). The proportions of ear nose throat (ENT) and

| Lab Parameters                  | No. (%)                  |
|---------------------------------|--------------------------|
| Leukocytosis                    | 2 (22.2)                 |
| Anemia                          | 3 (33.3)                 |
| Thrombocytopenia                | 0 (0.0)                  |
| Elevated ESR                   | 6 (66.7)                 |
| Elevated serum creatinine       | 2 (22.2)                 |
| Abnormal creatinine clearance   | 2 (22.2)                 |
| ANCA Positive                   | 8 (88.9)                 |
| ANCA Negative                   | 1 (11.1)                 |
| c ANCA Positive                 | 5 (55.6)                 |
| p ANCA Positive                 | 3 (33.3)                 |
| PR3 Positive (n = 4) (not done = 4) | 4 (100.0)               |
| PR3 Negative (n = 4) (not done = 4) | 0 (0.0)                 |
| MPO Positive (n = 4) (not done = 4) | 0 (0.0)                 |
| MPO Negative (n = 4) (not done = 4) | 4 (100.0)               |
Table 3. Therapy in 9 ocular-GPA patients.

| Therapy                        | No. (%) |
|--------------------------------|---------|
| Prednisolone                   | 9 (100.0) |
| Methyl Prednisolone            | 3 (33.3)  |
| Oral Cyclophosphamide          | 4 (44.4)  |
| Intravenous Cyclophosphamide   | 4 (44.4)  |
| Azathioprine                   | 4 (44.4)  |
| Methotrexate                   | 4 (44.4)  |
| Infliximab                     | 1 (11.1)  |
| Rituximab                      | 2 (22.2)  |

Table 4. Comparison of ocular GPA and non-ocular GPA patients.

| Characteristic                  | Ocular GPA (n = 9) | Non-Ocular GPA (n = 14) | p value |
|--------------------------------|-------------------|-------------------------|---------|
| Age at disease onset (years)   | Mean ± SD         | Range                   | 0.893   |
|                                | 39.6 ± 17.2       | 11 - 57                 |         |
| M:F ratio                      | 3.5:1             | 1:1                     |         |
| ENT involvement                | 7 (77.8)          | 8 (57.1)                | 0.311   |
| Sino nasal involvement         | 7 (77.8)          | 6 (42.9)                | 0.111   |
| Cutaneous involvement          | 2 (22.2)          | 5 (35.7)                | 0.493   |
| Pulmonary involvement          | 6 (66.7)          | 9 (64.3)                | 0.907   |
| Renal involvement              | 2 (22.2)          | 9 (64.3)                | 0.049*  |
| Neurological involvement       | 1 (11.1)          | 1 (7.1)                 | 0.742   |
| Elevated Serum creatinine      | 2 (22.2)          | 5 (35.7)                | 0.493   |
| ANCA positive                  | 8 (88.9)          | 13 (92.9)               | 0.742   |
| c-ANCA positive                | 5 (55.6)          | 12 (85.7)               | 0.231   |
| p-ANCA positive                | 3 (33.3)          | 1 (7.1)                 | 0.231   |

*p value significant.

Sino-nasal involvement were higher in ocular GPA (77.8% each) compared to non-ocular GPA (57.1%, 42.9%) patients; however, they were not statistically significant. Similarly, c-ANCA were more prevalent in non-ocular GPA patients (85.7%) compared to ocular GPA patients (55.6%), though not significant statistically (p > 0.05). There was significant association of renal involvement with non-ocular GPA patients (64.3%) compared with ocular GPA (22.2%) patients (p = 0.049).

4. Discussion

Ocular involvement has been reported to occur in 14% - 61% GPA patients [1] [6] [17] [18] [19]. The frequency of 39.1% in our patients falls within this range. It is known to occur in both limited and severe forms of GPA and can be the ini-
tial symptom or occur in as high as 87% GPA patients at some time during the disease [1] [20] [21]. However, GPA with limited involvement of the orbit and/or the eye is seen rarely [22]. The Spanish registry of systemic vasculitis study reported that 24% of GPA patients had ocular involvement at diagnosis [23]. Ocular GPA often presents as stromal keratitis, blurred vision, and scleritis/episcleritis [7] [24] [25]. In our study scleritis/episcleritis was the most frequent ocular manifestation, which occurred in 55.6% patients compared to 10% - 87% in previous reports [1] [5] [7] [25] [26] [27]. Scleritis in GPA patients can be nodular, diffuse or necrotizing [27]. Our patients presented with nodular scleritis. Scleritis is reported to lead to vision loss and blindness if not adequately treated [27] [28]. Vision loss or total blindness has been reported in 4.3% - 37% GPA patients [7] [29]. Blurred vision was noted in 11.1% of our patients but blindness was not detected in any of them. Conjunctival inflammation with granuloma formation and ulceration has been reported frequently [10] [25] [30]. Studies have reported frequency of 27% - 100% of conjunctival inflammation in GPA patients [10] [25]. In our study 44.4%, patients had conjunctivitis. Uveitis has been reported in 23.9% GPA patients in a study compared to 11.1% in our patients [7].

The orbit is frequently affected in ocular GPA presenting as proptosis, lid edema, diplopia and vision loss [1] [11] [29] [31]. In our study, none of the patients had proptosis. However, lid edema, decreased vision and lacrimal gland involvement were observed. Sino nasal involvement has been reported in up to 69% of GPA patients with orbital disease [10] [32]. We found sinonasal involvement in 77.8% of GPA patients with ocular disease. Several studies have shown association of sino-nasal manifestations with orbital disease and lacrimal gland involvement in GPA patients [10] [25] [32].

The predominant findings of orbital biopsy are reported to be chronic fibrotic changes rather than the classic triad of vasculitis, tissue necrosis and granulomatous inflammation [33]. In our patients, eye CT showed granuloma and orbital/lacrimal gland biopsy showed non-necrotizing granulomatous vasculitis. Orbital biopsy showed small vessel vasculitis in majority of the patients in some studies [34].

In our study patients responded to treatment with corticosteroids, IV CYC, methotrexate, rituximab and infliximab. Corticosteroid treatment along with IV CYC administration has been shown to increase the life expectancy of GPA patients which is otherwise a fatal disease [1] [5] [35]. Rituximab has shown to be more effective in relapsing patients and treatment of retro-orbital disease [36] [37] [38] [39]. Treatment with infliximab as an adjuvant therapy to CYC and methotrexate has been reported in the treatment of necrotizing and non-necrotizing scleritis [40] [41]. Necrotizing scleritis without appropriate treatment can lead to significant morbidity and mortality in GPA patients [42].

Comparison of ocular GPA patients with non-ocular GPA showed that ocular patients had significantly low risk of renal involvement compared to non-ocular GPA patients. There was concomitant ocular and sino-nasal involvement more
frequently in ocular group compared to non-ocular GPA similar to previous studies, however in contrast to their finding; we did not find an association with of age at onset [25]. There was no significant association of ocular disease with other manifestations of GPA in our patients.

To the best of our knowledge this is the first study reporting the disease manifestations, therapy and outcome in ocular GPA patients from our region. Some of the limitations of our study are the small sample size and the cohort being drawn from a single institution which cannot be generalized to the entire Saudi population. The other limitation is the retrospective nature of our study.

5. Conclusion

The frequency of ocular manifestations in our GPA patients was similar to reports elsewhere, with the most frequent symptoms being eye pain and scleritis/episcleritis. The ocular involvement was associated with sino-nasal manifestations and significantly with low risk of renal involvement. Patients responded well to corticosteroid and IV CYC therapy and rituximab was more effective in relapsing patients. Ocular symptoms may be the first sign of GPA and early diagnosis and appropriate therapy is crucial to lowering the morbidity and vision loss in GPA patients.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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