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ARTICLE

Ophthalmic manifestations and visual outcomes of granulomatosis with polyangiitis: a retrospective multicentre study in Korea

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OBJECTIVES: To analyse the ophthalmic manifestations and treatment outcomes of Korean patients with granulomatosis with polyangiitis (GPA).

METHODS: One hundred twenty patients diagnosed with GPA by rheumatologists from January 1984 to March 2019 at three referral centres were retrospectively reviewed. Patients with ophthalmic symptoms were examined by ophthalmologists and underwent orbital imaging. Ophthalmic manifestations were divided into ocular involvement and ocular adnexal involvement. Multivariable logistic regression was used to examine the factors related to ocular, ocular adnexal, and optic nerve involvement. Visual improvement was defined as a best-corrected visual acuity gain of ≥2 Snellen lines, accompanied by improvements in optic nerve function.

RESULTS: Ophthalmic manifestations were observed in 50 patients (41.7%) during the median follow-up period of 6.7 years. Proteinase 3-anti-neutrophil cytoplasmic antibody (PR3-ANCA) positivity (odds ratio 3.19, 95% confidence interval 1.18–8.60) was an independent risk factor for ocular involvement, while sinonasal involvement (21.94, 2.54–189.69) and brain involvement (5.38, 1.50–19.31) were independent risk factors for ocular adnexal involvement. Antinuclear antibody (ANA) positivity was associated with optic nerve involvement (12.8, 1.80–90.5). Visual improvement occurred in 5 of 14 patients with optic nerve involvement, all of whom received intravenous (IV) immunosuppressive treatments beyond oral steroids within 2 months of visual impairment.

CONCLUSIONS: Ophthalmic involvement is common in Korean GPA patients and should be considered in the presence of PR3-ANCA, sinonasal or brain involvement. Patients with positive ANA have an increased risk of optic nerve involvement, and early IV immunosuppressive treatments beyond oral steroids are necessary to improve the visual outcome.

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INTRODUCTION

Granulomatosis with polyangiitis (GPA) is a systemic inflammatory disease that features a classic histological triad, consisting of granulomatosis, tissue necrosis, and angiitis of small- to medium-sized vessels [1–3], and is characterised by the presence of circulating anti-neutrophil cytoplasmic antibody (ANCA) in serum.

While GPA most commonly involves the upper and lower respiratory tract and the kidney [4], ophthalmic involvement has been known to be highly variable across the studies of GPA (21~87%) [5–8]. Ophthalmic involvement can occur in any part of the eye or ocular adnexa, and can lead to blindness if not treated properly [2, 3, 9, 10].

To date, studies on ophthalmic GPA have had small sample sizes due to the rarity of the disease and diverse organ involvement, and have been largely limited to Caucasians. Data in Asians have been even more limited, with case series studies of fewer than 20 patients [11, 12]. In this multicentre retrospective study, we analysed the clinical features and visual outcomes of ophthalmic GPA in Korea for the past 30 years.

MATERIALS AND METHODS

Study population

We identified patients who were diagnosed with GPA from January 1984 to March 2019 at three referral centres (Seoul National University Hospital, Seoul National University Bundang Hospital, Seoul Metropolitan Government–Seoul National University Boramae Medical Center) in Korea by retrospective medical record review. During the review, rheumatologists confirmed that all patients met the most recent criteria of GPA: the American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) 2017 provisional classification criteria [13]. Rheumatologists also checked whether patients fulfilled classification criteria for other rheumatic diseases, such as systemic lupus erythematosus [14]. The collected data included patient demographics, detailed ophthalmic and systemic manifestations, serologic results, and treatment outcomes. This study was conducted according to the tenets of the Declaration of Helsinki.

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The study was approved by the institutional review board/ethics committee of Seoul Metropolitan Government–Seoul National University Boramae Medical Center (IRB No. 10-2021-19).

Ophthalmic manifestations

All patients complaining of ophthalmic discomforts were thoroughly examined by ophthalmologists; the examinations included Snellen best-corrected visual acuity (BCVA), extraocular muscle (EOM) movement, ocular deviation, relative afferent pupillary defect, exophthalmometry, slit lamp examination and fundus examination. Contrast-enhanced computed tomography or magnetic resonance imaging of the orbit was also performed for all patients.

Orbital biopsy was performed for all cases in which the first presentation was isolated orbital inflammation. In the case of concurrent ophthalmic and systemic involvements, biopsy was performed in the most accessible area, such as sinus mucosa. Inflammatory involvement of ophthalmic areas where the biopsy is potentially harmful (for example, orbital apex and sclera) was determined as ophthalmic GPA, when the patient was diagnosed as GPA in other organs and the ophthalmic inflammation responded to immunosuppressive treatments. Ophthalmic conditions unrelated to GPA, such as chalazion, simple blepharitis, facial nerve palsy, cataract, primary glaucoma, viral/allergic conjunctivitis and radiation- or steroid-induced retinopathy, were excluded from ophthalmic GPA.

Ophthalmic manifestations were divided into two major categories of ocular involvement and ocular adnexal involvement. Ocular involvement, including keratitis, episcleritis/scleritis, and uveitis, was diagnosed clinically. Anterior or posterior uveitis [15] patients underwent fluorescein angiography and optical coherence tomography. Ocular adnexal involvement, including involvements of orbit, eyelid, lacrimal gland, lacrimal drainage system, cranial nerves III to VI, and optic nerve, was determined based on the clinical and radiological findings (for example, orbital space and/or EOM involvement for orbital disease, absence of orbital lesion for eyelid disease). Involvement of cranial nerves was defined as a specific pattern of EOM limitation associated with orbital apex or cavernous sinus lesion.

Optic nerve involvement was assessed by BCVA, relative afferent pupillary defect, colour vision testing and automated perimetry. The subtypes of optic nerve involvement, defined according to the imaging study, were as follows: compressive (mass-like lesion in orbital apex) or noncompressive (infiltrative lesion or absence of any lesion). The characteristics of patients with optic nerve involvement were also reviewed due to the high impact of optic nerve involvement on visual loss [6, 7]. Visual loss was defined as BCVA lower than 20/200 [16].

Systemic manifestations and serologic tests

Associated systemic manifestations during the whole follow-up period were classified as sinus or nose, lung, kidney, brain, and gastrointestinal involvement. The presence of clinical items included in the ACR/EULAR 2017 criteria [13] or enhanced lesion in systemic imaging studies (for example, pachymeningeal or hypophyseal lesion for brain involvement) was considered as systemic manifestations of GPA. Brain involvement also included infarctions during active inflammatory phase of GPA. Kidney involvement included microhaematuria with > 5 red blood cells per high power field [17]. Gastrointestinal involvement included mesenteric vasculitis, recurrent GI bleeding, and granuloma in colonoscopic biopsy [18]. Tissue biopsy confirmed the involvement of GPA in sinus or nose, and kidney.

At the time of GPA diagnosis, antinuclear antibody (ANA; reference value: 1:40x), rheumatoid factor (RF; reference value: 15 IU/mL), and ANCA tests were routinely performed. Cytoplasmic ANCA or perinuclear ANCA was detected by indirect immunofluorescence, and proteinase 3 (PR3)-ANCA and myeloperoxidase (MPO)-ANCA levels were measured by antigen-specific enzyme-linked immunosorbent assays. ANCA tests were repeated to assess treatment responses during the follow-up period, and patients who showed at least one positive result during the follow-up period were considered ANCA-positive. For lacrimal gland enlargement, serum anti-Ro antibody was checked to exclude Sjogren syndrome.

Treatment strategy and outcomes

Treatments varied based on the category and severity of ophthalmic manifestations. For ocular involvement, topical steroid eyedrops and oral nonsteroidal anti-inflammatory drug were initially prescribed. If there was no response within 1 week, oral prednisolone (Pd; 0.5~1.0 mg/kg/day) was added. Triamcinolone injection was applied in refractory cases to oral Pd, mainly subconjunctivally or intravitreally for posterior uveitis cases. For ocular adnexal involvement, oral Pd (1.0 mg/kg/day) or methylprednisolone (methyl-Pd) combined with oral cyclophosphamide (CYC; 100 mg/day) were used. For optic nerve involvement and other ophthalmic involvements refractory to oral immunosuppressants, intravenous (IV) treatment regimen was determined by comprehensively considering disease burden, systemic comorbidities, and accessibility to biologics. In general, IV methyl-Pd pulse (1 g/day, 3 days) was used as an induction therapy with subsequent oral Pd (1.0 mg/kg/day) tapering by 5 mg every 1 to 4 weeks until reaching a long-term maintenance dose of 5 mg/day. Some patients with optic nerve involvement received empirical oral Pd (0.8~1.0 mg/kg/day) before being diagnosed with GPA. Additional IV CYC pulse (15 mg/kg/month, 6 months) was applied for patients with concurrent systemic involvements such as brain, cranial nerves, lung, and kidney involvements. Since 2012, IV rituximab (375 mg/m^2/week, 4 weeks) was administered as an alternate to IV CYC pulse [19]. Patients with general conditions unacceptable to IV methyl-Pd pulse were treated by IV CYC pulse or IV rituximab, combined with oral Pd. Visual improvement was defined as a BCVA gain of ≥2 Snellen lines, accompanied by improvements in optic nerve function. Radiologic improvement was classified into two categories: complete or partial response. Complete response refers to no apical lesion on follow-up radiological images after treatment, while partial response refers to obvious decrease of apical lesion.

Statistical analysis

The Mann-Whitney U test was used for comparison of continuous variables, and Fisher's exact test was used to compare categorical variables. The Kaplan-Meier method was applied for the survival analysis of ophthalmic involvement. Logistic regression analysis was used to evaluate the independent association of risk factors with ocular involvement, ocular adnexal involvement and optic nerve involvement. Cytoplasmic ANCA and perinuclear ANCA positivities were not used as variables for logistic regression due to their strong correlation with PR3-ANCA and MPO-ANCA. A p value cutoff of 0.20 was used to select covariates for inclusion in the multivariable logistic regression. A two-sided p value< 0.05 was considered to be statistically significant.

RESULTS

One hundred twenty patients with GPA were identified, 92 of whom had ophthalmic symptoms and were examined by ophthalmologists. Finally, 50 patients (41.7%) were found to have ophthalmic involvement of GPA. Among 13 ANA-positive ophthalmic GPA patients, no patient met classification criteria for systemic lupus erythematosus, and most of the systemic tissue biopsy (9/11) showed granulomatous inflammation with vasculitis. Anti-Ro antibody was negative in all tested cases ($n = 10$). The demographics and clinical characteristics of these 50 patients are presented in Table 1. The median age at GPA diagnosis was 55.6 years, and the patients were followed up for a median of 6.7 years.

Characteristics of ophthalmic involvement

The 19 patients (38%) with initial ophthalmic involvement showed a median delay of 1.6 months (interquartile range [IQR], 0.7–6.9) until GPA diagnosis, which was significantly shorter than the delay of 6.0 months (IQR, 2.0–17.9) in patients without initial ophthalmic involvement ($p = 0.04$, Mann-Whitney U test). Additionally, isolated initial ophthalmic involvement ($n = 9$) did not delay the diagnosis of GPA (1.9 vs. 3.1 months, $p = 0.59$). Visual loss as an initial ophthalmic presentation ($n = 12$) was caused mostly by optic nerve involvement ($n = 11$).

Ophthalmic involvement occurred throughout the course of the disease, and approximately half of the patients had ophthalmic involvement at 10 years after the initial presentation of GPA (involvement probability: 44.7%, 95% confidence interval [CI], 33.8–55.6) (Fig. 1). Bilateral ophthalmic involvement was marginally associated with episcleritis/scleritis (78% vs. 50%, $p = 0.07$, Fisher's exact test) and cytoplasmic ANCA positivity (76% vs. 46%, $p = 0.07$). Sinonasal involvement (88% vs. 59%), brain involvement (34% vs. 16%), gastrointestinal involvement (14% vs. 0%) and PR3-ANCA positivity (50% vs. 29%) were more common in patients

Table 1. Demographics and clinical characteristics of 50 patients with ophthalmic granulomatosis with polyangiitis.

	n (%)
Male sex	26 (52.0)
Age at initial presentation, median (IQR), years	54.5 (38.3–63.0)
Age at diagnosis, median (IQR), years	55.6 (40.8–64.6)
Time from initial presentation to diagnosis, median (IQR), months	3.1 (1.1–15.4)
Follow-up period, median (IQR), years	6.7 (3.6–15.9)
Initial involvement	
Ophthalmic and systemic	10 (20.0)
Isolated ophthalmic	9 (18.0)
Isolated systemic	31 (62.0)
Time to ophthalmic involvement, median (IQR), months	16.1 (6.1–61.8)
Bilaterality	30 (60.0)
Site of ophthalmic involvements	
Ocular involvement	24 (48.0)
Cornea	10 (20.0)
Episclera/sclera	18 (36.0)
Uvea (anterior or posterior)	5 (10.0)
Ocular adnexal involvement	35 (70.0)
Orbit	23 (46.0)
Eyelid	13 (26.0)
Cranial nerves (III to VI)	10 (20.0)
Lacrimal gland	5 (10.0)
Lacrimal drainage system	7 (14.0)
Optic nerve	14 (28.0)
Serologic tests, positive/tested (%)	
Antinuclear antibody (+)	13/39 (33.3)
ANCA testing	
Proteinase 3-ANCA (+)	23/46 (50.0)
Myeloperoxidase-ANCA (+)	10/46 (21.7)

ANCA anti-neutrophil cytoplasmic antibody, *IQR* interquartile range.

with ophthalmic involvement than in those without ophthalmic involvement.

Risk factors for ocular involvement and ocular adnexal involvement

During the whole follow-up period, ocular involvement and ocular adnexal involvement were presented in 24 patients (48%) and 35 patients (70%). Gastrointestinal involvement (21% vs. 6%), PR3-ANCA positivity (62% vs. 34%), and RF-positivity (50% vs. 35%) were more common in patients with ocular involvement than in those without ocular involvement. In patients with ocular adnexal involvement, sinonasal involvement (97% vs. 60%), brain involvement (43% vs. 15%), and ANA-positivity (43% vs. 18%) were more common than in those without ocular adnexal involvement.

Multivariable logistic regression analysis revealed that only PR3-ANCA positivity (odds ratio [OR] 3.19, 95% CI 1.18–8.60) was an independent risk factor for ocular involvement (Table 2). For ocular adnexal involvement, sinonasal involvement (OR 21.94, 95% CI 2.54–189.69) and brain involvement (OR 5.38, 95% CI 1.50–19.31) were independent risk factors.

Characteristics and risk factors for optic nerve involvement

Most optic nerve involvement was compressive involvement (11/14, 79%). Brain involvement (64% vs. 22%) and ANA positivity (70% vs. 21%) were more common in patients with optic nerve involvement than in those without optic nerve involvement. Only ANA positivity was associated with optic nerve involvement (OR 12.8, 95% CI 1.80–90.5). ANA positivity rate in noncompressive involvement (3 of 3) was higher than in compressive involvement (4 of 7).

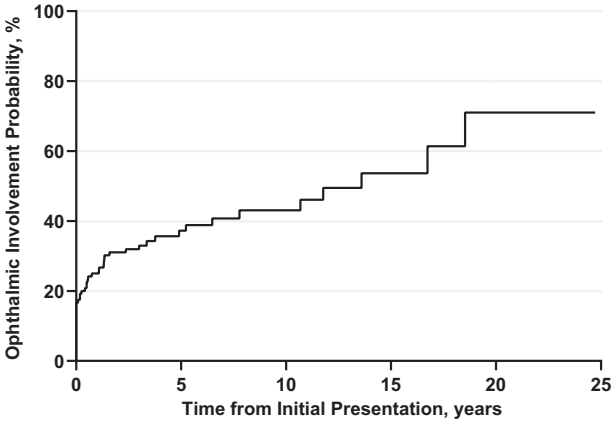

Fig. 1 Kaplan-Meier analysis of the cumulative probability of ophthalmic involvement after the initial presentation of granulomatosis with polyangiitis.

Treatment outcomes of ophthalmic manifestations

Overall, 11 patients had permanent visual loss, which was significantly associated with optic nerve involvement ($p < 0.001$, Fisher's exact test). The most common cause of visual loss was compressive optic nerve involvement ($n = 6$), followed by non-compressive optic nerve involvement ($n = 3$), keratitis ($n = 1$), and retinal vasculitis ($n = 1$).

Detailed characteristics, treatment regimens and outcomes of optic nerve involvement were listed in Supplementary Table 1. Three patients presented generalized optic disc pallor at GPA diagnosis, despite a prior history of prolonged oral Pd therapy. They showed radiologic partial responses to delayed IV CYC pulse and/or IV methyl-Pd pulse (range of delay: 20, 142, and 288 months), but no recovery of visual function.

Other 11 patients with optic nerve involvement were treated to rescue visual function (range of delay: 0–9 months) had variable treatment regimens. Empirical oral steroids were prescribed for 5 patients. Progression of visual impairment initially halted in 2 patients, but eventually progressed to visual loss at 1~3 months of oral Pd tapering in all 5 patients. IV methyl-Pd pulse was mainly used for an induction therapy, except for two patients received IV rituximab due to uncontrolled blood glucose. Visual improvement occurred in 5 patients, all of whom received early (within 2 months of visual impairment) IV immunosuppressive treatments beyond oral steroids. With early IV immunosuppressive treatments, compressive involvement showed better visual improvement than noncompressive involvement (4 of 5 vs. 1 of 3).

Ocular adnexal involvement, episcleritis/scleritis, and keratitis resolved after a median follow-up of 5.6 years, 3.2 years, and 2.5 years, respectively. These manifestations caused diverse sequelae, including orbital socket contracture, orbitonasal fistula, nasolacrimal duct obstruction, scleral necrosis requiring conjunctival autograft, and progressive corneal opacity.

DISCUSSION

This study retrospectively reviewed ophthalmic manifestations of GPA at multiple referral centres in Korea. This is the largest case series of ophthalmic GPA in Asia, and the sample size permitted statistical analyses to be performed. In our study, ophthalmic involvement in GPA patients was found in up to half of GPA patients (41.7%). Ocular adnexal involvement was more common than ocular involvement, and was associated with sinonasal or brain involvement. Poorer visual prognosis was associated with

Table 2. Multivariable logistic regression analysis of risk factors for ocular involvement and ocular adnexal involvement of granulomatosis with polyangiitis.

	Ocular involvement		Ocular adnexal involvement	
Variables	**Odds ratio (95% CI)**	***p* value**	**Odds ratio (95% CI)**	***p* value**
Male Sex	0.71 (0.28–1.78)	0.46	2.74 (0.85–8.89)	0.09
Systemic manifestations				
Sinus or nose	1.30 (0.47–3.61)	0.62	21.94 (2.54–189.69)	0.005
Lung	0.74 (0.30–1.83)	0.52	0.72 (0.32–1.59)	0.41
Kidney	1.05 (0.41–2.71)	0.92	0.64 (0.26–1.53)	0.31
Brain	1.47 (0.54–4.02)	0.45	5.38 (1.50–19.31)	0.01
Gastrointestinal	3.25 (0.78–13.59)	0.11	1.44 (0.39–5.26)	0.58
Serologic results				
Rheumatoid factor (+)	1.85 (0.65–5.22)	0.25	0.29 (0.08–1.05)	0.06
Antinuclear antibody (+)	0.76 (0.23–2.55)	0.66	2.36 (0.70–8.01)	0.17
Proteinase 3-ANCA (+)	3.19 (1.18–8.60)	0.02	1.53 (0.66–3.55)	0.32
Myeloperoxidase-ANCA (+)	1.04 (0.38–2.87)	0.94	0.44 (0.17–1.15)	0.09

ANCA anti-neutrophil cytoplasmic antibody, *CI* confidence interval.

optic nerve involvement. Early immunosuppressive treatment beyond oral steroids in optic nerve involvement allowed improvement of visual outcomes.

Patients who initially presented with ophthalmic involvement were diagnosed earlier than GPA patients without initial ophthalmic involvement. In contrast to a study in France [7], isolated ophthalmic involvement preceding systemic involvement did not delay the GPA diagnosis. A larger proportion of patients with initial visual loss were included in our study, so referrals to tertiary medical centres would have been made earlier. The larger number of doctor consultations and imaging scanners in Korea may have allowed the early detection of ocular adnexal involvement with sinonasal involvement and lowered the risk of delayed diagnosis of GPA [20, 21].

Several articles have shown that ophthalmic GPA is accompanied by a high proportion of sinonasal involvement and PR3-ANCA positivity [22–24]. Previous GPA studies in East Asia also showed a higher prevalence of ophthalmic involvement in the PR3-ANCA-positive group than in the MPO-ANCA-positive group (40.0–58.8% vs. 23.5–27.8%) [22, 24, 25]. However, ophthalmic involvement has included a vast range of clinical presentations in these articles. We categorized ophthalmic manifestations of GPA into ocular involvement and ocular adnexal involvement, and showed that the two categories differently associated with systemic manifestations and serologic results.

Ocular adnexal involvement was associated with sinonasal involvement and brain involvement. Orbital disease may develop from the contiguous extension of adjacent sinonasal involvement [2, 3, 10, 26]. Brain involvement, such as pachymeningitis, can be associated with ocular adnexal involvement via direct extension to the orbital apex or cranial nerves III to VI involvement [26]. In contrast to ocular adnexal involvement, ocular involvement in GPA was associated with PR3-ANCA positivity. Since GPA is generally characterised by a high rate of cytoplasmic ANCA or PR3-ANCA positivity [27], the PR3-ANCA test may have limited clinical significance for the prediction of ocular involvement. However, PR3-ANCA positivity rates were relatively lower in some studies of East Asia [22, 25] and even lower than the MPO-ANCA-positivity rates. Therefore, PR3-ANCA positivity will have more clinical significance in this area.

ANA positivity was a significant risk factor for optic nerve involvement. ANA-positive rates were 70% in optic nerve involvement, and 3 of 3 in noncompressive subtype of optic nerve involvement in the present study. These are higher than ANA-positive rates in GPA involving any organ (14~45%) and ophthalmic GPA (33~46%) of our cohort and previous studies [28–30]. Some specific types of ANA, such as anti-double strand DNA antibody, are known to directly cause autoimmune disease by immune complex formation [31]. However, the role of ANA in optic nerve involvement is still uncertain in the present study. A larger study including multiple ethnicities with results of ANA subtypes and renal biopsy will be helpful to clarify the association between ANA positivity and optic nerve involvement, especially for noncompressive involvement.

Visual improvement in patients with optic nerve involvement occurred only if they received IV immunosuppressive treatment beyond oral steroids within 2 months of visual impairment. The visual function of patients treated with oral steroids alone deteriorated to visual loss regardless of regimen. Even if the visual function initially improved due to empirical oral steroids, it may be unhelpful because further diagnostic work-ups for GPA such as ANCA test and biopsy can be deferred. Although it is difficult to draw firm conclusions through statistical analysis due to the small numbers and heterogenous treatments of patients in this retrospective study, it could be said that prompt diagnosis and early IV immunosuppressive treatment beyond oral steroids is a necessary condition for visual improvement. Intravenous steroids is well-known to be more effective than oral steroids during the active phase of thyroid eye disease, especially for patients with optic nerve dysfunction [32]. Noncompressive optic nerve involvement showed relatively poor visual outcomes, as expected, because it included ischemic optic neuropathy and optic neuritis, which are known to have abrupt onset with less significant improvement [33].

Table 3 compares the clinical features of patients with ophthalmic GPA among different countries. Males and females were almost equally affected, as in previous studies. The age at initial presentation was 54.5 years old, similar to Europe [8, 26, 34], and slightly higher than China [11].

Our results and review of previous literature suggest racial differences in patterns of ophthalmic manifestations in GPA. Orbital disease was the most common ophthalmic presentation in Asian studies [11, 12], whereas European and American studies showed episcleritis/scleritis as the most common presentation [5, 7, 8, 26, 29, 35, 36]. Although most of these European and American studies did not explicitly state how orbital disease was assessed, the only study discussing radiological findings performed orbital imaging studies in nearly all patients (92%) [5].

Table 3. Comparative characteristics of patients with ophthalmic granulomatosis with polyangiitis in different countries.

	Current study Korea	Jiang et al. [11] China	Gheita & Abd El Latif [29] Egypt	Woo et al. [37] Australia	Stavrou et al. [8] UK	Perez-Jacoiste Asin et al. [7] France	Bullen et al. [6] USA	Hinojosa-Azaola et al. [5] Mexico
Total no. of patients	50	19	46	29	31	63	40	46
Male sex, *n* (%)	26 (52)	10 (53)	22 (48)	17 (59)	21 (68)	33 (52)	21 (53)	22 (48)
Age at diagnosis, years	55.6	38.9	46.2	49	52.5	46.1	54.0	46.2
Follow-up period, years	6.7	-	-	4.5	4.1	4.2	5.5	6.5
Ophthalmic manifestation, *n* (%)								
Bilaterality	30 (60)	-	32 (70)	-	-	16/55 (29)	-	-
Orbit	**23 (46)**	**12 (63)**	12 (26)	**20 (69)**[a]	2 (7)	13 (21)	**18 (45)**	3 (7)
Episclera/Sclera	18 (36)	2 (11)	**40 (87)**	-	**12 (39)**	**36 (57)**	15 (38)	**27 (59)**
Optic nerve	14 (28)	7 (37)	-	5 (17)	2 (7)	6 (10)	9 (23)	6 (13)
Final visual loss	12 (24)	3 (16)	2 (4)	5 (17)	2 (7)	10 (16)	4 (10)	11 (24)
Systemic manifestation, *n* (%)								
Ear-nose-throat	46 (92)	14 (74)	44 (96)	20 (69)	-	54 (86)	38 (95)	45 (96)
Nervous system	18 (36)	3 (16)	-	-	-	13 (21)	7 (18)	1 (4)
ANCA, positive/tested (%)								
Cytoplasmic ANCA	21/47 (45)	12/19 (63)	46/46 (100)	15/29 (52)	28 (90)	47/59 (80)	-	-
Perinuclear ANCA	5/47 (11)	7/19 (37)	5/46 (11)	3/29 (10)	1/31 (3)	9/59 (15)	-	32 (69)
Proteinase 3-ANCA	23/46 (50)	-	-	-	-	50/61 (82)	-	-
Myeloperoxidase-ANCA	10/46 (22)	-	-	-	-	6/61 (10)	-	8 (17)

ANCA anti-neutrophil cytoplasmic antibody.
Bold indicates the most common category of ophthalmic manifestation.
[a]Cases with features of orbital or adnexal disease were included, and episcleritis/scleritis was not counted.

Optic nerve involvement was more frequent in Asians, usually in the form of compressive involvement. In a pooled analysis of two large randomised controlled trials of ANCA-associated vasculitis [36], nonwhite race was associated with higher odds of having orbital disease. Therefore, prompt orbital imaging should be included in the ophthalmic assessment for Asian GPA patients.

Our study has several limitations, including its retrospective design. Although this is the largest study in Asia to our knowledge, it is still a small number to reach statistical significance. Patients with mild ocular symptoms may have been missed because only patients who visited or were referred to the ophthalmology clinic were reviewed. Some patients who had already received different treatments for optic nerve involvement before referral to our 3 centres were also included in this study, and this heterogeneity of initial treatment of optic nerve involvement may have acted as a bias in statistical analysis. Future prospective studies with larger numbers of patients are warranted to further investigate the ophthalmic manifestations of GPA.

In conclusion, ophthalmic involvement is a common presentation of GPA in Korea. Ophthalmological assessment should be considered in the presence of PR3-ANCA, sinonasal or brain involvement. Patients with positive ANA are more likely to have optic nerve involvement. An early diagnosis and IV immunosuppressive treatment beyond oral steroids should be rendered to improve the visual outcome.

Supplemental information is available at Eye's website.

Summary Table

What was known before

- Granulomatosis with polyangiitis (GPA) is a systemic inflammatory disease characterised by the presence of circulating anti-neutrophil cytoplasmic antibody (ANCA) in serum.
- Ophthalmic involvement of GPA has not been well investigated in Asians.

What this study adds

- Proteinse 3-ANCA positivity was associated with ocular involvement of GPA in Korean patients.
- Antinuclear antibody positivity was associated with optic nerve involvement.
- Early intravenous immunosuppressive treatments beyond oral steroids is necessary to improve the visual outcome.

DATA AVAILABILITY

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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AUTHOR CONTRIBUTIONS

MKY collected the data and wrote the paper. EHK, HC designed the study. HWK, EHK, NK, HC, SIK recruited the subjects. EHK, HC, SIK revised the manuscript and approved the final version of manuscript.

COMPETING INTERESTS

The authors declare no competing interests.

ETHICS APPROVAL

Institutional review board approval was obtained, and the study was performed in accordance with the principles of the Declaration of Helsinki.

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