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# Clinical significance of ocular manifestations in granulomatosis with polyangiitis: association with sinonasal involvement and damage

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## Abstract

Ocular involvement is present in 50–60% of granulomatosis with polyangiitis (GPA) patients and can affect any part of the ocular globe. The present study describes ophthalmologic manifestations, association with systemic symptoms, disease activity and damage in GPA. A cross-sectional study was conducted including patients with GPA who underwent rheumatologic and ophthalmologic evaluation. Demographics, comorbidities, ophthalmologic symptoms, serologic markers, radiographic studies, disease activity and damage were assessed. Descriptive statistics, correlation, univariable logistic regression analyses, Student's *t*, Mann–Whitney *U*, Chi-square and Fisher's exact tests were performed. Fifty patients were included, 60% female, the median age was 56 years, disease duration 72.5 months. Nineteen (38%) patients had ocular manifestations at GPA diagnosis, scleritis being the most frequent; 27 (54%) patients presented ocular involvement during follow-up, repeated scleritis and dacryocystitis being the most common manifestations. Concomitant ophthalmic and sinonasal involvement was present in 12 (24%). Ocular and ENT damage occurred in 58% and 70%, respectively. Epiphora and blurred vision were the most frequent symptoms; scleromalacia and conjunctival hyperemia (27%) the most frequent clinical abnormalities. Ocular involvement at diagnosis was associated with concomitant ocular and sinonasal involvement at follow-up (OR 4.72, 95% CI 1.17–19.01, $p=0.01$). Ocular involvement at follow-up was associated with age at GPA diagnosis (OR 0.94, 95% CI 0.90–0.99, $p=0.03$), VDI (OR 1.29, 95% CI 1.03–1.61, $p=0.02$), and ENT damage (OR 5.27, 95% CI 1.37–20.13, $p=0.01$). In GPA, ocular involvement is frequent, therefore, non-ophthalmologist clinicians should be aware of this manifestation to reduce the risk of visual morbidity and organ damage.

**Keywords** Granulomatosis with polyangiitis · Ocular involvement · Sinus involvement · Disease activity · Damage

## Introduction

Anti-neutrophil cytoplasmic antibodies (ANCA)-associated vasculitides (AAV) are chronic, systemic, and relapsing autoimmune diseases of unknown etiology, characterized by necrotizing small-vessels inflammation and circulating ANCA, comprising three main clinical entities: granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA) [1, 2]. Disease presentation, subsequent course and severity are heterogeneous, ranging from life organ-threatening manifestations to milder forms of the disease, with delays in early diagnosis being a common feature.

The main distinctive features of GPA are the presence of granuloma, ear, nose, and throat (ENT) involvement, pulmonary manifestations, glomerulonephritis and positivity for proteinase 3 (PR3)-ANCA [3]. The eye is considered an immune-privileged site, with a high predisposition

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to develop anti-inflammatory and immunosuppressive mechanisms to prevent the consequences of inflammation [4]. Moreover, the eye is the only organ where the vasculature can be directly visualized without invasive tests [5].

Ophthalmologic involvement in GPA is common in both limited and systemic forms of the disease; it can affect any part of the eye and/or orbit, occurs in approximately 50–60% of the patients and is the presenting symptom in 8–16% of them [6–8]. Ocular disease is usually orbital and occurs due to pseudotumor or granulomatous inflammation, as an extension from the adjacent paranasal sinuses (contiguous), or as a result of focal vasculitis (non-contiguous) [3, 8, 9]. The most common clinical findings are proptosis, scleritis, episcleritis, retinal, and optic nerve vasculitis, nasolacrimal duct obstruction, uveitis, and dacryocystitis [6, 10]. Vision loss is reported between 20 and 50% because of optic nerve compression, retinal and optic nerve vasculitis, globe perforation from necrotizing scleritis, or peripheral ulcerative keratitis [3, 8, 11].

Diagnosis of the ocular involvement requires a complete ophthalmologic evaluation, serologic and imaging studies [computed tomography (CT) and/or magnetic resonance imaging (MRI)], whereas the orbital tissue biopsies are invasive and positive results are only seen in 50% of the cases, with necrotizing vasculitis and obliteration of the vessel lumen being infrequent findings [6, 12, 13].

Clinical and prognostic features of AAV in patients from Europe, Japan and North America have been described in several studies; however, clinical information regarding Hispanic patients with AAV is scarce [14, 15].

Because the ocular involvement is a frequent manifestation often associated with permanent sequelae and disability, the present study aimed to describe the characteristics of the ophthalmologic manifestations and the association with systemic symptoms, disease activity and damage in a group of Hispanic patients with GPA.

## Materials and methods

### Study patients

A cross-sectional study was conducted including patients > 18 years old with established diagnosis of GPA according to the 1990 American College of Rheumatology Classification Criteria and/or definition by the 2012 Chapel Hill Consensus [16, 17]. Patients with diagnosis of other autoimmune diseases were excluded. All patients were recruited consecutively from the outpatient clinic of the Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, a tertiary care Institution in Mexico City.

### Data collection and measures

All patients underwent a complete rheumatologic and ophthalmologic evaluation. Information regarding demographics, comorbidities and clinical variables, including disease duration, type of disease (limited or systemic), current treatment, and positivity (ever) for ANCA was retrieved. Acute phase reactants, including erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were assessed on the day of evaluation. Information regarding ocular manifestations at GPA diagnosis and during follow-up was retrieved retrospectively from the medical records. Radiologic findings including orbital CT or MRI were also considered. Histological results of orbital, sinus or lacrimal glands biopsies were recovered when available.

Disease activity and damage were assessed on the day of evaluation using the Birmingham Vasculitis Activity Score for GPA (BVAS/GPA) and the Vasculitis Damage Index (VDI) [18, 19], respectively. The ocular items were excluded from the BVAS/GPA score to assess extraophthalmic disease activity.

Patient's perception of ocular symptoms was evaluated with a questionnaire where each symptom was described (e.g., palpebral inflammation, ocular pain, red painful eyes, etc). In addition, patient's global assessment of the disease was evaluated using a visual analogue scale ranging from 0 (remission) to 10 mm (maximum activity).

### Compliance with ethical standards

The hospital Institutional Review Board (Comité de Ética en Investigación) approved the study on September 25th, 2017 (Reference IRE-2335-17/18-1), and informed consent was obtained from all individual participants included. All procedures performed involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

### Statistical analysis

Descriptive statistics was used. Continuous variables were expressed as mean ± standard deviation (SD), or median with minimum and maximum range, whereas categorical variables were expressed as counts with percentages. Differences between patients with and without ocular involvement were evaluated using the Student's *t* test or Mann–Whitney *U* test for continuous variables, and Chi-square or Fisher's exact test for categorical variables. Correlation analysis using Spearman's rho test with Bonferroni correction, and univariate logistic regression

analyses were performed to estimate associations between significant variables ($p \leq 0.10$) identified in the bivariate analyses. Odds-ratios (OR) and 95% confidence intervals (95% CI) were calculated. A value of $p < 0.05$ was considered. All analyses were performed using Stata (Stata Corp; College Station, Texas USA), version 12.0.

## Results

Fifty patients were included, 60% female gender, with a median age of 56 years (24–82), and disease duration of 72.5 months (0–469). Most of the patients (92%) had systemic disease and were ANCA-positive (96%). Current therapy comprised prednisone in 31 (62%) and azathioprine in 24 (48%) of the patients; other immunosuppressants were used in < 20% of the patients, whereas 6 (12%) patients in remission were not receiving immunosuppressants. Table 1 summarizes the demographic and clinical characteristics of the patients.

**Table 1** Clinical and demographic characteristics

| Variable | *n* (%) or median (min–max) |
|---|---|
| Sex, female/male, *n*/*n* | 30/20 |
| Current age, years | 56 (24–82) |
| Age at GPA diagnosis, years | 49 (16–76) |
| Disease duration, months | 72.5 (0-469) |
| Systemic disease | 46 (92) |
| Limited disease | 4 (8) |
| ANCA positivity | 48 (96) |
| Anti-PR3 positivity, *n*+/*n* (%) | 34/49 (69) |
| Anti-MPO positivity, *n*+/*n* (%) | 8/46 (17) |
| *Comorbidities* | |
| Hypertension | 22 (44) |
| Dyslipidemia | 22 (44) |
| Diabetes mellitus | 12 (24) |
| Smoking | 6 (12) |
| *Current treatment* | |
| Prednisone | 31 (62) |
| Azathioprine | 24 (48) |
| Methrotrexate | 8 (16) |
| Rituximab | 8 (16) |
| Mycophenolate mofetil | 3 (6) |
| Cyclophosphamide | 1 (2) |
| No immunosuppressants | 6 (12) |

*GPA* granulomatosis with polyangiitis, *ANCA* anti-neutrophil cytoplasmic antibodies, *anti-PR3* anti-proteinase 3, *anti-MPO* anti-myeloperoxidase

### Ocular involvement characteristics

Nineteen patients (38%) had ocular involvement at GPA diagnosis. At this point, scleritis was the most frequent manifestation, present in nine patients (18%). During follow-up, 27 (54%) patients presented ocular affection. Repeated scleritis in 15 (30%), and dacryocystitis in 9 (18%) patients were the most frequent manifestations during follow-up. Concomitant ophthalmic and sinonasal involvement was present in 12 (24%) patients. Radiologic studies were available in 46 patients and abnormalities were observed in 35 (76%) of them. Sinusitis was the most common radiologic abnormality, present in 25 patients (54%), followed by septal perforation in 19 (41%), and lateral cartilage collapse in 17 (37%). Table 2 shows the ocular manifestations at diagnosis and follow-up while Table 3 summarizes the radiological findings.

At evaluation, the assessment of disease activity and damage showed a BVAS/GPA total score of 1 (0–17) (excluding the ocular items), while total VDI score was 5.5 (0–11). Ocular and ENT damage was present in 29 (58%) and 35 (70%) patients, respectively. The most frequent manifestation of ocular damage was cataract, present in 21 (42%) patients, while the most frequent ENT damage manifestation was chronic sinusitis with radiological damage in 26 (52%) patients. Interestingly, those patients who developed cataracts ($n = 21$) had significantly longer disease duration than those who did not develop

**Table 2** Ocular manifestations at diagnosis and during follow-up

| Ocular manifestation | At diagnosis *n* (%) | During follow-up *n* (%) |
|---|---|---|
| Number of patients | 19 (38) | 27 (54) |
| Scleritis | 9 (18) | 15 (30) |
| Proptosis | 3 (6) | – |
| Peripheral ulcerative keratitis | 3 (6) | 1 (2) |
| Uveitis | 2 (4) | 3 (6) |
| Optic nerve compression | 2 (4) | 1 (2) |
| Dacryocystitis | 1 (2) | 9 (18) |
| Dacryoadenitis | 1 (2) | – |
| Scleromalacia | 1 (2) | 1 (2) |
| Retinal artery occlusion | 1 (2) | 2 (4) |
| Lacrimal occlusion | – | 3 (6) |
| Episcleritis | – | 3 (6) |
| Enucleation | – | 2 (4) |
| Fistula | – | 2 (4) |
| Conjunctivitis | – | 2 (4) |
| Optic neuropathy and pachymeningitis | – | 2 (4) |
| Corneal ulceration | – | 2 (4) |
| Ischemic optic neuropathy | – | 1 (2) |

**Table 3** Radiological imaging findings

| Radiological findings ($n=46$) | $n$ (%) |
|---|---|
| Radiologic abnormalities | 35 (76) |
| Sinusitis | 25 (54) |
| Septal perforation | 19 (41) |
| Lateral cartilage collapse | 17 (37) |
| Bone erosions | 10 (22) |
| Exophthalmos | 7 (15) |
| Lacrimal gland enlargement | 6 (13) |
| Mastoiditis | 5 (11) |
| Granulomas | 4 (9) |
| Otomastoiditis | 4 (9) |
| Pseudotumor | 2 (4) |
| Pachymeningitis | 2 (4) |
| Extraconal fat herniation | 2 (4) |

this complication ($n=29$) (median of 102 vs 43 months, $p=0.004$). Median ESR was 9 mm/h (1–63), and CRP 0.45 mm/dl (0.03–9.18). Table 4 displays the specific BVAS/GPA and VDI items.

Forty-three (86%) patients referred at least one ocular symptom in the questionnaire. Epiphora, blurred vision and photophobia were the most frequent symptoms, present in 20 (40%), 20 (40%), and 17 (35%) patients, respectively. In this regard, significantly more patients with cataract referred photophobia compared to patients without cataract (11% vs 6%, $p=0.03$), a finding that may suggest an association between these manifestations. Other symptoms less frequently referred by the patients included dryness (32%); ocular pain (31%); palpebral inflammation (29%); visual loss (25%); lacrimal gland obstruction (16%), and red painful eyes (12%). Patient's global assessment of disease had a median of 2 mm (0–9), in accordance with the low BVAS/GPA score values.

The ophthalmologic evaluation showed that at least one clinical abnormality was evident in 31 patients (62%), excluding visual acuity impairment. Scleromalacia and conjunctival inflammation/hyperemia were the most frequent findings, present in 13 (27%) patients. Blindness in either eye, a severe manifestation, was present in 12 (24%) patients, while exophthalmos and epiphora were observed in 10 (20%). Other abnormalities were detected in < 20% of the patients and are depicted in Table 5. Manifestations such as ophthalmoplegia, sclerouveitis, anterior or posterior uveitis, ciliary vessels vasculitis, optic nerve edema, endophthalmitis, corneal perforation, retinal occlusion or hemorrhage, choroidal granulomas or choroidal vasculitis were absent at the moment of evaluation.

**Table 4** Assessment of disease activity and damage

| Variable | $n$ (%) or median (min–max) |
|---|---|
| *BVAS/GPA total score* | 1 (0–17) |
| General | 5 (10) |
| Cutaneous | 2 (4) |
| Mucous membranes[a] | 1 (2) |
| ENT | 28 (56) |
| Cardiovascular | 1 (2) |
| Gastrointestinal | 0 |
| Pulmonary | 5 (10) |
| Renal | 10 (20) |
| Nervous system | 5 (10) |
| Other | 3 (6) |
| *VDI total score* | 5.5 (0–11) |
| Musculoskeletal | 9 (18) |
| Skin/mucous membranes | 6 (12) |
| Ocular | 29 (58) |
| ENT | 35 (70) |
| Pulmonary | 9 (18) |
| Cardiovascular | 13 (26) |
| Peripheral vascular disease | 5 (10) |
| Gastrointestinal | 0 |
| Renal | 24 (48) |
| Neuropsychiatric | 21 (42) |
| Other | 17 (34) |
| *Ocular damage* | |
| Cataract | 21 (42) |
| Blindness in one eye | 11 (22) |
| Optic atrophy | 6 (12) |
| Visual impairment/diplopia | 5 (10) |
| Retinal change | 4 (8) |
| Blindness in second eye | 2 (4) |
| Orbital wall destruction | 1 (2) |
| *ENT damage* | |
| Chronic sinusitis/radiological damage | 26 (52) |
| Hearing loss | 17 (34) |
| Nasal bridge collapse/septal perforation | 17 (34) |
| Nasal blockade/chronic discharge/crusting | 11 (22) |
| Subglottic stenosis (with surgery) | 5 (10) |
| Subglottic stenosis (no surgery) | 2 (4) |

*ENT* ear, nose, and throat, *BVAS/GPA* Birmingham Vasculitis Activity Score/granulomatosis with polyangiitis, *VDI* Vasculitis Damage Index

[a]Excluding ocular items

Regarding the histological studies, only four patients underwent biopsy of orbital tissue, paranasal sinuses or lacrimal glands. The findings showed giant cells, necrosis,

**Table 5** Ophthalmologic abnormalities detected during the evaluation

| Sign | Either eye *n* (%) |
|---|---|
| Scleromalacia | 13 (27) |
| Conjunctival inflammation/hyperemia | 13 (27) |
| Blindness | 12 (24) |
| Exophthalmos | 10 (20) |
| Epiphora | 10 (20) |
| Altered campimetry | 9 (18) |
| Dacyocystitis | 9 (18) |
| Keratoconjunctivitis sicca | 4 (8) |
| Ptosis | 3 (6) |
| Palpebral edema/inflammation | 3 (6) |
| Optic neuropathy | 3 (6) |
| Extraocular muscular involvement | 2 (4) |
| Orbital granuloma | 2 (4) |
| Proptosis | 2 (4) |
| Nasal conjunctive fistulas | 2 (4) |
| Ulcerative peripheral keratitis | 2 (4) |
| Scleritis | 2 (4) |
| Diplopia | 1 (2) |
| Retinal vasculitis | 1 (2) |
| Retinal exudates | 1 (2) |

inflammatory infiltrate, sclerosis, dacryoadenitis and hyalinized fibrosis of lacrimal glands.

### Association between ophthalmic involvement and other clinical variables

Correlation analysis including the variables of disease duration, ocular involvement, radiological abnormalities, disease activity and damage, acute phase reactants, ophthalmologic manifestations and symptoms showed only significant association between radiographic granulomas and clinical proptosis (Spearman's rho = 0.69, $p = 0.001$), and between extraconal fat herniation and scleritis (Spearman's rho = 0.69, $p = 0.0001$).

Patients with ocular involvement at diagnosis ($n = 19$) were compared to those patients without the manifestation ($n = 31$). The former group showed more frequency of concomitant ocular and sinonasal involvement during follow-up (42% *vs* 13%, $p = 0.03$), with no other significant difference between groups (Supplementary Material 1). Univariate logistic regression analysis confirmed that ocular involvement at diagnosis was associated with concomitant ocular and sinonasal involvement at follow-up (OR 4.72, 95% CI 1.17–19.01, $p = 0.01$).

Moreover, the analysis comparing patients with ocular involvement at follow-up ($n = 27$) and patients without the manifestation ($n = 23$), showed that the former group was younger at GPA diagnosis (41 vs 53 years, $p = 0.04$) and had longer disease duration (102 vs 43 months, $p = 0.01$). They also had higher accrued damage (VDI 6 vs 4, $p = 0.02$) and specifically higher frequency of ENT damage (85% vs 52%, $p = 0.01$), without other significant differences between groups (Supplementary Material 2). Univariate logistic regression analysis confirmed the association between ocular involvement at follow-up and age at GPA diagnosis (OR 0.94, 95% CI 0.90–0.99, $p = 0.03$), VDI (OR 1.29, 95% CI 1.03–1.61, $p = 0.02$), and ENT damage (OR 5.27, 95% CI 1.37–20.13, $p = 0.01$), while disease duration did not reach statistical significance (OR 1.00, 95% CI 0.99–1.01, $p = 0.05$).

## Discussion

In this study of 50 patients with mainly systemic and stable GPA and median disease duration of 6 years, 38% had ocular involvement at GPA diagnosis and 54% during follow-up. The most frequent ocular manifestation was scleritis. Concomitant ophthalmic and sinonasal involvement was found in 24%, and more than half of the patients had radiological sinusitis, as well as ocular and ENT damage. Ocular symptoms were referred by 86% of the patients and clinical abnormalities during the ophthalmological examination were found in 62% of them.

The findings of the present study are in keeping with those of a recent study by Gheita et al. where 46 patients with GPA referred to a tertiary care ophthalmic clinic in Egypt were included [4]. Blurred vision and scleritis/episcleritis were the most frequent ocular manifestations in their study, and similar to the present findings, retinal changes were infrequent. Unlike this study, they described uveitis in 24% of their patients and high disease activity at the time of evaluation determined by a mean BVAS score of 30.8 [4].

Conjunctival inflammation/hyperemia was one of the most frequent findings in the ophthalmological evaluation in the present study, similar to a retrospective report of 19 GPA patients from China, where this manifestation was present in 100% of them [20].

A study derived from randomized controlled trials included 377 AAV patients to characterize the patterns of ocular involvement. The results showed that 17% of the patients had ocular involvement at study entry, with conjunctivitis/episcleritis, scleritis, and retro-orbital mass/proptosis being the most common ocular manifestations, in agreement with current results. An association of non-white race with retroorbital mass/proptosis, as well as female gender and positivity for PR3-ANCA with scleritis was described [21].

In a study from The Spanish Registry of Systemic Vasculitis, the frequency of ophthalmic involvement at diagnosis in patients with GPA was lower than that of the present cohort (44/184, 24%, vs 19/50, 38%) [1]. Ocular manifestations in

the Spanish cohort included conjunctivitis, episcleritis, anterior uveitis, retinal vasculitis and optical nerve vasculitis, opposed to the current results, where uveitis, retinal changes and optical nerve involvement were infrequent. Furthermore, Ungprasert et al. also reported lower rates of inflammatory ocular disease in AAV patients from a retrospective single-center cohort study, where 183/1171 (15.6%) of the patients were affected; and, similar to the present findings, scleritis was the most common ocular manifestation [22].

A higher prevalence of ocular involvement in the current study compared to the previous studies could be explained by several reasons. First, the present study included only GPA patients that usually have a higher frequency of ocular involvement compared to the other forms of AAV (i.e., MPA and EGPA). Second, the current study assessed the manifestations at disease diagnosis and during follow-up, compared to other studies where ocular involvement was assessed at specific time points; and third, the present study defined ocular involvement considering the entire spectrum of ophthalmologic manifestations instead of the items included in the BVAS score exclusively.

Sinonasal involvement is common in GPA and has been reported in up to 69% of patients with orbital GPA. Similar to the current results, previous studies have demonstrated the presence of sinonasal involvement (e.g., opacification of the sinuses, mucosal thickening), and radiographic bony changes in patients with GPA presenting orbital inflammatory disease with lacrimal gland involvement [12, 20, 23, 24]. These findings support the notion that AAV should be considered in the differential diagnosis of any patient who presents with orbital inflammation and sinonasal involvement, regardless of other symptoms and/or ANCA status [22]. It also highlights the importance of the multidisciplinary approach and raises the question of whether the concomitant ocular and sinonasal involvement could be considered a particular clinical GPA phenotype with prognostic implications.

A great proportion of the patients referred at least one ocular symptom at evaluation. Epiphora, caused by nasolacrimal outflow obstruction, was also a common symptom referred by 52% of the patients in a study from Australia and New Zealand that included 29 patients with orbital and adnexal GPA [24].

Although there is no reliable pathognomonic imaging feature in GPA, radiologic abnormalities were observed in 76% of the patients in the present study. It is worth noting that sinonasal compartment involvement was frequent, whereas orbital pseudotumors were not, despite being a common imaging finding in GPA [25, 26]. Regarding to the histological studies, few of the patients had biopsy, being chronic fibrotic changes the predominant findings rather than the classic triad of vasculitis, tissue necrosis and granulomatous inflammation. In this sense, Ahmed et al. described a constellation of pathologic findings in 13 patients with limited ophthalmic GPA, including granulomatous foci, collagen necrosis, neutrophils/nuclear dust, plasma cells and infiltrating eosinophils [23].

In the current study, patients with ocular involvement at follow-up had higher damage accrued compared to patients without the manifestation. The most frequent presentation of ocular damage was cataract. In this regard, patients that developed cataract had longer disease duration than those who did not present this complication, a finding that suggests that this specific manifestation could be associated with the effects of treatment (specifically cumulative doses of steroids) rather than the disease itself.

The present study has potential limitations. The radiologic studies were not performed at the time of evaluation but rather at different points during follow-up. Not all patients had biopsy of orbital tissue, paranasal sinuses or lacrimal glands. Most of the patients had stable disease at the time of evaluation, which prevented the correlation of the ophthalmologic findings with other clinical manifestations. Moreover, most of the patients were ANCA-positive; therefore, the comparison of the ocular involvement in ANCA-positive and -negative patients was not possible. Conclusions regarding treatment/response were not feasible given the nature of the study design.

Strengths of the current study include the ophthalmologic evaluation of all patients by a single ophthalmologist, the inclusion of clinical and radiographic manifestations, the assessment of disease activity and damage. Moreover, information regarding ocular manifestations at diagnosis and during follow-up was collected and the evaluation of the patients' perspective of ocular symptoms was considered. The recruitment of patients with systemic rather than only limited forms of the disease, belonging to other clinics besides ophthalmology prevented potential recruitment bias leading to overestimations.

In conclusion, clinical and subclinical ophthalmic involvement is a common feature at diagnosis and during follow-up in patients with GPA, it is associated with concomitant sinonasal affection and has impact on ocular and ENT damage. Therefore, non-ophthalmologist clinicians should be aware of this important manifestation to reduce the risk of visual morbidity and organ damage.

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## Compliance with ethical standards

**Conflict of interest** AHA, AGC, AJF and CRG declare that they have no conflict of interest.

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