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Ocular involvement in granulomatosis with polyangiitis: A single-center cohort study on 63 patients

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ABSTRACT

Objective: To analyse the ocular manifestations of patients with GPA, their treatment and outcome.
Methods: Retrospective cohort study performed at the National Referral Center for Vasculitis, Cochin Hospital, Paris (France), from January 2005 to December 2015. Among 308 patients with a new diagnosis of GPA in accordance with the American College of Rheumatology classification criteria and/or revised Chapel Hill nomenclature definitions, we identified those with ocular involvement and a subsequent follow up in our center.
Results: The prevalence of ocular involvement in our GPA series was 38.6%; 63 patients were analysed with a median follow-up of 50.5 months (IQR: 17.8–82.8). Scleritis (18 patients, 28.6%) and episcleritis (18 patients, 28.6%) were the most common ophthalmologic manifestations, followed by orbital disease (13 patients, 20.6%). Bilateral involvement and visual acuity loss was seen in 29.1% and 16.7% of patients, respectively. Ocular involvement was the first GPA manifestation in 9 patients (14.3%), concomitant with systemic manifestation in 36 (57.1%), and occurred only during follow-up in 18 (28.6%). The indication for GPA treatment was suggested by ocular involvement in 12 patients (19.0%), by systemic features in 40 (63.5%) and by both ocular and systemic involvement in 11 (17.5%). Remission of ocular involvement was achieved in 51 patients (80.9%). In the remaining 12 (19.1%), symptoms persisted or even worsened, finally leading to rituximab (RTX) therapy in 8 of them (66.7%). Altogether, when used as first line or for refractory disease, ocular remission was achieved in 11 of the 12 cases (91.7%) treated with RTX versus 34 of the 47 cases (72.3%) treated with CYC ($P = .260$). Eye disease relapsed in 14 patients (22.2%). RTX allowed achievement of remission in 8 of them (57.1%). In the remaining six, other immunosuppressive drugs were used.
Conclusions: Scleritis and episcleritis are the most common ocular manifestations in GPA, most of the time associated with other systemic manifestations. In > 40% of cases, ocular manifestations were refractory to initial treatment or recurrent and led to RTX prescription, which appeared to be useful in these situations.

1. Introduction

Granulomatosis with polyangiitis (GPA, Wegener's) is an ANCA-associated vasculitis characterized by necrotizing granulomatous inflammation, usually involving the upper and lower respiratory tract, and small-vessel necrotizing vasculitis [1]. There is a broad heterogeneity in the clinical features at disease onset, especially in limited forms [2–5]. The clinician must be aware of the different manifestations of this disease to avoid a diagnostic delay, since prompt recognition of GPA leads to the early introduction of the appropriate therapy and, therefore, prevents disease progression and sequelae [6,7].

Eye involvement is common in GPA and may be the presenting

Abbreviations: GPA, granulomatosis with polyangiitis; ENT, ear-nose-throat; PUK, peripheral ulcerative keratitis; PR3, proteinase 3; MPO, myeloperoxidase; CYC, cyclophosphamide; GC, glucocorticoids; RTX, rituximab; AZA, azathioprine; MTX, methotrexate; PE, plasma exchange; NSAID, non-steroidal anti-inflammatory drug; iv, intravenous

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isolated sign leading to the diagnosis [8]. Any segment of the eye can be affected but orbital granuloma is the most specific manifestation [9–13]. High variability has been reported in the prevalence of GPA ocular involvement, ranging from 23 to 58% [3–5,14]. Moreover, most reports were published before 2005 or included only a small number of patients [3,4,8,14–16].

The objectives of the present study were to analyse the ocular manifestations of GPA, their treatment and outcomes, in a large French single-center cohort of GPA patients diagnosed after 2005.

2. Material and methods

2.1. Study population and settings

We conducted a retrospective cohort study at the National Referral Center for Vasculitis at Cochin Hospital, Paris, France. Patients with a new diagnosis of GPA from January 2005 to December 2015 who presented ocular involvement were identified from the database of the referral center and were analysed. Patients who consulted in the referral center but had no follow-up in our institution were excluded. Medical records of patients with ocular involvement were individually reviewed by one of the authors (MAPJA). The study fulfilled good clinical practices and the Declaration of Helsinki principles.

2.2. Data and definitions

To be included, patients had to have a diagnosis of GPA in accordance with the American College of Rheumatology classification criteria [17] and/or revised Chapel Hill nomenclature definitions [18]. Ophthalmologic manifestations associated with GPA included [9–13]: 1) orbital disease due to vasculitis, tissue necrosis and granulomatous infiltration of extraocular muscles and lachrymal glands. Patients with isolated nasolacrimal duct obstruction were excluded since it can be considered secondary to ear-nose-throat (ENT) involvement [13]; 2) eyelid involvement that may include blepharitis, lid granuloma, chalazion and trichiasis; 3) scleritis, episcleritis or conjunctivitis; 4) corneal inflammation such as interstitial keratitis or peripheral ulcerative keratitis (PUK); 5) anterior, intermediate and/or posterior uveitis; 6) retinal involvement as a consequence of vasculitis of blood vessels of the retinal circulation; and 7) optic nerve involvement (ischemic optic neuropathy, optic neuritis or compressive optic neuropathy in the setting of orbital inflammatory disease). Data on demographics, clinical manifestations, laboratory investigation, treatment and outcomes were collected. GPA treatment was defined as suggested by ocular involvement in cases of isolated ocular involvement or when only eye manifestation was severe, posing a risk for visual function (e.g. optic nerve compression, necrotizing scleritis), or progressive (e.g. bilateralization of scleritis or episcleritis); suggested by systemic involvement when systemic symptoms predominated with only mild ocular involvement (i.e. conjunctivitis, blepharitis, episcleritis); or suggested by both ocular and systemic involvement in the other cases. Criteria for remission and response were defined in accordance with the EULAR recommendations [19,20]. Remission was defined as an absence of disease activity with a Birmingham Vasculitis Disease Activity Score (BVAS) of zero under stable low dose of prednisone < 7.5 mg/day [21]. Response was defined as > 50% decrease in the BVAS and an absence of new vasculitis signs. Refractory vasculitis was defined as unchanged or increased disease activity after four weeks of treatment with daily oral cyclophosphamide (CYC) (2–3 mg/kg) and glucocorticoids (GC) or pulse-intermittent high-dose CYC (15 mg/kg or 0.6–0.7 g/m^2 body surface area) with GC, or lack of response, defined as < 50% reduction in BVAS and/or lack of improvement of at least one major item, after 4–6 weeks of treatment, or chronic persistent disease, defined as presence of at least one major or three minor items on the BVAS despite 8 to 12 weeks of treatment. Relapse was defined as a recurrence of disease activity or first appearance of at least one BVAS item attributable to active GPA after entering remission.

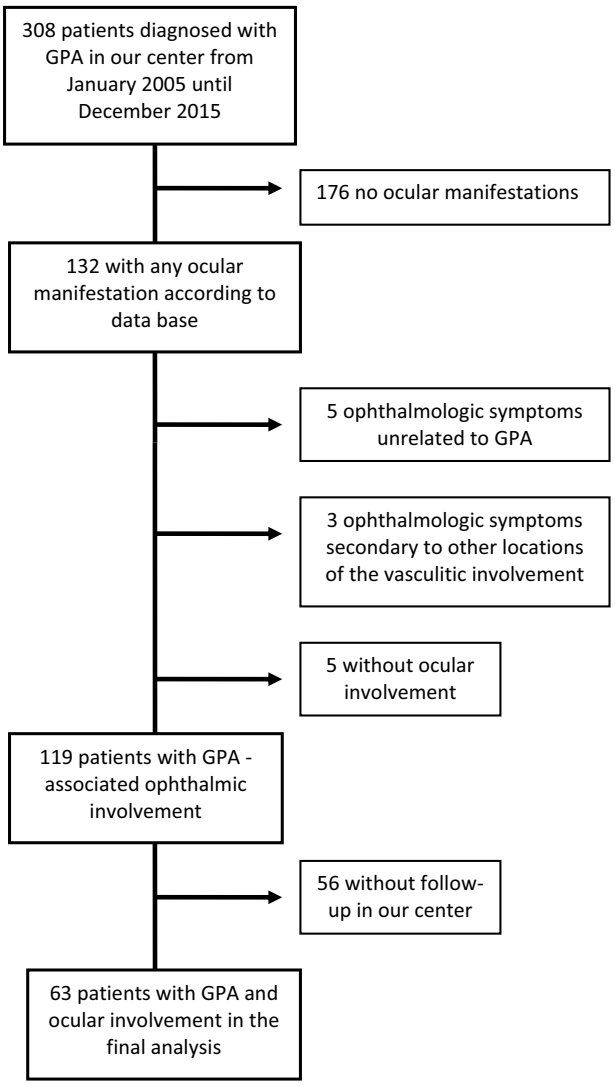

Fig. 1. Flow chart.

2.3. Statistical analysis

Quantitative data were shown as mean ± standard deviation (SD) or the median with interquartile ranges (IQR). Qualitative variables were expressed with frequencies and 95% confidence intervals (CIs). Categorical variables were compared using Chi-square test or Fisher exact test, whereas Student's *t*-test or Mann-Whitney *U* test were applied for continuous variables. Statistical analysis was performed using SPSS v. 15.0 (Statistical Package for Social Sciences Inc., Chicago, IL, USA).

3. Results

3.1. Patients and demographics

We retrieved a total of 308 patients with a new diagnosis of GPA from January 2005 until December 2015 in our center (Fig. 1). Any ocular manifestation was mentioned for 132 of them, but thirteen patients were excluded after the review of their medical records: five because their ophthalmologic symptoms were unrelated to GPA (one ocular lymphoma, one glucocorticoid-induced retinopathy, one ethambutol-induced retinopathy and two cataracts), three because their ophthalmologic symptoms were secondary to ENT or neurologic

Table 1
Demographics and clinical characteristics of ocular involvement in patients with GPA.

Variable[a]	Number of patients (%)
Age, yrs. (mean ± SD) (63)	46.1 (± 16.2)
Sex (male) (63)	33 (52.4%)
Ethnicity (63)	
Caucasian	54 (85.7%)
Arabic	6 (9.5%)
Black African	1 (1.6%)
Hispanic	2 (3.2%)
Type of eye disease (63)	
Episcleritis	18 (28.6%)
Scleritis[b]	18 (28.6%)
Orbital disease	13 (20.6%)
Conjunctivitis	6 (9.5%)
Keratitis	1 (1.6%)
Uveitis	1 (1.6%)
Retinal vasculitis	3 (4.7%)
Optic nerve involvement	2 (3.2%)
Palpebral involvement	1 (1.6%)
Type of scleritis (18)	
Diffuse anterior scleritis	13 (72.2%)
Diffuse anterior scleritis complicated with PUK	2 (11.1%)
Nodular anterior scleritis	2 (11.1%)
Necrotizing scleritis	1 (5.6%)
Symptoms at diagnosis (62)	
Ocular redness	27 (43.6%)
Ocular pain	14 (22.6%)
Proptosis/exophthalmos	11 (17.7%)
Diplopia	2 (3.2%)
Visual acuity loss[c]	5 (8.1%)
Photophobia	1 (1.6%)
Blurring vision	1 (1.6%)
Palpebral inflammation	1 (1.6%)
Laterality of eye involvement (55)	
Unilateral	39 (70.9%)
Bilateral	16 (29.1%)
Systemic symptoms	61 (96.8%)
General symptoms	30 (47.6%)
ENT	54 (85.7%)
Lung	33 (52.3%)
Renal	28 (44.4%)
Neurologic	13 (20.6%)
Timing of eye involvement (63)	
Ophthalmic involvement first[d]	9 (14.3%)
Systemic involvement first	18 (28.6%)
Both ocular and systemic involvement at onset	36 (57.1%)

PUK: peripheral ulcerative keratitis. ENT: ear/nose/throat involvement.

[a] Values in parenthesis in the first column indicate the number of patients for whom data were available.

[b] Scleritis presented with other ocular manifestation in 5 cases: uveitis (2), PUK (2) and optic neuritis (1).

[c] A total of ten patients (16.7%) presented visual acuity loss at diagnosis or during the evolution of the disease.

[d] Type of ocular involvement in those with ophthalmic manifestations first included: 4 patients with orbital disease, 1 with scleritis, 1 episcleritis, 1 with a combination of scleritis and uveitis, 1 with optic neuropathy and 1 with conjunctivitis.

involvement (one nasolacrimal obstruction secondary to nasosinusal inflammation, two cases of diplopia secondary to cranial pars involvement in the context of pachymeningitis and rhomboencephalitis respectively), and five since they were misclassified and had no ocular involvement. The prevalence of ocular involvement in our series was 38.6% (119/308). Fifty-six patients were subsequently excluded due to lack of follow-up. A total of 63 patients were finally analysed, with a median follow-up of 50.5 months (IQR: 17.8–82.8) after the ocular involvement onset. Their mean age at diagnosis of GPA was 46.1 years (SD = 16.2), 52.4% were males and 85.7% were Caucasian (Table 1).

3.2. Ocular manifestations

The most common ophthalmologic manifestations were episcleritis (18 patients, 28.6%) and scleritis (18 patients, 28.6%), followed by orbital disease (13 patients, 20.6%). Five patients had several concomitant ocular manifestations at the same time, with scleritis present in all cases. Most patients had diffuse anterior scleritis, but peripheral ulcerative keratitis (PUK) was associated in two patients (Table 1). The most common ophthalmic presentation symptom in the cohort was ocular redness (27 patients, 43.6%), followed by ocular pain (14 patients, 22.6%) and proptosis/exophthalmos (11 patients, 17.7%). Ten patients (16.7%) presented visual acuity loss at diagnosis or during the follow-up, 4 (40%) as a consequence of optic nerve compression due to orbital disease, 2 (20%) due to optic neuropathy, 2 (20%) due to retinal vasculitis and 2 (20%) due to scleritis. Nine patients (14.3%) complained about diplopia; all of them had orbital disease.

Ocular involvement was bilateral in 16 patients (29.1%). Bilateral ocular involvement was slightly higher in the case of scleritis and/or episcleritis (11/30–36.7%), but no differences were found when comparing with frequency of bilateralism in other types of ophthalmologic manifestations ($P = .175$).

3.3. Systemic manifestations

Sixty-one patients (96.8%) had other systemic manifestations, either at diagnosis or during the evolution of the vasculitis. The frequencies of the different systemic manifestations were: 54 (88.5%) ear/nose/throat (ENT) involvement (more commonly crusty rhinitis, chronic sinusitis and otitis), 33 (54.1%) lung involvement (more commonly lung nodules, followed by alveolar haemorrhage), and 28 (45.9%) renal disease. General symptoms (fever, asthenia, weight loss) were present in 30 patients (49.1%).

3.4. Sequence in ocular involvement

Ocular involvement was the first GPA manifestation in 9 patients (14.3%), was concomitant with systemic manifestation in 36 (57.1%), and occurred only during follow-up of the disease in 18 cases (28.6%) (Table 1). Two patients with orbital inflammation and exophthalmos never experienced systemic symptoms during evolution after a median follow-up of 69 and 95 months, respectively. The seven other patients with isolated ocular symptoms at the disease onset, who subsequently developed systemic manifestations, all had ENT involvement in the evolution of the disease. In the 36 cases with both ocular and systemic symptoms present at disease onset, ENT involvement was the most common systemic manifestation (32 patients, 88.9%), followed by lung involvement (22 patients, 61.1%) and renal disease (20 patients, 55.6%).

When ophthalmologic manifestations preceded systemic symptoms, GPA diagnosis was made after a median delay of 791 days (IQR: 105–1147), compared to 31 days (IQR: 0–92) when systemic symptoms were concomitant or the first manifestation of the disease ($P < .0001$). In patients who presented with isolated ocular involvement, median time to diagnosis of GPA tended to be shorter in cases of orbital disease compared with other ocular manifestations: 120 (IQR: 45–305) and 974 (IQR: 616–1255) days, respectively ($P = .071$).

3.5. ANCA and histology

ANCA-IFI tests were positive at the time of GPA diagnosis in 59 patients (93.7%) and negative in the remaining four (6.3%). Among them, 47 (79.7%) had cytoplasmic ANCA (c-ANCA)-pattern, nine (15.3%) perinuclear (p-ANCA)-pattern and three (5.0%) undetermined pattern. From a total of 61 patients for whom ANCA-ELISA test results were available, anti-proteinase-3 (PR3) ANCA were detected in 50 (81.9%), anti-myeloperoxidase (MPO) in 6 (9.8%), and negative in 5.

Table 2
Distribution of ANCA subtype for every type of eye disease and for the different timing of eye involvement during the evolution of the disease.

	PR3-ANCA [50]	MPO-ANCA [6]	Negative ANCA [5]	*P*
Type of eye disease[a]				0.865
Orbital disease (13)	10 (76.9%)	1 (7.7%)	2 (15.4%)	
Episcleritis (17)	14 (82.4%)	3 (17.6%)	0	
Scleritis (17)	14 (82.4%)	1 (5.9%)	2 (11.8%)	
Conjunctivitis (6)	5 (83.3%)	0	1 (16.7%)	
Keratitis (1)	1 (100%)	0	0	
Uveitis (1)	1 (100%)	0	0	
Palpebral involvement (1)	1 (100%)	0	0	
Retinal vasculitis (3)	3 (100%)	0	0	
Optic nerve involvement (2)	1 (50%)	1 (50%)	0	
Timing of eye involvement[a]				0.525
Ophthalmic involvement first (9)	6 (66.7%)	2 (22.2%)	1 (11.1%)	
Systemic involvement first (16)	13 (76.5%)	2 (11.8%)	2 (11.8%)	
Ocular and systemic involvement at onset (35)	31 (88.6%)	2 (5.7%)	2 (5.7%)	

PR3 = proteinase 3; MPO = myeloperoxidase.
[a] Values in parenthesis in the first column indicate the number of patients for whom ANCA determination was available.

No differences were observed in the distribution of ANCA subtype according to the type of eye disease or the timing of eye involvement during the evolution of the disease, with PR3-ANCA most commonly found in all cases (Table 2).

A biopsy to support the diagnosis was undertaken in 34 patients (54%), being renal biopsy the most common (23.5%).

3.6. Treatment

3.6.1. Treatment before ocular involvement

All but one of the eighteen patients diagnosed with ocular manifestations during the course of GPA had received systemic treatment before the onset of the ophthalmologic involvement. They had received oral glucocorticoids (GC), combined with another immunosuppressive drug as induction treatment in sixteen of them: intravenous (iv) cyclophosphamide (CYC) in eleven (68.8%), oral CYC in one (6.3%), azathioprine (AZA) in 2 (12.5%), methotrexate (MTX) in one (6.3%) and rituximab (RTX) in one (6.3%). Among the eleven patients treated with iv CYC before ocular involvement, one required switching to RTX due to lack of responsiveness to initial therapy (progression of bronchial stenosis despite iv CYC: 8 infusions of 500 mg/m^2 within 5 months). Fourteen patients (77.7%) had achieved complete remission before the ocular disease onset, with previous withdrawal of maintenance treatment in 7 cases and still under maintenance treatment in the remaining 7 (AZA in three cases, MTX in one, GC in one, and biannual RTX in two cases). Two patients (11.1%) were still receiving iv CYC induction treatment when ocular symptoms appeared. One patient (5.5%) had refractory ENT symptoms and was under oral CYC and GC when ocular manifestations developed, despite correct adherence to treatment.

3.6.2. Treatment at ocular symptom onset

Table 3 shows the treatment initiated when ophthalmic involvement was diagnosed. The indication for GPA treatment was driven mainly by the systemic manifestations in 40 (63.5%), by ocular involvement in 12 (19.0%), and by both in 11 patients (17.5%). In three of the 40 patients in whom treatment was mainly driven by systemic manifestations, topical agents were added to the treatment for the eye manifestations (blepharitis, conjunctivitis and episcleritis in each case). Six of those 23 patients in whom ocular involvement was part of the treatment decision had non-severe ocular affectation and received topical agents (non-steroidal anti-inflammatory drugs or GC) in two cases (one episcleritis and one conjunctivitis), oral GC in two (conjunctivitis treated with 10 mg/day of oral prednisone and mild orbital involvement due to extension of sinusitis treated with 30 mg/day of oral prednisone), combination of topical and systemic GC in one (bilateral episcleritis) or trimethoprim-sulfamethoxazole in one (mild orbital involvement). In the remaining seventeen patients, ocular involvement was more severe (ten cases with orbital infiltration with exophthalmos, three cases with optic neuritis, three with retinal vasculitis and one with progressive scleritis with bilateralization). Treatment consisted of a combination of systemic GC and either CYC (n = 12), AZA or MTX (n = 3) or RTX (n = 2). Debulking or decompression orbital surgery was not performed in any case.

3.7. Outcomes of ocular involvement

Remission of the eye involvement was achieved in 51 patients (80.9%) within 6 to 12 months. In twelve patients (19.1%) the ocular manifestations persisted or worsened despite systemic treatment, leading to therapeutic immunosuppressive intensification: five had orbital disease, five scleritis, one episcleritis and one optic neuropathy. Nine of the cases were considered refractory, since the first-line treatment had consisted of GC and CYC. The remaining three cases had not responded to a first-line treatment with GC and AZA or MTX. Switching to GC and CYC was conducted in two of them, without response and refractoriness of the ocular involvement. In the other case, RTX was given to achieve remission. In those patients with refractory eye involvement, RTX was the most commonly-used drug to achieve remission, administered in 8 cases (66.7%): four with refractory scleritis, three with refractory orbital disease, and one with orbital disease without response to first-line treatment with GC and MTX. Other treatments for refractory eye involvement included oral CYC (two cases with scleritis), intravenous methylprednisolone combined with mycophenolate mofetil (one case with optic neuropathy) or infliximab (one case with orbital disease). Remission was initially observed in the seven of the cases treated with RTX (87.5%). In the remaining case treated with RTX, progressive exophthalmos required high doses of intravenous methylprednisolone, intravenous immunoglobulin and two extra doses of RTX (375 mg/m^2), to eventually achieve remission. Altogether, when used as first-line or for refractory disease, ocular remission was achieved in 11 of the 12 cases (91.7%) treated with RTX versus 34 of the 47 cases (72.3%) treated with CYC (P = .260).

Twenty-seven patients (42.8%) experienced at least one relapse, involving the eye in 14 cases (22.2%) (Table 4). In six cases the relapse was exclusively ophthalmic (more commonly in orbital disease and optic neuropathy) and in the remaining eight (mainly scleritis and episcleritis), included a combination of ocular and systemic manifestations. Ocular relapses were significantly more common in patients with MPO-ANCA-associated disease (5/6, 83.3%), comparing with those with PR3-ANCA (8/50, 16%) or ANCA-negative (1/5, 20%) disease (P = .001). In 12 cases (85.7%) ocular manifestations were the same as at diagnosis. There were no significant differences in the risk of ocular relapse depending on the type of eye involvement (P = .583). Relapses were observed in five cases of scleritis (27.8% of all scleritis), three cases of episcleritis (16.6% of all episcleritis), three cases of orbital disease (23% of all orbital disease), one case of optic neuropathy (50% of all optic neuropathy cases), two cases of keratitis (100% of all keratitis), one case of conjunctivitis (50% of all conjunctivitis). A second ocular relapse was seen in five cases and a third ocular relapse in two. Initial treatment approach included systemic immunosuppression in all cases except one case of mild scleritis treated with topical non-steroidal anti-inflammatory drug (NSAID). RTX was the initial treatment in five cases and finally used in a total of 8 patients (57.1%) to achieve remission of inflammatory eye disease.

Despite remission of the vasculitis, ocular sequelae persisted in eight cases: retro-orbital fibrosis with mild exophthalmos in four, entropion

Table 3
Treatment of GPA administered when ocular involvement was diagnosed.

Treatment	GPA manifestations				
	Isolated ophthalmic involvement	Ophthalmic involvement + ENT manifestations[b]		Ophthalmic involvement + lung and/or renal involvement and/or other systemic manifestation	
		Suggested by ophthalmic manifestation ± ENT	Mainly suggested by ENT manifestation	Suggested by both ophthalmic and systemic manifestations	Mainly suggested by systemic manifestations
Topical ocular treatment	2 (3.2%)	0	0	0	0
Oral GC + topical ocular treatment	1 (1.6%)	0	0	0	0
Systemic GC	1 (1.6%)[1]	1 (1.6%)[6]	0	0	1 (1.6%)
TMP-SMX	1 (1.6%)	0	0	0	0
Topical ocular treatment + systemic treatment (oral GC+ iv CYC or oral GC + iv RTX)	0	0	1 (1.6%)[8]	0	2 (3.2%)[14]
iv methylprednisolone + iv CYC + oral GC	1 (1.6%)[2]	0	1 (1.6%)	5 (7.9%)[9]	11 (17.4%)
iv CYC + oral GC	0	2 (3.2%)[7]	3 (4.7%)	3 (4.7%)[10]	12 (19.0%)
Oral CYC + oral GC	0	0	1 (1.6%)	1 (1.6%)[11]	0
iv methylprednisolone + oral GC + AZA or MTX[a]	1 (1.6%)[3]	0	0	1 (1.6%)[12]	2 (3.2%)
AZA or MTX + oral GC	1 (1.6%)[4]	0	3 (4.7%)	0	1 (1.6%)
RTX + oral GC	1 (1.6%)[5]	0	0	1 (1.6%)[13]	2 (3.2%)

GC = glucocorticoids; iv = intravenous; CYC = cyclophosphamide; AZA = azathioprine; MTX = methotrexate; RTX = rituximab. ENT = ear/nose/throat.
[1] Low dose of oral GC (10 mg/day) for conjunctivitis.
[2] Severe exophthalmos, mass effect and optic nerve compression.
[3] Severe exophthalmos.
[4] The patient was under maintenance treatment with GC + AZA when exophthalmos developed, so the doses of GC and AZA were increased.
[5] Optic neuritis combined with scleritis.
[6] Mild exophthalmos.
[7] Severe exophthalmos in one case and optic neuropathy with visual impairment in another.
[8] Topical ocular treatment for episcleritis and systemic treatment for severe ENT manifestations.
[9] Two patients with severe exophthalmos, two patients with retinal vasculitis and one patient with optic neuritis.
[10] One patient with retinal vasculitis, one patient with moderate exophthalmos and one patient with progressive scleritis with bilateralization.
[11] Orbital involvement with optic nerve compression.
[12] Orbital involvement with optic nerve compression.
[13] Severe exophthalmos.
[14] Topical ocular treatment for conjunctivitis and blepharitis and immunosuppressive treatment for systemic manifestations.
[a] In one patient mycophenolate mofetil was used instead of AZA or MTX (the patient had renal involvement).
[b] In 3 cases there were also arthralgia and/or cutaneous manifestations.

due to palpebral retraction in one, and residual loss of visual acuity in three (two cases with optical neuritis and one with scleritis).

4. Discussion

The present study, based on a large retrospective single-center cohort of GPA patients with a follow up period of 4 years, showed that scleritis and episcleritis are the most common ocular manifestations in GPA. In > 40% of cases, ocular manifestations were refractory to initial treatment or recurrent and led to RTX prescription, which appeared to be useful in these situations of refractoriness or recurrence.

The prevalence of ocular involvement in our cohort is similar to the one observed in previous series [3,4,14,22,23] and the characteristics of this subgroup of patients with eye involvement do not differ from usual GPA population in terms of demographics [24]. It was also shown that the prevalence of ocular involvement was similar in children-onset and adult-onset ANCA-associated vasculitides [25]. According to our series the most common ocular affectation was not the typical orbital granuloma, mentioned in the first description of the disease [26] or in overlap syndromes [27], but scleritis and episcleritis. This is in concordance with a recent study, published by Ungprassert et al [28] that reported a prevalence of scleritis and episcleritis of 24% and 21%, respectively, among a series of 152 patients with GPA. The aforementioned contrasts with older series [14,29], in which orbital disease was reported as the most frequent ocular manifestation, probably due to lack of recognition of scleritis and episcleritis as GPA manifestation, especially if they were the sole manifestation of the disease. A plausible explanation for this higher prevalence of scleral and episcleral involvement in GPA may be the anatomic characteristics of these eye segments, with a rich network of vessels that can be affected in the setting of small-vessel vasculitis [11] and a high content of collagen, particularly susceptible to granulomatous involvement [30].

Isolated GPA ocular involvement was scarcely reported in our series, with eye manifestations more commonly identified when occurring as a part of the wide clinical spectrum of the disease [16]. Concerning associated systemic manifestations, ENT involvement was evident in almost 90% of our patients. Regarding other systemic manifestations, we have found a prevalence of lung and renal disease of 52.3% and 44.4% respectively, lower than the reported rates of 80–90% for both manifestations from GPA population in older series [2–4]. Such differences could be related to an increased awareness of GPA nowadays and description of limited forms more commonly than in the past, reflecting an earlier diagnosis. In fact, current series like the one by Solans-Laque et al [5] report frequencies of lung and renal involvement around 55–60% in patients diagnosed with GPA after 2000, but it remains highly variable according to the speciality recruitment.

There were only two patients in our cohort who never developed other manifestations of the disease after a median follow-up of more than six years. Both of them had orbital inflammation. Since other ocular manifestations could be more difficult to identify as GPA manifestations, it is possible that the prevalence of isolated ocular involvement may be underestimated [23]. In fact, the median time to diagnosis of GPA was approximately 25 times longer when ophthalmic manifestations preceded systemic symptoms, especially if such ocular manifestation was different from orbital disease. Ophthalmologists should consider a diagnosis of GPA when dealing with refractory or

Table 4
Characteristics and evolution of the 14 patients with ocular relapses.

	First ocular manifestation	First ocular relapse	Associated systemic symptoms	Time to relapse	Treatment of first ocular relapse	Ocular response to treatment	Second ocular relapse	Associated systemic symptoms	Time to second relapse	Treatment of second relapse	Third ocular relapse
1	Scleritis	Scleritis	ENT	59 days	Oral GC + RTX	Yes	Scleritis	No	233 days	Oral GC + RTX	Scleritis[1]
2	Scleritis	Episcleritis	No	201 days	Oral CT	Yes	Scleritis	No	164 days	iv CYC	Episcleritis[2]
3	Scleritis	Scleritis	No	681 days	Topical GC + oral GC + MTX	Yes	Scleritis	No	244 days	Topical GC	No
4	Scleritis	Scleritis	General symptoms[3]	224 days	RTX	Yes	No	–	–	–	–
5	Scleritis (combined with keratitis)	Keratitis	ENT	60 days	Oral GC + AZA + RTX	Yes	Scleritis	ENT	1248 days	RTX	No
6	Episcleritis	Episcleritis	ENT	671 days	Oral GC + AZA	Yes	Episcleritis	Renal	2160 days	RTX	No
7	Episcleritis	Episcleritis	ENT	1630 days	Oral GC + AZA	Yes	No	–	–	–	–
8	Episcleritis	Episcleritis	Lung[4]	2608 days	Oral GC + iv CYC + PE[5]	Yes	No	–	–	–	–
9	Orbital disease	Episcleritis	No	1156 days	Topical NSAID	Yes	No	–	–	–	–
10	Orbital disease	Orbital disease	ENT + general symptoms	46 days	Oral GC + RTX	Yes	No	–	–	–	No
11	Orbital disease	Orbital disease	No	959 days	RTX	Yes	No	–	–	–	–
12	Optic neuropathy	Optic neuropathy	No	92 days	RTX	Yes	No	–	–	–	–
13	Keratitis	Keratitis	No	62 days	Topical GC + oral CT	Yes	No	–	–	–	–
14	Conjunctivitis	Conjunctivitis + blepharitis	ENT	914 days	Oral GC + MTX	Yes[6]	No	–	–	–	–

ENT = ear/nose/throat, GC = glucocorticoids; iv = intravenous; CYC = cyclophosphamide; AZA = azathioprine; MTX = methotrexate; RTX = rituximab; PE = plasma exchange, NSAID = non-steroidal anti-inflammatory drug.

[1] RTX was used to control the third ocular relapse.
[2] RTX was used to control the third ocular relapse.
[3] General symptoms include: fever, asthenia, anorexia and/or weight loss.
[4] Pulmonary haemorrhage.
[5] Plasma exchange was used due to pulmonary haemorrhage.
[6] There was ocular response to the treatment, but iv CYC was required to control extraocular symptoms (ENT).

recurrent isolated scleritis or episcleritis [8,31], which may be the presenting symptoms of GPA, whereas they are extraordinarily infrequent as the first manifestation of other diseases such as rheumatoid arthritis [32]. Moreover, once they suspect that patients with isolated ocular inflammation could have a GPA, they should refer them for a careful assessment looking for pauci-symptomatic systemic manifestations of GPA, with periodic revaluations if no other manifestations are initially found.

As observed in our cohort, ocular disease may evolve in parallel or isolated from other GPA manifestations. Scleritis was the most commonly recurrent ocular manifestation, in up to 30% of the cases, relapsing in association with other systemic manifestations in two thirds of the cases, confirming that scleritis could be a surrogate marker of disease activity [9]. On the other hand, orbital disease and optic nerve involvement relapses were more commonly independent from other systemic manifestations. Surprisingly, we have observed a higher rate of ocular relapses in patients with MPO-ANCA-associated disease. A recent study focused on ocular manifestations of ANCA-associated vasculitis did not find significant differences in the rates of ocular recurrence in accordance with ANCA specificity, with rates of recurrence of 24% for PR3-ANCA, 26% for MPO-ANCA and 15% for negative ANCA-associated disease [28]. Our findings on a limited number of patients should be confirmed in other studies as they contrast with most previous studies that have observed a higher risk of relapses in patients with PR3-ANCA specificity [33].

Since ocular involvement occurred mostly in the setting of other systemic manifestations of GPA, treatment was more often suggested by the extra-ophthalmologic manifestations. Orbital disease and optic nerve affectation constituted an exception, due to the severity of the involvement and the repercussion over the visual function. Topical ocular treatment was generally used for mild ocular involvement, such as conjunctivitis or blepharitis. In refractory and relapsing cases of ocular involvement, RTX constituted an important therapeutic tool, being finally required in almost two thirds of refractory ocular manifestations and more than a half of all relapsing ocular symptoms, not only for controlling vasculitis (scleritis/conjunctivitis/optic ischemic neuritis), but also in some cases of granulomatous involvement such as orbital disease. Previous reports have observed less frequent remission in patients with granulomatous manifestations such as retro-orbital granuloma and endobronchial disease treated with RTX [34–36], but recent trials have also demonstrated the usefulness of RTX in controlling such manifestations [37,38]. The overall prognosis of ANCA-associated vasculitides has improved [39] and actually, no patient in our series required debulking or decompression orbital surgery, thanks to the control of orbital disease with rescue treatment with RTX.

Some limitations of our study are its retrospective design, the absence of a routinely ophthalmologic exam for all GPA patients, and the possible lack of recognition and referral to our center of very limited ophthalmic manifestations of GPA. Despite the above shortcomings, our study has several strengths, such as being a large modern series with all patients diagnosed after 2005, with a more homogeneous management of the disease and the introduction of RTX for the treatment of GPA, a long follow-up period that allows us to evaluate the outcomes of the ocular involvement, and a detailed description of treatments received.

In conclusion, ocular involvement is not an uncommon manifestation of GPA, but may be under-recognized, especially when it is the first symptom of the disease. Clinicians must be aware of this involvement, since it reflects activity of GPA and requires systemic immunosuppressive drugs to control the symptoms. Rituximab appears to be a useful tool in inducing remission and controlling relapses in patients with ocular involvement of GPA and also after failure of CYC to control the disease.

Author contributions

Dr. Pérez-Jacoiste Asín had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Pérez-Jacoiste Asín, Charles, Guillevin, Puéchal.

Acquisition, analysis, or interpretation of data: Pérez-Jacoiste Asín, Charles, Rothschild, Terrier, Brézin, Mouthon, Guillevin, Puéchal.

Drafting of the manuscript: Pérez-Jacoiste Asín, Puéchal.

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Ethics approval

The Ethics Committee of Cochin University Hospital approved the study (Decision AAA-2018-08011).

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None

Competing interests

The main investigators, Drs Rothschild, Terrier, Brézin, Mouthon, Guillevin, and Puéchal are employees of the Assistance Publique–Hôpitaux de Paris. All of them and Dr. Charles have conducted studies evaluating rituximab in which rituximab was given free of charge.

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