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Scleritis phenotype in Granulomatosis with Polyangiitis: experience from the international AIDA Network for Scleritis Registry

Jurgen Sota
University of Siena Faculty of Medicine and Surgery: Universita degli Studi di Siena
Andrea Hinojosa-Azaola
Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran
Eduardo Martín-Nares
Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran
Guillermo Arturo Guaracha-Basañez
Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran
Jiram Torres-Ruiz
Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran
Gaafar Ragab
Cairo University
Ahmed Hatem Laymouna
Cairo University
Mahmoud Ghanema
Cairo University
Amina Maher
Cairo University
Jessica Sbalchiero
University of Siena Faculty of Medicine and Surgery: Universita degli Studi di Siena
Valeria Caggiano
University of Siena Faculty of Medicine and Surgery: Universita degli Studi di Siena
Henrique Ayres Mayrink Giardini
Sao Paulo University Faculty of Medicine: Universidade de Sao Paulo Faculdade de Medicina
Juanita Téllez-Zambrano
Universidad Del Rosario
Juana Lozano-García
Universidad Del Rosario
Maria Camila Mosquera-Huertas
Universidad Del Rosario
Silvana Guerriero

University of Bari Aldo Moro: Universita degli Studi di Bari Aldo Moro

Rosanna Dammacco

University of Bari Aldo Moro: Universita degli Studi di Bari Aldo Moro

Maria Sole Chimenti

University of Rome Tor Vergata: Universita degli Studi di Roma Tor Vergata

Benedetta Monosi

University of Rome Tor Vergata: Universita degli Studi di Roma Tor Vergata

Elisabetta Greco

University of Rome Tor Vergata: Universita degli Studi di Roma Tor Vergata

Giuseppe Lopalco

University of Bari Aldo Moro: Universita degli Studi di Bari Aldo Moro

Pravin Hissaria

Royal Adelaide Hospital

Carla Gaggiano

University of Siena Faculty of Medicine and Surgery: Universita degli Studi di Siena

Marco Cattalini

University of Brescia: Universita degli Studi di Brescia

Piero Ruscitti

Universita degli Studi dell'Aquila

Samar Tharwatt

Mansoura University

Guillermo Ruiz-Irastorza

University of the Basque Country Faculty of Medicine and Nursing: Universidad del Pais Vasco Facultad de Medicina y Enfermeria

Maissa Thabet

University of Sousse: Universite de Sousse

Mario Fruschelli

University of Siena Faculty of Medicine and Surgery: Universita degli Studi di Siena

Giacomo Emmi

Hospital of Cattinara: Ospedale di Cattinara

Paola Parronchi

University of Florence: Universita degli Studi di Firenze

Maria Pia Paroli

Sapienza University of Rome: Universita degli Studi di Roma La Sapienza

José Hernández-Rodríguez

University of Barcelona: Universitat de Barcelona

Maite Sainz de-la-Maza

University of Barcelona: Universitat de Barcelona

Serena Bugatti

University of Pavia: Universita degli Studi di Pavia

Luciana Breda

Gabriele d'Annunzio University of Chieti and Pescara: Universita degli Studi Gabriele d'Annunzio Chieti Pescara

Maria Francesca Gicchino

University of Campania Luigi Vanvitelli: Universita degli Studi della Campania Luigi Vanvitelli

Ezgi Deniz Batu

Hacettepe University: Hacettepe Universitesi

Seza Ozen

Hacettepe University: Hacettepe Universitesi

Inés Hernanz Rodriguez

Fundacion Jimenez Diaz-UTE: Hospital Universitario Fundacion Jimenez Diaz

Luz Elena Concha Del Rio

Asociación para Evitar la Ceguera en Hospital Dr Luis Sánchez Bulnes: Asociacion para Evitar la Ceguera IAP Hospital Dr Luis Sanchez Bulnes

Perla Ayumi Kawakami-Campos

Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran

Mohamed Tharwat Hegazy

Al Jahra Hospital

Albero Balistreri

University of Siena: Universita degli Studi di Siena

Alejanda de-la-Torre

Universidad del Rosario: Universidad Del Rosario

Luca Cantarini

cantariniluca@hotmail.com

Universita degli Studi di Siena https://orcid.org/0000-0002-7352-1275

Claudia Fabiani

University of Siena Faculty of Medicine and Surgery: Universita degli Studi di Siena

Antonio Vitale

University of Siena Faculty of Medicine and Surgery: Universita degli Studi di Siena

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Jurgen Sota[1], Andrea Hinojosa-Azaola[2], Eduardo Martín-Nares[2], Guillermo Arturo Guaracha-Basañez[2], Jiram Torres-Ruiz[2], Gaafar Ragab[3], Ahmed Hatem Laymouna[3], Mahmoud Ghanema[3], Amina Maher[3], Jessica Sbalchiero[1], Valeria Caggiano[1], Henrique Ayres Mayrink Giardini[4], Juanita Téllez-Zambrano[5], Juana Lozano-García[5], Maria Camila Mosquera-Huertas[5], Silvana Guerriero[6], Rosanna Dammacco[6], Maria Sole Chimenti[7], Benedetta Monosi[7], Elisabetta Greco[7], Giuseppe Lopalco[8], Pravin Hissaria[9,10], Carla Gaggiano[1], Marco Cattalini[11], Piero Ruscitti[12], Samar Tharwatt[13,14], Guillermo Ruiz-Irastorza[15,16], Maissa Thabet[17], Mario Fruschelli[18], Giacomo Emmi[19,20], Paola Parronchi[21], Maria Pia Paroli[22], José Hernández-Rodríguez[23], Maite Sainz-de-la-Maza[24], Serena Bugatti[25], Luciana Breda[26], Maria Francesca Gicchino[27], Ezgi Deniz Batu[28], Seza Ozen[28], Inés Hernanz Rodriguez[29], Luz Elena Concha Del Rio[30,31], Perla Ayumi Kawakami-Campos[32], Mohamed Tharwat Hegazy[3,33], Albero Balistreri[34], Alejanda de-la-Torre[5], Luca Cantarini[1*], Claudia Fabiani[18*#], Antonio Vitale[1#]

[1]Rheumatology Unit, Department of Medical Sciences, Surgery, and Neurosciences, University of Siena and Azienda Ospedaliero-Universitaria Senese [European Reference Network (ERN) for Rare Immunodeficiency, Autoinflammatory, and Autoimmune Diseases (RITA) Center], Siena, Italy.

[2]Department of Immunology and Rheumatology, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico.

[3]Rheumatology and Clinical Immunology Unit, Internal Medicine Department, Faculty of Medicine, Cairo University, Giza, Egypt.

[4]Rheumatology Division, Faculdade de Medicina, Hospital das Clinicas (HCFMUSP), Universidade de Sao Paulo, Sao Paulo, Brazil.

[5]Neuroscience Research Group (NEUROS), Neurovitae Center for Neuroscience, Institute of Translational Medicine (IMT), School of Medicine and Health Sciences, Universidad del Rosario, Bogotá, Colombia.

[6]DiBrain department, University of Bari, Bari, Italy.

[7]Rheumatology, Allergology and Clinical Immunology, Department of Systems Medicine, University of Rome Tor Vergata, Rome, Italy.

[8]Department of Precision and Regenerative Medicine and Ionian Area (DiMePRe-J), Policlinic Hospital, University of Bari, Bari, Italy

[9]Department of Clinical Immunology and Allergy, Royal Adelaide Hospital, Adelaide, Australia.

[10]Department of Immunopathology, SA Pathology, Adelaide, Australia.

[11]Pediatric Clinic, University of Brescia and Spedali Civili di Brescia [European Reference Network (ERN) for Rare Immunodeficiency, Autoinflammatory, and Autoimmune Diseases (RITA) Center], Brescia, Italy.

[12]Rheumatology Unit, Department of Biotechnological and Applied Clinical Sciences, University of L'Aquila, L'Aquila, Italy.

[13]Rheumatology and Immunology Unit, Internal Medicine Department, Mansoura University, Mansoura, Egypt.

[14]Department of Internal Medicine, Faculty of Medicine, Horus University, New Damietta, Egypt.

[15]Faculty of Medicine and Nursery, University of the Basque Country, UPV/EHU, Leioa, Biscay, Spain.

[16]Autoimmune Diseases Unit, Biocruces Bizkaia Health Research Institute, Barakalko, Biscay, Spain.

[17]Internal Medicine Department, Farhat Hached University Hospital, Faculty of Medicine of Sousse, University of Sousse, Sousse, Tunisia.

[18]Unit of Ophthalmology, Department of Medicine, Surgery, and Neurosciences, University of Siena and Azienda Ospedaliero-Universitaria Senese [European Reference Network (ERN) for Rare Immunodeficiency, Autoinflammatory, and Autoimmune Diseases (RITA) Center], Siena, Italy.

[19]Internal Medicine, Immunology and Rheumatology Unit, Department of Medical, Surgical and Health Sciences, Cattinara University Hospital, Trieste, Italy.

[20]Centre for Inflammatory Diseases, Department of Medicine, Monash Medical Centre, Monash University, Clayton, VIC, Australia.

[21]Department of Experimental and Clinical Medicine, University of Florence, Florence, Italy.

[22]Uveitis Unit, Department of Sense Organs, Eye Clinic, Sapienza University of Rome, Rome, Italy.

[23]Autoinflammatory Diseases Clinical Unit, Department of Autoimmune Diseases, Hospital Clinic of Barcelona, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), University of Barcelona, Center of the European Reference Network (ERN) for Rare Immunodeficiency, Autoinflammatory and Autoimmune Diseases (RITA), Barcelona, Spain.

[24]Department of Ophthalmology, Hospital Clinic de Barcelona, IDIBAPS, University of Barcelona, Barcelona, Spain

[25]Division of Rheumatology, Department of Internal Medicine and Therapeutics (S.B.), Fondazione IRCCS Policlinico San Matteo, Università di Pavia, [European Reference Network (ERN) for Rare Immunodeficiency, Autoinflammatory and Autoimmune Diseases (RITA) Center], Pavia, Italy.

[26]Department of Paediatrics, University of Chieti-Pescara, Chieti, Italy.

[27]Department of Woman, Child and of General and Specialized Surgery, University of Campania "Luigi Vanvitelli", Naples, Italy.

[28]Pediatric Rheumatology Unit, Department of Pediatrics, Hacettepe University School of Medicine, Ankara, Turkey.

[29]Department of Ophthalmology, Hospital Universitario Fundación Jiménez Díaz, Madrid, Spain.

[30]Red de Investigación en Inmunología Ocular de Latinoamerica (RIOLAT), Santiago, Chile.

[31]Inflammatory Eye Disease Clinic, Hospital Dr. Luis Sanchez Bulnes, Asociacion para Evitar la Ceguera en Mexico (APEC), Mexico City, CDMX, Mexico.

[32]Department of Ophthalmology, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico.

[33]Internal Medicine Department, Rheumatology Unit, Jahra Hospital, Al Jahra, Kuwait.

[34]Bioengineering and Biomedical Data Science Lab, Department of Medical Biotechnologies, University of Siena and Azienda Ospedaliero-Universitaria Senese [European Reference Network (ERN) for Rare Immunodeficiency, Autoinflammatory and Autoimmune Diseases (RITA) Center], Siena, Italy.

#These authors equally contributed

***Corresponding authors:**

Luca Cantarini, MD, PhD; Research Center of Systemic Autoinflammatory Diseases, Behçet's Disease and Rheumatology-Ophthalmology Collaborative Uveitis Center, Department of Medical Sciences, Surgery and Neurosciences, University of Siena. Rheumatology Unit, Policlinico "Le Scotte", viale Bracci 1, 53100 Siena, Italy; **e-mail**: cantariniluca@hotmail.com

ORCID: 0000-0002-7352-1275

Claudia Fabiani, MD, PhD; Rheumatology-Ophthalmology Collaborative Uveitis Center, Ophthalmology and Neurosurgery Department, University of Siena, Siena, Italy; **e-mail**: claudia.fabiani@aidanetwork.com

ORCID: 0000-0003-4515-7741

Abstract

Objectives In this study we characterize scleritis features in GPA and assess differences with non-GPA-related scleritis.

Methods Data for this international registry-based study were retrieved from the AutoInflammatory Disease Alliance Network Scleritis Registry. Potential differences according to several demographic and clinical variables between GPA- and non-GPA-related scleritis were assessed via univariate analysis. Regression analysis was used to detect predictive factors for ocular complications and relapses.

Results A total of 170 patients (237 eyes) with non-infectious scleritis were enrolled. GPA was diagnosed in 31 of them. Anterior scleritis, the necrotizing pattern and ocular complications were significantly more frequent in GPA-related scleritis (p=0.029, p<0.0001 and p<0.0001, respectively). Regarding corneal involvement, we found a statistically significant higher prevalence in GPA-related scleritis (p=0.0005). The number of overall relapses throughout the disease course was significantly less prevalent among GPA patients with scleritis compared to non-GPA-related scleritis (7.7 *vs* 22.2 per 100 patient-years) (p=0.002). A diagnosis of GPA was independently associated with the development of ocular complications in the regression model (OR 5.547, p<0.0001).

Conclusion GPA-related scleritis is more likely to display necrotizing changes, corneal involvement and a higher likelihood of developing ocular complications, independently of the number of ocular relapses and concomitant uveitis. These characteristics carry an important prognostic value and suggest that patients with scleritis in the context of GPA should undergo a tight regular follow-up schedule to improve the overall long-term ocular prognosis.

Keywords

Scleritis, Wegener's granulomatosis, ocular prognosis, complications, peripheral ulcerative keratitis

Introduction

Granulomatosis with polyangiitis (GPA), formerly known as Wegener's granulomatosis, is a small vessel vasculitis characterized by necrotizing vasculitis and granulomatous inflammation that carries a high level of mortality and an unfavorable overall prognosis. GPA may affect virtually any organ and system [1]. Ophthalmic involvement occurs in roughly 40 to 50% of patients across several large-scale studies [2,3]. Various structures of the eye may be involved, including the orbit, episclera, conjunctiva, sclera, cornea, retina, optic nerve, uvea, eyelid and the nasolacrimal system. Scleritis, in particular, may be present in a considerable proportion of GPA patients and could precede extra-ocular manifestations in about 39% of them [3-5]. On the other hand, GPA is the most common form of vasculitis associated with scleritis and can lead to sight-threatening complications due to necrosis and tissue melting [5]. Whether scleritis in GPA patients follows a more aggressive and destructive course as opposed to other forms of scleritis remains unclear, as available evidence is confined to case series and small retrospective cohorts.

The aim of this study was to characterize scleritis in patients with GPA, assess its prognostic significance, and compare its clinical features and outcomes with those of idiopathic scleritis and scleritis associated with other immune-mediated systemic diseases.

Patients and Methods

Study design and participants

Data collected up to April 25th, 2026, from medical records of patients diagnosed with non-infectious scleritis were retrieved from the international AIDA Network Registry on Scleritis (an electronic-based, physician-driven registry developed to collect both retrospective and prospective on scleritis patients) [6].

The following data were extracted: gender, age at scleritis onset, age at scleritis diagnosis, associated systemic disease, autoantibodies detected, forms of GPA (systemic or localized), organs involved by GPA, scleritis anatomical classification according to Watson and Hayreh [7], pattern of scleritis

involvement (diffuse, nodular, necrotizing), uveitis, peripheral ulcerative keratitis (PUK), number of relapses, treatments given throughout disease course, and ocular complications developed from disease onset to the last follow-up visit. Scleritis severity was established according to the McCluskey score [8]. Diagnosis of GPA was established following the 2012 Chapel Hill Consensus Conference nomenclature and/or the 2022 American College of Rheumatology/European Alliance of Associations for Rheumatology classification criteria [9, 10]. Medical charts with more than 20% missing data across the variables of interest were excluded from the analysis. Patients with a previous history of ocular trauma or surgery, and those with an infectious etiology were also excluded. All patients were regularly followed up at scheduled appointments and in case of necessity (disease flare and/or safety issues).

Aims and Endpoints

The primary aim of the study was to characterize scleritis features of GPA patients and compare them with non-GPA patients affected by scleritis (either idiopathic or associated with other systemic immune-mediated diseases).

Secondary aims were established as: i) the influence of systemic diagnosis in severity score and ocular relapses, ii) predictive factors of the development of ocular complications and iii) the functional consequences of GPA in visual acuity.

The primary endpoint was analyzed by detailing scleritis characteristics of GPA patients in terms of anatomical classification, pattern (diffuse, nodular, necrotizing), ocular complications (excluding steroid-related complications), concomitant uveitis and corneal involvement (defined as the presence active inflammation such as PUK or its sequeale including peripheral corneal thinning/perforation and scars). These characteristics were later analyzed for potential statistical differences between patients diagnosed with and without GPA.

Secondary endpoints were investigated using: i) the detection of any statistically significant difference between patients with and without GPA in the mean scleritis severity score and mean number of relapses; ii) binary logistic regression with stepwise backward method to identify

predictive factors of the development of ocular complications; and iii) any difference in best corrected visual acuity (BCVA) at last follow-up between patients with and without GPA.

Ethical Statement

The present study adheres to the tenets of Declaration of Helsinki and received approval by the Local Ethics Committee of the University of Siena (Ref. No. 14951). All patients or their legal guardians have provided written informed consent.

Statistical Analysis

Analysis was conducted using IBM SPSS Statistics for Windows (IBM Corp., Armonk, NY, USA). Pairwise deletion was used to handle missing data. Consequently, the number of observations varied across correlations. Regarding descriptive statistics, mean and standard deviation (SD) or median and interquartile range (IQR) were used to describe quantitative variables as appropriate, whereas qualitative variables were reported as absolute frequencies alongside their percentages. The Shapiro-Wilk test was employed to assess the normality distribution of continuous variables. Cross-tables were analyzed by Pearson's Chi-square test or Fisher's exact test as required. For contingency tables with dimensions > 2 x 2, adjusted residuals were used for *post-hoc* analysis. Differences in median between groups were tested with the Mann–Whitney U test. The potential predictors of ocular complications were identified by binary logistic regression computed with the backward stepwise method. The threshold for statistical significance was set at a p-value of 0.05, and all tests were 2-sided.

Results

All 170 patients (237 eyes, female-to-male ratio 1.95) enrolled in the AIDA Scleritis Registry were included in the study. Mean ± SD age at scleritis onset was 43.1 ± 17.1 years and mean ± SD disease duration was 9.25 ± 7.61. Scleritis was bilateral and unilateral in 67 and 103 cases, respectively. GPA was diagnosed in 31 patients and all of them tested positive for proteinase-3 anti-neutrophil cytoplasmic antibodies. More detailed information of our cohort is provided in Table 1.

Scleritis in GPA patients presented as predominantly anterior (n=29, 93.5%) with a diffuse pattern (n=22, 70.9%) followed by necrotizing (n=6, 19.4%) and nodular pattern (n=3, 9.7%). Anterior scleritis and necrotizing pattern were significantly more represented in GPA-related scleritis (p=0.029 and p<0.0001 with an adjusted residual Z score of -3,0, respectively). Ocular complications were significantly more frequent in GPA-related scleritis ($p < 0.0001$). More in detail, irreversible ocular complications were detected in 21 GPA patients (67.7%) and in 42 non-GPA patients (30.2%). Figure 1 illustrates complications encountered in GPA-related scleritis. Regarding concomitant uveitis, no differences were detected between GPA-related scleritis and non-GPA-related scleritis (p=0.443). As for corneal involvement, we found a statistically significant prevalence in GPA-related scleritis (p=0.0005). Nine out of 31 GPA patients with scleritis (29%) exhibited corneal scars, corneal thinning or PUK whereas 10 out of 139 non-GPA scleritis patients (7.2%) experienced the same manifestations. PUK was then considered separately, and the statistical significance was maintained between groups (19.6% of GPA-related scleritis cases vs 7.2% of non-GPA patients with scleritis, p=0.036).

The number of overall relapses throughout disease course was significantly less prevalent among GPA patients with scleritis (7.7 events per 100 patient-year) compared to non-GPA-related scleritis (22.2 per 100 patient-year) (p=0.002). Given the different overall disease duration at last follow-up, a negative binomial regression was used to account for disease duration as well as treatment with disease modifying drugs and the difference between groups was maintained in the model. Patients with GPA-related scleritis were significantly less likely to experience an ocular relapse throughout disease course (OR 0.209, C.I. 0.084-0.516, p=0.001).

The mean severity score did not differ significantly between groups (p=0.147). Two variables were independently associated with the development of irreversible ocular complications in the regression model: a diagnosis of GPA (OR 5.547, C.I. 2.191-14.042, p<0.0001) and the presence of concomitant uveitis (OR 3.782, C.I. 1.461-9.789, p=0.006).

Concerning visual acuity, the impact of GPA was not significant in terms of BCVA measured at last follow-up assessment (mean ± SD BCVA was 8.50 ± 2.67 for GPA-related scleritis and 8.35 ± 2.50 for non-GPA-related scleritis, p=0.693).

Discussion

In our cohort, GPA-related scleritis presented predominantly as anterior scleritis with a diffuse pattern in 70% of cases and a necrotizing pattern in roughly 20% of patients, in keeping with the findings of Cocho et al [11-13]. The significant association with the necrotizing pattern aligns with previous studies reporting a higher prevalence of necrotizing scleritis among patients with systemic vasculitides, although percentages ranging from 22 to 79% [11-14]. Such differences in reported frequences are likely methodological rather than indicative of a true biological discrepancy. Possible explanations include the broad definition of the necrotizing pattern and referral bias, as tertiary referral ophthalmologic centers are more likely to recruit patients with an already severe ocular disease.

Overall, in our cohort, necrotizing scleritis occurred at a significantly higher rate in GPA-related scleritis compared to non-GPA-related scleritis. The detection of scleral necrotizing changes is highly suggestive of underlying systemic vasculitis. Therefore, even when a systemic diagnosis is still not yet established, such cases warrant prompt rheumatologic referral with a subsequent thorough diagnostic work-up, followed by regular rheumatologic follow-up, as eye disease may precede systemic findings and occur as the sole initial manifestation [15-17].

GPA can affect different eye structures outside the sclera, making it very challenging for ophthalmologists to thoroughly assess ocular involvement. In our cohort, 12.9% of GPA patients with scleritis presented with concomitant uveitis, and the difference with non-GPA-related scleritis was not significant (17.3% of patients). Contrarily, corneal involvement was significantly more prevalent in GPA-related scleritis with roughly 1 out of 3 patients displaying either PUK or its sequalae, such as peripheral corneal thinning and/or scars. Peripheral keratitis is frequently associated with scleritis

and develops in a considerable proportion of GPA-related scleritis, ranging from 11.1% to 50% across various studies [2, 3, 11, 12, 14, 15, 18, 19]. Therefore, similarly to what has been hypothesized with the necrotizing pattern, corneal involvement should also raise the suspicion of an underlying systemic vasculitis.

Regarding ocular complications, irreversible damage was encountered in nearly 70% of GPA patients with scleritis, more than twice as many complications detected in the non-GPA group. This finding was then confirmed in the multivariate regression analysis, demonstrating that the GPA group has 5.5-fold higher odds of developing ocular complications, in line with previous findings [20]. This could indicate that GPA is more severe and destructive to the sclera compared to idiopathic scleritis and other systemic immune-mediated diseases.

Taken together, the more frequent necrotizing pattern, the associated corneal involvement and the higher rate of ocular complications indicate an overall worse ocular prognosis. This in turn poses challenges from a therapeutic point of view since it may lead clinicians to reconsider systemic treatment despite an optimal control of the extra-ocular features.

Interestingly, the number of ocular relapses among patients with GPA-related scleritis was significantly lower, both in the univariate and multivariate analyses after correcting for disease duration and treatment courses. This could indicate that the severity of an individual ocular relapse carries a higher impact on ocular prognosis than the frequency of episodes. One episode of GPA-related scleritis could produce substantial tissue destruction and be more detrimental than repeated mild ocular inflammatory episodes. Nevertheless, in our cohort the greater phenotypic severity with a more complicated ocular disease was not reflected in a higher overall severity score. This could simply be due to the limitations of a composite severity score that may underestimate specific destructive features such as necrosis and corneal involvement and ignore other features like long-term complications.

Several limitations of this study should be acknowledged. First, the unavailability of standardized measures including the Birmingham Vasculitis Activity Score and Vasculitis Damage Index,

precluded a comprehensive assessment of the relationship between scleritis and systemic activity or damage. Second, the predominance of patients recruited from tertiary referral centers may have introduced referral bias toward more severe cases, potentially limiting the generalizability of our findings to patients with milder scleritis. Finally, the inclusion of a control group comprising other types of systemic vasculitis would have allowed a more specific assessment of whether the observed findings are unique to GPA or shared across systemic vasculitides.

In conclusion, patients affected by GPA-related scleritis are more likely to exhibit necrotizing changes, corneal involvement and a higher likelihood of developing ocular complications, independently of the number of ocular relapses. These characteristics carry important prognostic value and suggest that scleritis in the context of GPA should not be considered benign. This subgroup of patients should receive prompt aggressive treatment and undergo a tight regular follow-up schedule to minimize the risk of developing irreversible sight- and life-threatening manifestations.

Declarations

Conflict of Interest The authors declare that they have no conflict of interest.

Ethical Approval and concent to participate This study was approved by the Local Ethics Committee of the University of Siena (Ref. No. 14951). All patients or their legal guardians have provided written informed consent.

Consent to publications Not applicable

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CRediT authorship contribution statement JSo: Conceptualization, Data curation, Formal analysis, Investigation, Writing – original draft, Methodology, Project administration, Validation. AHA, EMN, GAGB, JTR, GR, AHL, MG, AM, HAMG, JTZ, JLG, MCMH, SG, RD, MSC, BM, EG, GL, PH, MC, PR, ST, GRI, MT, GE, PP, MPP, JHR, MSDLM, SB, LB, MFC, EDB, SO, IHR, LECDR, PAKC, MTH, ADLT: Writing – review & editing, Validation, Resources. JSb, VC, CG: Writing – review & editing, Project administration, Resources. AB: Data curation, Investigation,

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Table 1. Demographic and clinical characteristics of patients diagnosed with Granulomatosis with Polyangiitis-related scleritis.

Feature	GPA group	Non-GPA group
N° of patients	31	139
Gender	Females (n=18) Males (n=13)	Females (n=93) Males (n=45) Transexual (n=1)
Mean disease duration ± SD (years)	11.15 ± 7.22	8.79 ± 7.66
Clinical subgroup	Systemic (n=26) Localized (n=5)	NA
Organs involved	Nose (n=28) Ear (n=11) Throat (n=7) Lung (n=17) Kidney (n=20)	NA
Clinical features	Urinary sediment ≥ 5 red blood cells or red blood cell casts (n=20) Abnormal findings on chest radiograph (n=18) Nasal discharge (n=27) Oral ulcers (n=4)	NA
Ocular features accompanying scleritis	Ocular pain (n° of patients n=23) RE n=16 LE n=15	

	Orbital inflammation RE n=4 LE n=4 Conjunctival involvement RE n=4 LE n=1 Concomitant uveitis RE n=3 LE n=1	Concomitant uveitis RE n=16 LE n=14
Treatment courses with cDMARDs and bDMARDs	Rituximab n=19 Cyclophophamide n=8 Methotrexate n=2 Mycophenolate Mofetil n=1 Azathioprine n=1	Adalimumab n=16 Rituximab n=8 Infliximab n=5 Tocilizumab, Abatacept n=3, each Certolizumab Pegol n=2 Secukinumab n=2 Golimumab, Anakinra, Ustekinumab n=1, each Methotrexate n=23 Azathioprine, Mycophenolate Mofetil, Tacrolimus, Hydroxychloroquine, n=2, each Sulfasalazine (n=1) Cyclosporine n=1)

List of abbreviations: *bDMARDs* biologic disease-modifying anti-rheumatic drugs, *cDMARDs* conventional disease-modifying anti-rheumatic drugs, *GPA* granulomatosis with polyangiitis, *LE* left eye, *N°* number, *NA* not applicable, *RE* right eye, *SD* standard deviation

Figure legends

Figure 1. Ocular complications recorded throughout disease course in Granulomatosis with Polyangiitis patients.

Figures

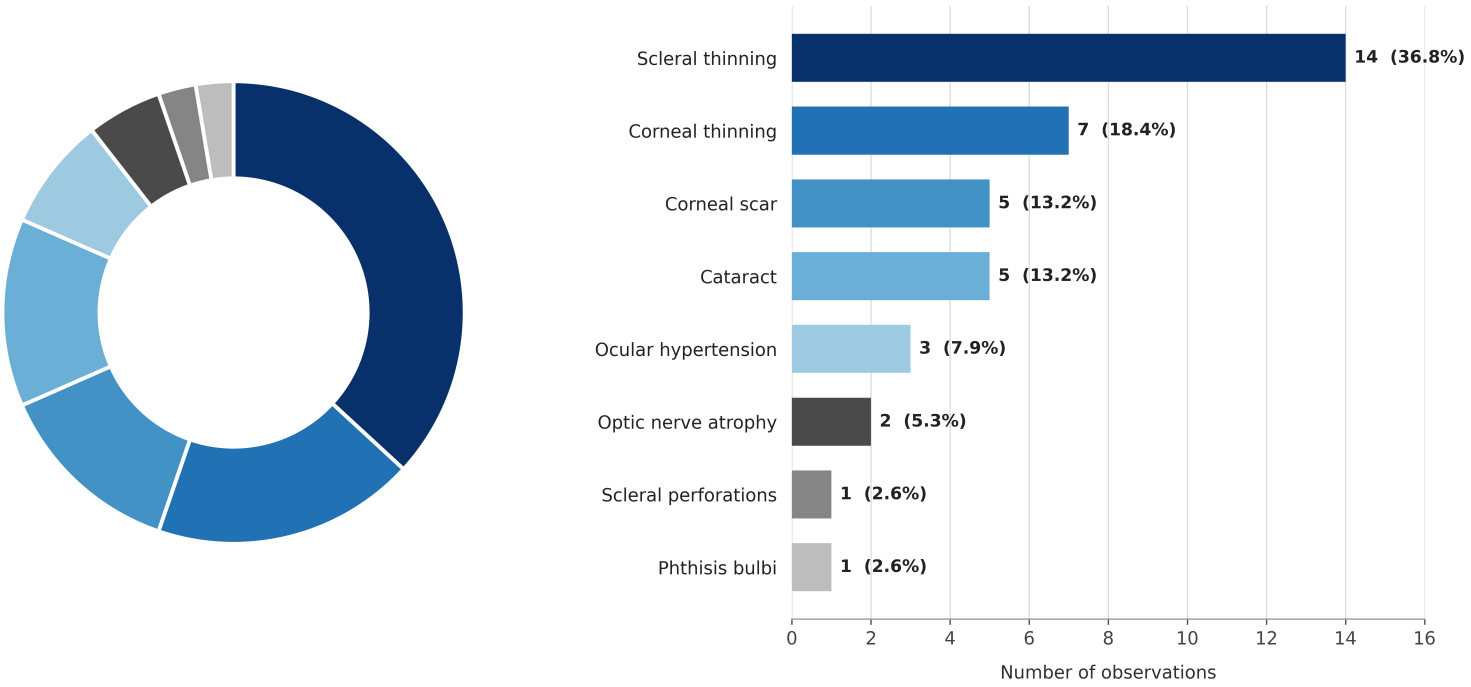


Figure 1

Ocular complications recorded throughout disease course in Granulomatosis with Polyangiitis patients.