Orbital masses in granulomatosis with polyangiitis are associated with a refractory course and a high burden of local damage

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Abstract

Objectives. To identify and characterize patients with orbital masses in a monocentric cohort of 1142 GPA patients followed up from 1990 until the end of 2010 with regard to disease stage, local orbital inflammation, course of disease and outcome and to assess the efficacy of immunosuppressive treatment.

Methods. All GPA patients fulfilling ACR criteria or Chapel Hill Consensus Conference definitions or who had localized GPA and who developed orbital masses were evaluated regarding the course and outcome of the orbital masses (assessed by MRI, ophthalmologist and ENT specialist), all other clinical manifestations, disease stages, ANCA status, immunosuppression and its side effects and surgical procedures.

Results. Of 1142 GPA patients 58 developed orbital masses during a median follow-up of 101.5 months (range 23–255 months). Forty patients fulfilled the inclusion criteria and had complete clinical assessments [44% females, median age 43 (20–74) years, 85% ANCA positive]. Seventy-five per cent (29/40) had systemic disease when orbital masses occurred; both orbits were affected in 30%. Seventy-two per cent had evidence of infiltration from paranasal sinuses. Under highly potent immunosuppression (mostly CYC and glucocorticoids), 41% were refractory, 24% had unchanged activity, 24% showed a response and 8.1% had complete remission. Forty-four per cent had relapses of orbital masses. Seventy-two per cent developed visual impairment, 19% suffered blindness. Blindness was associated with a longer time to remission and a relapsing and refractory course.

Conclusion. Orbital masses are a rare manifestation of GPA and are characterized by a refractory course and by a high rate of local damage. Patients with a refractory or relapsing course are at higher risk of developing blindness.

Key words: granulomatosis with polyangiitis, orbital masses, granulomatous lesions, cyclophosphamide.

Introduction

Orbital masses have been described as developing in 7–45% of granulomatosis with polyangiitis (GPA) patients [1–3] and account for 22% of all eye manifestations in GPA [3]. They most frequently evolve in one orbit (86%) and seem to either perforate from neighbouring structures such as paranasal sinuses or the nasal cavity or develop within the orbit itself [4, 5]. Orbital masses represent a serious organ manifestation that is associated with a high burden of disease and damage: patients may suffer from uncontrollable pain and sustain significant visual damage or blindness due to optic nerve compression by mass formation [1]. Furthermore, treatment-resistant orbital masses may cause severe local destruction and perforation of surrounding tissues (including cartilage and bone) leading to meningeal infiltration and cutaneous fistulas [6–8]. Orbital socket contracture may occur as a result of the formation of fibrous tissue [9].
Orbital masses in GPA have been shown to be slow responding and refractory towards CYC in a cohort of 85 GPA patients (6 with orbital masses) in the early 1980s [10]. This finding has been confirmed by small studies on 15–27 patients [3, 11]. In contrast to these reports, Fechner et al. [12] reported a favourable outcome in their 15 patients treated with a combination of CYC/glucocorticoids (GCs) and surgical procedures. Nevertheless, invasive procedures bearing the potential of local complications and damage may not be the treatment of choice for an autoimmune process and to reliably prevent relapses. Except for the study by Fauci et al. [10], the other studies were done by ophthalmology units without a standardized interdisciplinary follow-up.

Recently, orbital masses also have been shown to be resistant towards new therapeutic strategies such as rituximab (RTX; after failing to respond to CYC) in a significant proportion of patients treated in a standardized diagnostic and therapeutic approach [13].

The aim of this study was to systematically assess the outcome of GPA patients with orbital masses in a setting of a strict interdisciplinary and standardized diagnostic and therapeutic approach (including regular MRI, ophthalmology and ENT assessment). Patients were characterized retrospectively with regard to disease stage, course of the local inflammation (followed up by MRI), accompanying disease manifestations, effect of immunosuppressive therapy and damage.

**Methods**

**Patients and inclusion criteria**

All consecutive patients attending the centre in the period from June 1988 until January 2011 who fulfilled the classification criteria of the ACR [14] or the definition of the Chapel Hill Consensus Conference (CHCC) [15] for GPA or had localized GPA as defined earlier [16] and who developed orbital masses were included in the study and followed up retrospectively. Assessment of orbital masses by MRI plus ENT and ophthalmology assessment was mandatory for diagnosis and follow-up. The study was performed in accordance with the Declaration of Helsinki. Ethical approval was obtained from the University of Lübeck.

**Assessment of clinical manifestations, disease activity and damage**

All patients underwent standardized interdisciplinary clinical, laboratory and technical examinations as earlier described [16–18]. Patients were followed up at 3- to 6-monthly intervals, including a routine ophthalmology and ENT assessment. MRI of the head was done at first presentation regardless of symptoms and at any time a patient presented with new symptoms related to orbital or ENT activity. Furthermore, patients underwent MRI scanning at 3- or 4-monthly intervals under remission induction therapy. During periods of remission, MRI was done once a year regardless of symptoms. Disease stages were specified in accordance with European League Against Rheumatism/European Vasculitis Society (EULAR/EUVAS) definitions [19]; disease activity was defined according to the EULAR definitions [19] and measured using the Birmingham Vasculitis Activity Score (BVAS) version 3 [20]. Chronic damage was assessed by the Vasculitis Damage Index (VDI) [21]. The BVAS was applied retrospectively before 1999 and the VDI before 1997. Visual impairment was defined as a reduction of visual acuity ≤0.5 and blindness as a reduction of ≤1/50.

**Definition of remission, response and refractory disease of orbital masses by MRI**

MRI of the head was performed as described earlier [22]. T1- (axial and coronal) and T2-weighted (axial) spin echo imaging was performed with additional contrast enhancement in T1-weighted imaging (axial and coronal). Masses in orbits and sinuses appear as hypointense lesions in T1- and T2-weighted images. After gadolinium injection, homogeneous signal enhancement may be seen [4, 22] but may not be reliable for assessment of acute inflammation. Treatment response and remission were defined as a decrease in size or complete disappearance of orbital masses. Refractory disease was consistent with further enlargement of masses under treatment. Relapse of orbital masses was defined as the occurrence of new masses or enlargement of pre-existing masses that had been stable or shrinking on previous MRIIs. Orbital masses that were unchanged in two subsequent MRI scans after the initial scan (each scan 3–4 months apart) were considered as stable disease (unchanged). We differentiated between intra- and extracranial space, which is split by the intraocular muscles forming a cone within the orbit.

**Treatment procedures**

Treatment was adapted according to the activity and severity of disease manifestations as described earlier [16–18]. To assess treatment effects, patients were required to have a follow-up period of at least 6 months after starting remission induction. Orbital masses were regarded as organ-threatening manifestations and treated by CYC (2 mg/kg body weight oral or 15–20 mg/body weight i.v. every 2–3 weeks for at least 6 times) and GCs (1 mg/kg body weight initially) as standard remission induction except in patients with contraindications. Patients were switched to a maintenance regimen after achievement of remission, response or unchanged/stable disease as described earlier [16–18]. Maintenance treatment (including GC) was continued for at least 18 months. Refractory disease was treated by continued CYC treatment (in the 1990s). Patients were then either switched from i.v. to oral CYC or, if patients had already been pre-treated with oral CYC, they received intense oral CYC (2.5 mg/kg/day). Since 2000, biologics (TNF-α antagonists or RTX, with or without additional conventional immunosuppressant) have been used. Patients treated with RTX for refractory orbital masses (first manifestation or relapse) were also included in our previous report [13]. Patients with persistent refractory orbital masses on treatment with CYC plus biologics were switched to AZA-bolus
therapy [23] as rescue. Furthermore, resection of orbital masses or alcohol or GC injections were rescue treatment strategies. Enucleation was done when patients were blind but suffered from persistent uncontrollable pain. 

**Pneumocystis jirovecii** prophylaxis with trimethoprim/sulphamethoxazole (T/S) has been administered in the combination GC plus CYC since the year 2000. Patients have been educated by a standardized training programme [24] since 1994.

ANCA testing

ANCA testing was performed by indirect immunofluorescence test (IFT) using ethanol- and formalin-fixed leucocytes as screening assay and direct ELISA for the detection of target antigen, as previously described [16–18] and according to consensus guidelines [25].

Histology

Biopsy specimens were reviewed at the German Reference Center for Vasculitis (Department of Pathology, University of Lübeck, Germany) by two independent pathologists (as previously described) [16–18] and were considered diagnostic if at least two of the three features of ill-defined granuloma, small- to medium-size vessel vasculitis or geographic necrosis were present and the reviewers’ findings matched. Biopsy specimens were not routinely taken from orbital masses unless required to confirm the diagnosis of GPA.

Statistical analysis

Statistical analysis was performed using SPSS, version 18 (SPSS, Chicago, IL, USA). Chi-squared test, Mann–Whitney test and Wilcoxon test were used as appropriate. Analysis of relapses was done using Kaplan–Meier survival analysis. $P < 0.05$ was considered statistically significant.

**Results**

Patient characteristics

Of 1142 GPA patients seen from 1988 until January 2011, a diagnosis of GPA with orbital mass formation was suspected in 83 patients due to one or more of the following symptoms: proptosis, diplopia or orbital pain/cephalgia. Five patients were excluded because classification criteria were not fulfilled. Eighteen patients fulfilled GPA criteria and had orbital masses but an incomplete assessment during the first presentation and during follow-up. Forty patients were included in the analysis (Table 1). All 40 patients had one or more histology specimens of various organs compatible with GPA. Four patients had histology specimens from orbital masses, three of which were compatible with GPA. Two patients died within the observation period; death was not related to active disease in GPA.

Initial symptoms and time point of occurrence

At the initial presentation with orbital masses, 80% ($n = 32$) had orbital pain and/or cephalgia, 85% ($n = 34$) suffered from diplopia, 60% ($n = 24$) had proptosis and 47.5% ($n = 23$) had reduced eye motility; in 27.5% ($n = 11$) a reduction of visual acuity was detected ($\leq 0.5$). Thirty per cent of patients ($n = 12$) presented with orbital masses as first presentation; in the rest of the patients orbital masses developed later and occurred up to 276 months from diagnosis. Two patients had no eye-related symptoms and the orbital mass was detected by the MRI assessment routinely done every 12 months. In all other patients, the MRI assessment was done because of eye-related symptoms.

Location and origin of orbital masses

Patients either had evidence of per continuitatem infiltration or the origin of the orbital masses could not be definitely determined (no CTs available). In most patients, orbital masses seemed to originate from ethmoidal cells ($n = 23, 44.2$%), or from both ethmoidal cells and maxillary sinus ($n = 5, 9.6\%$) (Table 1). In these cases, patients had evidence of masses in the respective sinus with perforation of these masses into the orbit. All patients had extraconal involvement, some with evidence of extraocular eye muscle infiltration or even intraconal involvement (Table 1). Swelling of the eyelid was detectable in three patients (7.5%); four patients (10%) developed an orbito-nasal fistula. A significant proportion of patients had an encircled optic nerve on MRI.

We also analysed the MRIs done prior to the MRI in which the orbital mass was detected. In 28 patients, prior MRIs were available, while 12 patients presented with orbital masses as the first manifestation of GPA and no prior scans were available. Of these 28 patients (with involvement of 37 eyes), 15 (with involvement of 17 eyes, 45%) had evidence of masses in the sinuses in the prior scan. Nine patients (with later involvement of nine eyes, 24%) had no masses in the prior scan. In these nine patients, the prior scan occurred 5–12 months before the scan in which orbital masses were detected. Seven patients (with involvement of 11 eyes) developed orbital masses with no clear evidence of perforation (indeterminate group), three of whom had masses in ethmoidal cells/maxillary sinuses in the prior scan (supplementary Table S1, available as supplementary data at Rheumatology Online). In relapsing patients, the relapse most frequently occurred on the same side and at the same location (in 13 of 17 relapses, 76.5%; supplementary Table S2, available as supplementary data at Rheumatology Online).

Disease stages and organ manifestations at diagnosis, at manifestation of orbital masses and over the whole course

At the first manifestation of orbital masses, the majority of patients were in a systemic disease stage [$n = 18 (45\%)$ early systemic, $n = 11 (27.5\%)$ generalized] and about one-fourth of the patients had localized disease [$n = 11 (27.5\%)$] (supplementary Fig. S1, available as supplementary data at Rheumatology Online).

Thirty-seven patients were included in the analysis of organ manifestations, as three had an incomplete chart review (Fig. 1). At diagnosis of orbital masses, ENT activity, including sinusitis with mass formation in the sinuses...
eye involvement (other than orbital masses such as conjunctivitis and episcleritis) [35.1% (n = 13)] and cerebral involvement [24.3% (n = 9, five with pachymeningitis, four with cranial nerve paresis)] were most frequent. Active renal, lung, joint and peripheral neuropathy (excluding cranial nerves) were significantly less frequent at the manifestation of orbital masses than at diagnosis of GPA (renal 18.9% vs 43.2%, P = 0.003; lung 10.8% vs 40.5%, P = 0.002; joint 10.8% vs 35.1%, P = 0.005; polyneuropathy 2.7% vs 13.5%, P = 0.046).

Medication at diagnosis of orbital masses
Eighty per cent (n = 32) received immunosuppressive therapy at diagnosis of orbital masses; 15% (n = 6) were taking CYC (and GC) at diagnosis of orbital masses (supplementary Table S3, available as supplementary data at Rheumatology Online).

First-line remission induction, overall treatment effect (on all disease manifestations) and treatment effect on orbital masses
Thirty-seven patients had a follow-up of at least 6 months after remission induction therapy and were included in the analysis of treatment efficacy. Twenty-eight patients (75.7%) received GC plus CYC for remission induction, three patients (8.1%) received a combination of GC plus CYC and additional anti-TNF or additional RTX treatment (as orbital masses had developed under CYC treatment), one patient (2.7%) received RTX plus GC and five patients (13.5%) underwent other treatments mainly because of contraindications for CYC (three MTX, one AZA, one surgical decompression plus CYC + GC).

With respect to the overall treatment effect, 2 patients (5.4%) had a remission, 13 (35.1%) had a response and 22 (59.5%) were refractory. In most cases, refractoriness was due to treatment resistance of orbital masses (15 of 22

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patients, 68.2%); in 7 of 22 patients (31.8%) refractoriness was due to other disease manifestations.

Analysis of the treatment effect on orbital masses yielded the following results: 3 patients (8.1%) had a complete remission of orbital masses, 10 (27.0%) had a response (including the patient with surgical decompression), 9 (40.5%) had disease progression (refractory disease) (Fig. 2 and supplementary Figs S2 and S3, available as supplementary data at Rheumatology Online).

Treatment of refractory orbital masses (second-line therapy)

Patients with refractory orbital masses after first-line treatment received second-line treatment and underwent further analysis (n = 14). Four patients (28.6%) had a response, one (7.1%) was unchanged and nine (64.3%) had further disease progression (Fig. 2 and supplementary Table S4 and supplementary data on third- and fourth-line treatment effects, available at Rheumatology Online).

Relapses of orbital masses and treatment of relapses

A sufficient interdisciplinary follow-up after achieving remission/response was available for 34 patients. Fifteen of these 34 patients suffered from relapses or orbital masses during their follow-up (44.1%; median time to relapse 42 months, range 3–90 months) (supplementary Table S3, available as supplementary data at Rheumatology Online and supplementary Fig. S4). Most of them were under immunosuppressive treatment (n = 13, 86.78%; supplementary Fig. S5, as supplementary data available at Rheumatology Online). Most patients had unchanged disease (n = 7, 50%); six (42.8%) had disease progression and one (7.1%) a response (supplementary data on second- and third-line treatment of relapses, available at Rheumatology Online).

Surgical procedures

Five patients underwent six surgical procedures (two local resections for decompression, four enucleations; supplementary data on the effect of surgical procedures are available at Rheumatology Online).

Damage

VDI scores were available for 32 patients from diagnosis until the end of follow-up (Fig. 3). Orbital masses were associated not only with a high damage rate of eye structures but also of the ENT tract. Blindness developed in six patients (19%); all of these had evidence of an encircled optic nerve on MRI. However, not all patients with an encircled optic nerve (n = 25) developed blindness later on. Outside the eye and ENT tract, seven patients had polyneuropathy (21.9%), two CYC-induced cystitis (6.3%), one toxic bone marrow failure (3.1%), one granuloma of the hypophysis (3.1%), one chronic renal damage (3.1%) and one epilepsy (3.1%) at the end of follow-up (data not shown). Damage rates increased from first onset of the orbital mass until the end of follow-up (median VDI at onset of orbital mass: 1, range 0–9; median VDI at the end of follow-up: 3, range 0–9). One patient developed orbital socket contracture. Time to remission was significantly longer in patients who were blind after remission.
The induction of the first-time manifestation of the orbital mass and at the end of follow-up compared with patients who did not develop blindness (median time to remission 9 vs 24 months, \( P = 0.008 \) and 9 vs 18 months, \( P = 0.036 \), respectively) (supplementary Fig. S6, available as supplementary data at Rheumatology Online). There was a strong correlation between time to remission and blindness after remission induction of first-time manifestation of orbital mass (\( r = 0.545, P = 0.001 \) and \( r = 3.87, P = 0.029 \)). Patients who were blind after remission induction and at the end of follow-up had a refractory course significantly more often (3 of 3 vs 9 of 29, \( P = 0.019 \), and 5 of 6 vs 7 of 26, \( P = 0.01 \)) and relapses of orbital masses (5 of 6 vs 7 of 26, \( P = 0.01 \)). There was a significant correlation between VDI (after remission induction of first-time orbital mass/VDI at the end of follow-up) and time to remission (\( r = 0.465, P = 0.007 \) and \( r = 0.356, P = 0.044 \)).

Discussion

Orbital masses have been recognized as a resistant granulomatous manifestation in small cohorts [3, 10, 11, 16, 26], but have never been assessed in a large patient cohort before. We herein present the largest cohort of
GPA patients with orbital masses strictly followed by a standardized interdisciplinary approach. We found that the prevalence of orbital masses was lower than that reported before [1–3] and underpins the aggressive nature of this disease manifestation: 72% of patients had persistent visual impairment and 19% went blind in spite of intense immunosuppression. Furthermore, 41% of orbital masses were refractory (consistent with disease progression) to remission induction (mostly with CYC plus GCs), and relapses of orbital masses were frequent (44%) in spite of close follow-up and ongoing immunosuppression.

A possible explanation for the lower prevalence of orbital masses may be that this study was carried out in a rheumatology unit and not an ophthalmology or ENT unit to which patients may be admitted with symptoms related to orbital masses.

We reported earlier that RTX was partially efficient in the treatment of orbital masses refractory to CYC [13]. We cannot draw any conclusion with respect to the efficacy of RTX or anti-TNF as first-line treatment, as only a few patients received biologics as first-line therapy. RTX was partially effective for refractory orbital masses (as described before). Therefore, assessing the efficacy of biologics—in particular RTX—as first-line treatment seems an option for the future. Furthermore, approaches targeting the granulomatous lesion in a more specific way may be even more promising.

Orbital masses not only resulted in significant damage to the eye itself (e.g. with visual impairment in 72% and blindness in 19%) but were also associated with high damage rates for neighbouring structures. Orbital wall destruction and radiological damage of sinus walls were frequent and may be underestimated in our study due to the lack of CT data. Destruction occurred not only in the orbital wall adjacent to the masses but also in the nasal septum and cartilage of the nose, suggesting that the underlying local inflammation and not necessarily the mass formation itself may be responsible for the destructive process.

Patients who suffered blindness at the end of follow-up had a longer time to remission compared with patients who did not. The most common reason for blindness was optic atrophy. Patients who developed blindness had relapsing or refractory disease significantly more often. This is in line with Martinez del Pero et al. [27] who described an association of ENT relapses with an increase in ENT VDI.

Previous reports suggest that orbital masses arise from sinususes perforating into the orbit [2, 4, 28, 29]. One study reported that orbital masses may also develop within the orbit itself (5 of 16 patients, 31%) [4]. We confirm that orbital masses develop from perforation of masses. Orbital masses seemed to originate from ethmoidal cells, maxillary sinuses, nasal cavity or lacrimal gland. The majority of patients had evidence of sinusitis with mass formation in prior scans (45%), yet in some patients (24%) no masses were visible in the sinuses in the prior scan 5–12 months before the detection of orbital masses, suggesting that perforating masses from the sinuses may develop during this time span. Some patients with mass formation in the sinuses may therefore be at risk to develop orbital masses, although only a minority of these patients with masses in their sinuses (25–30% of our overall cohort, unpublished observation) present with orbital mass formation (5%). In one-fourth of patients we could not determine the origin of the orbital masses and had no clear evidence of perforation; however, we used MRI, which may not represent the best option to detect bone destruction. Bilateral involvement was frequent in our study, occurring in 30% of patients, which underlines the necessity of efficient immunosuppression in order to prevent significant visual impairment in both eyes.

As proptosis was present in only 60% of patients, we suggest generous performance of MRI/CT scans in cases of cephalgia, orbital pain or diplopia in any patient with GPA. Notably, at the time of orbital mass formation, all except two patients had eye-related symptoms and nearly 30% of patients had localized disease. Patients in systemic disease stages frequently had episcleritis/conjunctivitis and cerebral involvement (such as pachymeningitis resulting from local spreading), whereas classic vasculitic manifestations (e.g. glomerulonephritis) were less frequent compared with our overall cohort [17]. Physicians should be aware that orbital masses frequently occur in the absence of classic vasculitic activity.

To conclude, orbital masses are a resistant disease manifestation with a high frequency of complications such as persistent visual impairment, blindness, local destruction and perforation into neighbouring organs. CYC plus GC are not reliably efficient to induce a swift remission and to prevent damage.

The weakness of our study is its retrospective character including missing data sets for VDI and follow-up in some patients and the lack of combined imaging (MRI plus CT) to better assess the origin of orbital masses. The strength lies in its uniform and standardized diagnostic and therapeutic procedure, which allows some conclusions with respect to the course of disease and treatment efficacy. Systematic imaging and therapeutic studies are needed to better understand the pathophysiology of orbital masses and to develop efficient treatment strategies.

Rheumatology key messages
- Orbital masses in GPA seem to derive most frequently from paranasal sinuses via perforation.
- Orbital masses in GPA represent a refractory manifestation and do not reliably respond to CYC.
- Orbital masses in GPA are associated with high rates of persistent visual impairment and blindness.

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Supplementary data

Supplementary data are available at Rheumatology Online.

References


