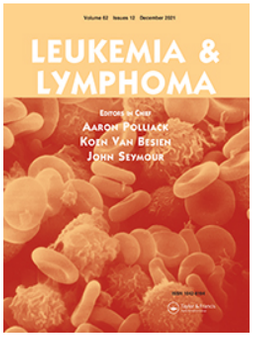

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ORIGINAL ARTICLE

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Monoclonal gammopathy of ocular significance (MGOS) – a short survey of corneal manifestations and treatment outcomes

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ABSTRACT

Monoclonal gammopathy of ocular significance (MGOS) is a rare subset of monoclonal gammopathy of clinical significance occurring secondary to plasma cell disorders and causing ocular manifestations. We identified 23 patients with paraproteinemic keratopathy (PPK) in the setting of monoclonal gammopathy of unknown significance (MGUS, 10), smoldering multiple myeloma (SMM, 3) or multiple myeloma (MM, 10). Many of these patients with PPK (11/23) presented decreased vision. All patients with MM and 40% of those with other diagnoses such as SMM and MGUS received systemic therapy with or without autologous stem cell transplantation. Four eyes of four patients were treated by penetrating keratoplasty. In most cases, neither ocular nor hematologic treatment afforded a durable improvement in the visual acuity (recurrence after a median of 11 months), despite initial responses. Further studies will be required to determine the optimal strategy to treat and prevent the relapse of ocular symptoms in patients with PPK.

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Introduction

Monoclonal gammopathies are disorders of clonal plasma cells which secrete an abnormal and nonfunctional immunoglobulin, typically composed of a heavy and a light immunoglobulin chain, but occasionally containing a light chain only (Bence-Jones protein) or rarely a heavy chain only. The most common gammopathies are monoclonal gammopathy of unknown significance (MGUS), multiple myeloma (MM) and Waldenström's macroglobulinemia (WM). MM is the second most frequent malignant hematologic disease, while the prevalence of MGUS is about 3–4% in the population at 50 years and increases with age [1–3]. The prevalence of MGUS is 5.3 percent among persons 70 years of age or older and 7.5% among those 85 years of age or older [1].

It was recently established that monoclonal gammopathies can lead to deposition of the monoclonal paraprotein in various organs, leading to clinically relevant functional impairments, which defines so-called monoclonal gammopathy of clinical significance (MGCS) [4–7]. A new term has been proposed for patients diagnosed with a monoclonal gammopathy resulting in significant clinical ocular manifestations: monoclonal gammopathy of ocular significance (MGOS) [8]. Ocular manifestations of monoclonal

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†Prof. Dr. N. Szentmáry and Prof. Dr. A. Jurczyszyn are shared last authors of the manuscript.
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plasma cell dyscrasias, related to either the monoclonal immunoglobulin or the plasma cells themselves, are rare [9–11].

The most common form of paraprotein deposition is found in the cornea, although paraprotein deposits have been described in any eye structure [11]. The most frequent ocular lesions are paraproteinemic keratopathy (PPK) (immunotactoid keratopathy) with a typically crystalline, but also non-crystalline morphology [12], paraproteinemic maculopathy [13] and orbital plasmacytoma [11].

Given the rarity of these conditions, optimal management strategies are not defined; the approach is dependent upon the underlying cause of the monoclonal gammopathy and whether or not the patient's vision is affected. Our goal was to collect data on MGOS in order to obtain a better understanding of the symptoms and diagnosis. The main focus was on patients with monoclonal gammopathy and coincident PPK. We characterized the hematologic disease and its course in parallel with that of MGOS. Finally, the local and/or systemic treatment and the outcomes, both ocular and hematologic, were recorded.

Patients and methods

In this international multicenter retrospective study, we collected data on patients with ocular disease related to a monoclonal gammopathy from collaborating centers in Chile, France, Germany, Italy, Poland, Spain and the United States. The retrospective data collection was based on a standardized study form and aggregated by the study coordinator. The patients' informed consent was not required since the study was retrospective and entailed no risk. Personal data were de-identified to ensure compliance with the General Data Protection Regulation of the European Union [14].

There were no other inclusion criteria besides monoclonal gammopathy with an ophthalmic manifestation. We initially grouped the ocular events in four categories: PPK, orbital plasmacytoma, paraproteinemic maculopathy and conjunctival disease. On the grounds that the term MGOS should be reserved for those entities related to decreased visual acuity due to or deposition of the M-protein in the eye, we excluded the plasmacytomas. The data concerning patients with paraproteinemic maculopathy and conjunctival disease were too incomplete to include them in the analysis. Therefore, the report focuses only on patients with PPK. The demographic data included age, race and sex, while hematologic and non-hematologic medical histories were also collected. The MM-related history included the staging, performance status, type of monoclonal protein, fluorescence *in situ* hybridization cytogenetic analysis, anti-MM therapy and autologous stem cell transplantation (ASCT). Acquired laboratory results included a complete blood count, renal and liver functions, a urine analysis for Bence-Jones proteins and a bone marrow analysis. Diagnostic procedures to evaluate and treat the eye disease were recorded, including ophthalmic pathology findings. Primary efficacy outcomes were the hematologic and ocular responses in patients with PPK. The hematologic responses were reported according to the International Myeloma Working Group (IMWG) response criteria [15].

Ophthalmic assessment

The ocular examination comprised slit-lamp biomicroscopy, *in vivo* confocal laser scanning microscopy (IVCM), magnetic resonance imaging (MRI), and histopathology in two individuals. The time between the hematologic diagnosis and the appearance of ocular manifestations was noted. The ophthalmic response to treatment was assessed by each local physician and split into three categories: complete, partial or no sight recovery.

Statistical analyses

Descriptive statistics, including counts and percentages, medians and ranges or inter-quartile ranges, were recorded for each parameter. Progression-free survival, defined as the time from diagnosis to progression or death, was calculated using the Kaplan-Meier method. Due to the small sample size and the rarity of ocular events, associations of factors contributing to treatment outcomes were not assessed by logistic regression. Analyses were performed with RStudio version 1.4.1106 and a graph was drawn using MedCalc® version 20.008 (MedCalc Software Ltd).

Results

Thirty-four consecutive patients were identified in retrospective chart reviews between 2006 and 2019 from clinical centers in seven countries [Germany ($n = 25$), Poland ($n = 3$), France ($n = 2$), Spain ($n = 1$), Italy ($n = 1$), Chile ($n = 1$) and the USA ($n = 1$)]. PPK was the most common ocular diagnosis ($n = 23$, 67.6%), followed by orbital plasmacytoma ($n = 8$),

Table 1. Baseline characteristics of the study population.

Characteristics	$N = 23$
Male, *n* (%)	12 (52.2%)
Age (years), median (IQR)	64 (58.0–71.5)
Hematologic disease, *n* (%)	
MGUS	10 (43.5%)
SMM	3 (13.0%)
MM	10 (43.5%)
WHO-PS, *n* (%)	
0 or 1	18 (78.3%)
≥2	5 (21.7%)
Bone marrow plasma cell infiltration (%), median (IQR)	10 (5–30)
Type of myeloma, *n* (%)	
IgG kappa	11 (47.8%)
IgG lambda	2 (8.7%)
IgA kappa	2 (8.7%)
IgA lambda	4 (17.4%)
Light chain – kappa	2 (8.7%)
Light chain – lambda	2 (8.7%)
ISS score, *n* (%)	
I	12 (52.2%)
II	6 (26.1%)
III	5 (21.7%)
R-ISS, *n* (%)	
I	8 (34.8%)
II	10 (43.5%)
III	5 (21.7%)
Serum creatinine (mg/dL), median (IQR)	0.96 (0.78–1.42)
Serum LDH, *n* (%)	
Normal	20 (87.0%)
Elevated	2 (8.7%)
Unknown	1 (4.3%)
Cytogenetic abnormalities, *n* (%)	
Standard risk	11 (47.8%)
High risk: del 17p, t (4;14) or t (14;16)	3 (13.0%)
Unknown	9 (39.1%)

The table lists the percentage or median of non-missing parameters.
IQR: inter-quartile range; LDH: lactate dehydrogenase; MGUS: monoclonal gammopathy of unknown significance; MM: multiple myeloma; SMM: smoldering multiple myeloma; WHO-PS: World Health Organization performance status; ISS: international staging system; R-ISS: Revised ISS.

paraproteinemic maculopathy ($n = 2$) and pathology of the conjunctiva ($n = 1$).

The ophthalmic diagnosis of PPK was made before the hematologic one in 3 cases (13.0%), simultaneously (within ±3 months) in 9 (39.1%) and after in 11 (47.8%). The median age was 64 years (range 37–86), with 52.2% male patients. The hematologic diagnoses were MGUS and MM (43.5% each) and SMM in 3 patients (13.0%). The paraprotein was an IgG in 56.5%, IgA in 26.1% and light chain in 17.4% of cases. Table 1 summarizes the patients' characteristics.

PPK was diagnosed by a slit-lamp examination and/or IVCM (Figures 1 and 2). Penetrating keratoplasty was performed in four eyes of four patients, which also allowed a histological evaluation; however, results were available only in two cases. Immunohistochemistry of the cornea in a patient with stromal flake-like PPK and MGUS of type IgG κ revealed red-stained kappa light chains between the connective tissue lamellae (Figure 1(E)). The corneal symptoms were bilateral in all cases. In 11 patients, PPK led to a decrease in visual acuity (monoclonal gammopathy with ocular significance, MGOS) while the remaining patients had heterogeneous, discrete findings which did not influence their vision.

The ophthalmic treatment included penetrating keratoplasty alone ($n = 1$) or in combination with treatment of the systemic disease ($n = 3$). In two of these patients, systemic therapy preceded keratoplasty. There was a recurrence of the PPK in these subjects after a median of 11.2 months (IQR: 7.7–11.8). Twelve individuals received only systemic treatment (Table 2). Seven patients, 5 with MGUS and 2 with SMM, did not receive any therapy and were only monitored. In this group, 3 patients were reported to have decreased vision (development of MGOS).

The median number of systemic treatment lines was 2 (range 1–3). Ten patients received one line, 5 patients two lines and 3 patients three lines of treatment, including 12 with ASCT. The details of the therapies with their respective hematologic and ophthalmic responses to the first line of treatment are reported in Table 2. The later lines of therapy included combinations of monoclonal antibodies (Mabs) with immunomodulatory drugs (IMiDs) (40%), proteasome inhibitors (PIs) (20%), IMiDs, Mabs, alkylating agents and combinations of PIs with IMiDs (10% each). A second keratoplasty was performed in one patient to treat recurrence of PPK, but the outcome was not available.

All patients displayed a hematologic response to systemic treatment following the first line of therapy. After a median follow-up of 39.2 months (95% CI: 24.7 – 55.1) in systemically treated patients, the best hematologic responses were 5 CR (33.3%), 4 VGPR (26.6%) and 6 PR (40.0%). The median progression-free survival was 27.8 months (95% CI: 4.4 – 27.8) (Figure 3). Overall, 6 of 11 patients with initially decreased vision (MGOS) achieved clinical improvement, 4 of them as a result of penetrating keratoplasty. However, these improvements were transitory and MGOS typically relapsed within one year (median: 11.2 months (IQR: 7.7–11.8) of the initial response. One patient died due to infection.

Discussion

The reasons for the deposition of monoclonal immunoglobulin in the cornea are unknown. Hypercupremic keratopathy results from uncommon physiochemical alterations of the monoclonal immunoglobulin which favor excessive copper binding [12,16]. The other syndromes might result from rare physiochemical changes in the monoclonal

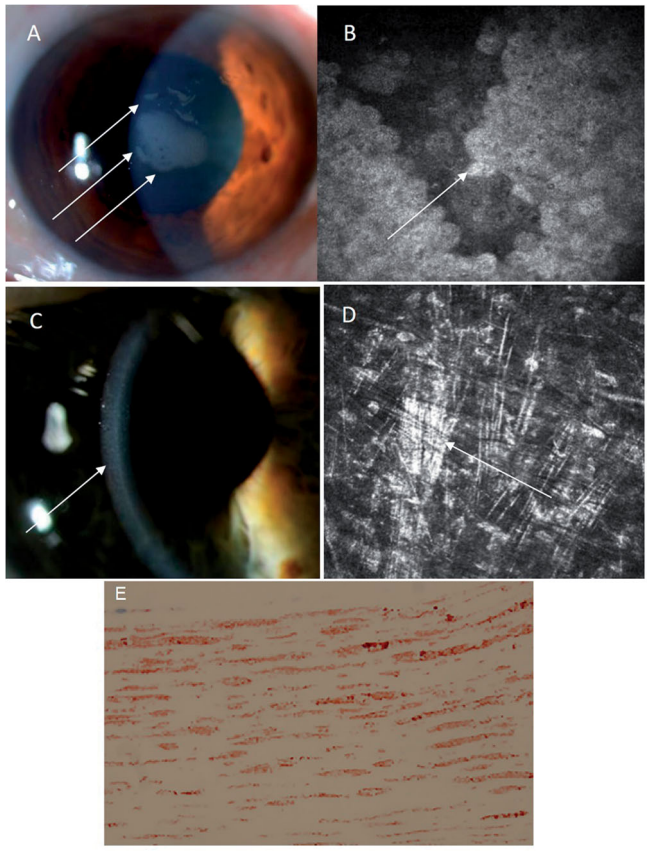

Figure 1. Slit-lamp (A) and *in vivo* confocal microscopic (B) images [Rostock Cornea Module of Heidelberg Retina Tomograph-III] of corneal deposits in monoclonal gammopathy of ocular significance (MGOS). There are whitish deposits in the anterior corneal stroma (A). Using confocal microscopy, no inflammatory cells could be visualized between the deposits or within the corneal stroma (B). Diffuse stromal flake paraproteinemic keratopathy under a slit-shaped light beam (C). Confocal microscopy shows extracellular hyperreflective needlelike stromal deposits at a depth of 284 μm (D) in the same patient as in (C). Immunohistochemistry of the cornea in a patient with stromal flake-like paraproteinemic keratopathy and monoclonal gammopathy of unknown significance of type IgG κ (E). Kappa light chains appear stained in red between the connective tissue lamellae of the corneal stroma.

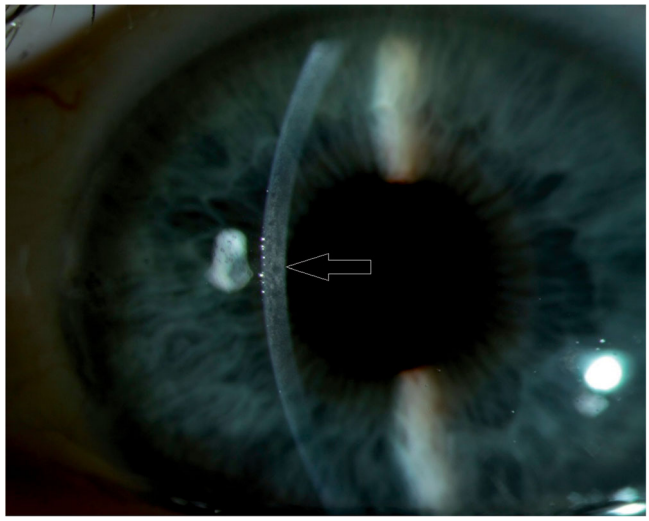

Figure 2. Slit-lamp image of a stromal corneal opacity in a patient with flake-like PPK due to MM type IgA lambda.

immunoglobulin favoring crystallization, although not all PPKs are crystalline. Monoclonal proteins may also be deposited in the conjunctival tissue. Additionally, less common ocular manifestations have been described, such as acute/chronic uveitis, delayed bilateral fibrinous anterior chamber reaction, dense

accumulation of copper in the lens capsule, cataract, glaucoma, Doyne's retinal dystrophy, maculopathy with or without retinal detachment, central retinal artery or vein occlusion and uveal effusion syndrome [17–26].

In monoclonal gammopathy of ocular significance (MGOS) there is decreased visual acuity, which impairs quality of life. The visual impairment represents a considerable additional burden in patients with MGUS, SMM or MM, who already suffer from psychological and physical distress [27,28]. In the PPK group, almost half of the patients had visual impairment (MGOS). Our knowledge regarding the treatment and prognosis of patients with PPK, the most common form of MGOS, is still limited. The condition is rare, but its prevalence is probably underestimated due to underdiagnosis and misdiagnosis. A recent secondary analysis of ocular health in patients receiving therapy for relapsed or refractory MM showed that 43% of them had an abnormal corneal epithelium, indicating that not only PPK, but also side effects of the therapy, belantamab/mafodotin in this study, can be a common complication of MM [29]. Pennisi et al. recorded a higher prevalence of lens opacity and dry eye syndrome in patients receiving active anti-myeloma therapy than in a control healthy population, emphasizing the occurrence of pleiomorphous ocular disorders linked to myeloma treatment [30].

This is to date the largest retrospective study [12,31,32] focusing on MGOS patients with monoclonal immunoglobulin deposits accumulating in the cornea and resulting in visual impairment. Typically, the ocular diagnosis was made with a slit-lamp and/or by IVCM after or at the time of the initial hematologic diagnosis, rarely before.

There is no universally accepted treatment management for patients with MGOS, due to PPK. Observation has until now been the standard care in MGUS and SMM [33,34]; however, as in monoclonal gammopathy of renal significance (MGRS), the standard care for

Table 2. Systemic therapies and eye management and their outcomes in paraproteinemic keratopathy.

Diagnosis	Treatment	Response	PPK recurrence
Number of patients with no hematologic or eye treatment: 7			
Number of patients with eye treatment only: 1			
MGUS	Keratoplasty	PR	Yes
Number of patients with both hematologic and eye treatment: 3			
MM	Ritux Dex	PR	Yes
	Keratoplasty	PR	
MM	Ritux Benda	PR	Yes
	Keratoplasty	PR	
MGUS	Rd + ASCT	PR	Yes
	Keratoplasty	PR	
Number of patients with hematologic treatment only: 12			
MM	CyBorD	CR	Yes
	No eye treatment	CR	
MGUS	VD + ASCT	CR	Yes
	No eye treatment	PR	
SMM	VRD	PR	Yes
	No eye treatment	PR	
MGUS	VD + ASCT	CR	–
	No eye treatment	No response	
SMM	VRD + ASCT	VGPR	–
	No eye treatment	No response	
MM	CyBorD	PR	–
	No eye treatment	No response	
MM	VRD + ASCT	PR	–
	No eye treatment	No response	
MM	CyBorD + ASCT	VGPR	–
	No eye treatment	No response	
MM	CyBorD	CR	–
	No eye treatment	No response	
MM	VD	PR	–
	No eye treatment	No response	
MM	VD + ASCT	PR	–
	No eye treatment	No response	
MM	CyBorD + ASCT	VGPR	–
	No eye treatment	No response	

PPK: paraproteinemic keratopathy; ASCT: autologous stem cell transplantation; CR: complete response; PR: partial response; VGPR: very good partial response; Ritux Dex: rituximab + dexamethasone; Ritux + Benda: rituximab + bendamustine; Rd: lenalidomide + dexamethasone; CyBorD: cyclophosphamide + bortezomib + dexamethasone; VRD: bortezomib + lenalidomide + dexamethasone; VD: bortezomib + dexamethasone.

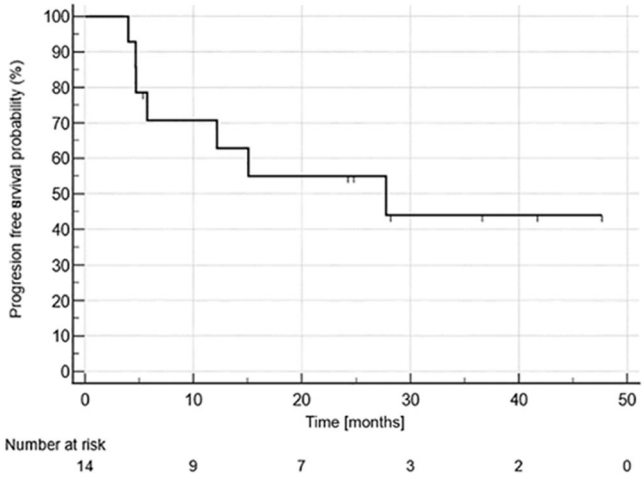

Figure 3. Progression-free survival of patients receiving systemic therapy.

compromised organ function should be systemic therapy.

The role of chemotherapy and ASCT in the treatment of PPK is controversial and based on the assumption that resolution of the paraproteinemia should stop the progression or induce reversal of the ocular symptoms. In our study, 40% of the patients received chemotherapy with or without ASCT. Although keratoplasty alone or in combination with systemic therapy and/or ASCT improved the visual acuity, similarly as in other reports, the improvements were transitory [9,31,32,35]. In the study group, all patients were treated with systemic therapy regimens based on new generation drugs, including monoclonal antibodies. All patients displayed a hematologic response, but even a complete hematologic response did not preclude ocular recurrence. In all cases, decreased visual acuity reappeared despite optimal systemic management of the underlying disease [36,37]. In contrast, it should also be noted, that in the study of Skalicka et al. [32] one patient had no PPK recurrence after repeat keratoplasty and without additional systemic treatment for 5 years. The preferred order of keratoplasty or chemotherapy could not be determined from the data of our present study, due to the small number of patients and the variations in their treatment. We nevertheless recommend that systemic therapy should precede keratoplasty to prevent recurrence in the corneal transplant.

Continuous systemic treatment, for example maintenance therapy similar in concept to post-transplant lenalidomide for MM, may be necessary to uphold the effect of treatment, even in patients with MGUS or SMM. Future studies will need to address the timing of keratoplasty and systemic chemotherapy and the role of maintenance therapy. Favorable ocular outcomes were rare in this survey, which precluded an analysis of predictors of sustained ophthalmic response. The resolution of ocular symptoms not affecting vision was likewise not evaluated. The rarity of the disease, retrospective nature of the study and patient selection also limit the generalizability of the results.

Conclusion

Ophthalmologists need to consider the diagnosis of MGOS in patients with bilateral corneal findings of unknown origin and it may be necessary to exclude monoclonal gammopathy. Patients with known paraproteinemia should undergo a slit-lamp examination to assess the possibility of ocular involvement. The treatment of MGOS is challenging. It includes surgical treatment of the affected cornea and systemic therapy, which is standard in patients with MM, but should also be incorporated into the management of cases of MGUS and SMM with significant ocular symptoms (i.e. MGOS). Patients with significant decrease of visual acuity treated surgically and/or systemically are at risk for corneal recurrence. The effect of therapy is rarely sustainable and this makes MGOS an entity with still unsatisfied medical needs.

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Author contributions

Conceptualization, LG, NS, AJ; data curation, LG, M AH, J WP, MM, KK, CP, AG, ZX, A WG, LR, GM, MK, WL, DV, NS, AJ; writing of original draft, LG,NS, AJ; reviewing and editing, LG, M AH, J WP, MM, KK, CP, AG, ZX, A WG, LR, GM, MK, WL, DV, NS, AJ.

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