



Case Report

# Successful Hematological Treatment of Monoclonal Gammopathy with Ocular Significance (MGOS)

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## Abstract

**Background:** The most common ocular symptom of monoclonal gammopathy is the appearance of corneal opacities. Our goal is to present a case with successful haematological treatment of monoclonal gammopathy with ocular significance (MGOS).

**Case Report:** Our patient was diagnosed with MGOS, with increasing corneal opacification and decreasing visual acuity. Following 4 cycles of plasma-cell-directed bortezomib and dexamethasone treatment (1,3mg/m<sup>2</sup> bortezomib subcutaneously and 20 mg dexamethasone orally), most of the corneal opacities disappeared or decreased in size and best corrected visual acuity of the patient increased.

**Conclusion:** In summary, in monoclonal gammopathy with ocular significance, plasma-cell-directed bortezomib-dexamethasone treatment may successfully decrease or diminish MGOS. The mechanism of corneal opacification and its disappearance has to be further analysed.

**Keywords:** Monoclonal gammopathy; Ocular significance; MGUS; MGOS

## Introduction

Monoclonal gammopathy includes various pathologies; in which plasma cells produce large amounts of abnormal, malfunctioning immunoglobulins, as a common feature. In most cases, these immunoglobulins are composed of a heavy and a

light chain, but sometimes they consist of a light chain only (Bence Jones protein) or, much more rarely, a heavy chain only. Monoclonal gammopathy of undetermined significance (MGUS), multiple myeloma (MM), and Waldenström macroglobulinemia are the most common plasma cell pathologies belonging to this category [1-4]. It has been known for a few years that in the case of monoclonal gammopathy, certain monoclonal Para proteins may be deposited in various organs, resulting in clinically manifest functional tissue damage. In such a case, we speak of monoclonal

gammopathy with clinical significance (MGCS) [5]. The term „monoclonal gammopathy with ocular significance”, (MGOS) was used for the first time in 2019. Karakus et al. presented a case of monoclonal gammopathy with only ophthalmic involvement (no other organ involvement could be verified) [6]. Solitary ophthalmic manifestations of monoclonal plasma cell dyscrasias are extremely rare. At the same time, several ophthalmic abnormalities have already been described in diseases with monoclonal gammopathy. Their symptomatology is mostly related to the haematological diseases and not to the deposition of Para proteins. These ophthalmic diseases include myositis, proposes, deposits in conjunctiva, acute or chronic uveitis, maculopathy, Doyme’s retinal dystrophy, central retinal artery, or vein occlusion [7-15]. The most common monoclonal gammopathy-specific ophthalmic abnormality is the appearance of corneal deposits. These were first described in 1934 by Meesmann [16]. The appearance of corneal deposits was later defined as paraproteinemic keratopathy or immunotactoid keratopathy [7,17]. In 2012, Lisch and his co-workers classified immunotactoid keratopathy (ITK) into 5 groups [17], and later on, they extended these into 11 distinct categories in 2016 [18]. These deposits are mostly bilateral, grey-white, yellowish, grey-brown, or polychromatic or maybe shiny dot-like crystals in any layer in the cornea [19]. With their changing clinical appearance, these can mimic many corneal diseases. Our work aims to present a successful haematological treatment of monoclonal gammopathy of ocular significance, through one specific case.

## Case Report

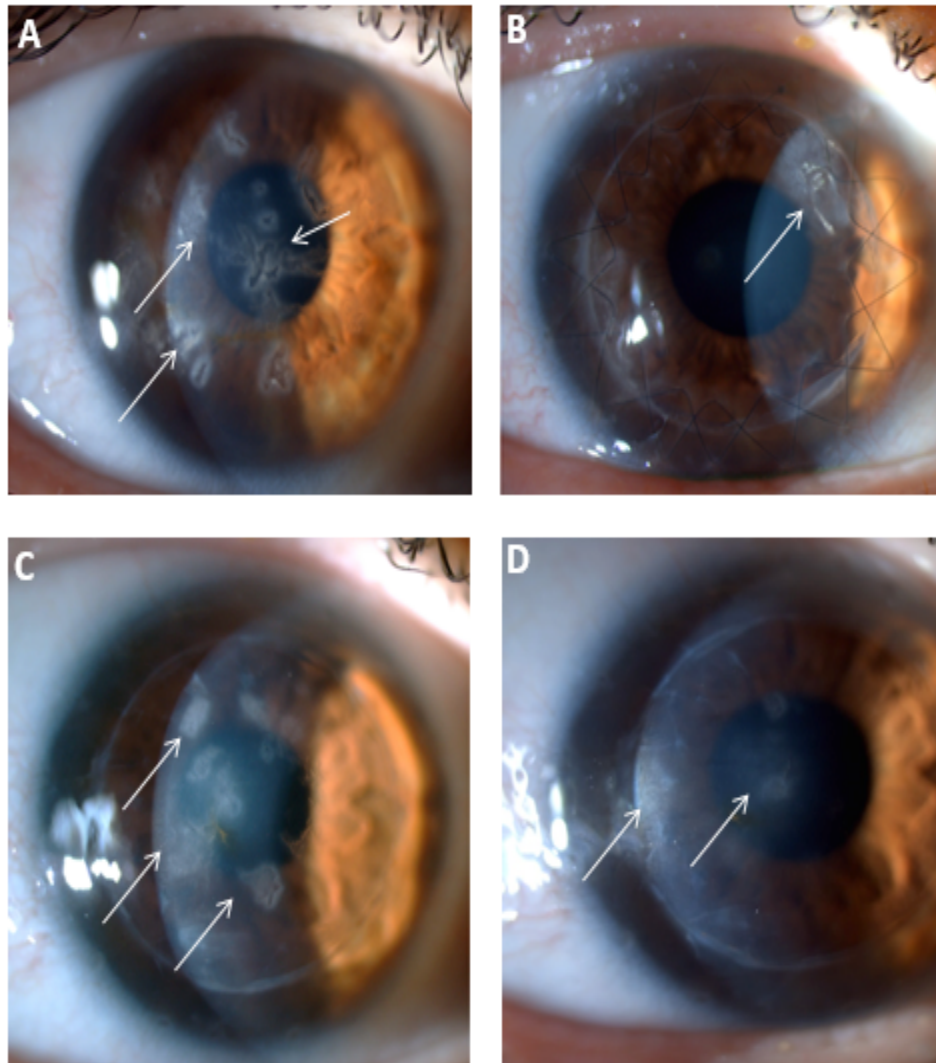
A fifty-year-old female patient, with high myopia, was referred to the Department of Ophthalmology of Semmelweis University in Budapest, due to her gradually deteriorating visual acuity in the right eye for 3 years. Slit-lamp examination revealed bilateral corneal opacities with blurred edges and a map-like pattern, which resulted in her deteriorating vision (Figure 1a). At this time point, her best-corrected visual acuity (BCVA) was 0.6 (logMAR 0.1) on her right and 1.0 (logMAR 0.0) on her left eye. No other ophthalmic abnormality could be verified. In her ophthalmic history, there were no prior ophthalmic surgery, injury, or other diseases. Her family history was negative for ophthalmic diseases and hereditary ophthalmic abnormalities.

In 2017, as the size of the corneal opacities gradually increased and the patient’s visual acuity decreased (her BCVA was 0.15 (logMAR 0.8) on the right, and 0.8 (logMAR 0.1) on the left eye) a penetrating keratoplasty has been performed on the right side to improve her best-corrected visual acuity. Histological analysis of the cornea confirmed the deposition of monoclonal proteins in the deep corneal stroma. Due to the suspicion of monoclonal gammopathy, serum electrophoresis has been performed, which verified a pathological amount of monoclonal protein with mobility at the gamma-globulin fraction. The subsequent bone

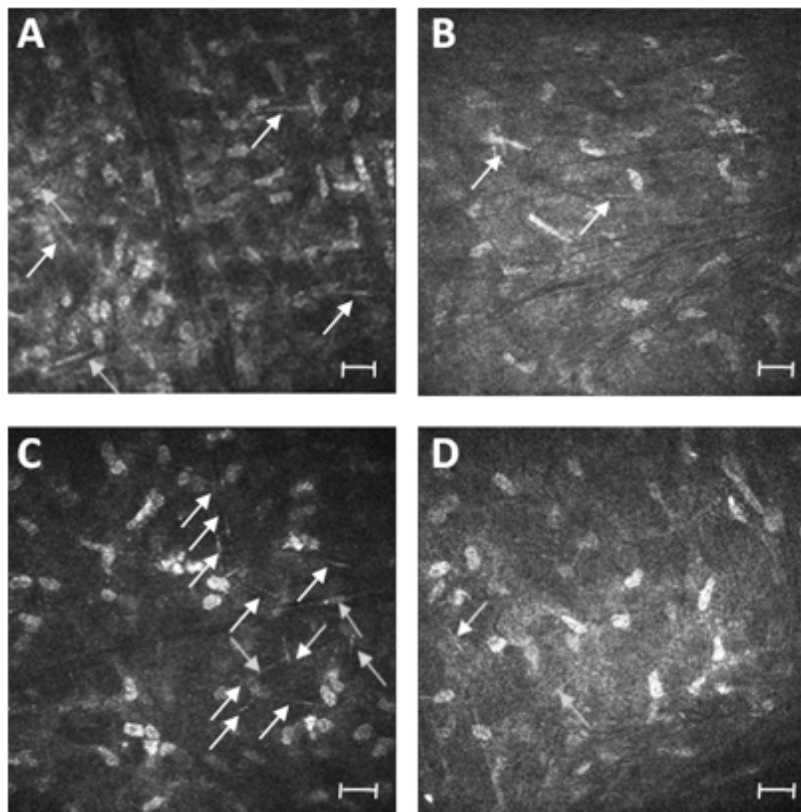
marrow biopsy verified 5-7% involvement of plasma cells (with an 8:1 kappa predominance). Besides the ophthalmic disease, no other organ involvement could be verified through detailed examination. Therefore, the diagnosis of monoclonal gammopathy of ocular significance (MGOS) was established. Donor adaptation was as usual and there was no rejection episode after corneal transplantation. However, at the 10th postoperative month, greyish-white corneal opacities, with unshar edges appeared at the transplant margin. These opacities were visible mainly in the upper nasal quadrant, and then in the lower temporal quadrant, next to the transplant interface (Figure 1b). At this time point, the best-corrected visual acuity of her right eye was 0.5 (logMAR 0.3). At the 15-month postoperative follow-up, after complete suture removal, the size of the opacities continued to increase (Figure c), and the best-corrected visual acuity deteriorated to 0.4 (logMAR 0.4). Meanwhile, the best corrected visual acuity of the non-operated left eye also decreased from 0.9 (logMAR 0.1) to 0.7 (logMAR 0.2).

Examination of the patient with in-vivo confocal microscopy (IVCM) (Heidelberg Retina Tomography with Rostock Cornea Module (Heidelberg Engineering, Heidelberg, Germany)) verified hyper reflective spikes in the corneal stroma of both eyes, at all examination time-points (PKP) (Figures 2a-c and Figure 3a). Before surgery, 5 hyper reflective stromal spikes were visible on the right side per micrograph, 10 months postoperatively this number decreased to 2, and then, 15 months after surgery increased again to 12 (Figure 2 a-c). On the left side, 15 months after corneal transplantation of the right eye, 13 hyperactive reflective spikes in the corneal stroma were visible (Figure 3a). Since the size of the opacities continued to increase for the subsequent control examinations, after haematological consultation, plasma-cell targeted treatment with a diagnosis of MGOS has been initiated. As a first step, systemic thalidomide treatment was administered (50 mg orally daily for 3 months), however, the patient’s ophthalmic status did not improve and the amount of serum Para proteins did not decrease. At the beginning of the systemic thalidomide treatment, the IgG kappa M-protein amount was 21.35 g/L, while the involved kappa light chain amount was 48.20 mg/L. Six months after the thalidomide treatment, serum M-protein was 19.91 g/L, and the kappa light chain was unchanged at 45.50 mg/L. Thereafter, as the second line of therapy, MGOS was treated with bortezomib and dexamethasone (bortezomib 1.3 mg/m<sup>2</sup> subcutaneously and dexamethasone 20 mg orally, weekly). The treatment was carried out in 4 cycles. After the fourth cycle, the majority of the corneal opacities were no longer visible or were significantly reduced in size (Figure 1d). For this time point, the patient’s best-corrected visual acuity (with hard contact lenses) improved to 0.6 on her right and 0.9 on her left eye. The amount of serum Para protein amount was reduced to 10.56 g/L and the amount of the kappa light chain to 25.50 mg/L, representing clinical benefit without

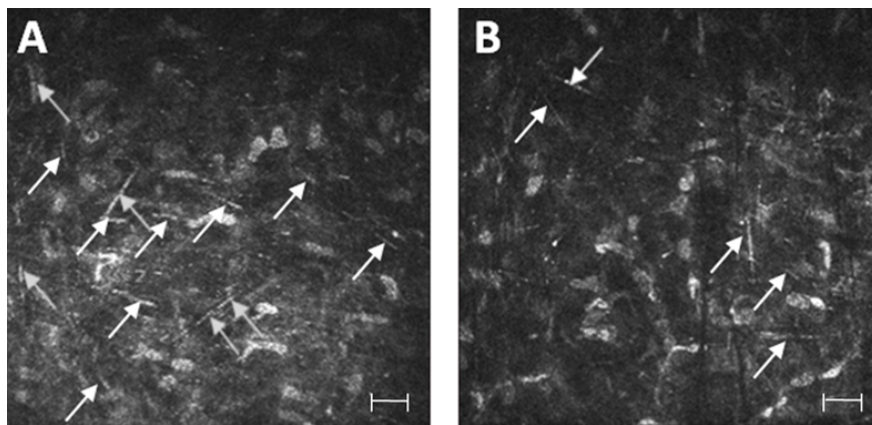
partial response. After the bortezomib-dexamethasone treatment, the number of hyper reflective spikes in the corneal stroma decreased to 2 per micrograph on the right, and 5 per micrograph on the left side (Figures 2d and 3b).



**Figure 1:** Posterior corneal stromal opacities with blurred edges in the patient’s right eye 7 months before penetrating keratoplasty (PKP) (A). Ten months postoperatively, greyish-white corneal opacities with indistinct edges appeared in the upper nasal quadrant next to the suture row (arrow) (B). Fifteen months after PKP, following suture removal, new, central corneal stromal opacities became visible in the donor cornea (C). After 4 cycles of bortezomib-dexamethasone chemotherapy, the size of all corneal opacities decreased and some of them disappeared (D).



**Figure 2:** *In vivo* confocal microscopy (IVCM) with stromal spike-like deposits (arrows) of the right corneal stroma at the first examination time-point (A), preoperatively, before penetrating keratoplasty (PKP) (B), postoperatively (C) and after bortezomib-dexamethasone treatment (B). Scale bar: 50  $\mu$ m.



**Figure 3:** *In vivo* confocal microscopy (IVCM) with stromal spike-like deposits (arrows) of the left corneal stroma at the first examination time-point (A) and after bortezomib-dexamethasone treatment (B). Scale bar: 50  $\mu$ m.

## Discussion

The primary clinical goal in monoclonal gammopathy is to extend the patient's life while preserving/maintaining the best possible quality of life. In addition, the aim is to prevent disease complications and reduce side effects when treatment is required. The therapeutic decision should always depend on the patient's clinical condition and personal preferences [20]. According to current professional recommendations, MGUS without clinical symptoms requires close follow-up, but systemic treatment is not required. At the same time, if MGUS transforms into a symptomatic malignant disease (e.g. multiple myeloma), it is justified to start antineoplastic therapy [21]. Antineoplastic drugs have undergone significant development in the last decades and the clinical application of many new groups of drugs could be initiated. Among the novel agents, thalidomide (an imid drug used as an immunomodulatory) has been the mainstay of multiple myeloma treatment since the early 2000s. Lenalidomide and pomalidomide are also drugs belonging to the imid class. These compounds have higher activity and a different spectrum of side effects [21,22]. Imides are used in combination with corticosteroids, alkylating agents, or other chemotherapeutic agents. The first-in-class proteasome inhibitor drug, bortezomib was registered in the EU in 2005. It is administered intravenously or more commonly subcutaneously in combination with a corticosteroid, often in triplets. It is also one of the most commonly used treatment methods for multiple myeloma in Hungary [23,24]. In the case of immunotactoid keratopathy, visual acuity does not change in some cases; therefore, treatment is not mandatory. However, partial, or full-thickness corneal transplantation (PKP) can also be performed in case of severe visual impairment. Nevertheless, according to literature data, the recurrence of ITK is very likely to occur, even after therapy/surgery (9), as we also experienced in our case. Successful systemic treatment has already been carried out in a few cases in MGOS. In 2012, Klingenstein et al. reported on the reduction of corneal opacity size after 4 cycles of bortezomib/dexamethasone treatment [25]. Froussart et al. described a decrease in corneal opacity size following chlorambucil treatment [26]. In 2015, Milmann et al. reported on the improvement of visual acuity and corneal opacities following cyclophosphamide, etoposide, and dexamethasone therapy [9]. In the literature, we also found a case report [27] on hyper reflective stromal spikes in the corneal stroma, similar to our present work [28]. Many substances could be deposited in the corneal stroma. These include e.g. amyloid, chloroquine, ciprofloxacin, gold, and iron [27,29-30]. At the same time, in such cases, no hyper reflective stromal spikes could be verified using *in vivo* confocal microscopy [7,9,31]. Using IVCM, even sub epithelial nerves could be falsely interpreted, as hyper reflective stromal spikes. However, in our subject, the hyper reflective stromal spikes have also been located in the deeper corneal stromal layers in both eyes; therefore, these could be easily

differentiated from nerves. These hyper reflective stromal spikes may correspond to immunoglobulin deposits (which are not visible with slit-lamp examination but can be verified using IVCM), or to systemic drugs deposited in the corneal stroma (systemic treatment of the haematological disease). As at the time of the first ophthalmic examination, our patient still did not receive any systemic treatment, but the hyper reflective stromal spikes could already be verified, presumably, their appearance corresponds to stromal immunoglobulin deposition. Nevertheless, an accurate evaluation of this phenomenon still requires further investigation. In conclusion, plasma cell-targeted bortezomib-dexamethasone treatment can successfully reduce or eliminate corneal stromal opacities in MGOS. The exact mechanisms, through which corneal deposition or clearance occurs, still have to be verified.

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