

Decrease in Bilateral Corneal Deposits After Bortezomib/Dexamethasone Chemotherapy in Monoclonal Gammopathy: Case Report

A. Klingenstein*, W.J. Mayer and A. Kampik

Ludwig-Maximilians University, Department of Ophthalmology, Klinikum der Universität München, Campus Innenstadt, Mathildenstr. 8, D-80336 Munich, Germany

Abstract: *Purpose:* To evaluate changes of bilateral crystalline corneal deposits *via* biomicroscopic photography and *in vivo* confocal microscopy (IVCM) after systemic chemotherapy in a patient with monoclonal gammopathy.

Methods: Ophthalmological examination, slit-lamp biomicroscopic photography and IVCM of each corneal quadrant were performed before and after 4 cycles of combined bortezomib and dexamethasone chemotherapy.

Results: IVCM revealed mainly subepithelial crystalline deposits not affecting keratocytes or antigen presenting cells. After therapy, corneal opacity in slit-lamp biomicroscopic photography and crystalline deposits decreased visibly. Visual acuity remained stable. Subjective symptoms (haziness, photophobia) improved.

Conclusions: This patient suffered from initially unknown monoclonal gammopathy manifesting in bilateral corneal deposits. Crystalline corneal deposits may be associated with systemic disorders such as monoclonal gammopathy. Correct diagnosis is crucial as systemic treatment may improve not only ophthalmological symptoms. Penetrating keratoplasty alone may lead to relapse.

Keywords: Corneal deposits, crystallins, *in vivo* confocal microscopy, monoclonal gammopathy, paraproteinemia.

INTRODUCTION

A 64 year-old white male patient was referred to our center for corneal transplantation due to bilateral corneal dystrophy. He reported increasing blurred vision and photophobia.

Ophthalmological findings

Best corrected visual acuity (BCVA) was 20/30 on both eyes. Slit-lamp examination showed bilateral diffuse opacities of unknown etiology mainly located in the anterior stroma (Figure 1a). There were no epithelial alterations. On the left side, there was a small subepithelial corneal scar located paracentrally. Otherwise, there were no abnormalities of the anterior or posterior segments of the eye. Goldmann applanation tonometry (GAT) was normal. Endothelial cell number count showed 2037 cells/mm² on the right and 1946 cells/mm² on the left eye which was slightly reduced compared to age-related reference [1]. Corneal crystalline deposits had first been detected 6 years before (BVCA 20/25 on both eyes) (Figure 2).

Internistic Findings

Medical history revealed arterial hypertension which was treated by calcium channel blocker (lercanidipine

10mg) and angiotensin II receptor antagonist (candesartan 8mg). The patient suffered from known chronic renal insufficiency. Serum creatinine levels were known to be elevated between 2.1-2.4mg/dl. Further enquiry revealed elevated serum levels of immunoglobulin G (1950mg/dl) which had first been diagnosed two years earlier. Serum protein electrophoresis showed a monoclonal IgG kappa band. Kappa- and lambda-chains in urine were elevated (ratio 22.0). Bone marrow punctuation showed plasma-cell infiltration between 5-10% (kappa-subtype) excluding plasmacytoma. C-/p-/x-Anti-Neutrophil-Cytoplasmic Antibodies were negative.

METHODS

The patient underwent a complete ophthalmologic examination, including objective and subjective refraction, slit-lamp biomicroscopy, intraocular pressure measurement with GAT and dilated fundus examination. At internistic work-up, blood and urine samples were analyzed. Cast nephropathy due to monoclonal gammopathy was verified by renal biopsy. Four cycles of bortezomib/dexamethasone chemotherapy were applied by the treating oncologist. Slit-lamp biomicroscopy and IVCM (Heidelberg Retina Tomograph II, Rostock Cornea Module; Heidelberg Engineering GmbH) were performed before and after systemic chemotherapy in the center and corneal periphery of all 4 quadrants (3, 6, 9, 12 o'clock).

*Address corresponding to this author at the Ludwig-Maximilians University, Department of Ophthalmology, Klinikum der Universität München, Campus Innenstadt, Mathildenstraße 8, D-80336 Munich, Germany; Tel: +49 89 5160 3811; Fax: +49 89 5160 5160; E-mail: Annemarie.Klingenstein@med.uni-muenchen.de

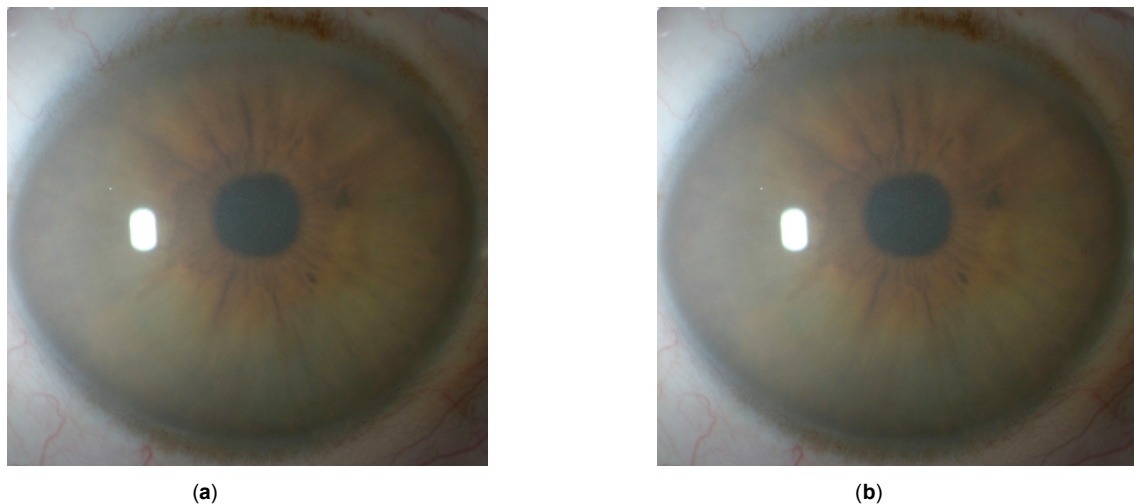


Figure 1: Bilateral intrastromal crystalline deposits in the entire cornea. Diffuse stromal infiltration before therapy (magnification x6) (a). Decrease of corneal opacity after four cycles of bortezomib/dexamethasone chemotherapy (magnification x6) (b).

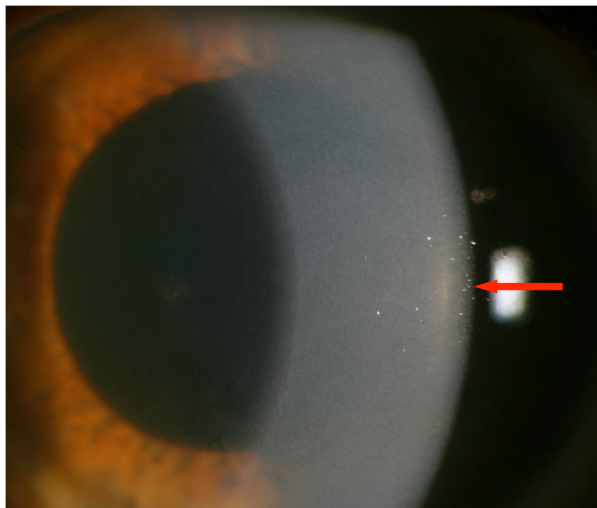


Figure 2: Corneal deposits in 2005 (magnification x10).

RESULTS

Before chemotherapy, IVCM showed bilateral, peripherally accentuated, mainly subepithelial, highly reflective crystalline deposits neither affecting keratocytes nor antigen presenting dendritic cells. Figure 3 demonstrates roundish, hyperreflective deposits with a diameter of approximately $10\mu\text{m}$ (3a and 3c). Keratocytes were evenly distributed in the anterior stroma (Figure 3e and 3f).

After four cycles of bortezomib / dexamethasone therapy, there was a visible decrease in corneal opacification in slit-lamp biomicroscopic photography (Figure 1b).

In confocal microscopy, crystalline deposits diminished in every quadrant (Figure 3b and 3d). The

number of antigen presenting cells did not increase in the corneal center nor in the periphery after therapy. Visual acuity remained stable. The patient reported improvement of symptoms (haziness, photophobia).

Kidney biopsy revealed intraluminal and lysosomal crystalline protein deposits, compatible with cast nephropathy. Vascular and tubulointerstitial damage was consistent with hypertensive genesis, while protein fragments and granular and phagocytic epithelial cells and macrophages gave evidence for dys- / paraproteinemia. Subsuming all internistic findings, monoclonal gammopathy of undetermined significance (MGUS) was diagnosed. After 4 cycles of bortezomib / dexamethasone therapy, serum IgG decreased from 1950mg/dl to 985mg/dl.

DISCUSSION

Different single-case reports have described corneal involvement in systemic hyperparaproteinemia [2-4]. Yet, the incidence of corneal alterations in monoclonal gammopathy is reportedly quite low [2, 5].

In monoclonal gammopathy, intracorneal deposits may present within all corneal layers [6]. In IVCM, Steinberg *et al.* reported the highest density of protein deposits in the epithelium and anterior stroma [6]. In this patient, reflective deposits were mainly located subepithelially. Due to possible heterogenous clinical presentation, differential diagnoses include various corneal dystrophies; amongst others Meesman's or Reis-Bückler's corneal dystrophy, Schnyder's crystalline dystrophy, deep filiform dystrophy and lattice dystrophy. Systemic associations include cystinosis

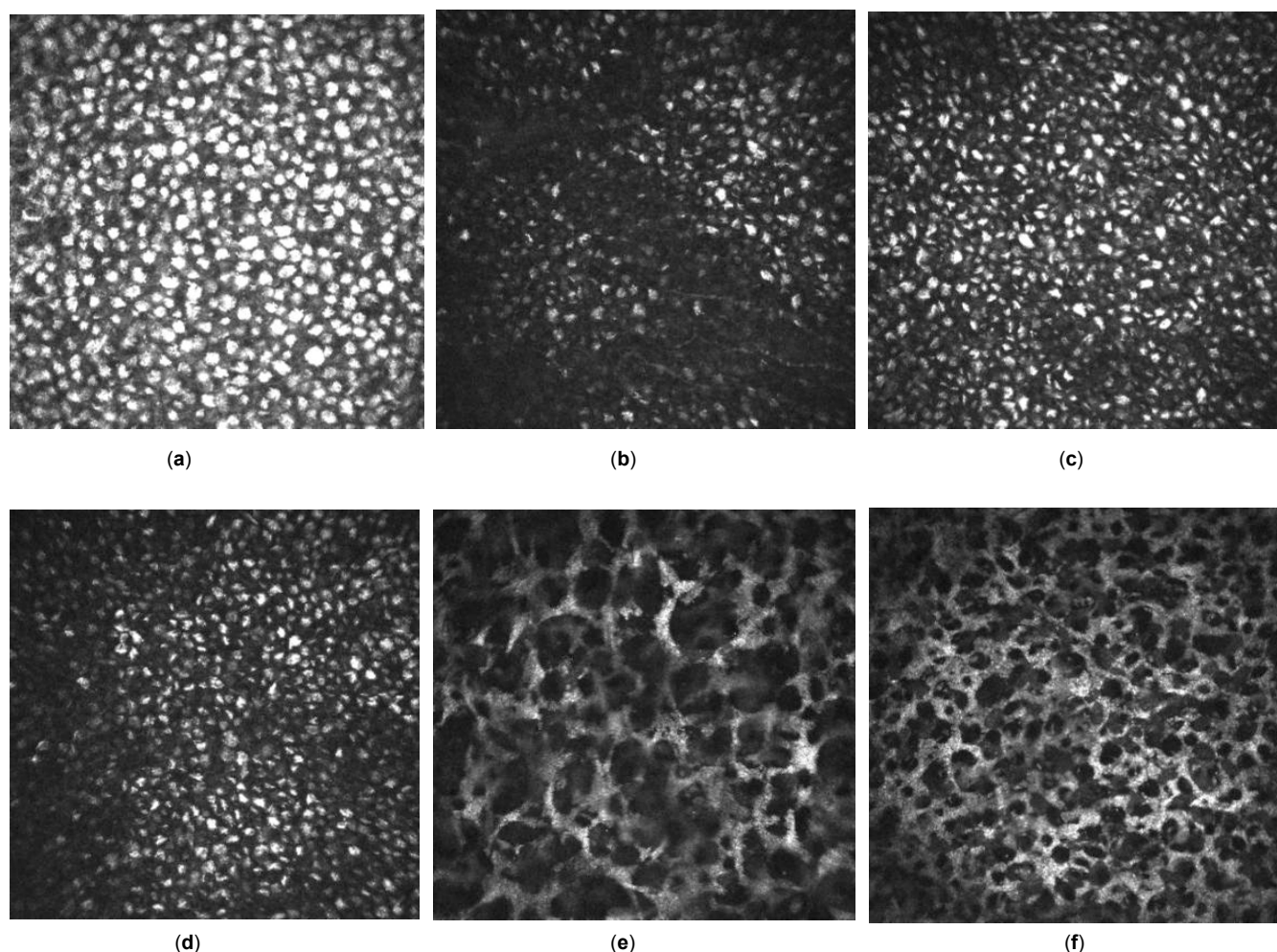


Figure 3: IVCM images of hyperreflective deposits (approximate diameter of 10 μ m) (**3a** located centrally, **3c** in the periphery). Distribution of keratocytes in the anterior stroma (Figure **3e** centrally and **3f** in the periphery), display 400x400 μ m. Decrease of intrastromal crystalline deposits after therapy (Figure **3b** centrally and **3d** in the periphery), display 400x400 μ m.

and multiple myeloma. It is important to differentiate between merely corneal affections and serious systemic diseases possibly requiring systemic therapies. Advanced age at presentation in a patient presenting with unusual corneal deposits of unknown etiology may argue for multiple myeloma [7].

Local therapeutic options include superficial keratectomy and lamellar keratoplasty. In cases with severe loss of visual acuity, penetrating keratoplasty is advised [8], but relapse in the grafted cornea [9] without systemic treatment has been reported [10]. In monoclonal gammopathy, systemic chemotherapeutic treatment (e.g. bortezomib / dexamethasone) is an option. Although limited treatment options are available to reduce the appearance or effects of corneal crystals [11], ocular symptoms resolved in this patient and visual acuity remained stable after 4 cycles of systemic therapy. At follow-up examination 6 months later, the situation was unchanged. The patient reported no further ocular complaints.

Ophthalmologists should be aware that crystalline deposits may be associated with monoclonal gammopathy.

CONFLICTS OF INTEREST

None of the authors have any conflicts of interest to disclose.

FINANCIAL SUPPORT

None.

REFERENCES

- [1] Wilson RS, Roper-Hall MJ. Effect of age on the endothelial cell count in the normal eye. *Br J Ophthalmol* 1982; 66(8): 513-5.
<http://dx.doi.org/10.1136/bjo.66.8.513>
- [2] Garibaldi DC, Gottsch J, de la Cruz Z, Haas M, Green WR. Immunotactoid keratopathy: a clinicopathologic case report and a review of reports of corneal involvement in systemic paraproteinemias. *Surv Ophthalmol* 2005; 50(1): 61-80.
<http://dx.doi.org/10.1016/j.survophthal.2004.10.002>

- [3] Aronson SB, Shaw R. Corneal crystals in multiple myeloma. *Arch Ophthalmol* 1959; 61: 541-6.
<http://dx.doi.org/10.1001/archophth.1959.00940090543007>
- [4] Auran JD, Donn A, Hyman GA. Multiple myeloma presenting as vortex crystalline keratopathy and complicated by endocapsular hematoma. *Cornea* 1992; 11: 584-5.
<http://dx.doi.org/10.1097/00003226-199211000-00017>
- [5] Bourne WM, Kyle RA, Brubaker RF, Greipp PR. Incidence of corneal crystals in the monoclonal gammopathies. *Am J Ophthalmol* 1989; 107: 192-3.
- [6] Steinberg J, Eddy MT, Katz T, Matthiessen E, Fricke OH, Richard G *et al.* Bilateral crystalline corneal deposits as first clinical manifestation of monoclonal gammopathy: a case report. *Case Report Ophthalmol* 2011; 2(2): 222-7.
<http://dx.doi.org/10.1159/000330334>
- [7] Nakatsukasa M, Sotozono C, Tanioka H, Shimazaki C, Kinoshita S. Diagnosis of multiple myeloma in a patient with atypical corneal findings. *Cornea* 2008; 27(2): 249-51.
<http://dx.doi.org/10.1097/ICO.0b013e31815b82cd>
- [8] Font RL, Matoba AY, Prabhakaran VC. IgG-kappa immunoglobulin deposits involving the predescemetic region in a patient with multiple myeloma. *Cornea* 2006; 25(10): 1237-9.
<http://dx.doi.org/10.1097/01.ico.0000240094.78095.f5>
- [9] Beebe WE, Webster RG Jr, Spencer WB. Atypical corneal manifestations of multiple myeloma. A clinical, histopathologic, and immunohistochemical report. *Cornea* 1989; 8: 274-80.
- [10] Koo H, Oh DH, Chun YS, Kim JC. A case of crystalline keratopathy in monoclonal gammopathy of undetermined significance (MGUS). *Korean J Ophthalmol* 2011; 25(3): 202-5.
<http://dx.doi.org/10.3341/kjo.2011.25.3.202>
- [11] Chou JL, Sink ML. Corneal crystals: a precursor to cancer. *Optom Vis Sci* 2011; 88(4): E543-7.
<http://dx.doi.org/10.1097/OPX.0b013e31820bb227>

Received on 01-04-2012

Accepted on 28-04-2012

Published on 25-06-2012

<http://dx.doi.org/10.6000/1927-7229.2012.01.01.15>