

Ocular crystal deposition leading to a diagnosis of multiple myeloma: a report of 2 cases and review of the literature

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ABSTRACT

Corneal crystal deposition due to multiple myeloma is a rare ocular manifestation caused by elevated immunoglobulin levels in the eye. It presents with decreased visual acuity and crystalline deposits in the corneal epithelium or stroma. We describe here two cases of myeloma crystal deposition in the eye, one of which involved crystal deposition in a Laser-Assisted in situ Keratomileusis (LASIK) interface, and one that demonstrated rapid and complete response of corneal crystals with induction chemotherapy (to our knowledge, the first such cases in the literature). We also present a brief review of the literature. A 50-year-old woman presented with decreased vision and crystal deposition in her LASIK interface. This led to a diagnosis of IgG multiple myeloma and treatment with melphalan and prednisone improved her vision to 20/20, but did not completely resolve the corneal crystals. Similarly, a 53-year-old woman presented with foggy vision and dense ocular crystalline deposits. Work-up revealed smoldering myeloma, and the patient was managed conservatively until she developed end-organ damage including anemia and lytic bone lesions. Systemic therapy was initiated, and the crystal deposits resolved completely. With these cases, we hope that clinicians will recognize these unusual ocular manifestations, and consider myeloma in the differential diagnosis. Further research is warranted, but in light of the observed response to therapy and the significant patient burden associated with vision loss, it may be prudent to consider systemic therapy for myeloma-associated ocular disease (though this is not the current convention), potentially with bortezomib.

BACKGROUND

Plasma cell dyscrasias including monoclonal gammopathy of undetermined significance

(MGUS) and multiple myeloma may cause ocular pathology by various mechanisms: direct infiltration, extramedullary plasmacytomas leading to mass effect, hyperviscosity syndrome,

ciliary cysts, or immunoglobulin deposition [1, 2, 3]. More specifically, myeloma can cause crystalline or non-crystalline deposits in the cornea – this finding tends to occur during the late phase of the disease, but may be the initial manifestation of the underlying asymptomatic gammopathy [4, 5]. Given the rarity of this presentation, these systemically-well patients are often mistakenly diagnosed with primary corneal diseases such as lattice dystrophy, Schnyder's crystalline dystrophy, or cystinosis that cause ocular irritation and mimic myeloma keratopathy [1, 6].

Cases of crystalline keratopathy in multiple myeloma have previously been described in the ophthalmic literature; it is a rare ocular manifestation present in approximately 1% of patients with a monoclonal gammopathy and is associated with a poor prognosis [1, 7]. Symptoms may include photophobia, glare, decreased visual acuity, and irritation, all primarily caused by immunoglobulin deposition (crystal) in the corneal epithelium or stroma [7, 8].

We describe here two unique cases of ocular crystalline deposition that led to a diagnosis of multiple myeloma, and discuss the importance of this rare finding along with implications for treatment and future recommendations.

CASE 1

A 50-year-old woman, a recently retired nurse, had a routine and uncomplicated LASIK eye surgery with a perfect 20/20 result. Previous history included rheumatoid arthritis with a hip replacement, small bowel obstruction secondary to frozen pelvis requiring loop colostomy, cervical cancer requiring hysterectomy and radiation 22 years prior, peripheral neuropathy, neurogenic bladder, and a right foot ulcer; there was no previous ocular history other than refractive error.

A year after the patient's LASIK, slit-lamp exam revealed crystal formation at the edges of the left flap interface, with no decreased vision. Subsequently, she developed similar crystal appearances in the right eye, initially observed as small iridescent zones resembling fibreglass bits scattered across the visual axis zone bilaterally (Figure 1). This was likely not diffuse intralamellar keratitis or epithelial ingrowth, and we elected to follow the patient conservatively. A year later,

there was an increase in crystal formation and a decrease in vision (left eye now 20/40), and the crystals were extending outside of the interface and into the deeper stroma. The patient underwent operative lifting of the flap and scraping of crystals twice, and her vision reverted to 20/20, likely due to the operative decrease in crystal burden. Testing of the surgical specimens revealed no growth or visible organisms, nor any indication of the underlying pathology. Despite numerous ophthalmologists and multiple investigations, she remained without a clear diagnosis.

Over the next year, the patient's vision remained relatively stable, with the occasional glare and haze, and management remained expectant. The crystals were increasing (especially on the left), and had clearly extended into the adjacent unoperated cornea, leading to speculation that the deposition was likely unrelated to the surgery itself. At this point, crystal deposition secondary to some form of systemic disease was suspected.

Subsequently, after an exhaustive work-up, a serum protein electrophoresis with immunofixation revealed an IgG kappa monoclonal gammopathy. Bone marrow aspirate and biopsy (including a sternal marrow aspirate) was attempted unsatisfactorily. End-organ disease was identified and included an L5 lytic lesion and kappa light chain proteinuria. She was diagnosed with IgG monoclonal gammopathy and kappa light chain proteinuria, and possible myeloma (initially described as "light chain deposition disease").

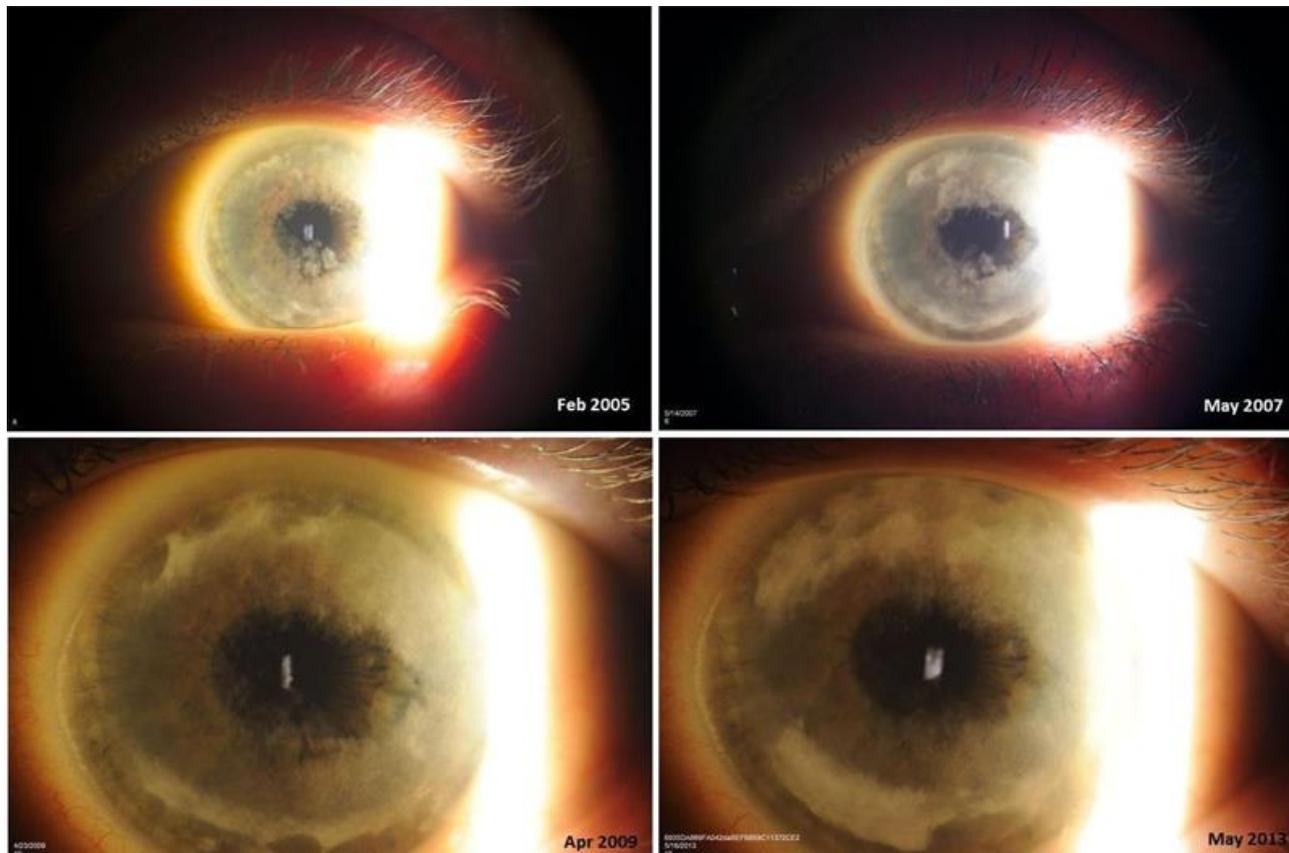
Given the inconclusive bone marrow results and end-organ manifestations (including the LASIK crystals), the decision was made to proceed with a less aggressive treatment for presumed myeloma with melphalan and prednisone for seven cycles. She then went on to receive plasmapheresis for 5 months, with marginal improvement of the corneal deposits. Her disease went into remission and her vision improved to 20/25 in both eyes, with some ongoing peripheral haziness of the left eye.

Six years later, the patient remains in very good partial response, and continues to be managed expectantly. Her unaided vision is 20/20 bilaterally, but there is residual left eye "blurriness" with only a small central clear

aperture surrounded by the deposits ([Figure 1](#)). Unfortunately, the crystals have become worse

over time and are encroaching further on to the visual axis zone.

Figure 1: Worsening of crystalline deposits in the LASIK interface in a 50-year-old woman [2005-2013]



CASE 2

A 53-year-old woman and retired hospital unit clerk initially presented with eight months of progressively “foggy” vision. Apart from hypertension and panic disorder, she had no previous medical history or ocular abnormalities. Initial ophthalmic assessment revealed a visual acuity of 20/30 (right eye) and 20/25 (left eye). Slit-lamp examination identified numerous iridescent flecks/crystals in the corneal subepithelium and anterior stroma, mostly distributed through the interpalpebral fissure area in both eyes and extending over 7 mm vertically ([Figure 2](#)). Cystinosis was suspected, but biopsy was consistent only with nonspecific crystal deposition disease and negative for cystine crystals and amyloid.

Further work-up revealed a smoldering

myeloma with IgG kappa monoclonal protein on protein electrophoresis, IgG level of 36.1, and 30-50% clonal plasma cell involvement on bone marrow biopsy. The patient was initially managed conservatively with serial quantitative immunoglobulin levels, serum and urine electrophoreses, and ophthalmic assessments as she had no evidence of myeloma related end organ damage (i.e normal calcium, renal function, hemoglobin, and skeletal survey).

Approximately three years later, she developed a mild anemia, increasing IgG levels, and progressively blurry and foggy vision, but still had a normal skeletal survey, serum calcium, and creatinine. Slit-lamp exam revealed densely packed crystalline deposition in both eyes, now extending beyond the previously noted interpalpebral fissure. A decision was made to treat with bortezomib and dexamethasone for

four cycles followed by high dose melphalan and autologous stem-cell transplantation. The monoclonal protein level reduced throughout her treatments and her vision began to improve significantly after her third cycle. Her inpatient course following autologous stem cell transplantation was complicated by febrile

neutropenia and neutropenic enterocolitis. Subsequently, the patient received a course of thalidomide maintenance for 1 year post transplant, at which point she attained a complete response (CR) with no detectable monoclonal protein by protein electrophoresis or immunofixation.

Figure 2: Bilateral corneal crystal (immunoglobulin) deposition associated with multiple myeloma in a 53-year-old woman

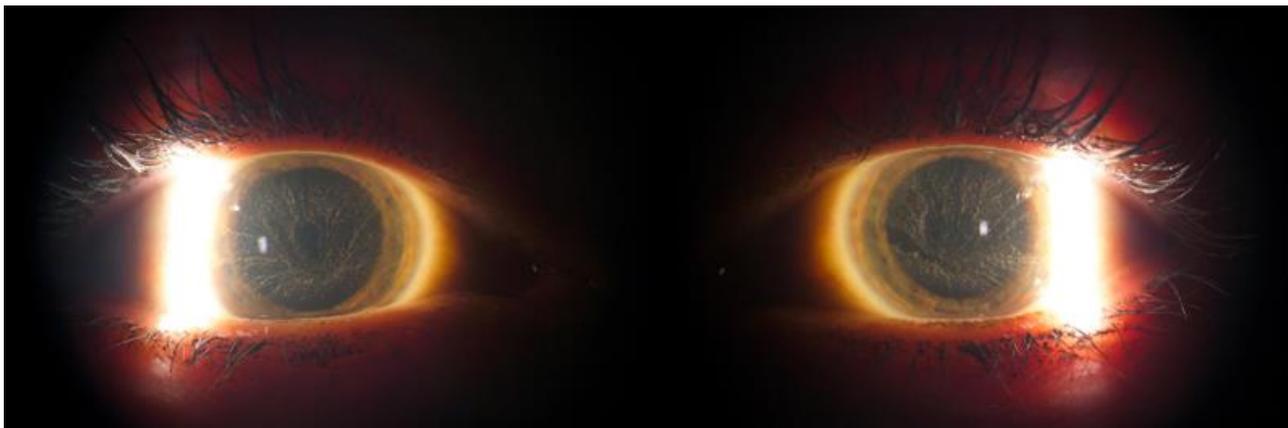
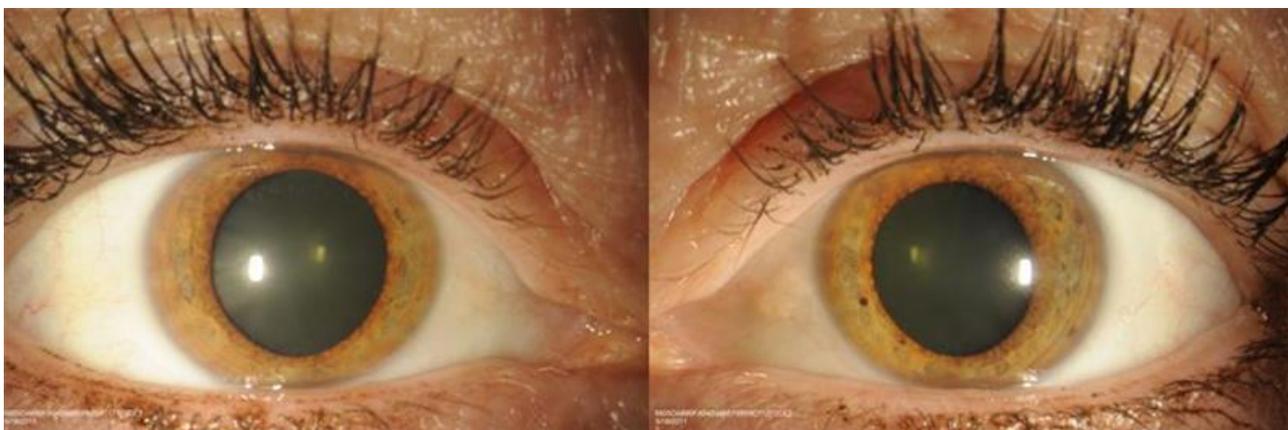


Figure 3: Resolution of bilateral corneal crystals in Figure 2



On repeat ophthalmic assessment a year later, she was noted to have 20/20 vision in both eyes with no visible corneal crystals ([Figure 3](#)) – implicating that these deposits were an ocular manifestation of multiple myeloma. Currently, four years after treatment, this patient's myeloma remains in CR and is followed expectantly.

DISCUSSION

Ocular involvement in multiple myeloma has previously been described in the literature,

but treatments and responses have been varied ([Table 1](#)). Most cases involve corneal crystalline deposits and vision changes as the initial manifestation of myeloma, thereby leading to hematologic evaluation, diagnosis, and treatment with both surgery and/or chemotherapy. Disease remission and some regression (or stability) of crystals with improved vision have been documented. There have been no previous cases, however, of crystal deposition in the LASIK interface.

Table 1: Summary of case reports of corneal involvement in multiple myeloma.

Study	Patient (Age/Sex)	Manifestation	Treatment	Clinical Course
Beebe <i>et al.</i> (1989) [11]	52 M	Bilateral subepithelial corneal deposits and anterior stromal haze (amorphous / non-crystalline)	Penetrating keratoplasty, chemotherapy (melphalan, prednisone)	Recurrence in graft, poor response to chemotherapy, profound loss of vision
Chou <i>et al.</i> (2011) [7]	51 M	Bilateral diffuse corneal subepithelial and anterior stromal crystals	Conservative (topical steroids), then chemotherapy (regimen not documented)	Underlying MGUS converted to myeloma, crystals stable
Font <i>et al.</i> (2006) [10]	52 M	Bilateral immunoglobulin deposits in corneal predescemetic region	Penetrating keratoplasty, chemotherapy (regimen not documented)	Regained vision, some recurrence in the right eye, systemically well
Hsueh <i>et al.</i> (2004) [8]	62 F	Bilateral crystalline deposits in corneal stroma	Chemotherapy (melphalan, prednisone)	No vision loss, stable crystals
Huang <i>et al.</i> (2012) [16]	45 F	Bilateral peripheral corneal crystalline deposits	Chemotherapy (thalidomide)	Vision stable, crystals decreasing
Kleta <i>et al.</i> (2004) [6]	49 F	Bilateral corneal epithelial and stromal crystals	Not documented	Unknown
Kwartz <i>et al.</i> (1993) [5]	65 M	Bilateral full thickness corneal crystals + proptosis due to orbital involvement	Orbital radiation, chemotherapy (vincristine, doxorubicin, dexamethasone)	Rapid initial response, relapse 6 months later
Nakatsukasa <i>et al.</i> (2008) [3]	67 F	Diffuse gray-white deposits in corneal epithelium and anterior stroma	Chemotherapy (melphalan, prednisone) and removal of corneal epithelium + cataract	Improved vision and clear cornea
Perry <i>et al.</i> (1993) [17]	52 M	Bilateral corneal intraepithelial crystals	Chemotherapy (regimen not documented)	Remission, crystals mostly resolved

The pathophysiology of crystal deposition is still largely unclear, but is thought to be related to increased IgG levels (less commonly, IgA) in the tears, aqueous, and limbal vessels of the eye. This then manifests as crystalline deposits usually in the corneal epithelium or stroma, possibly due to spontaneous crystallization of the protein [2, 7, 8, 9].

According to previous case reports, control

of the systemic condition usually improves ocular symptoms, but the crystals usually demonstrate only partial resolution or stability with chemotherapy regimens. Definitive management is surgical (superficial keratectomy and penetrating or lamellar keratoplasty), which is successful only in conjunction with systemic disease control, though this still does not preclude a recurrence of immunoglobulin deposition in the graft [10, 11]. Furthermore, surgery may produce

sub-optimal visual results, and complications such as glaucoma and cataracts. Other conservative measures include sunshades, antireflective coatings, and artificial tears. The use of topical steroids remains controversial [7].

The above cases describe ocular immunoglobulin deposition as an initial manifestation that led to a diagnosis of multiple myeloma; the crystals then had a significant clinical response to treatment of the underlying disease with chemotherapy. In the first case, crystal deposition occurred in the LASIK interface, the first such patient in the literature. This appears to be a rather rare ocular manifestation of multiple myeloma, as well as a unique place for crystal deposition. As in the second case, chemotherapy led to a clinical improvement, but this case also provides unique options for future treatment. Though the patient's vision has remained stable, if the visual axis is once again compromised, we may consider simply amputating the LASIK flaps through a lamellar keratoplasty to reduce crystal load. However, the patient may eventually require deep anterior lamellar keratoplasty or even a penetrating graft. This same case has been reported previously in the ophthalmologic literature by Nichols et al. in 2008, but was characterized as "light chain deposition disease" with an emphasis on refractive surgery and causes of crystal keratopathy as opposed to the systemic nature of the underlying myeloma (which we are now aware of) [12]. Moreover, regular follow-up over the subsequent five years confirms now that the crystals are still worsening, which addresses the epidemiology of this finding and demonstrates the clinical significance of both the ocular deposition and the underlying disease. Here, we present this case in combination with another case of crystal deposition as examples of an initial ocular manifestation that led to a diagnosis of multiple myeloma without other obvious diagnostic features.

In the second case, bortezomib, a proteasome inhibitor, was seemingly responsible for a rapid and complete resolution of crystals, but the underlying mechanism remains unclear. To our knowledge, this is the first case to demonstrate such a significant clinical and ocular response without surgery. Previous literature describes only partial resolution of corneal crystals

(decrease in size/number) with older chemotherapeutic regimens such as vincristine and daunorubicin [11].

LASIK is the most frequent type of refractive corneal surgery and is considered among the most successful elective procedures, with over 16 million procedures performed worldwide and 95% of patients reporting satisfaction with the outcome. The procedure involves flap formation (interface) in the upper layers of the cornea, followed by laser treatment of the refractive error. Differentiating between various interface complications is important for rapid diagnosis and appropriate treatment to ensure minimal visual sequelae [13, 14]. However, there is a dearth of literature on abnormal LASIK interface deposition, particularly immunoglobulin-related. In our case, we hypothesize that the interface may have simply acted as a conduit and allowed an easier route for the deposition of crystals early in the disease process. Further research will need to be undertaken to elucidate the actual mechanism.

The diagnosis of multiple myeloma requires at least 10% clonal plasma cells in the bone marrow, serum or urine monoclonal protein, and myeloma related organ dysfunction (at least 1 of CRAB criteria: hypercalcemia [serum Ca > 2.88 mmol/L], renal insufficiency [serum Cr > 177 μ mol/L], anemia [Hb < 100 g/L or > 20 g/L below lower limit of normal], or bone disease [lytic lesions, osteopenia, pathologic fractures]) [15]. Typically, in the absence of the CRAB criteria, ocular disease alone is not an indication to initiate systemic therapy. However, this convention may not be appropriate, given our patients' rapid response to chemotherapy and the significant patient burden associated with decreased vision (loss of function, quality of life, employment, independence, etc.). The push to treat may be further supported by newer agents such as bortezomib, which may produce crystal resolution. Further research is certainly needed, but it appears that with further understanding of the pathophysiology and burden of crystal deposition, chemotherapy may become indicated for ocular disease in multiple myeloma.

Lastly, ocular/corneal findings may present months or years before systemic manifestations, and may cause significant morbidity [11]. As such, we suggest that patients diagnosed with multiple

myeloma are at least asked about visual changes and/or screened by an optometrist if possible.

CONCLUSION

We describe here two cases of ocular crystal deposition as the initial finding that led to a diagnosis of multiple myeloma. The cases are unique, as they demonstrate crystal deposition in a previously-normal LASIK interface, and rapid and complete resolution of crystals with chemotherapeutic treatment of the underlying myeloma; no other such patients have previously been reported in the literature. Crystal deposition in myeloma is an uncommon but significant occurrence that brings into question the indications to initiate therapy for the underlying disease in light of end-organ damage that is not CRAB-related (i.e. ocular manifestations such as keratopathy). It may be prudent to screen for ocular disease in patients that are diagnosed with multiple myeloma, but further research is certainly warranted to evaluate whether systemic treatment is actually of clinical benefit in this situation, particularly for patients who suffer significant morbidity and burden due to decreased vision.

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CONSENT

Written informed consent was obtained from these patients for publication of these case reports and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

LIST OF ABBREVIATIONS

LASIK – Laser-Assisted in situ Keratomileusis

MGUS – Monoclonal gammopathy of unknown significance

CR – complete response

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

AUTHORS' CONTRIBUTIONS

VB was responsible for acquiring the data and drafting the manuscript; CCH, LM, RM, and BDN were involved with the clinical management of the patients and with revising and editing the manuscript. All authors read and approved the final manuscript.

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