Crystalline keratopathy in monoclonal gammopathy of undetermined significance

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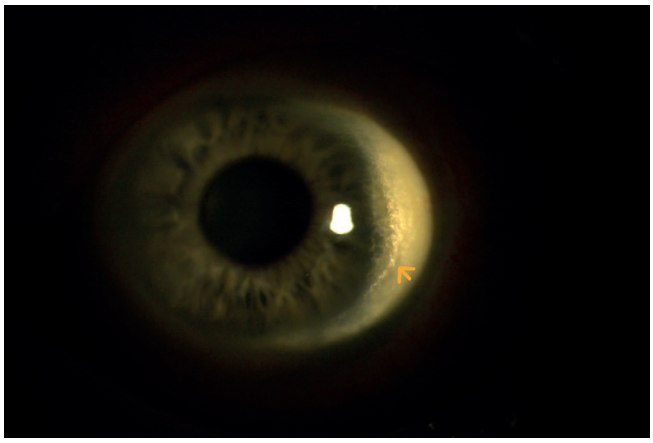

Figure 1: A slit-lamp image showing crystalline deposits at the peripheries of the cornea.

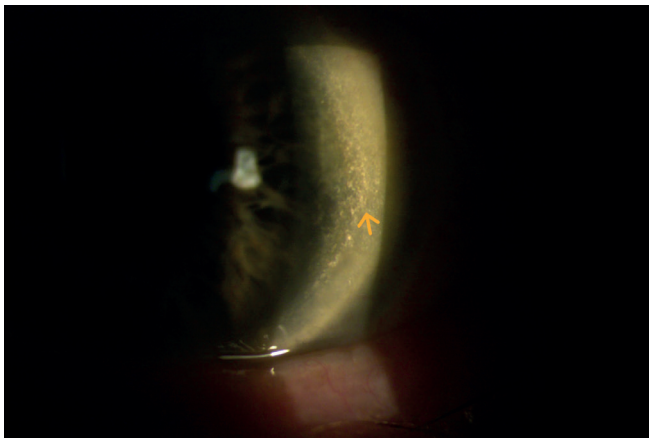

Figure 2: A slit-lamp image showing a magnified image of crystalline deposits.

Monoclonal gammopathies encompass a group of plasma cell disorders characterised by the excessive production of abnormal monoclonal immunoglobulins in the bloodstream [1]. This category includes multiple myeloma, monoclonal gammopathy of undetermined significance (MGUS), amyloidosis and other lymphoproliferative disorders.

Monoclonal gammopathy of undetermined significance is a common preneoplastic haematological condition with a conversion rate of 1% per year to multiple myeloma or other systemic gammopathies [2]. Its prevalence increases with age, from 1.7% in patients below 60 years to 6.6% in individuals aged 80 years and above [3]. Typically, MGUS is diagnosed incidentally, with patients generally asymptomatic at the time of diagnosis.

The three primary diagnostic criteria for MGUS are as follows: (a) a serum paraprotein level below 30g/L; (b) less than 10% of clonal plasma cells in the bone marrow; and (c) the absence of end-organ damage associated with multiple myeloma, such as hypercalcaemia, renal impairment, anaemia, and lytic bone lesions [1]. The term 'paraprotein' is used interchangeably with non-functional monoclonal immunoglobulin as both are produced by abnormal clonal plasma cells.

Paraproteinemic keratopathy (PPK) is an ocular manifestation of monoclonal gammopathies where paraprotein deposits are found within the cornea. The presentation of PPK can be highly variable with different shapes, patterns and locations within the cornea [4]. The crystalline deposits on the cornea may resemble various conditions such as infections, corneal dystrophies and systemic conditions such as cystinosis [5]. Additionally, crystalline deposits may be the first presentation of an underlying lymphoproliferative disorder. It is crucial to conduct a comprehensive assessment, including a thorough history, slit-lamp examination, detailed systemic workup and appropriate referral to address the potentially serious haematological condition of MGUS.

Case presentation

A 71-year-old female with a medical history of irritable bowel disease, non-insulin-dependent diabetes mellitus, osteoarthritis, and gastric angiodysplasia presented to the eye clinic with recurrent episodes of bilateral anterior uveitis. Over the past four years, she has experienced up to eight episodes of acute anterior uveitis, all of which were successfully managed with a tapering regimen of topical steroids. Previous investigations for bilateral acute anterior uveitis yielded normal results, leading to a diagnosis of 'idiopathic' acute anterior uveitis.

However, despite previously responding to a tapering course of steroids alone, this episode presented as more severe and resistant to topical steroids. Her vision deteriorated to 0.46 logMAR in the right eye and counting fingers in the left eye, despite no evidence of posterior segment inflammation and no pathology detected on an ultrasound scan. Both corneas appeared cloudy, with a central corneal thickness of 590µm in the right eye and 597µm in the left eye. Additionally, an evident ring of crystalline keratopathy was observed in both eyes, which was previously perceived as the corneal arcus (Figures 1, 2). Due to the thickened corneas, her intraocular pressures were 34mmHg in the right eye and 28mmHg in the left eye. Subsequently, she was referred to the glaucoma specialist team for further management of the newly raised intraocular pressures. She was treated for anterior uveitis with a tapering course of topical steroid (prednisolone 1%) over six weeks, cyclopentolate 1% twice a day for three weeks, and dorzolamide 2% twice a day for raised intraocular pressures.

A comprehensive systemic workup, including serological tests (toxoplasmosis, tuberculosis, HIV and hepatitis), immunological studies (complement levels, lupus screening, ANCA, HLA-B27, ACE, rheumatoid factors, and serum and urine protein electrophoresis) and blood tests (renal function test, full blood count and calcium levels) were conducted to rule out other causes of bilateral and

recurrent anterior uveitis. Further radiological tests, such as chest X-ray and computerised tomography (CT) skeletal survey were performed to exclude sarcoidosis and multiple myeloma.

Systemic blood investigations revealed an increased IgA Kappa level of 15g/L with a distinct band in the gamma region. This finding was correlated with normal renal function, haemoglobin and the calcium level. The patient was promptly referred to the haematology team for further investigations and management. Based on the low serum paraprotein levels, normal blood results and the absence of lytic lesions on the CT skeletal survey, a diagnosis of MGUS was made. Systemically, the patient continues to be monitored by the haematology team, as 1% of patients with MGUS may develop multiple myeloma [2]. From the ocular perspective, a diagnosis of crystalline keratopathy associated with MGUS was established. The patient continues to be monitored by the corneal team for the progression of corneal deposits, intraocular pressures, and any recurrence of inflammation.

Discussion

Monoclonal gammopathy of undetermined significance is a preneoplastic disorder of plasma cells, characterised by a low level of myeloma protein and the absence of myeloma-related end-organ damage [6]. Ophthalmic involvement was previously reported as a rare consequence of MGUS [7]. Borne, et al. investigated 100 patients with systemic gammopathies and they found that only one patient had crystalline deposits on their cornea, highlighting the significance of this rare association [8]. Another study estimated an incidence of less than 1% in patients with systemic gammopathies such as multiple myeloma, macroglobulinemia, amyloidosis and MGUS-related crystalline keratopathy [7]. However, Al Hariri, et al. reported an exceptionally high prevalence of PPK (29%) in patients (n=45) with systemic gammopathies when they utilised in vivo confocal laser scanning microscopy to visualise the crystalline deposits [9].

The terms 'paraproteinemic keratopathy' and 'crystalline keratopathy' have been used interchangeably. Crystalline keratopathy is generally employed as a broader term to describe the crystalline nature of corneal deposits, typically occurring in the epithelial and stromal layers. This condition may result from various factors such as infections, medication-induced effects, corneal dystrophy and systemic conditions including cystinosis and lymphoproliferative disorders [10]. Paraproteinemic keratopathy specifically relates to lymphoproliferative disorders that generate high levels of serum paraproteins, leading to their deposition within different layers of the cornea [10]. The appearance of crystalline keratopathy varies in morphology and distribution depending on the condition. For instance, infectious crystalline keratopathy forms distinctive fine branch-like deposits within the anterior stroma of the cornea, whereas polychromatic cystine crystals are commonly found in the cornea, conjunctiva or trabecular meshwork in patients with cystinosis [11,12].

The presentation of PPK varies significantly. Patients may present asymptomatically or with reduced vision, depending on the corneal thickness and the extent of crystal deposits [5]. Some studies have found an association between the level of serum paraprotein and the extent of crystal deposits [5,13]. In this study, the patient was found to have elevated IgA kappa paraproteins, leading to a diagnosis of MGUS. This diagnosis helped to explain the extent of the corneal deposits and corneal thickness observed. Additionally, she experienced recurrent acute anterior uveitis, which is a rare finding in the literature. Only one study conducted by Ormerod, et al. reported a patient with recurrent uveitis and a background of IgG Kappa monoclonal gammopathy in 1988 [13]. Paraproteinemic keratopathy is typically discovered incidentally or misdiagnosed with conditions such as arcus senilis, infectious crystalline keratopathy, corneal dystrophy or ocular cystinosis [4]. The limited clinical signs and highly variable appearance of deposits make the diagnosis of PPK challenging for clinicians.

A recent literature review identified 17 distinct patterns of paraproteinemic deposits in patients with MGUS [5]. These deposits can range in appearance from colourless to polychromatic opacities, with various layouts in different layers of the cornea. The most common presentation is iridescent crystalline deposits throughout the stroma, although previous literature has also described granular deposits and peripheral corneal rings [14]. Additionally, some studies have noted the progression of peripheral deposits towards the centre over time, correlating with the advancement of systemic disease [5,15].

Multiple research projects have hypothesised that immunoglobulins are transported to the cornea via several pathways [16,17]. These pathways may involve immunoglobulins diffusing from the aqueous fluid in the anterior chamber through the tear film or the perilimbal vasculatures. Balderman and Lichtman found that IgG-kappa light chains are the most prevalent isotype to form corneal crystals [4,7]. However, the exact mechanism behind why certain immunoglobulin molecules have a higher tendency to crystallise and deposit in specific locations remains unclear, which complicates the treatment of MGUS-related PPK [4].

Current practice suggests treating the underlying systemic condition, with no specific ocular therapy is recommended for asymptomatic patients [6]. Some studies have proposed that adequate control of MGUS can improve ocular symptoms in patients, while others have shown no improvement in ocular symptoms despite treating the systemic disease [4,18]. Penetrating keratoplasty has been offered for patients with severe vision loss and irreversible corneal involvement. However, recurrence of corneal deposits has been reported within a year of corneal transplant, depending on the severity of MGUS [18]. It has been recommended that penetrating keratoplasty be considered for patients with stable systemic conditions to reduce the risk of recurrence [10]. Overall, the most effective treatment for PPK involves treating the underlying systemic gammopathies, thereby reducing paraprotein depositions within ocular tissues.

Conclusion

Prompt identification of crystalline keratopathy is crucial, as it may indicate life-threatening systemic conditions such as cystinosis and multiple myeloma that warrant urgent systemic work-up. Patients diagnosed with MGUS should undergo regular follow-up assessments, including monitoring serum paraprotein concentrations and whole-body CT scans to track disease progression. This study highlights the importance of recognising a potentially life-threatening systemic condition manifesting as an ocular condition. Close collaboration among various specialties is essential to develop an appropriate treatment plan for the patient.

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Declaration of competing interests:
None declared.