Atypical Gout-Associated Band Keratopathy

Sara Moses, OD; Lisa Schifanella, OD, MS; Ellen Prewitt, OD, FAAO

Abstract
Band keratopathy is a chronic condition that involves the deposition of crystals in the anterior layers of the cornea. There are many etiologies, both ocular and systemic, that can result in the formation of these crystals. These conditions include chronic ocular inflammation, hypercalcemia, and gout. Herein we report a case of band keratopathy due to gout and discuss the possible systemic etiologies and management of band keratopathy.

Case Report
A 55-year-old retired African American male presented with dry eye complaints and mild blurry vision. He reported that comfort was improved with the use of artificial tears, but that his vision remained blurry. Over the prior two years he had been followed for a slowly progressing peripheral band keratopathy OU. His medical history was significant for type 2 diabetes, hypertension, sleep apnea, alcohol dependence, and chronic pain.

Best corrected visual acuities measured 20/40² OD and 20/30- OS and showed no improvement with pinhole testing. Extraocular muscle and pupil functions were normal in each eye. Intraocular pressures were 16 mmHg OD and 14 mmHg OS.

Slit lamp examination revealed normal lids and adnexa. The band keratopathy had progressed across the inferior cornea OU but was not yet within the visual axis of either eye. Dilated fundus examination revealed significant cataracts and an unremarkable posterior segment in each eye.

Due to the progressive nature of the presumed calcific band keratopathy, labs were ordered including complete blood count (CBC), basic metabolic panel (Chem-8), angiotensin-converting enzyme (ACE), lysozyme and uric acid. A chest x-ray was also ordered to rule out sarcoidosis. The results, summarized in Table 1, revealed no significant abnormalities, particularly no elevation of uric acid levels. Consequently, the band keratopathy was presumed idiopathic and treated with artificial tears three times per day in each eye. The patient was also sent for cataract surgery in order to improve visual function.

Initial best corrected visual acuities following cataract surgery were 20/20 in each eye. However, over the course of a year, vision was reduced to the 20/25 level OD and 20/40 level OS, with no improvement by pinhole testing. Slit lamp examination revealed progression of band keratopathy in each eye and was now within the visual axis of the left eye (Figures 1&2).

Due to the advancement of band keratopathy, blood work was repeated for magnesium, phosphorous, and uric acid levels. Results of lab testing revealed elevated uric acid levels (Table 2), which suggested a possible diagnosis of gout. The patient was referred to his primary care physician who confirmed the diagnosis and began treatment with 100 mg of allopurinol daily. Subsequent eye examinations have revealed no progression of band keratopathy in either eye since initiation of treatment for gout. The patient was referred to a corneal specialist for evaluation due to the reduction in visual acuity, and the determination was made to continue with artificial tear therapy and monitoring for the time being.

<p>| Table 1. |</p>
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<thead>
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<th>Lab Test</th>
<th>Result</th>
<th>Reference Range</th>
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<tr>
<td>BUN</td>
<td>11</td>
<td>7-18 mg/dL</td>
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<tr>
<td>CO2</td>
<td>31</td>
<td>18.4-27.4 mEq/L</td>
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<tr>
<td>Creatinine</td>
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<td>Potassium</td>
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<td>Sodium</td>
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<td>136-146 mmol/L</td>
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<tr>
<td>Uric acid</td>
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<td>ACE</td>
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<tr>
<td>Calcium</td>
<td>9.5</td>
<td>8.9-10.4 mg/dL</td>
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</tbody>
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The authors have no financial or proprietary interest in any material or method mentioned in this article. This article has been peer reviewed.
**Discussion**

Band keratopathy is an opacification of the cornea due to deposition of crystals in Bowman’s layer. Typically, the band begins in the corneal periphery, slowly progressing centrally and toward the visual axis. Eventually, the deposits coalesce in a horizontal band-like plaque from limbus to limbus. The deposits are most frequently composed of calcium, although other particles, such as cystine or uric acid, can also have a similar presentation.

The appearance of the plaques can range from flat and visually insignificant gray-white opacities to bulky flakes with devastating visual consequences. The plaques characteristically have a “cheesy” appearance with clear holes in the opacified band which aids in the differentiation between band keratopathy and other corneal dystrophies or opacities. These holes occur where corneal nerves pass through Bowman’s membrane and inhibit the deposition of crystals.

Visual acuity and ocular discomfort depend on the severity and location of the disease. As the deposits collect within the cornea, the epithelium can become rough and irregular. If the corneal epithelium degrades, recurrent corneal erosions may occur.

The development of the plaques in band keratopathy is thought to be a result of a chemical imbalance between the cornea and the tear film. Precipitation of the plaques into the cornea occur with an increase in calcium levels in the tear film or when the pH of the ocular surface becomes basic; occasionally both occur simultaneously. Broadly speaking, the levels of tear film calcium increase with elevated serum calcium levels as well as with significant evaporation of the tears. These conditions arise in keratitis sicca and a variety of systemic conditions that produce hypercalcemia such as end-stage renal disease and hyperparathyroidism. Ocular surface pH has been shown to increase with chronic ocular inflammation, such as in uveitis and with corneal endothelial compromise.

**Ocular Associations**

A strong association exists between band keratopathy and chronic ocular inflammation from sarcoidosis, Vogt Koyanagi Harada syndrome, and HLA B-27-related disorders such as juvenile idiopathic arthritis and ankylosing spondylitis. In the case of sarcoidosis, the link is theorized to be related to elevated serum calcium and vitamin D levels. Although ocular involvement with sarcoidosis commonly presents as uveitis, iris granulomas, or periphlebitis, band keratopathy occurs in 4-5% of ocular sarcoidosis cases. For patients with HLA-B27 associated uveitis, Verhagen et.al showed that band keratopathy tends to develop in eyes with reduced vision, and that the band keratopathy itself is rarely the cause of acuity loss.

Ocular surgeries and injections are also known to be associated with band keratopathy. The long-term presence of silicone oil in the eye after retinal detachment repair has been shown to increase the risk of band keratopathy. This is especially true when the silicone oil enters the anterior chamber and contacts the corneal endothelium. Doostdar et.al proposed that because silicone is known to promote calcium absorption in bones, it

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**Table 2.**

<table>
<thead>
<tr>
<th>Lab Test</th>
<th>Result</th>
<th>Reference Range</th>
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<tbody>
<tr>
<td>Magnesium</td>
<td>2.3</td>
<td>1.6-3 mg/dL</td>
</tr>
<tr>
<td>Phosphorus</td>
<td>2.9</td>
<td>2.3-4.3 mg/dL</td>
</tr>
<tr>
<td>Uric acid</td>
<td>8.7</td>
<td>2.6-7.2 mg/dL</td>
</tr>
</tbody>
</table>

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**Figure 1.**

**Figure 2.**
where the alkaline pH is more favorable to deposition. Stromata allow precipitation in the anterior layers of the cornea. The elevated concentrations of phosphate and calcium in the corneal endothelium resumes extracting water from the cornea, allowing excess phosphate and calcium to diffuse from the tissue. Endothelial dysfunction during periods of inflammation may result from the use of tissue plasminogen activator (tPA) in post cataract inflammation; possibly due to the phosphate buffer in the tPA preparation or as a result of endothelial compromise. Case reports describing development of band keratopathy following use of tPA in post cataract surgery have been reported.

There has been one reported case of band keratopathy associated with iridocorneal endothelial syndrome (ICE). In ICE syndrome, the corneal endothelial cells are replaced by migrating epithelial-like cells resulting in endothelial dysfunction, corneal edema, and stromal changes. In 2018 Zygoura et al published a case of recurrent band keratopathy associated with ICE. The case demonstrated recurrent inflammation and hypercalcemia due to a systemic condition. The list of possible disease entities associated with band keratopathy is unknown. When there is no evidence of an ocular inflammatory condition present in the setting of band keratopathy, it becomes necessary to assess for systemic cause. Lab testing is extremely useful in detecting the systemic conditions associated with band keratopathy. A typical panel of labs for band keratopathy will include CBC, Chem-8, uric acid, ACE, and lysozyme. The Chem-8 will provide information relating to kidney function and electrolyte levels, including serum calcium levels. The CBC, ACE, and lysozyme assist in assessing for chronic systemic inflammation. ACE and lysozyme, particularly when combined with a chest x-ray, are useful in detecting sarcoidosis, while uric acid evaluates for gout. Hypercalcemia is the primary etiology for band keratopathy due to a systemic condition. The list of possible disease entities that can result in hypercalcemia is extensive and includes end stage renal disease, hyperparathyroidism, sarcoidosis, milk-alkali syndrome, Paget disease of bone, disoid lupus, erythematous, malignancy, tuberous sclerosis, and excessive vitamin D. As serum calcium levels rise, the concentration of calcium in the tears also elevates. Under alkaline or evaporative conditions, the calcium can precipitate and deposit within the anterior layers of the cornea resulting in the development of band keratopathy.

The association between end stage renal disease (ESRD) and band keratopathy has long been discussed. As kidney function deteriorates, it is common to also develop renal hyperparathyroidism resulting in elevated serum calcium and phosphate levels. In 2016, Weng et al investigated the risk of band keratopathy development in ESRD. Compared to controls, there was shown to be a 12.21 times higher risk of developing band keratopathy in ESRD patients. It has even been suggested that band keratopathy may be one of the most frequent ocular complications relating to ESRD. Although most patients with ESRD will be aware of their kidney failure, it is important to assess kidney function when the etiology of band keratopathy is unknown.

Systemic medications and supplements must also be considered when determining the etiology of band keratopathy. Medications such as lithium and denosumab have been associated with elevated serum calcium and the development of band keratopathy. Lithium use has been associated with hypercalcemia and parathyroid gland enlargement. Denosumab is commonly used for postmenopausal osteoporosis as it inhibits RANKL, a nuclear factor kappa-B ligand that regulates osteoclastic bone resorption. In 2019 Nguyen et.al reported a case of band keratopathy development after initiation of denosumab therapy. It was suggested that the denosumab therapy caused an imbalance in calcium and phosphate levels resulting in the corneal calcific deposits. In addition, Calcium supplements are often emphasized as therapy for treatment and prevention of osteoporosis. However, elevated calcium may also promote a local increase of calcium and subsequent deposition resulting in band keratopathy. There are also case reports describing development of band keratopathy after the use of tissue plasminogen activator (tPA) in post cataract inflammation; possibly due to the phosphate buffer in the tPA preparation or as a result of endothelial compromise. Endothelial dysfunction during periods of inflammation may allow excess phosphate and calcium to diffuse from the aqueous into the stroma. When conditions normalize and the endothelium resumes extracting water from the cornea, the elevated concentrations of phosphate and calcium in the stroma allow precipitation in the anterior layers of the cornea where the alkaline pH is more favorable to deposition.

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intake combined with absorbable alkali can result in a triad of hypercalcemia, acute kidney injury, and metabolic alkalosis known as milk-alkali syndrome.\(^3\) Band keratopathy can also present in this condition. Milk-alkali syndrome was initially common due to over-treatment of peptic ulcer disease but has recently increased due to the emphasis on calcium in treatment for osteoporosis.

Band keratopathy is also a frequent complication of cystinosis, a rare autosomal recessive storage disorder. This disease results in cystine crystals accumulating in cells throughout the body due to a defect in a membrane protein carrier.\(^3\) The systemic effects include endocrine dysfunction, neurologic deterioration, myopathy, and blindness. The condition usually results in the need for a kidney transplant. The ocular complications leading to vision loss include retinopathy, glaucoma and corneal disease. As the crystals deposit throughout the body, they can also deposit within the cornea, trabecular meshwork, iris, and retina. Corneal deposits typically present within the first year of life and do not always present as band keratopathy.

Familial band keratopathy is a very rare cause of band keratopathy and there have only been a few cases reported. A complete systemic and ocular workup must be completed before determining the cause to be familial. Although no specific gene has been identified for familial band keratopathy, mutations in the human NBC1 gene have been associated with renal tubular acidosis, band keratopathy, and cataracts.\(^3\) Unfortunately, cases of familial band keratopathy appear to have higher rates of recurrence after treatment as the underlying condition cannot be resolved.

**Gout**

One of the less common etiologies of band keratopathy is gout, also known as monosodium urate crystal deposition disease. Uric acid is a product of purine metabolism that is primarily excreted through the kidneys. Although its exact biological function is unknown, it has shown some antioxidant activity and may be useful as an indicator of cell death.\(^1\) Over the course of this disease, uric acid levels in the blood stream rise and begin to deposit in various locations throughout the body. These uric acid depositions, called tophi, have a predilection for joints, particularly in the lower extremities, and result in inflammatory outbreaks. Although many patients with elevated uric acid may remain asymptomatic for years, the overall course tends to be one of exacerbations and remissions.

The classic presentation for a patient with gout is a 30 to 60-year-old male with obesity, hypertension, and alcohol dependence. There is a 3% prevalence of gout among American adults. The primary risk factors for gout include obesity, cardiovascular disease, diabetes, chronic kidney disease, alcohol consumption, and age. Systemic manifestations include gout flare of a single joint, polyarticular gout flare of multiple joints, tendons, or bursas, and tophaceous gout in soft tissue. Depending on the location and size of the tophi, the discomfort can range from mild irritation to debilitating pain.

The ocular manifestations are dependent on the location of the tophi within the ocular structures. These uric acid deposits have been found in the eyelids, bulbar conjunctiva, cornea, trabecular meshwork, and even the retina.\(^3\) The resulting ocular conditions can include retinal vein occlusions, iridocyclitis, ocular hypertension, dry eye disease, and band keratopathy.\(^1,10,12\) Interestingly, band keratopathy resulting from gout is unique in that the deposits are made of uric acid crystals instead of calcium crystals.

The initial management of gout is focused on risk reduction including reducing consumption of alcohol and sugar, weight loss, and managing comorbidities. When gout flares inevitably arise, they are managed with systemic steroids or NSAIDs to control inflammation. These can be taken orally or injected into the specific gouty flare. When these two management strategies are insufficient or when the disease is causing damage to organs, reduction of systemic uric acid levels is attempted. Typically, patients with this level of gout are given medications such as allopurinol or losartan which promote the excretion of uric acid. As urate levels fall, the tophi depositions throughout the body are occasionally reabsorbed. Although reabsorption of the tophi can be beneficial, the main goal of therapy is to reduce gout flares and prevent disease progression.

**Management**

Due to the varied presentations of band keratopathy, management is dependent on each individual patient. Corneal topography will give a sense of the extent of focal irregularities and their potential effect on vision. In all cases, the underlying etiology must be investigated and managed in attempt to prevent progression of the ocular and potential systemic disease. Treatment of an underlying condition such as uveitis or hypercalcemia may allow the band keratopathy to resolve without aggressive treatment.\(^6,9\) Patients with mild symptoms of discomfort or decreased vision are treated with artificial tears, gels, and/or ointments. These ocular lubricants promote a healthy tear film and can discourage the deposition of crystals into the cornea. For more moderate to severe cases of band keratopathy with corneal erosions, bandage soft or scleral gas permeable contact lenses can be used to improve both comfort and vision.

Surgical intervention is frequently utilized for visually significant or painful band keratopathy cases. The most common surgical procedure for band keratopathy involves chelation with ethylene-diamine-tetra-acetic acid (EDTA).\(^7\) In order to reach the underlying keratopathy, the epithelium needs to be removed. This removal can be accomplished under topical anesthetic either mechanically, or with alcohol. When used, alcohol allows the epithelium to be elevated, removed, preserved and then replaced after completion of the procedure. In theory, this improves comfort after the procedure. After epithelial debridement, the calcium plaques are exposed and can be removed either mechanically or with EDTA. When EDTA is used, it is applied to the plaques, either in a well, sponge, or
pledget. As a chelator, EDTA binds to the calcium in the lesion resulting in the dissolution of the plaques on the cornea. This often takes several minutes and multiple applications of EDTA. Once the plaques have been removed, the corneal surface is often still irregular. Many surgeons elect to smooth the surface with a diamond burr or phototherapeutic keratotomy (PTK). After the procedure, the resulting corneal abrasion is often treated with a bandage contact lens with or without an amniotic membrane transplant (AMT). Small studies have shown that a combination method involving EDTA, PTK, and AMT can reduce healing time and reduce recurrence.

Conclusion

Determining the underlying etiology of band keratopathy, whether ocular or systemic, is critical in the management of patients presenting with this condition. When ocular etiologies are absent, lab testing can often provide the information we need to give the patient an appropriate referral for systemic diagnosis. As systemic conditions are not static, lab tests may return normal in early stages and should be reordered if progression is noted. For many of these patients with conditions such as sarcoid, end-stage renal disease, and gout, co-management with other medical professionals is essential for comprehensive care.

Bibliography