INTRODUCTION

Climatic droplet keratopathy (CDK) is an acquired degeneration of the cornea. There are many synonyms of this entity including Bietti’s band-shaped nodular dystrophy, Labrador keratopathy, spheroidal degeneration, chronic actinic keratopathy, oil droplet degeneration, elastoid degeneration, keratinoid corneal degeneration, hyalin degeneration and Nama keratopathy. This diversity is related to the variation in the geographic distribution of this entity. Bietti made his initial clinical observation in southwest region of Saudi Arabia. The disease occurs in areas where exposure to ultraviolet (UV) light is excessive.

CLINICAL FINDINGS

Climatic droplet keratopathy consists of a degenerative change that occurs in the cornea and is characterized by the accumulation of aggregates of small golden-yellow globules of various sizes that accumulate in the subepithelial layers of the cornea (Fig. 1). The accumulation of this material occurs near the limbus in early stages and may progress toward the center of the cornea in the horizontal meridian with a band-shaped fashion. The accumulation of the globules primarily involves Bowman’s layer; however, it may occur in the subepithelial area and superficial layers of the stroma once Bowman’s layer is disrupted. The deposits in the epithelium may damage the corneal epithelium and the band-shaped configuration may extend to the center leading to decrease in vision.

Two types of CDK are recognized. Primary CDK is characterized by corneal lesions that occur without other ocular or corneal disorders. Secondary CDK is associated with other ocular disorders, corneal vascularization and scarring. The predisposing factors appear to be similar, and these types of CDK occur more frequently in men than women. It is presumed that exposure to environmental irritants, such as evaporation and microtrauma caused by windblown dust and UV radiation, may predispose to CDK. UV light from solar irradiation is considered as a main causal factor which is common to all geographic locations. Recurrence of CDK may occur in patients undergoing penetrating keratoplasty (PKP). CDK globular aggregates may occur in the corneal graft and usually in the center of the graft (Fig. 2). In Saudi Arabia, the use of the veil by women may have decreased the incidence of CDK.

Keywords: Climatic droplet keratopathy, cornea, corneal degeneration, annexin, UV light, pterygium, amyloid, corneal amyloidosis, Labrador keratopathy, actinic keratopathy
CDK. The preponderance of men probably reflects their outdoor activities and exposure to environmental irritants such as sand, dust, wind and sunlight.

Table 1 demonstrates the clinical differences between primary CDK and secondary CDK. Patients with primary CDK have bilateral disease with aggregates of golden-yellow spherules that appear in a band-shaped configuration. The disease can be variable from mild limbal deposits to extensive subepithelial globules. Patients with primary CDK have the spherules without any vascularization or corneal scarring. On the other hand, secondary CDK is characterized by the presence of corneal scars and vascularization with large and small yellow globules invading the epithelium, basement membrane, Bowman’s layer and superficial stroma. There may be scarring within the adjacent layers of the cornea. The location of the globules depends on the degree of Bowman’s layer disruption and the location of the corneal scars. Scars may be peripheral or central. The deposition is not always in a band-shaped configuration and can occupy the areas of the corneal scar (Figs 3 and 4). The disease may be either unilateral or bilateral, while patients with primary CDK, the lesions are usually symmetrical and bilateral. In cases with unilateral vascularized corneal scars, the CDK occurs in the eye with corneal scars and may not occur in the eye with clear cornea. The conjunctiva may be involved in patients with primary CDK especially nasally.

Lattice lines may be seen in some patients with CDK (Fig. 5). The lattice lines are fine, short, measuring 1–3 mm in length.45 The lattice lines are discrete, appearing clinically exactly like lattice lines in lattice dystrophy of the cornea. Some of the lines are seen deep in the stroma and not only in the superficial layers of the cornea. Fine gray-

![Fig. 2: Recurrence of globules of CDK in the corneal graft](image1)

![Fig. 3: Golden globules of CDK over a vascularized corneal scar. Patient had no CDK in the contralateral clear cornea](image2)

![Fig. 4: Aggregates of elevated yellow globules in a patient with CDK](image3)

Table 1: Differences between primary and secondary CDK

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<tr>
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<th>M &gt; F</th>
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<tr>
<td>Sex</td>
<td>Bilateral</td>
<td>Unilateral</td>
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<tr>
<td>Laterality</td>
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<tr>
<td>Associated corneal disease</td>
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<tr>
<td>Corneal scar</td>
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<td>+</td>
</tr>
<tr>
<td>Corneal vascularization</td>
<td>-</td>
<td>+</td>
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<tr>
<td>Conjunctival involvement</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Pattern</td>
<td>Constant band-shaped (start at limbus)</td>
<td>Variable (start anywhere)</td>
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<tr>
<td>Shape</td>
<td>Spheroidal</td>
<td>Nodular-globular</td>
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<tr>
<td>Family history</td>
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<tr>
<td>Predisposing factors (solar radiation, dust, etc.)</td>
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<tr>
<td>Verhoeff’s elastic stain</td>
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<td>Masson trichrome stain</td>
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ish fleck-like opacities are sometimes dispersed in between the lines and beside the globules of the CDK. The lattice lines can be central or peripheral. The deposition of slight golden-yellow globules is variable from a few settled globules to aggregate or diffuse globules occupying the central portion of the cornea. The lattice lines are usually observed among elderly patients from the age of 60 years and are observed in both primary and secondary CDK. Lattice lines are bilateral in 82% of the cases and usually appear late in life. The lattice lines in CDK appear to be similar to the lines in lattice dystrophy of the cornea, but they occur late in life in the absence of family history and may be superficial and deep in the cornea. The lattice lines are not associated with recurrent painful corneal erosions and do not interfere with vision in patients with primary CDK. The lattice lines are usually non-arborizing and found to lack orientation. The lines are thin, glossy and randomly placed occupying the superficial layers of the cornea and close to the spherules of CDK. Amyloidosis of the cornea has been previously described in association with trachoma, keratoconus, phlyctenulosis and corneal trauma as well as uveitis. The accumulation of amyloid in corneas with CDK may be non-specific. The pathogenesis of the composition of amyloid in the cornea is not clear. Kedar and associates and Cohen and Connors have previously described amyloid degrading factors in the human serum that prevents the deposition of amyloid AA in the tissue. It is believed that a decrease in the serum amyloid degrading activity may precede the accumulation of amyloid in the tissues. The association of CDK with corneal amyloidosis is not well understood. One may postulate that the key factors that lead to the deposition of CDK proteins in the cornea may allow deposition of amyloid proteins in the same tissue. Amyloidosis of the cornea may be the result of connective tissue activity subsequent to multiple microtraumas by sand, dust, UV rays and other factors. The type of amyloid seen in tissue with CDK is associated with protein AP. Environmental factors causing CDK may also play a role in deposition of amyloid in the cornea.

Cataract and pseudoexfoliation are common among patients with CDK. Iris atrophy has also been observed in patients with CDK. Urrets-Zavalia and associates studied the iris in patients with CDK. They had 23 patients with CDK and 13 control individuals living in a semi-desert area of Argentina in the Patagonia region. Nineteen out of 23 patients with CDK had bilateral disease. Patients had corneal hypoesthesia and sectorial depigmentation. Atrophy of the inferior iris was observed in 38% of the eyes with CDK. In patients with severe CDK, there was decrease in corneal sensitivity and atrophy of the exposed iris. In the Patagonia region of Argentina, 86% of the patients with CDK were males and the mean age of patients with CDK was 65 years.

Grading of CDK has been classified into three grades: Grade 1, mild spherule deposition near the limbus; Grade 2, moderate spherule deposition with band-shaped haziness and Grade 3, large yellow aggregates of subepithelial droplets spherules reaching the central part of the cornea. Another grading of the condition depending on the severity is as follows: trace (small number of deposits in one eye or only at the end of the interpupillary strip in each eye (if bilateral); Grade 1 (sparring of central cornea with involvement of medial and lateral interpupillary strips); Grade 2 (affected central cornea but no effect on visual acuity); Grade 3 (central cornea is affected with reduced vision) and Grade 4 (elevated nodules in addition to the findings of Grade 3).

**HISTOPATHOLOGY AND ELECTRON MICROSCOPY**

In primary CDK, Hematoxylin and Eosin (H&E) stained sections of the cornea show evidence of homogeneous proteinaceous globular deposits of variable sizes that are noted in the superficial layers of the cornea (Figs 6 and 7). The globules are mainly seen along Bowman’s layer which may show disintegration by the globular deposits. The spherules are then seen in the subepithelial space disrupting the basement membrane and the superficial stroma. The subepithe-
Electron microscopic study of the globules in patients with CDK reveals aggregates of extracellular electron dense round to oval globules among the collagen fibrils of the superficial stroma (Fig. 11). The globules are of different sizes and cause disruption of Bowman’s layer and the basement membrane of the epithelium.

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**PROTEOMIC ANALYSIS AND PATHOGENESIS**

The corneal globular deposits of patients with CDK were dissected and surgically removed from corneas of 9 patients suffering from CDK. The globules were weighed and homogenized. The total protein concentration was 71.91±17.95 µg protein/mg of wet tissue. The electrophoretic pattern of proteins from the globules showed major protein bands ranging between 20 and 30 kilo daltons (kDa). One of the major bands corresponded to a molecu-
lar weight of 67 K. The solution of globules did not give any immunoprecipitating line which suggests that the 67 K band may not be serum albumin. Proteins deposits have been previously shown to contain amino acids, such as tryptophan, tyrosine, cysteine and cystine, which are not normally found in the corneal stroma. A high tryptophan and tyrosine content is also reported.

Quantitative analysis of N-linked glycoproteins in tear fluid of CDK patients showed no appreciable difference between the control and the CDK samples. Kaji and associates studied the accumulation of D-beta-aspartic acid-containing proteins in surgically removed corneal tissue with CDK. D-beta-aspartic acid accumulates in the body with advancing age. The D-beta-aspartic acid-containing proteins may be found in a partial unfolding of proteins leading to the aggregation of proteins in CDK. CDK may be caused by an aggregation of advanced glycation and products, and modified proteins resulting from UV radiation and aging.

Holopainen et al. studied the activation of matrix metalloproteinase (MMP)-2, MMP-9, MMP-8 and MMP-13, and their tissue inhibitors (TIMP)-1, TIMP-2 in tear fluids of patients with CDK. They included 17 patients and 10 control subjects living in the Patagonia region of Argentina. They determined the MMPs and TIMPs of metalloproteinase by immunofluorescence in lieu of immunofluorometric assay (IFMA), gelatin zymography and quantitative Western immunoblot analysis in tear samples. They detected an upregulation and increase the level of MMP-9 and MMP-2 in the tear fluids in patients with CDK, whereas latent and active MMP-8 levels were significantly enhanced in controls only. There was no statistically significant difference in the level of MMP-13 between the CDK group and the control group. TIMPs where found as part of complexes in the TIMP-1 that were significantly lower in patients than in controls. This study demonstrated that MMP-2 and MMP-9 tear levels were significantly elevated and may have resulted in delay in corneal re-epithelialization and corneal scarring. Elevated levels of MMP-8 suggest a protective mechanism from recurring corneal traumas. The reduced expression of TIMP-1 in CDK, such as deficient antiproteolytic shield, which may lead to rendering the corneas of patients with CDK vulnerable to enhanced MMP activity.

The SDS-polyacrylamide gel electrophores (SDS-PAGE) (Invitrogen Inc., Carlsbad, CA) has shown that the proteins in the CDK globules consist of the molecular mass varying between 20 and 300 kDa with a major fraction appearing to be of a molecular mass of 67 kDa. Immunohistochemical studies in surgical specimens of patients with CDK studied with monoclonal antibodies to N-(carboxymethyl)-l-lysine (CML), N-(carboxyethyl)-l-lysine (CEL), pyrroline, pentosidine and imidazolone have shown these moieties to be immunoreactive for protein modifications in CDK. Menegay et al. carried out proteomic analyses of superficial corneal specimens obtained from patients with CDK during PKP. Bioinformatic analysis was performed to determine the biochemical pathway of identified proteins. CDK specimens procured from the cornea of patients undergoing PKP were subjected to protein analysis. The specimens were homogenized and proteins were fractionated over 4–20% gradient SDS-PAGE. The proteins (10 µg) fractionated on the gels were stained with blue gel stain (GelCode; Pierce Biotechnology, Inc., CA). The protein bands were excised, destained, reduced,
Environmental factors and aging play an important role in the pathogenesis of CDK. CDK is prevalent in areas that are characterized by high solar radiation and exposure to atmospheric irritants. Solar irradiation, high temperature, and persistent winds carrying particles of sand, dust or ice can provoke subtle microtrauma to the cornea leading to microerosions of the epithelium which may play a role in CDK. Lifetime exposure to these climatic conditions may constitute major risk factors to CDK; therefore, CDK mostly occurs in adults—predominantly in men who are exposed to solar irradiation. A high prevalence of pinguecula, pterygium, cataract and pseudoexfoliation has been reported in patients with CDK compared to age-matched control subjects. Advanced age of patients and rigorous climatic and environmental features of the region are the major contributing factors to CDK. Life-time exposure to these climatic conditions may provoke subtle microtrauma to the corneas leading to microerosions of the epithelium which may play a role in CDK. Lifetime exposure to these climatic conditions may constitute major risk factors to CDK; therefore, CDK mostly occurs in adults—predominantly in men who are exposed to solar irradiation. A high prevalence of pinguecula, pterygium, cataract and pseudoexfoliation has been reported in patients with CDK compared to age-matched control subjects. Advanced age of patients and rigorous climatic and environmental features of the region are the major contributing factors to CDK. In Britain, the disease is uncommon but it mostly manifests in persons with outdoor activities. Dry eye syndrome does not appear to play a role in the pathogenesis of CDK. Corneal hypoesthesia in patients with CDK has been reported and this may also add insult and injury due to exposure to environmental irritants which might not be felt by patients. The advanced grading of the CDK may help to correlate with the decrease in corneal sensitivity. Analysis of CDK globules in corneas undergoing PKP has shown high protein content. Recurrence of CDK may occur in patients with CDK. One of the authors has seen one case that occurred 18 months after PKP suggesting that proteins accumulation following exposure to environmental irritants may occur practically in some of these patients with CDK. Al-Rajhi and associates reported two cases of recurrence of the disease in the corneal graft three and a half years following lamellar keratoplasty and six years following PKP. Primary CDK occurs in individuals without previous corneal disorders, and secondary CDK occurs in patients who have previous corneal disease and scarring. The origin of the abnormal material deposited in the cornea may be the corneal blood vessels, limbal blood vessels, tears and abnormal corneal vascularization. Chronic irritation of the eye may lead to exudation of plasma proteins from the limbal and conjunctival vessels or from the neovascular network of the corneal scars. The presence of Annexin A1 and Annexin A2 as well as GAPDH is interesting because these proteins are known for

**Annexin and GAPDH**

Annexin and glyceraldehyde 3-phosphate dehydrogenase (GAPDH) were among the proteins that were identified in patients with CDK using monoclonal antibodies to annexin and GAPDH. These two proteins were identified by immunohistochemical analysis in control specimens. Annexin A1 was found in the periphery but not in the center of the cornea, while in patients with CDK annexin was captured in abundance from the central portion of the cornea. Prominently associated with droplets, immunohistochemical analysis of corneas with CDK showed a strong presence of annexin and GAPDH in the droplets and the other diffused presence in the rest of the cornea. Annexin A1 and, to a lesser extent, Annexin A2 as well as GAPDH are known for membrane fusion. Annexin A1 has been previously implicated in the formation of fibrotic deposits in the lungs, in cultured lung cells after irradiation. Annexin and GAPDH therefore act as membrane fusion allowing cells to adhere to the collagen. Proteomic identification and immunohistochemical observation of the droplets suggest an elevated presence of GAPDH and annexin in the droplets and not a complete lack of them in the normal cornea. The increased accumulation of GAPDH and annexin in CDK compared with normal cornea is intriguing and justified further investigations. The lack of suitable animal model in CDK makes it hard to study. The proteomic analysis and the pathways that lead to accumulation of proteins in the cornea of patients with CDK remain to be elucidated in the cornea of patients with CDK.

Environmental factors and aging play an important role in the pathogenesis of CDK. CDK is prevalent in areas that are characterized by high solar radiation and exposure to atmospheric irritants. Solar irradiation, high temperature associated with aridity and constant microtrauma to the cornea by sand, wind and dust may lead to deposition of proteins in the cornea. The disease has also been described in Labrador Region in Canada where solar radiation, reflection and wind may play a role in the pathogenesis. There is exposure to high solar UV irradiation in certain regions of the world such as North Africa, the Red Sea and certain parts of Australia and Argentina. Repeated and persistent winds carrying particles of sand, dust or ice can provoke subtle microtrauma to the cornea leading to microerosions of the epithelium which may play a role in CDK. Lifetime exposure to these climatic conditions may constitute major risk factors to CDK; therefore, CDK mostly occurs in adults—predominantly in men who are exposed to solar irradiation. A high prevalence of pinguecula, pterygium, cataract and pseudoexfoliation has been reported in patients with CDK compared to age-matched control subjects. Advanced age of patients and rigorous climatic and environmental features of the region are the major contributing factors to CDK. In Britain, the disease is uncommon but it mostly manifests in persons with outdoor activities. Dry eye syndrome does not appear to play a role in the pathogenesis of CDK. Corneal hypoesthesia in patients with CDK has been reported and this may also add insult and injury due to exposure to environmental irritants which might not be felt by patients. The advanced grading of the CDK may help to correlate with the decrease in corneal sensitivity. Analysis of CDK globules in corneas undergoing PKP has shown high protein content. Recurrence of CDK may occur in patients with CDK. One of the authors has seen one case that occurred 18 months after PKP suggesting that proteins accumulation following exposure to environmental irritants may occur practically in some of these patients with CDK. Al-Rajhi and associates reported two cases of recurrence of the disease in the corneal graft three and a half years following lamellar keratoplasty and six years following PKP. Primary CDK occurs in individuals without previous corneal disorders, and secondary CDK occurs in patients who have previous corneal disease and scarring. The origin of the abnormal material deposited in the cornea may be the corneal blood vessels, limbal blood vessels, tears and abnormal corneal vascularization. Chronic irritation of the eye may lead to exudation of plasma proteins from the limbal and conjunctival vessels or from the neovascular network of the corneal scars. The presence of Annexin A1 and Annexin A2 as well as GAPDH is interesting because these proteins are known for
membrane fusion. They allow the adhesion of the epithelial cells to the collagen. Annexin A1 has been implicated in the formation of fibrotic deposits in the lungs in cultured lung cells after irradiation. Transforming growth factor-beta-induced protein was also found in high levels. This is a 68 kDa protein which may play a role in amyloid deposits in the cornea.21-25

PREVENTION AND MANAGEMENT

Climatic droplet keratopathy may be prevented by wearing UV blocking sunglasses in areas of sand and dust. Side protectors of the sunglasses may have to be placed to prevent exposure to environmental irritants. Avoiding solar irradiation and repeated microtrauma of the cornea may also prevent the formation of CDK golden spherules.

Treatment of patients with mild CDK requires topical lubricants. The treatment is mostly symptomatic. There is no specific treatment for the resolution of CDK spherules. In patients with corneal scarring and CDK globules involving the central part of the cornea where the pathology is anterior, the vision may be compromised. Such corneal pathology may be treated with phototherapeutic keratectomy (PTK) or lamellar keratectomy with significant visual improvement if the deeper layers of the cornea are not involved.26-28 PTK may also be required for patients undergoing cataract surgery to improve visualization. Superficial lamellar keratectomy using automated microkeratomes may be used for patients with irregular CDK, and the flap can be removed. The association of pterygia, cataract and pseudoexfoliation is frequent clinical finding in patients with CDK.29 Patients may require phacoemulsification with posterior chamber intraocular lens implantation and excision of pterygium. It is recommended that patients with CDK who have pterygium undergo excision of pterygium with conjunctival autotransplantation.

REFERENCES


