Corneal Infection Associated with Diabetes: A Case Study & Literature Review

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Abstract: A 54-year-old woman with a history of type 2 diabetes presented with concern for sudden eye pain, photophobia, and redness of the eye. History, physical examination and comprehensive lab tests, yielded a diagnosis of corneal keratopathy. She responded poorly to the initial management of moxifloxacin 5% and homatropine 2%. A multi-faceted approach involving strict glycemic control and antibiotic therapy was then adopted. Through dietary management and pharmacotherapy, the patient's clinical disposition improved, highlighting the importance of glycemic control when managing diabetic keratopathy.

Keywords: Diabetic keratopathy, Moxifloxacin, Homatropine, Hyperglycemia, Diabetes, Corneal abnormality.

INTRODUCTION

Diabetic keratopathy is a disorder that doesn't represent a specific clinical or pathological entity and has therefore been ignored by both doctors and scientists. However many cases of vision impairment are attributed to diabetic keratopathy. Diabetic keratopathy includes several symptomatic corneal conditions that induce superficial pointed keratopathy and persistent corneal epithelial erosion [1]. The latter may be found particularly after vitreoretinal surgery, where oedematous and cloudy corneal epithelium, often removed manually to restore clarity, results in a poorly healing corneal epithelial surface postoperatively in diabetic patients. De-novo epithelial erosion may also persist despite routine clinical treatment of corneal erosions. Poorly healing epithelial surfaces predispose patients to infectious bacterial and fungal keratopathies [1].

Being a common cause of vision loss worldwide, diabetic keratopathy should garner more attention both in research and in clinical practice. Understanding the mechanism of diabetic keratopathy will allow for the development of improved diagnosis and management strategies.

The transparent and outermost layer of the eye is known as the cornea. The multi-layered corneal epithelium, through its tight junctions among surrounding cells, helps in protecting the eye against infections. The regenerating cells in the basal cell layer provide a smooth ocular surface [2, 3]. Any disturbance in these layers can lead to eye infections, stromal ulceration, and reduced visual acuity [4, 5]. The corneal smoothness and transparency are sustained by a tear film comprising of mucin, aqueous, and lipid layers. The majority of optical pathologies are corneal epithelium abrasions. Failure of re-epithelization within

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10-14 days of corneal damage will result in persistent corneal epithelial defects [PEDs] even with subsequent regular supportive management [5]. PEDs can lead to eye infections and vision loss if left untreated.

Excess glucose can damage corneal nerve fibers [6-8]. Therefore, corneal nerve deterioration is commonly found in diabetic keratopathy [9]. The corneal nerve serves a defensive role by maintaining the epithelial integrity of the cornea [10]. Prolonged hyperglycemia will significantly decrease corneal nerve fiber sensitivity [11]. Therefore, corneal sensitivity could be used to clinically diagnose diabetic keratopathy [11].

Hyperglycemic patients who undergo intraocular surgical procedures are at a much higher risk of acquiring epithelial defects and corneal abrasions [12]. Diabetics show a delay in re- epithelialization of the cornea [13], likely attributed to corneal nerve damage and corneal basement membrane imperfections. This can lead to the recurrent epithelial defects characteristic of diabetic keratopathy [14].

Hyperglycemia can lead to corneal ulceration and epithelial erosion [15], that become difficult to manage through conventional treatments [10]. Delay in treatment of epithelial defects can lead to diabetic keratopathy [16]. In the diabetic cornea, accumulated advanced glycation end products (AGEs) reduce epithelial cell migration to the site of injury, leading to delayed wound healing and recurrent erosions, requiring invasive cataract and pan retinal photocoagulation procedures [17].

Corneal erosion, or the unprompted breakdown of the corneal epithelium [18, 19], is another complication of diabetic keratopathy. Diabetics are at increased risk of corneal abrasion, detachment of the corneal basement membrane and subsequent erosion [20]. There are many corneal conditions such as stromal infiltration, opacity, and corneal epithelial dysfunction, which have a great impact on developing corneal erosion. For this reason, corneal erosion is one of the most important clinical manifestations in diabetic keratopathy [21].

The normal corneal density is maintained by the balance between cell differentiation, proliferation, migration, and cell death. Altered maturation and accumulation of glycogen granules epithelial layer [14], as well as decreased innervation of the corneal epithelium are characteristic of diabetic keratopathy [23].

Hyperglycemia can lead to corneal thickening; studies indicate that there is an increased central corneal thickness (CCT) in diabetics relative to healthy individuals. The duration of hyperglycemia is associated with corneal thickening. Epithelial and endothelial dysfunction of the hyperglycemic cornea results in stromal edema, the greatest contributor of corneal thickening [20]. Other causes of increased corneal thickness include augmented AGE formation, and collagen crosslinking induced by glycation.

EPITHELIAL WOUND HEALING

The corneal epithelium is composed of stratified squamous cells and is divided into 3 layers. The deepest layer is the basal layer, the middle 2-3 cell layers are composed of a wing layer, while the outermost layer is composed of a superficial layer [26]. The corneal healing procedure utilizes numerous growth factors, receptors, and degradation proteins [27]. In response to injury of the corneal epithelium, interleukin-1 (IL-1), and tumor necrosis-alpha (TNF-α) is released. In response to interleukin-1, keratocytes produce keratocyte growth factor and hepatocyte growth factor that affects epithelial cell migration and propagation. Transforming growth factor-beta and insulin-like growth factors control the progression of epithelial cells and stromal keratocytes [28]. During wound healing, epithelial migration and re-epithelialization are facilitated by thymosin-β4 while migration and proliferation of keratocytes are controlled by platelet-derived growth factors (PDGFs). Corneal sensation and preservation of tear film are mediated by Nerve growth factor (NGF) [29]. It takes 7-14 days for the epithelial layer of damaged cornea to heal. The healing process involves a highly controlled cascade of growth factors, migration, proliferation, remodeling of the extracellular matrix, and apoptosis [30]. The stroma can adhere to the regenerated epithelial layer only after epithelialization occurs through hemidesmosomes attached to fibrils [31]. PEDs usually spread into the stromal layer, triggering stromal melting, secondary ulceration, and stromal damage. This results in a persistent epithelial defect that is unable to heal in 7-14 days [32].

EPIDEMIOLOGY

Persistent epithelial defects [PED] of the cornea is a rare condition, with a prevalence of less than 200,000. cases of PED occurring in the United States annually [33]. Diabetic keratopathy almost occurs in 47-64 % of hyperglycemic patients. Research indicates that amongst children exposed to mechanical ventilation,

almost 25% grow a corneal epithelial deficiency [34]. Moreover, pars plana vitrectomy is associated with a high occurrence of postoperative PED [35].

ETIOLOGY

Normal corneal epithelial wound healing is impacted by defective epithelial adhesion, limbal stem cell deficiency, inflammation, and neurotrophic, as described below. The propagation of myofibroblasts results in PEDs, extracellular matrix disorders and corneal opacities.

DEFECTIVE EPITHELIAL ADHESION

Fibril connections and hemidesmosomes help the basal epithelial cells adhere to the basement membrane. Persistent corneal epithelial defects be the result of poor basement membrane and faulty epithelial linkages [36]. Recurrent corneal erosion will lead to an overproduction of matrix metalloproteinases resulting in disturbances of the basement membrane and abolished fibril networks between the epithelium and basement membrane, leading to PED [37]. Deterioration of the cornea in Salzmann's nodular degeneration, band keratopathy, or bullous keratopathy, can produce in PEDs due to atypical development of the basement membrane and faulty adhesion mechanisms [32].

LIMBAL STEM CELL DEFICIENCY

After any injury to the corneal epithelium, corneal epithelial stem cell migration plays a crucial role in the regeneration of tissues. Persistent epithelial defects, scarring, and stromal melting can occur as a result of limbal stem cell deficiency. Domestic cleaning solutions, fertilizers, and alkali induced chemical damage from lye can cause severe limbal stem cell deficiency [38].

INFLAMMATION

Cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-1 (IL-1) facilitate inflammation and release of keratocyte growth factors that initiate propagation and migration of epithelial cells. Over-activity of TNF-α, IL-1, and other inflammatory cytokines can result in PED due to disturbances of corneal wound healing by numerous inflammatory settings. These conditions include infectious keratitis, peripheral ulcerative keratitis, Stevens-Johnson syndrome, Sjögren's syndrome, and rheumatoid arthritis [39].

NEUROTROPHIC

In the human body, the cornea is one of the highly innervated tissues which takes neurotrophic factors and neural perception from the ophthalmic division of the trigeminal nerve [39]. Due to systemic and local injury to the trigeminal nerve, neurotrophic persistent corneal epithelial defects can lead to reduced corneal sensation. The loss of corneal innervation results in deterioration of tissue, with the epithelium being most vulnerable to impairment. This results in epithelial defects and deprived corneal healing [40]. Moreover, reduced blink frequency, tear formation, and Meibomian gland excretion can further damage the epithelium, and injury to corneal nerves can lead to dry eye syndrome [41].

CASE REPORT

Our patient was a 54-year-old woman with a history of type 2 diabetes diagnosed 14 years ago. Other pertinent medical conditions included obesity and hypercholesterolemia. She presented to the hospital clinic with sudden pain, photophobia, and erythema of her right eye for the last 2 days. She had no recent history of trauma or contact lens use. She reported frequent urination, extreme fatigue, blurry vision, and numbness in the feet and hands. The patient had 7 previous visits to the hospital for a diabetic emergency within the last six [6] months, with the most recent being 20 days before presentation. During the past year, she gained 20 pounds. Since the last admission, she was referred to a dietician, who recommended weight loss of at least 10 pounds. To this end, she has increased her exercise in the last three [3] weeks.

The patient took glyburide 2.5mg every morning, which she stopped taking due to dizziness, mild agitation, and sweating. She currently takes atorvastatin 10mg daily for hypercholesterolemia.

She does not test her blood glucose levels at home. Her diet predominantly includes carbohydrates in the form of pasta and bread. Her medical records indicated that her HbA1c has never been less than 6.5%, and that her HbA1c 2 months ago was 12.4%. She had no surgeries or hospitalization, and her immunizations are up to date. Her blood pressure had been measured at 126/84, 132/90, 125/88 on separate occasions during the past year.

PHYSICAL EXAMINATION

On physical examination, the patient was in mild distress initially. Vital signs included a temperature of

36.7°C; respiratory rate of 14 breath/min; blood pressure of 132/ 78 mm Hg; and a pulse rate of 72 beats/min. The patient's sense of hearing was intact and normal. The oropharynx was clear. Her neck was mobile, with no jugular venous distension. On cardiovascular exam, rate and rhythm was normal, and there were no murmurs, rubs or gallops. There were no rales, rhonchi, or wheezing on auscultation of the chest. The chest wall was not tender to palpation. Bowel sounds were normal, and the abdomen was soft and non-tender, without guarding or hepatosplenomegaly. There was no evidence of cyanosis or clubbing on the patient's extremities. She had a normal range of motion and muscle strength in all extremities and reflexes were normal. Cranial nerves II through XII were intact.

On ophthalmologic examination, her visual acuity was 20/20 on the right eye, and 20/40 on the left eye. There was a small 1.5 x 2 mm anterior stromal infiltrate in the left cornea, with a superimposing epithelial defect and circumcorneal congestion. The adnexa and eyelids were normal. There was a mild decrease in corneal sensation indicating the loss of a corneal reflex. Fundoscopic examination revealed non-proliferative diabetic retinopathy. Corneal scraping revealed a small number of gram-positive cocci and no signs of any fungal infection.

LABORATORY TESTING

The patient was admitted into the emergency department and her electrocardiography findings revealed no abnormalities. Urine toxicology was negative for alcohol, barbiturates, benzodiazepines, cocaine, opioids, tricyclic antidepressants, and amphetamines. The complete blood cell count revealed an elevated white blood cell count of 17700/uL and decreased hemoglobin of 11.7g/dL. Urinalysis revealed no abnormalities. A complete metabolic panel revealed hyperglycemia, with glucose of 340mg/dL, and bicarbonate of 27mEq/L (Table **1**).

TREATMENT

A broad spectrum topical antibiotic (moxfloxacin 0.5% every 2 hours), and cycloplegics (homatropine 2% 3 times daily) were used to treat the patient's condition. Despite the regimen, the patient's corneal ulcer failed to resolve. The patient's blood glucose meanwhile was increasing, which prompted the endocrinologist to increase the patient's insulin dose. This led to the reduction of the patient's blood sugar one week later. By adopting a strict hyperglycemic control, and continuing the antibiotic and cycloplegic therapy, the patient's diabetic keratopathy and ulcer resolved after 2 months. A combined administration of moxifloxacin 0.5% and homatropine 2% effectively improved visual acuity, leading to a gradual decrease of the stromal infiltrates and resolution of the epithelial defect after two months of treatment.

DISCUSSION

Diabetic keratopathy was documented when vitrectomy was done on the patient for corneal epithelial healing problems as a result epithelium was removed [18]. Diabetic patients have a 47- 67% probability of developing diabetic keratopathy [42]. Contact lens use can increase the severity of keratopathy by exaggerating susceptibility to microbial keratitis and corneal ulceration [43].

Diabetic keratopathy is a continuous corneal epithelial abnormality due to deviancy from the regular wound healing process. As seen in our patient, diabetic keratopathy is unresponsive to the treatment unless the underlying hyperglycemia is managed [44]. Further studies should elucidate the degree and molecular mechanisms associated with diabetic neuropathy and keratopathy [16]. As compared to cataracts or diabetic retinopathy, patients suffering from diabetic keratopathy do not have noticeable symptoms. Pathogenic processes involved in diabetic keratopathy include oxidative stress and chronic low-grade inflammation. However, the molecular pathways leading these pathogenic events are not completely understood [45]. The histological features of the cornea are influenced by corneal optical density and corneal transparency [46].

Diabetic keratopathy is one of the most common types of corneal diseases that may occur in both type 1 and type 2 diabetes [47]. As exemplified by our patient, prolonged hyperglycemia can have profound effects on the retina, damaging each layer of the corneal structure, leading to decreased corneal optical density and associated complications, such as irritation and nubecula [46].

Patients with diabetic keratopathy, such as ours, will benefit from routine clinical supervision for corneal damage, as well as treatment with topical medication.

Monitoring for subclinical defects can prevent the development of symptomatic diabetic corneal problems. These subclinical defects include irregularities in the shape of corneal epithelial and

endothelial cells, basement membrane thickening, and reduced corneal sensation. These subclinical irregularities are closely correlated to the development of symptomatic corneal situations in hyperglycemia.

Table 1: Summary of the Result of Comprehensive Blood Cell Count, Urinalysis and Comprehensive Metabolic Panel

Sr. No.	Urine Analysis	Analyte Value
1.	Glucose	340mg/dl
2.	White blood cell count	17700/µl
3.	Human chorionic gonadotropin	Negative
4.	Blood urea nitrogen	15mg/dl
5.	Red blood cell count	$4.37 \times 10^{6/}$ µl
6.	Color	yellow
7.	Creatinin	1.08 mg/dl
8.	Hemoglobin	11.7mg/dl
9.	Appearance	Clear
10.	Sodium	137 mEq/L
11.	Hematocrit	39.2%
12.	Specific gravity	1.122
13.	Potassium	3.8 mEq/L
14.	Mean corpuscular volume	79.7 µm³
15.	PH	6.1
16.	Chloride	101 mEq/L
17.	Mean corpuscular hemoglobin	27.9 pg/cell
18.	Nitrogen	Negative
19.	Carbon dioxide	27 mEq/L
20.	Mean corpuscular hemoglobin concentration	34.7 g/dl
21.	Glucose	Negative
22.	Calcium	12 mg/dl
23.	Red cell distribution width, coefficient of variation	12.8%
24.	Ketones	Negative
25.	Ethanol	<13.0 mg/dl
26.	Red cell distribution width, standard deviation	43.7 fl
27.	Protein	Negative
28.	BUN/ Creatinine ratio	21.1
29.	Platelet count	267 10^{3}/µl
30.	Blood	Negative
31.	Osmolality	274.3 mOms/kg
32.	Mean platelet volume	10.5 fl
33.	Bilirubin	Negative
34.	Amino gap	7 mEq/L
35.	Urobilirubin	0.3 mg/dl
36.	Glomerular filteration rate	70 ml/min/1.73 m^2
37.	Leukocyte esterase	Negative
38.	Drug screen	Negative
39.	Microscopy	N/A

CONCLUSION

Assessment of the ocular surface of diabetic patients is crucial to prevent complications such as diabetic keratopathy. With the rise in prevalence of diabetes, diagnostic and management strategies for diabetic keratopathy should be developed. Our case highlights how prolonged hyperglycemia can lead to corneal ulceration. Additionally, this case suggests that before pathological procedures are performed, a detailed evaluation of morphological and functional aspects of the cornea should be done on diabetic patients.

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