DOI: 10.17816/OV11125-33

CLINICAL AND ETIOLOGICAL CHARACTERISTIC, CLASSIFICATION AND TREATMENT OF ASEPTIC CORNEAL ULCERS

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For citation: Brzheskaya IV, Somov EE. Clinical and etiological characteristic, classification and treatment of aseptic corneal ulcers. *Ophthalmology Journal*. 2018;11(1):25-33. doi: 10.17816/OV11125-33

Received: 12.01.2018 Accepted: 20.02.2018

✧ ***Introduction.*** Aseptic corneal ulcers are among rare, but severe, torpid diseases. ***The aim*** is to study the etiology, develop a clinical classification of the corneal aseptic ulcer, and determine the tactics of their treatment. ***Material and methods.*** A total of 40 patients (47 eyes) were examined when admitted as emergency with an aseptic ulcer of the cornea. In addition to routine examination methods, the optical coherence tomography was performed, ulcer area and depth were recorded, and the collagenolytic activity of the tear fluid was also determined. The defect closure with a biological transplant (amniotic membrane preserved in glycerin, allogeneic sclera, autogenous tissues – a free flap of the sclera or a pedicle flap of the conjunctiva). The procedure was completed by blepharorrhaphy or flap covering with a soft contact lens. ***Results.*** Initial procedures were successful in 34 eyes out of 47 (72.3%). In the remaining 13 cases, repeated surgeries were required: in 11 cases – during first three months, and in 2 cases – between 4 and 12 months. In two patients with high lytic tear activity (more than 700 kU/ml) repeated procedures were performed twice, due to rapid lysis of the amniotic membrane during 14 days. ***Conclusion.*** All patients with a progressive aseptic corneal ulcer need surgical treatment in the form of its coverage with a biological tissue of allo- or autogenous nature. Anterior stromal ulcers should preferably be covered with a free amniotic flap, and the posterior stromal ulcers should be closed with an autoconjunctival-tenon pedicle flap or with a free flap of the sclera. High collagenolytic activity of the tear fluid is the main cause of biological tissue lysis. Primary and repeated plastic surgery allowed a reliable replacement of the corneal ulcer defect area with scar tissue.

✧ ***Keywords:*** aseptic corneal ulcer; diagnostics; surgical treatment; amnioplasty.

КЛИНИКО-ЭТИОЛОГИЧЕСКАЯ ХАРАКТЕРИСТИКА, КЛАССИФИКАЦИЯ И ЛЕЧЕНИЕ АСЕПТИЧЕСКИХ ЯЗВ РОГОВИЦЫ

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Для цитирования: Бржеская И.В., Сомов Е.Е. Клинико-этиологическая характеристика, классификация и лечение асептических язв роговицы // Офтальмологические ведомости. – 2018. – Т. 11. – № 1. – С. 25–33. doi: 10.17816/OV11125-33

Поступила в редакцию: 12.01.2018 Принята к печати: 20.02.2018

✧ ***Актуальность.*** Асептические язвы роговицы относятся к числу редких, но тяжёлых, торпидно протекающих заболеваний. ***Цель:*** изучить этиологию, разработать клиническую классификацию асептической язвы роговицы, а также определить тактику её лечения. ***Материал и методы.*** Обследованы 40 пациентов (47 глаз), поступивших по неотложной помощи с асептической язвой роговицы. У всех

кроме традиционных методов обследования выполняли оптическую когерентную томографию, фиксировали площадь и глубину язвы, а также определяли коллагенолитическую активность слезы. Всем выполнено закрытие дефекта биологическим трансплантатом (амниотической оболочкой, консервированной в глицерине, аллогенной склерой, аутотканями — свободным лоскутом склеры или лоскутом аутоконъюнктивы «на ножке»). Операцию завершали блефарорафией либо покрытием лоскута мягкой контактной линзой. ***Результаты.*** Первично выполненные операции оказались успешными на 34 глазах из 47 (72,3 %). В остальных 13 случаях потребовались повторные вмешательства: на 11 глазах — в течение первых трёх месяцев, а на 2 — от 4 до 12 месяцев. Причём двум больным с высокой лизисной активностью слезы (более 700 КЕ/мл) повторные операции выполняли дважды в связи с быстрым лизированием амниотической оболочки в течение 14 дней. ***Заключение.*** Все больные с прогрессирующей асептической язвой роговицы нуждаются в хирургическом лечении в виде её покрытия биологической тканью алло- или аутогенной природы. Переднестромальные язвы предпочтительнее закрывать свободным амниотическим лоскутом, а заднестромальные — аутоконъюнктивально-теноновым лоскутом «на ножке» или свободным лоскутом склеры. Высокая коллагенолитическая активность слезы является основной причиной лизиса биологической ткани. Первичные и повторные пластические операции позволили надёжно заместить зону язвенного дефекта роговицы рубцовой тканью.

✧ ***Ключевые слова:*** асептическая язва роговицы; диагностика; хирургическое лечение; амниопластика.

INTRODUCTION

Corneal disorders and injuries are one of the leading causes of impaired vision or even blindness. Corneal injuries are responsible for approximately 1.5–2.0 million new cases of monocular blindness annually [1, 11, 12].

Although corneal ulceration is rare, it is a potentially devastating condition that is exceedingly difficult to treat. In 8%–9% of cases, the disease results in anatomical loss of the eye; 17% of patients undergo enucleation due to ineffective treatment [1, 8].

Vender and Golt have classified corneal ulcers as infectious and aseptic without elaborating the clinical details in their classification [6]. Unfortunately, the issues associated with aseptic corneal ulcers were poorly covered, whereas the treatment of patients with neurotrophic keratitis combined with lagophthalmos was primarily described [10, 14]. However, the damage to the facial or trigeminal nerves after surgical excision of a large cerebellopontine angle neurinoma is not a unique cause of noninfectious corneal ulcers. Their development can be triggered by keratitis of various etiology (7.7%), rheumatoid arthritis (4.4%), wearing contact lenses (2.5%), and dry eye syndrome (2.3%) [23]. Several systemic disorders, such as Sjögren syndrome, Stevens–Johnson syndrome, rosacea, and vitamin A deficiency, play a significant role in corneal ulceration [21, 24]. Some authors [20, 26] have described corneal ulcers in patients with surgical trauma to the cornea and damage to the ciliary nerves after cataract extraction. Impaired innervation and insufficient blood supply to the cornea after herpetic keratitis, burns, and surgical injuries can also result in persistent corneal ulcers [18, 20, 22, 26].

One of the main difficulties lies in the fact that physicians are not always prepared to take adequate measures, owing to the rarity of this disease. Lee at al. found that only 15.9% of patients with corneal ulcerations admitted to eye hospitals for emergency care in the United States were diagnosed with noninfectious corneal ulcers [23].

Of note, corneal epithelial defects that do not heal within 3 weeks should be considered persistent or chronic [25]. The currently available pharmacotherapy is often ineffective; therefore, many ophthalmologists are inclined to perform surgery. The main aim of surgery is to perform corneal ulcer closure and prevent its further progression. It can be achieved by therapeutic corneal transplantation, when the affected corneal area is replaced by an allogeneic corneal graft [7]. However, it is impossible to perform corneal transplantation for all patients, particularly in emergency cases, when timely keratoplasty allows preservation of the corneal tissue and occasionally even obtaining high visual acuity. In recent years, the number of corneal grafting surgeries in Russia has been significantly reduced due to the existing shortcomings in the Russian transplant legislation that substantially limit the ability to obtain donor material.

Difficulties associated with obtaining a donor cornea necessitate the selection of alternative biological materials to repair corneal ulcers, including preserved allogeneic sclera [1, 15] and native or preserved amniotic membrane [2, 12, 16, 21, 22, 24]. These tissues have been successfully used in our hospital for

many years. Autoconjunctival grafting is also currently widely used. The problem of selecting an optimal surgical technique is being actively discussed [1, 3, 9, 10, 14].

Despite the achievements in ophthalmic surgery, the treatment of corneal ulcers remains challenging.

In light of the aforementioned aspects, the present study aimed to analyze the etiology of aseptic corneal ulcers in patients admitted to emergency care units, develop their clinical classification, and determine an optimal treatment strategy.

MATERIAL AND METHODS

This study included 40 patients (47 eyes) with aseptic corneal ulcers admitted to the emergency ophthalmic unit of the Saint Petersburg Mariinsky Hospital between 2010 and 2016. The cohort comprised 14 males (35%) and 26 females (65%) aged between 23 and 87 years.

All patients admitted to the hospital were examined according to a generally accepted standard algorithm, which aimed at the detection of corneal disorders. Additionally, the corneal structure was analyzed, the area and depth of the lesion were measured, and the lysis activity of the ulcerative process was evaluated. The corneal structure was analyzed by optical coherence tomography (OCT) using the Visante OCT 1000 system (Carl Zeiss Meditec Inc.). The Canon IXUS145 camera was used to obtain ulcer images and assess its characteristics. The camera lens was placed on the ocular of the slit lamp with the following standard conditions: ×8 magnification, diffuse illumination with a maximum open slit, and direct focal illumination with a narrow slit. The lysis activity of ulcerative process was measured using a method based on the assessment of the drying rate of a mixture containing the lavage fluid of the conjunctival cavity and collagen gel [5].

The analysis of clinical data revealed that all study participants required surgical treatment (i. e., overlaying the area of the corneal ulcer with a biological tissue).

All plastic surgeries were intended to completely repair the corneal defect with a biological graft to restore corneal integrity and activate reparation. Amniotic membrane preserved in glycerol (prepared in our hospital), allogeneic sclera (Alloplant LLC, Ufa, Russia), and autografts, including scleral free flaps and conjunctival pedicle flaps, were used. All plastic surgeries were complemented by blepharorrhaphy or flap covering with a soft contact lens.

The biological material for corneal defect closure was selected according to the ulcer depth. Allogeneic and autologous scleral flaps and conjunctival pedicle flaps were used in patients with corneal perforations and descemetocele. In patients with deep ulcers without involvement of Descemet's membrane, the cornea was repaired using two layers of the amniotic membrane. Patients with paralytic lagophthalmos additionally underwent medial or lateral canthoplasty or blepharoplasty (the Kuhnt–Szymanowski procedure) to reduce the palpebral fissure height and partially prevent corneal dryness.

RESULTS AND DISCUSSION

Table 1 describes the main pathological conditions underlying corneal ulceration, duration of the xerotic process, and ulcer characteristics. All patients were divided into three groups according to the etiology of the ulcerative process.

Group 1 included 17 patients (24 eyes) with corneal ulcers developed due to systemic diseases. The group primarily comprised individuals with Sjögren syndrome (12 patients, 17 eyes) aged between 59 and 87 years. Upon examination, mature corneal ulcers located in various parts of the cornea were detected. In six patients, ulcer-associated tissue decay led to the development of descemetocele, whereas in 11 patients, it resulted in perforation of Descemet's membrane. Ultimately, 15 eyes were found to have a visual acuity between light perception and 0.05, whereas the remaining 2 eyes had a visual acuity of 0.1–0.2. Low visual acuity was caused by centrally and paracentrally located corneal ulcers. In other cases, the ulcer was located on the corneal periphery. Two patients (a male and a female) aged 54 and 43 years developed aseptic corneal ulcers with perforation in one eye due to the rare systemic disorder, Stevens–Johnson syndrome. They had centrally located ulcers that caused significant reduction of visual acuity (to 0.005). Rosacea was diagnosed in two female patients aged 23 and 43 years; one had monocular corneal ulceration with perforation, whereas the other had ulcers in both eyes that emerged with an interval of 11 months. The visual acuity was reduced to 0.1 in the case of peripherally located ulcers and to light perception in the case of centrally located ulcers. One female patient aged 49 years had pronounced vitamin A deficiency and developed corneal ulcers with perforation in both eyes with an interval of 2 years. She had a visual acuity of 0.005, owing to the central and paracentral location of the ulcers.

Group 2 comprised 14 patients (14 eyes) with corneal ulcers associated with various corneal disorders.

The majority of patients in this group (10 individuals aged between 25 and 71 years) received earlier treatment for unilateral herpetic keratitis. Impairments in corneal trophics led to the progression of corneal lysis with a formation of descemetocele in 3 eyes and corneal perforation in 4 eyes. Two patients from this group (aged 73 and 83 years) developed deep corneal ulcers within 2–3 months after cataract extraction performed through a long (6–7 mm) limbal incision. Such incisions lead to a decreased tactile sensitivity of the superior part of the cornea [26]. In one patient, the ulcerative process involved the Descemet's membrane; the other patient developed descemetocele. Two patients (aged 35 and 51 years) developed corneal ulcers within 6 months after a grade 3 alkali burn in the cornea. In one patient, the ulcerative process involved Descemet's membrane; the other patient developed descemetocele.

Group 3 included 9 patients (9 eyes) with corneal ulcers that developed due to paralytic lagophthalmos induced by facial nerve damage during surgical excision of a cerebellopontine angle schwannoma ($n = 5$) or acute stroke with facial nerve palsy ($n = 4$). Moreover, the operated patients had damage to the trigeminal nerve, which affected tactile and trophic innervations of the cornea. These patients developed deep corneal ulcers within 4–6 months postoperatively.

Table 1

Basic forms of pathology, revealed in patients with aseptic corneal ulcer, and some features of their manifestations

Таблица 1

Базовые формы патологии, установленные у больных с асептической язвой роговицы, и некоторые особенности их проявлений

Diseases	n/n^1	Actual Age of Patients and Their Age Groups, years ($M \pm m$)								Duration of Xerotic Process, months		
		n	22–35	n	36–60	n	61–74	n	75–90	up to 6	6–12	over 12
1. Systemic diseases:												
• Sjögren syndrome	12/17	–	–	2	59.0 ± 0	2	70.0 ± 3.0	8	80.0 ± 1.6	3	4	5
• Vitamin A deficiency	1/2	–	–	1	49.0	–	–	–	–	–	–	1
• Stevens–Johnson syndrome	2/2	–	–	2	48.5 ± 5.6	–	–	–	–	–	2	–
• Rosacea	2/3	1	23.0	1	43.0	–	–	–	–	1	1	–
2. Corneal diseases:												
• Herpetic keratitis	10/10	2	25.0	3	47.7 ± 4.4	5	68.4 ± 2.0	–	–	8	2	–
• Surgical trauma	2/2	–	–	–	–	1	73.0	1	83.0	2	–	–
• Chemical burn	2/2	1	35.0	1	51.0	–	–	–	–	2	–	–
3. Eyelid diseases:												
• Paralytic lagophthalmos after surgical excision of a schwannoma	5/5	2	27.0 ± 2.0	3	42.7 ± 4.5	–	–	–	–	5	–	–
• Paralytic lagophthalmos after acute stroke	4/4	–	–	–	–	1	72.0	3	83.7 ± 3.4	–	4	–
Total	40/47	6	–	13	–	9	–	12	–	21	13	5

Note: n – number of patients; n^1 — number of eyes

All corneal ulcers had various locations and depth of the stromal defect (Table 2). Corneal ulcers up to Descemet's membrane were identified in 12 eyes, primarily in patients with corneal or eyelid diseases. Descemetocele was observed in patients with systemic disorders (7 eyes) and corneal disorders (5 eyes). Corneal perforations were primarily found in patients with systemic diseases (17 eyes), after multiple episodes of herpetic keratitis (4 eyes), and in one patient (1 eye) with paralytic lagophthalmos developed after acute stroke.

The majority of patients had very low visual acuity, which was strongly associated with ulcer location [0.001–0.01 in 29 eyes (61.7%), 0.02–0.05 in 14 eyes (29.8%), and 0.1–0.2 in 4 eyes (8.5%)].

By analyzing specific characteristics of various aseptic corneal ulcers, a clinical classification that allows the establishment of a final diagnosis for each patient (Table 3) was developed. Multiple characteristics were allocated to classify the ulcerative process according to its etiology, location, area and depth of the ulcer and the degree of collagenolytic activity of the conjunctival fluid.

Patients with perforating corneal ulcers underwent surgery within 3–4 h after admission to the hospital;

Table 2

Characteristics of identified corneal ulcers in terms of their degree of destructiveness and topographic features

Таблица 2

Характеристика выявленных язв роговицы по степени их деструктивности и топографическим особенностям

Diseases	Depth of the Stromal Defect of the Cornea						Location of the Pathological Focus					
	Up to the Descemet's Membrane		with Descemetocele		with Perforation of Descemet's Membrane		Central and/or Paracentral		Peripheral		Subtotal	
	n^1	%	n^1	%	n^1	%	n^1	%	n^1	%	n^1	%
1. Systemic diseases:												
• Sjögren syndrome	–	–	6	35.3	11	64.7	11	64.7	6	35.3	–	–
• Vitamin A deficiency	–	–	–	–	2	100.0	–	–	–	–	2	100.0
• Stevens–Johnson syndrome	–	–	–	–	2	100.0	2	100.0	–	–	–	–
• Rosacea	–	–	1	33.3	2	66.7	2	66.7	1	33.3	–	–
2. Corneal diseases:												
• Herpetic keratitis	3	30.0	3	30.0	4	40.0	1	10.0	6	60.0	3	30.0
• Surgical trauma	1	50.0	1	50.0	–	–	1	50.0	1	50.0	–	–
• Chemical burn	1	50.0	1	50.0	–	–	1	50.0	–	–	1	50.0
3. Eyelid diseases:												
• Paralytic lagophthalmos after surgical excision of a schwannoma	5	100.0	–	–	–	–	–	–	–	–	5	100.0
• Paralytic lagophthalmos after acute stroke	2	50.0	1	25.0	1	25.0	1	25.0	3	75.0	–	–

Note: n – number of patients; n^1 — number of eyes

the remaining patients were operated no later than the next day.

Surgical treatment was given for 47 eyes in 40 patients with aseptic corneal ulcers of various origin and depth. Different biological materials were applied to repair corneal ulcers (Table 4). Most frequently, the amniotic membrane was used due to its high plasticity. It was used in all study participants as an independent two-layer flap (17 eyes), as a filling material placed under an autoconjunctival Tenon's flap (23 eyes), or under a free allogeneic/autologous scleral flap (7 eyes).

To maintain the transplanted flap in the correct position on the cornea, temporary blepharorrhaphy was performed (30 eyes), or the cornea was covered with a soft contact lens (17 eyes).

During pre- and postoperative periods, all patients received antibacterial and anti-inflammatory agents, including eye drops (0.3% solution of ofloxacin and 0.09% solution of bromfenac) and parabulbar injections (dexamethasone and gentamicin). Patients with high collagenolytic activity of conjunctival fluid (>700 KU/mL) additionally received eye drops containing Gordox (antienzymatic agent) and Hemodesum in the ratio of 1:1. During the postoperative period, all patients received artificial tears containing natural polysaccharides [4, 19]. Patients with systemic diseases additionally received general anti-inflammatory therapy coordinated by a healthcare professional.

Long-term follow-up demonstrated that primary surgeries were effective in 34 of 47 eyes (72.3%). The remaining 13 eyes required repeated surgeries, 11 eyes within 3 months postoperatively and 2 eyes within 4–12 months postoperatively. In two patients, surgery was repeated twice because of severe systemic disorders and high collagenolytic activity of conjunctival fluid (>700 KU/mL), resulting in immediate (within 14 days) lysis of the amniotic membrane, which was in direct contact with the ulceration area.

The visual acuity in the long-term postoperative period depended on the ulcer location and involvement of the optical portion of the cornea. The visual acuity remained relatively low, up to 0.04 in 33 eyes (70.2%) with centrally and paracentrally located ulcers, 0.05–0.1 in 12 eyes (25.5%), and 0.2 to 0.3 in 2 eyes (4.3%) with peripherally located ulcers.

Several patients developed postoperative complications, including ocular hypertension in 7 eyes (14.9%) and complicated cataract in 3 eyes (6.4%). The administration of local hypotensive therapy normalized the ocular tonus. Patients with complicated cataract underwent surgical treatment; however, the final visual acuity remained low (0.05–0.1) due to corneal opacity.

CONCLUSION

1. Aseptic corneal ulcers can be caused by systemic disorders (Sjögren syndrome, Stevens–Johnson syndrome, and rosacea) or local disorders (herpetic keratitis and paralytic lagophthalmos) leading to severe trophic impairments in the cornea.
2. All patients with progressive aseptic corneal ulcers require surgical repair of corneal defects with allogeneic or autologous tissue grafts.
3. The anterior stromal ulcers should be repaired with amniotic membrane flaps, whereas the posterior stromal ulcers should be repaired with autoconjunctival Tenon's pedicle flaps or allogeneic/autologous scleral flaps.
4. High collagenolytic activity of conjunctival fluid in the operated eye is one of the main causes of graft lysis.
5. Primary and repeated (13.7% of cases) plastic surgeries allowed positive results to be achieved: the reliable replacement of affected areas with scar tissue.

The authors declare no conflict of interest and no competing financial interest

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Table 3

Clinical classification of corneal ulcers

Таблица 3

Клиническая классификация язв роговицы

Classification Based on					
Etiology	Location on the Corneal Surface	Affected Area of the Cornea	Degree of Damage to the Cornea	Degree of Collagenolytic Activity of the Conjunctival Fluid	Outcome
Infectious: • Bacterial • Fungal • Parasitic • Viral Aseptic: • Associated with systemic diseases • Associated with a long-term corneal disorder • Associated with lagophthalmos of various genesis	• Paralimbal • Paracentral • Central	• Small (up to 25% of the total corneal area) • Medium (between 25% and 50% of the total corneal area) • Subtotal (between 50% and 75% of the total corneal area) • Total (over 75% of the total corneal area)	Grade 1. Superficial (epithelial) Grade 2. Stromal: a) anterior stromal (up to half corneal thickness) b) posterior stromal (more than half corneal thickness) c) with a descemetocele d) with perforation of Descemet's membrane	Grade 1: between 301 and 500 KU/mL Grade 2: between 501 and 700 KU/mL Grade 3: over 701 KU/mL	• Formation of a limited vascularized leukoma that does not require keratoplasty • Formation of a vascularized leukoma that requires keratoplasty

Table 4

Types of biological material used for the primary covering of different types of aseptic corneal ulcer

Таблица 4

Виды биологического материала, использованного для первичного покрытия различных видов асептической язвы роговицы

Clinical Characteristics of the Corneal Ulcer	Diseases	Total Number of Eyes	Biological Tissues and Number of Surgeries			
			Free two-Layered Flap	Autoconjunctival Tenon's Pedicle Flap With an Amnion Base	Free Scleral Flap With an Amnion Base	
					Autologous	Allogeneic
Anterior stromal	Corneal diseases	5	4	1	–	–
	Eyelid diseases	7	5	2	–	–
Posterior stromal with a descemetocele	Systemic diseases	7	3	4	–	–
	Corneal diseases	5	4	1	–	–
	Eyelid diseases	1	1	–	–	–
Posterior stromal with perforation of Descemet's membrane	Systemic diseases	17	–	12	1	4
	Corneal diseases	4	–	2	1	1
	Eyelid diseases	1	–	1	–	–
Total		47 (100%)	17 (36.2%)	23 (48.9%)	2 (4.3%)	5 (10.6%)

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