

Newly Acquired Herpetic Epithelial Keratitis After Penetrating Keratoplasty without Previous History of Herpetic Keratitis

Herpetik Keratit Geçmiş Olmadan Penetran Keratoplasti Sonrası Yeni Edinilmiş Herpetik Epitelyal Keratit

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ABSTRACT Objective: Herpes simplex virus (HSV) infection may develop either by reactivation of latent HSV in its endogenous foci or exogenous transmission from the transplanted donor cornea after penetrating keratoplasty (PK). In the current study, we aimed to determine the clinic and treatment outcomes of patients without previous history of HSV infection who had newly acquired herpetic epithelial keratitis (HK) after PK. **Material and Methods:** The medical records of patients who underwent PK for reasons outside of corneal scars due to the HK between January 1995 and February 2016 were retrospectively screened. **Results:** The incidence of newly developed HK was 1.09% (17/1559). The mean interval between PK and HK was 30.41±39.31 months (range 1-139 months). Dry eye was present in 82.3%, corneal neovascularization in 41.2% and systemic diseases in 23.5% cases with newly acquired HK after PK. At the time of the diagnosis of HK; 82.3% of cases were using topical steroids, 23.5% of cases oral steroids and 11.8% of cases topical cyclosporine-A. In 17.6% cases HK developed after the secondary surgeries following PK. **Conclusion:** The diagnosis of HK immediately came to mind and treatment was started at once especially in persistent and atypical epithelial defect on corneal grafts. Herpetic epithelial keratitis should be remembered that it can be develop any time after PK.

Keywords: DNA polymerase, simplexvirus; keratitis, herpetic; corneal ulcer; keratoplasty, penetrating

ÖZET Amaç: Herpes simpleks virüsü (HSV) enfeksiyonu ya latent HSV'nin endojen odaklarında yeniden aktivasyonu veya penetran keratoplastiden (PK) sonra nakledilen donör korneadan eksojen iletim yoluyla gelişmektedir. Penetran keratoplasti sonrası yeni herpetik epitelyal keratit (HK) tanısı almış olan ve daha önce herpes simpleks virüs enfeksiyonu öyküsü olmayan hastaların klinik ve tedavi sonuçlarını belirlemek amaçlandı. **Gereç ve Yöntemler:** Herpetik keratit dışı kornea skar nedeniyle Ocak 1995 ile Şubat 2016 arasında PK yapılan hastaların tıbbi kayıtları retrospektif olarak tarandı. **Bulgular:** Yeni gelişen HK insidansı %1.09 (17/1559) idi. Penetran keratoplasti ile HK gelişim arasındaki süre ortalama 30,41±39,31 ay idi (1-139 ay). Herpetik keratit gelişen olguların %82,3'ünde kuru göz, %41,2'sinde kornea neovaskülarizasyonu ve %23,5'inde sistemik hastalıklar mevcuttu. Herpetik keratit teşhisi sırasında; olguların %82,3'ü topikal steroid, %23,5'i oral steroid ve %11,8'i topikal siklosporin-A kullanıyordu. Olguların %17,6'sında HK, PK'yı takip eden ikincil ameliyatlardan sonra gelişmiştir. **Sonuç:** Penetran keratoplasti sonrası herpetik epitelyal tanısı, özellikle kornea greftlerinde kalıcı ve atipik epitel defektlerinde hemen akla gelmeli ve tedavi başlanmalıdır. Herpetik epitelyal keratit PK'dan sonra herhangi bir zamanda gelişebileceği unutulmamalıdır.

Anahtar Kelimeler: DNA polimeraz, simpleks virüsleri; keratit, herpetik; korneal ülser; keratoplasti, penetran

Herpes simplex virus (HSV) is one of the most common viruses acquired by humans and by the age of 60, more than 90% of the population is latently infected with HSV.^{1,2} Herpes simplex virus is a neu-

rotropic microorganism which can uniquely stay dormant in trigeminal and autonomic ganglia innervating the site of primary infection for the lifetime of the host.^{2,3}

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After keratoplasty HSV infection may develop either by reactivation of latent HSV in its endogenous foci in trigeminal ganglia and the host's own cornea or by exogenous factors such as fever, social stress, fatigue, hypothermia, hyperthermia, skin irritation, immunosuppression and UV-B exposure, trauma, and surgical manipulation of the trigeminal ganglion.⁴⁻⁸ The another source of HSV infection is exogenous transmission from the transplanted donor cornea.⁹

Recurrent herpetic ocular infection is one of the most common indications for penetrating keratoplasty (PK) owing to creating visual morbidity by developing corneal scar, neovascularization, thinning, and occasionally perforation.¹⁰⁻¹² Recurrent herpetic keratitis (HK) on corneal graft can result in a persistent epithelial defect, graft rejection or failure.¹²⁻¹⁴ There is a limited number of studies on the herpetic epithelial keratitis after PK without previous history of HK after PK.^{15,16} These two studies have focused on endogenous factors (topical corticosteroid usage, graft failure, secondary surgeries such as suture removal) for HSV activation after PK. On search with PubMed, using key words "herpetic keratitis" and "penetrating keratoplasty", we were not able to find any articles on association between new onset HK after PK on corneal graft and dry eye or systemic disease. Therefore, it is essential to identify the pathologies and conditions encountered in patients during the diagnosis of HK after PK. We aimed to investigate the characteristics of patients with herpetic epithelial keratitis after PK without previous history of HK and its association with dry eye, neovascularization and systemic diseases.

MATERIAL AND METHODS

This study was approved by the ethics committee of Ankara Training and Research Hospital (Ankara, Turkey) and it conforms to the principles of the Declaration of Helsinki (2008- Clinical Trial Protocol Number: 5307). It retrospectively reviewed the medical records of patients who underwent PK for reasons other than corneal scars due to the herpetic keratitis between January 1995 and February 2016.

DIAGNOSIS OF HSV KERATITIS

The criteria for diagnosis of HSV keratitis with typical dendritic keratitis after PK were based only on the

clinical findings of HSV infectious keratitis and the respond to the treatment of HSV keratitis. The diagnosis of HSV keratitis with atypical epithelial lesion was based on the differential diagnosis and respond to the treatment of HSV keratitis as in the study of Rezende et al.¹⁵

TREATMENT OF HSV KERATITIS

The treatment for new onset HSV keratitis after PK was modified according to whether the infection was epithelial and/ or stromal. In epithelial keratitis; topical cyclopentolate HCl 1% (Sikloplejin, Abdi İbrahim, İstanbul, Turkey) two times a day, acyclovir ointment 3% (Zovirax, Glaxosmithkline, Draxis-Pharma, Canada) five times a day, and moxifloxacin 0.5% (Vigamox, Alcon, Forte Worth, TX, USA) five times a day were started and topical steroid use was discontinued. In stromal keratitis the dosage of prednisolone sodium phosphate 1% (Predforte, Allergan, Irvine, CA, USA) was reduced to two times a day. Oral acyclovir 5x400 mg (Asiviral, Terra Pharma, ToprakPharma, İstanbul, Turkey) was started. After the infection was controlled, the dose was gradually reduced and 2x400 mg was used prophylactically for 1 year.¹⁷ Oral corticosteroid was started at a dose of 0.5 mg/kg/day for intense inflammation. The dosage was adjusted according to the clinical status of the patients.

TREATMENT OF GRAFT REJECTION

Topical corticosteroids were started on an hourly basis and oral steroids at a dose of 1 mg/kg/day in patients with graft rejection after PK. Oral CsA was not used in any of the cases.

Demographic properties, surgical indications, follow-up time, time between PK and new onset HK on graft, intrasurgical and postsurgical complications, topical and systemic therapies, and additional surgical procedures were recorded.

The descriptive statistics and frequencies were calculated using The Statistical Package for the Social Sciences 16.0 (SPSS Inc. Chicago, IL, USA).

RESULTS

Our study revealed that HK developed for the first time after PK in 17 of 1559 cases who underwent PK

due to reasons other than corneal scars caused by herpetic keratitis. The demographic properties and the clinical features of the patients are shown in Table 1. The mean age was 41.82±12.09 years (range 15-55 years); 10 subjects were male and 7 were female. The mean interval between PK and HK was 30.41±39.31 months (range 1-139 months). The mean follow-up duration was 48.06±3.33 months (range 12–126 months).

Herpetic keratitis occurred within the first 6 months in 6 eyes (35.3%), between 6 and 12 months in 2 eyes (11.9%), between 12 and 24 months in 3 eyes (17.6%), between 24 and 60 months in 3 eyes (17.6%), and after 60 months in 3 eyes (17.6%).

At the time of the diagnosis of HK, none of the patients had a history of febrile illness, trauma, long-term exposure to sunlight and UV-B. Two of 7 (28.6%) female patients were in their menstrual cycle.

The pathologies and conditions encountered in patients during the diagnosis of HK after PK were investigated (Table 2). Systemic disease was present in 4 patients (23.5%), of which 2 (11.8%) had diabetes mellitus (DM) and the other 2 (11.8%) had rheumatoid arthritis (RA). Neovascularization was present in 7 cases (41.2%), of which 5 cases developed neovascularization before PK and 2 cases after PK.

Fourteen cases (82.3%) had dry eye. The study population had a mean break-up time (BUT) of 6.81±2.19 (3-12) seconds; 12 of them had a history of artificial tear drops use while 2 cases had a history of additional use of topical cyclosporine A (CsA) (Restasis; Allergan, Irvine, CA, USA).

The usage patterns and the dosage of the drugs were provided in Table 1. Four-

TABLE 1: Clinical data and characteristics of cases with new onset of HK after PK.

Case	Gender	Age	Primary Diagnosis of PK	Time interval between PK and HK (month)	Type of HK on grafts	Localization of the HK	The number of recurrence	Follow-up time (month)	Graft Status
1	F	23	Corneal dystrophy	8	Epithelial	Inferior	2	24	Failure
2	M	47	Descematocele	9	Epithelial+stromal	Central	1	28	Clear
3	M	49	Scar secondary to bacterial keratitis	5	Epithelial	Central	1	13	Clear
4	M	46	Keratoconus	13	Epithelial	Central	2	38	Clear
5	F	50	Corneal dystrophy	13	Epithelial	Temporal	1	24	Clear
6	M	54	Bullous keratopathy	11	Epithelial	Central	2	39	Clear
7	F	15	Keratoconus	46	Epithelial	Central	1	56	Clear
8	F	31	Scar secondary to trauma	15	Epithelial	Inferior	3	66	Clear
9	M	48	Scar secondary to trauma	72	Epithelial	Temporal	1	88	Clear
10	M	43	Scar secondary to bacterial keratitis	32	Epithelial	Inferior	1	45	Clear
11	M	55	Scar secondary to bacterial keratitis	6	Epithelial	Central	3	12	Clear
12	M	53	Scar secondary to bacterial keratitis	24	Epithelial	Central	1	48	Failure
13	M	23	Keratoconus	139	Epithelial+stromal	Inferior	2	188	Clear
14	M	48	Descematocele	3	Epithelial	Superior	1	12	Clear
15	F	32	Keratoconus	26	Epithelial	Temporal	1	33	Clear
16	F	54	Scar secondary to trauma	1	Epithelial	Central	4	89	Failure
17	F	30	Keratoconus	104	Epithelial	Superior	1	156	Clear

HK: Herpetic keratitis, HSV: Herpes simplex virus, PK: Penetrating keratoplasty.

TABLE 2: The pathologies and conditions encountered in patients during the diagnosis of HK after PK.

Case	Systemic disease	Dry eye	Vascularization use (dosage)	Topical steroid use (dosage)	Topical CsA (dosage mg/daily)	Oral steroid use infection	Previous bacterial rejection	Previous graft surgeries	Secondary
1		+		+ (2x1)	-	-	-	-	
2	RA	+	360°	+ (1x1)	-	-	-	-	
3		-		+ (4x1)	-	-	-	-	
4		+		+ (8x1)	-	+ (60)	-	+	Suture removal
5		-		+ (1x1)	-	-	-	-	
6	DM	+	180°	+ (1x1)	+ (4x1)	-	-	-	
7		+		+ (4x1)	-	-	-	-	Cataract surgery
8		+	120°	+ (6x1)	-	+ (40)	-	+	
9	DM	+	120°	-	-	-	-	-	
10		+	90°	+ (8x1)	-	+ (80)	-	+	
11		+		+ (3x1)	-	-	-	-	
12		-		-	-	-	-	-	
13		+		+ (3x1)	-	-	+	-	
14	RA	+		+ (6x1)	+ (4x1)	-	-	-	
15		+		+ (4x1)	-	-	+	-	
16		+	360°	+ (12x1)	-	+ (60)	-	+	
17		+	90°	-	-	-	-	-	TRAB

CsA: Cyclosporine-A, DM: Diabetes Mellitus, RA: Rheumatoid arthritis, TRAB: Trabeculectomy.

teen cases (82.3%) were using topical steroids at the time of the diagnosis of HK. Topical steroid was used for routine anti-inflammatory prophylaxis in 7 cases (41.2%), for graft rejection in 4 cases (23.5%), following secondary surgical interventions after PK in 2 cases (11.8%), and for bacterial infection in 1 case (5.9%). Oral steroid was used for graft rejection in 4 cases (23.5%). Two cases (11.8%) were found to sustain bacterial keratitis before HK.

Herpetic keratitis was identified after secondary surgical interventions following PK in 3 cases (17.6%). In the first case, the patient developed graft rejection three days after the removal of the keratoplasty sutures. Herpetic keratitis developed 1 week after commencement of topical and oral steroids. In the second case HK developed 2 weeks after cataract surgery that was performed after PK. In the third case, HK was identified 1 month after trabeculectomy (TRAB) surgery for glaucoma that persisted despite treatment following PK.

Two cases (11.8%) that suffered HK underwent amniotic membrane transplantation in addition to medical treatment. While all cases had graft transparency before HK, graft transparency was lost in three cases (17.6%) who later underwent re-PK.

DISCUSSION

Corneal transplantation is the most common and successful tissue transplantation performed worldwide.¹⁸ The major factors affecting graft survival are appropriate host and donor selection, surgical technique, and the management of all possible complications after PK. Since it was reported that typical dendrites were rarely seen in newly acquired HSV keratitis, and that stromal keratitis with edema could be confused with graft re-

jection, the diagnosis of HK immediately came to mind and treatment was started at once especially in persistent and atypical epithelial defect on corneal grafts.^{11,15,19} Remeijer et al. reported that the rate of new onset HK was 0.85% over a period of 15 years; in the current study, comprising a period of nearly 21 years, the incidence was 1.09%.¹⁶

The first mechanism of the reactivation of a latent HSV in patients who had PK without previous history of HSV is the possibility of transmission of virus through the donor cornea. Remeijer et al. proposed that HSV-1 DNA was positive in 48% (40/83) of patients with HK and 4% (15/367) in patients without HK.¹⁷ Kaye et al. reported the presence of three different HSV-1 DNA sequences in patients who underwent PK for nonherpetic reasons.⁵

After keratoplasty HSV infection may also develop by endogenous reactivation of latent HSV in the recipient's trigeminal nerve and/or cornea.^{2,4,5} As the HSV-1 DNA of patients with HK was found to be approximately 100-times greater than the patients without HK, Hill and Clement proposed that the recipient's corneal rim contains enough HSV-1 DNA that might reactivate, migrate to the transplanted cornea, and cause an immune response.²⁰ HSV can be reactivated in the graft after PK due to a systemic disorder of the recipient, corneal vascularization, dissection of corneal nerves during surgery, use of topical or systemic steroids and immunosuppressive agents, secondary surgeries, and suture removal.

The association between new onset of HK after PK and dry eye or systemic disease has not been studied. Four (23.5%) of our cases had systemic disorders, of whom 2 had DM and 2 had RA. Both DM and RA are chronic, progressive, inflammatory, and multisystem disorders that are characterized by dry eye. These cases frequently have dysfunctional lacrimation and reduced ocular defense mechanism, putting them at lifetime risk of post-PKP herpetic re-activation.

Corneal incisions from radial keratotomy and disruption of corneal nerves during PK trigger HSV reactivation in the trigeminal ganglion and its subsequent release from the nerve endings in the cornea.^{2,21,22} Rezende et al., in a 14-case series of new-onset HK after PK, proposed that severing corneal

nerves during PK could provide a strong stimulus for HSV-1 reactivation because the nerve density of the corneal epithelium is 300 to 600 times that of skin.¹⁵ The ocular HSV occurs six times more frequently in patients who had undergone PK for nonherpetic corneal disease.^{2,15} In addition to the intraoperative trauma, topical steroids given from the first postoperative day in the absence of concomitant antiviral therapy can also increase the viral load and play a role in the reactivation of latent HSV-1.^{12,21,22} Remeijer et al. reported that 77.8% (14/18) of newly acquired HK cases used topical steroid and 50% (7/14) of them used steroids at high dose (four to six times daily).¹⁶ Rezende et al. reported that 71% (10/14) of cases used topical steroid more frequently than once a day, with 20% (2/10) of these having used steroid at high dose due to the graft rejection and 10% (1/10) having used topical CsA in addition to topical steroid.¹⁵ In our study, 82.3% of the cases had a history of topical steroid usage, 57.1% of them used topical steroid more than four times a day. Among these, 23.5% used oral steroid for graft rejection (between 40-80 mg daily), and 11.8% topical CsA four times daily for dry eye.

In this study, at the time of the diagnosis of HK, 14 cases (82.3%) had dry eye; 12 of them had a history of tear drops use and 2 had a history of topical CsA use in addition to tear drops. PK surgery may lead to dry eye by both transecting corneal nerves during corneal dissection and by causing inflammation at the healing phase.²³ Dry eyes are more prone to infectious complications due to disturbed ocular defense mechanisms.²⁴

Cytotoxic CD8 T cells play an important role and CD4 T helper cells are also involved in the clearance of infectious HSV. Because CsA is a potent T-cell immunosuppressant, herpetic recurrence is thought to be triggered by systemic CsA.^{25,26} None of our cases were using oral CsA at the time of diagnosis but two of our patients were using topical CsA for dry eye. Topical CsA has been successfully used for the management of dry eye disease and ocular surface disorders requiring immunomodulatory therapy and to suppress inflammation.²⁷ Although it has been reported that topical CsA reduces corneal inflammation, enhances visual acuity, reduces corneal

vascularization in non-necrotizing HK, recurrent cases having been observed upon the discontinuation of the drug; hence, topical CsA was stopped in two patients after the diagnosis was made as more large-scale studies are needed for the use of topical CsA during herpetic epithelial keratitis.^{23,26}

It was reported that the interval between the transplantation and the new onset of the keratitis varied from 1 day to 13 years and mostly 2 years, especially in the 1st year (61%).^{15,16} We observed that HK commonly developed in the first 6 months (35.3%) and beyond 1 year its risk was increased after graft failure and secondary surgeries. We attributed this finding to a more intense surgery-associated inflammation and topical steroid use in the first 6 postoperative months and to the use of topical steroid, oral steroid, and topical cyclosporin-A without using concomitant antiviral therapy in the later periods.

The initial site of the disease is still controversial. Unlike Biswas, Nicholls et al., in an experimental animal model, demonstrated that the graft-host junction was the region from which the release and spread of virus occur.^{4,14} Neovascularization is a serious risk factor for HSV recurrences, immune rejection, and graft failure following high-risk keratoplasty.²⁸ The site of neovascularization at the host cornea is also suitable for the beginning and spread of the HSV-1 due to the transport of cellular and serum components of inflammation and host immune responses.²⁸ Garcia et al. demonstrated that corneal neovascularization was an important preoperative clinical factor indicative of actual inflammation in the diseased cornea due to the significant correspondence between the presence of preoperative clinical corneal neovascularization and the histopathologic presence of inflammation in the same corneal specimens after removal at PK.²⁹ In our study, 7 cases (41.2%) had vascularization before the diagnosis of HK. We attributed the lack of a significant association between the presence of vascularization and initial HK quadrant to a small number of subjects. However, it was observed that vascularization occurred at the central part of the HK graft in 3 eyes that featured vascularization of 180° or above, while it developed in the quadrant of vascularization in 4 eyes with a vascularization of below 180°.

Graft survival in HK cases is affected by the presence of vascularization, number of attacks, attack intensity, and treatment response.²⁹⁻³¹ Bachmann et al. found that corneal vascularization increased the risk of graft failure with a risk ratio of 1.32, with the risk increasing as more quadrants were involved.³² Goodfellow et al. reported that patients who had experienced a rejection episode were more than twice as likely to have a failed graft at 5 years.³⁰ In that 17-case series, graft transparency could not be achieved and re-PK was performed in 2 cases with combined epithelial and stromal keratitis and 1 case with a vascularization of 360 degrees and 4 attacks of epithelial keratitis.

Our study has some limitations. First, since the viral cultures were not performed, we can not rule out the possibility that we have misclassified the epithelial defects without dendritic form and keratouveitis as herpetic as emphasized in the study of Rezende et al.¹⁵ But all eyes were treated successfully after antiviral treatment was initiated. It is also often difficult to claim that we have caught all herpetic keratitis episodes. Second, a risk analysis for factors that could cause HK activation could not be performed since no control group comprising cases who underwent PK for reasons other than HK and those who did not develop HK could not be formed. Third, the types and dosages of medications used for steroid (topical, oral) therapy after PK were not the same over the 21-year study period. Topical CsA is available since 2002.²³ The evaluation for dry eye was not performed after PK in every patient, and whenever it was done, the same tests were not used for every patient, and the effects of the preservatives found in eye drops administered for dry eye on graft survival were not studied. Dry eye evaluation was based on patient symptoms and clinical signs and BUT specified in medical records. There is a need for conducting multicenter prospective studies to reveal the association between recurrent and newly developed herpetic cases and dry eye.

CONCLUSION

The diagnosis of herpetic epithelial keratitis should come to mind immediately especially in patients with atypical or persistent epithelial defects. Patients

should be thoroughly evaluated for the presence of systemic diseases and dry eye, and it should be always remembered that post-PK neovascularization, topical and oral treatments, and secondary surgeries may trigger the development of HK. As HK was more prevalent in cases undergoing PK compared to the normal population, it should not be forgotten that there is a lifetime HK risk after PK even in persons without a history of HK.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: Evin Şingar, Ayşe Burcu, Firdevs Örneç; **Design:** Evin Şingar, Züleyha Yalnız Akkaya; Ayşe Burcu; **Control/Supervision:** Ayşe Burcu, Züleyha Yalnız Akkaya **Data Collection and/or Processing:** Evin Şingar, Züleyha Yalnız Akkaya, Ahmet Kaderli; **Analysis and/or Interpretation:** Evin Şingar, Ayşe Burcu, Züleyha Yalnız Akkaya, Ahmet Kaderli; **Literature Review:** Evin Şingar, Firdevs Örneç; **Writing the Article:** Evin Şingar, Züleyha Yalnız Akkaya; **Critical Review:** Züleyha Yalnız Akkaya, Ayşe Burcu.

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