A Clinical Study on Peripheral Ulcerative Keratitis of Non-Infective Aetiology

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ABSTRACT

BACKGROUND

Peripheral ulcerative keratitis (PUK) is a destructive inflammatory disease of the juxta-limbal corneal stroma that is caused by various infectious and non-infectious ocular and systemic diseases. Certain morphologic and immunologic characteristics of peripheral cornea make it more vulnerable to inflammatory reactions and necrosis. Early diagnosis and prompt treatment prevent blindness due to this devastating inflammatory condition. We wanted to study the aetiology, clinical features and outcome of various treatment modalities of peripheral ulcerative keratitis of non-infective aetiology.

METHODS

54 eyes of 40 patients with peripheral ulcerative keratitis of non-infective aetiology were evaluated and treated with either medical or surgical therapy or both in a tertiary care centre and were followed up. The total study duration was 12 months.

RESULTS

60 percent of cases were males (24 / 40). The most common age group affected was 60 - 70 years (32.5 %) and the mean age in our study group was 57.7 ± 18.33 years. 65 % were unilateral (26 / 40). In our study 15 eyes (27.77 %) had meibomitis. 13 % of eyes had mild involvement, 40.8 % eyes had moderate involvement, 46.2 % eyes had severe involvement. Severe involvement was the most common presentation. The incidence of perforated PUK in the study group was 20.37 % (11 / 54 eyes). 45 % were found to have unknown aetiology. Of the remaining, the most common aetiology was Mooren's ulcer (32.5 %) followed by rheumatoid arthritis (20 %) and Systemic Lupus Erythematosus (2.5 %). Among 54 eyes, the resolution of signs of active PUK was seen in 50 eyes (92.59 %) after treatment. Visual acuity improvement noted on comparison of mean of pre-treatment visual acuity 0.90 with standard deviation 0.39 and the mean of post treatment visual acuity 0.62 with standard deviation 0.37 logarithm of minimum angle of resolution units with P value is < 0.001 which is significant. For perforated peripheral ulcerative keratitis eyes, patch graft was found to be successful in 87.5 %. Peritomy was successful in 100 % and peritomy with amniotic membrane graft was successful in 70 %.

CONCLUSIONS

In our study, male patients were more than female and the commonest presentation was unilateral. Most common aetiology was idiopathic followed by Mooren's ulcer, rheumatoid arthritis and systemic lupus erythematosus. Mild to moderate cases respond well to medical management. Severe cases need immunosuppressants. Perforated cases needs surgical intervention especially patch graft which is better in achieving good anatomical integrity and enhanced visual acuity. Early referral of patients with peripheral ulcerative keratitis to a tertiary care centre helps in early treatment which is beneficial in avoiding blindness.

KEYWORDS

Peripheral Ulcerative Keratitis, Non Infective, Immunosuppressants, Patch Graft

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DOI: 10.18410/jebmh/2020/622

How to Cite This Article:
Arumugam S, Vadivelu SD, Senthilkumar NK, et al. A clinical study on peripheral ulcerative keratitis of non-infective aetiology. J Evid Based Med Healthc 2020; 7(50), 3050-3054. DOI: 10.18410/jebmh/2020/622

Submission 25-07-2020,
Peer Review 01-08-2020,
Acceptance 18-10-2020,
Published 14-12-2020.

BACKGROUND

A crescent-shaped destructive inflammation at juxta limbal corneal stroma, with associated epithelial defect, presence of stromal inflammation, and progressive stromal degradation and thinning defines peripheral ulcerative keratitis. Progressive necrosis of the corneal stroma, can lead to perforation and blindness. The peripheral cornea is different from central cornea in morphologic and immunologic characteristics and it is prone to inflammatory reactions.

Unique Features of the Peripheral Cornea

Peripheral cornea is 1 mm in thickness which is greater than the central cornea. Epithelium is tightly adherent to underlying structures and epithelial stem cells are highly concentrated in the peripheral cornea. It has more access to blood vessels and lymphatics. Endothelial cells in peripheral cornea have maximum mitogenic activity. Collagen fibres are loosely arranged, and nerve fibres are less dense in the peripheral cornea wherein the central cornea is heavily innervated. Peripheral cornea depends upon the blood vessels from the edge of the cornea for nutrients whereas the central cornea derives its nutrients from aqueous humour. The membrane associated Mucins MUC 4 is present in higher levels in the periphery which may be associated with serum albumin from the capillaries of peripheral cornea.

- Unique immunological features of peripheral cornea are more concentration of Langerhans cells, IgM, C1 (first component of complement cascade), immune complexes due to diffusion from limbal vessels because of its large size.

Matrix Metalloproteinases in PUK

Activated matrix metalloproteinase I (MMP-I or collagenase I), is a lytic enzyme against type I collagen of corneal extracellular matrix, has been identified as causative agent of PUK. It is also suggested that MMP-I is produced by the keratocytes or infiltrating macrophages. The local imbalance between collagenases such as MMP-1 and the tissue inhibitors such as TIMP-1 results in rapid keratolysis and PUK.

MMP-8 (a neutrophil collagenase) is expressed in inflammatory conditions and it is important in wound healing and tissue remodelling. Production of MMP-2 & MMP-9 has been implicated in the progression of PUK and causes perforation by breaching the basement membrane. If peripheral cornea encounters any inflammatory stimulus due to microbial organisms invasion, trauma, malignancy, immune complex deposition due to systemic immune diseases, or dermatologic conditions it may result in activation of local and systemic immune responses, which results in leucocytes recruitment and complement pathway activation.

Mooren's ulcer was the leading cause of collagen vascular diseases, infections are next important causes of PUK in developing countries.[1] Mooren's was first described by Bowman in 1849, then by McKenzie in 1854 as "a chronic serpiginous ulcer". Mooren's ulcer is an idiopathic condition without any diagnosable systemic disorder and with no associated scleritis.[2] It may be an autoimmune corneal disease which is difficult to manage and can cause blindness.[3] To rule out the underlying aetiology, there should be thorough historical review of systems.[4] Cell mediated immune mechanisms appear to be important in aetiopathogenesis of PUK and a combination of corticosteroids and cyclosporine is therefore probably the regimen of choice.[5] Infliximab is an alternative to cases not responding to corticosteroids and methotrexate.[6]

In recent days biological therapy such as antagonists of B cells (rituximab), T cells (abatacept), TNF-α (etanercept, infliximab), IL-1 (anakinra), IL-6 (tocilizumab) has been included in clinical applications.[7]

Tauber et al[4] graded corneal ulceration in PUK based on the depth of thinning as:

- Grade 1 - < 25 percent
- Grade 2 – 25 - 50 percent
- Grade 3 – 50 - 75 percent
- Grade 4 – 75 - 100 percent

Images 1a, 1b, 1c show slit lamp images of PUK of grade 2, grade 3 and grade 4 respectively.

Indications for systemic immunosuppression with chemotherapeutic agents include:

1. PUK with active systemic autoimmune disorders such as rheumatoid arthritis, polyarteritis nodosa, relapsing polychondritis, Wegener's granulomatosis.
2. PUK associated with scleritis.
3. PUK associated with ocular vasculitis.
4. Bilateral PUK with simultaneous involvement.
5. Non-responding PUK after adequate medical and surgical therapy.

Cases with impending or actual corneal perforation may require more extensive surgery, including lamellar or penetrating keratoplasty, to maintain the integrity of the globe.[8] Various surgical modalities for PUK includes peritomy, peritomy with amniotic membrane graft, and patch graft. Recent study recommends tuck-in Tenon Patch Graft (TPG) for perforations up to 5 mm size for which it is a safe, inexpensive and an effective technique[9]. Our study aims to analyse the aetiology, clinical presentation, outcome of various treatment modalities of PUK of non-infective origin.

METHODS

In this prospective interventional case study, a hospital based sequential sampling of cases was adopted as sampling method. The Institutional Ethics Committee, Madras Medical College approved the study and prior informed consent was obtained from all participants. Case recruitment period was 6 months (from 01/11/2017 to 30/04/2018) and follow up period was 6 months (from 01/05/2018 to 31/10/2018).

54 eyes of 40 patients who presented and were diagnosed as PUK of non-infective aetiology at Cornea Services Department, RIOGOH (Regional Institute of Ophthalmology and Government Ophthalmic Hospital), Madras Medical College, Chennai were included in our study.

A detailed history of the patient, complete general and systemic examination was done. Best corrected visual acuity using Snellen chart, intraocular pressure measurement using noncontact tonometry / rebound tonometry, detailed slit lamp anterior segment evaluation and complete posterior segment examination was done.

Corneal smear examination with gram staining and KOH (Potassium Hydroxide Preparation) mount, complete urine and blood investigations to rule out any underlying infectious and non-infectious aetiology was done. Patients were referred to general physician and rheumatologist for expert opinion.

Cases were managed medically or surgically according to the aetiology and severity. Immunosuppressive, oral methotrexate 10 mg / wk. along with folic acid and oral azathioprine 1 mg / kg / day were given to severe cases and who had underlying collagen vascular disease after rheumatologist opinion. Cases presented with perforation and cases which had perforation during treatment and non-responding cases were managed surgically.

Outcome of the treatment, resolution of signs, visual acuity improvement were assessed in the follow up period of six months. Outcome was named successful when the ulcer became epithelized, avascularised and stable and named failure when there was persistent epithelial defect with persistent vascularisation and progressive thinning.

Inclusion Criteria

1. Patients presenting with peripheral ulcerative keratitis of non-infective aetiology.
2. Age >18 years.

Exclusion Criteria

Peripheral degenerative conditions such as Terrien's marginal degeneration, senile furrow degeneration.

RESULTS

Statistical method: Paired t-test was used to calculate the significance level. A Type 1 error of 0.05 was considered as significant. The study was conducted on 54 eyes of 40 patients, of which 60 % were male and 40 % were female. The most common age group affected was 60 - 70 years (32.5 %) (Figure 1) The mean age in our study group was 57.7 ± 18.33 years. Out of 40 patients 26 (65 %) had unilateral presentation and 14 (35 %) had bilateral presentation. In this study group 13 % of eyes had mild involvement, 40.8 % eyes had moderate involvement, 46.2 % eyes had severe involvement. Severe involvement was the most common presentation. This classification has taken into account both the extent of clock hours involvement & depth of thinning. In our study mean grade of depth of ulceration at presentation was 2.57. The incidence of perforated PUK in the study group was 20.37 % (11 / 54 eyes). The number of cases with perforation at the time of presentation was 7 eyes & during the course of therapy was 4 eyes. In our study 15 eyes (27.77 %) had meibomitis. In this study group, 45 % were found to have unknown aetiology. Of the remaining, commonest was Mooren's ulcer (32.5 %), rheumatoid arthritis (20 %) followed by systemic lupus erythematosus (2.5 %).

Among 54 eyes, resolution of signs of active PUK was seen in 50 eyes (92.59 %) after treatment. Among the various surgical modalities, patch graft was successful in 87.5 % (7 out of 8 eyes), peritomy was successful in 100 % (2 out of 2 eyes) and peritomy with amniotic membrane graft was successful in 70 % (7 out of 10 eyes).

Images 2a, 2b are pre- and post-operative images of peritomy with amniotic membrane grafting and patch graft of PUK affected eyes. Table 1 and 2 show medical and surgical management of PUK affected eyes.

Comparison of visual acuity shows there is significant improvement between pre-treatment and post treatment visual acuity. The mean of pre-treatment visual acuity was 0.90 (LogMAR) with standard deviation 0.39 and the mean of post treatment visual acuity was 0.62 (LogMAR) with standard deviation 0.37 and the p value is < 0.001 which is significant. Table 3 shows comparison of mean of pre- and post-treatment visual acuity in LogMAR (Logarithm of the Minimum Angle of Resolution).

Among the various surgical modalities, patch graft had visual acuity improvement from mean pre-treatment vision 1.29 (LogMAR) to mean post treatment vision 0.85 (LogMAR) and the P value was < 0.05 which is significant. For peritomy, mean pre-treatment visual acuity was 0.55 and mean post treatment mean visual acuity was 0.1 and the p value was 0.05.

Among the peritomy with AMG (Amniotic Membrane Graft) cases, the pre-treatment mean visual acuity was 0.99 and post treatment mean visual acuity was 0.84 and p value is > 0.05 which is not significant. Table 4 shows comparison of mean pre-treatment and post treatment visual acuity for patch graft, peritomy and peritomy with AMG.

Limitation here was the number of eyes undergone patch graft was 8 and the number of eyes undergone peritomy was only 2 and peritomy with AMG was 10. There was gross difference in number of eyes which underwent patch graft or peritomy with AMG or peritomy alone.

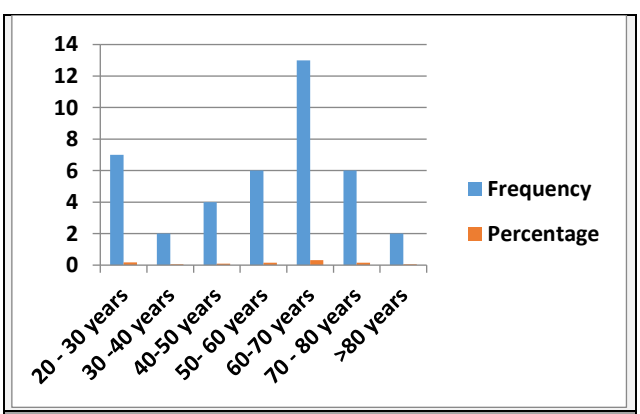

Figure 1. Age Distribution in the Study Group

	Medical Management	Outcome
Mild N = 7	Topical prednisolone acetate 1 % n = 3 Topical + oral steroids n = 4	Cornea epithelised, avascularised and stable for all cases
Moderate n = 22	Topical prednisolone acetate 1 % + oral steroids n =16	Cornea epithelised, avascularised and stable for all cases. 4 eyes had mild progression which was controlled after peritomy (2 eyes) and peritomy with AMG (2 eyes).
	Topical prednisolone acetate 1 % + topical cyclosporine 0.05 %+ oral steroids n = 6	
Severe N = 25	Topical +oral steroids n = 2	Success n = 1 (50 %) Failure (Requiring Surgery) n= 1 (50 %)
	Topical cyclosporine 0.05 % + oral steroids n = 7	Success n = 0 Failure (Requiring Surgery) n= 7 (100 %)
	Topical steroid + cyclosporine +oral steroids n = 7	Success n = 4 (57.14 %) Failure (Requiring Surgery) n= 3 (42.8 %)
	Topical meds +systemic methotrexate / azathioprine n = 9	Success n = 4 (44.44 %) Failure (Requiring Surgery) n= 5 (55.55 %)

Table 1. Medical Management and Outcome of Treatment of PUK Affected Eyes

	Surgical Management	Outcome	Percentage (Outcome)
Mild N = 0	-	-	-
Moderate n = 4	Peritomy (conjunctival resection) n = 2	Good anatomic integrity Healthy and stable cornea	100 %
	Peritomy with AMG n = 2	Better visual acuity	100 %
Severe n = 16	Peritomy with AMG n = 8	Good anatomic integrity Healthy and stable cornea Better visual acuity n = 5	62.5 %
		Persistent inflammation Progressive thinning Unable to maintain anatomic integrity n = 3	37.5 %
	Patch graft n = 8	Good anatomic integrity Healthy and stable cornea Better visual acuity n = 7	87.5 %
		Persistent inflammation Progressive thinning Unable to maintain anatomic integrity n = 1	12.5 %

Table 2. Surgical Management and Its Outcome in PUK Affected Eyes

Variable	Time Point	n	Mean	S.D.	P-Value
Visual acuity (LOGMAR)	Pre treatment	54	0.90	0.39	< 0.001
	Post treatment	54	0.62	0.37	

Table 3. Comparison of Pre- and Post-Treatment Visual Acuity in LogMAR

Surgical Therapy	Variable	Time Point	n	Mean	S.D.	P-Value
Patch Graft	Visual acuity (LOGMAR)	Preoperative	8	1.29	0.15	< 0.05
		Postoperative	8	0.85	0.49	
Peritomy	Visual acuity (LOGMAR)	Preoperative	2	0.55	0.05	0.05
		Postoperative	2	0.1	0.14	
Peritomy with AMG	Visual acuity (LOGMAR)	Preoperative	10	0.99	0.28	> 0.05
		Postoperative	10	0.84	0.40	

Table 4. Comparison of Pre- and Post-Operative Visual Acuity in LogMAR for Various Surgical Modalities

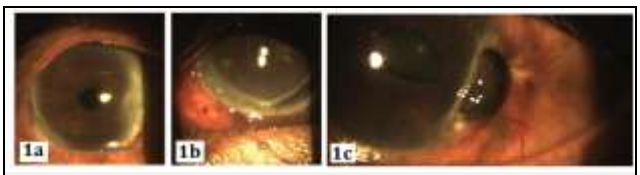

Image 1a, 1b, 1c. Slit Lamp Images of PUK of Grade 2, Grade 3 and Grade 4 Respectively

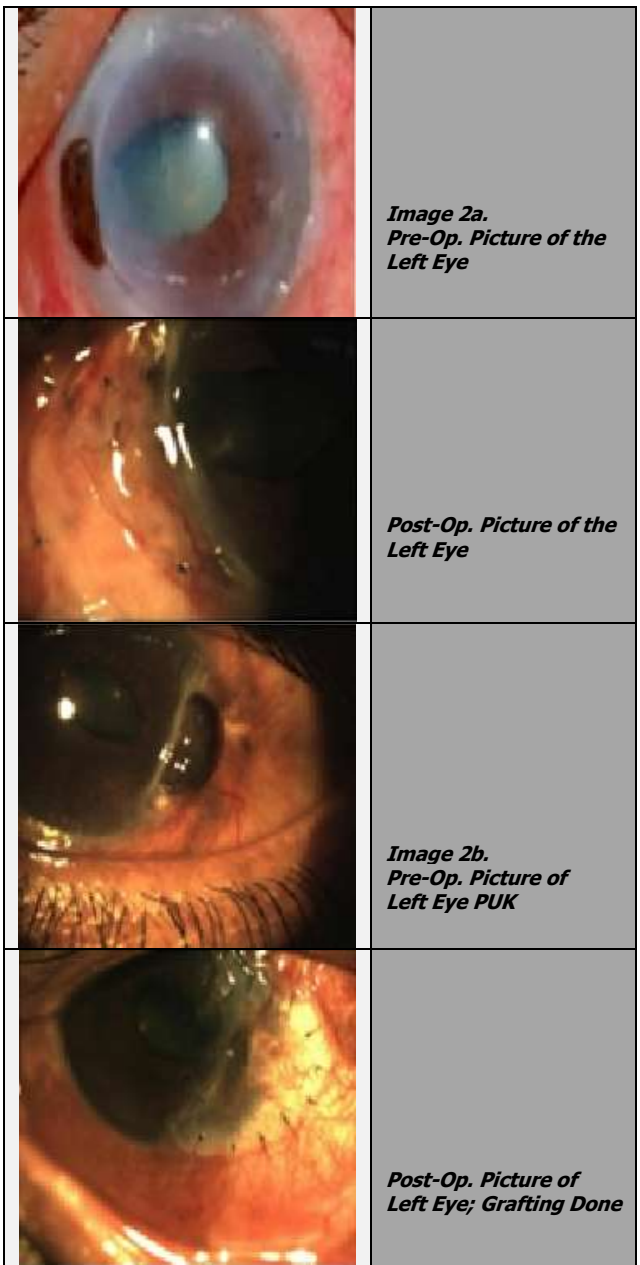

Image 2a.
Pre-Op. Picture of the Left Eye

Post-Op. Picture of the Left Eye

Image 2b.
Pre-Op. Picture of Left Eye PUK

Post-Op. Picture of Left Eye; Grafting Done

Image 2a, 2b. Pre- and Post-Operative Images of Amniotic Membrane Grafting and Patch Graft of PUK Affected Eyes

DISCUSSION

In our study the maximum number of patients (32.5 %) were in 60 - 70 years age group. The mean age in our study group was 57.7 ± 18.33 years. Sixty percent of cases were men and forty percent cases were women. It is similar to Sharma et al study in which sixty percent of cases were men and the mean age was 45.5 ± 17.9 years.[1] In our study unilateral cases were 65 % (26 / 40) and bilateral cases were 35 % (14 / 40). Unilateral presentation was the most common presentation. Sharma et al study also showed unilateral presentation (83 %) is more common than bilateral presentation.[1]

In our study mean grade of depth of ulceration at presentation was 2.57 which is comparable to another study conducted by Tauber et al in which the mean depth of ulceration was grade 2.[4] In our study 15 eyes (27.77 %) had

meibomitis. It is comparable to Sharma et al study where meibomitis was present in 22.3 % of eyes (17 / 76).[1] In our study 32.5 % (13 / 40) had Mooren's ulcer followed by rheumatoid arthritis 20 % (8 / 40). This is similar to Sharma et al study in which the Mooren's ulcer was the most common aetiology 31.5 % (24 / 76 eyes) followed by systemic collagen vascular diseases.[1]

Medical Management

Topical cyclosporine eye drops alone were given to 18.5 % eyes (10), topical steroids prednisolone acetate 1 % eye drops were given 55.6 % of eyes (30), both were given to 25.92 % eyes (14). Oral steroids were given to 94.44 % of eyes (51 / 54). Systemic immunosuppressants oral methotrexate 10 mg / wk. were given to 8 cases (14.81 %) and oral azathioprine 1 mg / kg / day was given to 1 patient (1.85 %) as these eyes had severe PUK and associated with underlying systemic collagen vascular disease. Treatment was successful in all mild cases which received medical management alone. It is similar to Sharma et al study, where the mild cases treated with medical therapy alone was successful in all eyes.[1]

Surgical Management

In our study group, the eyes undergone patch graft was 8 (14.81 %), peritomy (conjunctival resection) was 2 (3.7 %) and peritomy with AMG was 10 eyes (18.52 %). 7 out of 8 eyes (87.5 %) that had undergone patch graft, 2 eyes that had undergone peritomy (100 %) and 7 out of 10 eyes (70 %) that had undergone peritomy with AMG were able to maintain good anatomic integrity, healthy and stable cornea with better visual acuity. 1 eye which had undergone patch graft and 3 eyes which had undergone peritomy with AMG had persistent inflammation and progressive thinning and unable to maintain anatomic integrity, which were treated with penetrating keratoplasty.

In our study, surgical treatment achieved success in 80 % of eyes totally (16 / 20). It is similar to Sharma et al study in which the surgical treatment was successful in 83.3 % (30 / 36 eyes).[1] In our study on comparison of mean of pre- and post-treatment visual acuity, visual acuity improvement noted with P value of < 0.001 which was significant. Sharma et al study had reported improvement in post treatment mean visual acuity with p value of 0.085 for mild cases, 0.160 for moderate cases, 0.001 for severe cases.[1]

CONCLUSIONS

The key in peripheral ulcerative keratitis is identifying the aetiology. Treatment should be tailored on individual basis and appropriate surgical intervention should be selected and performed when necessary. Mild to moderate cases respond well to medical therapy. Systemic Immunosuppressants are helpful in severe PUK & PUK associated with collagen vascular disorders, which should be started in collaboration with rheumatologist. Surgical intervention especially patch grafts give good anatomical integrity, stable cornea and enhanced visual acuity. Early referral of patients with peripheral ulcerative keratitis to a tertiary care centre helps in early treatment which helps in avoiding blindness.

Data sharing statement provided by the authors is available with the full text of this article at jebmh.com.
Financial or other competing interests: None.
Disclosure forms provided by the authors are available with the full text of this article at jebmh.com.

REFERENCES

[1] Sharma N, Gautam S, Himanshu S, et al. Demographic profile, clinical features and outcome of peripheral ulcerative keratitis: a prospective study. The British Journal of Ophthalmology 2015;99(11):1503-1508.
[2] Sangwan VS, Zafirakis P, Foster CS. Mooren's ulcer: current concepts in management. Indian J Ophthalmol 1997;45(1):7-17.
[3] Chen J, Xie H, Wang Z, et al. Mooren's ulcer in China: a study of clinical characteristics and treatment. Br J Ophthalmol 2000;84(11):1244-1249.
[4] Tauber J, de la Maza SM, Hoang-Xuan T, et al. An analysis of therapeutic decision making regarding immunosuppressive chemotherapy for peripheral ulcerative keratitis. Cornea 1990;9(1):66-73.
[5] Squirrell DM, Winfield J, Amos RS. Peripheral ulcerative keratitis 'corneal melt' and rheumatoid arthritis: a case series. Rheumatology (Oxford) 1999;38(12):1245-1248.
[6] Thomas JW, Pflugfelder SC. Therapy of progressive rheumatoid arthritis-associated corneal ulceration with infliximab. Cornea 2005;24(6):742-744.
[7] Cao Y, Zhang W, Wu J, et al. Peripheral ulcerative keratitis associated with autoimmune disease: pathogenesis and treatment. Journal of Ophthalmology 2017;2017:7298026.
[8] Raizman MB, de la Maza SM, Foster CS. Tectonic keratoplasty for peripheral ulcerative keratitis. Cornea 1991;10(4):312-316.
[9] Sharma N, Deepali S, Maharana PK, et al. Tuck-in tenon patch graft in corneal perforation. Cornea 2019;38(8):951-954.