Demographic Characteristics, Clinical Presentations, and Risk Factors Impacting Visual Outcomes in Peripheral Ulcerative Keratitis

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Purpose: To assess the demographic characteristics, ophthalmic and systemic presentations, and risk factors impacting the outcomes in patients diagnosed with peripheral ulcerative keratitis (PUK).

Methods: This retrospective study includes patients diagnosed with PUK at a tertiary care center over 13 years. A descriptive analysis of the demographics, clinical history, and presentation was performed. A reverse risk analysis was performed to assess the PUK resolution in patients with underlying autoimmune and non-autoimmune etiologies. Finally, we evaluated the correlation between treatment duration and final best corrected visual acuity (BCVA) and continuous and categorical variables.

Results: A total of 58 eyes of 51 patients with a mean age of 59.67 ± 13.41 years diagnosed with PUK were included in the study; 58.82% were female. The resolution duration was significantly shorter in patients with autoimmune etiologies (vs. non-autoimmune etiologies, $P = 0.028$) and female patients (vs. male patients, $P = 0.008$). The BCVA worsened in patients with non-autoimmune etiologies after treatment ($P = 0.17$). Despite worse BCVA at presentation in patients with underlying autoimmune etiologies, significantly better final vision outcomes were observed ($P = 0.04$). Linear regression analysis showed that longer treatment duration ($P = 0.001$; $R^2 = 0.1704$) and worse vision ($P = 0.002$; $R^2 = 0.1502$) at presentation were the primary risk factors of poor vision outcomes. Similarly, the treatment duration was significantly longer in male compared with female patients ($P < 0.001$; $R^2 = 0.2027$).

Conclusions: The clinical outcomes in PUK with underlying autoimmune disorders were observed to be better than non-autoimmune etiologies, which may be attributed to the early detection of the PUK-related changes and aggressive medical management. A delayed diagnosis of PUK leads to poor vision outcomes.

Key Words: peripheral ulcerative keratitis, keratitis, corneal ulcers, PUK

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Peripheral ulcerative keratitis (PUK) is a potentially devastating ocular inflammatory disorder affecting the juxtalimbal area of the cornea.[1] It usually presents with crescent-shaped stromal thinning and persistent epithelial defect with or without associated scleritis.[2] The clinical characteristics of PUK depend on the underlying ocular or systemic disorder.[3] The etiological causes of PUK are classified into infectious and non-infectious and further categorized into ophthalmic and systemic diseases. It is essential for the ophthalmologists to maintain high clinical suspicion and perform thorough investigations to confirm the underlying causes that lead to PUK. More than half of the PUK cases are associated with autoimmune disorders such as rheumatoid arthritis, granulomatosis with polyangiitis, systemic lupus erythematosus, polyarteritis nodosa, progressive systemic sclerosis, Sjögren disease, relapsing polychondritis, and giant cell arteritis.[4] Among these, PUK is most commonly associated with granulomatosis with polyangiitis in the later stages of the disease.[5] Ocular and systemic infections have been reported to be the second most common causes of PUK, accounting for one fifth of all the cases.[6] PUK is associated with ocular infections in ~20% of cases, and a bacterial organism is found to be the cause in more than 70% of these cases. The systemic infections that may eventually cause PUK include *M. tuberculosis*, *C. trachomatis*, hepatitis B and C, and Varicella Zoster viruses.[2,7–9]

In some patients with PUK, no underlying etiological cause can be identified. These cases are classified as Mooren ulcer and have been reported to constitute about 30% of the PUK cases.[6] Mooren ulcer presents as chronic, painful, peripheral serpiginous ulcer occurring at the periphery of the cornea. It progresses toward the central cornea with distinct overhanging edges.[10,11] The diagnosis of Mooren ulcer is made after all the other underlying etiologies associated with PUK have been ruled out.

Although the epidemiological evidence in the literature suggests low PUK incidence (0.2–3 per million population per year), it has a devastating impact on the patient due to the

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possibility of progressive thinning and ulceration leading to corneal perforation and vision loss.[12–14] In this study, we evaluate the associated factors and management outcomes in one of the largest cohorts of patients diagnosed with PUK at a tertiary eye care center in the United States.

METHODS

This single-center, retrospective study was conducted at the UPMC Vision Institute, University of Pittsburgh School of Medicine. The study received approval from the Institutional Review Board and Ethics Committee of the University of Pittsburgh. The study was conducted in compliance with the Health Insurance Portability and Accountability Act of 1996 and in strict compliance with the tenets of the Declaration of Helsinki. The patients diagnosed with PUK between January 2007 and December 2022 were included in the study, and their clinical charts were reviewed.

The treating ophthalmologists diagnosed PUK based on the ophthalmic presentation of a crescent-shaped ulceration in the periphery of the cornea within 2 mm of limbus, presence of inflammatory infiltrate, and keratolysis and stromal thinning.[2,3,15–17] We extracted demographic and clinical information from the electronic patient records including sex, age at presentation, laterality, and initial and final best corrected visual acuity (BCVA). At presentation, the patient records were also assessed for risk factors that are typically associated with PUK including chronic dry eye disease, ocular abrasions, contact lens use, infectious keratitis, allergic conjunctivitis, uveitis, lid laxity, glaucoma, blepharitis, orbital cellulitis, scleritis, rosacea, tarsorrhaphy, scleromalacia, and herpetic eye disease.[2] A detailed systemic history including autoimmune disorders diagnosed in the patients by a rheumatologist before presentation was also recorded from the electronic health record.

Corneal scrapings were performed in the presence of corneal infiltrate. In addition, polymerase chain reaction tests were performed to detect Herpes Simplex Virus, Adenovirus, and Acanthamoeba infections, whenever applicable. The management plan for patients with PUK was evaluated by the treating physician depending on the severity of the disease. The primary care team was involved when necessary. The treatment modalities included topical and systemic drugs and adjunctive treatment such as serum drops, bandage contact lens, cyanoacrylate application, punctal plug placement, tarsorrhaphy, and surgical interventions such as penetrating keratoplasty and crescentic lamellar transplantation. "Duration of resolution" was defined as the time taken for complete closure of an epithelial defect, where as "treatment duration" was defined as the period for which the treating ophthalmologist prescribed topical treatment for the patients. The size of the epithelial defect was measured during slitlamp examination. The largest dimensions were measured using slitlamp light beam.

Statistical Analysis

Prism 9 (GraphPad Software LLC, Boston, MA) was used for statistical analysis. Student *t* tests were used to calculate *P*-values for continuous variables. The data are presented as mean ± SD. For demographic data analysis, patients with bilateral presentation were considered a single event, whereas for clinical data and visual outcomes data analysis, each eye was considered a separate event. Pearson correlation test was performed to assess the correlation between the epithelial defect size and initial and final visual acuity. Reverse Kaplan-Meier (K-M) survival analysis was used for comparing the duration of PUK resolution in patients with and without associated autoimmune disorders. The statistical significance for the reverse K-M test was assessed by log-rank (Mantle-Cox) test. BCVAs were converted from Snellen to LogMAR as per standardized criteria.[18] We performed simple linear regression analysis to assess the factors impacting vision outcomes (ie final BCVA) and PUK treatment duration using SPSS Statistics for Macintosh, Version 27.0 (IBM Corp., Armonk, NY). The factors analyzed included age, sex, history of autoimmune disease, defect size, BCVA at presentation, duration of ocular symptoms at presentation, and treatment duration. A *P*-value of less than 0.05 was considered statistically significant.

TABLE 1. Demographics, Clinical Presentation, and Ophthalmic History of Patients Diagnosed With Peripheral Ulcerative Keratitis

		Percentage
Age [mean (SD) in yr]	59.67 ± 13.41 (Range: 27–84)	
Sex (n)		
Female	30	58.82
Male	21	41.17
Laterality (n)		
Unilateral	44	86.27
Bilateral	7	13.73
Mean BCVA (at presentation, LogMAR)	0.41 ± 0.07	
Duration of ocular symptoms before presentation [mean ± SD in d]	17.79 ± 24.22	
Defect size [mean ± SD in mm^2]	12.47 ± 11.75	
Primary clinical presentation		
Corneal thinning	40	68.96
Recurrent epithelial defect	27	46.55
Corneal infiltrate	15	25.86
Ophthalmic history*		
Dry eye disease	34	66.67
Meibomian gland disease	15	29.41
Allergic conjunctivitis	12	23.53
Recurrent infectious keratitis	8	15.69
Cataract surgery	7	13.73
Lid laxity	5	9.80
Contact lens use	4	7.84
Uveitis	4	7.84
Glaucoma	4	7.84
Scleritis	3	5.88

*Risk factors reported in >5% of the patients in the cohort.

RESULTS

The study included 58 eyes of 51 patients, including 30 female patients (58.82%). The mean age of patients was 59.67 ± 13.41 years (Table 1). About half of the patients in the cohort were older than 60 years (52.94%), and the mean BCVA at presentation was 0.41 ± 0.07 LogMAR. The patients were diagnosed with PUK after 17.79 ± 24.22 days of ocular symptoms. The mean epithelial defect size at presentation was 12.47 ± 11.75 mm^2. There was a significant correlation between epithelial defect size and BCVA at presentation (P = 0.008; Fig. 1). The clinical presentations included corneal thinning (40 eyes, 68.97%), recurrent corneal epithelial defects (27 eyes, 54.55%), and corneal infiltrate (15 eyes, 25.86%). A corneal perforation was reported in 4 eyes (6.90%).

Associated ocular findings included history of dry eye disease (34 eyes, 58.62%), blepharitis, meibomian gland dysfunction (15 eyes, 25.86%), allergic conjunctivitis (12 eyes, 20.69%), recurrent infectious keratitis (8 eyes, 13.79%), and history of cataract surgery (7 eyes, 12.09%; Table 1). In addition, uveitis and scleritis had been previously diagnosed in 4 (7.84%) and 3 (5.88%) patients, respectively. 45 patients (88.23%) had a history of atopy. The systemic history of the patients is summarized in Table 2. Autoimmune diseases were the most common risk factor associated with PUK (35, 68.66%), including rheumatoid arthritis (23, 45.10%), Sjogren disease (4, 7.84%), ulcerative colitis (4, 7.84%), psoriasis (3, 5.88%), systemic lupus erythematosus (2, 3.92%), and ankylosing spondylitis (2, 3.92%; Table 2). A higher proportion of female patients diagnosed with PUK had an autoimmune etiology (30, 73.33%) compared with male patients (13, 61.90%)

The microbiological investigations revealed coagulase-negative Staphylococci in 9 patients. The mean treatment and resolution duration for the patients was 591.26 ± 94.27 (median: 244.5 days) and 394.34 ± 121.80 days (median: 71.5 days), respectively. The duration of disease resolution in

TABLE 2. Systemic History in Patients Diagnosed With Peripheral Ulcerative Keratitis*

	n	%
Allergies	45	88.24
Hypertension	27	52.94
Tobacco smoking	14	27.45
Hyperlipidemia	10	19.61
Cardiac disorders	9	17.65
Chronic kidney disease	8	15.69
Asthma	7	13.73
Substance abuse	5	9.80
Diabetes mellitus	4	7.84
Cancer	4	7.84
Viral hepatitis	4	7.84
Cerebrovascular disease	3	5.88
Chronic obstructive pulmonary disease	3	5.88
Autoimmune diseases		
Rheumatoid arthritis	23	45.10
Sjogren disease	4	7.84
Ulcerative colitis	4	7.84
Psoriasis	3	5.88
Systemic lupus erythematosus	2	3.92
Ankylosing spondylitis	2	3.92
Raynaud disease	1	1.96
Granulomatosis with polyangiitis	1	1.96
Crohn disease	1	1.96

*Systemic diseases with >5% prevalence in the cohort.

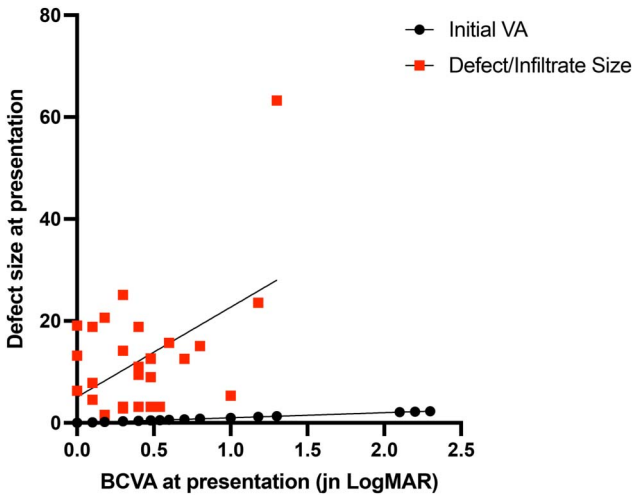

FIGURE 1. Correlation between the BCVA and epithelial defect size at presentation.

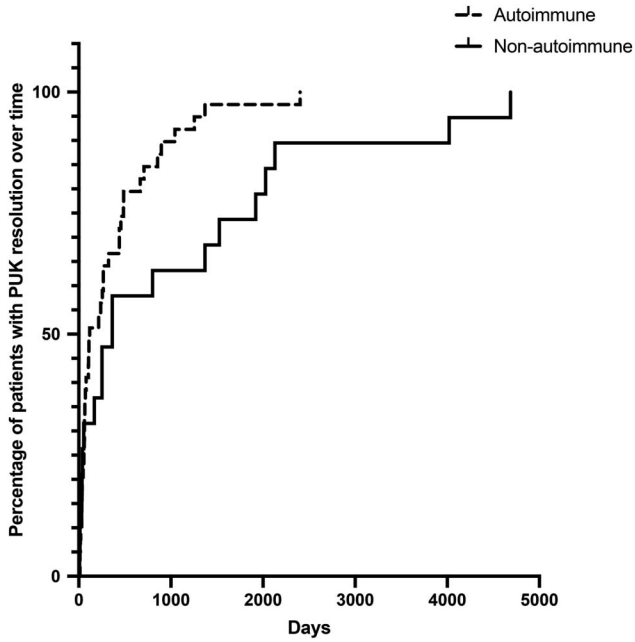

FIGURE 2. Reverse Kaplan-Meier survival analysis comparing the duration of PUK resolution in patients with underlying autoimmune and non-autoimmune etiologies.

female patients (277.5 ± 62.34 days) was significantly shorter than male patients (1035.75 ± 261.18 days, P = 0.008). The duration of resolution in PUK cases with underlying autoimmune disorder (252.43 ± 59.55 days, median: 68 days) was shorter than non-autoimmune (685.63 ± 137.28 days, median: 252 days), which was confirmed by reverse K-M survival analysis (P = 0.028; Fig. 2).

Treatment modalities included artificial tears for symptomatic relief (51, 100%), topical corticosteroids [including prednisolone 1% (25, 49.02%), fluorometholone 0.1% (24, 47.06%)], topical cyclosporine (14, 27.45%), and topical antibiotics [fluoroquinolones (46, 90.20%), moxifloxacin (36, 70.59%); Table 3]. The adjunctive treatments included use of serum eye drops (21, 41.18%), bandage contact lens (14, 27.45%), and cyanoacrylate tissue adhesive and amniotic membrane transplantation (7, 13.73%). Three patients (5.88%) presented with corneal perforation and required penetrating keratoplasty. During the treatment, 2 patients were diagnosed with new-onset glaucoma (3.92%) and 1 patient presented with epithelial defect and nodular scleritis (1.96%).

TABLE 3. Medical and Adjunctive Management in Patients Diagnosed With Peripheral Ulcerative Keratitis

	n	%
Steroids		
Topical anti-inflammatory		
Prednisone forte	25	49.02
Fluorometholone	24	47.06
Topical cyclosporin (Restasis)	14	27.45
Oral steroids	37	72.55
Topical antibiotics		
Fluoroquinolone drops	46	90.20
Erythromycin	19	37.25
Ciprofloxacin	13	25.49
Ofloxacin	9	17.65
Gatifloxacin	7	13.73
Fortified tobramycin	7	13.73
Fortified cefazolin	7	13.73
Trimethoprim + Polymyxin	6	11.76
Tobramycin + Dexamethasone	5	9.80
Miscellaneous drugs		
Artificial tears	51	100.00
Vitamin C	22	43.14
Topical lubricant eye gel	9	17.65
Oral immunosuppressants		
Methotrexate	14	27.45
Hydroxychloroquine	8	15.69
Adalimumab	6	11.76
Leflunomide	5	9.80
Infliximab	3	5.88
Rituximab	2	3.92
Cyclophosphamide	2	3.92
Mycophenolate	2	3.92
Etanercept	2	3.92
Abatacept	1	1.96
Adjunctive management		
Serum eye drops	21	41.18
Bandage contact lens	14	27.45
Cyanoacrylate tissue adhesives	7	13.73
Amniotic membrane transplantation	7	13.73
Punctal plug placement	5	9.80
Punctal cautery	4	7.84
Conjunctival resection	4	7.84
Tarsorrhaphy	3	5.88
Penetrating keratoplasty	3	5.88

The mean final LogMAR VA was 0.36 ± 0.64 (vs. 0.41 ± 0.51 at presentation). At presentation, the PUK patients with associated autoimmune diseases (0.46 ± 0.59 LogMAR) presented with worse VA compared with non-autoimmune etiologies (0.30 ± 0.28 LogMAR). The final VA (0.46 ± 0.67 LogMAR) in PUK associated with underlying non-autoimmune etiologies worsened after resolution (0.30 ± 0.28 LogMAR, P = 0.17), whereas the final VA significantly improved after resolution in PUK associated with autoimmune disorders (0.31 ± 0.64 vs. 0.46 ± 0.59 LogMAR, P = 0.04; Fig. 3). The factors and conditions associated with final BCVA and treatment duration using linear regression are shown in Table 4. The final BCVA in patients with PUK depended on the duration of treatment (P = 0.001; 95% CI, 245.15–952.59) and initial BCVA (P = 0.002, 95% CI, 0.1122–1.5056). Time to resolution was significantly longer in male compared with female patients ($P < 0.001$, 95% CI, −0.00047 to −0.00015).

DISCUSSION

This retrospective study conducted at a tertiary care center assessed the patient characteristics, clinical presentations, and visual outcomes in 58 eyes of 51 patients diagnosed with peripheral ulcerative keratitis. The duration of treatment and resolution were typically less than 2 years. The demographic characteristics of our patient cohort is similar to that reported in the previous studies.[6,12] As reported previously, PUK tends to have a female preponderance: 60% of the

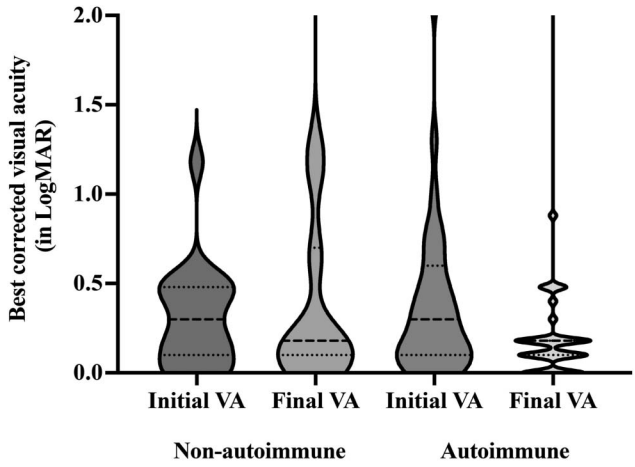

FIGURE 3. Initial and final BCVA in PUK patients with underlying non-autoimmune and autoimmune etiologies.

TABLE 4. Linear Regression Model Assessing the Factors Associated With Vision Outcomes and Treatment Duration in Patients With Peripheral Ulcerative Keratitis

				95% CI	
	Multiple R^2	β	*P*	Lower Bound	Upper Bound
Age (in yr)	0.00006	0.167	0.952	−5.405	5.739
Treatment duration (in d)	0.1704	598.9	0.001	245.15	952.59
Sex (female vs. male)	0.0239	−0.119	0.246	−0.323	0.0845
Systemic autoimmune disease (Yes vs. No)	0.0063	−0.056	0.551	−0.246	0.1331
Defect size (in mm^2)	0.0060	1.754	0.687	−7.095	10.603
BCVA (at presentation, in LogMAR)	0.1502	0.3089	0.002	0.1122	0.5056
Duration of ocular symptoms (at presentation, in d)	0.0063	2.761	0.594	−7.599	13.120
Dependent variable: Final BCVA					
Age (in yr)	0.013	−0.0021	0.376	−0.0071	0.0027
Sex (female vs. Male)	0.2027	−0.0003	<0.001	−0.00047	−0.00014
Systemic autoimmune disease (Yes vs. No)	0.0007	−0.00002	0.838	−0.00018	0.00015
Defect size (in mm^2)	0.00096	−0.00052	0.873	−0.0071	0.0061
BCVA (at presentation, in LogMAR)	0.0062	0.000056	0.555	−0.00024	0.00013
Duration of ocular symptoms (at presentation, in d)	0.032	0.0055	0.2283	−0.0035	0.0146

Dependent variable: Duration of resolution.

patients in our cohort were female as well.[12] More than 85% of the patients had unilateral PUK and presented with corneal thinning, recurrent epithelial defect, and anterior chamber inflammation. Sharma et al[6] reported a similar number of patients with unilateral PUK, whereas another study by Srinivasan et al had fewer patients with unilateral disease.[6,19] Many patients in the current study presented after a prolonged period (~2–3 weeks) of ocular symptom onset, thus large epithelial defects (~12 mm^2) were observed which impacted the BCVA. Interestingly, despite the delay in the presentation, very few patients had corneal perforations, significantly lower than the previous studies. However, it may be noted that most of the patients were previously receiving treatment from their primary ophthalmologist and were only referred to us due to the refractory nature of the disease.

More than 60% of the patients in our cohort had a history of autoimmune disorders. Among these patients, 45% had a history of rheumatoid arthritis and a few patients had been diagnosed with more than 1 autoimmune disorder. Previously, Eiferman et al[20] have reported rheumatoid arthritis to be the primary non-infectious cause of PUK in 34% of the patients. Mooren ulcer was the second most common cause of PUK (37.25%). A similar proportion of PUK associated with Mooren ulcer has been reported in previous studies.[6,21] The inflammatory responses that lead to PUK have been associated with history of previous traumatic events such as ocular trauma or surgery. Srinivasan et al[19] observed that patients with PUK had a history of ocular trauma (26%) and surgery (37%). Similarly, Sharma et al[6] also reported a history of ocular trauma (4%) and surgery (28%) in their study. A similar proportion of patients with PUK had a history of similar inciting factors, that is, ocular trauma (3 patients, 5.88%) and surgery (11 patients, 21.57%) in our cohort.

The management strategy for PUK is variable and depends on the underlying etiologies and presenting symptoms and severity. Since many patients with PUK have an underlying autoimmune disease, the treating ophthalmologists tailor a treatment plan in close coordination with the rheumatologist. The ophthalmologists use adjunctive treatment modalities depending on the severity of the disease. In our study, patients were treated with serum eye drops and bandage contact lenses to improve patient symptoms. In addition, procedures such as punctal plug placement and cauterization were performed for the preservation of natural or artificial tears and improve the quantity of the tear film.[22] In severe cases, amniotic membrane transplantation and tissue adhesives may be used to stabilize the cornea in the cases with severe corneal thinning and descemetocele.[23,24]

In our cohort, artificial tears were prescribed to all the patients for symptomatic relief, whereas topical steroids were prescribed to more than 75% to suppress the ocular surface inflammation. Almost all the patients on topical steroids were also prescribed systemic (oral) steroids. In patients with a history of infectious keratitis, the treatment was based on confirmation of the causative organism from microbiological results. However, the cultures of only patients came back positive with coagulase-negative *Staphylococci* as most of the patients were already on prescribed ongoing topical antibiotic treatment. In our study, only 3 patients presented with corneal perforation during the treatment and needed surgical intervention. We observed that the BCVA in patients with non-autoimmune etiologies worsened in the patients, whereas the final BCVA in patients with an underlying autoimmune disorder was better than the presenting BCVA. Although the initial BCVA depended on the epithelial defect size, the visual outcomes in patients with PUK after treatment did not have a significant correlation with it. Interestingly, we observed the PUK resolution time in patients with underlying autoimmune etiologies was significantly shorter than in those with non-autoimmune etiologies, which we attribute to aggressive systemic immunosuppressive management in these patients supplemented by topical immunosuppression.

The primary limitation of this study is incomplete reporting inherent to retrospective studies, which leads to imprecision and variable effect sizes. Since our practice is a tertiary care center, most of the patients were referred to us by their primary ophthalmologists. At presentation, most of the patients were already prescribed topical steroids and antibiotics; therefore, the severity of the disease and underlying cause could not be assessed in some of the patients. Moreover, since this study includes patients who were treated by multiple ophthalmologists over a prolonged duration, the management plan was variable and tailored according to the presentation, severity of the disease, and subjective preferences of the treating physician. A prospective study is warranted to propose definitive criteria for diagnosis of PUK, which will further lead to standardized treatment protocols.

In conclusion, patients with PUK often present with severe disease and require comprehensive ophthalmic and systemic evaluation to assess the underlying etiologies and tailoring an aggressive management plan accordingly. Since autoimmune disorders are the primary causes of PUK in many patients, high clinical suspicion and close coordination between the patient's ophthalmologist and rheumatologist is necessary for timely management of PUK.

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