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An Analysis of Therapeutic Decision Making Regarding Immunosuppressive Chemotherapy for Peripheral Ulcerative Keratitis

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We reviewed our experience in the management of 47 patients (61 eyes) with peripheral ulcerative keratitis (PUK) to establish guidelines for appropriate indications to consider institution of systemic chemotherapy. Fifty-three percent of patients had a systemic disease as the etiology of PUK; one fourth of these were newly diagnosed as a result of meticulous history taking. The histologic demonstration of vasculitis in ocular tissue was the crucial step in deciding on chemotherapy in more than half of our patients. The presence of scleritis was highly associated with active vasculitis. Twelve of 14 patients with bilateral PUK required chemotherapy. Recommendations for an approach to therapy of PUK are presented.
Key Words: Peripheral ulcerative keratitis—Chemotherapy—Surgery—Vasculitis.

The concept of the peripheral cornea as a uniquely definable anatomic region has emerged in the ophthalmic literature in recent years. Several authors have addressed those aspects of vascular supply, lymphatic drainage, antigen presentation, and T-cell subpopulations that contribute to the predilection of this region of the cornea to be involved in local and systemic immunologic diseases and reactions (1,2).

Because of the multiple and varied etiologies of peripheral ulcerative keratitis (PUK) (Table 1), appropriate management of patients often includes both medical and surgical approaches. Although several studies have been published advocating diverse approaches to this difficult management problem (3–11), it has proven difficult to design a well-controlled evaluation of treatment options. In many patients, PUK can be stabilized by the application of tissue adhesive, without adjunctive medical or surgical therapies. However, abundant documentation has accumulated showing that in the presence of an active immunologic process, tectonic procedures such as application of tissue adhesive, lamellar keratoplasty, and penetrating keratoplasty may be palliative or temporizing, but inadequate to prevent recurrence of ulceration (4,12–14). Nevertheless, no clear guidelines exist regarding appropriate indications for limiting treatment strategies to tectonic surgical approaches and/or the application of tissue adhesive versus proceeding with conjunctival resection or the institution of systemic chemotherapy. Difficulties determining a precise diagnosis in patients with PUK further complicate the issue.

As a primary and tertiary referral center, we have had the opportunity to evaluate and treat patients with PUK due to a variety of conditions. This report reviews those historical, clinical, laboratory,

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TABLE 1. *Etiologies of peripheral ulcerative keratitis*

Infectious ocular	Bacterial (*Staphylococcus, Streptococcus, Gonococcus*)
	Viral (herpes simplex virus, herpes zoster ophthalmicus)
	Amoebic (*Acanthamoeba*)
	Fungal
Infectious systemic	Varicella-zoster virus
	Gonococcal arthritis
	Dengue fever
	Leishmaniosis
Noninfectious ocular	Traumatic, postsurgical
	Metaherpetic
	Neuroparalytic
	Exposure keratitis
	Mooren's ulcer
	Sicca syndrome
	Carcinoma
Noninfectious systemic	Vasculitides
	rheumatoid arthritis, Wegener's granulomatosis, relapsing polychondritis, systemic lupus erythematosus, giant cell arteritis, Sjögren's syndrome, Polyarteritis nodosa, Churg-Strauss
	Other autoimmune disorders
	Graft-versus-host disease, Progressive systemic sclerosis
	Dermatologic conditions
	Rosacea, psoriasis, cicatricial pemphigoid, Stevens-Johnson syndrome
	Others
	leukemia, porphyria

and biopsy features that were helpful to us in reaching a specific etiologic diagnosis, and it describes our approach to making the decision to initiate systemic chemotherapy in patients with PUK.

MATERIALS AND METHODS

We reviewed the records of all patients with noninfectious peripheral corneal ulceration seen on the Immunology Service at the Massachusetts Eye & Ear Infirmary between January 1977 and December 1987. For the purposes of this review, PUK was defined as crescent-shaped peripheral corneal stromal ulceration with epithelial defect adjacent to the corneoscleral limbus with an intrastromal white blood cell infiltrate visible on biomicroscopic slit-lamp examination.

Historical features, including prior ocular disease or surgery and a comprehensive review of systems (rheumatologic, dermatologic, gastrointestinal, genitourinary, respiratory–pulmonary, and neurologic) were recorded. The onset of ulceration was characterized as either acute (onset of symptoms within 2 weeks of presentation), subacute (onset of symptoms within 3 months of presentation), or chronic (onset of symptoms >3 months before presentation). Specific diagnoses were ascribed as the etiologic basis for PUK in the presence of specific diagnostic findings. The diagnosis of rheumatoid arthritis was based on published criteria of the American Rheumatological Association (15). Wegener's granulomatosis was diagnosed in the presence of biopsy-proven necrotizing granulomas and vasculitis of the upper and lower respiratory tract with or without a focal necrotizing glomerulonephritis (16). Suspected Wegener's granulomatosis was diagnosed if biopsy was inconclusive despite a typical clinical presentation. Rosacea was diagnosed clinically based on characteristic facial skin features. A diagnosis of relapsing polychondritis was made based on the presence of typical clinical features and histologic findings consistent with published biopsy characteristics (17). A diagnosis of Mooren's ulcer was based on ocular clinical characteristics, including circumferentially and centrally progressive ulceration with a negative workup for other etiologies. If no specific diagnosis could be reached, cases were classified as idiopathic.

Visual acuity, laterality, intraocular pressure, and detailed results of the biomicroscopic slit-lamp examination were recorded. Corneal sensation and lacrimal function by Schirmer test with anesthetic were recorded. Clinical disease activity was described by the degree of corneal ulceration and inflammation. Corneal ulceration was graded from 0 to 4 according to the following: <25% depth of ulceration = 1, 25–50% = 2, 50–75% = 3, and 75–100% = 4. Inflammation was graded from 0 to 4 by the degree of injection and/or swelling of the bulbar conjunctiva, episclera, or sclera. The presence of uveitis was graded from 0 to 4 according to the number of cells in the anterior chamber. Scleral involvement was further characterized as diffuse, nodular, or necrotizing according to clinical appearance. All examinations and gradings were performed by the same physician (C.S.F.) and were confirmed by a second examiner to assure consistency and reproducibility.

Results of laboratory evaluation, including serum chemistry, serology, hematologic and immunologic assays, and radiographic studies were recorded. The extent of workup varied widely among patients according to the ease of reaching a certain diagnosis; however, in most cases, complete blood count, erythrocyte sedimentation rate, VDRL, fluorescent treponemal antibody-absorption, renal function studies, urinalysis, rheumatoid factor, antinuclear antibody, C3, C4, circulating immune complexes, and chest radiography were performed.

In the majority of patients, tissue biopsies were obtained for diagnostic purposes, sometimes at the

time of a surgical therapeutic procedure. Biopsies were taken from the bulbar conjunctiva adjacent to the ulcerating cornea. In selected cases, episcleral, scleral, and/or corneal tissue were also excised and analyzed. Details of tissue handling and processing for light microscopy, and for immunofluorescence and immunoperoxidase stainings have been previously published (18). The presence of vasculitis, perivasculitis, granulomas, eosinophils, mast cells, and neutrophil or lymphocytic infiltrate was documented. Vasculitis was defined as neutrophil invasion of the vessel wall with fibrinoid necrosis seen by light microscopy; immunoreactant deposition in the vessel wall seen by immunofluorescence and/or immunoperoxidase microscopy was accorded equal importance in the diagnosis of presumptive vasculitis.

Treatments used in these patients with PUK included conjunctival resection with or without the use of tissue adhesive, other tectonic surgical techniques such as lamellar and penetrating keratoplasty and scleral transplantation, and systemic chemotherapy. Our therapeutic approach was based on the following algorithm: once PUK was diagnosed, conjunctival resection with or without application of tissue adhesive was performed. Chemotherapy was initiated if (a) active vasculitis was present (on histologic or clinical grounds, e.g., necrotizing scleritis), (b) bilateral Mooren's ulcer was diagnosed, or (c) ulceration was progressive despite tectonic procedures and/or conjunctival resection. Doses of chemotherapeutic agents used and guidelines for patient monitoring have been published elsewhere (4,12,13,18,19). Measures of patient outcome included visual acuity gain or loss and progression or stabilization of the degree of corneal ulceration.

RESULTS

Forty-seven patients (61 eyes) form the data base for this report, including 25 men and 22 women, with a mean age of 65 years (range 34–89). Mean follow-up was 20 months (range 1–120).

Historical Aspects

Twelve patients gave a history of ocular disease before their initial examination in our Immunology Service, including rosacea in four, keratitis sicca in two, alkali burn in one, herpes simplex virus (HSV) keratitis in one, episcleritis in one, and pseudophakic bullous keratopathy in one patient. Two patients were diagnosed as having Mooren's ulcer before their referral to us. Thirty-five patients (75%) had no history of ocular disease before the development of PUK.

Twenty-five of 47 patients (53%) had a systemic disease as the etiology of their PUK. All 16 patients with rheumatoid arthritis gave a history of many years of prior arthritis; one of them did not have the diagnosis of rheumatoid arthritis established before presentation. Two of the six patients with Wegener's granulomatosis had been previously diagnosed and treated for systemic manifestations of this disease and were in remission and not receiving therapy at the time of onset of PUK. Comprehensive review of systems led to the discovery of a systemic disease in seven patients; diagnoses in this group included rheumatoid arthritis (one patient),Wegener's granulomatosis (four patients), relapsing polychondritis (one patient), and leukemia (one patient).

Clinical Aspects

Visual acuity at initial examination ranged from 20/20 to light perception (mean acuity 20/284). Twenty patients (21 eyes) presented with acuities of 20/400 or worse. The corneal ulceration was acute in 7, subacuted in 27, and chronic in 28 patients. There were no significant differences in final diagnoses between these groups. Fourteen patients had bilateral PUK; diagnoses in this group included rheumatoid arthritis (seven patients), Mooren's ulcer (six patients), and leukemia (one patient).

Mean ocular inflammation for the entire group was graded 2.0, with 14 eyes grade 1, 24 eyes grade 2, 17 eyes grade 3, and 2 eyes grade 4. The mean degree of corneal ulceration at presentation was grade 2 (25–50% depth ulceration); 15 patients had <25%, 17 had 25–50%, 12 had 50–75%, and 15 had 75–100% ulceration. Table 2 summarizes etiologic diagnoses for these groups. The degree of inflammation or of corneal ulceration at presentation was not believed to be helpful in limiting the differential diagnosis.

Table 3 summarizes the etiologic diagnoses observed in patients with PUK and scleritis. Scleritis occurred in 17 patients; 5 (6 eyes) had diffuse, 6 (6 eyes) had nodular, and 12 (15 eyes) had necrotizing scleritis (Fig. 1). Episcleritis was observed in 5 of the 47 patients, including 2 with rheumatoid arthritis, 2 with Mooren's ulcer, and 1 with suspected Wegener's granulomatosis.

A marked corneal infiltrate at the edge of ulceration was noted in 16 patients; final diagnoses in these patients included rheumatoid arthritis (5 patients), Mooren's ulcer (7 patients), Wegener's granulomatosis (3 patients), and rosacea (1 patient).

TABLE 2. *Final diagnoses according to depth of ulceration*

Depth of ulceration	Final diagnosis	No. of eyes
<25%	Rheumatoid arthritis	7
	Wegener's granulomatosis	2
	Relapsing polychondritis	1
	Mooren's ulcer	3
	Rosacea	1
	Leukemia	1
25–50%	Rheumatoid arthritis	6
	Mooren's ulcer	6
	Wegener's suspect	1
	Idiopathic	3
	Leukemia	1
50–75%	Rheumatoid arthritis	3
	Mooren's ulcer	4
	Wegener's suspect	1
	Idiopathic	3
75–100%	Rheumatoid arthritis	6
	Mooren's ulcer	5
	Wegener's granulomatosis	1
	Wegener's suspect	1
	Rosacea	1
	Sebaceous cell carcinoma	1
	Herpes simplex virus type 1-associated vasculitis	1

Seven patients had uveitis at presentation (mean grade 1.5) and none had retinal vasculitis.

Biopsy and Laboratory Aspects

Histologic findings from biopsies performed in 38 patients are summarized in Table 4. Twenty patients had active vasculitis (Fig. 2); etiologic diagnoses in these patients included rheumatoid arthritis (nine patients), Wegener's granulomatosis (three patients), suspected Wegener's granulomatosis (two patients), relapsing polychondritis (one patient), HSV-1 keratitis (one patient), Mooren's ulcer (one patient), and idiopathic PUK (three patients). Twenty patients had marked mast-cell involvement in the inflammatory process. Eight patients had granulomas seen in biopsies of ocular tissue.

Nine patients did not have biopsies performed, including three with a known diagnosis of Mooren's ulcer and one with a known diagnosis of Wegener's granulomatosis. In five patients with rheumatoid arthritis biopsies were not done, including one patient with necrotizing scleritis, and three patients with central perforations treated by application of tissue adhesive. In these nine patients, the decision to treat with chemotherapy was made without the aid of a biopsy.

Certain clinical and laboratory features were associated with the subsequent demonstration of vasculitis on biopsy. Ten of the 12 patients who had

TABLE 3. *Final diagnoses in patients with peripheral ulcerative keratisis and scleritis*

Scleritis type	Final diagnosis	No. of patients
Nodular	Rheumatoid arthritis	2
	Sebaceous cell carcinoma	1
	Mooren's ulcer	1
	Wegener's granulomatosis	2
Necrotizing	Rheumatoid arthritis	7
	Wegener's granulomatosis	2
	Wegener's suspect	2
	Relapsing polychondritis	1

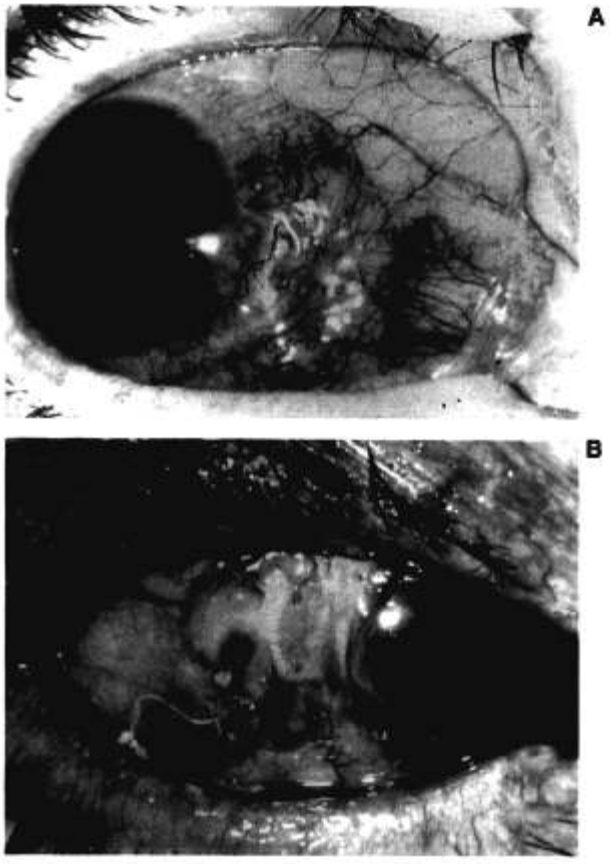

FIG. 1. Different manifestations of scleritis may be associated with peripheral ulcerative keratitis (PUK) and active vasculitis demonstrable on biopsy of ocular tissue. **A:** Nodular scleritis associated with PUK in an 80-year-old woman with rheumatoid arthritis. **B:** Necrotizing scleritis associated with PUK in a 69-year-old woman with rheumatoid arthritis.

TABLE 4. *Biopsy characteristics*

	No. of patients
Vasculitis	20
Perivasculitis	12
Eosinophils	4
Mast cells	20
Granuloma	8

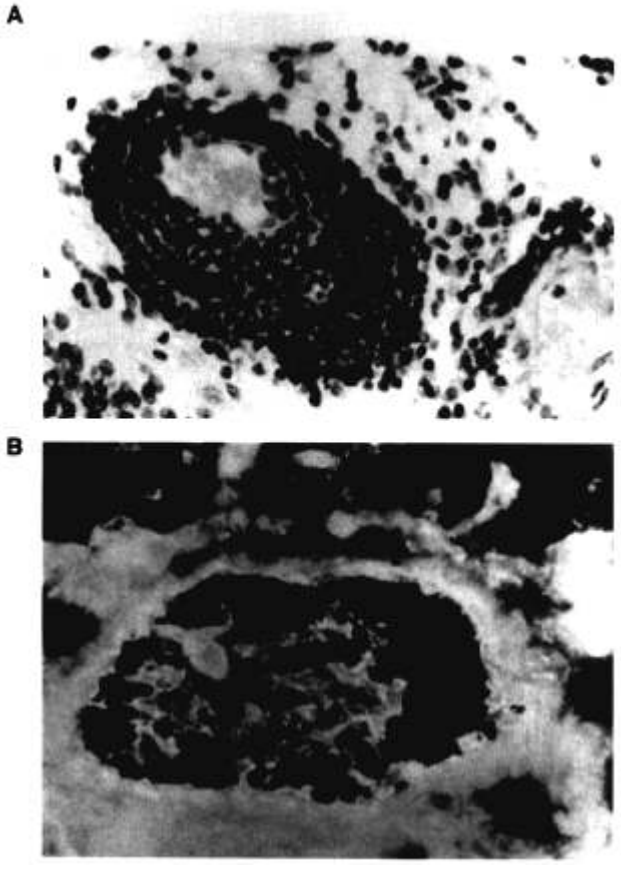

FIG. 2. A: Light microscopy, H&E stain, conjunctiva. Perivasculitis and granulomatous vasculitis. Note in particular the granulomatous reaction around the central vessel with vascular wall invasion by inflammatory cells (× 45). **B:** Immunofluorescence microscopy. Rhodamine-conjugated rabbit anti-human IgM antibody has been used in incubation on resected conjunctiva. Note the brilliant "staining" of the vascular wall, signifying the deposition of IgM in the vessel wall (cryostat section × 104).

necrotizing scleritis noted on initial examination were subsequently found to have active vasculitis. Nine of the 11 patients with rheumatoid arthritis in whom biopsies were done had active vasculitis. All nine patients had intercurrent scleritis—seven necrotizing and two nodular. All eight patients with granulomas on biopsy had active vasculitis. This group included three patients with Wegener's granulomatosis, one Wegener's suspect, two with rheumatoid arthritis, one with HSV keratitis, and one with idiopathic PUK.

No laboratory parameter was found that was consistently helpful in reaching an etiologic diagnosis. As expected, certain tests were valuable in confirming a clinically suspected diagnosis. A high-titer rheumatoid factor was detected in all 11 patients with rheumatoid arthritis tested, including all 9 patients with vasculitis. Circulating immune complexes (Raji cell assay) were detected in 9 of 10 patients with and only 4 of 11 patients without vasculitis demonstrated on tissue biopsy ($p < 0.05$). Peripheral corneal stromal infiltrates were detected in 5 of 13 patients with vasculitis and only 3 of 11 patients without vasculitis ($p = NS$).

Outcome

Six of seven patients who did not have vasculitis and who were not treated with chemotherapy remained stable long-term after conjunctival resection; this group included one patient with suspected Wegener's granulomatosis, one with rosacea, one with Mooren's ulcer, and three with idiopathic PUK. One patient with sebaceous cell carcinoma underwent enucleation.

Eleven patients (17 eyes) without vasculitis were treated with chemotherapy (eight with Mooren's ulcer, two with rheumatoid arthritis, and one with leukemia). All remained stable or improved after surgery and chemotherapy. Eight of the 18 patients without vasculitis required tectonic procedures emergently for preservation of the globe (Fig. 3).

Eighteen of 20 patients (20 eyes) with vasculitis were treated with chemotherapy; etiologic diagnoses for this group were as described previously. Seventeen of the 18 patients treated with chemotherapy had no progression of their ulceration in the long term. Twelve of the 18 patients (15 eyes) with vasculitis treated with chemotherapy required tectonic procedures emergently. Two patients with vasculitis (one with HSV keratitis and one with idiopathic PUK) were not treated with chemotherapy based on clinical judgment regarding the extent of ulceration and degree of inflammation; they were carefully followed for progression of PUK. Both were stabilized, after conjunctival resection and tissue adhesive in one case, and lamellar keratoplasty in the other.

Patients with vasculitis had no net change in vision during the course of the study; in contrast, patients without vasculitis had a mean loss of 2.3 Snellen lines ($p < 0.05$). These differences are in large part a reflection of the poor visual outcome in the subgroup of eight patients with bilateral Mooren's ulcer (without vasculitis), who had a mean loss of 2.0 Snellen lines.

DISCUSSION

PUK represents a final pathway common to many diseases. Dermatologic, neurologic, traumatic, infectious, and postinfectious disorders, abnormalities of eyelids or eyelashes, and systemic

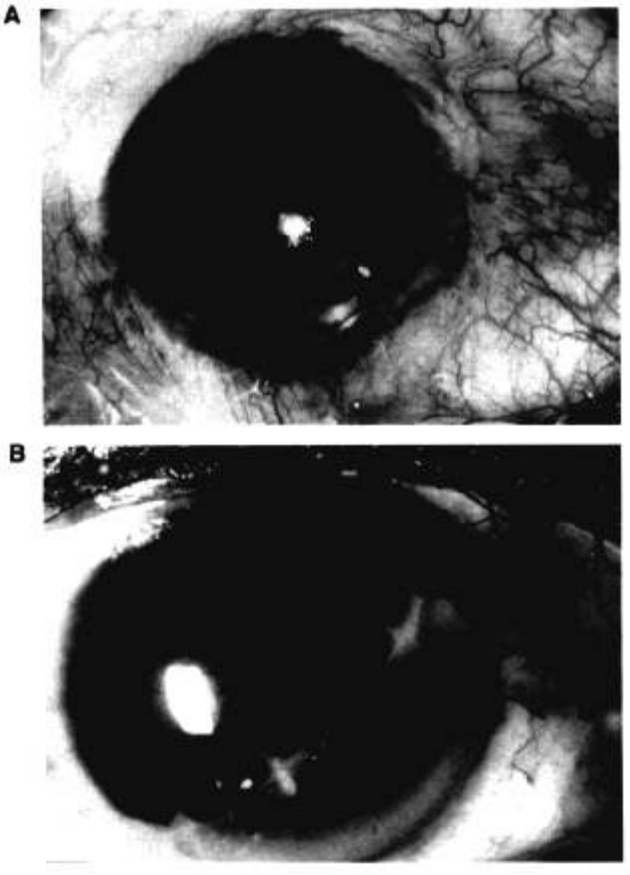

FIG. 3. A: A 33-year-old man with bilateral Mooren's ulcer, status postevisceration in 1976 after perforation of the left eye. The right eye first became involved 10 months before the photograph shown. Ulceration has progressed despite two conjunctival resections. Vision is 20/200 due to corneal distortion. **B:** Seven months after A, status postconjunctival resection, superficial keratectomy, lamellar corneoscleral grafting, and institution of cyclophosphamide therapy. The globe has remained stable without recurrent ulceration. Vision is 20/30 with spectacle correction.

and local autoimmune diseases must all be considered in the differential diagnosis of peripheral corneal ulceration. Discussions of the overall strategy for diagnostic approach to PUK have been published (1,3–5,7) and are beyond the scope of this report. Antimicrobial therapy, systemic tetracycline, lid hygiene, correction of anatomical lid and lash abnormalities, and lubrication regimens (including punctal occlusion and temporary or permanent eyelid closure) can be helpful in some of these entities. More aggressive management strategies such as immunosuppression will be needed in cases associated with systemic or local autoimmune diseases, many of which are potentially fatal and/or highly destructive of the eye(s) (1,3,4,7,8,12). This report attempts to identify historical, clinical, laboratory, and biopsy features of patients with PUK that may aid in the decision to initiate systemic chemotherapy.

The most important finding to emerge from this analysis is the observation that there is no simple recipe for establishing a diagnosis. The difficult task of seemingly endless diagnostic detective work would appear to have no short cuts, as far as we can determine from analysis of our 47 cases. Meticulous historical review of systems (with subsequent studies to pursue leads) and evaluation of biopsied tissue were the two diagnostic endeavors we found most fruitful. Abnormalities of the dermatologic, rheumatologic, genitourinary, and respiratory systems, including physical findings of necrotic skin ulcers, subcutaneous nodules, arthritis, ear or nose cartilaginous inflammation, and hematuria were critical clues that led to the detection of previously undiagnosed and potentially lethal systemic vasculitis in six of our patients. All had undergone prior negative workups, in some instances several times. These patients made up 25% of the group in which PUK was associated with a systemic disease, and these findings emphasize the importance of the eye as a barometer for occult, potentially lethal systemic disease and the importance of continual vigilance and repeated systemic investigations in these patients.

Certain clinical features of the ocular examination were identified as possible markers of active ocular vasculitis. Necrotizing scleritis on initial examination was associated with active vasculitis on biopsy in 10 of 12 patients. In this regard, we should note previous reports of the frequent association of necrotizing scleritis with systemic vasculitis and death from vasculitic lesions of vital organs in patients with rheumatoid arthritis (4,13,20–22). All our patients with rheumatoid arthritis and active vasculitis also had active scleritis. It is of note that two patients with rheumatoid arthritis and *nonnecrotizing* nodular scleritis also had active vasculitis, and one patient with necrotizing scleritis *did not* have vasculitis found on biopsy. It should be stressed that vasculitis in ocular tissues may be segmental or focal, and a single negative biopsy result cannot be considered conclusive.

Two additional clinical features were associated with either vasculitis on biopsy and/or relentless progression of the destructive ocular process despite aggressive conventional therapy. A marked corneal infiltrate at the edge of ulceration was present in 16 patients, eight of whom had active vasculitis (five with rheumatoid arthritis and three with Wegener's granulomatosis). Although bilateral PUK was associated with active vasculitis in only two of 14 patients (both with rheumatoid arthritis),

12 of these 14 required treatment with chemotherapy to save the globes and/or the patient's life. This was so for five patients with Mooren's ulcer, one with leukemia, and six with rheumatoid arthritis. Six of the 13 patients with Mooren's ulcer in this study had bilateral involvement.

Laboratory evaluation provided the key findings to establishing a definite etiologic diagnosis in only two patients. Although a "shotgun" approach to the use of laboratory tests is unjustified, with laboratory evaluation designed by careful review of systems, the yield may be much higher. In this study, detection of circulating immune complexes was significantly more frequent in patients with vasculitis than in patients without vasculitis. Radiologic findings, such as lung infiltrates or sinus disease, provided important clues in the discovery of subtle but widespread systemic involvement of a vasculitic process that would otherwise have been thought to be limited to the eye in five patients who gave positive responses to questions about lung and sinus symptoms. Because of the lethal consequences of missing the diagnosis in the necrotizing vasculitides (4,13), it is probably reasonable to recommend the routine performance of certain tests that have a high likelihood of detection of these serious diseases. We recommend evaluation of complete blood counts, sedimentation rate, rheumatoid factor, circulating immune complexes, urinalysis, and chest and sinus radiography in all patients with PUK, whether or not there is a history that suggests a more benign etiology.

Biopsy of ocular tissues was the critical step in our decision making with regard to the institution of chemotherapy in almost half the patients in this study. It should be emphasized that the performance of a conjunctival biopsy may, in many cases, be therapeutic in that resection of conjunctiva removes, ableit transiently, immunocompetent cells capable of liberating proteolytic enzymes and chemotactic factors from the area of ongoing ulceration (9,10,23–25).

The value of histopathology centered on the presence or absence of vasculitis in the tissue. In cases without evidence of an active vasculitic process (except for Mooren's ulcer and patients with an established systemic vasculitidity), systemic chemotherapy was withheld and patients were followed closely. Six of seven patients in this category not treated with chemotherapy had PUK stabilized without recurrence. All of these patients had undergone conjunctival resection and/or application of tissue adhesive.

Patients with progressive bilateral Mooren's ulcer were an exception to this approach, and were treated with systemic chemotherapy. The inexorable course of ulceration in patients with bilateral Mooren's ulcer has been well documented in the literature (10,26), as have the excellent results possible with the use of systemic chemotherapy (12,13). In patients suspected clinically of having Mooren's ulcer, the absence of vasculitis was helpful in making this diagnosis of exclusion (27,28).

In patients with known systemic vasculitic diseases (rheumatoid arthritis, Wegener's granulomatosis, relapsing polychondritis), the demonstration of vasculitis in ocular tissue in the presence of destructive corneal ulceration implied possible systemic involvement with the same vasculitic process. It has been observed that ocular findings of a vasculitic process often precede systemic findings of the same process (1,4,13). Immunosuppressive therapy can be lifesaving in this group of patients.

In patients *suspected* of having a systemic vasculitic disease as the basis for progressive PUK, but without a definite diagnosis, the demonstration in ocular tissue of a destructive vasculitic process provided additional justification for the institution of chemotherapy. Based on our experience in managing such patients, we believe that chemotherapy should be strongly considered in patients with idiopathic PUK and evidence of vasculitis. It is probably impossible to perform a prospective, randomized, masked, and controlled study to address this critical issue; nonetheless, our results with the approach described herein have been highly successful in this group of patients.

Visual acuity is typically worse in patients with PUK than would be expected, as judged by central corneal clarity, because of surface distortion and irregular astigmatism. Although therapies used were able to halt progressive corneal ulceration, recovery of vision was less than complete. Despite this disappointment, our primary goals were achieved in the majority of patients with destructive PUK; none of our patients died during the follow-up period and no globe was enucleated as a result of progressive, uncontrollable corneal ulceration.

Based on our experience as reported previously, we would suggest that ophthalmologists and their chemotherapist colleagues consider cytotoxic chemotherapy for patients with peripheral ulcerative keratitis whenever (a) PUK is associated with potentially lethal vasculitic disease, such as rheumatoid arthritis, relapsing polychondritis, polyarteritis nodosa, or Wegener's granulomatosis; (b) PUK is associated with ocular vasculitis demonstrated by histopathologic analysis of ocular tissue on which biopsy was done; (c) PUK is bilateral and/or progressive in cases diagnosed as Mooren's ulcer; or

(d) PUK is unresponsive to aggressive conventional medical and surgical therapy, provided no contraindication to chemotherapy exists.

We would caution that the chemotherapeutic program should be administered by a physician who, by virtue of education and training, is expert in such treatment and in the early recognition and management of drug-induced complications.

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