Microbial Keratitis—the False Negative

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Summary

The investigation of presumed microbial keratitis includes microscopy and culture of corneal specimens obtained by scraping the infiltrated cornea. Routine microscopy fails to identify the infecting organism in about 15% of cases. We discuss the problems presented by 20 such eyes which required further investigation. We present a diagnostic algorithm aimed at reducing the delay in identifying the pathogen and increasing the rate of positive culture. This is important since unusual pathogens may require treatment with drugs other than the 'first line' broad spectrum combination of an aminoglycoside and a cephalosporin. The algorithm allows sequential restaining and reculturing of specimens for more thorough investigation. In addition to the use of special stains and culture conditions, it presents indications for further corneal scrapes and biopsies.

Uncontrolled infection resulted in five perforations and penetrating keratoplasty was indicated in 11 cases. The visual outcome for these patients was poor with fewer than 30% achieving 6/12 acuity. The delay in diagnosis increases morbidity and this should be significantly reduced by adopting the algorithm we propose.

Presumed microbial keratitis must be investigated to identify or exclude a pathogenic organism. Positive identification may lead to a modification of the therapeutic strategy if the pathogen is not expected to be sensitive to the initial broad spectrum therapy.¹ Until the infective cause is identified, however, it is essential to initiate intensive topical antimicrobial treatment. A combination of fortified broad-spectrum antibiotics such as an aminoglycoside (15 mg/ml gentamicin) and a cephalosporin (50 mg/ml cefuroxime) is chosen since most bacteria are susceptible to these. Previous experience^{1,2} suggests that routine Gram staining of scrapes from corneal ulcers indicates the presence of pathogens in about 75% of cases which are thought to be infected. A problem arises when there is progressive corneal infiltration, but no organisms are identified on microscopy or on culture.

Prior low-dose or inappropriate antibiotic therapy may modify the infective process and the growth of laboratory cultures. Further corneal scrapes for inoculation of cultures should be performed after treatment is discontinued for 24 or 48 hours.

Reports of unusual pathogens such as *Nocardia* sp., *Mycobacteria* sp. and *Acanthamoeba* sp.^{3–11} have increased clinical awareness of infection which may not be diagnosed by routine methods, particularly if perfunctory. We have pursued the diagnosis in 20 eyes of 19 patients with 'culture-negative keratitis', further investigating them by special techniques. The majority proved to be infected and investigations revealed unusual pathogens.

Methods

Patients were identified from the database of

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the Cornea Clinic, Moorfields Eye Hospital. They had been managed for presumed microbial keratitis between 1983–1989. Some patients had started treatment prior to referral, but without clinical response. Initial laboratory investigations were negative in each case. Further investigations were prompted by continuing clinical suspicion of infection.

Routine investigation of microbial keratitis at Moorfields Eye Hospital during the study period, included Gram stain of a smear, direct plating of scrapes onto blood agar, Sabouraud slope, inoculation of meat broth, brain-heart infusion and thioglycollate broth. Other investigations were performed on request.

The routine method of corneal scraping was as follows:

- (1) The infiltrated corneal tissue was first exposed by removing mucopurulent discharge from the surface of the ulcer.
- (2) The involved cornea was scraped, using a sterile needle or Kimura spatula, at the advancing edges of the infiltration, both around the periphery and in the base of the ulcer.
- (3) The specimen was smeared onto a clean glass slide for the purpose of Gram staining, or by request for special staining, such as Periodic Acid Schiff for fungi.
- (4) Specimens were obtained at the same time for inoculation of the media outlined above. Special media were inoculated on request, such as non-nutrient agar seeded with *Escherichia coli*, for suspected *Acanthamoeba*.

For patients wearing contact lenses, these and any cleaning, storage and wetting solutions available were also cultured.

Patients were treated first with topical broad-spectrum antibiotic therapy (an aminoglycoside plus a cephalosporin), but without evidence of clinical response. The initial investigations being negative, further specimens were obtained in an effort to establish the diagnosis. These specimens included a repeat corneal scrape ($n = 20$) in addition to corneal biopsy ($n = 8$) or excisional keratoplasty ($n = 8$). Treatment was withheld for 24 or 48 hours prior to these further biopsies.

Biopsy specimens were obtained in the operating theatre by aseptic technique using a

corneal trephine (2 or 3 mm) and lamellar dissection. The advancing edge of the corneal infiltrate was included and an effort was made to ensure the biopsy was as deep as possible, aiming to include the stroma deep to the abscess. This is particularly important when seeking to obtain viable acanthamoebae. The biopsy provided material for both culture and histology (Table III).

Penetrating keratoplasty (PK) was performed in 11 eyes (mean follow-up 27.8 months) of which five had perforated (three without identification of a pathogen). One excisional lamellar keratoplasty was also performed.

It became apparent that there was significant diagnostic delay in the cases designated 'culture negative'. We therefore considered how the management of such cases may be improved in future. We developed an investigative algorithm (Tables I–III) which may be applied to specimens from corneal scrapes in cases where a laboratory diagnosis is not made by routine methods. Indications for corneal biopsy and excisional keratoplasty are included. The scheme aimed to improve the prognosis for patients by increasing the chances of identifying a pathogenic organism.

Results and Case Reports

The cases are summarised in Table IV and representative case histories are outlined. Cases are considered according to clinical criteria.

Repeat corneal scrape

Case 1: A 55-year-old stableowner developed a corneal abscess following an abrasion sustained while working in the stables. Initial corneal scrapes were negative both on microscopy and culture. Topical chloramphenicol was not therapeutic and the patient was referred to Moorfields Eye Hospital. A fungus was suspected given the farmyard exposure and a further corneal scrape was stained by Grocott methenamine silver. The silver impregnation showed black staining hyphae, the morphological diagnosis suggesting *Curvularia sp.* (Fig. 1). Cultures remained negative, but special media containing vegetative matter or animal dung were not used. It was not appreciated at the time that some plant

Table 1

fungi require specially supplemented agar to grow. The infection responded to combined treatment; topical miconazole 1% and clotrimazole 1%.

Corneal biopsy

Case 4: A 57-year-old farmer developed a corneal abscess following minor trauma. The cornea was scraped and *Aspergillus* sp. was cultured. He was treated with topical econazole 1% and clotrimazole 1% to which the fungus was sensitive, but corneal infiltration progressed steadily. A further corneal scrape confirmed *Aspergillus*, but subsequently a biopsy was performed which initially yielded *Aspergillus fumigatus*. Later, cultures also grew *Fusarium* sp. which was sensitive to amphotericin 1% and natamycin 1%, but resistant to the imidazoles (used to treat the *Aspergillus*). Thus polymicrobial infection was identified by performing corneal biopsy, the more important pathogen, *Fusarium* sp., having been 'culture negative' by routine corneal scraping.

Excisional keratoplasty

Case 7: A 66-year-old soft contact lens wearer

developed unilateral keratitis after wearing a spare pair of unsterilised lenses stored in saline for several months. Initial corneal scrapes were microscopy and culture negative. Acanthamoeba was suspected some weeks later and corneal scrapes were repeated for immunofluorescence and culture on non-nutrient agar seeded with *E. coli*. These investigations were also negative, but the clinical response to anti-amoebic therapy supported the clinical diagnosis. PK was later performed for bullous keratopathy with a persistent epithelial defect (this had been complicated by streptococcal crystalline keratitis). Acanthamoeba cysts were demonstrated, by immunofluorescence, deep in the excised host tissue (Fig. 3) and this may have been identified by corneal biopsy.

Review of excised corneal specimens

Case 11: An 87-year-old lady had undergone irradiation for a basal cell carcinoma involving the upper lid, which resulted in a reduced pre-corneal tear film. She was also diabetic and wore a contact lens for correction of aph-

Table II

CULTURE
Specimens obtained by corneal scrape are inoculated on these culture media
Blood or chocolate agar for 48 hrs at 37°C
Sabouraud agar for 48 hrs at 35°C
Brain-heart infusion broth for 1 week at 37°C
Thioglycollate broth for 1 week at 37°C
For negative results at 48 hrs:
Blood and chocolate agar in 4% CO ₂ for 5 days at 35°C
Subculture brain-heart infusion on blood and chocolate agar and reincubate
Subculture thioglycollate broth on prereduced blood agar and incubate anaerobically
Incubate Sabouraud agar at 30°C and subsequently at 25°C for 2 weeks
For negative results at 1 week:
Rescrape for inoculation on special media:
Reduced blood agar anaerobically (Capnocytophagia)
Lowenstein-Jensen (Mycobacteria)
Non-nutrient, <i>E. coli</i> -seeded agar (Acanthamoebae)
Chlamydia, virus transport media
For negative results at 2 weeks:
Consider corneal biopsy or excisional lamellar or penetrating keratoplasty
plus culture on all media above
For infection threatening scleral invasion or perforation:
consider excisional keratoplasty plus culture on all media above

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nia. A corneal infiltrate supervened and was scraped prior to treatment with broad spectrum antibiotics initially followed by clotrimazole 1%. A therapeutic bandage lens was later applied. The eye remained inflamed and progressive stromal thinning was managed by excisional penetrating keratoplasty (8 mm host excision). Histopathology demonstrated active keratitis, but no organisms were seen by Gram stain. The tissue was later restained by the modified Ziehl-Neelson technique which revealed *Nocardia* organisms. The patient was not specifically treated in the absence of a microbiological diagnosis at the time. The graft remains clear over a 36-month post-operative follow-up period.

Clinical Response

Case 14: A 26-year-old man developed unilateral keratitis while wearing soft contact lenses. *Pseudomonas sp.* were cultured from the contact lens case two months later, but the corneal disease had the appearance of a herpetic disciform lesion. It was, however, unresponsive to antiviral drugs and the clinical appearance of a ring infiltrate, on presen-

tation to Moorfields, was consistent with *Acanthamoeba* infection. Corneal scrapes were repeatedly negative, including immunofluorescent staining for *Acanthamoeba*. A clinical response was achieved with combination therapy of anti-amoebic drugs Brolene and neomycin. Minimal scarring resulted in 6/12 vision, hence the presumptive diagnosis was not confirmed by biopsy or excision.

Exclusion of microbial keratitis

This implies a thorough investigation of possible infection and allows alternative diagnoses to be considered although it may not be possible to exclude fastidious pathogens.

Case 19: A 42-year-old lady developed an epithelial defect and keratitis induced by excessive ultraviolet irradiation. She was treated with copious topical anaesthetic for three days. Stromal oedema then persisted with recurrent epithelial erosions. At five weeks subepithelial infiltrates were observed suggestive of microbial, possibly *Acanthamoeba*, keratitis. Corneal scrapes were microscopy and culture negative, including specific microscopy and cultures for *Acanthamoeba*. A cor-

Table III

neal biopsy was performed two months later when a new curvilinear opacity appeared. It was also negative for *Acanthamoeba*. The epithelium healed with a bandage contact lens and topical steroid and antibiotic. The stromal oedema gradually resolved, leaving central corneal scarring. This clinical course is consistent with corneal toxicity due to topical anaesthesia (in this case a combined preparation containing naphazoline 0.005% and benoxinate 0.05%) which can cause irreversible endothelial and stromal damage.

A diagnosis of microbial keratitis was confirmed in 13/20 (65%) cases designated 'culture negative' keratitis. Repeat corneal scrapes with conventional microscopy and culturing sufficed in three cases. Special stains or culture techniques were required to make the diagnosis in 10 cases. Mean delay in making the diagnosis was 13 weeks. Five corneal perforations occurred spontaneously at a mean interval of eight weeks after the onset of infection. The pathogens identified were not sensitive to the broad spectrum antibiotic regime of gentamicin plus cefuroxime in 10/13

cases. Appropriate therapy was commenced with a mean delay of 9.7 weeks after onset of symptoms on the basis of either clinical suspicion ($N = 5$) or identification of the pathogen ($N = 8$). Visual outcome was 6/12 or better for 5/13 cases shown to have microbial keratitis. Visual outcome for the subgroup requiring PK ($N = 10$) was 6/12 or better for 4/10 cases (mean follow-up = 28 months).

Discussion

We have been concerned that 'routine' investigations alone do not identify the cause of infection in a significant percentage of patients with presumed microbial keratitis and that the indications for further analysis should be defined. We investigated cases reported to be 'culture-negative' where there was a strong clinical suspicion of microbial keratitis. The special investigations outlined in Tables I–III identified a pathogenic organism in 13/20 (65%) of cases. As there was no defined diagnostic strategy for these cases, there was considerable delay both in identifying the pathogen and initiating appropriate

Table IV

Case No.	Age	Event	Investigations	Initial topical Rx	Diagnostic investigation	Diagnosis
Repeat corneal scrape						
1.	55	Abrasion (stables)	Corneal scrape (1)	Chloramphenicol	Grocott stain	Curvularia
2.	64	Hard CL	Corneal scrape (3)	Chloramphenicol	4% CO ₂ incubation	Nocardia
3.	59	Neuropathic	Corneal scrape (3)	Gentamicin Econazole	30°C culture	Aspergillus
Corneal biopsy						
4.	57	Abrasion (farmyard)	Corneal scrape (2)	Econazole Clotrimazole	Repeat culture 30°C	Aspergillus/Fusarium
5.	70	Bullous keratopathy	Corneal scrape (1)	Gentamicin	Repeat culture	Serratia
6.	34	Soft CL	Corneal scrape (2)	Gentamicin Cefuroxime Fucithalmic	Immunofluorescence <i>E. coli</i> seeded agar	Acanthamoeba
Excisional keratoplasty						
7.	66	Soft CL	Corneal scrape (3)	Gentamicin Cefuroxime Antivirals	Histology Immunofluorescence	Acanthamoeba
8 (R).	35	Saturn CL	Corneal scrape (1)	Antivirals	Histology Immunofluorescence	Acanthamoeba
8 (L).	35	Saturn CL	Corneal biopsy Corneal scrape (1)	Antivirals	Histology Immunofluorescence	Acanthamoeba
9.	71	PK suture abscess	No scrape	Penicillin	Histology Gram stain	Streptococcus viridans
10.	33	HSK	Corneal scrape (1)	Penicillin	Grocott positive	Unidentified
Review of excised corneal specimens						
11.	87	Dry eye + CL (post-irradiation)	Corneal scrape (1)	Gentamicin Cefuroxime Clotrimazole	Acridine orange	Nocardia
12.	60	Dry eye + PK (rheumatoid perforation)	—	PO Erythromycin	Acridine orange	Nocardia
13.	78	Bullous keratopathy	Corneal scrape (1) Corneal biopsy	Gentamicin Cefuroxime	Gram stain	Streptococcus viridans
Clinical response						
14.	26	Soft CL	Corneal scrapes (2)	Antivirus	Ring abscess	Acanthamoeba
15.	22	Soft CL	Corneal scrapes (1)	Antivirus	Ring abscess	Acanthamoeba
Exclusion of microbial keratitis						
16.	68	Myeloid leukaemia	Corneal scrapes (3)	Gentamicin Penicillin	Culture negative	Sterile infiltrate
17.	58	None	Corneal scrape (2) Corneal biopsy	Gentamicin Cefuroxime	Anterior segment fluorescein angiography	Scleritis
18.	24	GPCL	Corneal scrape (1)	Gentamicin Methicillin	Culture negative	CL related infiltrates
19.	42	Abrasion	Corneal scrape (2) Corneal biopsy	Naphazoline 0.005% Benoxinate 0.05%	Culture negative	Abuse of topical anaesthetic
20.	22	Abrasion	Corneal scrape (2)	Gentamicin Cefuroxime	Patch skin testing	Artefacta Dermatitis

therapy. This delay probably resulted in avoidable morbidity, including five corneal perforations. Organisms not previously recognised as pathogenic for keratitis, such as atypical mycobacterium, nocardia, anaerobic

bacteria, listeria and plant fungi such as *Sphaeropsis subglobosa*³⁻¹⁷ are being reported with increasing frequency in the literature. A logical diagnostic strategy is likely to be the most effective way of either identifying the

Table IV cont.

Case No.	Specific Rx	Rx delay (days)	Complications and further Rx	Final VA
Repeat corneal scrape				
1.	Clotrimazole + Miconazole	39	Scar	6/6
2.	Rifampicin + Vancomycin	189	Lamellar keratoplasty	6/60
3.	Clotrimazole	90	Perforation + PK	CF
Corneal biopsy				
4.	Natamycin + Amphotericin	39	Uncontrolled infection + PK	6/18
5.	Gentamicin	15	Failed PK	LP
6.	Brolene Neomycin	42	Perforation + PK	LP
Excisional keratoplasty				
7.	Brolene Neomycin	51	PK	6/36
8 (R).	Brolene Neomycin	80	PK	6/9
8 (L).	Brolene Neomycin	80	PK	6/9
9.	Penicillin	32	PK	6/12
10.	Penicillin	47	Perforation + PK	6/12
Review of excised corneal specimens				
11.	—		Perforation + PK	6/24
12.	—		Endophthalmitis + evisceration	NLP
13.	—		PK + subsequent 2° IOL Endophthalmitis + PK	LP
Clinical response				
14.	Brolene Neomycin	92	Corneal scar	6/12
15.	Brolene Neomycin	88	Corneal scar	6/12
Exclusion of microbial keratitis				
16.	Steroids		ECCE + IOL	6/18
17.	Steroids		Perforation + PK	NLP
18.	Steroids		None	6/9
19.	Steroids		Corneal scarring	6/24
20.	Occlusive taping		None	6/6

presence of known pathogens or screening for 'new' ones.

These considerations prompted us to derive a comprehensive diagnostic algorithm, encompassing both microscopy and culture. It pro-

vides a logical approach for investigating patients who may otherwise be doomed to a misleading diagnosis of 'sterile' keratitis, when infection is suspected. The algorithm represents an important departure from

Fig. 1 Methenamine silver stain showing branching fungus (*Curvularia* sp.).

Fig. 3 Immuno-fluorescent antibody stain showing *Acanthamoeba* sp. in paraffin-embedded section of cornea.

acceptance of a 'culture-negative' diagnosis and should allow earlier identification of unusual pathogens. The principles of the algorithmic approach are applicable to the more rapid diagnostic tests which are now being developed for clinical use.¹⁸ These include the *Limulus* amoebocyte lysate assay (for Gram negative organisms), fluorescein-conjugated

Fig. 2 Modified Ziehl-Neelson stain showing *Nocardia* in paraffin-embedded section of cornea.

Fig. 4 Haematoxylin-eosin stain showing *Streptococcus* sp. between corneal lamellae of excised graft tissue.

lectins, electron microscopy with negative staining, specific fluorescein-conjugated antibody tests, enzyme immunoassay and nucleic acid hybridisation reactions. An algorithmic approach to the investigation of presumed infection should provide the most efficient use of existing and future resources. By sequential re-staining and re-incubating, the original

specimens can be re-exploited to give the best chance of gaining a positive result without performing unnecessary additional biopsies.

It is held that 86% of bacterial keratitis is caused by staphylococci, streptococci, pseudomonads or enterobacteriaceae.² This is the continuing rationale for adopting the Gram stain for initial microscopy and for instituting combined aminoglycoside and cephalosporin therapy. The remaining 14% of infections are caused by pathogens which are more difficult to identify and a proportion of these are designated 'culture-negative'. The problem differs in tropical and subtropical regions where fungal infection may account for as much as 50% of microbial keratitis. Early identification of the organism is vital if useful vision is to be preserved.

Microscopy

Microscopy may provide an early guide to appropriate therapy. It has been reported that the Gram stain is reliable in about 75% of single infections and 37% of mixed infections.² Acridine orange has recently been found more sensitive than Gram stain.¹⁹ It should be used as a 1% solution with an acid buffer to stain bacteria orange against a dark background (green cells and tissue debris), seen under ultra-violet light. This can be done before applying Gram stain for examination under white light. In addition, some fungi will be identified by Giemsa staining as recommended by Jones.¹

We propose an algorithm for special staining (Table I) which should be followed when investigations are negative for keratitis of presumed microbial aetiology. This includes the use of reversible stains such as modified and full Ziehl-Neelson stains, before re-cycling the specimens and applying end-stains such as methenamine silver.

Cultures

Preliminary identification of pathogens by microscopy should be confirmed by positive cultures. These also provide for antimicrobial sensitivity testing. A problem arises when organisms do not grow under routine conditions of incubation. We propose an algorithm (Table II) which should be followed in this event. It may be possible to achieve positive

cultures without inoculating further media; if antibiotics were administered prior to the scrape, colonies may grow in broth culture (which dilutes any antimicrobial present) given extra incubation time. Some organisms may grow slowly on sub-optimal media, such as mycobacteria on blood agar, and 'negative' cultures should not be discarded as occurs routinely in busy laboratories at 48 hours, but re-incubated for five days in 4% CO₂. Micro-aerophilic or capnophilic organisms such as *Nocardia* (Case 2) may require conditions of 4% CO₂ in a special incubator. Some organisms, including fungi (Case 3) and *Acanthamoeba* mutants are temperature-sensitive, requiring incubation at 25°C, 30°C or 35°C. The role of special media is discussed in the context of repeat corneal scrapes and biopsies. It should be borne in mind that organisms such as *Listeria* and various anaerobic organisms may cause infection and these should also be looked for.

Repeat Corneal Scrape

The original corneal specimen may not yield a pathogenic organism despite the application of supplementary stains and changes in the conditions of incubation. In the absence of clinical response to treatment with broad spectrum antibiotics, further corneal scrapes are indicated (Cases 1–3). These should be performed after 24 hours without antibiotic administration. In addition to conventional media, including broth cultures, special media should now be considered; Lowenstein-Jensen agar for *Mycobacteria*, non-nutrient agar seeded with *E. coli* for *Acanthamoeba* and virus transport media (Table II). Some plant fungi are particularly exigent, requiring agar impregnated with autoclaved vegetable matter or animal dung.²¹ This may have been the reason for negative *Curvularia* cultures on Sabouraud agar (Case 1). Incubation conditions may be modified, exposing cultures for example to 4% CO₂ which will reveal capnophilic organisms (Case 2).

Corneal Biopsy

Chronic progressive microbial keratitis due to an unidentified pathogen is an established indication for corneal biopsy; corneal scrapes may be too superficial to obtain infected tis-

sue. In longstanding acanthamoebic keratitis, for example, cysts tend to be detectable only in the deeper stroma (Cases 6 and 7).¹⁰ We believe this may explain the negative acanthamoeba cultures in cases 14 and 15. Mid-stromal crystalline keratopathy may require biopsy when it occurs in the absence of an epithelial defect (especially related to infected suture-tracks in grafts) when it is inaccessible to scraping (Case 9).

Progressive keratitis due to unsuspected polymicrobial (Case 4) or fungal infection (as an alternative explanation to microbial resistance) should be considered when there is incomplete response to therapy appropriate for the identified pathogen. Keratectomy has been advocated for suspected fungal disease¹ and chronic keratitis.²² We recommend that such biopsies be adopted for acute culture negative cases and suspected polymicrobial infection which have previously been scraped and thoroughly analysed according to the proposed algorithms for microscopy and culture.

Excisional Keratoplasty

Excisional lamellar or penetrating keratoplasty is a potentially therapeutic procedure²³⁻²⁴ (e.g. Cases 2 and 11), but in untreated infection, residual pathogens in the host cornea represent a threat to graft survival. Case 12 demonstrates this problem; perforation necessitated grafting but recurrent infection supervened at the graft-host interface in the absence of appropriate therapy. A diagnosis of *Nocardia* keratitis was only made when the histopathology was reviewed. Endophthalmitis followed and the infection was ultimately identified from the evisceration specimen. By adopting the diagnostic algorithm an earlier diagnosis may achieve an improved prognosis in future. Progressive infection which threatens corneal integrity may require emergency keratoplasty and all involved tissue must be excised. In combination with specific antimicrobial therapy this should minimise the risk of recurrence.

'Sterile' Keratitis

A variety of clinical diseases may give rise to non-infected corneal ulcers²⁵ including chemical injuries, Mooren's ulceration, auto-

immune collagen-vascular disease, exposure, neuroparalytic and nutritional disorders. These ulcers may become infected as a secondary event and it is wise to exclude this, especially where the clinical signs become atypical of the condition suspected. Infection may be complicated by scleritis, particularly when this is uncontrolled and progressive. Hence the conditions may co-exist, complicating the diagnostic problem. Neither scleritis nor infection were conclusively demonstrated in four atypical cases with infiltrates thought to be infective. One of these had myeloproliferative disease (Case 16). The other two (Cases 17 and 18) responded to intensive topical and pulsed systemic steroids, without antibiotics, which is suggestive of scleritis.

Corneal infiltrates which are truly sterile are a recognised complication of contact lens wear.²⁶ They are considered to represent the response to a number of different stimuli; contact lens solutions, hypoxia and hypersensitivity to microbial antigens. They tend to be multiple and lack significant associated anterior chamber inflammation. These infiltrates were often associated with epithelial defects and generally measured less than 1 mm (Case 18). It is, however, accepted that they should be investigated to exclude infection.

Corneal toxicity from topical anaesthetic administration, particularly in the presence of an epithelial defect, is well recognised²⁷ but not frequently observed in current practice. It may masquerade as microbial keratitis (Case 19) and should be investigated. Endothelial damage may be sufficiently severe to result in corneal decompensation requiring PK.

Artefactual damage should always be a diagnosis of exclusion which entails investigation for microbial infection or systemic autoimmune disease. It is more readily made in the presence of contact dermatitis (Case 20) and skin testing may suggest the likely agent involved.

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