

Adenovirus Type 8 Epithelial Keratitis: The Development, Accompanying Signs, and Sequelae

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This chapter shows the development of Ad8 keratitis in patients of whom all but one (Case 8) were exposed to the virus during a nosocomial outbreak of EKC. The infection was transmitted either directly in the Clinic or by infected contacts. Since in clinical practice infections with various adenovirus serotypes cannot be distinguished from each other, Ad8 can serve as a model of a sequence events common to all of them. In the absence of causative treatment, the cases presented in this chapter show the natural course of the disease. Cortisone eye drops were not used except for a couple of days during the acute stage in one patient (Case 8) because of an initial diagnostic error.

In *time perspective*, lacking better indicators, the duration of the keratitis at presentation is related to the onset of symptoms as reported by the patient, which of course does not tell when exactly during the course of the disease the corneal epithelium became affected. It might have occurred early, as shown in Case 1 presenting about 30 h. after the onset of symptoms.

The morphological components of adenovirus epithelial keratitis are few (Chap. 1) and the *course of the disease* rather stereotype: first to appear are superficial cyst-like structures; either concurrently with them, or shortly thereafter, appear rounded/abnormal cells, individual or grouped. During the next few days, the numbers of both tend to increase, and the rounded/abnormal cells show propensity to heap-up; this phenomenon eventually results in larger lesions termed adenovirus *epithelial infiltrates*. The cyst-like structures are first to clear. The numbers of rounded/abnormal cells, on the other hand, diminish only slowly, and in some patients they persist for many months or even years after the acute disease had subsided.

These are patients who develop a *sequela* of adenovirus epithelial keratitis termed *subepithelial infiltrates*. Clinically, this denomination seems to apply to *light-reflecting flecks* or *opacities*, mild or dense, few or many, present after the

integrity of the epithelial surface has been restored as judged by the absence of fluorescein staining. Published *histological preparations* have shown subepithelial accumulations of inflammatory cells, but at what point of time the subepithelial stroma becomes involved seems unknown. In vivo, there is no abrupt change, there is the same cellular component as before, and the only indicators of subepithelial involvement are structures implying damage to the lamellar composition of the superficial stroma the initial stages of which are difficult to detect. Since the cells appear the same during the course of the disease, I have chosen (Chap. 1) to use the purely descriptive term rounded/abnormal cells irrespective of their possible nature throughout the book. Concerning the subepithelial infiltrates, the *terminology* is even more challenging. After having pondered the question for a while, I found it practical to use the term in accordance with the clinical application, i.e., also in cases in which no clear subepithelial stromal involvement has been captured. The substructure, the superficial location, and the development of subepithelial infiltrates are shown in Case 10 (cf. also Chap. 4).

Diagnostic errors occurring during the period of time elapsing between symptom onset and (in the context) the diagnostic adenovirus epithelial infiltrates highlight the importance of familiarity with the appearance of the early corneal manifestations: With the slit lamp, the cornea appears dusty but not lustreless; a careful observation discloses the presence of light-reflecting dots and, with fluorescein sodium, many surface elevations. If attention is not paid, patients with *accompanying signs* of anterior uveitis are easily diagnosed with primary uveitis, particularly those with a history of a recurrent one (Cases 3 and 8). Very tricky are also nosocomial infections superimposed on preexisting corneal epithelial diseases (Cases 9 and 10); before an outbreak is discovered, they tend to be erroneously attributed to allergic reactions to treatment.

Case 1: EKC: An Occupational Hazard

Case Report

A 40-year-old woman presented with irritation, foreign body sensation, tearing, and redness of the right eye, all starting about 30 h. before examination. The lids were slightly swollen, the eye moderately injected, the conjunctiva showed follicular hyperplasia and, with fluorescein sodium, myriads of green dots; with the slit lamp, the corneal epithelium appeared slightly hazy. The left eye was white. Adenovirus infection was suspected. The fellow eye became affected 3 days later but less severely.

The photographs of the right cornea were taken at presentation and 5, 12, and 20 days, and 2 months after the onset of symptoms.

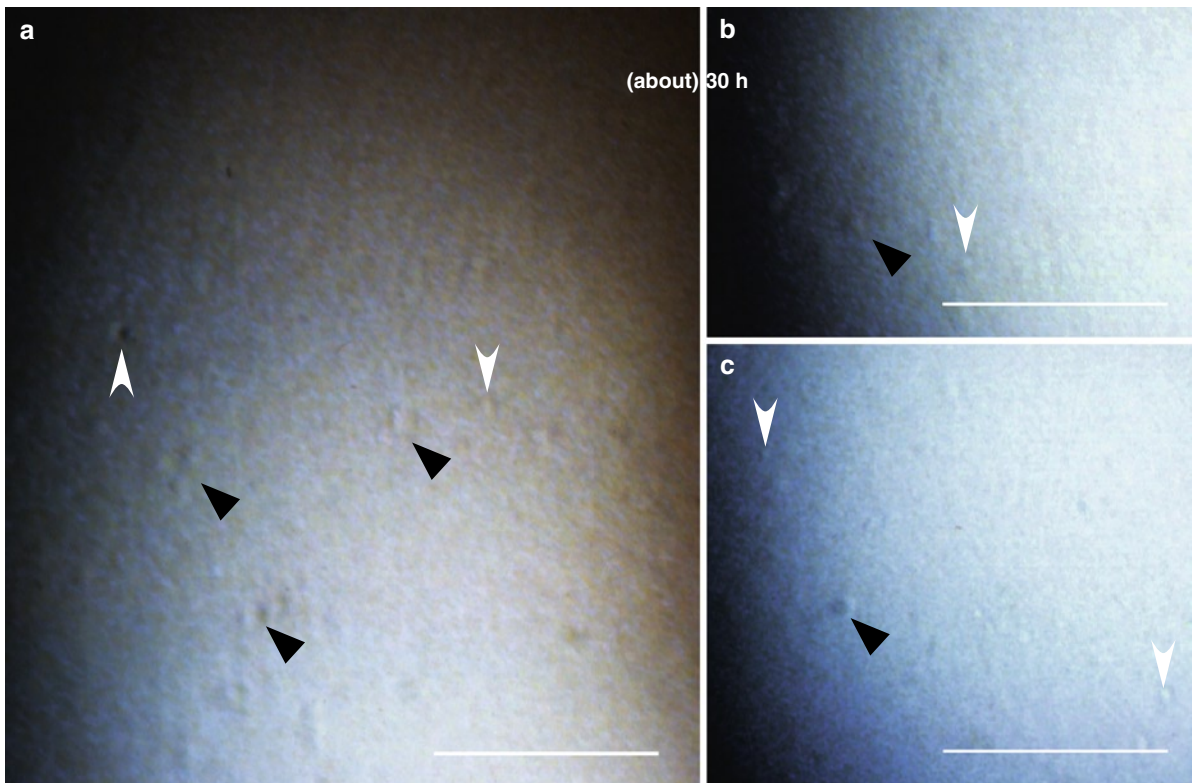


Fig. 2.1 (a–c) About 30 h after the onset of symptoms, the corneal epithelium shows discrete rounded cyst-like structures (*black arrowheads*). The smaller structures (*white arrowheads*) might represent rounded/abnormal cells (cf. Fig. 2.2, opposite page)

Comment

It is uncommon to see a patient presenting that early after the onset of symptoms. This patient was a staff member whose symptoms had started during a just discovered outbreak of nosocomial infection.

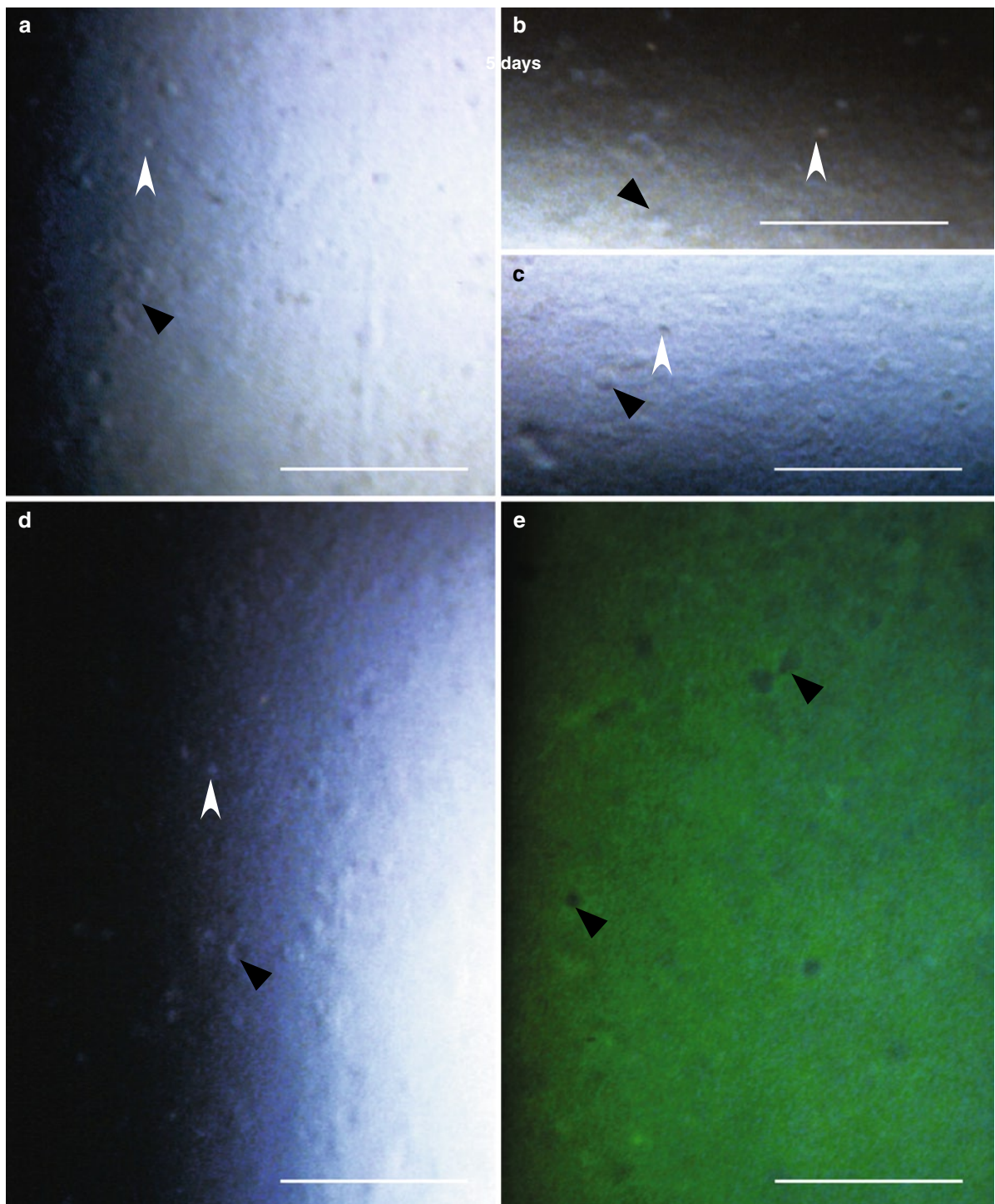
EKC: An Occupational Hazard (Case 1, cont.)

Fig. 2.2 (a–e) Five days after symptom onset. In (a–d) are visible rounded/abnormal cells (*white arrowheads*) and many rounded cyst-like structures (*black arrowheads*) which (e) are protruding (dark; *arrowheads*) in the tear film stained green with fluorescein. (Cf. Figs. 2.6 and 2.7)

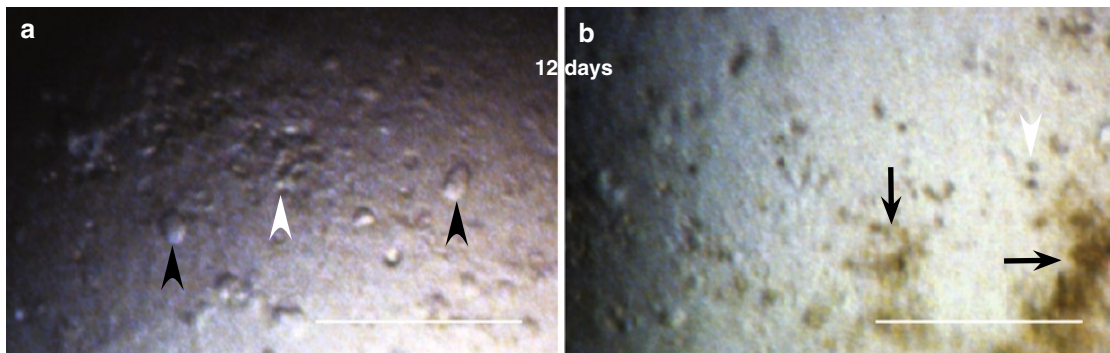
EKC: An Occupational Hazard (Case 1, cont.)

Fig. 2.3 (a, b) Twelve days after symptom onset, the epithelium is heavily disturbed. It shows many rounded/abnormal cells (white arrowheads), individual or grouped, and distinct epithelial cysts (black arrowheads). In places, the cells seem mixed with cell debris (b, arrows). (Adapted from [4])

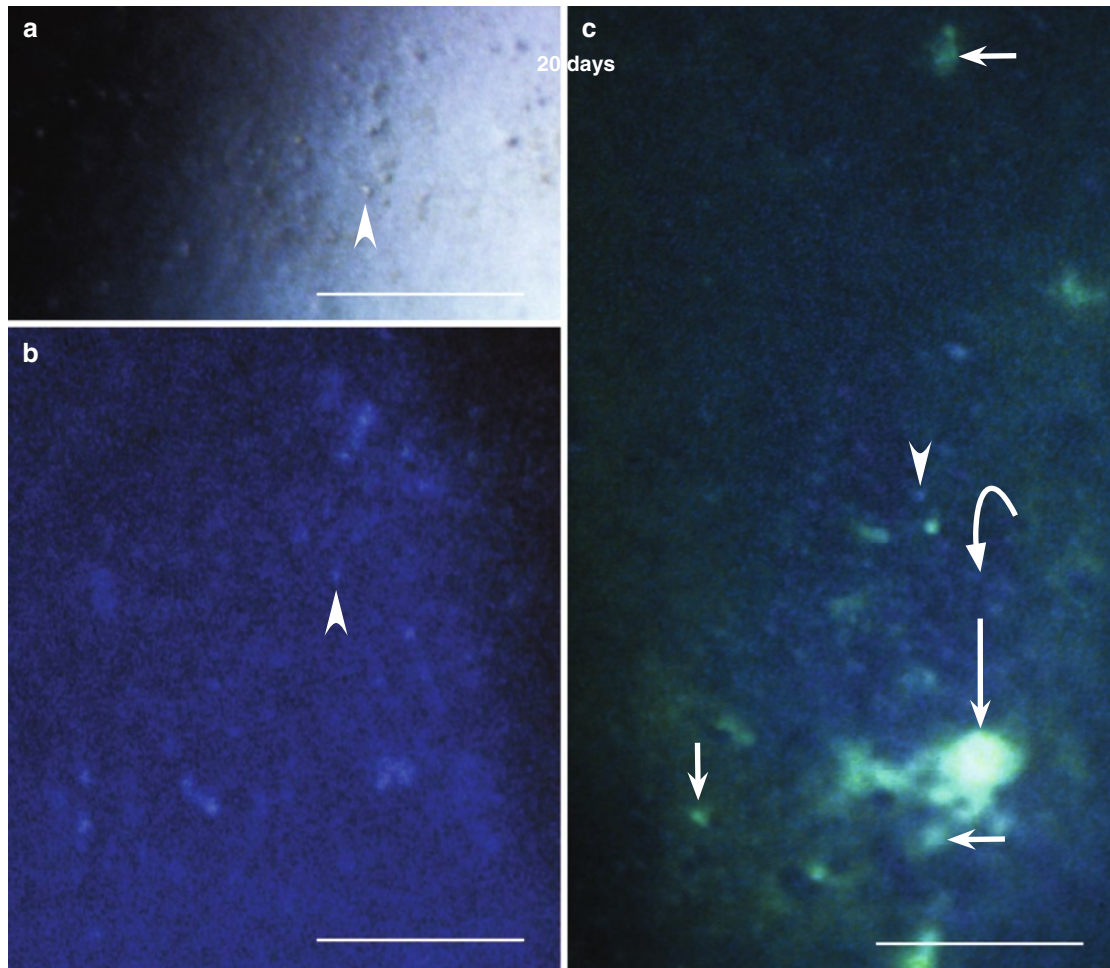


Fig. 2.4 (a–c) Twenty days after symptom onset, the epithelium shows (a) rounded/abnormal cells (arrowhead); they are (b, c) light reflecting (arrowheads). (c) With fluorescein are visible brilliantly green dots, individual (short arrows) or grouped (long arrow), and surface elevations (dark; bowed arrow)

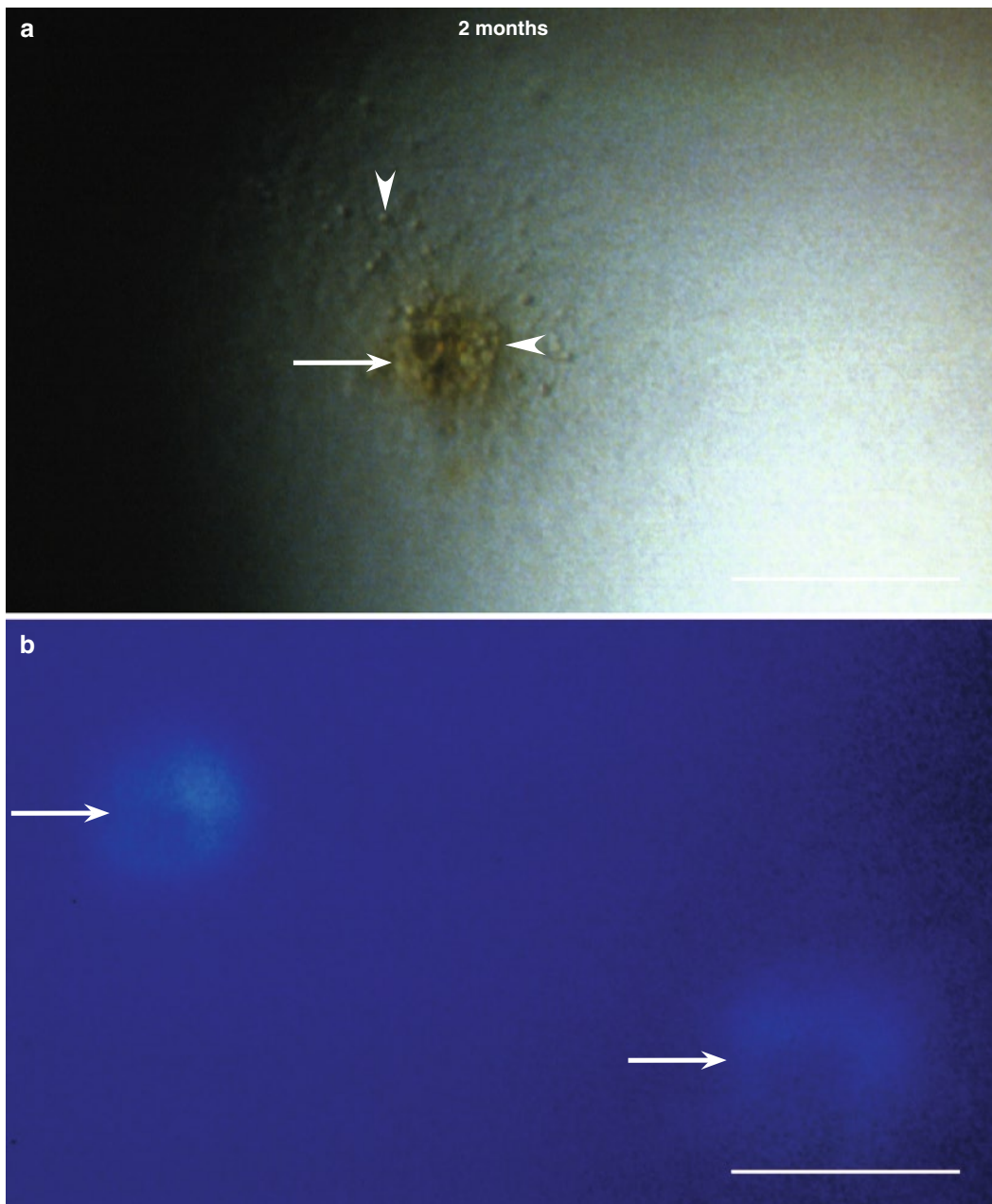
EKC: An Occupational Hazard (Case 1, cont.)

Fig. 2.5 (a, b) Two months after symptom onset (a) a lesion (arrow) that contains rounded/abnormal cells (arrowhead) is visible; such cells (arrowhead) are also present outside it. (b) Two lesions staining green with fluorescein (blue filter)

Comment

Sometimes, new surface disruptions occur long after the surface has been restored. Cf. Figs. 4.14 and 4.27.

Addendum

This patient developed dense subepithelial opacities/infiltrates that only gradually faded away.

Case 2: A Sequel of a Friendly Visit

Case Report

A 77-year-old man was referred to the Eye Clinic by a general practitioner because of a left-sided conjunctivitis of 4 days duration. The left eye was injected, the conjunctiva swollen, and the cornea showed many dust-like epithelial dots and folds of the Descemet's membrane. The right eye was white. Adenovirus was suspected. The following day, the patient presented again because of worsening of symptoms. The right eye was slightly injected and showed many follicles in the lower fornix, and the symptoms in the left eye were more severe. The source of the infection was traced to a contact with a close friend who had contracted nosocomial infection.

Three months after onset, the right cornea showed two discrete subepithelial opacities/infiltrates and the left cornea several dense ones. 7.5 months after onset, the right cornea was clear and the periphery of left one showed a few discrete subepithelial opacities.

The photographs of the left cornea were taken 5 and 19 days, and 3 and 7.5 months after the onset of symptoms.

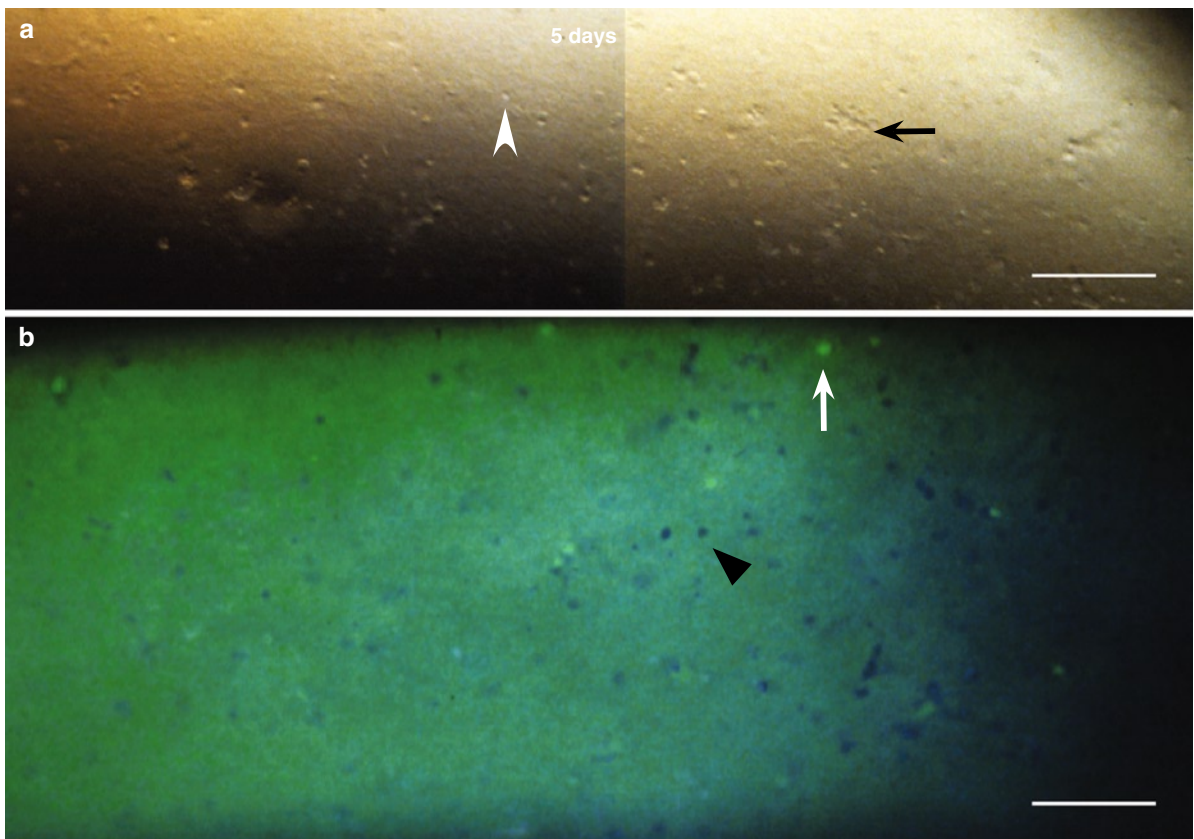


Fig. 2.6 (a, b) Five days after symptom onset. Survey. (a) Without staining, the epithelium shows many fine dots spread over the surface, individual (arrowhead) or grouped (arrow). (Composed photograph.) (b) With fluorescein are visible many rounded dark (arrowhead) and some brilliantly green (arrow) dots. For details see Fig. 2.7 (opposite page)

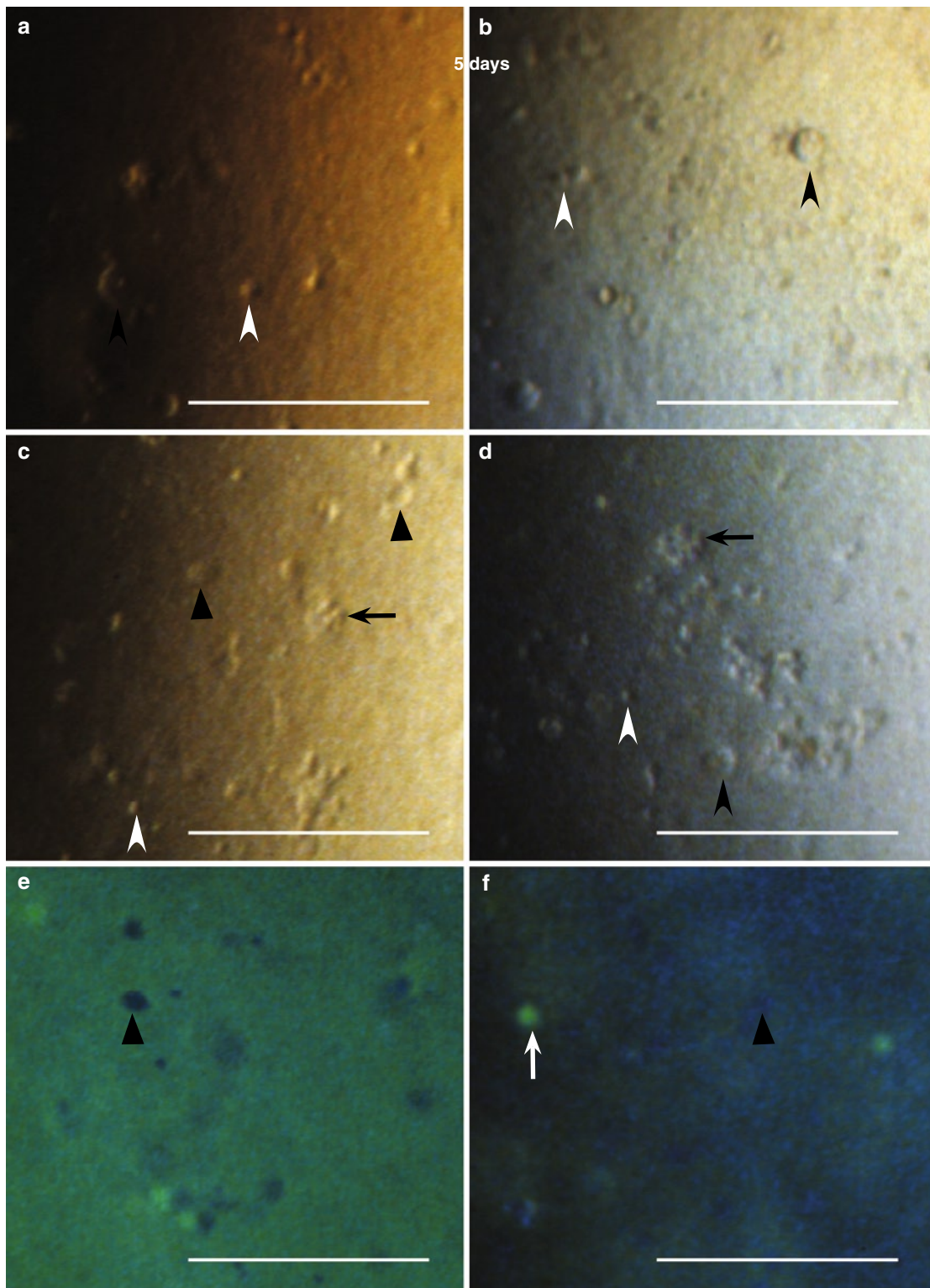
A Sequel of a Friendly Visit (Case 2, cont.)

Fig. 2.7 (a–f) The cornea shown in Fig. 2.6. Visible are (a–d) rounded/abnormal cells, individual (*white arrowheads*) or grouped (*arrows*), (c) cyst-like changes (*black arrowheads*), and (b and d) epithelial cysts (*black arrowheads*). (e, f) With fluorescein are visible small protrusions (dark; *arrowheads*) in the green stained tear film and a few green dots (*arrow*)

A Sequel of a Friendly Visit (Case 2, cont.)

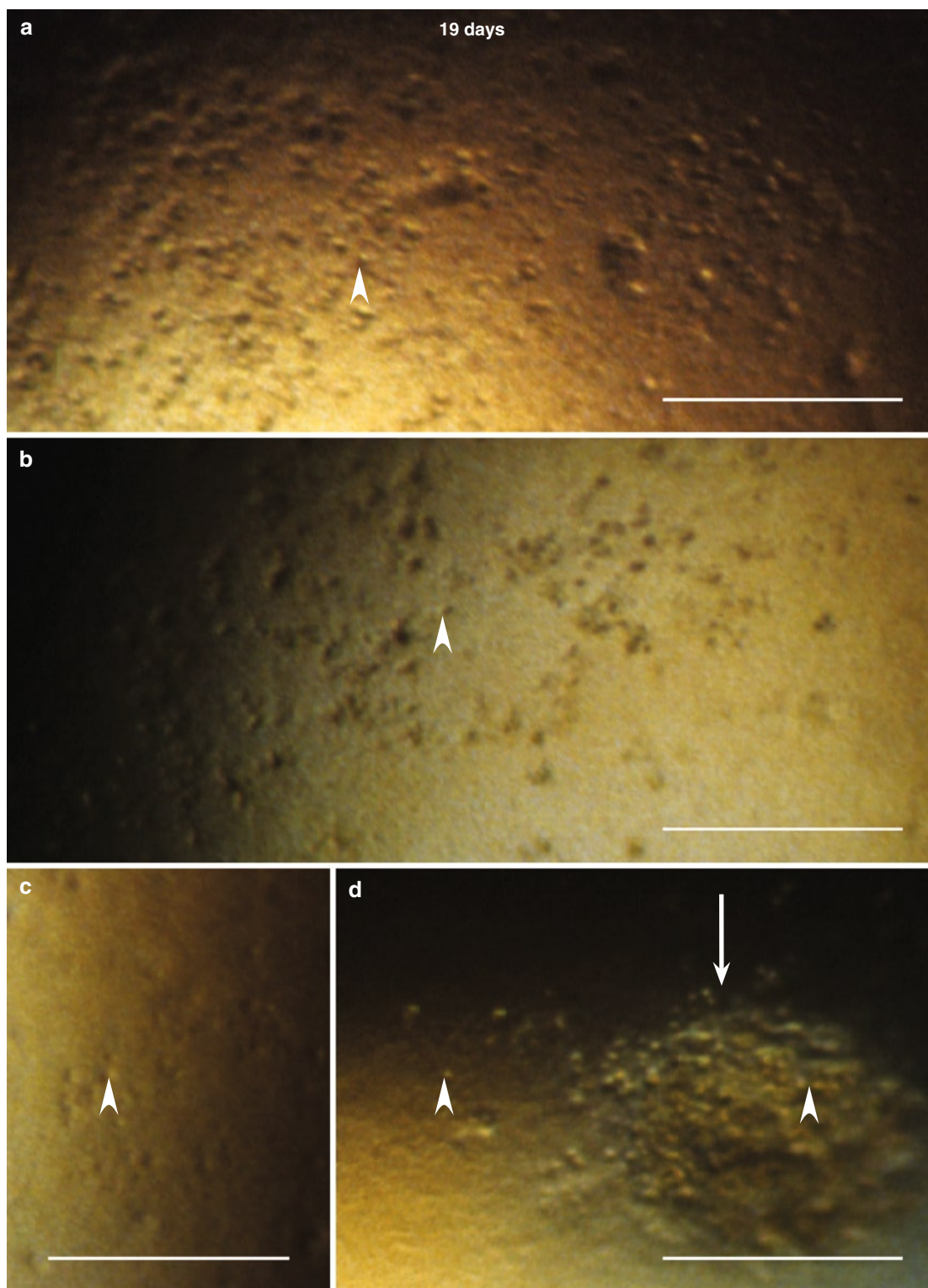


Fig. 2.8 (a–d) Nineteen days after symptom onset, the cornea shows many rounded/abnormal cells (*arrowheads*), in (d) heaped-up in a distinct epithelial infiltrate (*arrow*). (d; adapted from [4])

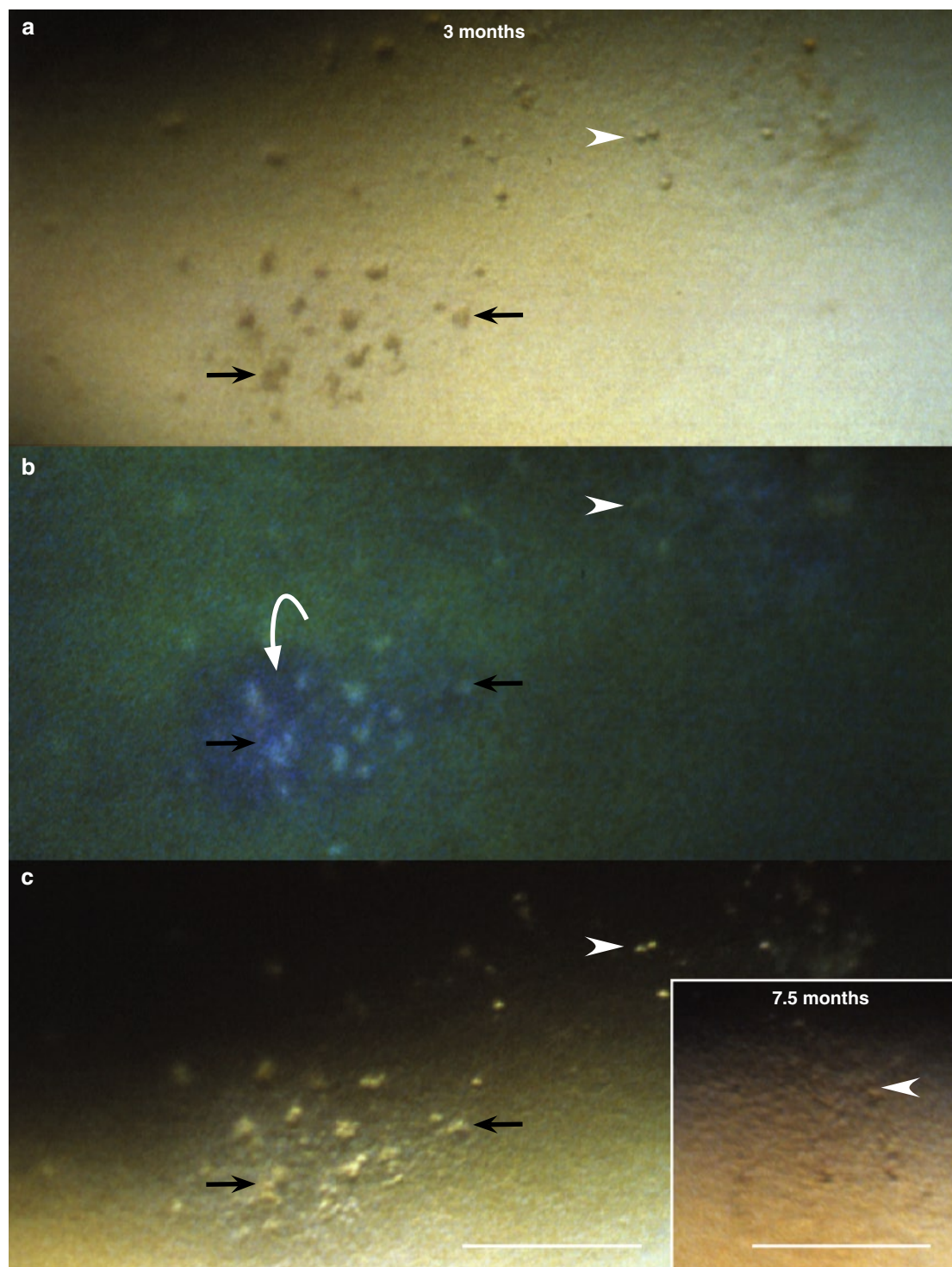
A Sequel of a Friendly Visit (Case 2, cont.)

Fig. 2.9 (a–c) Three months after symptom onset, the cornea shows subepithelial opacities/infiltrates containing rounded/abnormal cells, individual (*arrowheads*) or grouped (*black arrows*); (b) shows their light-reflecting property and a surface elevation (dark; *bowed arrow*). (The black arrows and the arrowheads are placed in corresponding locations.) *Inset*: rounded/abnormal cells (*arrowhead*) present 7.5 months after onset

Case 3: Anterior Uveitis and Nosocomial Infection

Case Report

A 74-year-old woman treated with cortisone eye drops for right-sided anterior uveitis. Nine days after the last visit, she presented again because of augmenting redness and irritation in the fellow eye. Both eyes were slightly injected and the corneae showed discrete dust-like epithelial dots. Four days later, when the lids were swollen and the corneae additionally showed folds of the Descemet's membrane, adenovirus was suspected. Six weeks after symptom onset, the eyes were white and the corneae clear. She never developed subepithelial opacities/infiltrates.

The photographs of the left cornea were taken 9 and 15 days after the onset of symptoms.

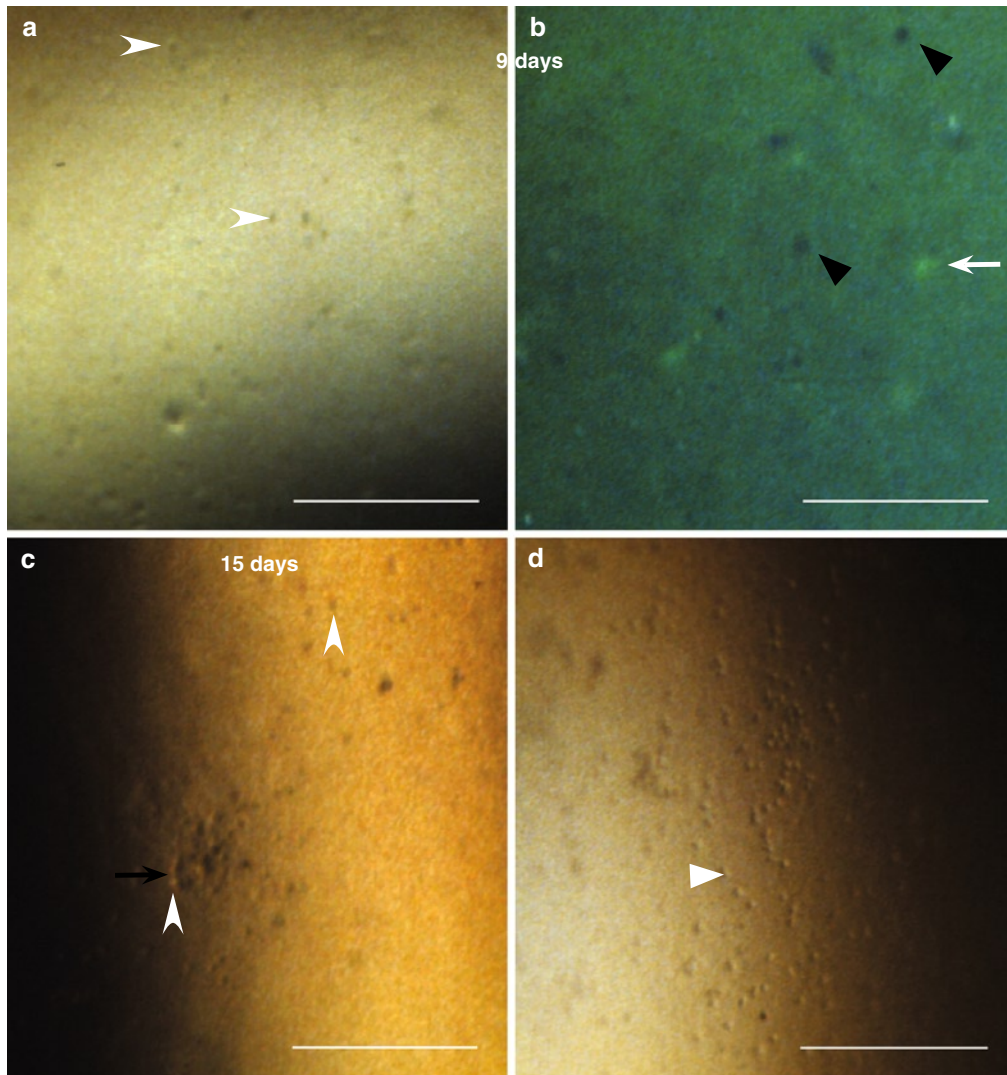


Fig. 2.10 (a–d) Nine days after symptom onset, the cornea shows (a) rounded/abnormal cells (arrowheads) and (b) rounded protrusions (dark; arrowheads) and green dots (arrow) in the tear film stained green with fluorescein. (c) Rounded/abnormal cells (arrowheads), in places grouped (arrow) are still present 15 days after onset. (d) shows, for comparison, inflammatory cells (arrowhead) attached to the endothelium during a mild anterior uveitis present 15 days after the onset of symptoms relatable to Ad8 infection

Case 4: A Case of a Caring Wife

Case Report

This 87-year-old woman, who had administered eye drops to her husband with nosocomial infection, presented with bilateral keratoconjunctivitis 4 days after symptom onset. She developed many subepithelial opacities/infiltrates still present 2 years later.

The photographs of the left cornea were taken 17 days after symptom onset.

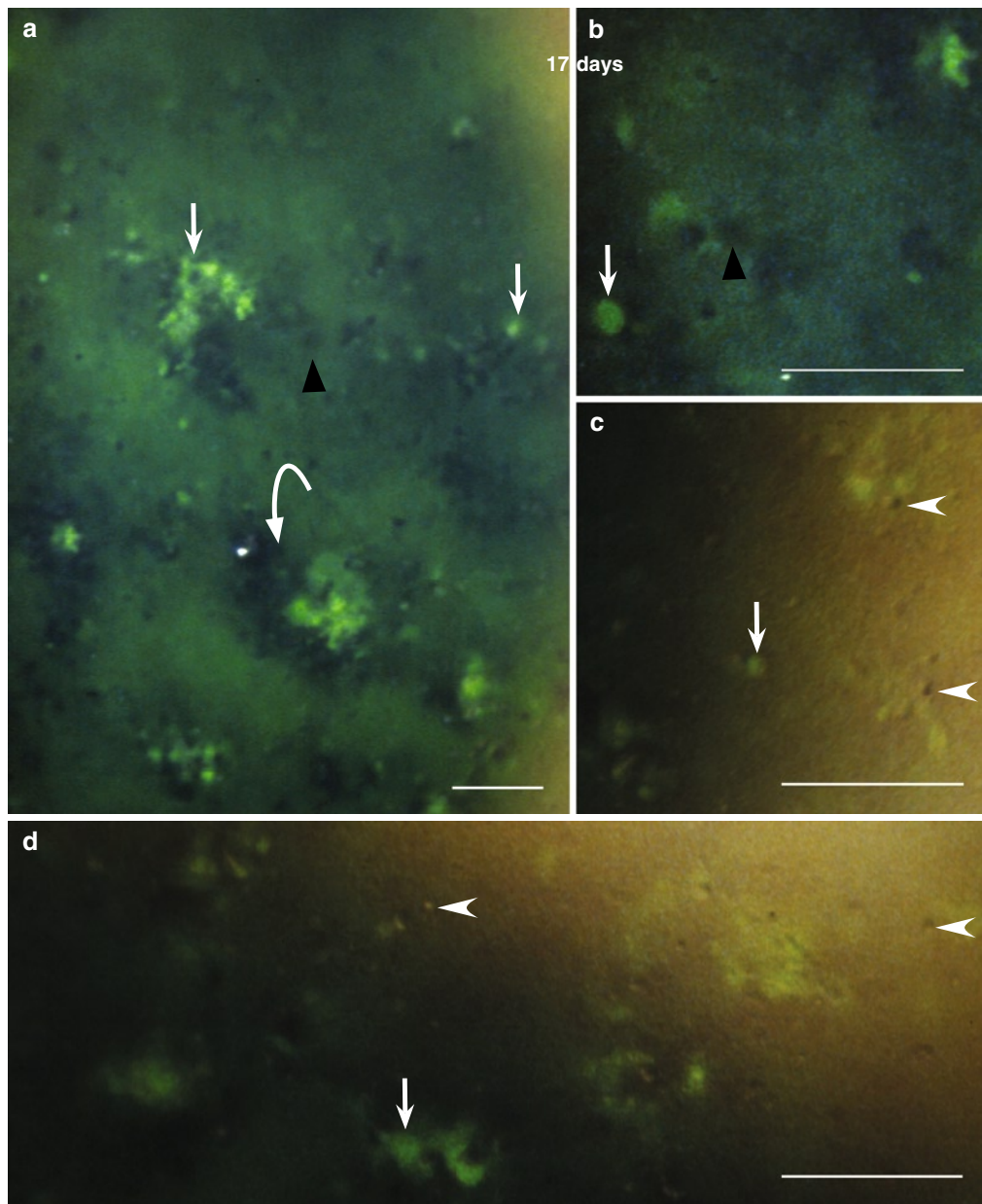


Fig. 2.11 (a–d) A heavy disturbance of the epithelial architecture highlighted with fluorescein. (a, b) show surface elevations (dark; bowed arrow and arrowheads) and brilliantly green dots (straight arrows). In (c, d) are visible green dots (arrows) and rounded/abnormal cells (arrowheads)

Case 5: Nosocomial Infection After Suture Removal

Case Report

A 85-year-old woman presented with irritation and foreign body sensation in her left eye. An old corneal suture after a previous cataract operation was removed. Sixteen days later she presented again, this time because of irritation and redness in both eyes that had started a week earlier (9 days after her first visit). The lids were swollen, the conjunctivae injected and swollen, and the corneae showed fine epithelial dots and folds of the Descemet's membrane. Nosocomial adenovirus infection was suspected. She developed discrete subepithelial opacities/infiltrates in both corneae; only a few very faint ones with no visual consequences were present 7 months after symptom onset.

The photographs of the left cornea were taken 2 weeks, 4 weeks, and 7 months after the onset of symptoms.

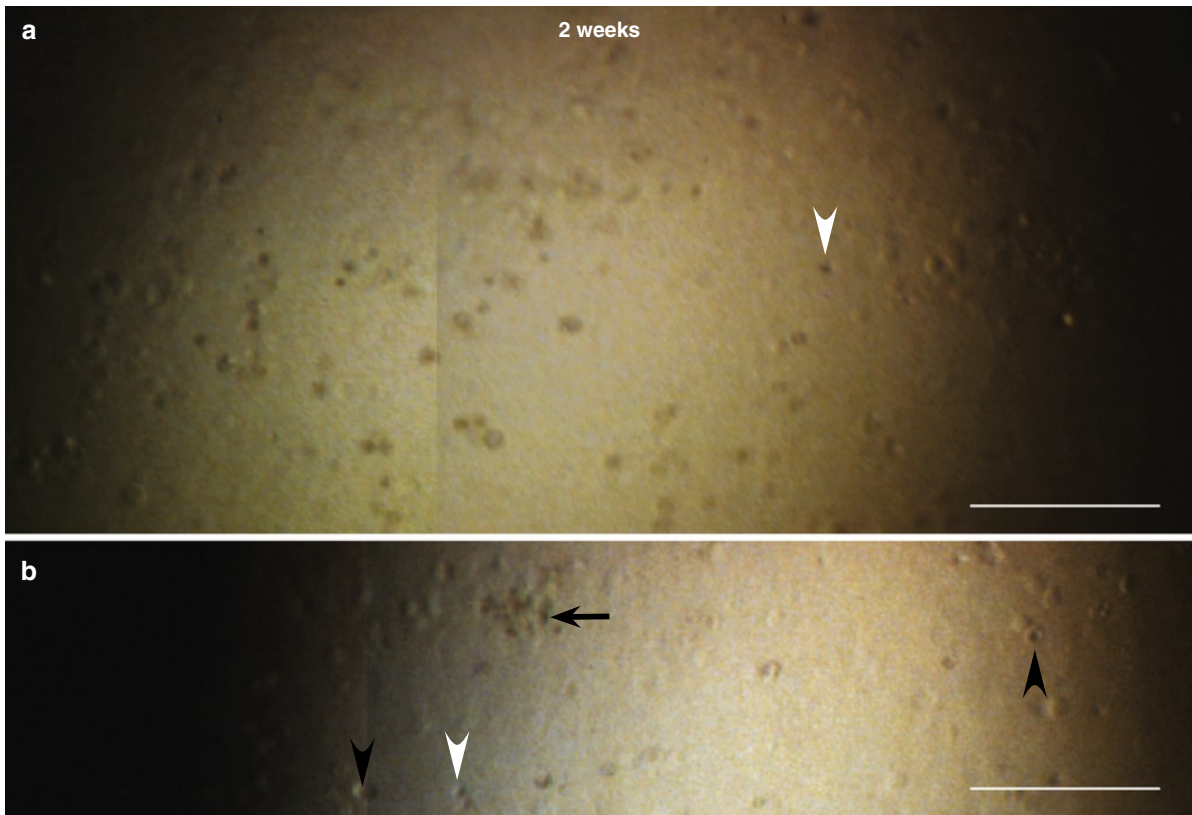


Fig. 2.12 (a, b) Survey of corneal epithelial changes captured 2 weeks after the onset of symptoms. The epithelium shows many rounded/abnormal cells (*white arrowheads*), in places grouped (*arrow*), and many small cysts (*black arrowheads*) spread over the surface (composed photographs). For details see Fig. 2.13 (*opposite page*)

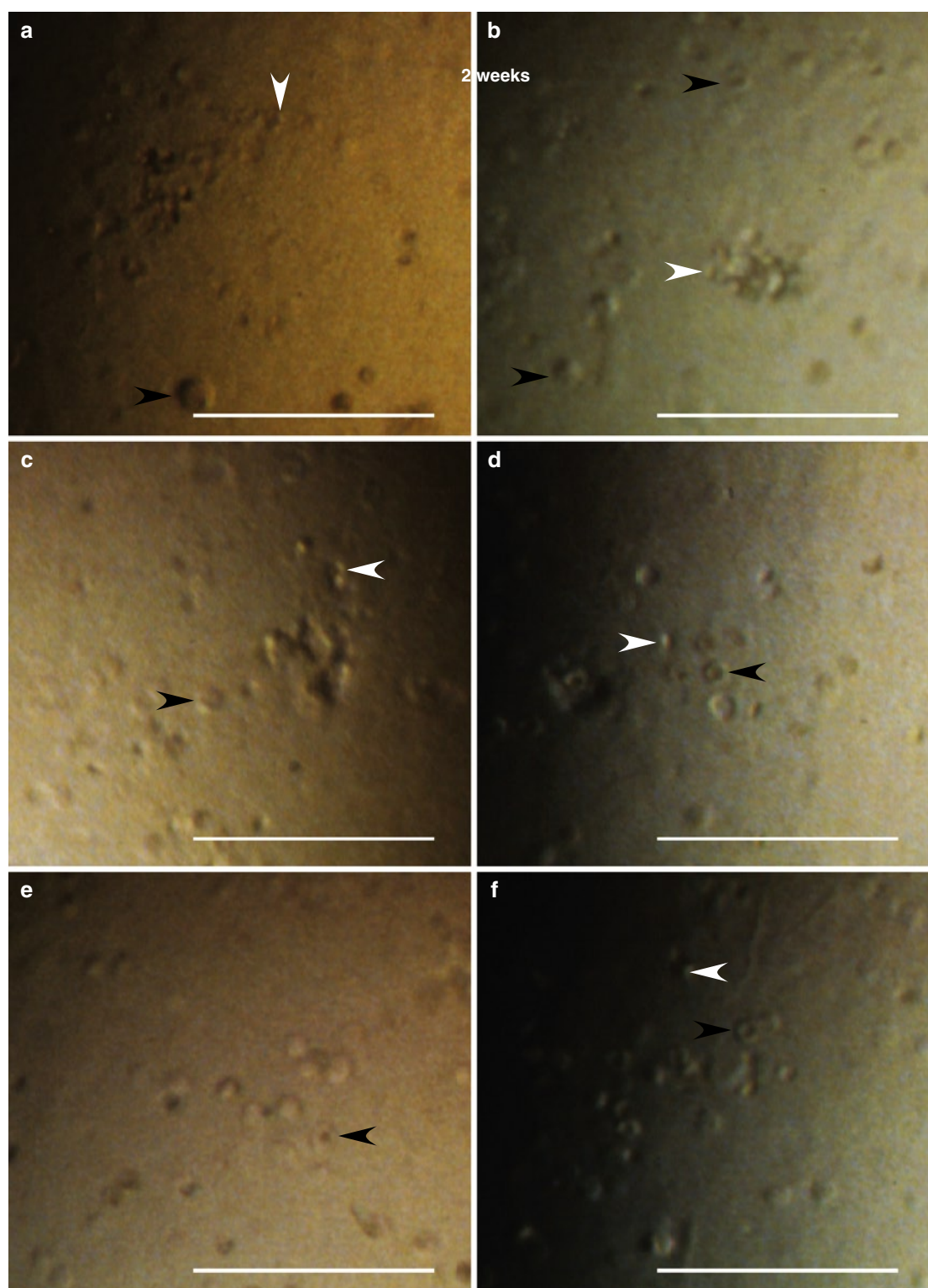
Nosocomial Infection After Suture Removal (Case 5, cont.)

Fig. 2.13 (a–f) Two weeks after symptom onset. The epithelium is heavily disturbed. It shows many rounded/abnormal cells (white arrowheads) and small cysts (black arrowheads); of these, many contain a rounded cell. (This phenomenon is unspecific)

Nosocomial Infection After Suture Removal (Case 5, cont.)

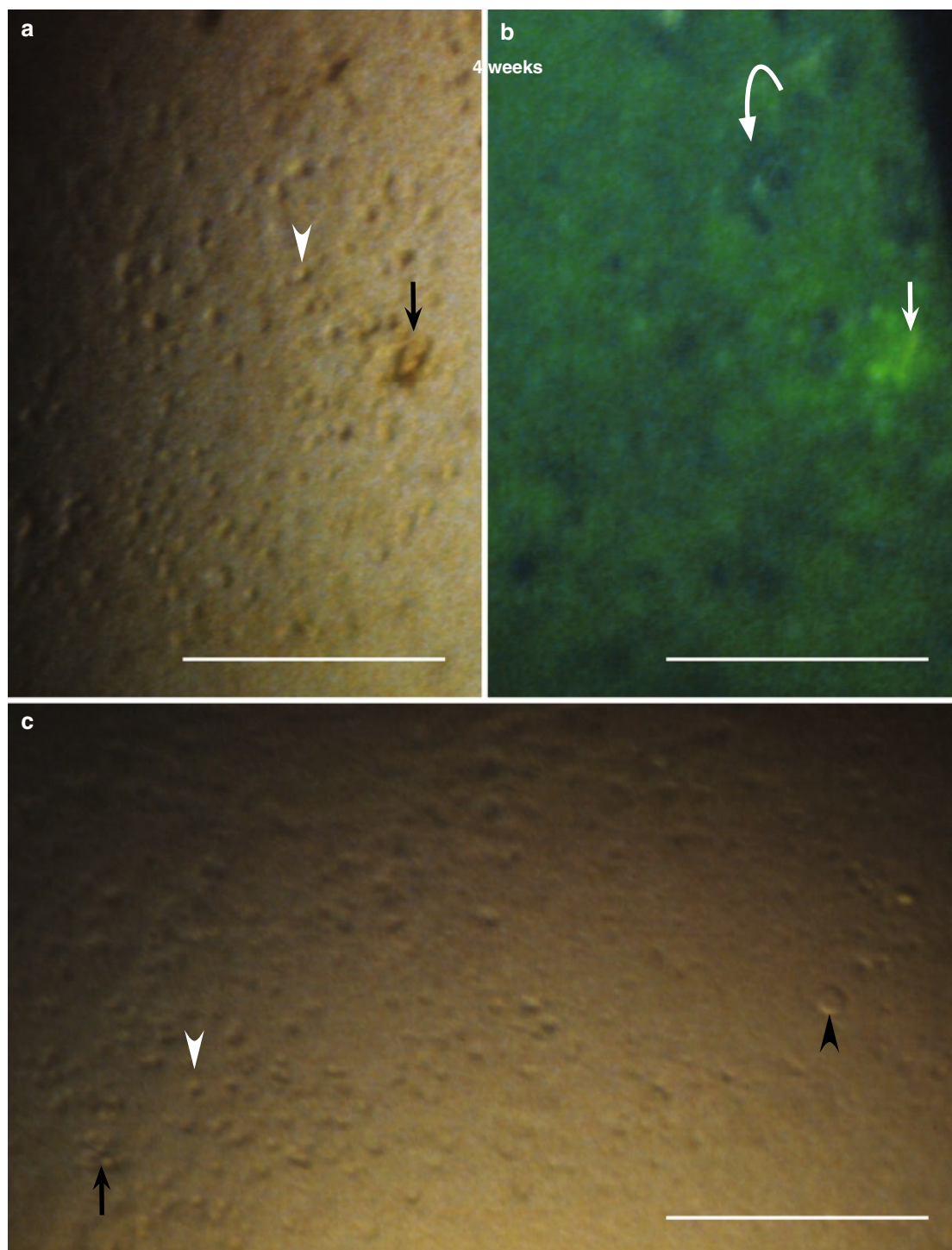


Fig. 2.14 (a–c) Four weeks after symptom onset, the epithelium shows (a and c) many rounded/abnormal cells, individual (white arrowheads) or grouped (arrows) and a cyst (black arrowhead). (b) In the tear film stained green with fluorescein are visible surface elevations (dark; bowed arrow) and brilliantly green dots (short arrow)

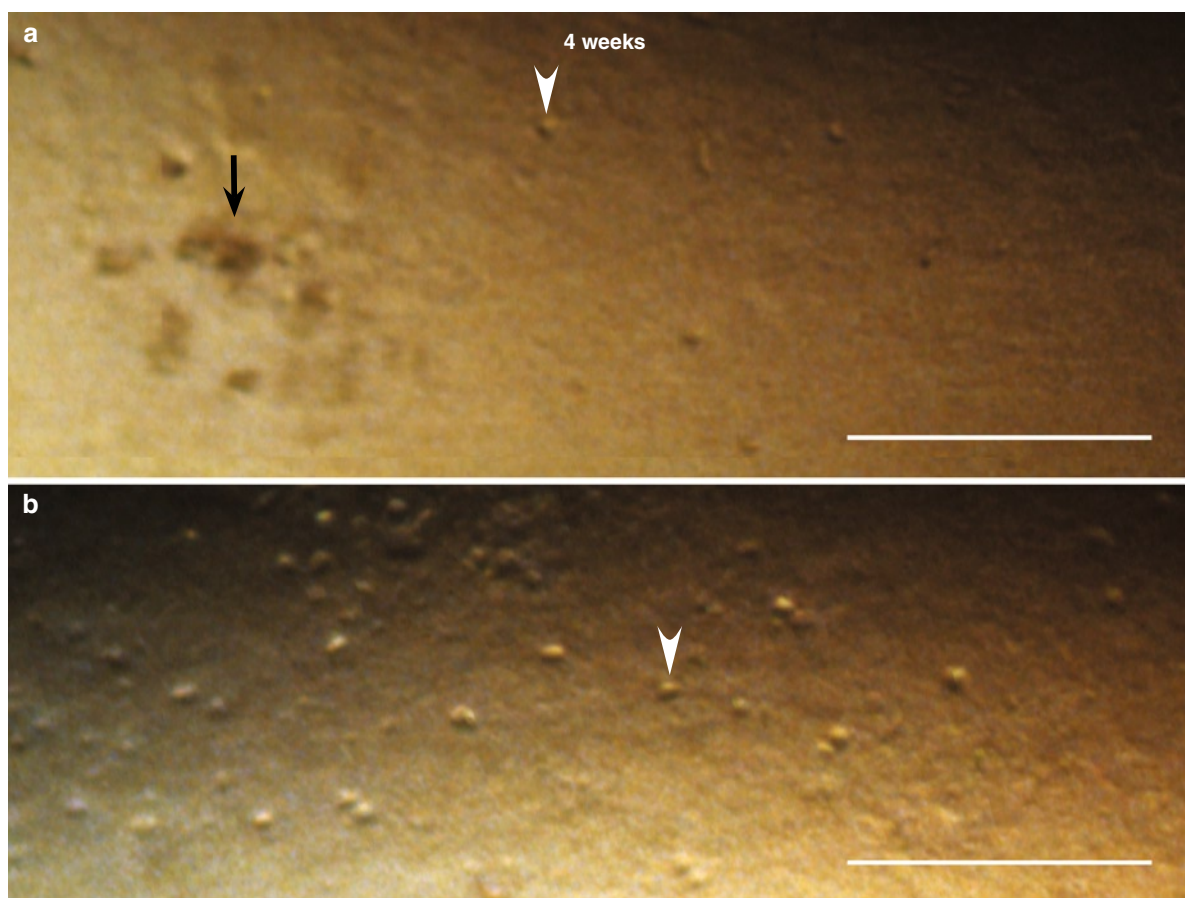
Nosocomial Infection After Suture Removal (Case 5, cont.)

Fig. 2.15 (a, b) Different areas of the same cornea as in Fig. 2.14 showing rounded/abnormal cells (*arrowheads*); in the group indicated by *arrow*, the cells seem mixed with cell debris

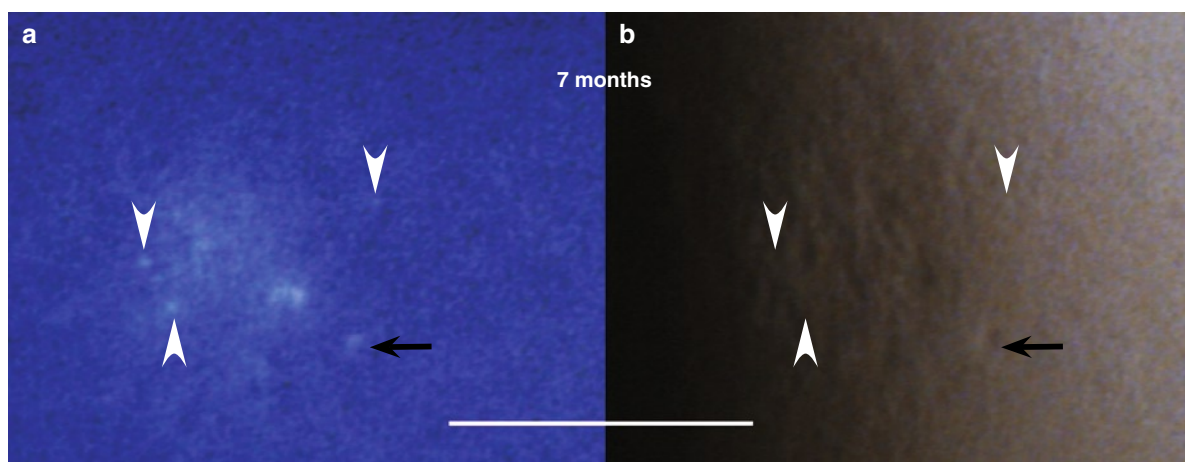


Fig. 2.16 (a, b) Seven months after epithelial keratitis the cornea shows (a) faint subepithelial opacities /infiltrates containing a few light-reflecting rounded/abnormal cells, individual (*arrowheads*) or grouped (*arrows*). (The markers are placed in corresponding locations)

Case 6: Nosocomial Infection After Applanation Tonometry

Case Report

Six days after a visit to the Eye Clinic, a 62-year-old woman with glaucoma woke up with redness and irritation in the left eye. The eye was slightly injected and the lower fornix showed follicular hyperplasia; the cornea appeared normal. A week later, both eyes were injected and within a further 5 days developed many corneal epithelial infiltrates. Sixteen months after onset, the left cornea showed many dense subepithelial opacities/infiltrates.

The photographs of the left cornea were taken 12 days and 7 weeks after the onset of symptoms.

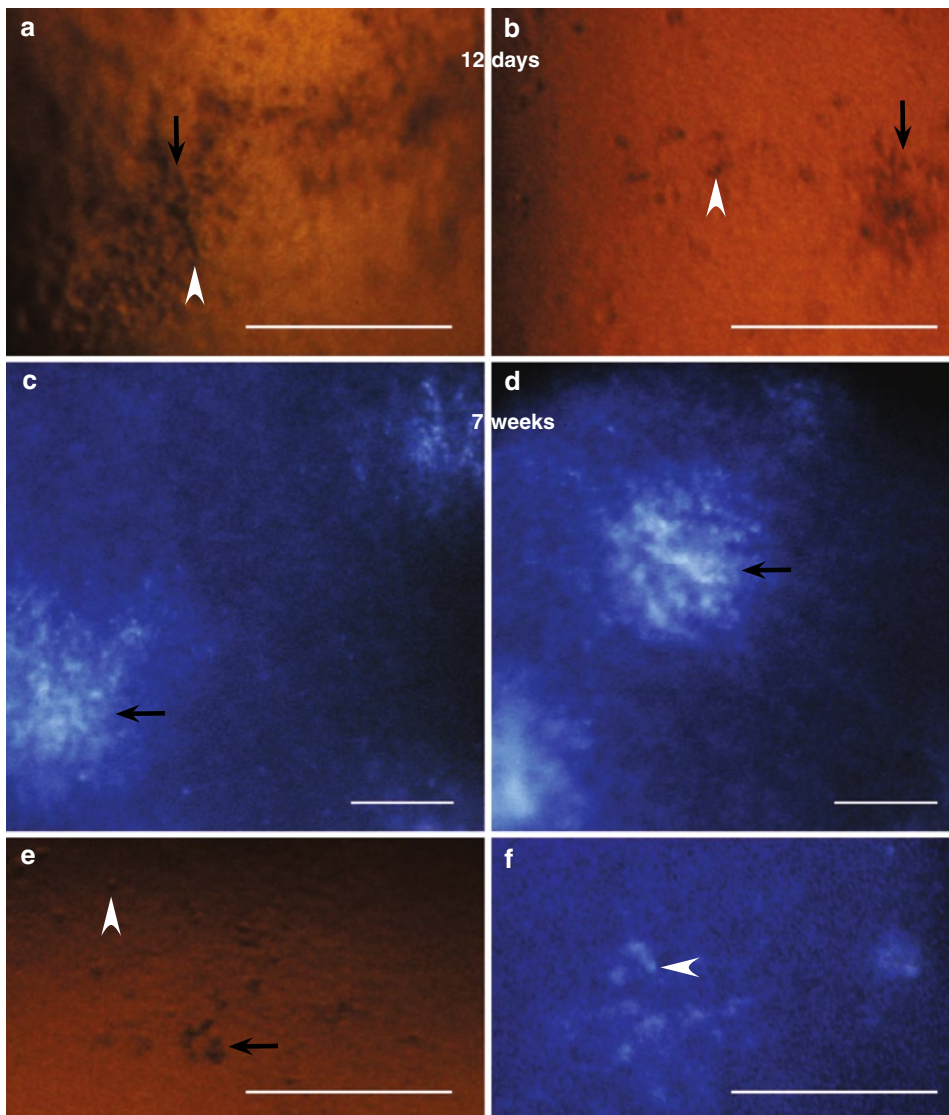


Fig. 2.17 (a, b) Twelve days after symptom onset are visible rounded/abnormal cells, individual (*arrowheads*) or heaped-up and apparently mixed with cell debris (*arrows*). (c, d) Subepithelial opacities/infiltrates 7 weeks after symptom onset (*arrows*). (e) Rounded/abnormal cells, individual (*arrowhead*) or grouped (*arrow*) are (f) light-reflecting (*arrowhead*). (Cf. Figs. 2.4, 2.21, 2.26, 2.27)

Case 7: A Woman Infected by a Caring Relative

Case Report

To this 77-year-old woman, the virus was transmitted by a relative (herself mother of a patient with nosocomial infection) who was nursing her. She suffered a severe bilateral keratoconjunctivitis starting in the left eye and subsequently developed many subepithelial opacities/infiltrates interfering with vision in both eyes.

The photographs of the left cornea were taken 4 weeks and 17 months after the onset of symptoms.

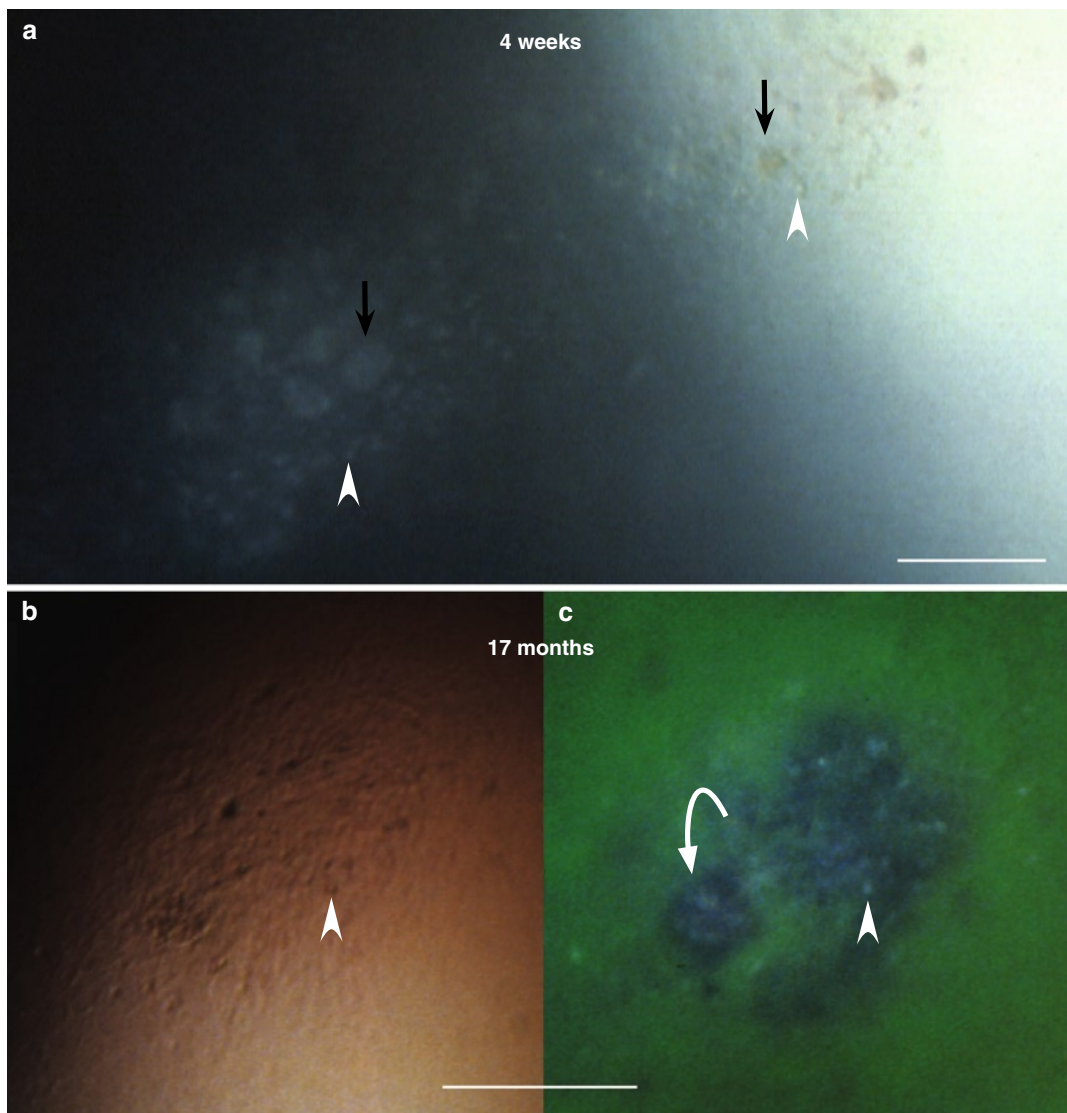


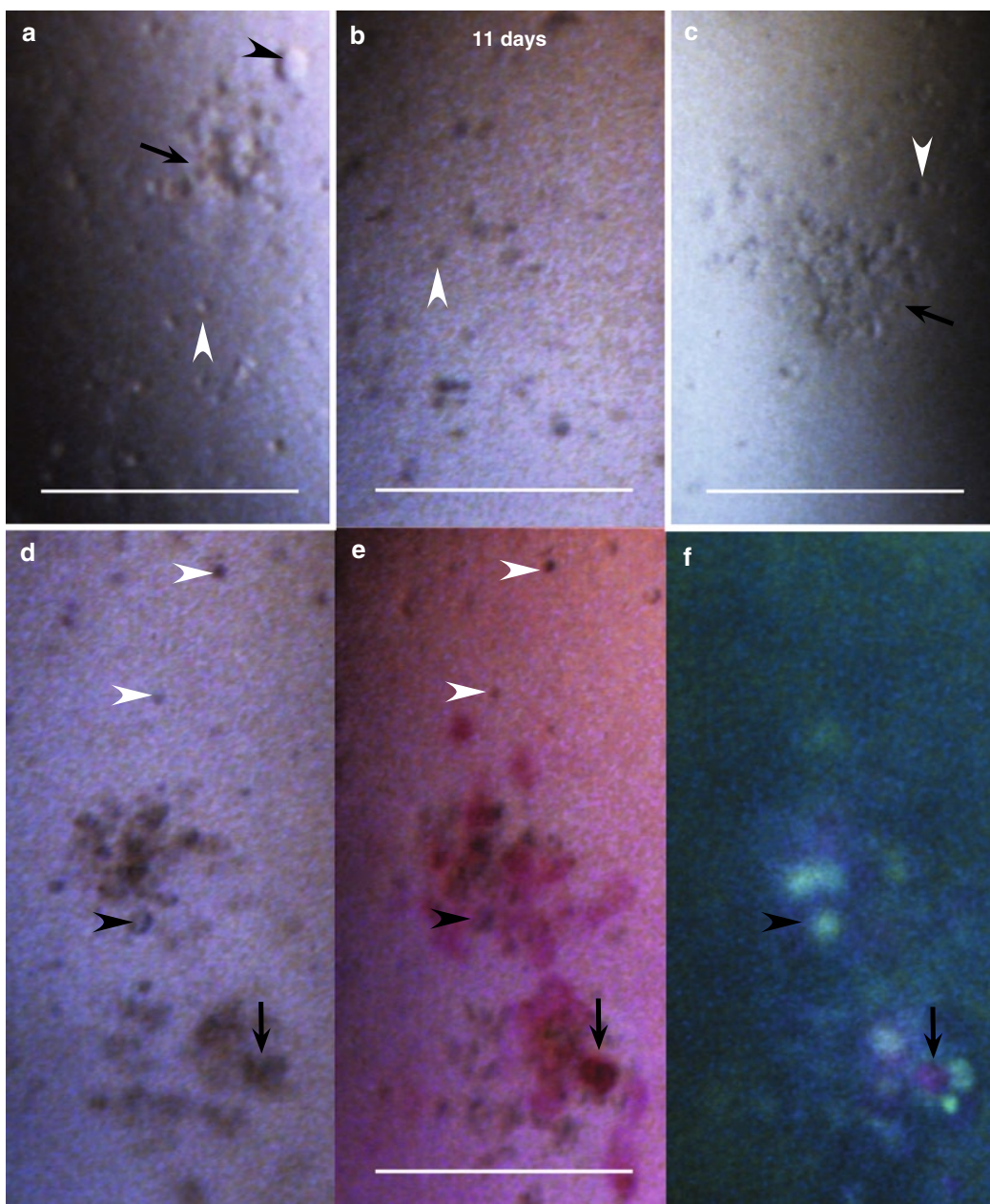
Fig. 2.18 (a) Four weeks after symptom onset, the cornea shows rounded/abnormal cells, individual (*arrowheads*) or grouped (*arrows*). (b–c) Subepithelial opacities/infiltrates containing rounded/abnormal cells (*arrowheads*) 17 months after onset. In (c) are visible surface elevations (*dark, arrow*) present in the same area as in (b); the surface appears intact. (The arrowheads are placed in corresponding locations)

Case 8: A Potential Source of a Nosocomial Outbreak

Case Report

In a 76-year-old woman with a history of recurrent bilateral anterior uveitis and corneal marginal infiltrations, an incipient adenovirus infection was confused with an incipient recurrence of anterior uveitis. She stopped using steroid eye drops after a few days because of symptom worsening. At presentation, 10 days later, both eyes were injected, and the cornea showed dust-like epithelial keratitis; the right cornea additionally showed folds of the Descemet's membrane. Adenovirus was suspected; laboratory tests revealed Ad8.

The photographs of the left cornea were taken 11 and 20 days after the onset of symptoms.



A Potential Source of a Nosocomial Outbreak (Case 8, cont.)

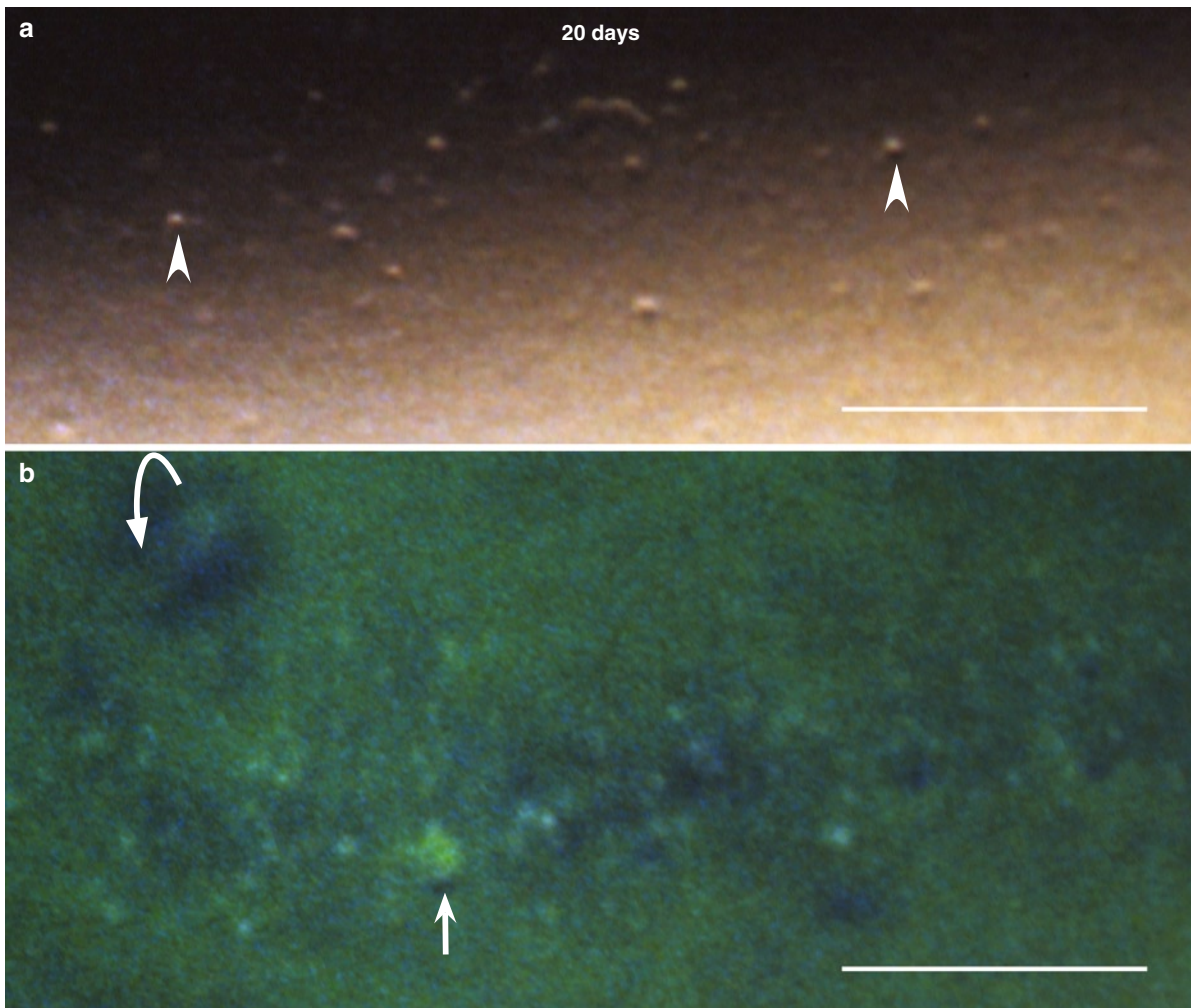


Fig. 2.20 (a, b) Twenty days after symptom onset, the cornea still shows (a) many rounded/abnormal cells (*arrowheads*) and (b), with fluorescein, surface elevations (*bowed arrow*) and a few green stained dots (*short arrow*)

Addendum

The patient had acquired the infection in Central Europe. With an outbreak of nosocomial Ad8 infection fresh in mind, the awareness of the danger was still high and there was only one secondary case.

The patient was followed for a further 1.5 years because of recurrent anterior uveitis. She developed only one very faint peripheral subepithelial opacity. Dry eye was diagnosed 4 months after the infection.

Fig. 2.19 (a–f) (Opposite page) Eleven days after symptom onset. The epithelium shows (a–d) many rounded/abnormal cells, individual (*white arrowheads*) or grouped (*arrows*) and a cyst (*black arrowhead*). (e, f) Show the same area as (d). (e) Damaged surface cells stain red with rose bengal. (f) Between red stained cells are visible fluorescein stained dots (green, *arrowhead*). (The markers are placed in corresponding locations)

Case 9: Nosocomial Infection in a Contact Lens Wearer

Case Report

A 28-year-old contact lens wearer presented in the Emergency Department because of irritation and redness in both eyes. At that occasion, and 4 days later, the corneal epithelium showed unspecific superficial changes suggestive of contact lens overwear. Six days after the second visit he presented again because of symptom worsening in both eyes. The corneal epithelium showed only a fine epitheliopathy but there were new findings: lid swelling, follicular hyperplasia, conjunctival injection, all severe, and a painful swelling of a preauricular lymph node. These findings were strongly suggestive of adenovirus infection. A week later, the symptoms were less severe but both corneae showed many epithelial infiltrates.

The photographs of the left cornea were taken at that occasion, about 10 days after the onset of symptoms relatable to adenovirus infection.

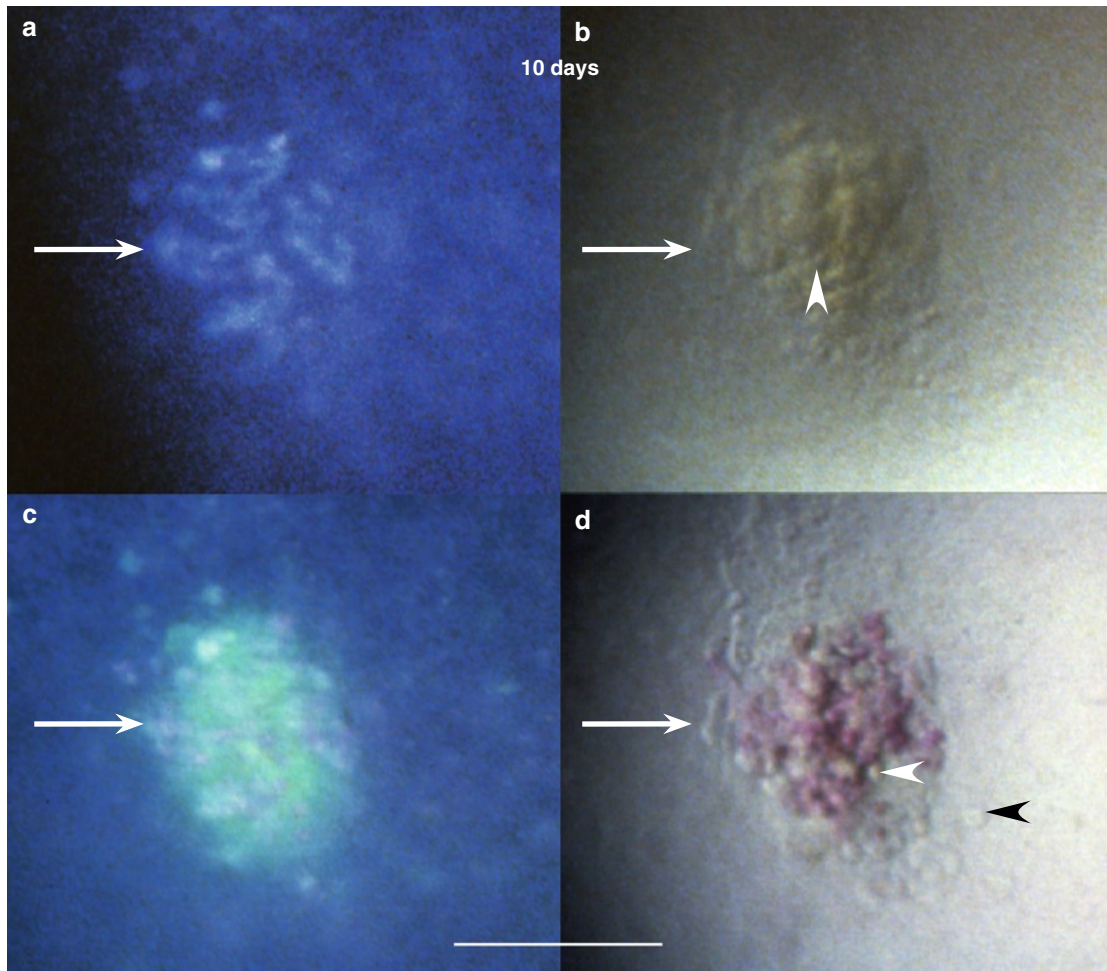


Fig. 2.21 (a–d) This epithelial infiltrate (arrows), captured about 10 days after symptom onset (a) is light-reflecting, (b) contains rounded/abnormal cells (arrowhead), (c) shows a circumscribed green fluorescein staining, and (d) red rose bengal staining of damaged superficial cells/cell debris. In (d) are also visible rounded/abnormal cells (white arrowhead) and a few adjacent cysts or cyst-like structures (black arrowhead). (The arrows are placed in corresponding locations)

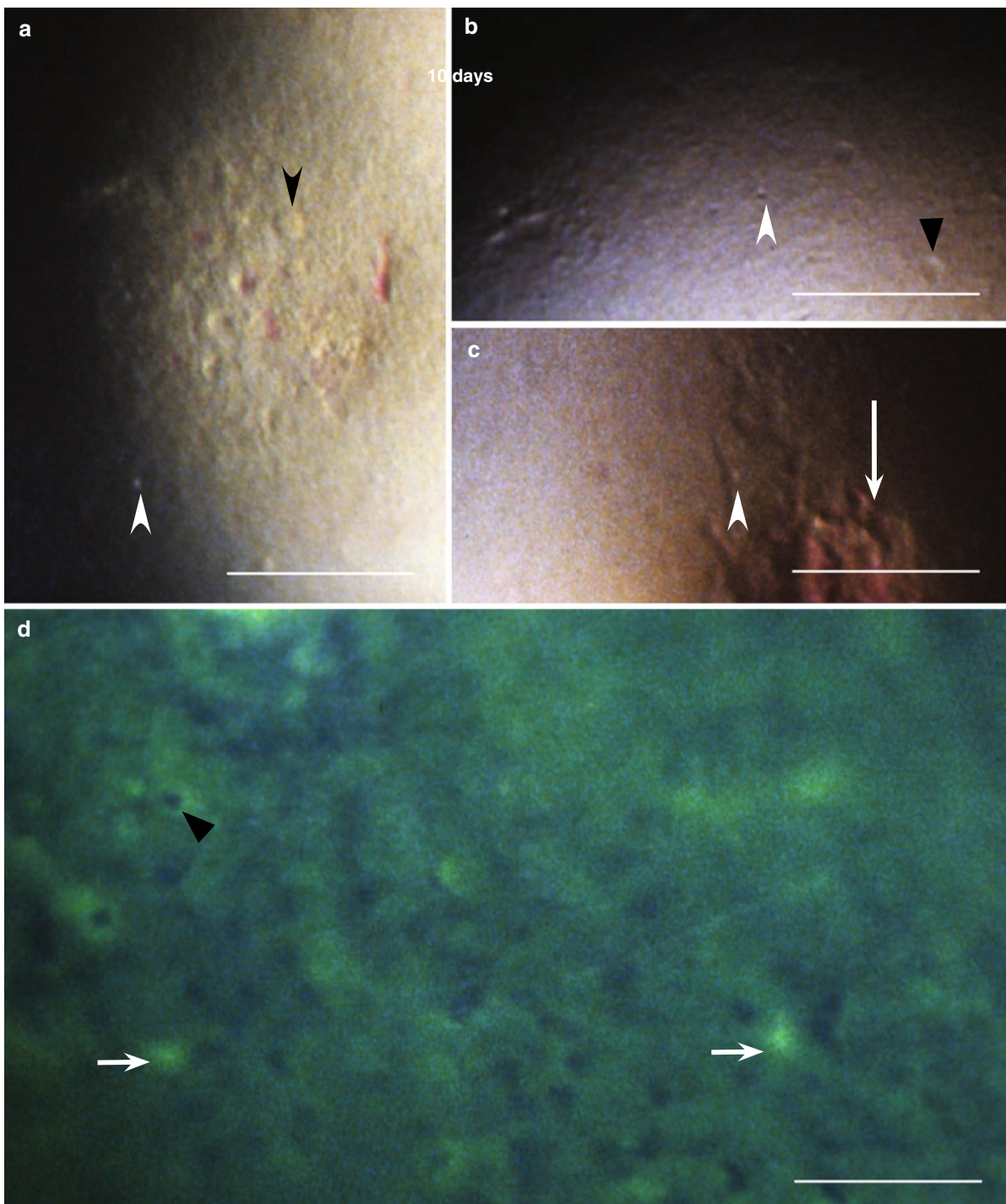
Nosocomial Infection in a Contact Lens Wearer (Case 9, cont.)

Fig. 2.22 (a–d) Different areas of the same cornea as in Fig. 2.21 show (a–c) rounded/abnormal cells (*white arrowheads*) and cysts or cyst-like structures (*black arrowheads*). In (c) is additionally visible a part of an epithelial infiltrate (*arrow*), and in (d), with fluorescein, many small surface elevations (*dark; arrowhead*) and a few brilliantly green dots (*arrows*)

Case 10: Nosocomial Infection in Corneal Erosion

Case Report

A 53-year-old woman was pecked in her left eye by her pet bird. A clean epithelial erosion was treated with antibiotic ointment. Seventeen days later, she was referred by a practitioner back to the Eye Clinic because symptom worsening. In the left eye, the lids were swollen, the conjunctiva injected and swollen, and the cornea showed a large erosion; the remaining epithelium was swollen and there were folds of the Descemet's membrane. In addition, she had symptoms also in the fellow eye, for 4 days; that eye was moderately injected and the corneal epithelium appeared dusty. Nosocomial Ad8 infection was suspected. After a further 2 days, the right cornea showed epithelial infiltrates. The erosion in the left eye healed within a further 3 days, but the cornea started to show many epithelial infiltrates. Dense subepithelial opacities/infiltrates interfering with vision developed in both corneae; they were still present a year after the infection.

The photographs of the right (not traumatized) cornea were taken 6 and 7 days; 4, 6, and 9 weeks; 3, 5, and 8 months; and 1 year after the onset of symptoms.

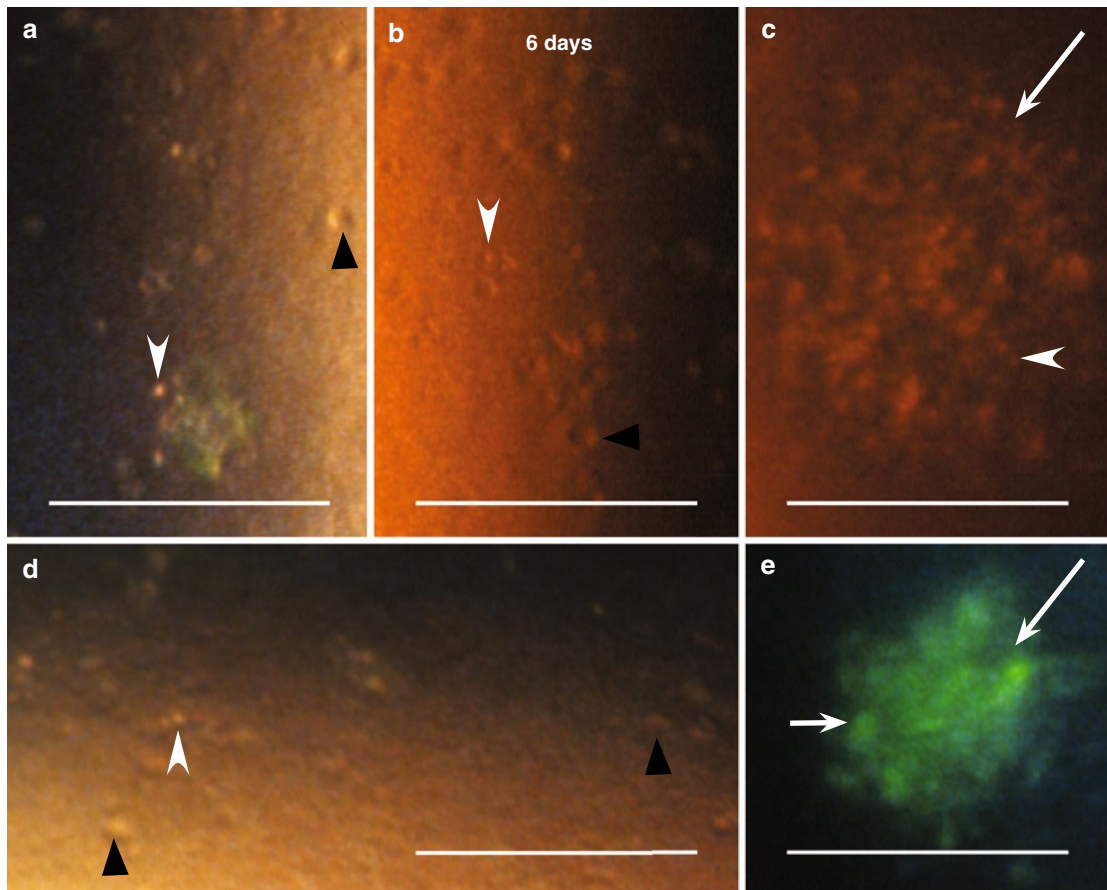


Fig. 2.23 (a–d) Six days after symptom onset, the epithelium shows many rounded/abnormal cells (*white arrowheads*), individual or heaped-up (*c*, *arrow*) and cyst-like structures (*black arrowheads*). (*e*) With fluorescein, the surface of an infiltrate (*long arrow*) shows brilliantly green dots (*short arrow*); there is no diffusion into the surroundings

Nosocomial Infection in Corneal Erosion (Case 10, cont.)

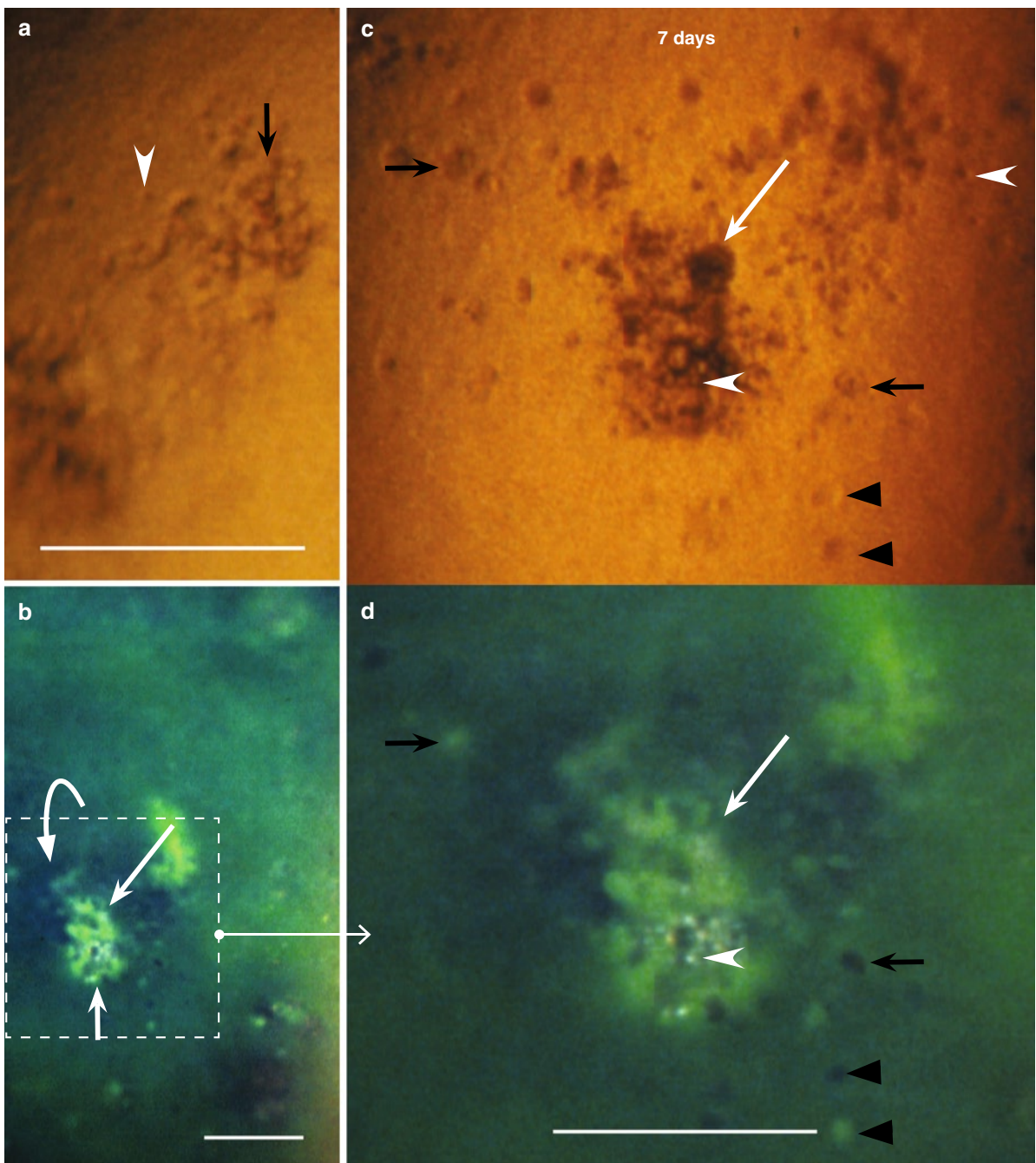


Fig. 2.24 (a) Seven days after symptom onset are visible rounded/abnormal cells, individual (*arrowhead*) or grouped (*arrow*). (b) Survey showing circumscript green staining (*short arrow*) of epithelial infiltrates (*long arrow*) and adjacent surface elevations (dark; *bowed arrow*). The area in frame is shown at higher magnification in (c) and (d). (c) The lesion (*arrow*) contains accumulated rounded/abnormal cells (*white arrowhead*) apparently mixed with cell debris. Rounded/abnormal cells, individual (*white arrowhead*) or grouped (*black arrows*) and cyst-like structures (*black arrowheads*) are visible in the surroundings. (d) Some groups of rounded/abnormal cells (*black arrows*) and some cyst-like structures (*black arrowheads*) stain brilliantly green, others are protruding (*dark*) in the green stained tear film. (In c and d, the arrows and the black arrowheads are placed in corresponding locations)

Nosocomial Infection in Corneal Erosion (Case 10, cont.)

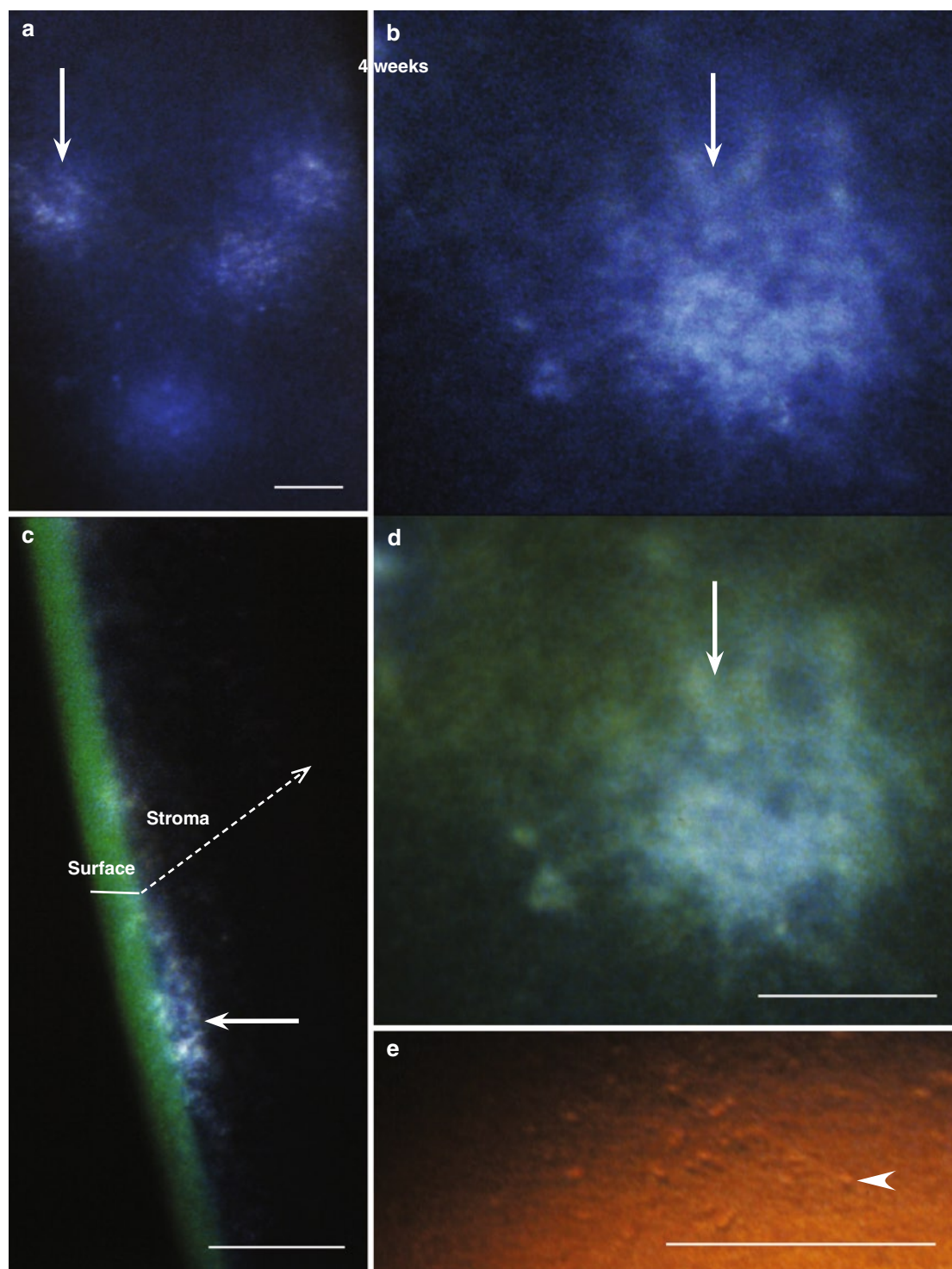


Fig. 2.25 (a–e) Four weeks after symptom onset, the cornea shows subepithelial opacities/infiltrates (arrows). (a) Survey. (b) The infiltrate (arrow) consists of more or less light-reflecting areas, has indistinct edges, (c) is superficially located below (c, d) an apparently intact surface, and (e) contains rounded/abnormal cells (arrowhead). (The arrows in b and d are placed in corresponding locations)

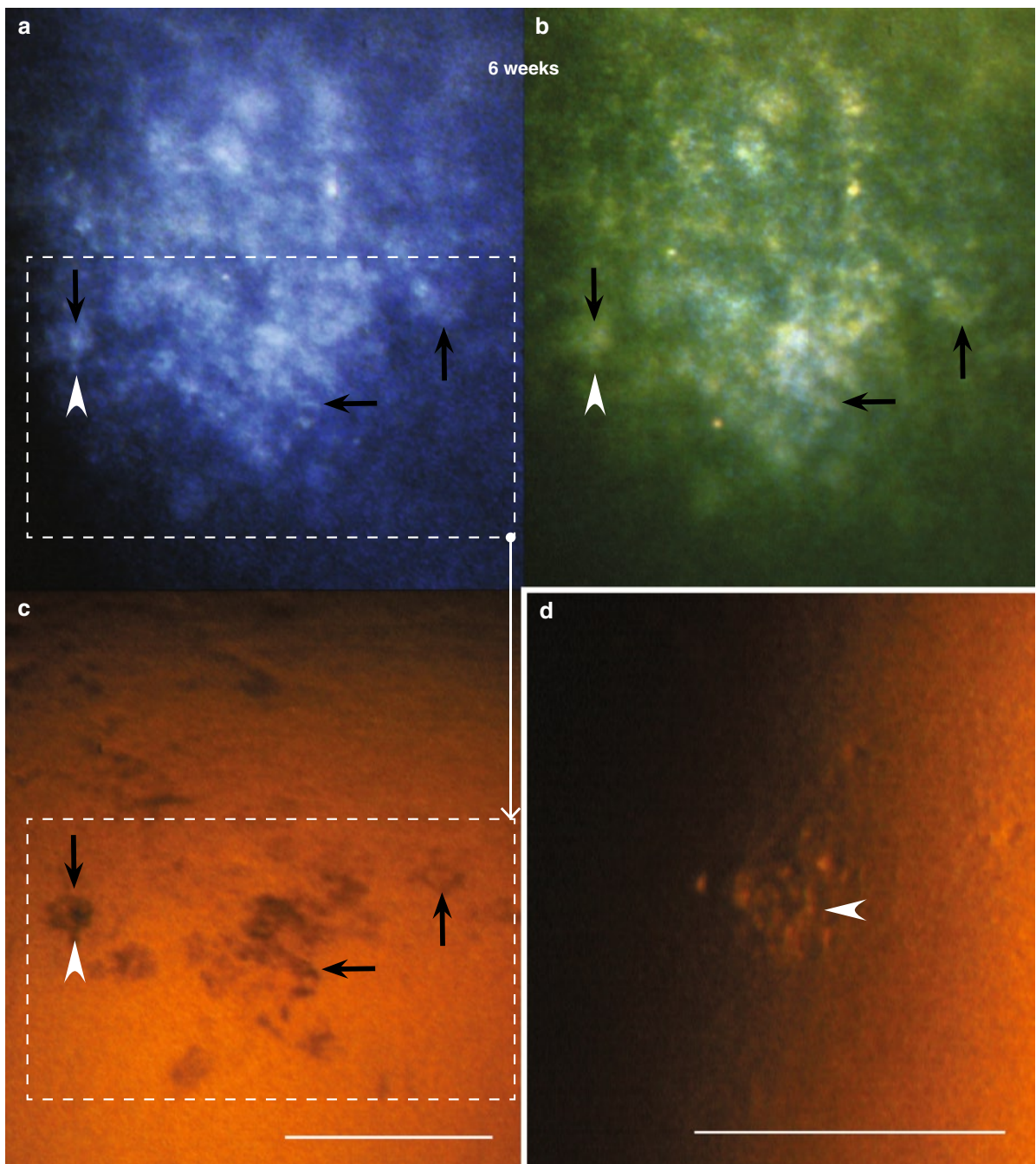
Nosocomial Infection in Corneal Erosion (Case 10, cont.)

Fig. 2.26 (a–d) Six weeks after symptom onset. (a) A subepithelial opacity/infiltrate with indistinct edges. (b) With fluorescein, the overlying epithelium appears intact. (c) The light-reflecting areas show rounded/abnormal cells (*arrowhead*); the cells seem mixed with light-reflecting material suggestive of cell debris. (The markers are placed in corresponding locations.) (d) A different area showing the presence of grouped rounded/abnormal cells (*arrowhead*)

Nosocomial Infection in Corneal Erosion (Case 10, cont.)

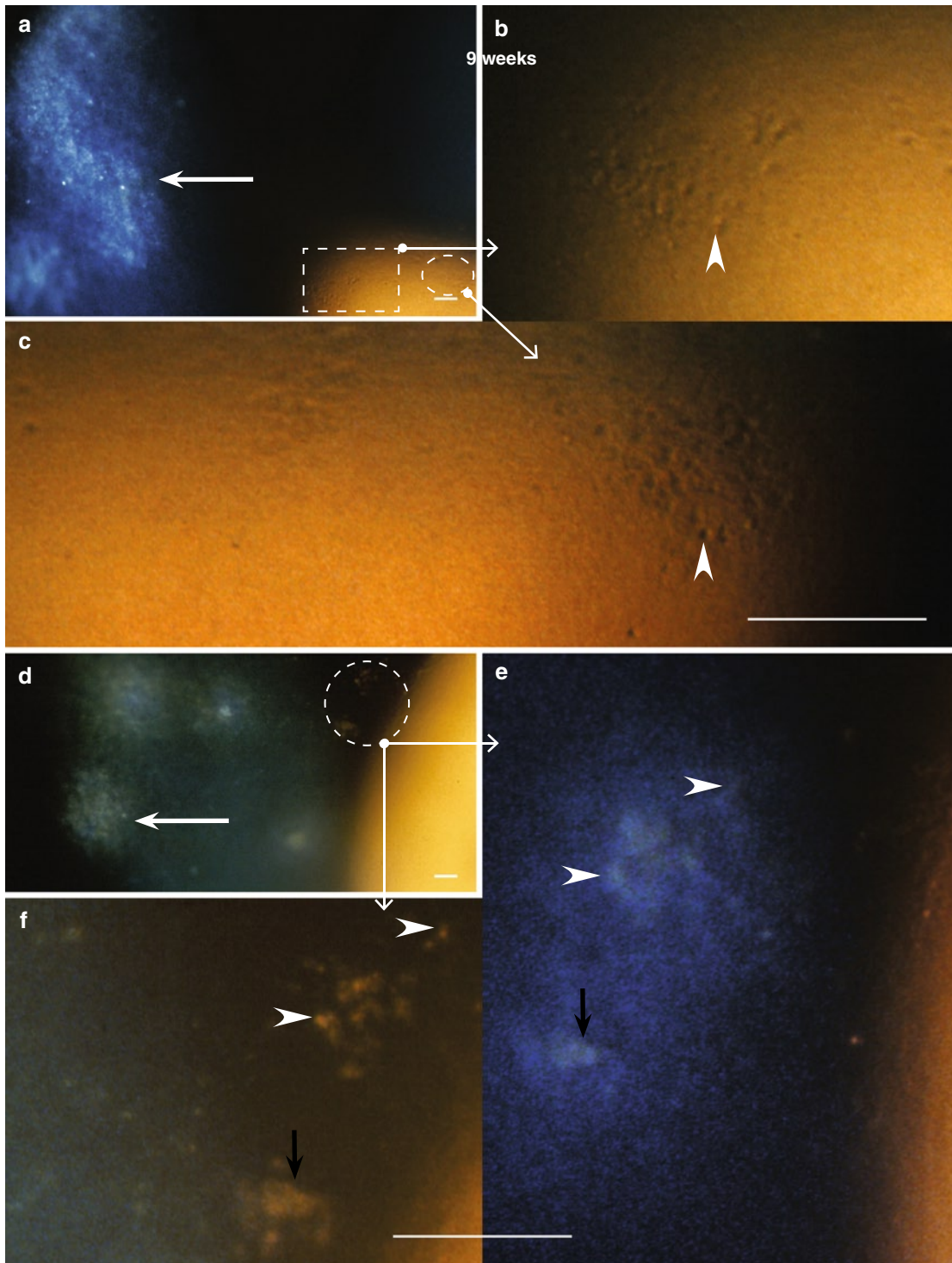


Fig. 2.27 (a–f) Nine weeks after symptom onset, the cornea shows (a and d) many subepithelial opacities/infiltrates (arrows) located below (d) an apparently intact surface. (b, c) show at higher magnification the areas indicated by frames in (a); rounded/abnormal cells are visible in both (arrowheads). (e, f) show at higher magnification the area indicated by frame in (d). In (f) are visible groups of rounded/abnormal cells (arrowheads), in places possibly mixed with cell debris (arrow), and in (e) their light-reflecting property. (The markers are placed in corresponding locations)

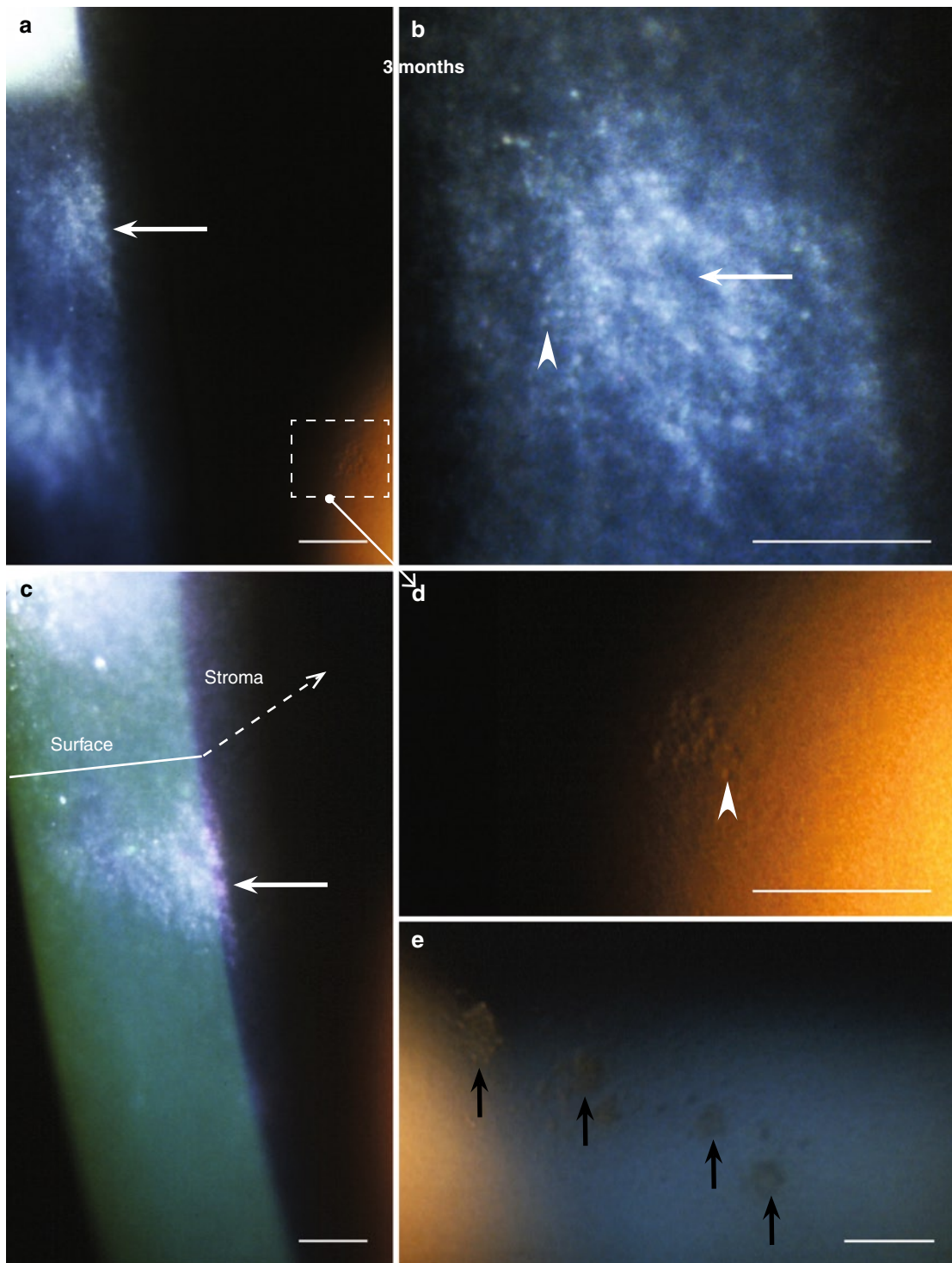
Nosocomial Infection in Corneal Erosion (Case 10, cont.)

Fig. 2.28 (a–e) Three months after symptom onset. (a, b) The subepithelial opacities/infiltrates (arrows) contain (b) light-reflecting dots (arrowhead). (c) Shows their location below an apparently intact surface, (d) the presence of rounded/abnormal cells (arrowhead) in the area indicated by frame in (a), and (e) groups of rounded/abnormal cells (arrows). (The arrows in a and b are placed in corresponding locations)

Nosocomial Infection in Corneal Erosion (Case 10, cont.)

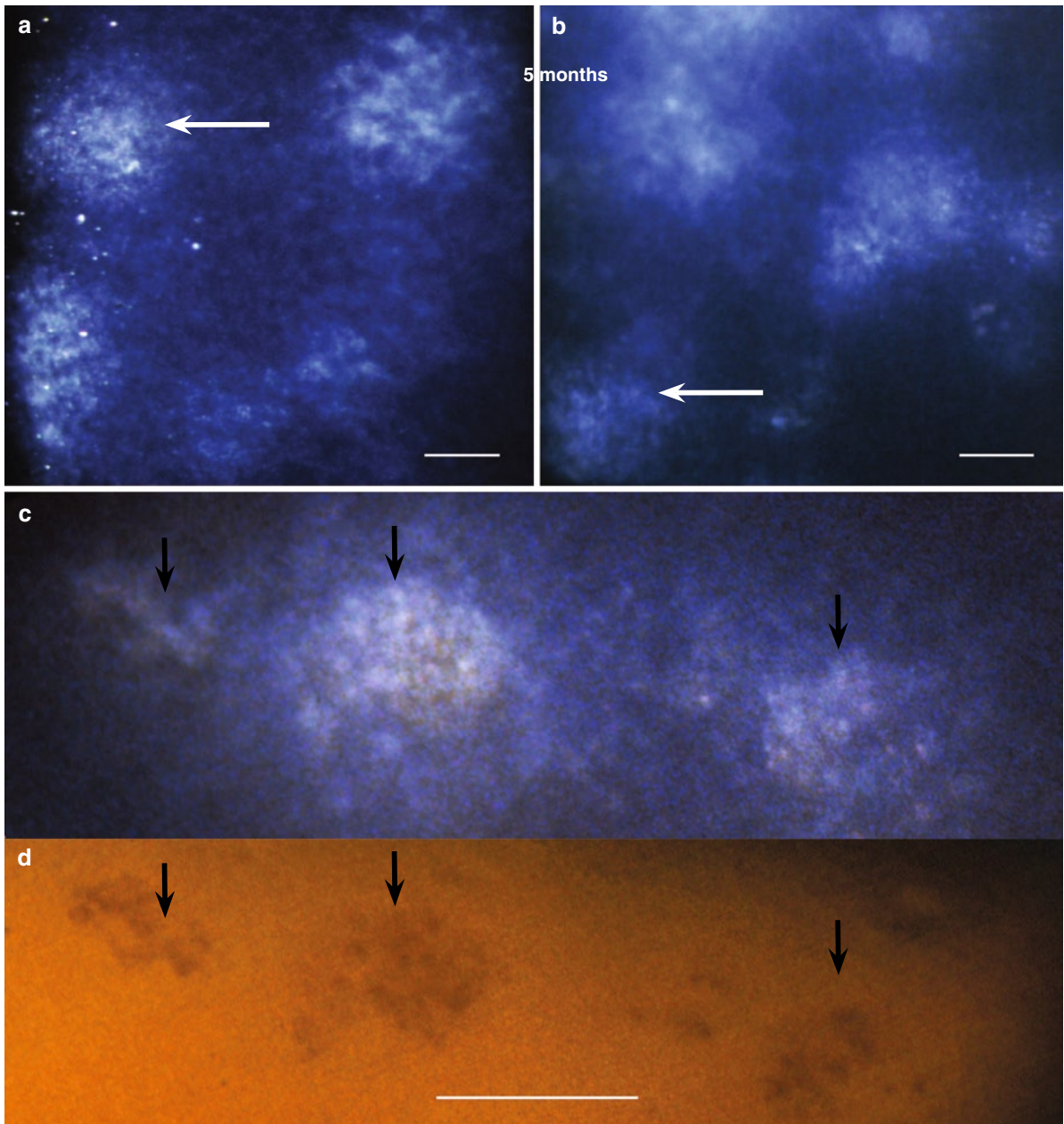


Fig. 2.29 (a–d) Five months after symptom onset, the cornea shows (a, b) subepithelial opacities/infiltrates (arrows). In (c, d) are visible groups (arrows) of rounded/abnormal cells. (The arrows in c and d are placed in corresponding locations)

Nosocomial Infection in Corneal Erosion (Case 10, cont.)

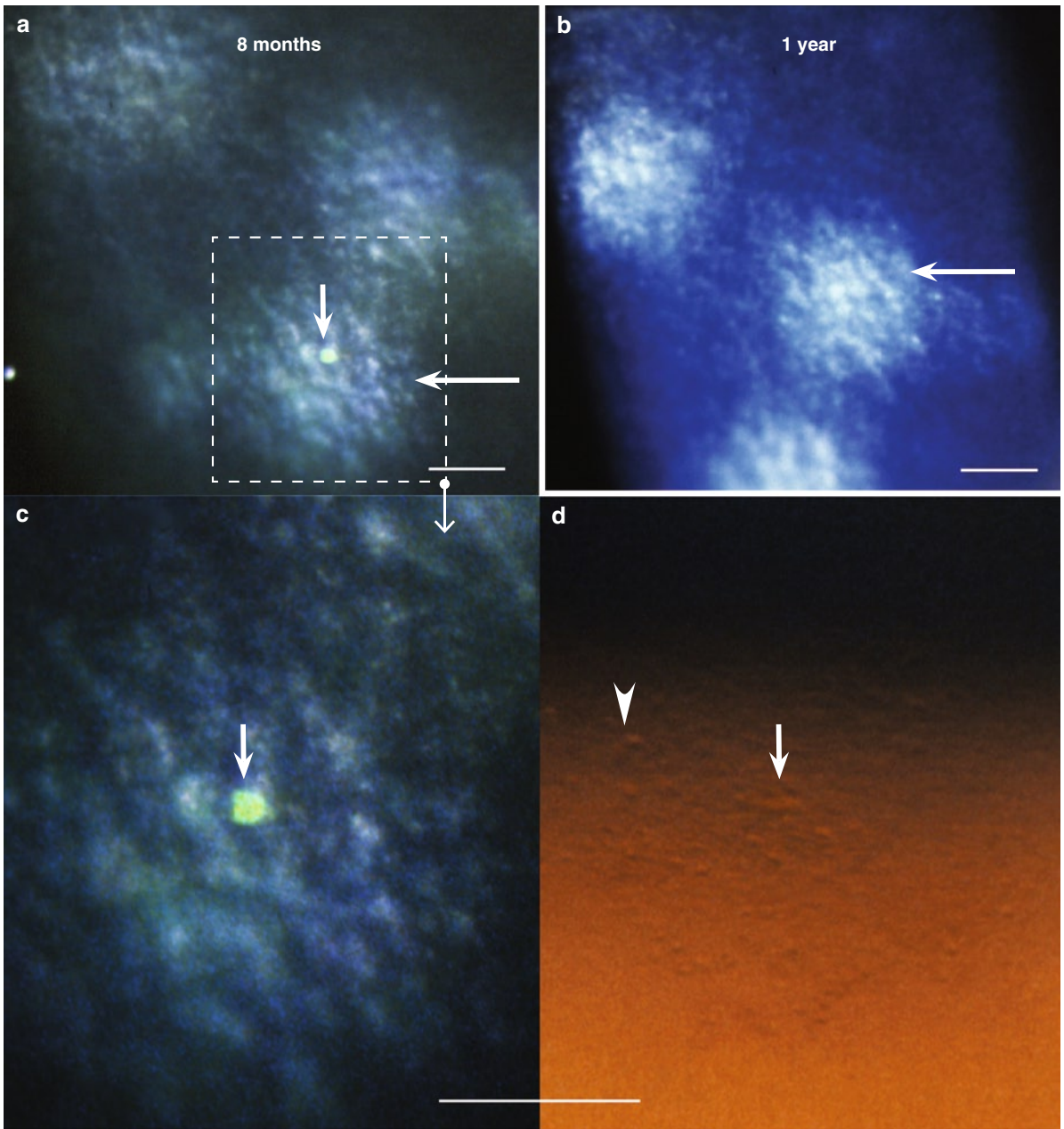


Fig. 2.30 (a–d) The appearance of subepithelial opacities/infiltrates (*long arrows*) (a, c, and d) 8 months and (b) 1 year after the onset of symptoms. The infiltrate indicated by *short arrow* in (a) is shown at higher magnification in (c, d). (c) Fluorescein visualizes a small surface disruption (*arrow*). (d) The infiltrate contains rounded/abnormal cells (*arrowhead*). (The short arrows in a, c, and d are placed in corresponding locations)

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