

The Dynamics of Varicella-Zoster Virus Epithelial Keratitis in Herpes Zoster Ophthalmicus

The morphology of an individual VZV lesion reflects a sequence of events triggered by the virus impact on corneal epithelial cells. When seen in time perspective, it becomes evident that the morphology of the lesions at each moment is a result of an ongoing, highly dynamic process that involves not only the destructive action of the virus but also an action of natural healing forces. Serial observations reveal that the shapes of the lesions change rapidly (as fast as within 24 hours). This feature is relatable to two phenomena: partly a disappearance of diseased/damaged cells in some locations and, as judged by the absence of ulcerations, their substitution by fresh ones, and partly an appearance of new sites of damage in adjacent areas. The first phenomenon implies that in some locations the virus noxious action has ceased and the second one that new infections in new locations have occurred. In larger lesions, this process results in their changing shapes; in smaller lesions located at some distance from each other the same is demonstrated by their coming and going.

The VZV lesions presented in this chapter have been captured in patients treated with an antiviral drug in vitro arresting the virus replication (acyclovir, 800mg five times a day) administered for a week. It is notable that: (a) new lesions continued to develop after the treatment was started; these lesions were morphologically indistinguishable both from those which had developed before that and from those developing after the treatment was stopped; and (b) that the features of VZV epithelial keratitis in treated patients were indistinguishable from the natural course of the disease observed in patients not treated with antiviral drugs (cf. Chap. 3). And the same applied to lesions treated with topical acyclovir (Chap. 3).

In the absence of a detectable effect of treatment (so clearly visible in HSV infections) in conjunction with the absence of knowledge on how rapidly invading abnormal (inflammatory?) cells appear, it is possible that in patients subsequently developing subepithelial opacities in the same areas some images captured both virus-damaged and invading cells (Case 2, Figs. 2.12–2.13 and Case 3, Figs. 2.21–2.22). Before the surface is restored, a distinction between the two is not possible.

Case 1: Changing Shapes of a Large VZV Lesion

Case Report

An 82-year-old healthy man with typical HZO rash in the left side of the forehead and blisters on the upper lid. The symptoms had started 3 days previously. The left eye was injected, and the cornea showed a large VZV pseudodendrite. He was treated with acyclovir, 800 mg five times a day, for a week. The photographs were taken on day 1 (at presentation) and on days 4 and 7.

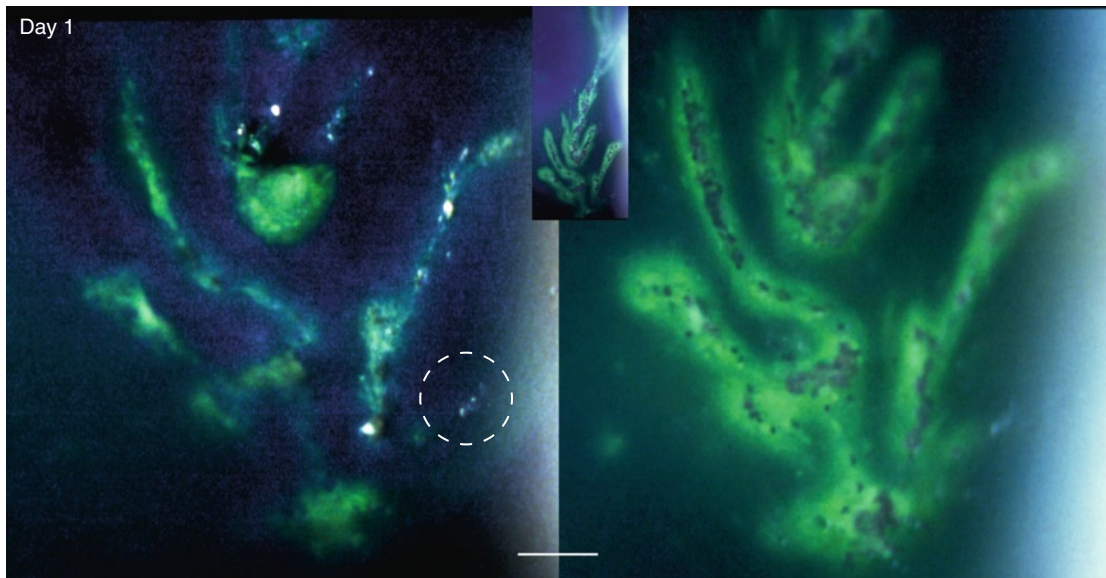
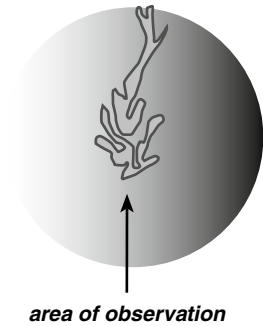


Fig. 2.1 Day 1 (before treatment). The lower part of a large VZV lesion (pseudodendrite, *inset*) consists of several smaller lesions located close to each other. *Left*: Tear fluid stained green with fluorescein sodium penetrates into the lesions through surface disruptions. *Right*: A couple of minutes later and after application of rose bengal. With ongoing diffusion, the lesions appear larger but the pattern is preserved. Diseased surface elements stain red with rose bengal. (The area within frame is shown at higher magnification in Fig. 2.4, *overleaf*)

Fig. 2.3 (*Opposite page*) Day 7 (6 days of acyclovir treatment). The lesion has changed shape again (*inset*). *Left*: This photograph taken shortly after the application of fluorescein sodium captured the yellow (adherent) fluorescein staining of the light-reflecting plaques (*white arrows*) present concurrently with incipient diffusion into the lesion (green staining). The dye additionally visualizes fine wavy lines close to the lesion (*arrowhead*) and a cyst (*black arrow*). *Right*: After a couple of minutes and application of rose bengal. As on days 1 and 4, the lesion appears larger because of the green staining. Rose bengal stains the same surface plaques as adherent fluorescein. Also in this picture, the fine wavy lines (*arrowhead*) are visible. For further details see Fig. 2.7, *overleaf*. (The markers are placed in corresponding locations)

Changing Shapes of a Large VZV Lesion (Case 1, cont.)

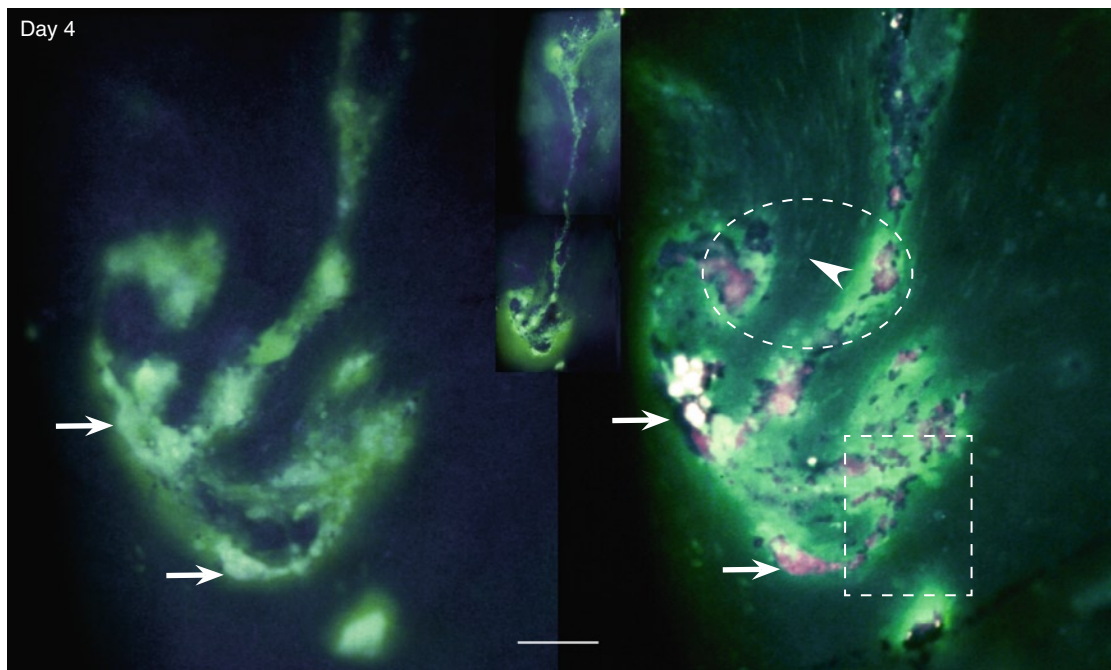
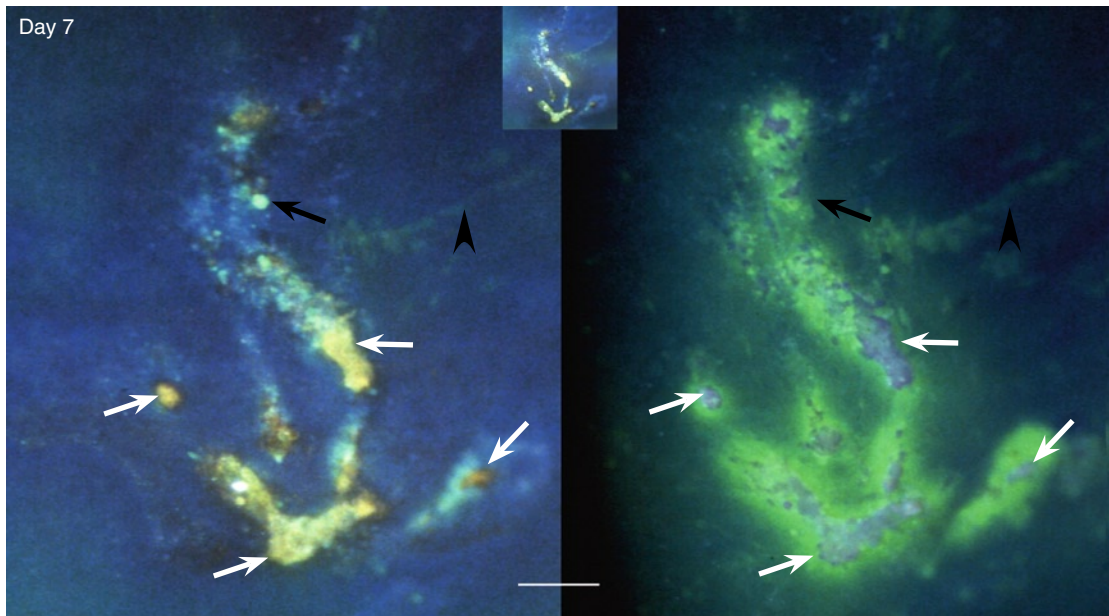


Fig. 2.2 Day 4 (3 days of acyclovir treatment). The pseudodendrite has changed shape (*inset*). As before, it consists of several adjacent smaller lesions and shows the same staining features (cf. Fig. 2.1). *Left*: Tear fluid stained green with fluorescein sodium penetrates into the lesions; confluent surface debris appears as strongly light-reflecting plaques (*arrows*). *Right*: A couple of minutes later and after application of rose bengal. The lesions appear larger, but the pattern is preserved. Fusiform cells parallel the lesions (*arrowhead*). For details, see Fig. 2.5 (*rectangular frame*) and Fig. 2.6 (*oval frame*), *overleaf*. (The arrows are placed in corresponding locations.) Comment: In the inset is visible that the lesion is slightly raised above the surrounding epithelium; the green staining adjacent to its lower part is caused by pooling of green stained tear fluid in a tear meniscus



VZV Corneal Epithelial Lesions (Case 1, cont.)

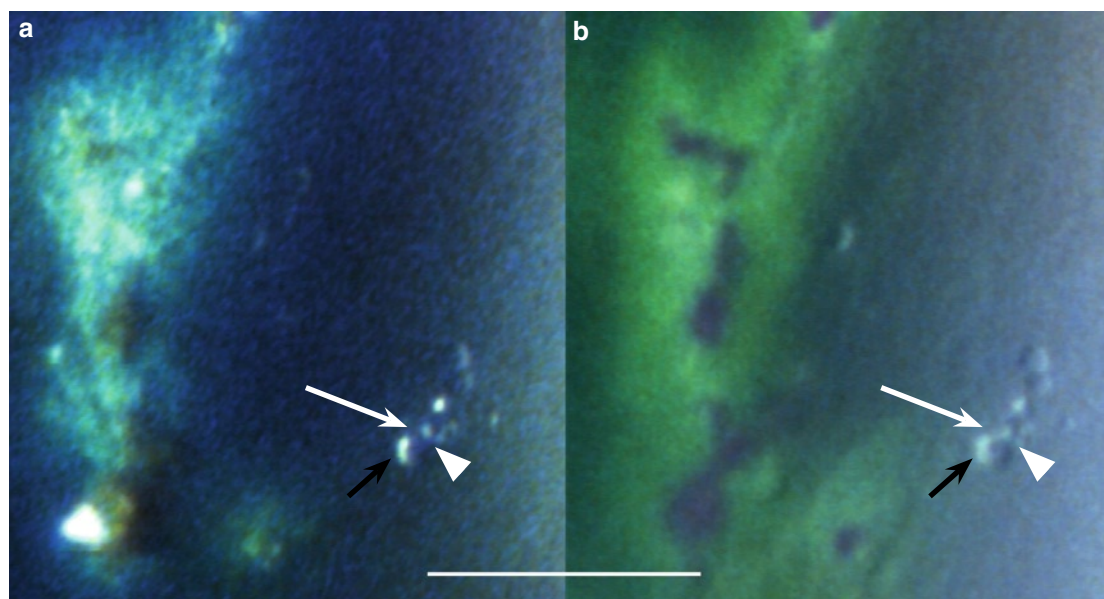


Fig. 2.4 Day 1. Close view of the area indicated by frame in Fig. 2.1, (a) shortly after the application of fluorescein and (b) a minute or two later. An incipient VZV lesion (*white arrows*) close to the main one shows swollen/rounded cells (*arrowheads*) and small cysts (*black arrows*). (The markers are placed in corresponding locations)

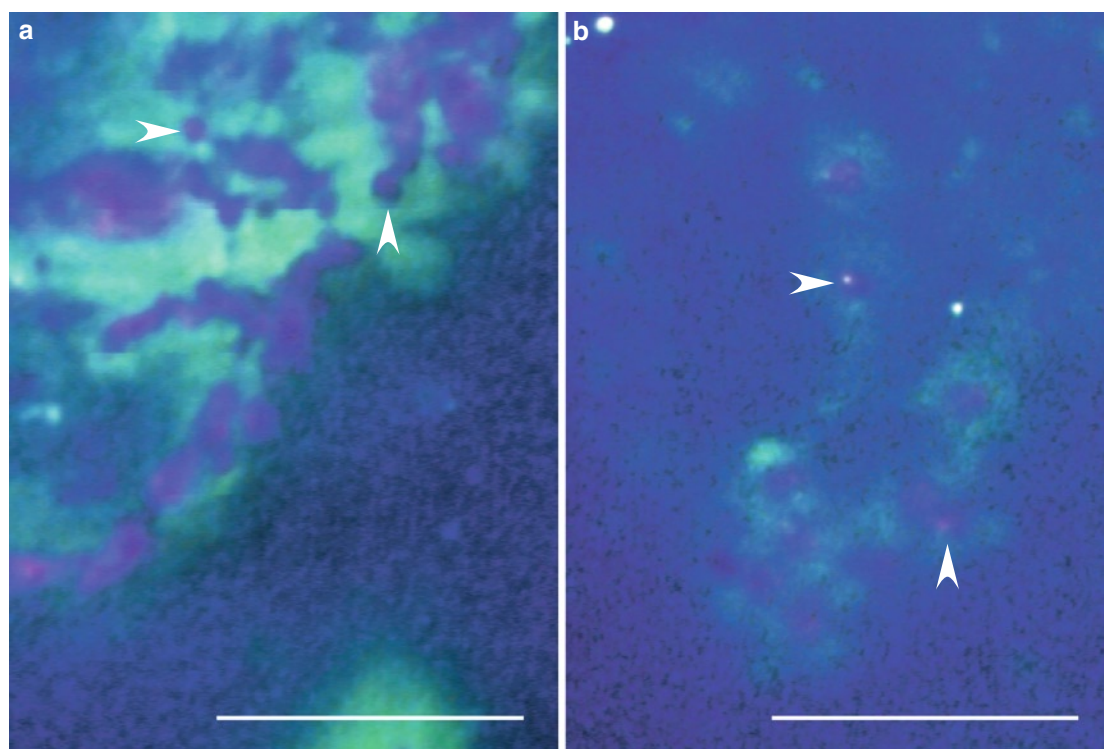


Fig. 2.5 Day 4. (a) This part of the VZV lesion (indicated by rectangular frame in Fig. 2.2) shows fluorescein diffusion into the epithelium (*green*) and degenerating surface cells/cell debris staining red with rose bengal (*arrowheads*). (b) Also this area, located distally from the main VZV lesion, shows diseased surface cells (*arrowheads*) and fluorescein diffusion into their surroundings

VZV Corneal Epithelial Lesions (Case 1, cont.)

Fig. 2.6 Day 4. Close view of the area indicated by oval frame in Fig. 2.2. Green fluorescein staining (*arrow-heads*) visualizes fusiform cells paralleling the lesion

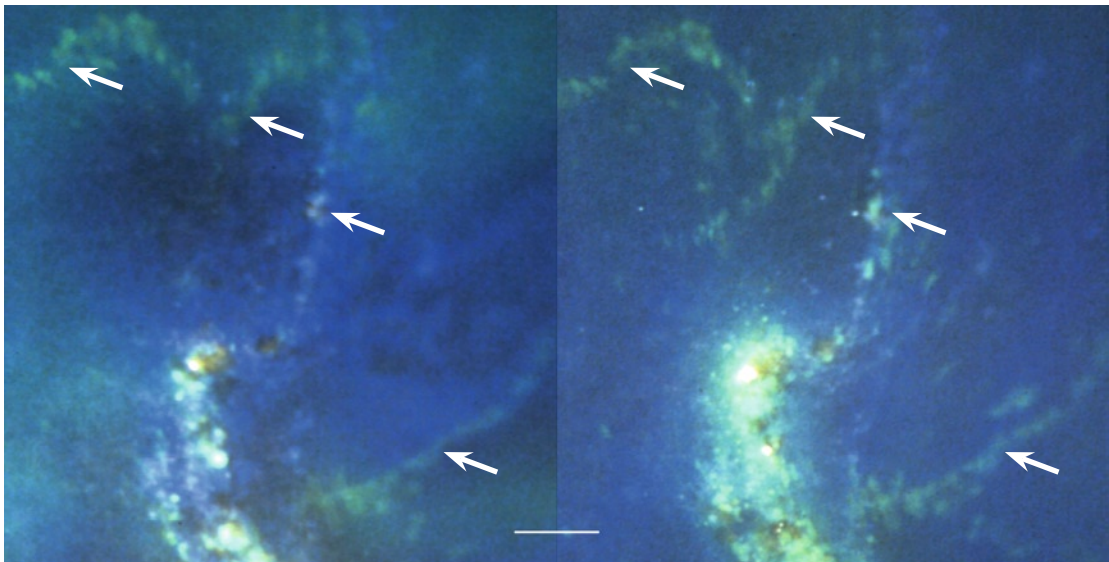
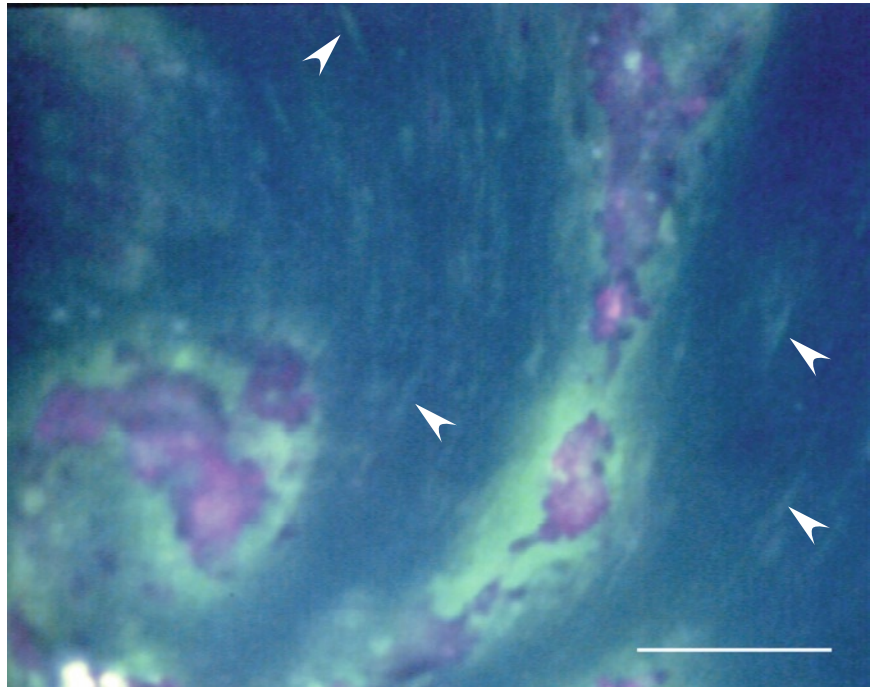


Fig. 2.7 Day 7. Wavy lines (*arrows*) showing green stained cystic spaces. *Left*: shortly after the application of fluorescein sodium. *Right*: a minute or two later; there is no fluorescein diffusion around these lines. The origin of these lines is uncertain. (The arrows are placed in corresponding locations)

Addendum

Two weeks after onset of the first (cutaneous) symptoms, all VZV lesions were gone. The cornea showed a faint subepithelial shadow. Four weeks after onset, when last seen, the cornea appeared normal.

Case 2: Changing Shapes of a Smaller VZV Lesion

Case Report

A 66-year-old man with left-sided headaches for a week and redness of the left eye for 3 days. The left side of the forehead and of the nose showed incipient vesicles. The left eye was slightly injected, and a VZV pseudodendrite was present in the nasal part of the cornea. Acyclovir p.o. (800 mg five times a day for a week) was started. On the following day, the pseudodendrite was still present, and a new, small one appeared in the nasal upper part of the cornea. The anterior chamber showed a few cells which disappeared within a few days. The photographs were taken on day 1 (at presentation), and days 2, 3, 4, 8, 10, 15, 24, and after 7 weeks.

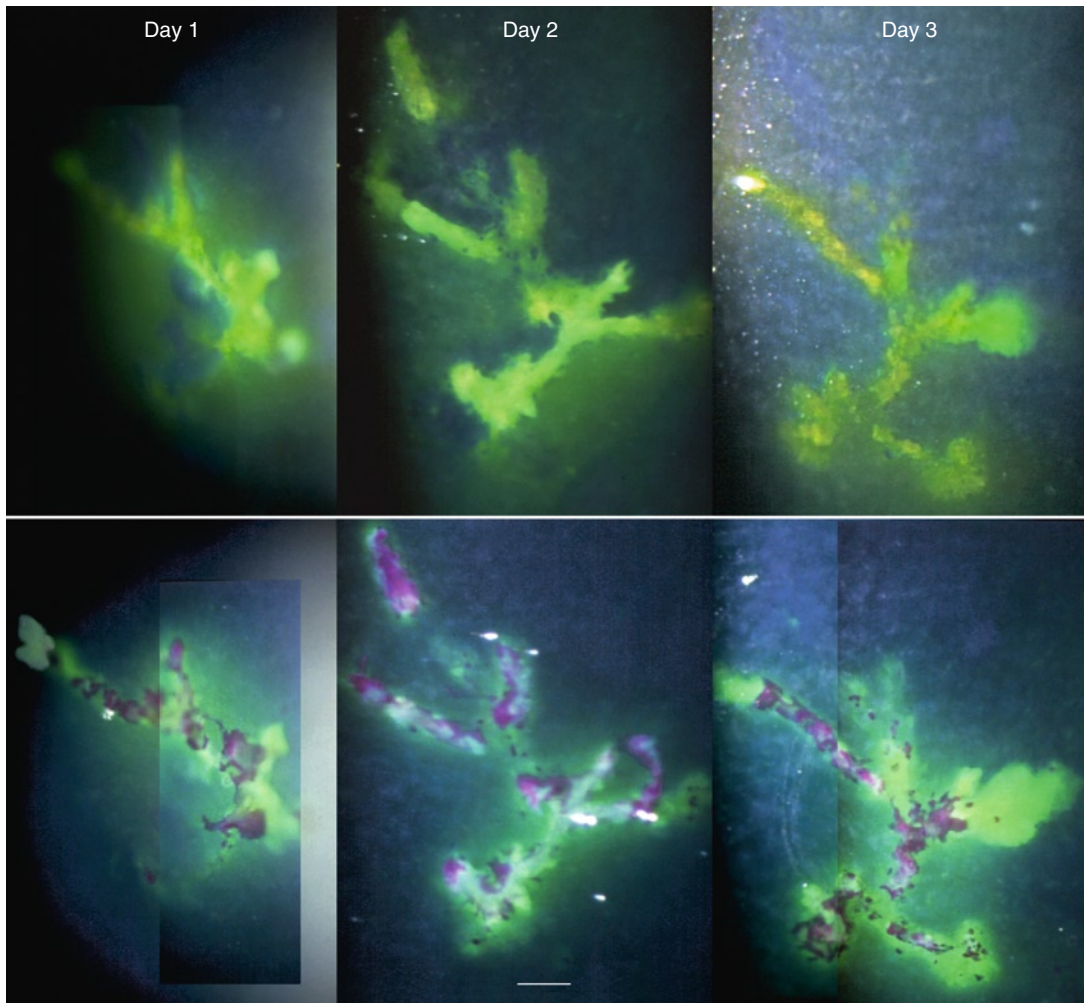
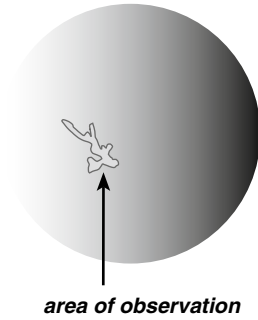
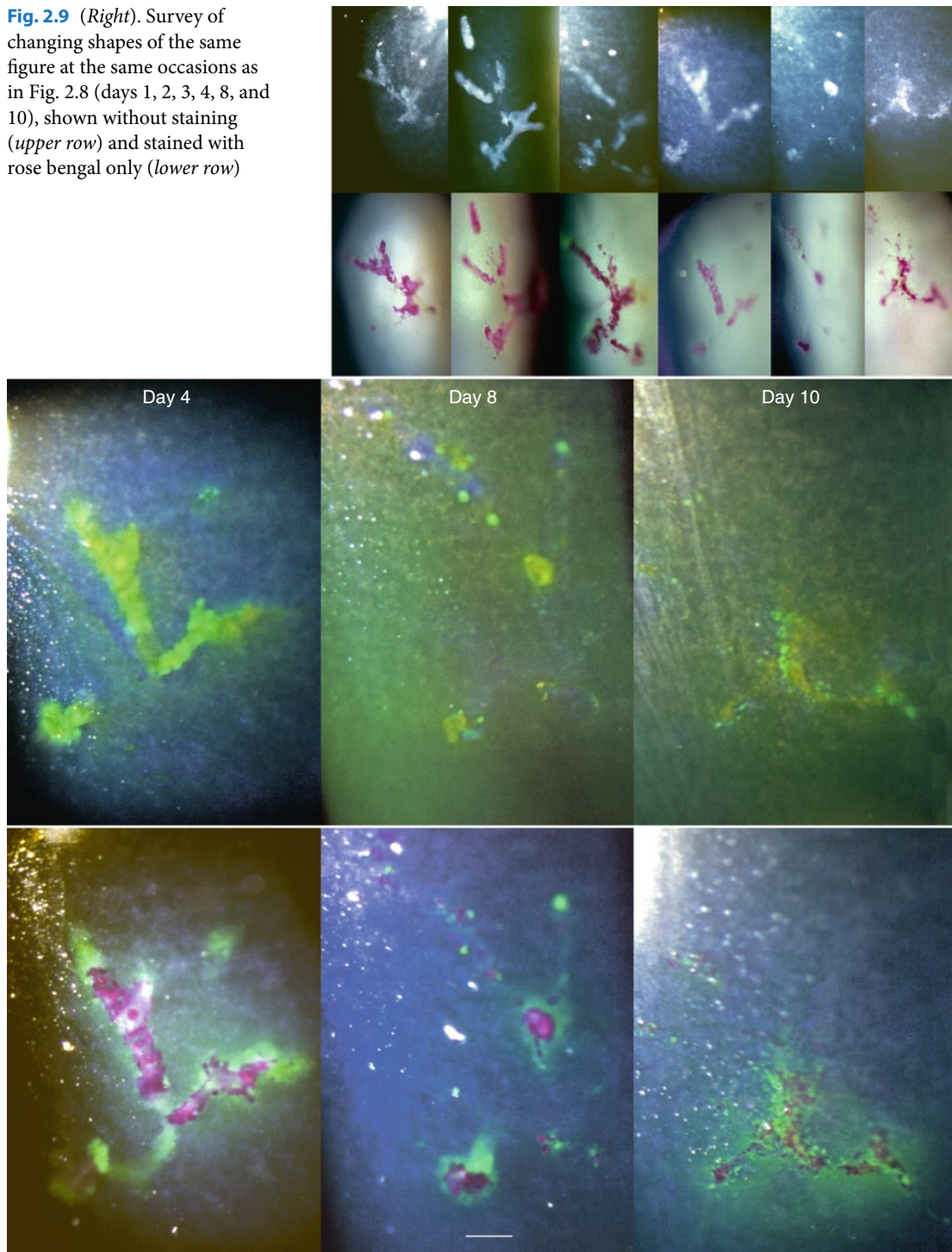


Fig. 2.8 This and opposite page. Day 1 (before treatment) – day 10. Survey at low magnification of changing shapes of a pseudodendrite captured on days 1, 2, 3, and (opposite page) days 4, 8 and 10. The upper row shows the figure stained with fluorescein sodium, the lower row with addition of rose bengal

Already after 24 h, the “same” lesion located in the nasal part of the cornea is not the same. Its shape changes but, in the absence of reference points others than the figures themselves, the exact locations of

Changing Shapes of a Smaller VZV Lesion (Case 2, cont.)

Fig. 2.9 (*Right*). Survey of changing shapes of the same figure at the same occasions as in Fig. 2.8 (days 1, 2, 3, 4, 8, and 10), shown without staining (*upper row*) and stained with rose bengal only (*lower row*)



preceding and subsequent changes cannot be pinpointed (cf. Fig. 2.26). On day 10, the appearance of the lesion is still compatible with a VZV infection. For some details see Figs. 2.10–2.13. (Day 1 and day 3, lower row, are composed photographs.) (Day 1, upper row, adapted from [9], day 1–day 4, lower row, adapted from [7])

VZV Corneal Epithelial Lesions (Case 2, cont.)

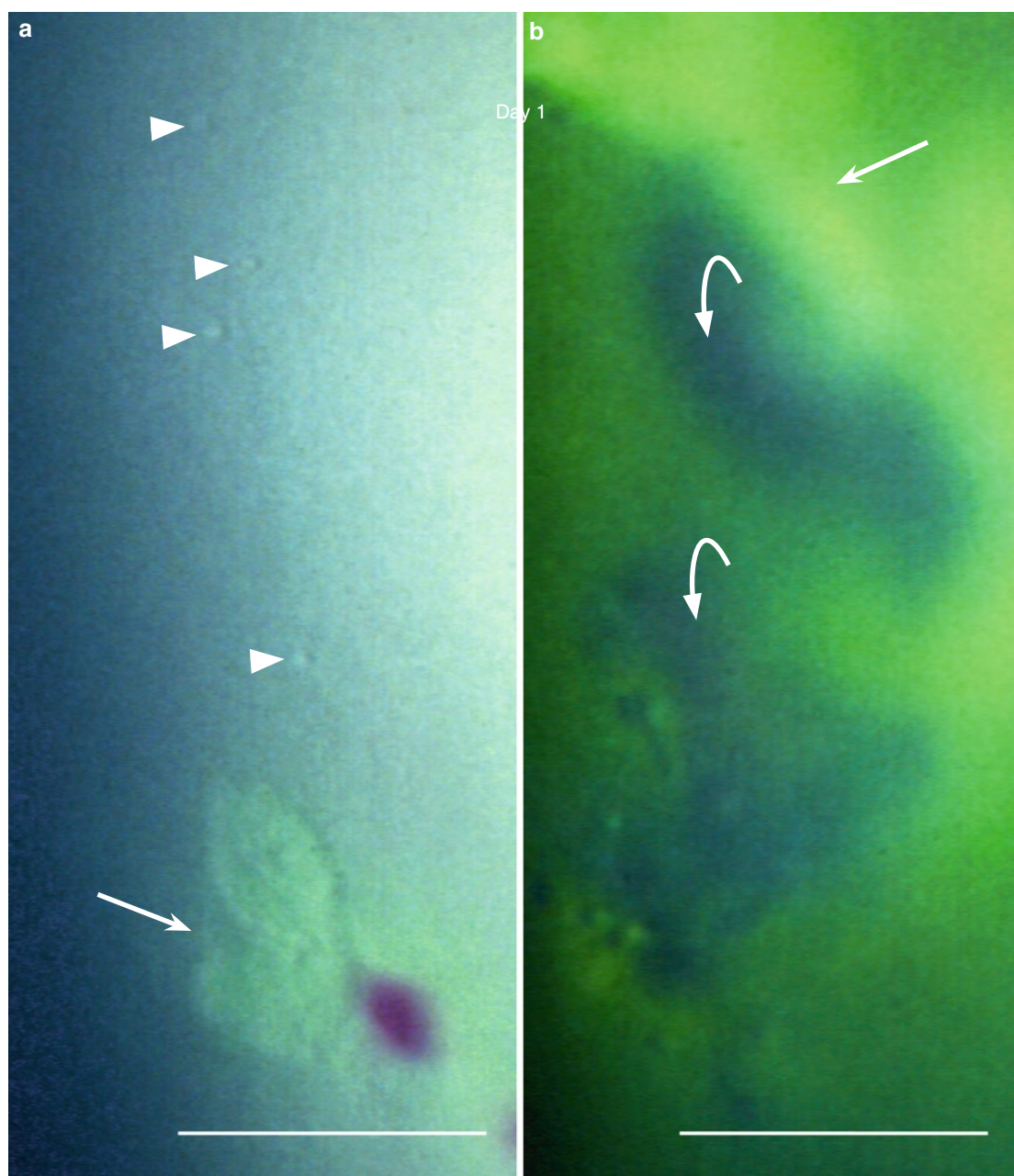


Fig. 2.10 Day 1, before treatment. (a) Individual swollen/rounded cells (*arrowheads*) present close to the left upper part of the lesion (*arrow*). (b) Surface elevations (*dark, bowed arrows*) in apposition to the lesion (*straight arrow*) staining yellow with fluorescein

VZV Corneal Epithelial Lesions (Case 2, cont.)

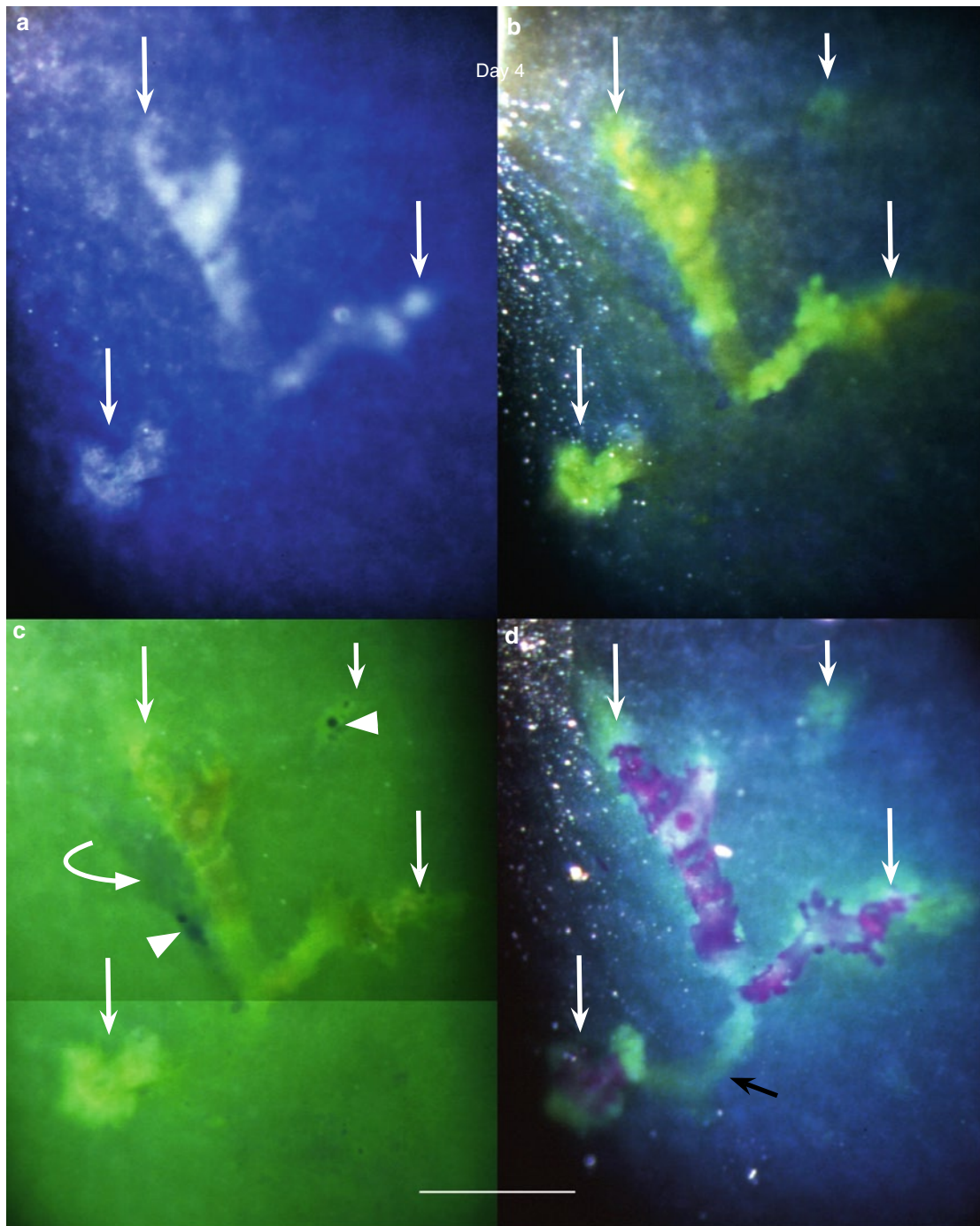


Fig. 2.11 Day 4, 3 days of acyclovir treatment. (a) shows light-reflecting surface plaques (arrows) before staining, (b) an early staining with fluorescein sodium revealing an additional, incipient lesion (short white arrow); (c) swollen/rounded cells (arrowheads) and a surface elevation (bowed arrow) in apposition to the lesion (protruding in the green stained tear film refreshed after a blink), and (d) rose bengal staining of surface plaques; in the lower part is visible an additional green fluorescein staining connecting the lesions (black arrow). (The long white arrows are placed in corresponding locations; (c) composed photograph)

VZV Corneal Epithelial Lesions (Case 2, cont.)

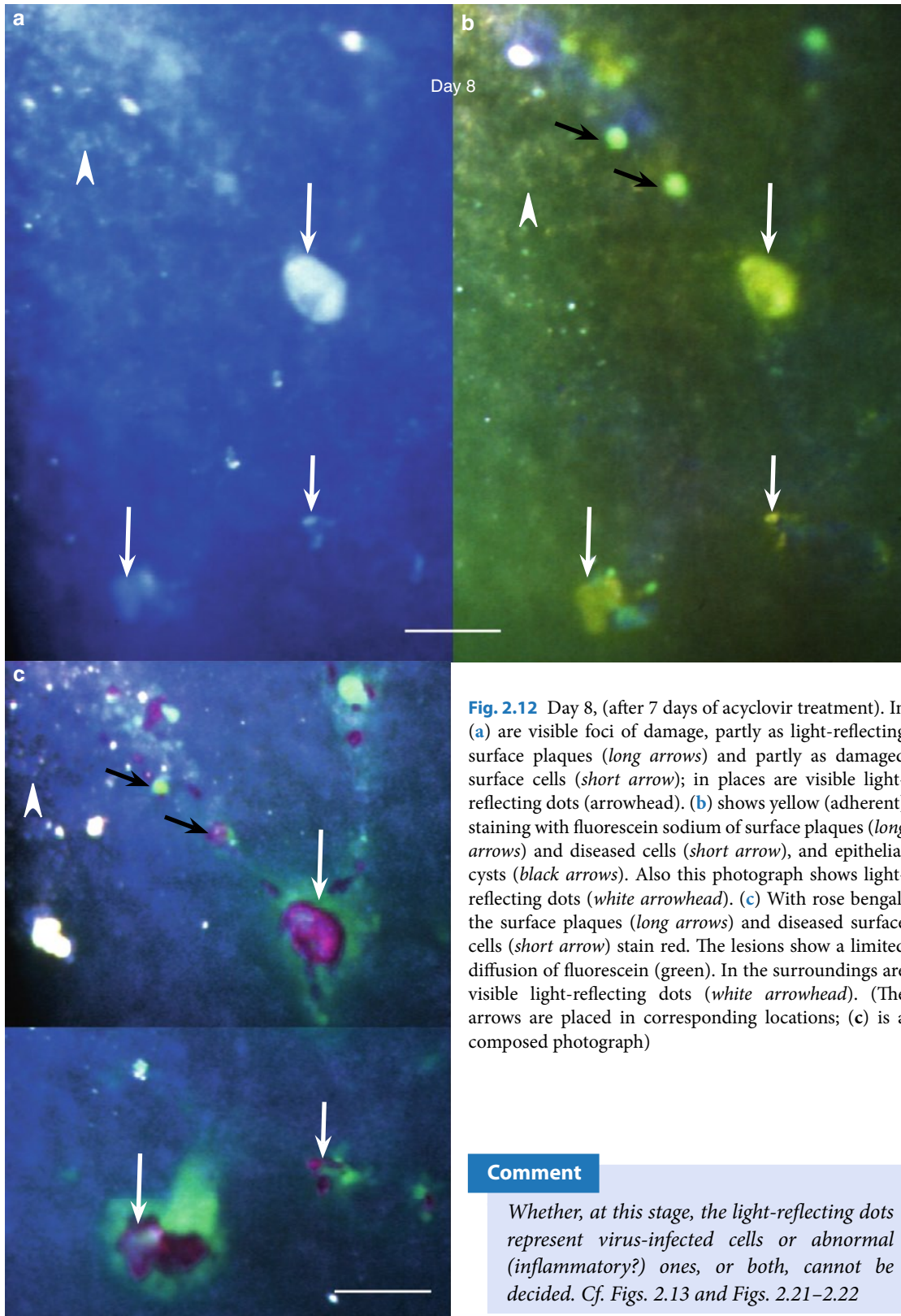


Fig. 2.12 Day 8, (after 7 days of acyclovir treatment). In (a) are visible foci of damage, partly as light-reflecting surface plaques (*long arrows*) and partly as damaged surface cells (*short arrow*); in places are visible light-reflecting dots (*arrowhead*). (b) shows yellow (adherent) staining with fluorescein sodium of surface plaques (*long arrows*) and diseased cells (*short arrow*), and epithelial cysts (*black arrows*). Also this photograph shows light-reflecting dots (*white arrowhead*). (c) With rose bengal, the surface plaques (*long arrows*) and diseased surface cells (*short arrow*) stain red. The lesions show a limited diffusion of fluorescein (green). In the surroundings are visible light-reflecting dots (*white arrowhead*). (The arrows are placed in corresponding locations; (c) is a composed photograph)

Comment

Whether, at this stage, the light-reflecting dots represent virus-infected cells or abnormal (inflammatory?) ones, or both, cannot be decided. Cf. Figs. 2.13 and Figs. 2.21–2.22

VZV Corneal Epithelial Lesions (Case 2, cont.)

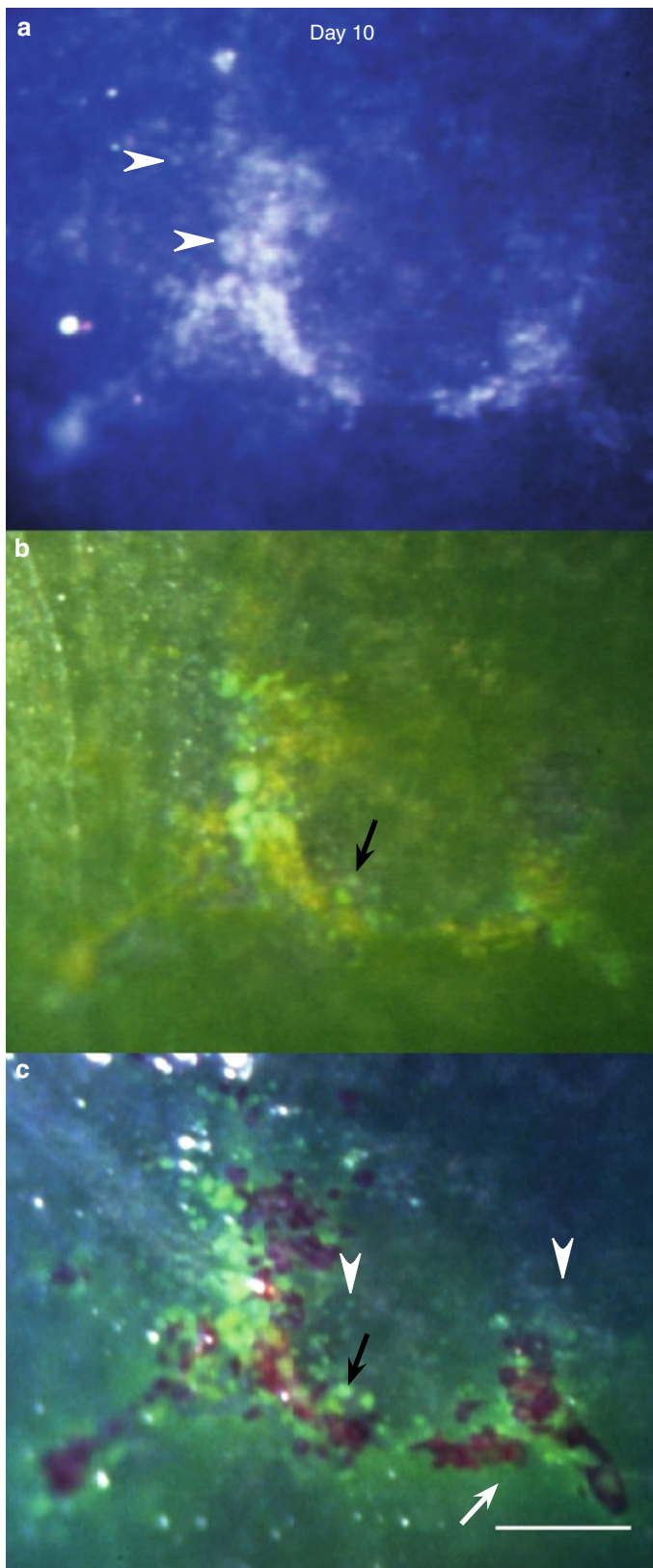


Fig. 2.13 This figure, captured on day 10 (3 days after the treatment was stopped), is still compatible with a result of VZV infection

(a) Before staining are visible many light-reflecting dots, agglomerated or individual (*arrowheads*)

(b) Fluorescein sodium visualizes diseased surface cells and cell debris (yellow staining) and small cystic spaces (*arrow*)

(c) Diseased surface cells and cell debris are clearly visible after the application of rose bengal. The staining is in places confluent, and there is still a limited diffusion of green stained tear fluid (*white arrow*). Also this photograph captured light-reflecting not-stainable dots outside the figure (*arrowheads*). (The black arrow points to the same cyst as in [b])

Subepithelial Opacities: A Sequela of VZV Epithelial Keratitis (Case 2, cont.)

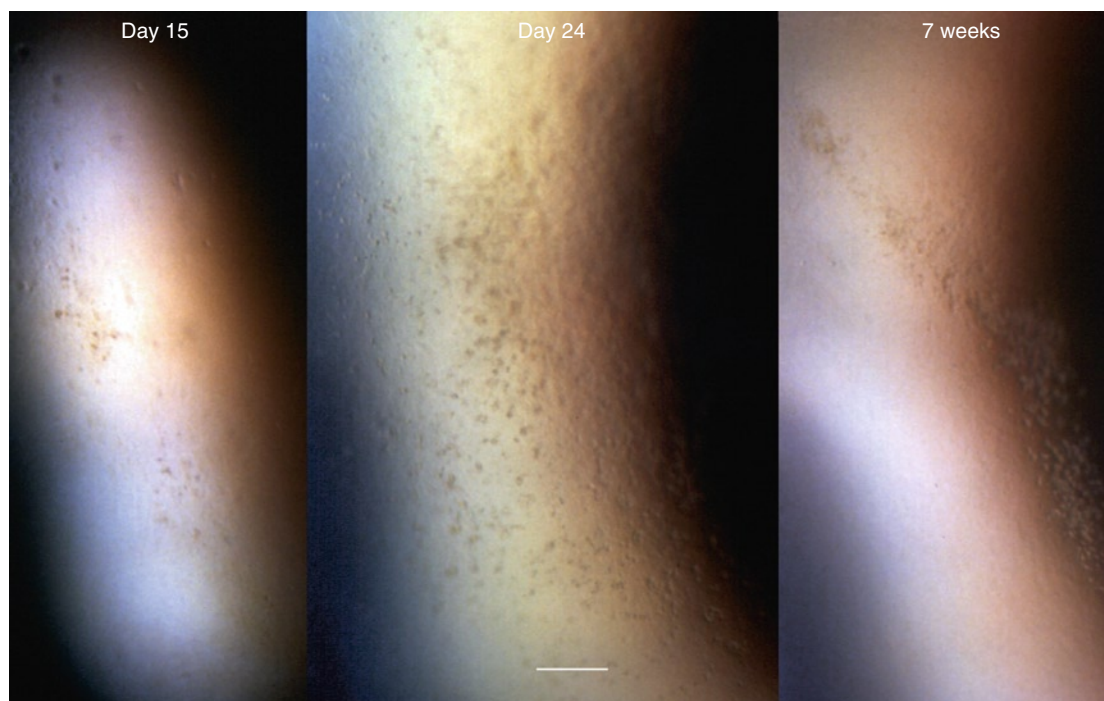


Fig. 2.14 All surface changes have disappeared. Abnormal cells situated about the level of the basement membrane (present on day 15, 24, and 7 weeks after onset in the area previously showing VZV epithelial lesions) appear as fine dots (shown at higher magnification in Figs. 2.15 and 2.16)

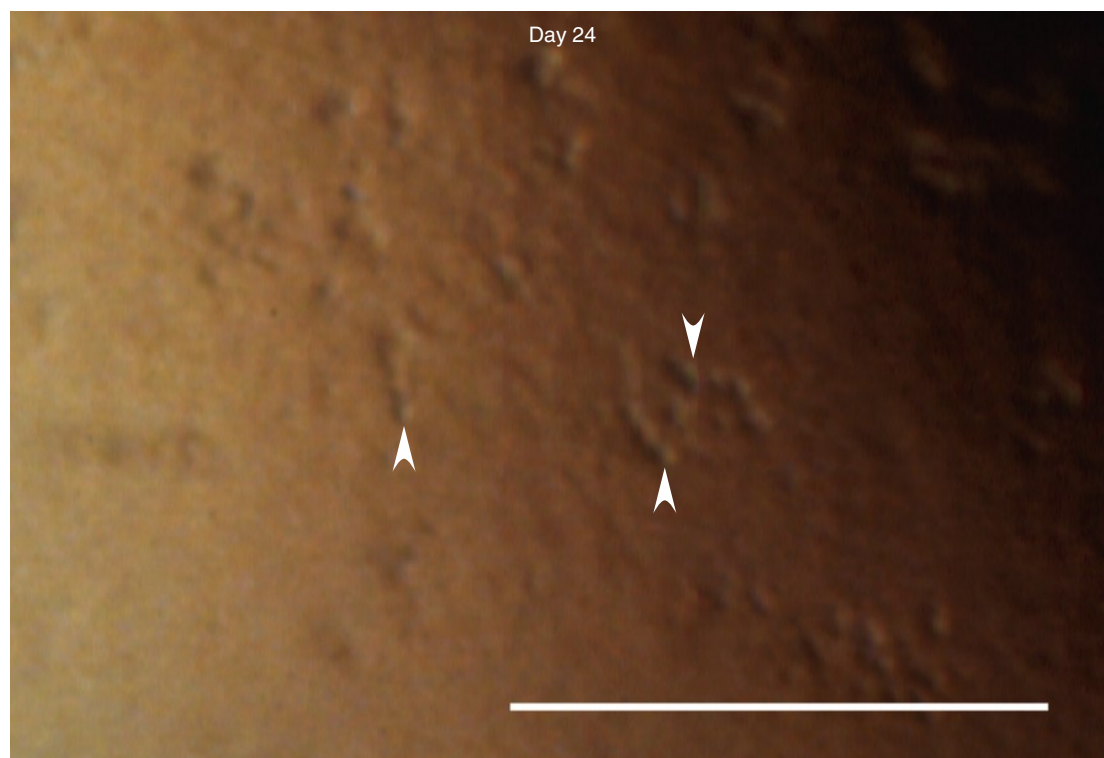


Fig. 2.15 Abnormal cells (*arrowheads*), individual or grouped, on day 24

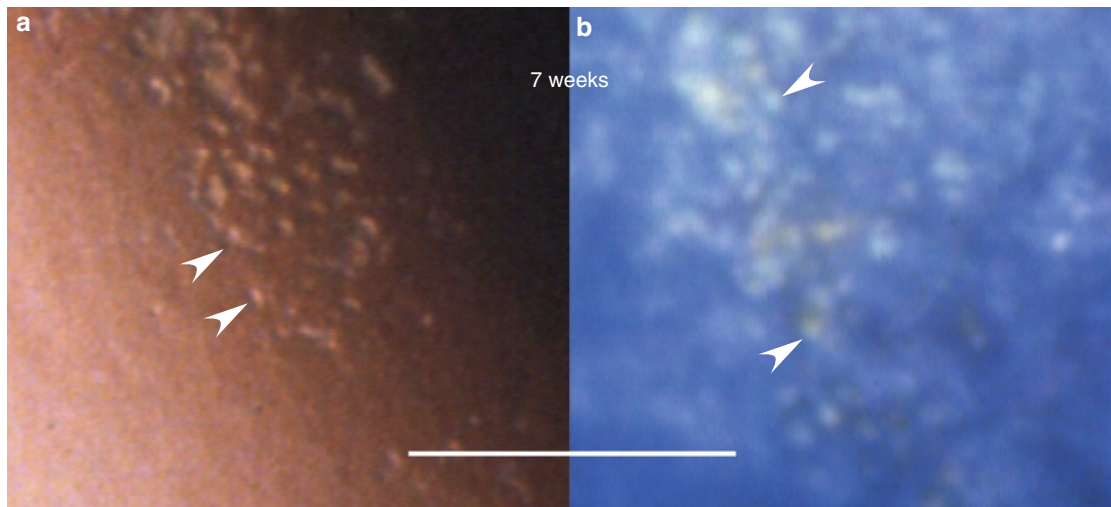
Subepithelial Opacities: A Sequela of VZV Epithelial Keratitis (Case 2, cont.)

Fig. 2.16 a–b Abnormal cells (*arrowheads*) 7 weeks after onset. In (**b**) is visible their light-reflecting property (not exactly the same areas)

Addendum

The skin lesions disappeared within a week leaving no scars. Three months after onset, the patient had no complaints, and the cornea showed no sequelae.

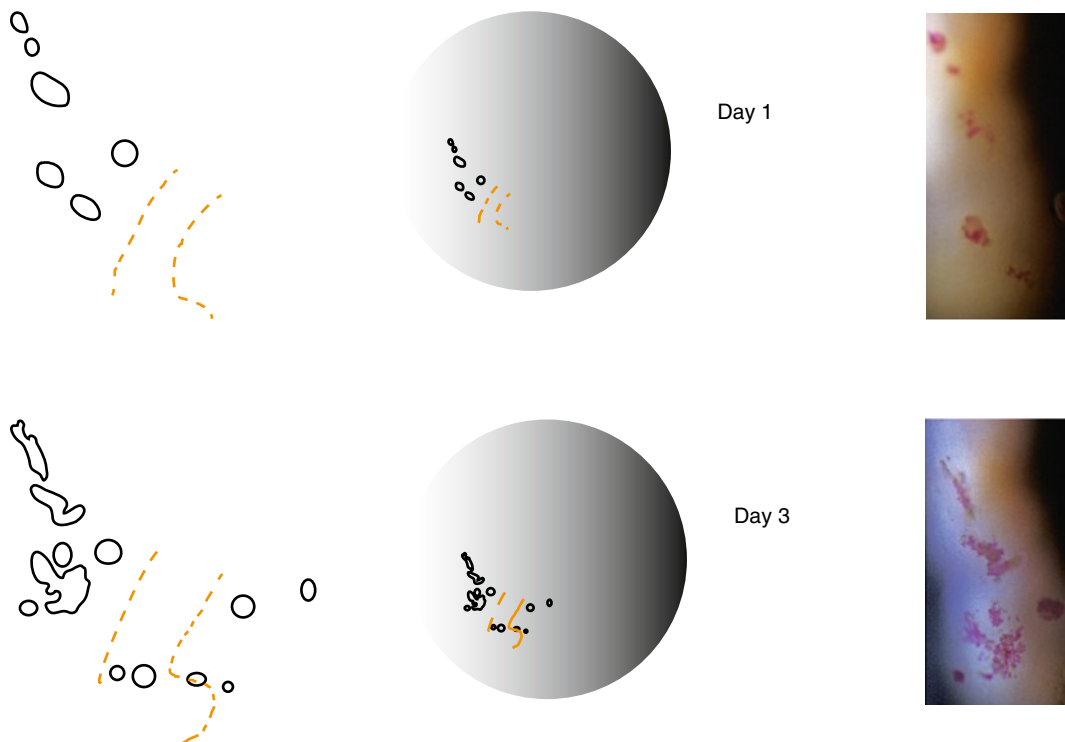
Case 3: Appearance and Disappearance of VZV Corneal Epithelial Lesions

Case Report

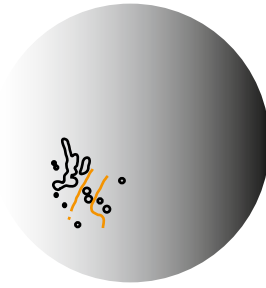
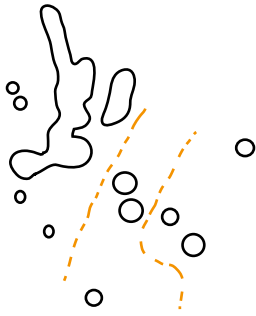
A 70-year-old healthy woman had had left-sided headaches and irritation in her left eye for 3 days. The eye was injected, the nasal part of the cornea showed a few small VZV epithelial lesions and the nasal part of the upper lid a group of small blisters. She was treated with acyclovir p.o., 800 mg five times a day for a week. While on treatment, she developed a typical HZO rash. New corneal epithelial lesions continued to appear at (or close to) the original site, and in other locations (subcentrally, in the prepupillary area, and close to the upper limbus). Ten days after onset (day 7 after presentation), the eye showed a mild anterior uveitis treated with topical cortisone. This treatment was slowly tapered.

The photographs were taken on day 1 (at presentation), and days 3, 5, 7, 9, 11, 14, and 16. The last VZV compatible epithelial lesion was observed on day 22 (not photographed).

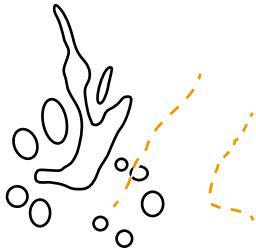
The following series of photographs shows a follow-up of the development of VZV epithelial lesions in the nasal part of the cornea, captured on days 1 and 3, and (opposite page) on days 5, 7, 9 and 11. The drawings, composed from several photographs, comprise also changes not staining with rose bengal. In the absence of reference points, they show the positions of the lesions in relation to their background, i.e., an iris structure visible in the photographs; its outlines are indicated in the drawings by the dotted orange lines. Because not exact, the drawings serve only orientation purposes; changes of individual structures cannot be pinpointed. Figs. 2.17–2.28 show some details captured at these occasions.



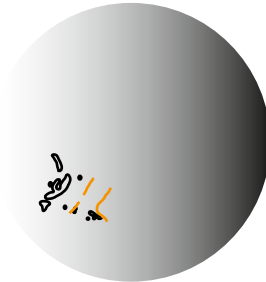
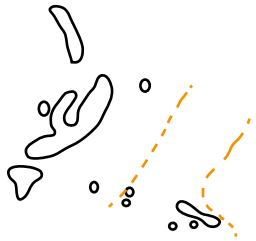
Appearance and Disappearance of VZV Corneal Epithelial Lesions (Case 3, cont.)



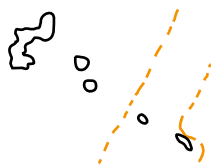
Day 5



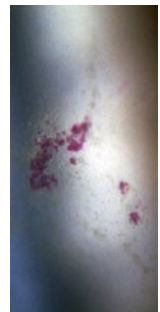
Day 7



Day 9



Day 11



VZV Corneal Epithelial Lesions (Case 3, cont.)

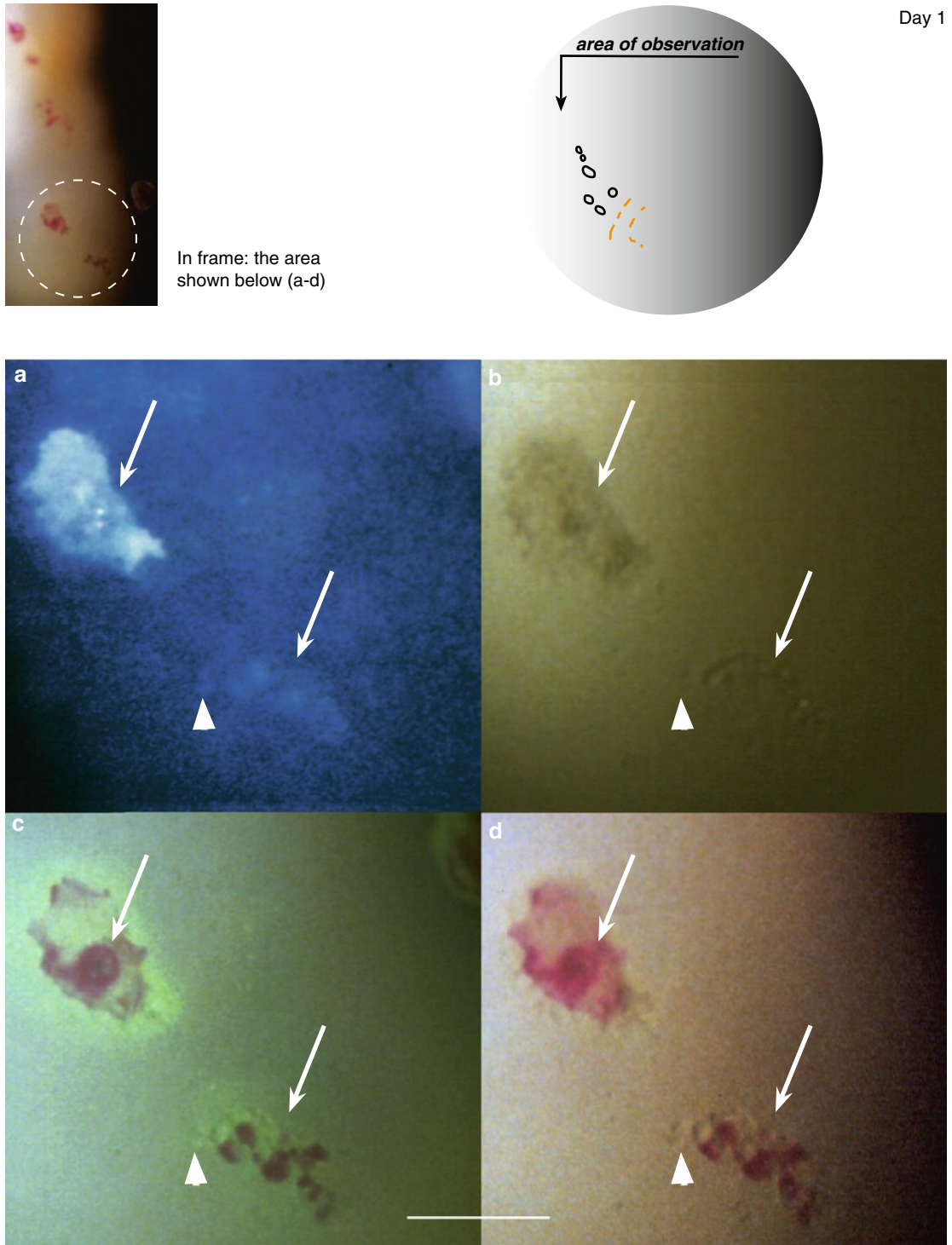


Fig. 2.17 a–d Before treatment. Two small VZV lesions (*arrows*) close to each other, one strongly light-reflecting and one less so. *Arrowheads* indicate swollen/rounded cells (visible in **b–d**). In (**c**) is visible a limited fluorescein diffusion and in (**c–d**) rose bengal staining of damaged surface cells/cell debris. (The markers are placed in corresponding locations)

VZV Corneal Epithelial Lesions (Case 3, cont.)

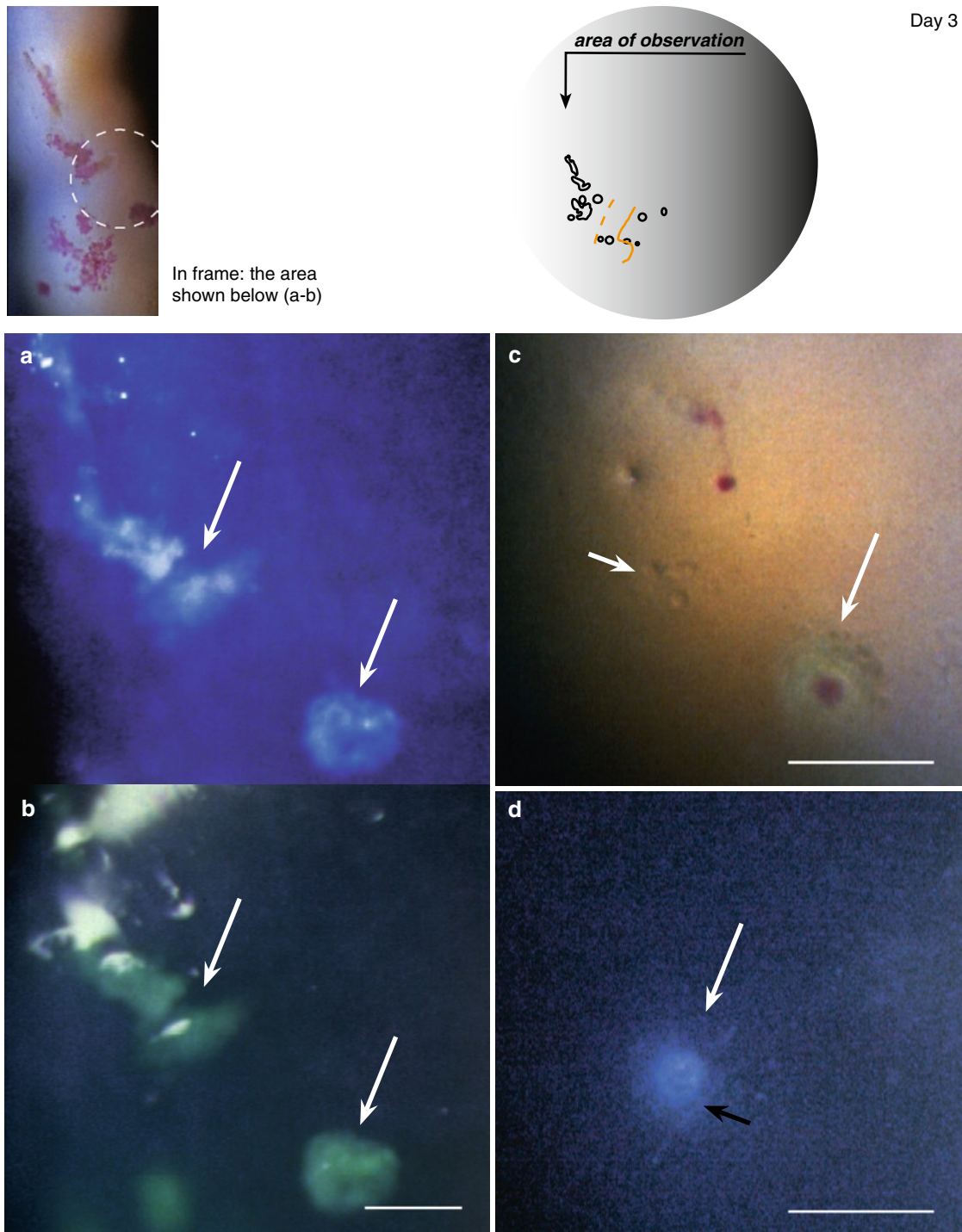


Fig. 2.18 After 2 days of acyclovir treatment. (a) The light-reflecting lesions (*arrows*) stain (b) green with fluorescein sodium. There is no diffusion into the surroundings. (The arrows are placed in corresponding locations.) (c) A rounded lesion (*long arrow*) present subcentrally stains green with fluorescein sodium and, in the center, red with rose bengal. Close to it is visible an incipient lesion (*short arrow*) that does not stain. (d) shows a light-reflecting lesion (*white arrow*) and a corneal nerve (*black arrow*)

VZV Corneal Epithelial Lesions (Case 3, cont.)

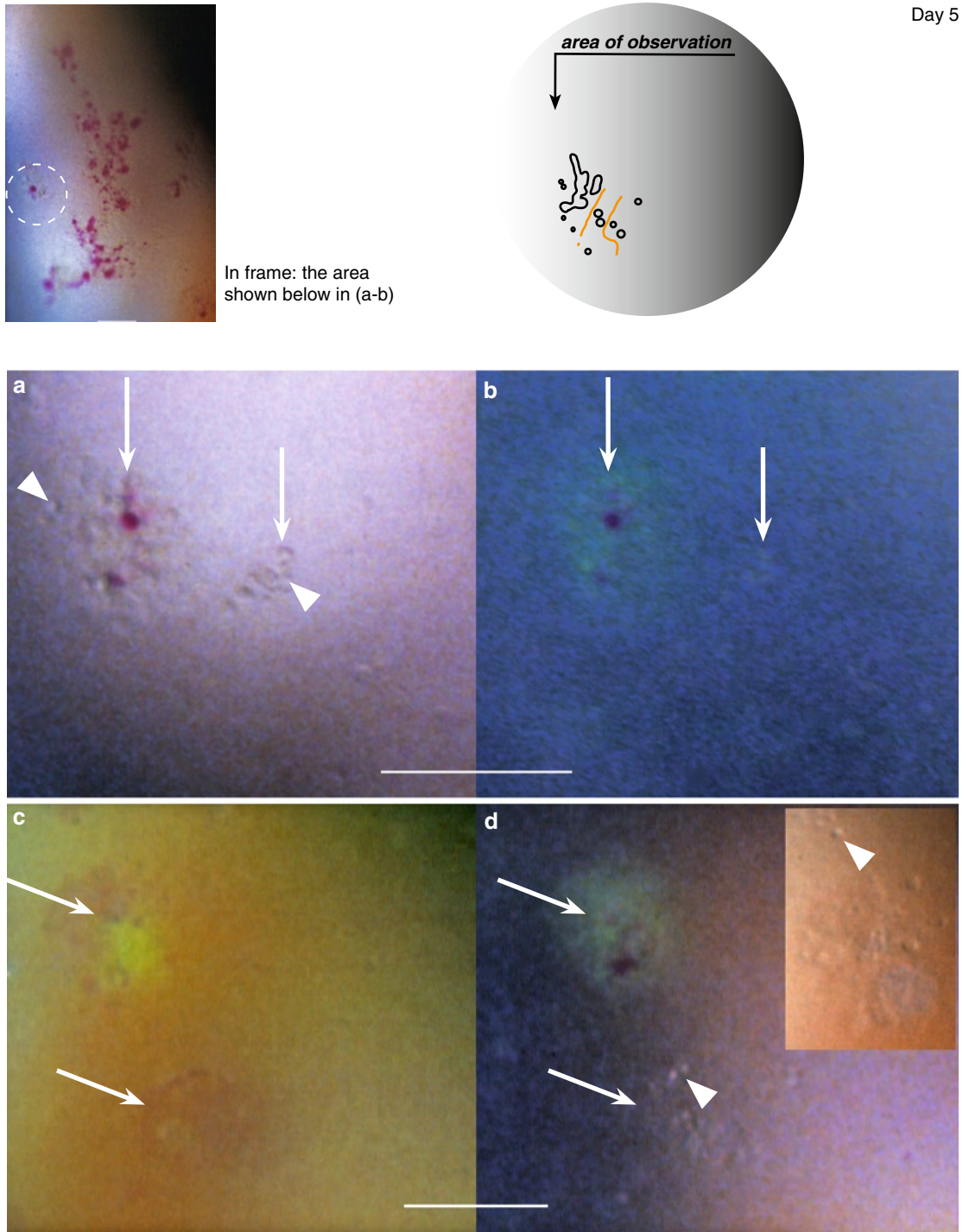


Fig. 2.19 After 4 days of acyclovir treatment. (a) Adjacent incipient lesions (*arrows*) containing swollen/rounded cells (*arrowheads*); (b) the left lesion shows fluorescein diffusion and a red staining of surface cells/cell debris. (The arrows are placed in corresponding locations.) (c–d) shows incipient lesions (*arrows*) that developed in a new (subcentral) location; they show the same staining as in (a–b). In (d) are visible swollen/rounded cells (*arrowhead*, cf. also *inset*). (The arrows are placed in corresponding locations)

VZV Corneal Epithelial Lesions (Case 3, cont.)

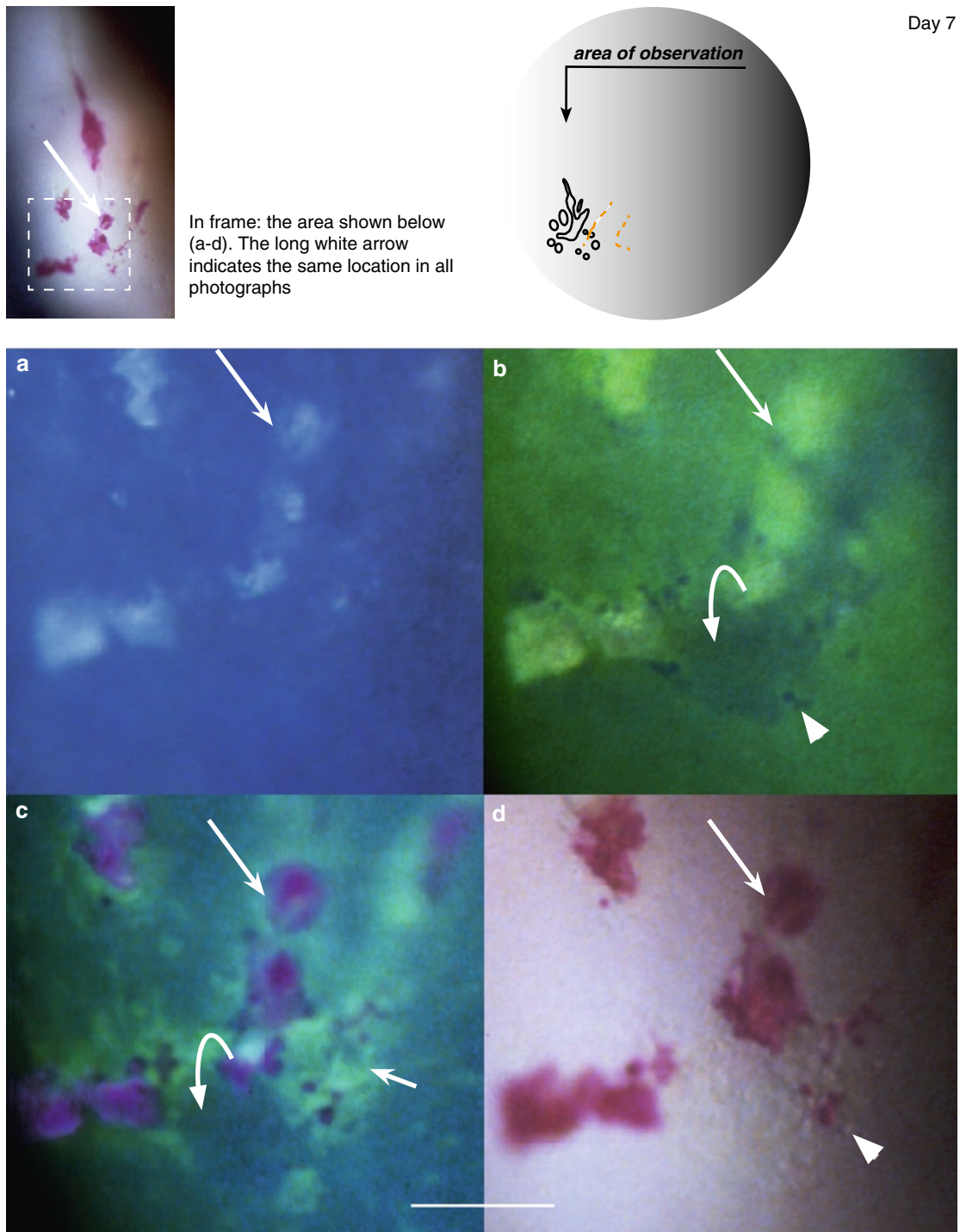


Fig. 2.20 After 6 days of acyclovir treatment. The lower part of the lesion shown above shows a VZV typical mixture of features: (a) light-reflecting surface plaques (*long white arrow*) appear (b) bright in the tear film stained green with fluorescein, and (c-d) stain red with rose bengal. Fluorescein visualizes protruding swollen/rounded cells (b, *arrowhead*), surface elevations (b and c, *bowed arrows*), and diffusion into the tissues (c, *short white arrow*). In (d) are additionally visible swollen/rounded cells (*arrowhead*). (Adapted from [7])

VZV Corneal Epithelial Lesions (Case 3, cont.)

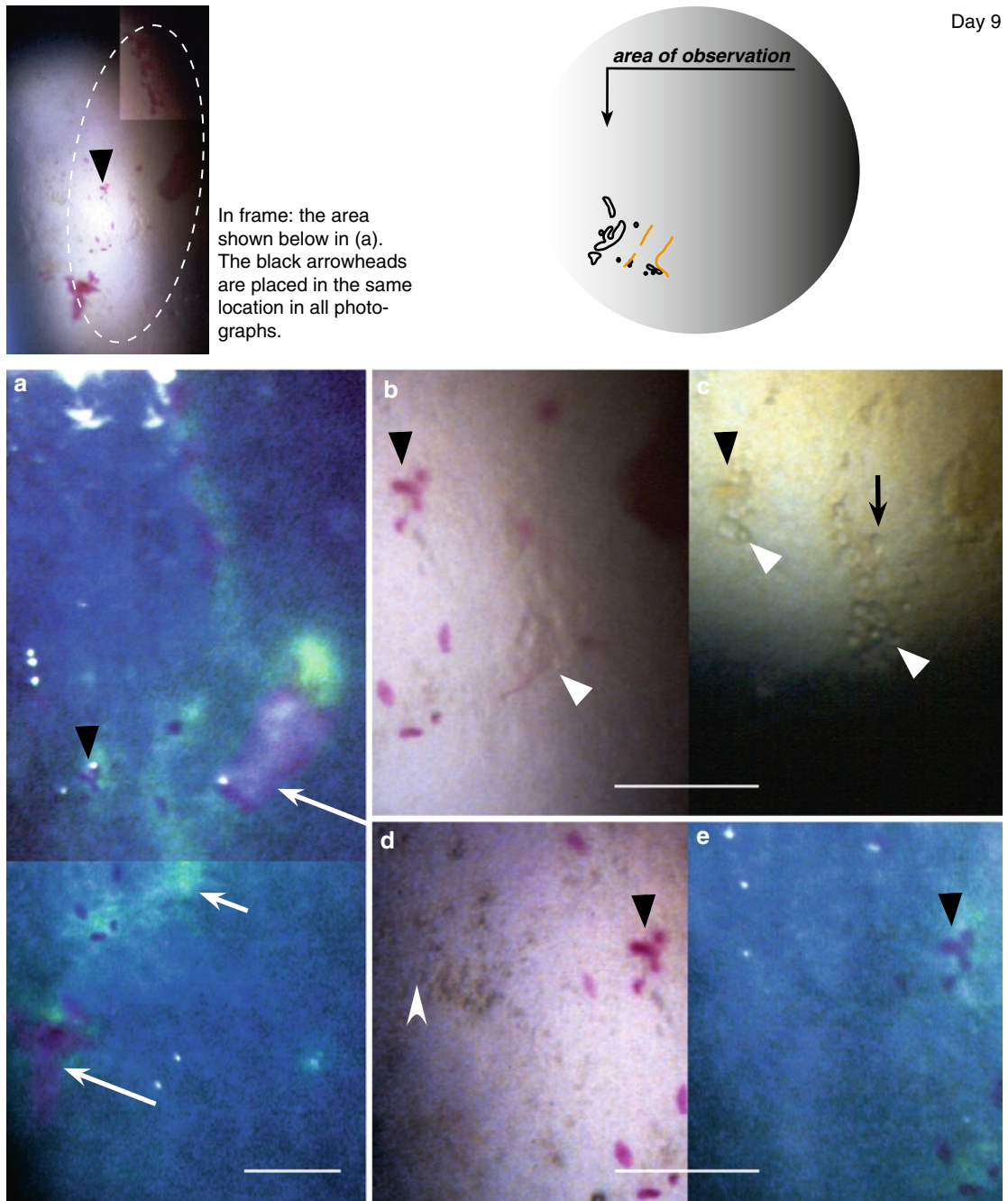


Fig. 2.21 (a) shows red staining of damaged cells (black arrowheads), surface plaques (long white arrows), and penetration of green stained tear fluid into the epithelium (short white arrow; composed photograph). In the pair of photographs (b and c) are visible swollen/rounded cells (white arrowheads) present in areas staining green in (a) and larger rounded structures (black arrow), probably cysts. (d and e) This pair of photographs shows an area to the left from the main lesion; it contains heaped-up abnormal cells (white arrowhead) but it does not stain. Cf. Fig. 2.22 and Figs. 2.23–2.24 (overleaf)

Comment

Similarly to Case 2 (Fig. 2.12–2.13), it is impossible, at this stage, to differentiate virus-infected cells from abnormal (inflammatory?) ones.

VZV Corneal Epithelial Lesions (Case 3, cont.)

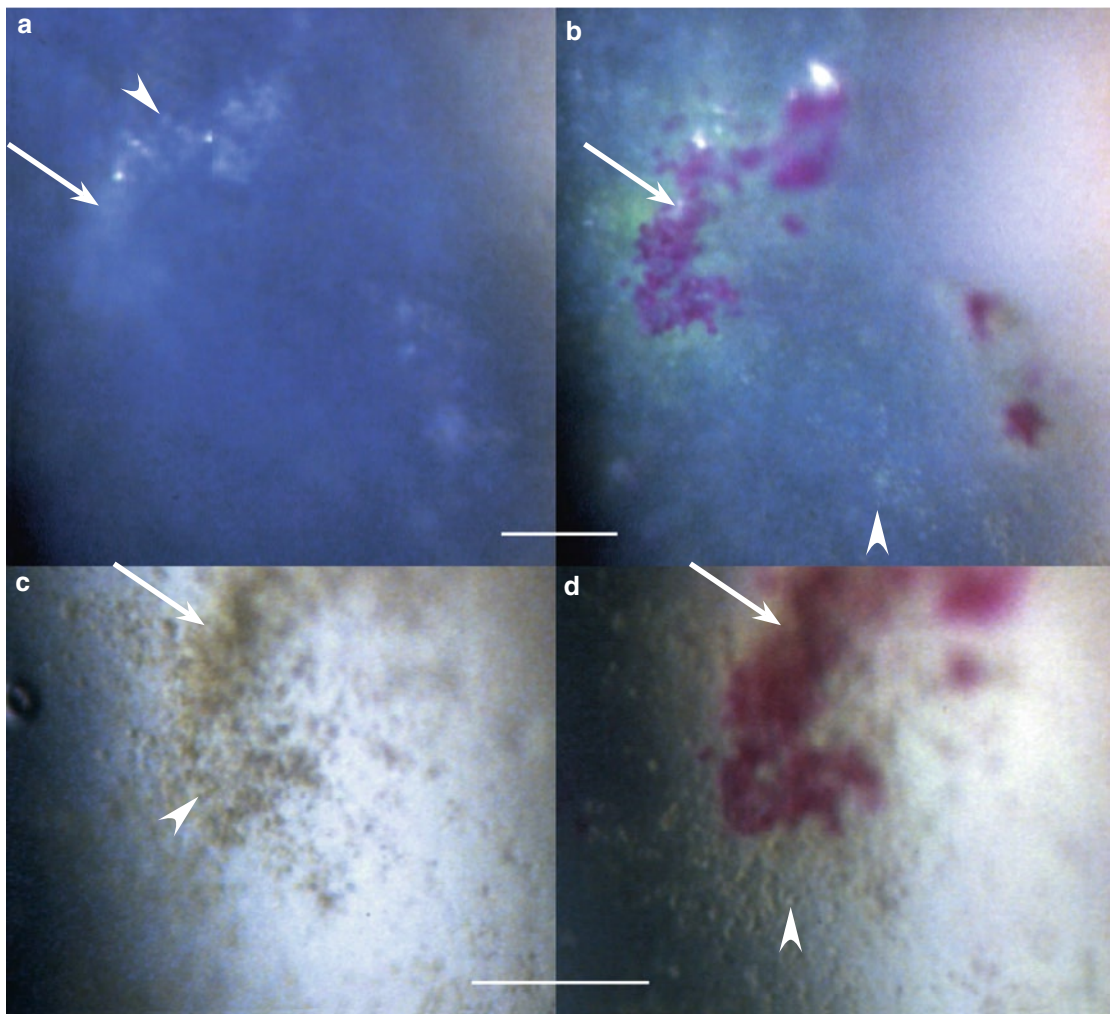
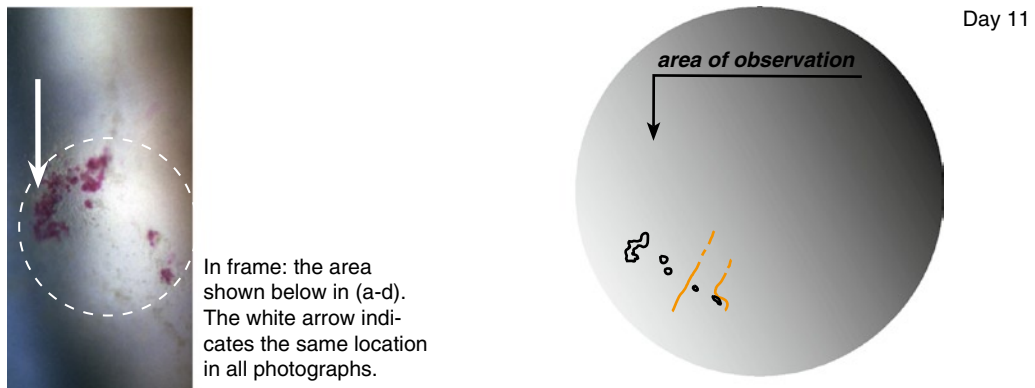


Fig. 2.22 These lesions (a) contain light-reflecting dots (*arrowhead*), (b) show rose bengal staining and a limited green fluorescein staining, and (c) seem composed of heaped-up rounded cells (*arrowhead*); also the surroundings show many rounded cells (b and d, *arrowheads*) in areas that do not stain. Cf. Figs. 2.21 and 2.23–2.24 (*overleaf*). At the same occasion (day 11), new incipient lesions were captured in a different area (Fig. 2.28)

VV Corneal Epithelial Lesions (Case 3, cont.)

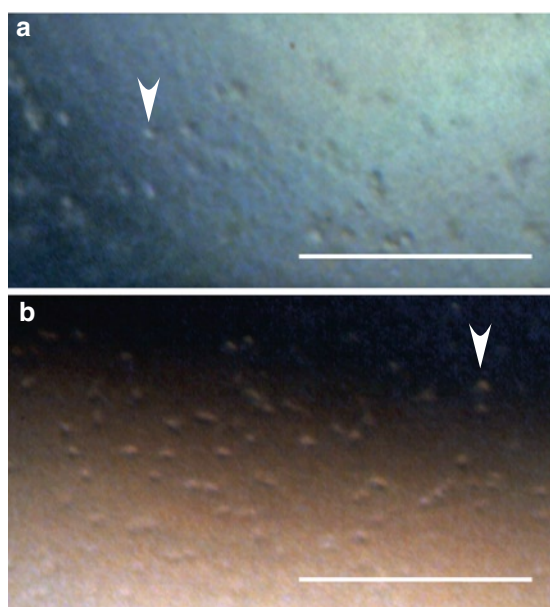
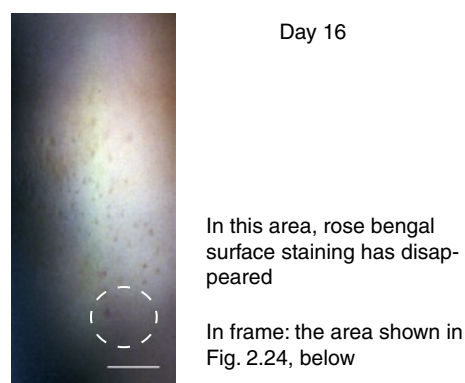
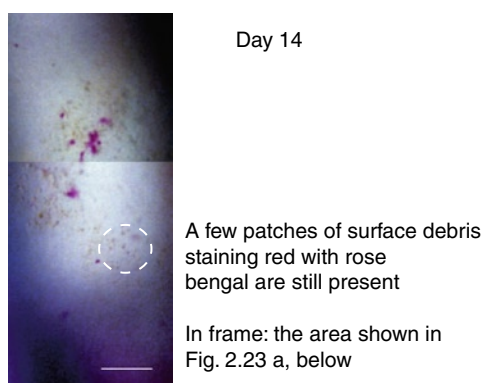


Fig. 2.23 (a) In this area, surface changes have disappeared. The rounded cells (*arrowhead*) probably represent abnormal cells situated about the level of the basement membrane. (b) For comparison, inflammatory cells (*arrowhead*) attached to the endothelium during anterior uveitis (captured on day 7)

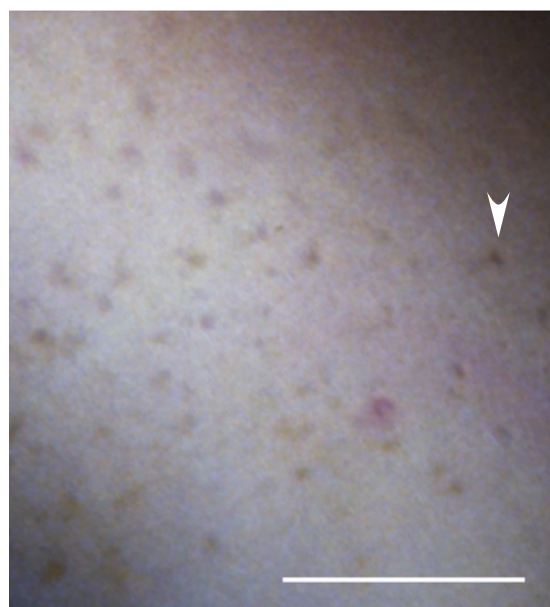


Fig. 2.24 Abnormal cells (*arrowhead*) situated about the level of the basement membrane

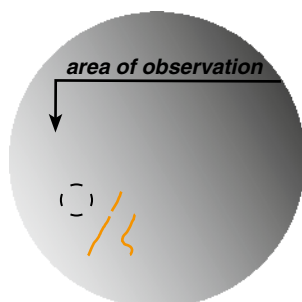
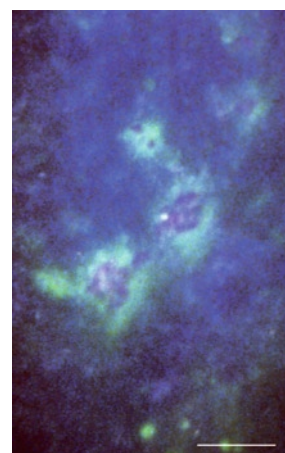


Fig. 2.25 (right) At the same occasion (day 16), the upper part of the cornea showed new VZV lesions



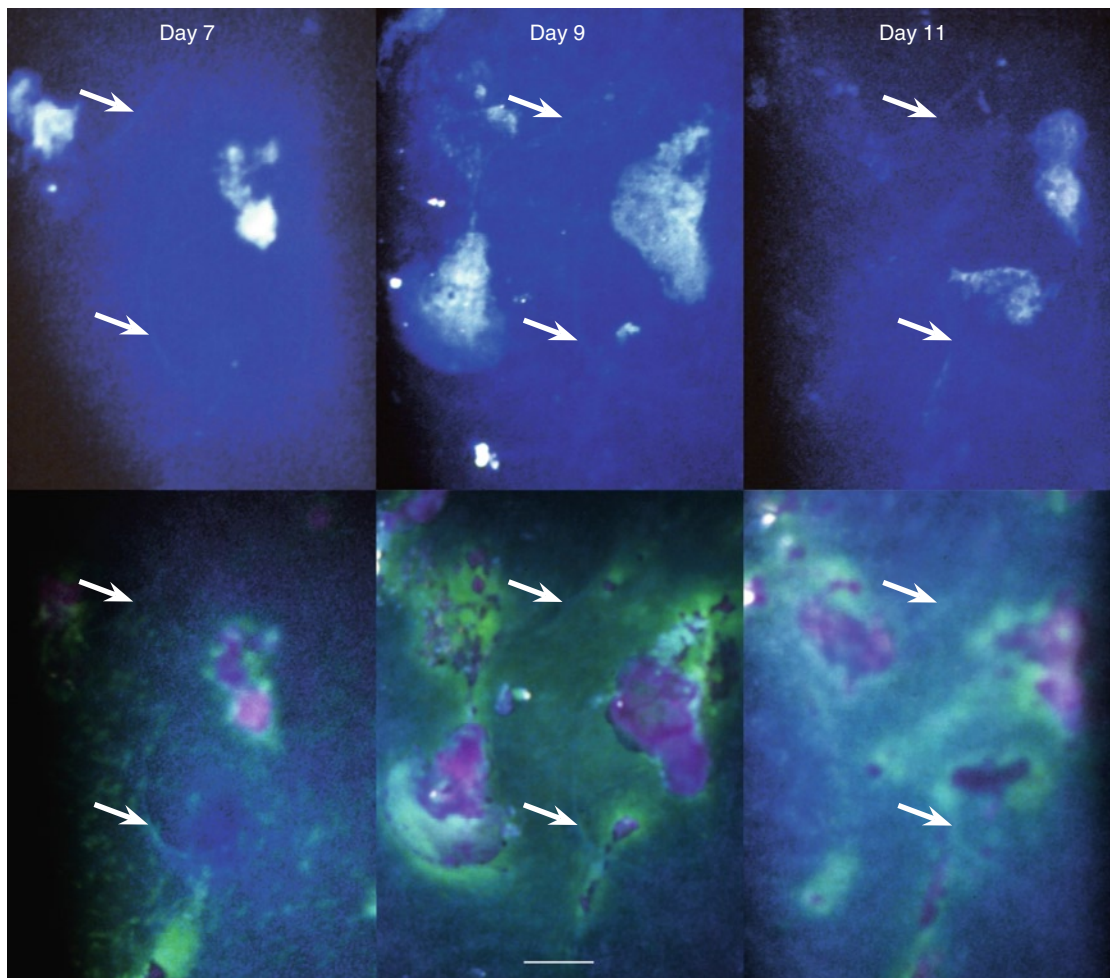
Development of VZV Corneal Epithelial Lesions in the Same Location (Case 3, cont.)

Fig. 2.26 Days 7, 9, and 11. The three pairs of photographs captured a rare occasion. By coincidence, VZV lesions developed centrally, in a location that showed grayish lines due to epithelial basement membrane dystrophy (*arrows*). The changing pattern within 48 h, caused by disappearance of some lesions, or their parts, concurrently with the appearance of new ones is well visible in relation to the dystrophy. The arrows are placed in corresponding locations, both before (*upper row*) and after staining with fluorescein sodium and rose bengal (*lower row*)

VZV Corneal Epithelial Lesions (Case 3, cont.)

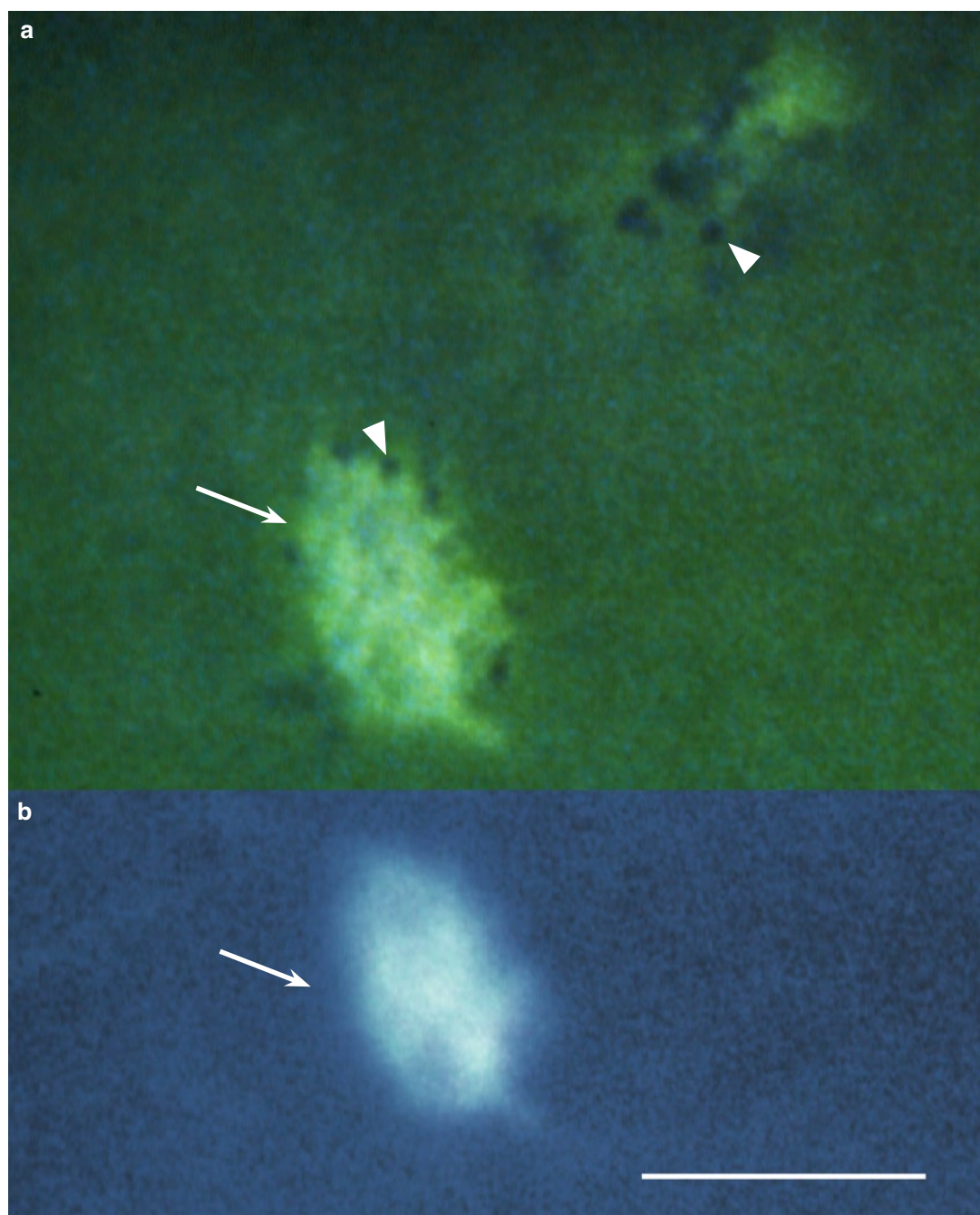


Fig. 2.27 Day 7, after 6 days of acyclovir treatment. (a) This lesion (*arrow*) located subcentrally shows swollen/rounded cells at the edges (*arrowhead*); similar cells are visible in the upper right corner (*arrowhead*). (b) shows the light-reflecting property of the same lesion. (The arrows are placed in corresponding locations.) Four days later, lesions with similar features were captured in a different area (cf. Fig. 2.28, *opposite page*)

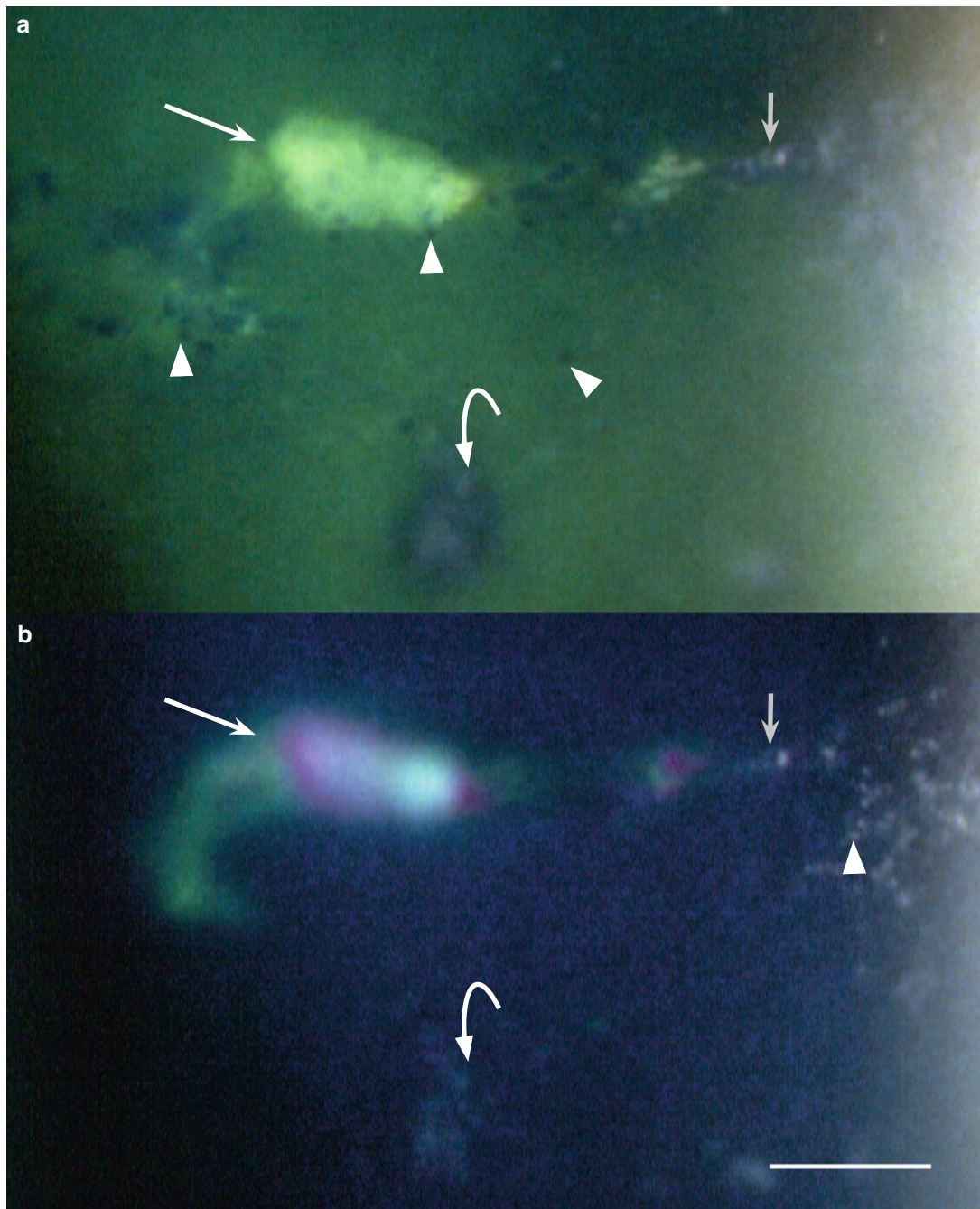
VZV Corneal Epithelial Lesions (Case 3, cont.)

Fig. 2.28 Day 11, 3 days after acyclovir treatment was stopped. This subcentral area shows (a) an incipient lesion (*bowed arrow*), a more advanced one (*long arrow*), and swollen/rounded cells (*arrowheads*); the gray arrow points to a small cyst. In (b), fluorescein has disappeared from the tear film: The incipient lesion (*bowed arrow*) does not stain; the more advanced lesion (*long arrow*) shows a limited green fluorescein staining, and rose bengal staining; to the right are visible swollen/rounded cells (*arrowhead*) and a small cyst (*gray arrow*). (The arrows are placed in corresponding locations)

Addendum

Three months after onset, when last seen, the patient was symptom-free. The cornea showed no sequelae of the infection; the only finding was epithelial basement membrane dystrophy.

Varicella-Zoster Virus Epithelial Keratitis in Herpes
Zoster Ophthalmicus

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