Varicella dendritic keratitis*

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Atypical dendritic keratitis has been described following herpes zoster infection. This is the first reported case of atypical dendritic keratitis following classical varicella infection. It also provides the first light and electron microscopic description of the varicella-zoster dendritic corneal lesion. The diagnosis is substantiated by the clinical appearance of the lesion and by the presence of serum antibody titers against varicella-zoster but not against herpes simplex. Cultures were negative for both viruses. The grayish intra-epithelial plaque-like appearance of the varicella-zoster dendritic lesion consists of unhealthy and dying cells in the middle layers of the corneal epithelium. These cells show a relatively sparse population of herpes-type virus particles.

Key words: case report, chickenpox, varicella, keratitis, varicella-zoster virus, dendritic keratitis, herpes zoster, herpes simplex, light and electron microscopy.

Dendritic corneal lesions were considered pathognomonic of herpes simplex virus (HSV) infection of the human or experimentally inoculated animal eye. Recently, two additional agents, both members of the herpes virus family, have been documented as causing such lesions. In 1972, Roberts and co-workers described a dendritic corneal lesion caused by Herpes virus felis (feline herpes virus) infection of the cat eye. In 1973, Pavan-Langston and McCulley established what had been suspected for a long time, that varicella zoster virus (VZV) was a cause of dendritic keratitis in herpes zoster ophthalmicus. They isolated VZV from atypical "medusa-like" dendritic lesions in three patients. That same year, Piebenga and Laibson provided more evidence for the existence of zoster dendritic keratitis by describing thirteen atypical dendritic lesions in nine patients with herpes zoster ophthalmicus. The dendrites were composed of "swollen and heaped up cells" giving the lesions a "linear gray, plaque-like character." Neither VZV nor HSV was isolated from these patients. Since five of them had no serum antibodies to herpes simplex, the authors attributed these atypical dendritic figures to herpes zoster infection.

Varicella (chickenpox) is caused by the same viral agent as herpes zoster. Therefore, one would not be surprised to find

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atypical dendritic keratitis following varicella infections. However, this entity has not been reported. The following external ocular conditions have been attributed to varicella: vesicles, pustules, and gangrene of the lids; phlyctenules and vesicles of the conjunctiva; vesicles, phlyctenules, punctate staining, disciform edema, deep keratitis, and ulceration of the cornea. Varicella has also been associated with uveitis, unilateral mydriasis, ocular palsies, internal ophthalmoplegia, optic neuritis, and encephalitis.1

In this paper, we present evidence to show that varicella may also cause atypical dendritic keratitis, grossly indistinguishable from that described following herpes zoster infection. This paper also provides the first documentation of the light and electron microscopic appearance of the varicella-zoster atypical dendritic lesion.

Materials and methods

Harvesting of the corneal epithelium. Removal of the corneal epithelium was carried out using the slit lamp biomicroscope and proparacaine anesthesia. A sterile Beaver No. 57 blade was used to demarcate and remove the involved epithelium.

Virus cultures. Conjunctival swabs and debrided corneal epithelial specimens were immediately inoculated into two tubes of human embryonic kidney (HEK) monolayer cultures maintained on minimal essential medium (Eagle) with 10 per cent fetal calf serum, 10 per cent NCTC 135, Amphotericin B, and penicillin. These tubes were incubated at 37° C and the medium was carefully changed every five to seven days leaving the epithelial fragments in the culture tube. After three weeks of observation when no cytopathic changes were noted, these cells were scraped and passed to fresh HEK tubes. These cultures were considered negative when no cytopathic effect was noted after an additional three weeks of incubation.

Serology. Complement fixation studies for VZV and HSV antibodies were kindly carried out by the Los Angeles County Public Health Laboratories. HSV neutralizing antibody determinations were carried out in our laboratory by methods previously described.5

Quantitative serum globulin determinations were carried out by a commercial medical laboratory using paper electrophoresis methods.

Electron microscopy. The debrided corneal epithelium was immediately immersed in cold, freshly prepared 1.5 per cent phosphate-buffered glutaraldehyde for at least one hour and then post-fixed in 1 per cent osmic acid. Specimens were dehydrated in graded alcohols and embedded in an Epon-Araldite mixture. Semithin sections were stained with toluidine blue and examined by light microscopy. Ultrathin sections were stained with lead citrate and uranyl acetate and examined by transmission electron microscopy.

Description of patient. A healthy eight-year-old white female developed typical chickenpox during a school epidemic in early February 1973. Craps of lesions developed over the entire trunk and extremities as well as the face including prominent involvement of the left outer canthus. There was no definite eye involvement or conjunctivitis. On May 10, 1973, the patient's mother noted the left cornea appeared hazy. That day, the patient was examined by her ophthalmologist.
Fig. 3. Light microscopy of atypical dendritic lesion shows some loss of surface cells and degeneration of the underlying middle layers of corneal epithelium. Some cells show what appear to be dark intranuclear inclusion. (Arrows.) Plastic embedded semi-thin section of specimen obtained Sept. 4, 1974. Stained with toluidine blue.

and found to have asymptomatic disciform edema of the left cornea with decreased corneal sensation. A tentative diagnosis of herpes simplex keratitis was made. The patient was started on treatment with idoxuridine (IDU). Subsequently, topical corticosteroids and atropine drops were added to the regimen. On June 4, 1973, "multiple small dendrites over the entire cornea, chiefly in the center" were noted. The poor response of the lesions to medication led to the patient's being seen at the Estelle Doheny Eye Foundation.

Examination on June 14, 1973, revealed a healthy asymptomatic youngster with an uncorrected visual acuity of 20/25 in the right eye and 20/50 in the left. The right eye appeared normal. The left eye showed no injection, but there was a round, central, 6 mm. in diameter area of mild stromal haze and edema. The epithelium overlying the area of disciform edema showed a large "medusa-like" gray intra-epithelial atypical dendritic figure which stained only moderately with fluorescein (Fig. 1). The presumptive diagnosis was varicella keratitis. The patient was maintained on atropine but both IDU and topical corticosteroid medications were discontinued. She was re-examined on June 18, 1973, with no further healing or change in the appearance of the atypical dendritic figure. Therefore, debridement of the involved corneal epithelium was carried out. Viral cultures were performed on the debrided corneal epithelium and a conjunctival swab specimen. Part of the epithelial specimen was fixed for electron microscopic study. Blood was drawn for serum antibody determinations.

In addition to the debridement, the patient was started on adenine arabinoside (ARA-A) 3 per cent ointment, atropine, and chloramphenicol drops. After the epithelium healed, topical corticosteroids were added to the regimen to suppress stromal keratitis and uveitis. Medications were slowly tapered and finally discontinued after a two-month period. The uveitis had cleared and the stromal haze had decreased to a point where uncorrected vision was 20/20 in the affected eye.

On Aug. 22, 1973, one week after discontinuation of all medications, the patient developed recurrent iritis and disciform edema with a decrease in visual acuity to 20/50. Prednisolone acetate 1 per cent drops four times a day rapidly improved the clinical condition. However, on Sept. 4, 1973, the patient presented with 13 small scattered atypical dendritic lesions which were grayish, intra-epithelial, and slightly raised (Fig. 2). The corneal epithelium was debrided. Specimens were submitted for viral and electron microscopic studies. The patient was restarted on ARA-A ointment and sulfacetamide drops with continuation of prednisolone acetate 1 per cent drops. Over the ensuing seven months, the medications have been tapered slowly and no recur-
Fig. 4. Note the almost completely degenerated surface epithelial cells of the atypical dendritic figure. The two cells lying directly below these show signs of early degeneration, including separation. Lead citrate and uranyl acetate stain, ×6,000. NB: All transmission electron micrographs are from specimens obtained Sept. 4, 1973.
Fig. 5. Higher power view of almost completely degenerative corneal epithelial cell containing herpes-like virus particles, some of which are enveloped. (Arrow) (N) Nuclear debris. Enveloped particles measured 190 to 220 nanometers. Lead citrate and uranyl acetate stain, x40,000. Reference line equals 220 nanometers.

rence of the dendritic figures has been encountered. However, the patient continues to have a low-grade smoldering iritis and faint stromal haze of the type frequently encountered in herpes zoster keratitis. The patient remains asymptomatic with a visual acuity of 20/30.

According to the mother, the patient had no other childhood exanthems, no serious illnesses, and only a rare upper respiratory infection. There was no history of cold sores or other manifestations of herpes simplex and/or herpes zoster-like infections, no previous eye abnormalities, and no use of systemic medication.

Results

**Virus culture studies.** In spite of very careful and thorough attempts to isolate virus from conjunctival swabs or corneal epithelial specimens taken on June 18, 1973 and Sept. 4, 1973, neither varicella zoster nor herpes simplex virus was isolated.

**Serological studies.** As shown in Table I, the patient had significant VZV complement-fixing antibody present in both specimens. Complement-fixing activity for herpes simplex virus was negative on both occasions and no neutralizing antibody was detected in the patient's undiluted serum. Quantitative serum globulin determinations were performed on serum obtained Sept. 19, 1973. The gamma A level was 82 mg. per 100 ml. (normal, 100 to 400 mg.). The gamma C level was 1,000 mg. per 100 ml. (normal, 1,000 to 1,600 mg.), and the gamma M level was 150 mg. per 100 ml. (normal, 40 to 160 mg.).

**Histologic studies.** Toluidine blue-stained sections of the atypical dendritic lesion of Sept. 4, 1973 (Fig. 3) show a loss of some superficial epithelial cells and advanced degeneration of many remaining cells. Some of the most highly involved cells
show what appears to be dark intranuclear inclusions. Low-power electron microscopic pictures of these areas show degenerating corneal epithelial cells with scattered nuclear debris (Fig. 4). Under higher magnification, in Figs. 5 and 6, typical herpes-like virus particles can be seen. The relative number of virions is small and few appear to have a normal and healthy morphologic appearance.

Discussion

What evidence can be marshalled to substantiate VZV as the cause of the atypical dendritic figures described in this paper? To the present, only two viral agents are known to cause human dendritic keratitis. They are HSV and VZV, both members of the herpes group. This atypical dendritic figure did indeed show herpes-type virus in affected cells. Virus particles were present in relatively small numbers and in poor morphologic condition, a finding more characteristic of VZV than HSV infection.9

There are additional facts favoring a VZV etiology. By history and by serologic evaluation, the patient had no previous infection with HSV while just prior to the keratitis she developed typical varicella and the expected antibody response to that infection. The lesion's clinical appearance was not typical of herpes simplex dendritic keratitis, but was indistinguishable from that associated with herpes zoster. VZV is very difficult to isolate from the eye,2,6 while HSV, usually present in high titer in steroid-treated eyes, should have been isolated with ease from the specimens taken on Sept. 4, 1973. However, no virus was
recovered even from cultures of the involved corneal epithelium. These negative results occurred though the patient had been off all antiviral medication for three weeks and had used topical steroids for two weeks prior to culture. This patient did exhibit a recurrence of dendritic keratitis, a characteristic usually attributed to HSV infections. But, we, and others, have noted this behavior in zoster dendritic keratitis as well.

Certainly the weight of evidence favors VZV as the etiologic agent. But, was the infectious process varicella or was it systemic herpes zoster? Systemic herpes zoster infection can mimic varicella, but it usually occurs in very ill or debilitated adults or in patients that are immune incompetent or immunosuppressed. By contrast, this healthy young patient, who has a totally benign medical history, contracted typical chickenpox from which she recovered rapidly. No initial zoster-like distribution followed by generalized lesions was encountered. Quantitative serum antibody determinations were normal, though gamma A levels were slightly low.

The clinical morphology of the varicella-zoster dendritic lesion is consistent with the light and electron microscopic findings. It is a gray intra-epithelial plaque-like lesion, which stains only moderately with fluorescein. While there is loss of some surface cells, the figure is made up of unhealthy and dying cells in the middle layers of the corneal epithelium. These cells are seen to support an indolent type of virus infection. In contrast, herpes simplex figures, both clinically and in experimental animals, are made up of areas of almost complete or complete loss of epithelial cells in the dendritic pattern. In this instance, one expects and finds a transparent lesion which stains rapidly and intensely as fluorescein dye penetrates the underlying stroma. In varicella-zoster atypical dendritic figures, the presence of many sick and dying cells probably imparts the gray appearance to the lesion, while the remaining relatively healthy basal cells lead to a less rapid and less intense fluorescein staining of the stroma.

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