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Corneal surface changes in Thygeson's superficial punctate keratitis: a clinical and noncontact photomicrographic *in vivo* study in the human cornea

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PURPOSE. *To elucidate mechanisms behind the morphology of Thygeson's superficial punctate keratitis (TSPK).*
METHODS. *Sixteen patients were examined with the slit lamp and photographed by noncontact photomicrography. The results were compared with morphology of epithelial keratitis in* herpes simplex *type 1 (HSV1),* varicella zoster *(VZV), and adenovirus type 8 (Ad8) infections, all previously studied by the same method, and with published histologic findings in TSPK.*
RESULTS. *In the photographs, the corneal epithelium showed various numbers of abnormal subsurface cells measuring about 10 µm in diameter, present individually, in small groups, or aggregated in larger lesions (coarse lesions with the slit lamp). The surface epithelium was well preserved, except in larger lesions, which showed surface debris. The morphology was unlike HSV1 and VZV epithelial keratitis, but strongly resembled epithelial changes occurring in Ad8 infections on day 5, and later, after the onset of symptoms.*
CONCLUSIONS. *TSPK shows a more widespread epithelial involvement than suspected with the slit lamp. Its morphology seems to reflect an action of a noxious agent targeted at the deeper epithelial layers, with the appearance of abnormal cells as a result. These might represent invading inflammatory cells, damaged intraepithelial ones, or both. The coarse lesions visualize areas of major involvement showing discernible signs of cell destruction. The similarity to Ad8 keratitis suggests that the source of the noxious agent might be located outside the cornea. The morphology, in conjunction with clinical features, is compatible with an immunologically mediated injury. The etiology remains unknown. (Eur J Ophthalmol 2004; 14: 85-93)*

KEY WORDS. *Cornea, Epithelium, Thygeson's keratitis*

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INTRODUCTION

Thygeson's superficial punctate keratitis (TSPK) is a clinical entity, in typical cases characterized by the presence of one, a few, or several (20 to 30) coarse granular opacities apparently localized in the corneal epithelium. Some patients develop subepithelial opacities. Historical review, description of the slit lamp appearance, and the natural course of the disease have been given elsewhere (1). In short, since Thyge-

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son's original report in 1950 on 26 patients (2), over 300 cases have been described in the literature. The disease runs a prolonged course, with numerous exacerbations causing ocular discomfort, irritation, photophobia and tearing, and remissions. It has been reported to occur in both sexes, at ages ranging between 2.5 and 70 years (3), and with duration ranging between 1 month (3) and up to 40 years (4). The origin of the disease is obscure. It seems neither contagious, nor associated with systemic illnesses, and, so far, no infectious agent has been identified as its regular cause. Bacteriologic studies revealed no significant ocular pathogen (1, 4, 5), and no virus has been detected, either by virus isolation tests in tissue cultures (3, 5, 6-8) or by electron microscopy (1, 3, 9). A significant association between TSPK and histocompatibility antigen HLA-DR3 implying a role of immune factors has been reported (1). The disease is extremely cortisone-sensitive; also topical cyclosporine A seemed effective (10-12). There are occasional patients meeting all criteria but lacking coarse granular opacities (atypical cases) (1, 7, 13). TSPK tends to be confused with HSV and/or adenovirus infections.

The scope of the present study was to examine the detailed *in vivo* morphology, and variations, of epithelial changes in TSPK by a high-magnification method requiring no contact with the corneal surface (14).

MATERIALS AND METHODS

Included were 16 patients seen from 1987 to 2003, 13 with typical (6 men, 10 women, mean age 24.8 years, range 6-81 years at onset) and 3 with atypical TSPK (2 men, 1 woman, mean age 62.7 years, range 50-81 years at onset). In 11 patients (nos. 1-7 and 13-16) previous medical records were available, and 5 (nos. 8-12) had a history compatible with TSPK. Laboratory tests concerning *herpes simplex* type 1 (HSV1), *varicella zoster* (VZV), and adenoviruses – i.e., virus isolation in tissue cultures, immunofluorescence (IF), and polymerase chain reaction (PCR) – were performed in six patients (Tab. I).

The photographs were taken by noncontact photomicrography (14) in various illumination modes, before and after staining with fluorescein sodium and rose bengal (both dyes 1%, no preservative). Ektachrome 100 or 200 ASA film was used. The findings were compared with HSV1 (15-17), VZV (18), and *adenovirus* type 8 (Ad8) (19) epithelial keratitis studied by the same method, and with histologic findings in TSPK (6, 9, 20).

RESULTS

Clinical features/course of the disease (Tab. I)

For the most part, the eyes were white. During exacerbations, some showed slight to moderate conjunctival injection. The 13 typical cases (nos. 1-13) showed various numbers (1 to about 30) of light-reflecting apparently intraepithelial granular punctuate lesions. The intervening epithelium seemed normal. Before diagnosis of TSPK, adenovirus infection was often suspected. In the three atypical cases (nos. 14-16), the corneae showed myriads of dust-like apparently intraepithelial opacities, sometimes aggregated in patterns reminiscent of dendritic figures. The picture was more diffuse; more widespread and larger aggregates, if present, were more difficult to identify as TSPK lesions. Before diagnosis of TSPK, HSV was suspected. In all cases, fluorescein sodium staining was limited to the lesions; there was no diffusion of dye into the surrounding and underlying tissues. Many lesions stained red with rose bengal. In five patients (nos. 1-3 and 6-7) subepithelial opacities without overlying epithelial changes were observed. They were fine and transient.

The disease was as a rule bilateral. Occasionally, the findings were unilateral in patients with previously observed bilateral involvement, or, conversely, initially unilateral involvement became bilateral; in two patients (nos. 8 and 9) the findings remained unilateral during the observation period. The disease ran a course of exacerbations, manifesting as eye irritation, tearing and photophobia, and remissions. The duration of symptom-free intervals, as reported by the patients, varied between 1 and 13 years. The corneae showed TSPK lesions also in the absence of symptoms (nos. 2, 3, 7, and 13); in three patients (nos. 3, 13, and 16), a spontaneous, complete disappearance of corneal changes in both eyes was observed. Topical cortisone drops were extremely effective; in the majority of the patients, a weak solution (prednisolone sodium phosphate 0.05%) was sufficient to eliminate the

TABLE I - CLINICAL DATA ON 16 PATIENTS WITH TYPICAL (nos. 1-13) AND ATYPICAL (nos. 14 -16) THYGESON'S KERATITIS

Patient no.	Sex/age at onset, yrs	Disease duration, yrs	Symptom-free intervals, yrs	Eye	Laboratory tests (all results negative)	Concurrent findings, eye/general disease
1	F/38	20	?	Both	VI: HSV, Ad IF: Ad	None known
2	F/20	16	None	Both	VI: HSV, Ad IF: HSV, VZV, Ad	None known
3	M/16	16	7	Both		None known
4	F/19	14	8	Both		–/Mb Crohn
5	M/23	20	None	Both		
6	F/36	20	11	Both	PCR: HSV	–/Muscle dystrophy
7	F/26	4	None	Both	PCR: Ad	None known
8	M/7	23	13	Left		None known
9	F/73	1	?	Right		None known
10	F/19	1 mo	None	Both		None known
11	M/19	6	None	Both	PCR: HSV, Ad	None known
12	F/20	2	None	Both		None known
13 *	F/6	9	5	Both		–/Alopecia
14	M/50	1.5	1	Both		Dry eye/febrile illness
15	M/81	3		Both		Cataract/–
16	F/57	12	4 remissions with duration 10 mo–5.5 yr	Both	VI: HSV, Ad IF: HSV, Ad	Dry eye, cornea guttata/febrile illness

*Filial granddaughter of Patient 16.
VI = Virus isolation in tissue culture; HSV = *Herpes Simplex* Virus; Ad = Adenovirus; IF = Immunofluorescence test; VZV = *Varicella Zoster* Virus; PCR = Polymerase chain reaction

symptoms and to reduce the findings. Patients with mild symptoms experienced relief with lubricating eye drops.

Laboratory examinations failed to prove HSV1, VZV, and/or adenovirus in the six patients tested.

A history of associated diseases was elicited in five patients: morbus Crohn (no. 4), facio-scapulo-humeral muscle dystrophy (no. 6), transient alopecia (no. 13), and a febrile illness preceding either a recurrence of eye symptoms (no. 14) or the first known attack of TSPK (no. 16).

Two patients, one with typical (no. 13) and one with atypical (no. 16) TSPK features, were members of the same family (granddaughter and paternal grandmother).

Report on two members of the same family

Case 13 (typical TSPK). A 9-year-old girl, a filial granddaughter of Patient 16 (below), had symptoms of recurrent eye irritation, tearing, and photophobia, all starting in 1990, at the age of 6. A medical record from 1992 described bilateral keratitis in white eyes, resolving with topical cortisone. When examined in 1993, both corneae showed several typical TSPK lesions. The same picture was observed in 1995 and in 1997. Since 1993, her symptoms were mild and of short duration, and no cortisone was used. In 1999, when last seen, both corneae were clear. Since then, as reported by her grandmother, the girl had no symptoms.

The patient's mother reported that the girl was healthy except for a history of alopecia in 1991-1992, a problem that remained unexplained and resolved spontaneously. She had *varicella* in 1993, about 3 years after the onset of ocular symptoms.

Case 16 (atypical TSPK). A 57-year-old healthy woman with irritation in the left eye, starting in March 1991 in conjunction with a febrile illness, presented in April 1991 because of blurred vision in her right eye for about a week. The eyes were white. Both corneae showed fine dust-like light-reflecting opacities, spread in a dendritiform pattern and apparently located in the deeper epithelial layers. Her symptoms were mild, and treated only with lubricating eye drops. Within 6 weeks, her visual acuity returned to normal, the right cornea showed only a few small cysts, and the left appeared normal. Virus isolation test was negative for HSV and adenovirus, and IF test from conjunctival scraping negative for adenovirus.

About 16 months later, in September 1992, the symptoms recurred in the left eye. The eye was white, and the cornea showed the same type of opacities as in April 1991. The patient was diagnosed with atypical TSPK. The symptoms resolved spontaneously within 5 weeks. The right eye remained uninvolved.

About 10 months later, in August 1993, the symptoms recurred in both eyes, starting as one small group of intraepithelial opacities in the right eye, and two in the left one, subsequently diffusely spreading over both corneae, and disappearing within 1 month. IF test in material scraped from corneal lesions was negative for HSV and adenovirus.

A fourth attack occurred 1 year later, in October 1994, in the left eye; the symptoms subsided spontaneously within 2 months, but the corneal changes did not disappear. The right eye had a new attack in February 1995, and shortly thereafter the opacities spread again over the left cornea. After that, the keratitis was waxing and waning but never disappeared completely in either eye. In November 1995, the more involved right eye was treated with prednisolone sodium phosphate 0.05% 3 times a day, and the keratitis resolved rapidly. The keratitis persisted in the left eye but the patient had no symptoms. In February 1996 because of blurred vision, she started to use the drops once daily also in the left eye, and the keratitis resolved. In March 1996, while she was using the drops every other day, the keratitis recurred in the right eye with very little symptoms. She did well on low-dose steroid but it was not until January 1997 that both corneae were clear. After that, the treatment was stopped, she was seen every 6 months, she had no symptoms, and both corneae remained clear. In October 2002, the symptoms recurred in the left eye and, again, rapidly resolved with prednisolone sodium phosphate 0.05% once daily.

In 1992, after the symptoms had resolved, the patient was found to have dry eyes (break-up time 1-2 seconds, Schirmer 1 test 2 mm of wetting in 5 minutes, the test repeated at several occasions during remissions) but no dry eye related corneal epithelial changes. Both corneae additionally showed endothelial changes (cornea guttata). She had no associated general illness.

Photographic findings (Figs. 1 and 2).

Before staining. In all patients, the smallest discernible entities were abnormal cells of about 10 µm in diameter, optically dense on retroillumination, and light reflecting on focal illumination. They were present individually, in small groups, or aggregated in larger lesions. Larger lesions had a broken pattern, on focal illumination visible as adjacent islands of more or less light reflecting material, and on retroillumination as variously dense areas. In some parts of them the abnormal cells were difficult to distinguish. All lesions had indistinct edges showing individual or grouped abnormal cells.

Staining with fluorescein sodium. Occasional dots stained yellow. Three patients exposed for potentially toxic substances (such as ciprofloxacine in no. 14, terracortril-polymyxine B in no. 15, and rose bengal in no. 16) showed green micropunctate staining. Areas containing small groups of abnormal cells appeared elevated (dark) in the green stained tear film. Larger lesions captured shortly after the application of the dye showed yellow surface staining, which, within short, transformed into green. In some lesions, both fluorescein staining modes (21) were captured in one photograph. The staining pattern was often broken by interspersed unstained areas. The green staining, appearing as variously large and partly confluent flecks, was limited to the lesions, and there was no further

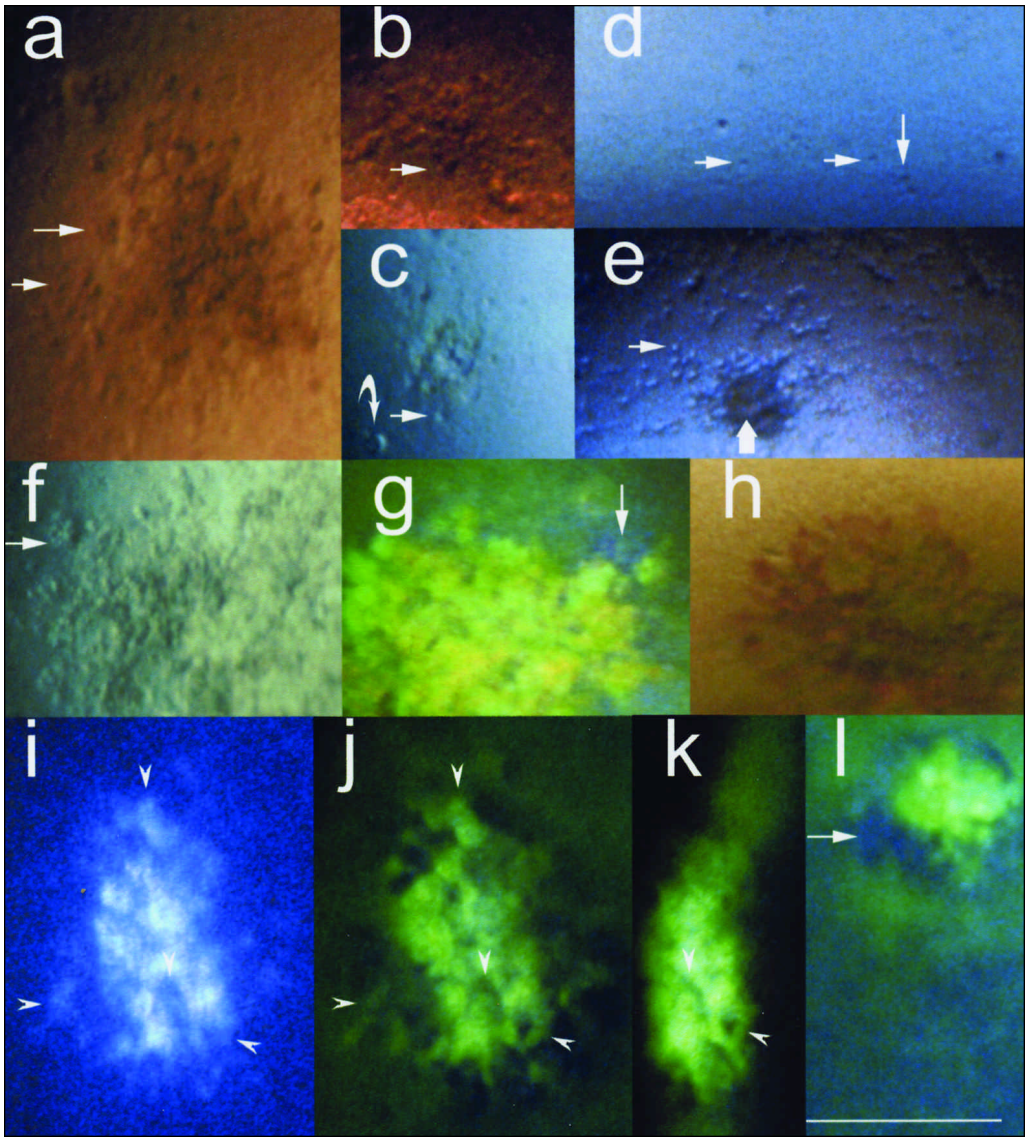

Fig. 1 - *Examples of corneal epithelial changes captured in 13 typical cases of Thygeson's superficial punctate keratitis. For comparison, inflammatory cells adhering to the corneal endothelium in anterior uveitis are shown in* **(e)**. *(Fluorescein sodium 1%, rose bengal 1%, bar 200 µm.)* **(a, b)** *Two lesions captured in the same cornea. The larger lesion* **(a)** *has a broken pattern; in some areas, abnormal cells are clearly visible (short arrow), in others difficult to distinguish. The indistinct edges show groups of abnormal cells (long arrow). The smaller lesion* **(b)** *contains many abnormal cells. Both lesions seem heaped-up. (Patient 3.)* **(c)** *A small lesion composed of more or less clearly visible abnormal cells (short arrow), and an adjacent cyst (bowed arrow). (Patient 4.)* **(d)** *This photograph shows that areas appearing normal with the slit lamp might contain abnormal cells, individual (short arrows), or grouped (long arrow). (Patient 5.)* **(e)** *Inflammatory cells (short arrow) adhering to the corneal endothelium resemble intraepithelial abnormal cells shown in* **(a-d)** *and* **(f)**. *A larger precipitate (fat arrow) appears optically dense. (A case of idiopathic anterior uveitis.)* **(f)** *A part of a large lesion consisting of many abnormal cells. Grouped abnormal cells (long arrow) are located at its indistinct edge. Some parts of the lesion appear more optically dense than others. (Patient 2.)* **(g)** *In a similar lesion as in* **(f)**, *fluorescein sodium staining captured shortly after the application of the dye reveals surface debris (yellow), penetration of the stained tear fluid into circumscript spaces (green), some unstained spaces (dark), and a surface elevation (dark) in an adjacent area containing a group of abnormal cells (long arrow). (Patient 1.)* **(h)** *A similar lesion as in* **(f, g)** *stained with rose bengal dye; some areas take up the dye, others appear unstained. (Patient 6.)* **(i-k)** *Three photographs of the same lesion; arrowheads indicate corresponding locations. On focal illumination* **(i)**, *the lesion shows more (white) and less (grey) light-reflecting patches. The similarity of patterns between the unstained epithelium* **(i)** *and the green staining with fluorescein sodium* **(j)** *indicates that the light reflections* **(i)** *are partly caused by damaged surface cells/surface debris below which the stained fluid penetrates. In a narrower light beam* **(k)**, *the lesion appears slightly elevated in the green stained tear film. There is no diffusion into the subjacent tissues. (Patient 2.)* **(l)** *With fluorescein sodium, this lesion shows similar features as in* **(i)**. *Elevated areas appear dark (long arrow). The green stained tear film in the lower part of the photograph appears mottled by incipient surface elevations. (Patient 2.)*

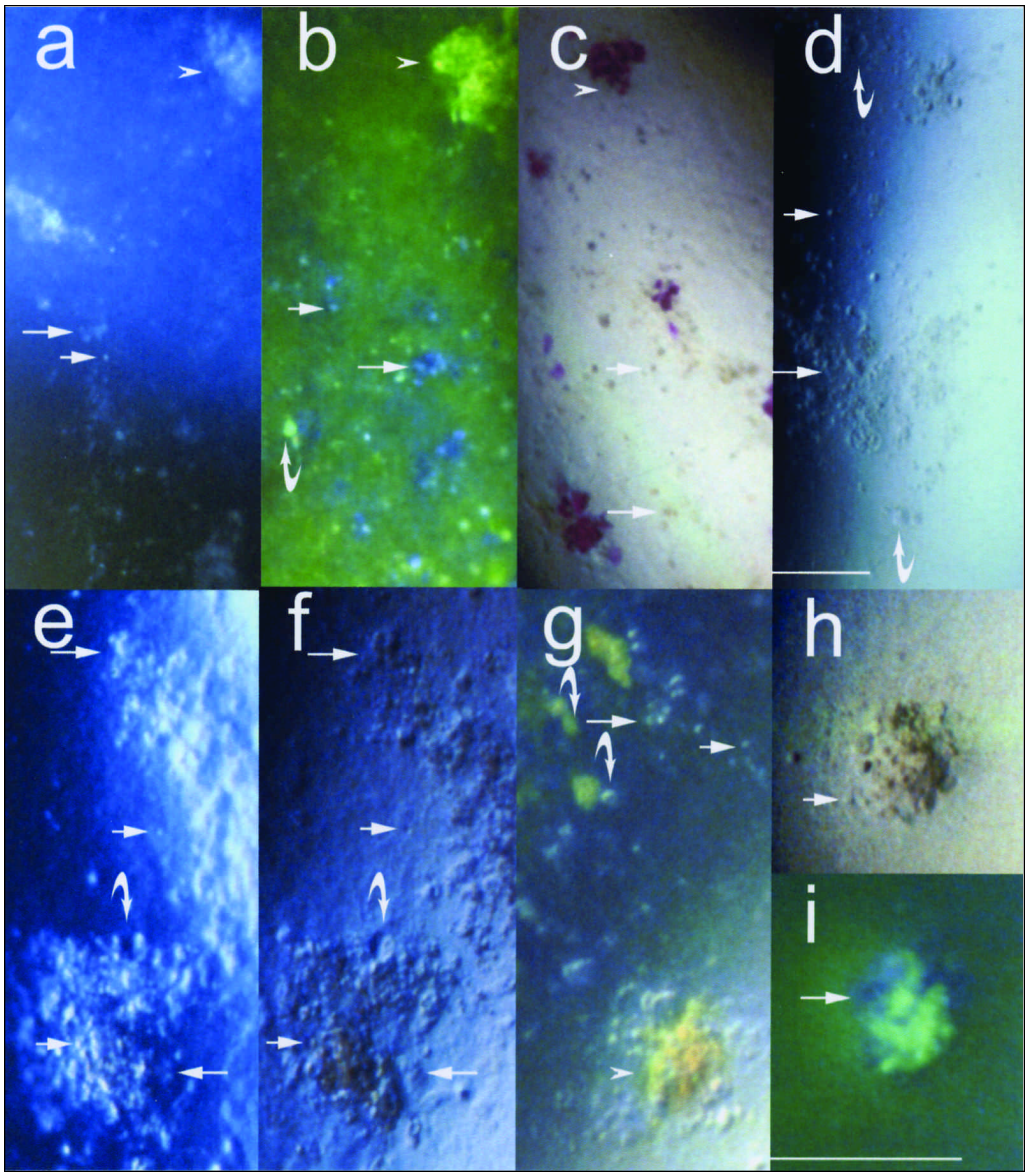

Fig. 2 - *Examples of corneal epithelial changes captured in three atypical cases and one typical case of Thygeson's superficial punctate keratitis (TSPK). (Fluorescein sodium 1%, rose bengal 1%, bars 200 µm.)* **(a-g)** *Atypical cases.* **(a-c)** *Three survey photographs taken in the same cornea show many abnormal cells spread over the surface, individually (short arrows), in groups (long arrows), or aggregated in larger lesions (arrowheads). The abnormal cells are light reflecting on focal illumination* **(a, b)**, *and optically dense on retroillumination* **(c)**. *Staining with fluorescein sodium* **(b)**, *captured immediately after the application of the dye, shows surface elevations (dark) in areas of grouped abnormal cells (long arrow), and some green stained cysts (bowed arrow). The larger lesion shows yellow staining of surface debris. There is no diffusion of the dye into the tissues. Rose bengal* **(c)** *stains surface debris red. (Patient 14.)* **(d)** *This cornea shows many abnormal cells (short arrow) arranged in dendritiform patterns, and many cysts (bowed arrows). At this occasion, there was no surface staining except for occasional cysts. (Patient 16; c.f.* **(g)**.*)* **(e-f)** *Agglomerates of abnormal cells captured in the same area. The individual (short arrows) and grouped (long arrows) cells are light reflecting on focal illumination* **(e)**, *and optically dense on retroillumination* **(f)**. *The lesion shows a broken pattern. The arrows are placed in corresponding locations. (Patient 15.)* **(g)** *In Patient 16 (shown also in* **(d)**), *the corneal epithelium showed one larger lesion (arrowhead) on one occasion. Fluorescein sodium staining, captured shortly after the application of the dye, reveals surface debris (yellow staining). The epithelium outside the lesion shows individual (short arrow) or grouped (long arrow) abnormal cells, and stained or unstained cysts (bowed arrows).* **(h, i)** *Lesion present in a case of a typical TSPK. Abnormal cells (short arrow) are visible on retroillumination* **(h)**. *Fluorescein sodium staining, captured a while after the application of the dye, reveals penetration of fluid into limited spaces (green) within the lesion, and surface elevations at its edges (dark, long arrow). There is no diffusion into the surrounding epithelium. (Patient 13, filial granddaughter of Patient 16, shown in* **(d)** *and* **(g)**).

diffusion. Comparison of light-reflecting properties and the green fluorescein staining of one and the same lesion showed a strong similarity of patterns.

Staining with rose bengal. Only a few occasional dots stained red. Larger lesions showed a broken red staining pattern.

Additional findings. Cystic changes appearing as vesicles of about 25 to 45 µm in diameter were captured in eight corneae, five with typical, and all three with atypical TSPK; the cysts were abundant in no. 16.

DISCUSSION

The present patients showed the same clinical features as reported in the literature, including absence of a consistent association with systemic diseases. Exceptional was the occurrence of TSPK in two members of the same family, because the disease has never been reported in relatives, or close contacts. Apparently, the grandmother and her filial granddaughter developed symptoms shortly apart in time; this might be interpreted as a coincidence, a transmission of infection between two individuals, or an exposure to an infectious agent of two individuals sharing some important genetic factors.

With the slit lamp, the hallmark of TSPK is coarse whitish epithelial lesions situated within a seemingly normal corneal epithelium. The diagnosis is more difficult in patients with clinical features compatible with TSPK, yet lacking this sign (atypical cases) (1, 7, 13). Coarse lesions confirming TSPK diagnosis might be observed occasionally during the course of the disease, but some patients might show little propensity to convert to the typical picture (for example, Patient 16).

By the present method, the elementary feature of TSPK was rounded cells of about 10 µm in diameter, abnormal to the corneal epithelium. The typical and atypical TSPK cases seemed to differ only in the distribution of these cells. In typical cases, the abnormal cells were predominantly accumulated in coarse lesions, and only few, easily overlooked with the slit lamp, were present outside them; in atypical cases, they were spread over the cornea, often in small aggregates, in combination with (nos. 14 and 15) or in the absence of (no. 16) coarse lesions.

Coarse lesions showed signs of cell destruction, or necrosis, manifesting as patches of light-reflecting surface material staining yellow with fluorescein sodium and/or red with rose bengal. The circumscript green staining with fluorescein sodium, revealing (semi) cystic spaces (22), seemed due to penetration of stained tear fluid below the surface debris. The absence of a further diffusion into the tissues implied participation of reparative forces aiming at preservation of surface integrity. Outside coarse lesions, the abnormal cells were clearly located below the superficial layer(s), which appeared well preserved. There was no significant surface staining, except for micropunctate fluorescein sodium (green) in iatrogenic damage (23) (nos. 14-16); the volume increase in areas containing grouped abnormal cells, manifesting as surface elevations (dark holes in the green stained tear film), was well sustained by the surface. The exact position in depth of the abnormal cells versus the epithelial basal membrane, and the superficial stroma, could not be estimated because of lack of reference points. The paucity of subepithelial opacities, however, and their mild and transient nature, indicated that the abnormal cells were located above that level. Cystic changes, captured in eight patients, were a sign of a concurrent edematous propensity.

The morphology seemed to reflect ongoing action of an (unknown) noxious agent targeted at the deeper epithelial layers. Apparently, the coarse lesions represented areas of major attack resulting in cell necrosis. The absence, or paucity, of coarse lesions in atypical cases implied that the elimination of the abnormal cells also occurred inconspicuously, probably by successive transportation to the surface from which they were shed. The reasons for the uneven distribution of TSPK epithelial changes remain unknown.

There are only a few histologic studies for comparison. Scraping of epithelial lesions in four cases showed slightly abnormal cells with vacuolated cytoplasm (6); material obtained in seven TSPK patients by lifting out typical lesions of the epithelium without scraping showed a mixture of necrosed cells, normal epithelial cells, and lymphocytes (9); a study, performed in 10 patients by the method of corneal replicas (24), reported the presence of rounded and swollen epithelial cells, and confluent degenerated ones (20). The results of different methods, however, are difficult to compare because the replicas concerned on-

ly the superficial layers stripped off via colloidine membrane. In areas outside typical lesions, the corneal replicas have shown edematous superficial epithelial cells (20); histologic examinations concerning the whole epithelial thickness in these areas seem missing.

The *in vivo* captured abnormal cells resembled inflammatory cells adhering to the Descemet's membrane in anterior uveitis (Fig. 1). They also resembled abnormal cells present in subepithelial opacities developing as sequelae of virus infections (25), and presumed to represent invading inflammatory ones; the few published histologic examinations concerning subepithelial opacities (caused by Ad8 infections) have shown lymphocytes (26) and histocytes (27). Despite the resemblances, interpretation of the present findings must be cautious, because damaged epithelial cells would appear similar.

The nature of TSPK causative agent remains obscure. A possible virus has been defying identification, and the present attempts only added further negative laboratory test results. Within limits of the used method, TSPK morphology diverges from epithelial damage caused by HSV1 and VZV viruses, mainly by the absence of clearly swollen epithelial cells protruding into the tear film, the absence of surface disruptions, and the absence of surface erosions (only HSV1). TSPK typical lesions have not been observed in HSV1 and VZV, and vice versa. In contrast, there is a strong morphologic similarity between TSPK and Ad8 caused epithelial changes appearing on day 5, and later, after the onset of symptoms (19). Such similarity is puzzling because it implies similar mechanisms working both in an apparently not contagious disease (TSPK), and a highly contagious one caused by a known virus (Ad8). A sure interpretation is hampered by the limited set of responses the cornea is provided with, and by the lack of knowledge on the exact nature of the abnormal cells, i.e., invading inflammatory cells, unspecific damage, or incipient virus cytopathic effect (CPE). At the same time, the conspicuous absence in both diseases of a clearly discernible virus CPE suggests that their morphology might be an expression of an unspecific or immunologic reaction. Suggestive of an immunologically mediated injury is the extreme effectiveness of topical steroids in eliminating TSPK signs and symptoms, and the recurrence of TSPK after the treatment is stopped. This point cannot be elucidated during the acute phase of virus infections because of the risk of promoting virus replication. Their sequelae (subepithelial opacities), however, show the same response to topical steroids as TSPK. Ad8 is a well-known example.

Subepithelial opacities is a feature TSPK shares with virus infections. In TSPK, an antiviral drug (iduridine) has been suspected as a cause (3, 6, 7), but they were reported also in untreated patients (1, 8). Of the present patients, 5/16 occasionally showed one or two fine homogenous opacities from which no informative photographs were obtained. According to the literature, however, the severity of such opacities shows large variations, and associated scarring has been reported (28, 29). In Ad8 infections, a similar variability studied during an outbreak seemed at least in part determined by the condition of the immune status of the host (30).

The TSPK causative agent might be a latent virus, which might or might not be located in the cornea. Both intra- and extracorneal sources of a noxious agent would be well compatible with the morphologic and clinical features of the disease, including recurrences after epithelial removal by scraping (3). Recurrences after removal of anterior stromal layers by photorefractive keratectomy (31) make perhaps a corneal location uncertain. The present findings show that the epithelial involvement in TSPK is more widespread over the corneal surface than suspected with the slit lamp. It is possible that TSPK morphology reflects an immunologically mediated injury.

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