Corneal surface changes in keratoconjunctivitis sicca. Part II: the mucus component. A non-contact photomicrographic *in vivo* study in the human cornea

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Abstract

Purpose Description of mucus on the corneal surface and in the precorneal tear film in keratoconjunctivitis sicca (KCS).

Methods In all, 24 patients with KCS examined with slit lamp and by non-contact photomicrography.

Results Material interpreted as mucus seemed to exist in three varieties: one optically dense, light reflecting, and with definite forms (fine threads, variously thick and long strands, sheet-like structures); one appearing as small clumps or patches of light-reflecting material adhering to the corneal surface; and one amorphous. All were present either *per se*, or in various combinations, with or without adherent cell debris. The mucus attached to abnormal (stainable) corneal surface cells.

Conclusions The formed material strongly resembles formed mucus found in samples from normal conjunctival surface; the light-reflecting clumps or patches adhering to the surface are possibly of the same origin. The nature of the amorphous material is unclear. Adherence of formed mucus to the corneal surface seems to be related to the presence of abnormal (stainable) surface cells.

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Introduction

The corneal surface is covered by a tear film serving clear vision, surface protection, and its

nutrition. One of the tear film components is mucus, a group of various mucins produced by the lacrimal glands, ocular surface epithelium, and conjunctival goblet cells. As found by laser interferometry, the precorneal tear film is composed largely of mucus.¹ The precorneal tear film mucus has been proposed to exist in the form of hydrated gel bound to membrane-bound mucins on the superficial corneal epithelium (glycocalyx); this form of mucus is presumed to serve optical clarity and ocular comfort.² Mucus showing definite morphological features has been reported on the conjunctival surface. Light microscopy, with the aid of India ink particles and filter impressions,³ and scanning electron microscopy in conjunctival biopsies,⁴ have shown that the normal conjunctival surface is covered by mucus in the form of strands, sheets, and granules. This form of mucus has been suggested to serve the elimination of exfoliated cells and extraneous particles adhering to the surface, by entrapping and removing them during blinks, and by subsequently transporting them to the fornices in which they appear as 'mucous thread'. This thread has been found to consist of variously thick fibres arranged in bundles and to contain various cells and amorphous material, and suggested to function as conveyor band transporting material to be removed towards the inner canthus where it is ultimately expelled.⁵

In healthy eyes, mucus is translucent and cannot be discerned with the slit lamp. With alcian blue staining mucus, small amounts of

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fine punctuate deposits or a very thin flat coating localised peripherally has been found in one-fifth of normal corneae.⁶ Excess of mucus occurs in irritative states such as infections, foreign bodies, and KCS. In KCS, alcian blue stained punctuate and membranous mucus deposits have been found to extend across the lower part of the cornea, and further on to the bulbar conjunctiva.⁶

The aim of the present study was to investigate *in vivo* morphology of (pre) corneal surface mucus in patients with KCS because of *bona fide* aqueous tear deficiency (Part I).

Patients and methods

In all, 24 of the patients presented in Part I, Table 1 (nos. 4–27, 23 women, one man, mean age 56.9 years, range 34–76 years) were examined by the same methods as in Part I (slit-lamp observations, non-contact photomicrography, staining with fluorescein sodium 1%, and rose bengal 1%).

Results

Before staining

With the slit lamp, the precorneal tear film showed floating particles. In some corneae, light-reflecting structures seemed to adhere to the surface. Light-reflecting structures adhering to the surface were captured in the photographs (not shown).

After staining

- Optically dense material with definite forms:
 - Fine threads, apparently lying free on the surface (Figure 1a) or attached at one (Figure 1b and d) or both (Figure 1c) ends to rose bengal stained cells *in situ* overlying green stained flecks (Part I) (Figure 1d); rose bengal stained cells/cell debris were adhering to them (Figure 1c and d). Whether or not the fine threads reflected light and stained with rose bengal was beyond resolution.
 - Various thick and long light-reflecting strands, without (Figure 1e) or with (Figure 1g) attached debris. Some strands were stretched and seemed to be sticking to the surface at several points (Figure 1e), others formed complex intertwined figures or meshworks (not shown), and some seemed to be lying free on the surface (Figure 1f and g). Occasionally, some of the attached strands suddenly changed appearance after a blink. Some strands stained red with rose bengal (Figure 1f), others appeared unstained (Figure 1e).

- Sheet-like structures, lying free on the surface (Figure 1h and j) or apparently adhering to it (Figure 1i). Some showed emanating strands and rounded holes (Figure 1h and i), others appeared folded or collapsed (Figure 1j). They seemed to be light reflecting; some stained with rose bengal (Figure 1i), others did not (Figure 1h and j).
- Small patches or small clumps of light-reflecting material, adhering to the surface (Figure 1d, inset) and staining brightly with rose bengal.
- Amorphous material staining red with rose bengal (Figure 1k), sometimes containing cells debris (Figure 1m) and air bubbles. It was adhering to or enveloped by folded sheet-like structures (Figure 1j), adhering to the strands (Figure 1m) or apparently lying free on the surface (Figure 1k).
- Additional findings were rose bengal stained clumps, apparently lying free on the surface and containing various amounts of cell debris (Figure 1l), and complex figures consisting of rose bengal stained or unstained strands, light-reflecting material and cell debris; they were attached at several points to areas of green flecks located close to each other (shown elsewhere⁷).

Discussion

In the interpretation of the findings, two possible sources of artefacts had to be considered: topical treatment and the staining with fluorescein sodium and rose bengal dyes. Topical treatment did not seem to be a factor in the patients who either did not use any, or were examined at least 1 h after the last drop of a tear substitute. Fluorescein sodium has no known toxic properties.⁸ The propensity of the light-reflecting material to adhere to the corneal surface was visible before staining with rose bengal, and thus seemed to be unrelated to the toxic effect on the epithelium of the dye.⁹ Lid squeezing because of the smarting property of rose bengal dye probably resulted in mechanical displacements. Material interpreted as mucus comprised three morphological variations, one with definite forms (threads, strands, sheets), one adhering to surface in small clumps or patches, and one amorphous. The additional material involved was cell debris.

The formed material showed striking similarities to formed mucus present on normal conjunctival epithelial surface (clusters, granular sheets and strands,³ and fine and coarser mucus strands, sheets and granules⁴). The mechanisms behind the development of strands and sheets on the normal conjunctival surface are not fully understood. It has been suggested that the strands are the result of sheets rolling up at their edges,³ or that the

Figure 1 Morphology of mucus on the corneal surface in patients with keratoconjunctivitis sicca (rose bengal 1%, fluorescein sodium 1%, bars 200 μ m). Fine threads, apparently lying free on the surface (a, arrow), may attach at one (b, d, arrows) or both (c, arrows) ends to red stained cells. Some threads are covered by material stained red with rose bengal, in (c) discernible as cell debris. The minifilament in (d) shows green staining around its attachment (arrow), and a strongly light reflecting (brightly appearing) free end. Inset (d): A patch of brightly red appearing material in an area showing red stained cells. Thicker strands (e), apparently interconnected by a transparent sheet rolling up at the edges (bowed lines, arrows; cf. also (h) and (i)) show darker spots (arrowheads) suggestive of ruptured and coiled interconnecting strands; the figure appears unstained with rose bengal. Another strand (f), partly coiled and with a fringed upper end, is lying apparently free on the surface; it stains vividly with rose bengal. A further strand (g) shows adherent granular material (cell debris). The partly collapsed sheet (h) shows centrally a rounded hole; the strands emanating from its edges appear unstained, and there is only a weak red shade within the sheet. Rounded holes are visible also in another sheet (i) staining with rose bengal; the stronger staining (arrow) seems to be because of folding resulting in a double layer of the sheet. A collapsed sheet with attached (or enveloping?) red stained material and cell debris is shown in (j). A clump of red stained amorphous material (k), a clump of cemented red stained cell debris (l), and amorphous material and cell debris attached to a strand (m, arrow) seem to be lying free on the surface.

sheets are the result of the flattening of thicker strands by the upper eyelid.⁴

In vivo, the single- or double-attached minifilaments seemed to be the result of threads and strands rolling between the tarsal and corneal surfaces, detaching from the conjunctiva, at random attaching to anchored abnormal (stainable) corneal surface cells, and attaching to themselves exfoliating cells and cell debris. The bonds to anchored cells seemed to be strong enough to withstand, at least for some time, the shearing action of the lids. When captured in appropriate illumination, areas around their attachments showed green fluorescein staining indicating disruptions in the epithelial barrier. This might have been due either to mechanical forces (such as tugging on the epithelium during blinks), or to attachments to abnormal cells present in preformed areas of green flecks (Part I). Also, the small patches and clumps of optically dense material (corresponding to clusters or granulae on the normal conjunctiva^{3,4}), as well as some of the sheet-like structures apparently detached in toto from the (superior tarsal?) conjunctiva, and more complex structures resembling mucus plaques reported previously in KCS¹⁰ adhered to abnormal surface cells.

The second component captured in the present study, the amorphous material, stained with rose bengal and seemed to have an adhesive quality, as seen by its propensity to adhere to or envelop the strands, and to cement exfoliated cells/cell debris. Whether or not this apparently sticky material also adhered to abnormal cells *in situ* and promoted adherences to the surface of the formed material could not be decided by present means. It is unclear whether the amorphous material represented an excess of mucus, perhaps corresponding to amorphous material found in normal eyes in the 'mucous thread',⁵ or mucus with altered composition.

The present 24 patients, 23 (95.8%) of whom had a systemic disease, represented the more severe end of KCS, as estimated by the extent of surface changes revealed with rose bengal dye. In this condition, 'mucus excess' is regularly seen with the slit lamp. Examined on a higher magnification level, this mucus appeared to consist partly of formed conjunctival mucus released in the tear film, and partly of amorphous material the composition of which is unclear. Under normal

conditions, formed conjunctival mucus does not adhere to the corneal surface. For unclear reasons, surface adherence occurs in a variety of disease conditions including KCS. In KCS, the propensity of formed conjunctival mucus to bind to the surface seems to be related to the presence of abnormal (stainable) surface cells. It is conceivable but not proven that the amorphous material might partly function as a mediator cementing formed mucus to diseased cells, and that its dissolution might be the mechanism behind the beneficial effect of mucolytic agents on filamentary keratitis¹¹ and corneal mucus plaques.¹⁰

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