CASE REPORTS

Primary lipid keratopathy: a morphological and biochemical assessment

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Lipid keratopathy is a term applied to conditions where lipid degeneration of the cornea occurs.[1–5] There are only a few cases of primary lipid keratopathy published to date,[1–5] and all of them report the morphological evaluation of a corneal button by different methods; in some of these cases identification of the lipids was tentatively made histochemically.[2–4] To our knowledge, however, no quantitative biochemical determination of lipids has been reported in this condition. We present a case of primary lipid keratopathy diagnosed by biochemical and ultrastructural analysis of a corneal button allied to the quantitative determination of neutral lipids in the aqueous humour, cultured skin fibroblasts, leucocytes, and blood plasma.

Case report

A 57-year-old woman exhibited a progressive golden yellow infiltrate in the temporal cornea of both eyes over a 12 year period. This infiltrate proceeded from the perilimbic areas and occupied the entire thickness of the stroma, being more dense in its posterior half and extending axially to cover the pupil (Fig 1a, b). At the end of the 12 year period, a few deep blood vessels, not present in the initial stage of the disease, reached the lesion from the clear adjacent corneoscleral limbus. Its central margins glistened, with many crystals present only in the posterior stroma; the overlying epithelium was intact and did not stain with fluorescein. In its initial stage (in 1980) the visual acuity was 20/20 in both eyes and worsened progressively until at the end stage of the disease VA was 20/200 (left) and 20/80 (right); the lens, the ocular fundi, and intraocular pressure were normal. There was no previous history of ocular disease or trauma and family history was irrelevant.

Determination of serum lipids revealed no alterations to chylomicrons, β, pre-β and α lipoproteins, throughout the 12 year period.

A penetrating keratoplasty was performed on the left eye. Postoperative recovery was normal with no evidence of recurrence at the 2 year follow up and VA recovered to 20/30.

The corneal button was sectioned into three parts to be used for electron microscopy, histochemical stainings, and analysis of lipids by high performance thin layer chromatography (HPTLC).

Ultra-thin sections demonstrated the presence of multiple needle-like cholesterol clefts dispersed throughout the corneal stroma. Lipid droplets were seen as grey, black, or clear vacuoles present in fibroblasts and histiocytes (Fig 2). Histochemical staining (oil red O and Sudan black B) indicated deposits of neutral fats and phospholipids. Lipids of the cornea, aqueous humour, cultured skin fibroblasts, leucocytes, and blood plasma from the patient and from controls (corneas and aqueous humour from donors at S João Hospital Eye Bank) were analysed.[6] Lipid separation was achieved by HPTLC; identification of the lipid spots was

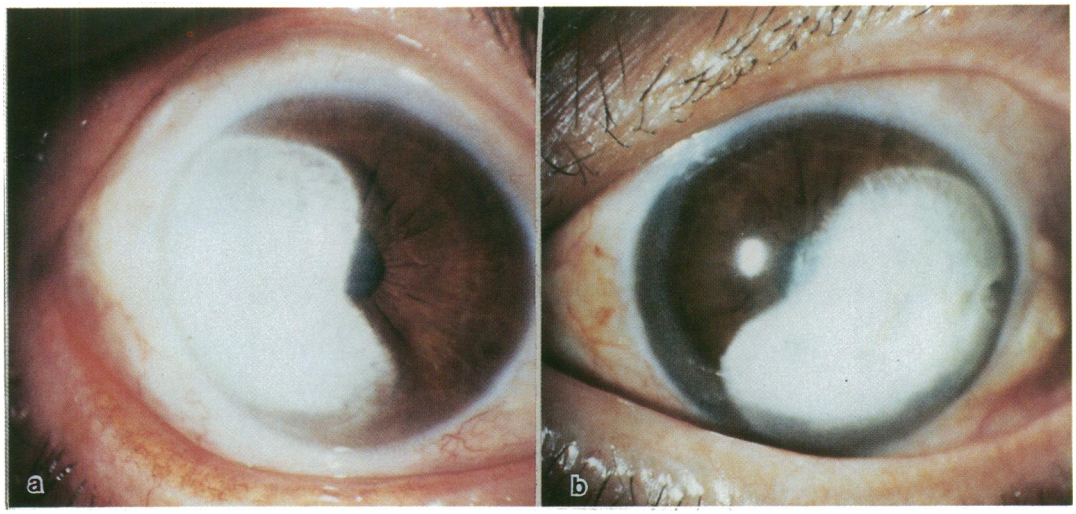

Figure 1 (a) Right cornea with temporal lipid infiltration extending into the visual axis. (b) Left cornea showing symmetrical lipid infiltrates (12 year follow up).

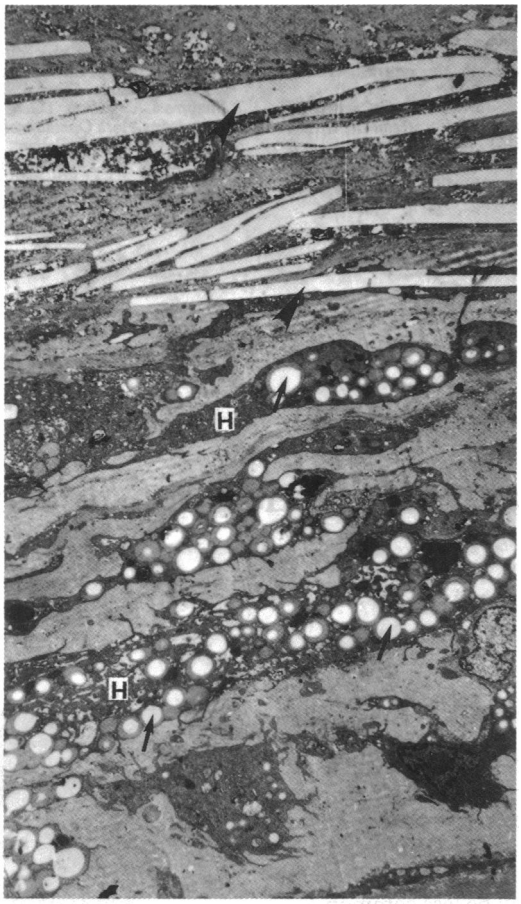

Figure 2 Electron micrograph of the corneal stroma showing histiocytes (H) with lipid vacuoles (arrows); extracellular cholesterol clefts (arrowhead) can be seen. ×3050.

done by comparison with appropriate standards and the lipid concentration was determined by densitometry.

The most striking biochemical finding was the increase of cholesterol and sphingomyelin concentrations in the cornea of the patient, being 6–11 times and six times respectively higher than in controls (Table 1). Only 12% of the cholesterol from the patient cornea was esterified in contrast to 52–68% found in controls. Since the concentration of the cholesteryl esters was similar in the cornea of the patient and the controls this gives a decrease in the cholesteryl esters/cholesterol ratio (8–16 times) in the cornea of the patient. In the aqueous humour no significant differences were found in the levels of cholesterol and cholesteryl esters between the patient and controls (Table 2). The concentration of neutral lipids in cultured skin fibroblasts and leucocytes (Table 1) and in the blood plasma (Table 2) were also determined. The activity of sphingomyelinase was also determined in cultured skin fibroblasts from the patient (108 nmol/h/mg protein; reference values: 82–216 nmol/h/mg protein, n=3).

Table 1 Quantitative distribution of neutral lipids in the cornea, cultured skin fibroblasts, and leucocytes

	Cornea			*Fibroblasts*		*Leucocytes*	
	Patient	*Control*	*Control*	*Patient*	*Control*	*Patient*	*Control*
	µg/100 mg fresh weight						
CE	64 (12%)[b]	92 (68%)[b]	83 (52%)[b]	8[a] (30%)[b]	7[b] (28%)[b]	18[a] (51%)[b]	13 (54%)[b]
C	487	44	78	19[a]	18[a]	17[a]	11
PE	31	28	18	35[a]	36	19	8
LacCer	nd	nd	nd	nd	nd	32	18
PC	89	48	24	33[a]	15	8	22
Sph	108	19	18	13[a]	10	8	11
Sph/C	0·22	0·43	0·23	0·68	0·56	0·47	1·00
CE/C	0·13	2·09	1·06	0·42	0·39	1·06	1·18

[a]Mean value (n=2).
[b]Percent of esterified cholesterol.
nd=not detected. CE=cholesteryl esters; C=cholesterol; PE=phosphatidylethanolamine; LacCer=lactosylceramide; PC=phosphatidylcholine; Sph=sphingomyelin.

Table 2 Quantitative distribution of the neutral lipids in the aqueous humour and blood plasma

	Aqueous humour		*Plasma*		
	Patient	*Control*	*Patient*	*Control*	*Control*
	mg/100 ml				
CE	4·2 (63%)[a]	3·8 (57%)[a]	71 (70%)[a]	67 (68%)[a]	51 (57%)[a]
C	2·5	3·0	30	32	38
GluCer	nd	nd	1·7	1·2	3·0
PE	nd	nd	3·6	3·3	8·1
PC	nd	nd	12	10	16
Sph	nd	nd	9·0	10	9·6
Sph/C			0·30	0·31	0·25
CE/C	1·68	1·27	2·37	2·09	1·34

[a]Percent of esterified cholesterol.
nd=not detected. GluCer=glucosylceramide.

Comment

The patient reported herein had a bilateral and symmetrical lipid keratopathy unrelated to previous vascularisation, inflammatory alterations or systemic lipid or lipoprotein disorders, and normal serum values which allowed the diagnosis of primary lipid keratopathy. Besides the histopathological features seen in this case, which are similar to previous reports,[1-5] the biochemical determinations performed in the cornea, aqueous humour, cultured skin fibroblasts, and leucocytes provided for the first time a more complete characterisation of the lipid infiltrates involved in this disorder.

Allowing for the fact that the accumulation of lipids in the cornea in the absence of vascularisation has been suggested to originate from the aqueous humour,[7] the comparison of blood plasma lipids and those present in the aqueous humour is important for the differential diagnosis of a local versus a systemic disorder. In this case, however, the cholesterol content of the aqueous humour was similar to the control values thus excluding this hypothesis. The cornea of our patient showed an increased accumulation of cholesterol (6–11 times) and sphingomyelin (six times) compared with the controls; however, similar increases in the reticuloendothelial system of the spleen, lymph nodes, and bone marrow are also a prominent finding in Niemann-Pick group of diseases.[8] The differential diagnosis was settled by quantification of the activity of sphingomyelinase in the cultured skin fibroblasts of the patient which showed values within the range of controls.

The overall observations support a disturbance in cholesterol and/or sphingomyelin metabolism restricted to the cornea. We suggest that the accumulation of cholesterol in the cornea of the patient might have been caused by an increase in lipid synthesis or by a decrease in esterification of cholesterol. Further studies on the cholesterol esterification process will be an important step for a better understanding of this condition.

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Serious corneal complication of 5-fluorouracil

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The success of filtering surgery in eyes with a poor prognosis can be improved by 5-fluorouracil (5-FU).[1-5] 5-FU is known to be potentially toxic to corneal epithelium and epithelial defects have been reported.[2 6] It has been suggested that the doses of 5-FU originally recommended were excessive and that with lower doses corneal problems may be less common.[7]

Case report

This case reports an adverse effect of 5-FU occurring in the left eye of an 81-year-old man who underwent a fornix based trabeculectomy to lower raised intraocular pressure uncontrolled by medical treatment. The patient had a 15 year history of open angle glaucoma, and the left eye had previously undergone an extracapsular cataract extraction (corneal section) with implantation of a posterior chamber lens. Before surgery both eyes had mild idiopathic band keratopathy (Fig 1) for several years, with intact overlying epithelium. The patient was diabetic and preoperatively he was receiving topical timolol and pilocarpine in the left eye. At surgery 0·2 ml (5 mg) of undiluted 5-FU was injected subconjunctivally in the inferior fornix with a further 5 mg of undiluted 5-FU the following day. At his first outpatient review 9 days following surgery a central corneal epithelial defect was noted and no further 5-FU was given (Fig 2).

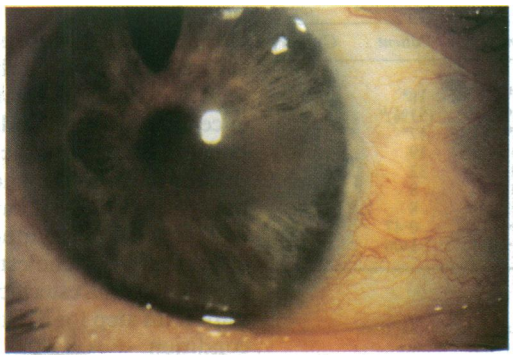

Figure 1 Band keratopathy in right eye of patient. The band keratopathy in the left eye undergoing trabeculectomy with 5-FU was identical to the appearance of the right eye preoperatively.

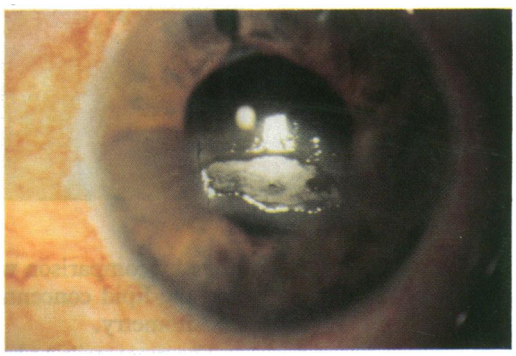

Figure 2 Corneal epithelial defect noted at 9 days following surgery in left eye.

The epithelial defect failed to heal despite topical treatment associated with padding. Because of discomfort due to the epithelial defect, a bandage contact lens was inserted into the eye 4 months later. This made the eye comfortable but no healing of the ulcer occurred. He subsequently presented with reduced visual acuity in the eye, associated with intense pain. Examination revealed the presence of a deep ulcer with a corneal abscess and hypopyon (Fig 3).

On intensive treatment with topical cefuroxime and gentamicin the infection was

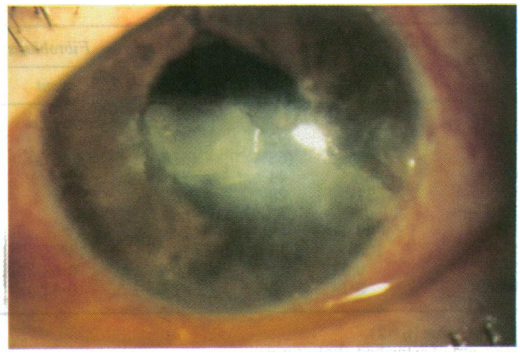

Figure 3 Corneal abscess in the left eye at 4 months postoperatively.

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