Extrinsic and idiopathic vernal keratoconjunctivitis? Two cases with dissimilar immunopathology

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SUMMARY Two clinically similar cases of vernal keratoconjunctivitis with dissimilar immunological data are reported. One patient had strikingly elevated IgE levels in both serum and tears, and his tear fluid contained specific IgE antibodies to a number of allergens. Conjunctival scrapings and peripheral blood samples showed marked eosinophilic reactions. The other patient showed normal values for tear and serum IgE; no IgE type antibodies to allergens were detected; and no local or systemic eosinophilic reactions were observed. The immunopathogenesis of these cases is discussed.

Vernal keratoconjunctivitis (VKC) is an inflammatory disorder of the conjunctival mucosa. The main symptoms are itching, photophobia, intense tearing, and a mucoid discharge that may stick the eyelashes together in bundles. On examination the most characteristic and persistent feature is a papillary hypertrophy of the upper tarsal conjunctiva ('cobblestones'). The cornea may be involved to varying degrees from a superficial punctate keratitis to indolent corneal ulceration.

The disorder is usually considered of allergic aetiology with mainly IgE intervention.¹ Elevated levels of IgE in serum and tears of the patients have been reported,^{2,3} and conjunctival scrapings reveal usually a considerable number of eosinophilic leucocytes.

In Israel the disease is endemic, with onset in early childhood, and often the symptoms fade and disappear towards adolescence. Most of the patients show strikingly increased tear IgE, but in more than 20% IgE levels are persistently normal.³ We describe here one patient of each of these groups.

Case reports

CASE 1

The patient was a boy born in 1975. As an infant he suffered from spastic bronchitis. Since 1977 he had been treated for VKC, initially with dexamethasone and hydrocortisone-neomycin ointment. In June 1979

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he was admitted to hospital with a serious aggravation—itching, severe photophobia, tearing, and red eyes. On examination he had hyperaemic sloppy conjunctivae, giant papillary hypertrophy of the upper tarsus, severe superficial keratitis with an area of considerable epithelial loss (right eye), and thick mucous discharge; the right eye seemed more seriously attacked than the left. Treatment with 2% sodium cromoglycate 4 times a day, and, when needed, 20% acetylcystein, apparently had a beneficial effect. Since then the patient has had persistent low-grade inflammation with 3 episodes of moderate aggravation, always more severe in the right than the left eye (December 1981, November 1982, May 1983).

CASE 2

The patient was a boy born in 1970. He had a history of spastic bronchitis and frequent rhinitis during 1972-6, and presented at the clinic in 1981 owing to prolonged complaints of itching, photophobia, excess tearing, and red eyes. On examination he had wet, hyperaemic eyes, with prominent papillary hypertrophy of the upper tarsal conjunctivae ('cobblestones') and ropy mucoid discharge. There was partial ptosis of both eyes, with superficial keratitis of the right and corneal ulceration of the left eye (1×2 mm). The giant papillae were treated with cryotherapy in addition to topical antibiotics, corticosteroids, and 2% sodium cromoglycate. The ulcer healed slowly. The boy was observed and treated in our clinic for 18 months.

Table 1 Prick tests to allergens (size of the induration zones (mm) after 15 min)

Allergen	Case 1	Case 2
House mite	9×7	0
House dust	5×5	0
Cat fur	4×5	3×3
Dog hair	4×4	0
Weed pollen	5×5	0
Chicken feathers	0	2×2
<i>Aspergillus fumigatus</i>	0	4×4
Milk, whole egg, grass pollen, <i>Penicillium notatum</i>	0	0
Histamine (control)	7×8	9.5×10.5

LABORATORY INVESTIGATIONS

Blood and tear samples were obtained periodically. The tear fluid was collected in microtubes from the lower fornix.⁴ From case 1, 9 blood samples and 16 tear samples from the right and 14 from the left eye were examined during 3 years. From case 2, 7 blood samples and 7 tear samples from each eye were collected during a period of 1½ years.

Serum albumin (HSA) was assayed by radial immunodiffusion.⁴ Tear and serum IgE levels were determined by solid-phase radioimmunoassay (PRIST, Pharmacia Ltd, Uppsala, Sweden). The limit for sensitivity was 0.5 IU/ml. Specific IgE antibodies to a series of allergens were assayed by the radioallergosorbent technique (RAST, Pharmacia Ltd). Results are expressed as percentage of radioactivity obtained with the commercial A grade standard (=100%). Fetal calf serum and serum from human cord blood were used as negative controls (2.0–4.5% of A grade).

Conjunctival scrapings and peripheral blood smears were stained with Giemsa's stain. Prick testing of the skin was performed with a set of 11 allergen extracts (Bencard Ltd, Brentford, UK).

Results

Prick tests. Table 1 shows that both patients reacted to a number of allergen extracts.

Table 2 Two cases of vernal keratoconjunctivitis

	<i>Eosinophils</i>		<i>Tear HSA</i> (mg/dl)	<i>IgE (IU/ml)</i>					
	<i>Conjunctival scraping per HPF</i>	<i>Blood % of WBC</i>	<i>Mean (±SD)</i>	<i>Serum</i>	<i>Tears</i>				
				<i>GM (+1SD)</i>	<i>Range</i>	<i>GM (+1SD)</i>			<i>Range</i>
						<i>OD</i>	<i>OS</i>		
Case 1	1–2	11–24	253.5 (±159.8)	990.1 (1390.3)	620.0–1575.0	127.4 (292.5)	93.8 (212.9)	14.8–580.0	
Case 2	0	1–2	409.1 (±459.3)	10.9 (26.4)	2.5–31.5	<0.5	<0.5	<0.5	

HPF=high-power field. WBC=white blood cells. OD=right eye. OS=left eye. GM=geometric mean. Mean tear HSA of tears from healthy eyes was 17.7 mg/dl.⁴ GM of tear IgE from healthy eyes was 0.92 IU/ml, and the highest level of tear IgE observed among the healthy controls was 6.6 IU/ml.³ (SI conversion: mg/dl×10=mg/l.)

Eosinophilic leucocytes. For case 1 an increased number of eosinophils were demonstrated in conjunctival scrapings and peripheral blood (total leucocytes=11–13×10⁹/l). In case 2 no eosinophilic leucocytes could be demonstrated in conjunctival scrapings, and 1–2% of leucocytes of the blood were eosinophils.

Tear HSA. The mean of tear HSA was for case 1 253.5±159.8 (±SD) and for case 2 409.1±459.3 mg/dl (Table 2). Tears from healthy controls contain 17.7±12.6 mg/dl HSA.⁴ (SI conversion: mg/dl×10=mg/l.)

Tear and serum IgE. The geometrical mean (GM) of serum IgE was 990.1 for case 1 and 10.9 IU/ml for case 2 (Table 2). GM for tear IgE for case 1 was 127.4 IU/ml for the right and 93.8 IU/ml for the left eye, but in tears from case 2 we could never demonstrate IgE (<0.5 IU/ml).

Specific IgE type antibodies. Table 3 shows the results of RAST for 17 allergens. The limit for a positive reaction was arbitrarily set at 10%, approximately the level obtained with the D grade standard. Tears of case 1 reacted with house mites and house dust, the 2 grasses, 2 moulds, and chicken feathers. The examinations were performed with serum samples which contained several times more IgE than the corresponding tear samples; in spite of this none of the above reactions were stronger with serum than with tears, and several were significantly weaker. Positive reactions were also obtained with the serum, but not with tears, to 2 food allergens (egg white and wheat).

With tears and serum from case 2 no significant reactions to any of the tested allergens were obtained.

Discussion

The 2 cases described are representative of 2 groups of VKC patients with dissimilar immunological data. About 80% of patients in our care show elevated tear IgE (>10 IU/ml and sometimes even >1000 IU/ml³) and marked eosinophilic reaction in the conjunctival

Table 3 Specific IgE antibodies (%) of tears (T) and serum (S)

Allergens	Case 1			Case 2	
	T	S	T/S	T	S
1 Dermatophagoides (house mites)	124.5	124.8	1.00	3.7	4.2
2 House dust	66.9	78.5	0.85	4.1	4.6
3 Cat epithelium	7.1	5.4		4.6	4.1
4 Dog epithelium	6.0	5.7		5.1	5.3
5 <i>Blattella germanica</i> (cockroach)	7.6	9.1		1.8	2.7
6 Vernal grass	12.6	8.1		3.0	3.4
7 Bermuda grass	51.0	22.8	2.24	4.3	4.5
8 <i>Cladosporium herbarum</i>	21.1	16.8	1.26	4.7	5.2
9 Olive	9.8	3.7		2.6	2.5
10 Egg white	5.3	12.5		3.5	4.3
11 Wheat	8.1	15.8		4.9	5.9
12 Orange	4.0	9.3		2.6	2.7
13 Milk (cow)	4.9	5.0		4.5	4.9
14 <i>Ambrosia elatior</i>	3.4	6.5		3.3	3.5
15 <i>Mucor racemosus</i>	18.8	8.8		4.0	3.7
16 Chicken feathers	41.2	24.2	1.70	3.5	3.6
17 Fish	3.4	3.8		1.7	2.0

Specific IgE values are indicated as a percentage of radioactivity obtained with the standard A of the RAST kit. For human cord serum and fetal calf serum 2.0–4.4% were obtained with all allergens.

The examinations of case 1 were performed with different specimens of tears (both eyes) and serum collected on the same day. For allergens 1–9 the total IgE content was: T=285 IU/ml; S=950 IU/ml; T/S=0.30. For allergens 10–14: T=73 IU/ml; S=645 IU/ml; T/S=0.11. For allergens 15–17: T=364 IU/ml; S=1065 IU/ml; T/S=0.34. For case 2 pools of tears containing <0.5 IU/ml and serum containing 17.7 IU/ml were used.

tissue, whereas about 20% of the patients show persistently normal tear IgE levels (see footnote, Table 2) and lack of eosinophilic reactions. Clinically we cannot distinguish between these groups. The 2 cases reported here were both typical for VKC. Case 2 was complicated by corneal ulceration, an infrequent sequela of epithelial damage, and his tear HSA levels were higher than for case 1 (Table 2). Tear HSA is a measure of vascular leakage but depends also on the tear flow.

Patients with bronchial asthma are usually divided into groups with high and low serum IgE ('extrinsic' and idiopathic ('intrinsic') respectively).⁵ However, in asthma patients it is usually not possible to assess the levels of IgE in the local secretion in a way comparable to the tear examinations. As possible causes of idiopathic asthma autoantibodies to IgE receptors or to IgE type immunoglobulin have been proposed.^{6,7} These hypotheses might be proposed for low IgE VKC, but further studies are needed to verify them. It is of interest that in spite of the persistently low serum and tear IgE case 2 showed some moderately positive prick tests; however, none of the RAST examinations revealed specific IgE antibodies in serum and tears.

For case 1 some (but not all) of the positive prick tests were confirmed by the RAST technique. It is of interest that for allergens for which both serum and tears were positive >10% in RAST (house mites, house dust, Bermuda grass, *Cladosporium herbarum*,

and chicken feathers) the tear/serum ratio for the strength of the RAST reaction exceeded by far the corresponding ratio for total IgE. It has been demonstrated that assays of the RAST type are not strictly quantitative.⁸ In spite of this the results shown in Table 3 for case 1 seem impressive. Serum samples which contained 3 times more IgE than the corresponding tear samples reacted only equally to or much more weakly than the tear samples with several of the allergens, although the assays were performed simultaneously and with the same batch of allergen discs. This may indicate that the tear IgE antibodies were essentially a product of local synthesis.⁹ Pollen-specific antibodies of the IgE type have been demonstrated by others in tears of VKC patients,^{10,11} but these authors did not look for IgE antibodies to other common allergens. Our results indicate that common allergens of wide ecological distribution may sensitise the tissue of the outer eye.

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