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Immunohistochemical characterization of epithelial cells in human lacrimal glands

II. Inflammatory and neoplastic lesions of lacrimal glands

Carl Michael Wilk[1], **Nadarajah Vigneswaran**[2], **Angelika Heese**[2], **Otto Paul Hornstein**[2], **and Gottfried O.H. Naumann**[1]

[1] Augenklinik mit Poliklinik der Universität Erlangen-Nürnberg, Schwabachanlage 6, D-8520 Erlangen, Federal Republic of Germany
[2] Dermatologische Klinik und Poliklinik der Universität Erlangen-Nürnberg, Hartmannstrasse 14, D-8520 Erlangen, Federal Republic of Germany

Abstract. The distribution of cytokeratins (CK), actin, lactoferrin (Lf), lysozyme (Ly), vimentin and S-100 protein was immunohistochemically investigated in paraffin-embedded specimens of five inflammatory and five neoplastic lesions of lacrimal glands (LGs). Atrophic acini in dacryoadenitis reacted with antibodies (ABs) KL1 and Pkk1 (CK 7, 8, 17, 18) in a manner similar to ducts. Apart from myoepithelial cells and some luminal-duct cells, the remaining epithelia in dacryoadenitis were negative with AB 34βE12 (CK 5). The number of AB HHF35 (actin)-positive myoepithelial cells was not altered in dacryoadenitis. Epithelia in dacryoadenitis reacted weakly but consistently with Lf while revealing weak and inconsistent staining for Ly. Vimentin was negative in epithelial cells in dacryoadenitis except in one case. S-100 protein was detected only in epithelia of inflammatory major LGs. Epimyoepithelial islands in lymphoepithelial proliferation reacted variably for CKs, Lf, Ly and vimentin and remained negative for actin and S-100. In pleomorphic adenomas, neoplastic cells showing duct-like differentiation (luminal) reacted consistently with CK 7, 8, 17, 18 and S-100 protein and inconsistently with CK 5, Lf and Ly but remained negative for actin and vimentin. Other neoplastic cells (ovoid/peripheral cells) stained consistently for CK 5, vimentin and S-100 protein and focally for CK 7, 8, 17, 18, actin, Lf and Ly. Spindle-form neoplastic cells found in the stroma exhibited vimentin and S-100 protein and, less frequently, actin. Determination of these antigens in pleomorphic LG adenomas may help to evaluate their prognosis.

Introduction

Swelling of the lacrimal gland (LG) can be inflammatory or neoplastic (lymphoid, epithelial or metastatic) in nature. The patient's history and clinical examination may help to establish a diagnosis: e.g. pleomorphic adenomas, in contrast to malignancies, usually have a long history of swelling without severe symptoms; swelling of the LG, associated with diminished basal as well as reflex tear volume, can be an expression of Sjögren's syndrome. Although CT scanning and nuclear magnetic resonance imaging give an impression of the size, formation, invasion and nature of the process with increasing sensitivity [13, 32], histopathological confirmations of these lesions are necessary to exclude malignancy and predict their future clinical behaviour [5, 6, 7, 9, 31].

In recent years immunohistochemistry has increasingly been used in ophthalmic pathology to diagnose or classify neoplasias and immunologically related diseases [11, 16, 21]. Immunodetection of cytokeratins (CKs), actin, lactoferrin (Lf), lysozyme (Ly), vimentin and S-100 protein in epithelial components of inflammatory and neoplastic salivary glands are widely used for the differential diagnosis of inflammatory and neoplastic lesions of salivary glands, to predict their clinical behaviour and to comprehend their patho-/histogenesis [2, 3, 17, 20, 25, 27, 29]. The expression patterns of these antigens in normal major and accessory LGs were reported by us in the first part of this study. As a continuation, we describe the altered distribution of these marker proteins associated with inflammatory and neoplastic changes in LGs.

Materials and methods

Formalin (10%)-fixed, paraffin-embedded surgical specimens of inflammatory ($n=5$) and neoplastic ($n=5$) LG lesions were retrieved from the files of the Eye Pathology Laboratory of the University Eye Hospital, Erlangen-Nürnberg. Table 1 delineates brief clinical and histopathological findings of the lesions. Details regarding antibodies and methods used to detect their bindings have been described in part I of this study.

Results

Histology

In chronic dacryoadenitis, there was a severe and diffuse infiltration of mononuclear cells, causing destruction of glandular parenchyma and atrophy of secretory cells. In the biopsies of cases 2 and 4, mild proliferation of ductal elements was noticed, whereas in the rest (cases 1, 3 and 5), only a few duct-like structures were found scattered among the inflammatory cells predominantly consisting of lymphocytes, plasma cells and, occasionally (cases 2 and 3), epitheloid and plurinucleated giant cells.

Similar destruction of glandular tissue, leaving a few duct-like structures without (case 6) and with (case 7) nests of epimyoepithelial cells among follicularly arranged lymphocytes, was observed in LGs showing either benign reac-

Offprint requests to: C.M. Wilk

Table 1. Clinical and histological details of the specimens

Case number	Age[a]/Sex	Type of lacrimal gland	Clinical diagnosis/reason for biopsy	Histology
1	50/F	Major	S/o lymphoma	Dacryoadenitis/non-granulomatosus
2	58/F	Major	S/o lymphoma	Granulomatosus dacryoadenitis
3	73/M	Major	S/o lymphoma	Granulomatosus dacryoadenitis
4	9 months/M	Major	S/o rhabdomyosarcoma	Dacryoadenitis/non-granulomatosus
5	77/F	Accessory	S/o conjunctival implantation cyst	Dacryoadenitis/non-granulomatosus
6	49/F	Major	S/o lymphoma	Benign reactive lymphoid hyperplasia
7	45/F	Major	S/o Sjögren's syndrome	Benign lymphoepithelial tumor
8	70/F	Major	S/o lymphoma	Non-Hodgkin's lymphoma
9	48/M	Major	S/o fibroma	Pleomorphic adenoma
10	55/F	Major	S/o lymphoma	Pleomorphic adenoma

S/o, suspected of having

[a] Age is shown in years unless otherwise indicated

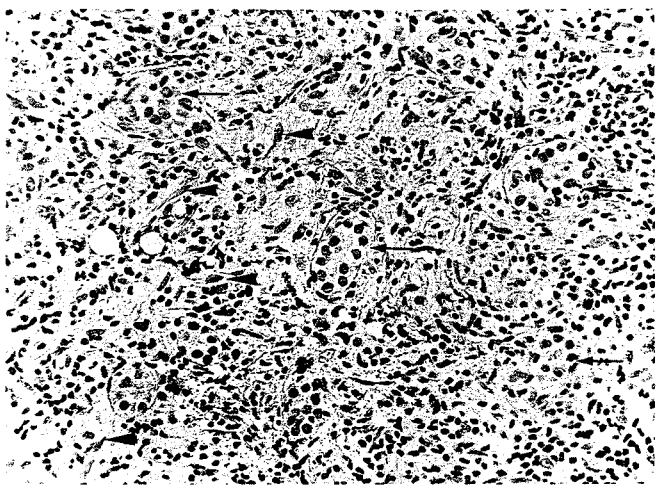

Fig. 1. Benign lymphoepithelial tumor of major lacrimal gland (case 7). Haematoxylin-eosin-stained section reveals proliferating lymphocytes and epimyoepithelial cell nests that are composed of cuboidal cells (*arrows*) forming duct-like structures and loosely arranged (*arrowhead*) polyhedral cells (original magnification, ×110)

tive lymphoid/lymphoepithelial hyperplasia or non-Hodgkin's lymphoma (Table 1). Epimyoepithelial cell nests were composed of closely packed cuboidal cells forming duct-like structures and loosely arranged polyhedral cells (Fig. 1). The polyhedral cells had prominent vesicular nuclei with an indistinct pale cytoplasma and were more often outlined by reticulin fibres; they frequently branched out from the duct-like structures, forming discrete strands in hyalin-transformed areas.

Both pleomorphic adenomas of LGs (cases 9 and 10) were mainly composed of cellular components (>50%) rather than myxoid stroma. Their neoplastic cells could be classified into four types based on morphology, localization and arrangement (Fig. 2): single- or double-layered cuboidal/columnar *luminal* cells, with an abluminal layer of round *peripheral* cells forming duct-like structures of different size, solid sheets or islands of *ovoid* cells and elongated *spindle-form* cells intermittently scattered throughout the myxoid stroma.

Immunohistology

Reaction patterns of anti-CK ABs KL1 and Pkk1 in inflammatory and neoplastic LGs was practically similar apart

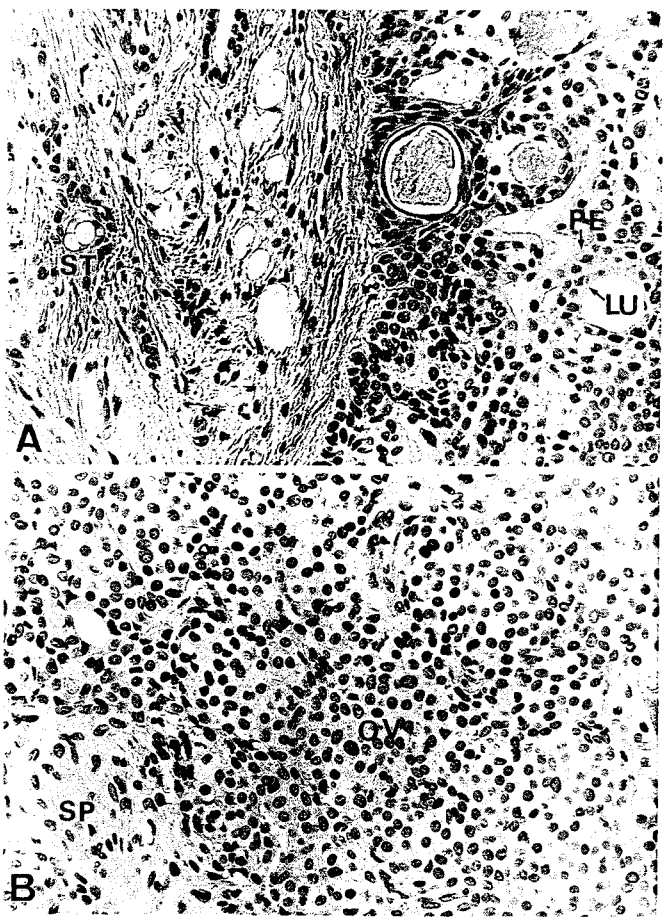

Fig. 2A, B. Different neoplastic cell types in pleomorphic lacrimal-gland adenomas (case 9 and 10, H & E-stained section). **A** *ST*, stroma; *LU*, luminal cells of duct-like structures; *PE*, peripheral cells of duct-like structures (original magnification, ×130). **B** *OV*, ovoid cells; *SP*, spindle-form cells (original magnification, ×130)

from differences in their staining intensity (Table 2). All ductal and atrophic acinar cells in both granulomatosus and non-granulomatosus dacryoadenitis were strongly and consistently reactive for both KL1 and Pkk1 (Table 2, Fig. 3). Most of the ductal and atrophic acinar cells in dacryoadenitis failed to react with the Anti-CK AB 34βE12, with the exception of the myoepithelial cells and a few isolated cells of duct-like structures revealing supranuclear cy-

Table 2. Reaction patterns of antibodies in inflammatory and neoplastic lesions of lacrimal glands

	KL1	Pkk1	34βE12	HHF35	Anti-Lf	Anti-Ly	Anti-Vimentin	Anti-S-100
Dacryoadenitis and lymphomas:								
Atrophic acinar cells	+++, 3	+++, 3	−, 0	−, 0	++, 3	+, 2	−, 0	++, 2/−, 0[a]
Ductal cells	+++, 3	+++, 3	+, 1	−, 0	++, 3	+, 3	−, 0	++, 2/−, 0[a]
Myoepithelial cells	−, 0	−, 0	+, 1	+++, 3	−, 0	−, 0	−, 0	−, 0
Epimyoepithelial islands:								
Cuboidal cells	+++, 3	++, 3	+, 1	−, 0	++, 3	++, 3	−, 0	−, 0
Polyhedral cells	−, 0	−, 0	−, 0	−, 0	++, 2	++, 2	+++, 3	−, 0
Pleomorphic adenomas:								
Luminal cells	+++, 3	+++, 3	+, 1	−, 0	++, 1	++, 1	−, 0	++, 3
Ovoid/peripheral cells	+++, 1	++, 1	+++, 3	+, 1	++, 1	++, 1	+++, 3	+++, 3
Spindle-form cells	−, 0	−, 0	−, 0	++, 1	−, 0	−, 0	+++, 3	++, 3
Myxoid stroma	−	−	−	−	+++	−	−	−

[a] Accessory lacrimal gland

Intensity of reaction: −, negative; (+), weak and focal; +, weak; ++, moderate; +++, strong
Amount of positive cells: 0, none; 1, 5%–25%; 2, 25%–50%; 3, 50%–100%

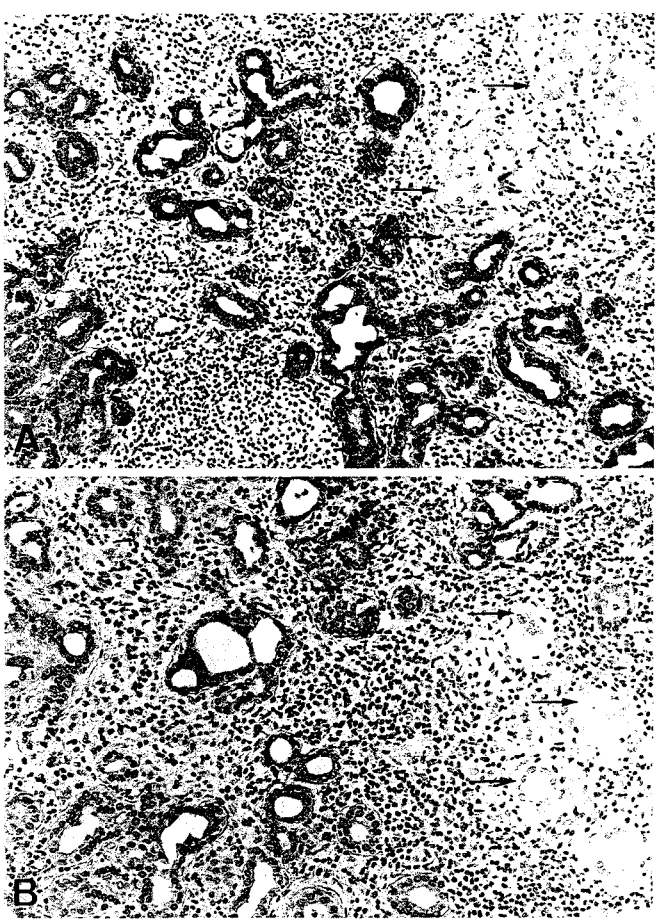

Fig. 3A, B. Chronic dacryoadenitis (granulomatosus) of major lacrimal gland (case 2). Atrophic acinar and ductal cells are strongly stained for cytokeratin; epitheloid and plurinucleated giant cells (*arrows*) are negative. **A** Reactive pattern of KL1 (original magnification, ×110). **B** Reactive pattern of Pkk1 (original magnification, ×110)

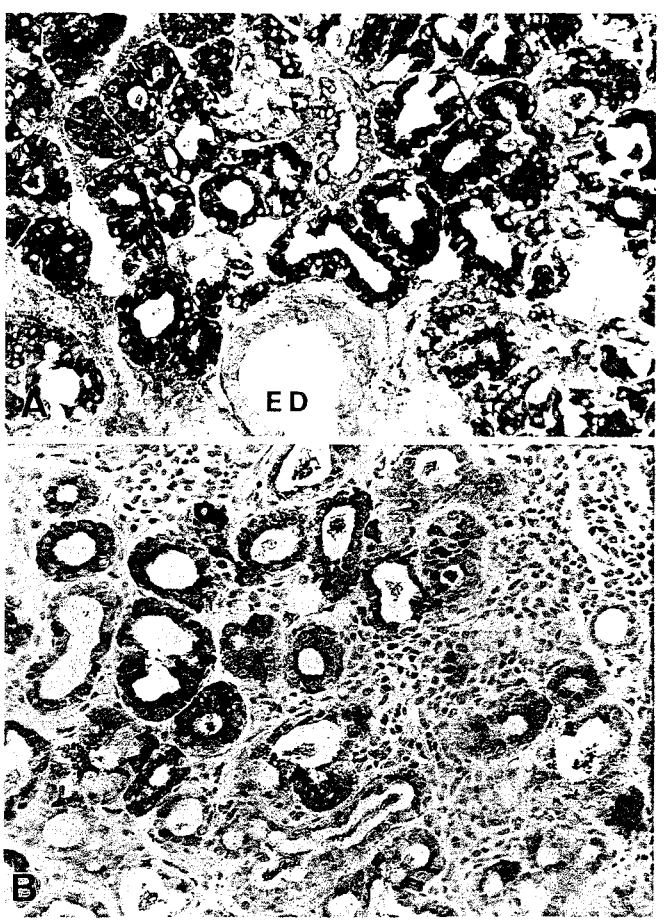

Fig. 4A, B. Dacryoadenitis (non-granulomatosus) of major lacrimal gland (case 4). **A** Intense lactoferrin staining in most of the atrophic acinar and ductal cells except for the excretory duct (*ED*) (original magnification, ×110). **B** Weak and inconsistent lysozyme positivity in a number of atrophic acinar and ductal cells (original magnification, ×110)

toplasmic immunostaining (Table 2). In contrast to normal LGs, the duct-like structures found in dacryoadenitis lacked the 34βE12-positive basal cells. Anti-muscle AB HHF35 revealed an intense cytoplasmic staining with myoepithelial cells of all remaining atrophic acini and smaller intralobular ducts found in dacryoadenitis. Intense Lf staining was seen in most of the acinar and ductal cells of LG with mild inflammation (case 4, Fig. 4A) except large excretory ducts,

unlike the remaining ones with advanced dacryoadenitis (cases 1, 2, 3 and 5), which exhibited weak but consistent immunostaining for Lf in their ducts and duct-like structures (Table 2). Cells of either atrophic acini or duct-like structures found in inflammatory LGs were weakly and infrequently positive for Ly (Table 2, Fig. 4B). Secretory material found in the lumina of dilated duct-like structures was positive for both Lf and Ly.

As in normal LGs, epithelia in dacryoadenitis also showed a negative reaction with vimentin except in case 4 which showed mild ductal proliferation (Table 2). In this case, vimentin positivity was found in a number of myoepithelial/basal cells and a few isolated luminal-duct and acinar cells (Fig. 5A). Nearly all epithelial cells in inflammatory major LGs were also reactive for S-100 protein, whereas those in the accessory LG with inflammation remained negative (Table 2, Fig. 5B).

Immunohistochemical distribution of these antigens in glandular epithelia of LGs affected by benign or malignant lymphomas (cases 6, 7 and 8) was almost similar to that in dacryoadenitis except for the epimyoepithelial islands in case 7 (Fig. 1). Epimyoepithelial islands revealed intense CK reactivity (KL1 & Pkk1) in their cuboidal cells, whereas the polyhedral cells lacked CK staining (Fig. 6A) but reacted strongly for vimentin (Table 2, Fig. 6B). On the other hand, both groups of cells revealed moderate but infrequent staining for Lf and Ly (Fig. 6C & D) while remaining negative for both S-100 protein and anti-muscle AB HHF35 (Table 2).

In pleomorphic adenomas, intense cytoplasmic staining of KL1 and Pkk1 was seen in luminal cells (double- or single-layer) and focal staining in a few ($<25\%$) ovoid cells, excluding the peripheral cells of all duct-like structures and spindle-shaped cells (Table 2, Fig. 7A). In contrast, all ovoid and peripheral cells of duct-like structures reacted strongly with anti-CK AB 34βE12 (Fig. 7B), whereas the luminal cells were either negative or only weakly and infrequently positive (Table 2). The spindle-shaped cells remained negative for all three anti-CK ABs (Table 2).

The reaction pattern of neoplastic cells with ABs to muscle (HHF35), Lf and Ly (Fig. 8) varied substantially between both pleomorphic adenomas examined. In case 9, most neoplastic cells were negative for HHF35, except for a weak reaction in a very few spindle-shaped and ovoid cells, whereas a considerable portion of ovoid and luminal cells (of this tumor) stained for Lf and Ly (Fig. 8A, B) (Table 2). In contrast, the other tumor (case 10) exhibited strong cytoplasmic staining with anti-muscle AB HHF35 in a number of spindle-shaped and ovoid cells (Fig. 8C) while showing a negative reaction for both Lf and Ly in nearly all neoplastic cells (Table 2). The myxoid stroma of both tumors stained strongly for Lf but not for Ly. All neoplastic cells, excluding the luminal cells of duct-like structures, revealed strong cytoplasmic staining for vimentin (Table 2, Fig. 9A). Intense cytoplasmic and nuclear S-100 protein reactivity was observed in all ovoid/peripheral cells, whereas in luminal and spindle-shaped cells this staining was weaker and often cytoplasmic (Table 2, Fig. 9B).

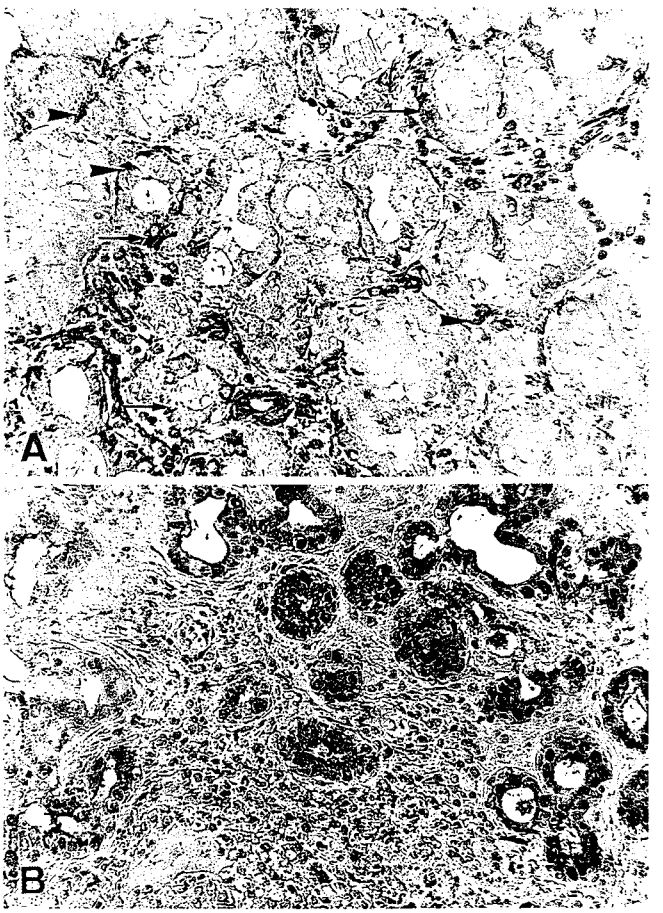

Fig. 5A, B. Dacryoadenitis (non-granulomatosus, case 4, **A**) and lymphoid hyperplasia (case 6, **B**) of major lacrimal gland. **A** Lacrimal gland with mild inflammatory changes reveals vimentin reactivity in a number of myoepithelial (*arrowhead*), acinar and ductal (*arrows*) cells (case 4; original magnification, $\times 150$). **B** Intense S-100 protein staining in most ducts and duct-like structures (case 6; original magnification, $\times 150$)

Discussion

The most frequent reason for diminished tear (both basic and reflex) secretions (keratoconjunctivitis sicca) is degeneration (atrophy) of major and/or accessory LGs. Atrophy of LGs can be due to aging or obstruction (e.g. caused by an accompanying tumor) or to chronic dacryoadenitis isolated from (e.g. sarcoidosis) or associated with Sjögren's syndrome.

Unlike the functionally active secretory cells that lack CK immunostaining, atrophic acinar cells of LGs were found to contain abundant CKs 7, 8, 17 and 18 (KL1 and Pkk1-reactive), similar to the mucous cells in chronic sialadenitis [20, 29]. This accumulation of CKs with the loss of secretory granules causes the atrophic acinar and ductal cells to look alike. On the other hand, the number of HHF35-reactive myoepithelial cells and their staining intensity did not vary between normal and inflammatory LGs and, thus, helps to differentiate ductal from atrophic acinar cells. These findings confirm previous reports from ultrastructural [27] and immunohistochemical studies [20] in sialadenitis that the structure and number of myoepithelial cells are usually not altered during inflammatory changes of salivary glands. In contrast to myoepithelial cells, 34βE12-reactive basal cells were nearly absent in dacryoadenitis. In salivary glands these basal cells are also found to be the most sensitive cells to undergo early inflammation-

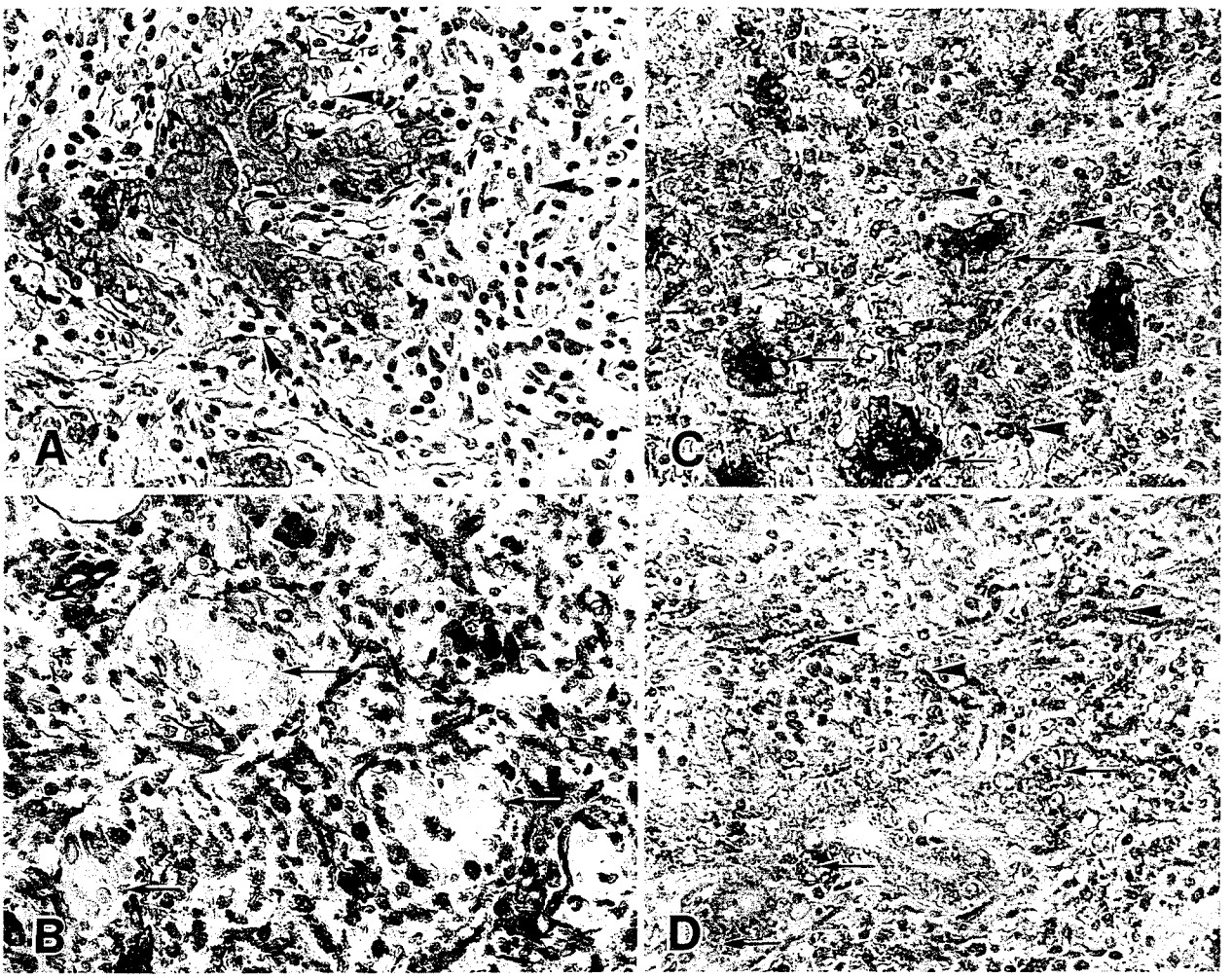

Fig. 6A–D. Immuno-reactive pattern of epimyoepithelial cell islands in major lymphoepithelial lacrimal-gland proliferation (case 7). **A** CK (KL1) reactivity is found only in cuboidal cells forming duct-like structures; polyhedral cells (*arrowheads*) in the periphery are negative (original magnification, ×250). **B** Polyhedral cells as well as lymphocytes are positive for vimentin, whereas cuboidal cells of duct-like structures (*arrows*) remain negative (original magnification, ×250). **C** Cuboidal (*arrows*) and polyhedral (*arrowheads*) cells reveal strong and weak lactoferrin staining, respectively (original magnification, ×250). **D** Cuboidal (*arrows*) and polyhedral (*arrowheads*) cells are weakly positive for lysozyme (original magnification, ×250)

associated degeneration [20]. Neoexpression of CK 5 (34βE12 reactivity) in some luminal cells of duct-like structures in dacryoadenitis may be attributed to the alteration of CK synthesis caused by inflammation.

LG epithelia in both chronic advanced dacryoadenitis and benign lympho/lymphoepithelial proliferations revealed a weak reaction for Lf and a weak and infrequent reactivity for Ly. This is due to the reduction in or lack of synthesis of these proteins by degenerating secretory cells and is in line with a previous report of diminished Lf and Ly levels in tears of patients with keratoconjunctivitis sicca [26]. A recent study reported that tear Lf concentrations in patients with keratoconjunctivitis sicca associated with Sjögren's syndrome are significantly lower than those in patients with isolated keratoconjunctivitis sicca [15]. This may be relevant to our finding that an intense Lf immunostaining was found in all glandular epithelial cells in case 4 with early inflammatory changes but not in association with any autoimmune disease. Therefore, it remains to be determined, using a greater number of cases, whether differences in Lf reactivity can be immunohistochemically demonstrated between dacryoadenitis of obstructive and autoimmune origin. However, an increase in Lf immunostaining is found in early obstructive sialadenitis [28, 29], and this is regarded as a non-immunoprotective response of glandular epithelia against secondary infections [29].

Glandular epithelia in the majority of inflammatory LGs revealed no vimentin reactivity, as do normal ones. However, as an exception, in one inflammatory major LG (case 4), most basal/myoepithelial cells were vimentin-reactive. Although vimentin is characteristic for non-muscular mesenchymal cells, certain undifferentiated embryonal and neoplastic cells of epithelial origin have been found to express vimentin in vivo and in vitro [18]. Since major LG achieves its full differentiation only during 3–4 years postnatally [12], the undifferentiated nature of LG obtained from a 9-month-old patient in case 4 may be responsable for the vimentin reactivity of its epithelia. A similar proliferative and undifferentiated nature could also be the reason for the presence of vimentin in the polyhedral cells of epimyoepithelial islands (case 7).

Recent studies on lymphoepithelial lesions of salivary

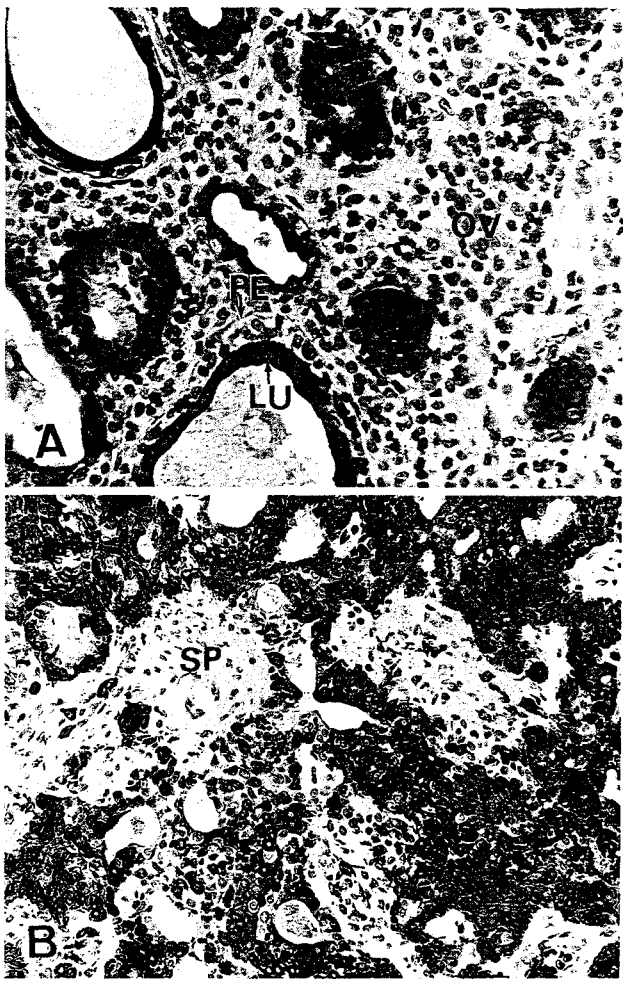

Fig. 7A, B. Cytokeratin-reactive pattern of neoplastic cells in pleomorphic lacrimal-gland adenoma. **A** Intense KL1 staining restricted to luminal (*LU*) cells of duct-like structures; peripheral (*PE*) and ovoid (*OV*) cells are mostly negative (case 9; original magnification, ×160). **B** Strong 34βE12 positivity in peripheral and ovoid cells; luminal cells are inconsistently positive; spindle-form cells (*SP*) are negative (case 9; original magnification, ×90)

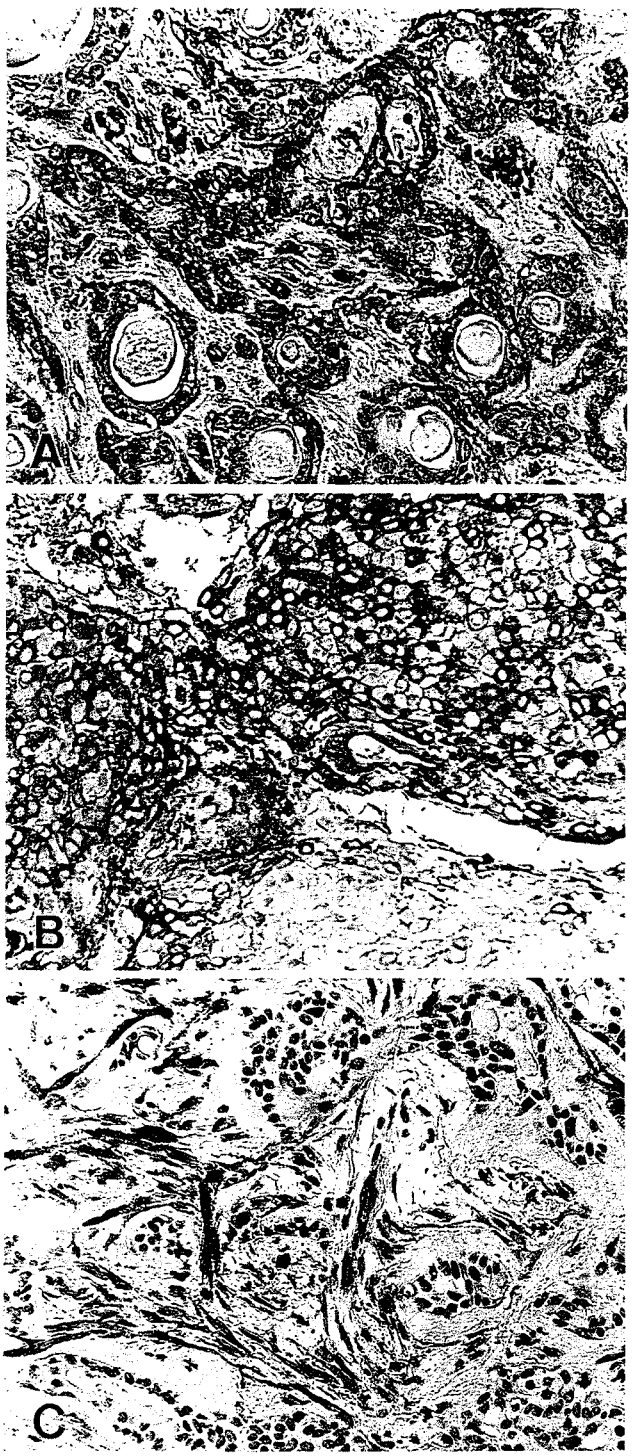

Fig. 8A–C. Distribution pattern of lactoferrin (Lf), lysozyme (Ly) and actin in pleomorphic lacrimal-gland adenoma. **A** Most of the neoplastic cells forming duct-like structures are stained for Lf (case 9; original magnification, ×160). **B** Ovoid cells in the same tumor are positive for Ly (case 9; original magnification, ×160). **C.** Another tumor reveals a number of actin-positive spindle-form neoplastic cells (case 10; original magnification, ×220)

glands reported the presence of CKs and collagen IV in most of the cells of epimyoepithelial islands, whereas these cells demonstrated neither actin nor myosin [19, 23]. Therefore, it was argued that the progenitors of these cells are ductal cells but not myoepithelial cells [19, 23], as once believed [24]. We demonstrated Ly and Lf in a similar type of cells in LG lesions, in addition to their lack of actin supporting their origin from ductal cells. The failure to demonstrate CK in the polyhedral cells of these islands in our study may be due to the low amount of CK in these cells, or their epitopes could have been masked by the presence of large amounts of hyalin [19] and vimentin. In LGs with lymphoid neoplasia, the behaviour of all glandular epithelia except the epimyoepithelial islands was immunohistochemically comparable with that of chronic dacryoadenitis.

Pleomorphic adenomas are the most frequent epithelial tumors of LGs as well as of major salivary glands [5, 6, 12, 25, 31]. They are also called benign mixed tumors since they were once thought to be composed of epithelial and mesenchymal elements [12]. However, on the basis of histological, ultrastructural and immunohistochemical features of pleomorphic salivary-gland adenomas [2, 14, 17], their histogenesis has been hypothesized as being the co-ordinated proliferation of intercalated ductal and modified myoepithelial cells with the synthesis of extracellular matrix [4].

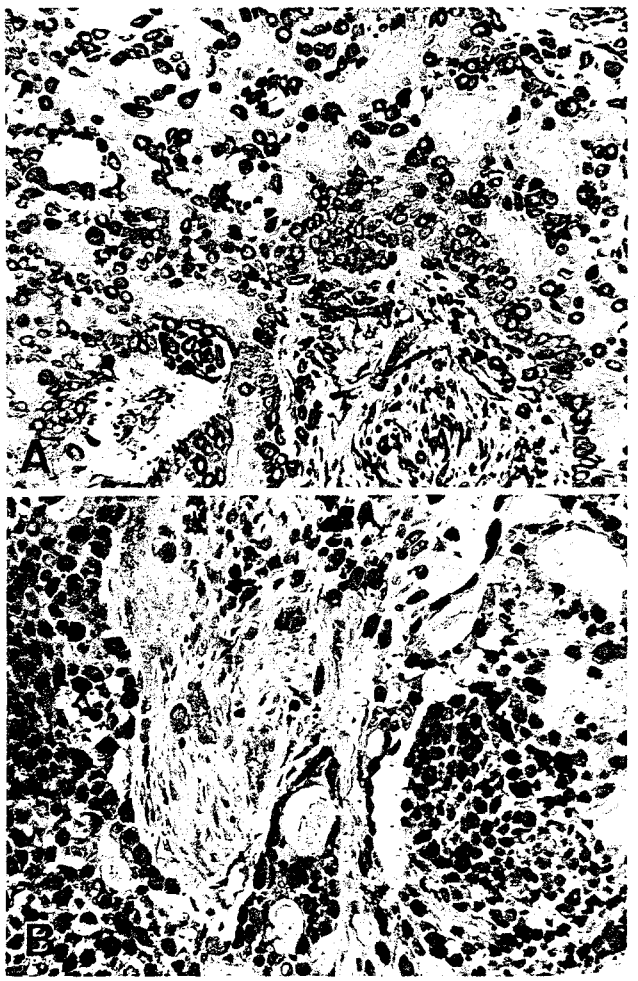

Fig. 9 A, B. Vimentin and S-100 protein reactivity in pleomorphic lacrimal-gland adenoma (case 9). **A** Peripheral, ovoid and spindle-form cells are positive for vimentin; luminal cells remain negative (original magnification, × 160). **B** Peripheral and ovoid cells reveal strong nuclear and cytoplasmic S-100 protein staining, whereas luminal and spindle-form cells are weakly stained (original magnification, × 160)

In both pleomorphic adenomas of LGs, the CK pattern of neoplastic luminal cells (KL1- and Pkk1-reactive) and that of ovoid/peripheral cells (34βE12-reactive) resemble that of the luminal-duct cells and basal/myoepithelial cells of normal LGs, respectively. However, the presence of Lf and Ly not only in neoplastic luminal cells but also in ovoid cells and the absence of actin in the majority of ovoid and spindle-form cells supports a recent report by Burns et al. [1] suggesting that all neoplastic cells of pleomorphic salivary-gland adenomas have a common clonal origin but show a differentiation potential of their entire ductal-acinar unit.

It is interesting to note that a considerable number of neoplastic cells in case 9 revealed Lf and Ly immunostaining while lacking reactivity for actin, whereas those in case 10 behaved vice versa. Moreover, a major proportion of the neoplastic cells in both tumors exhibited vimentin with CK 5 (ovoid/peripheral cells) or without CK (spindle-form cells). Conversely, in pleomorphic salivary-gland adenomas, vimentin reactivity was found to be highly variable as well in a minor proportion of neoplastic cells [2, 30]. In a recent study on a large number ($n=80$) of pleomorphic salivary-gland adenomas, only 25% of these tumors appeared to reveal a vimentin reaction pattern comparable with that observed in similar LG tumors examined in the present study [30]. Furthermore, 31% of these salivary-gland tumors are reported to express no vimentin in their neoplastic cells [30]. Vimentin reaction in these epithelial-derived neoplastic cells seems to be related to their proliferative/undifferentiated nature (e.g. ovoid and peripheral cells) and/or a modification in their differentiation pathway leading to that of mesenchymal cells (e.g. spindle-form cells). S-100 protein reactivity in nearly all neoplastic cells, with a strong cytoplasmic and nuclear reaction of ovoid/peripheral cells, is found to be common for pleomorphic adenomas of both LGs and salivary glands [3, 17]. In addition to pleomorphic adenomas, neoplastic cells of eccrine spiroadenoma and various metastatic adenocarcinomas are also reported to be reactive for S-100 protein [8, 10].

The presence of Lf and Ly reactivity in similar types of tumors in salivary glands was found to correlate well with their degree of epithelial differentiation [14]; thus, Ly staining in these tumors is suggested to be a reliable indicator for exclusion of their malignancy [22]. In contrast, the pleomorphic salivary-gland adenomas composed of more neoplastic cells showing positivity for CK 5, vimentin, actin and S-100 protein (nuclear and cytoplasmic) reactions (myoepithelial/basal-cell type differentiation) are reported to have a higher risk of malignant transformation [25]. Therefore, examination of the above-mentioned antigens in LG pleomorphic adenomas do not only help to understand their histogenesis but may also aid in evaluating their prognosis. Further investigations using a greater number of LG tumors are necessary to evaluate the use of these antibodies in the differential diagnosis of LG epithelial tumors.

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