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Lymphoepithelial duct lesions in Sjögren-type sialadenitis

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Abstract It is not clear, whether the so-called basal cells of the salivary striated ducts are an independent cell-type distinct from myoepithelial cells, making characterization of the cell proliferation typical of the duct lesions in Sjögren-type sialadenitis/benign lymphoepithelial lesion (BLEL) difficult. An immunohistochemical investigation including different cytokeratin subtypes, α-actin, Ki-67 and *Bcl*-2 was directed at the epithelial cytoskeleton in normal parotid parenchyma (*n*=8), BLEL (*n*=12), HIV-associated lymphoepithelial cysts (*n*=8) and palatine tonsils (*n*=8). There are profound morphological and functional differences between basal and myoepithelial cells in the normal salivary duct. Development of duct lesions in BLEL arises from basal cell hyperplasia of striated ducts with aberrant differentiation into a multi-layered and reticulated epithelium, characterized by profound alteration of the cytokeratin pattern. This functionally inferior, metaplastic epithelium is similar to the lymphoepithelial crypt epithelium of palatine tonsils. The often postulated participation of myoepithelial cells in duct lesions of Sjögren disease/BLEL cannot be supported. We regard the designations lymphoepithelial lesion and lymphoepithelial metaplasia as the most appropriate.

Key words Salivary glands · Lymphoepithelial lesion · Sjögren disease · Metaplasia · Cytokeratin filaments

Introduction

Sjögren-type sialadenitis is characterized histologically by the triad of lymphocytic gland infiltration, alteration of salivary ducts and parenchymal atrophy [1, 8, 14, 19, 34]. It is designated by different histomorphological terms, partly because of the controversial pathogenesis of the characteristic duct lesions. The term "Sjögren's syndrome" [36] is accepted as a predominantly clinical description of autoimmune disease of salivary glands. Godwin [16] introduced the term benign lymphoepithelial lesion (BLEL), which has become widely used [1, 2, 5, 8, 14, 20, 34]. Focusing on the pathogenesis of characteristic duct alterations, Morgan proposed the designation epimyoepithelial lesion, favouring a proliferation of myoepithelial cells [27]. Based on conventional and ultrastructural histology some groups supported this concept of a primary myoepithelial lesion, adding the more comprehensive term myoepithelial sialadenitis [5, 10, 12, 33, 34]. However, in a series of consecutive ultrastructural and immunohistochemical investigations the role of myoepithelial cells could not be substantiated [2, 20, 21, 28, 32, 38].

Analysis of the literature indicates that this confusion over terms is caused mainly by the disputed role of basally located cells in striated ducts. Some authors classify these cells as basket-type myoepithelial cells [4, 10, 12], while others regard them as an independent cell type (from this point on called basal cells; see [3, 11, 13, 15, 28, 38]. As a consequence of this difficulty, the formal pathogenesis of duct lesions in BLEL is also disputed: a proliferation of basal cells [18, 20, 21, 28, 32, 38] and proliferation of myoepithelial cells [1, 4, 5, 8, 10, 12, 14, 19, 34] have both been postulated.

We initially focused our immunohistochemical study on the morphological and functional relationship of myoepithelial and basal cells in the regular salivary duct, using a panel of subtypes of cytokeratin filaments. Cytokeratins (CK) represent the intermediate filaments of epithelial cells and contribute significantly to the function of different types of epithelia (see [24, 25]). Based on our findings in the normal duct, we investigated the pathogenesis of duct lesions in BLEL, with reference to the role of basal and myoepithelial cells. We included surgical specimens of palatine tonsils in our study, since the physiologically reticulated tonsillar crypt epithelium has been shown to be phenotypically similar to the fully

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Table 1 Monoclonal mouse antibodies (MAb) used in this study applied to antigens listed (all CK subtypes belong to the acidic (type I) CK group, *MW* microwave, *min* minutes, *conc* concentrated)

Antigen	MAb clone	Source	Pretreatment	Dilution of MAb	Method
Pan-keratin	5D3&LP34	Histoprime	30 min MW	conc	ABC
CK 10	DE-K10	Progen	30 min protease	1:10	APAAP
CK 13	Ks13.1	Progen	30 min MW	1:80	APAAP
CK 14	LL02	Serotec	30 min MW	1:10	APAAP
CK 18	Ks18.04	Progen	30 min protease	1:40	ABC
CK 19	Ks19.1	Progen	30 min protease	1:50	ABC
CK Ks8.12	Ks8.12	Sigma	20 min MW	1:100	APAAP
α-actin	asm-1	Boehringer	30 min MW	1:600	ABC
Bcl-2	124	DAKO	30 min MW	1:10	LSAB
Ki-67	MIB-I	Dianova	30 min MW	1:10	APAAP

Table 2 Immunohistochemical characterization of the epithelial cytoskeleton of normal salivary duct, reticulated epithelium of both salivary duct lesion and tonsillar crypts, and squamous epithelium of both large ductal cysts and tonsillar surface. Cytoplasmic staining intensity: no expression –, mild expression +, moderate expression ++, strong expression +++. Gain of CK-expression in lymphoepithelial metaplasia (CK 13) and squamous cell metaplasia (CK 10) is indicated by bold **+**

	Pan-keratin	CK 19	CK 18	CK 14	CK Ks8.12	CK 13	CK 10	α-Actin
Acinar cells[a]	++	–	+++	–	–	–	–	–
Intercalated duct cells[a]	+++	+++	+++	–	–	–	–	–
Oxyphilic cells of striated ducts[a]	+++	++	+++	–	–	–	–	–
Myoepithelial cells[a]	+++	+++	–	++	–	–	–	+++
Basal cells of striated duct[a], duct lesion and tonsillar epithelium	+++	+++	+	+++	++	–	–	–
Reticulated epithelium of salivary duct lesion (only suprabasal)	+++	+++	–/+	++	+++	**+++**	–/+	–
Reticulated epithelium of tonsillar crypts (only suprabasal)	+++	+++	–/+	++	+++	++	–	–
Squamous epithelium of large ductal cysts (only suprabasal)	+++	+++	–	++	+++	+++	**++**	**–**
Squamous epithelium of tonsillar surface (only suprabasal)	+++	–	–	–/+	+++	+++	–	–

[a] Five different cell types

developed duct lesions of BLEL. Furthermore, our group has recently presented evidence that the development of parotid lymphoepithelial cysts (LEC) in patients with human immunodeficiency virus (HIV)-1 infection is associated with alterations that have a striking phenotypical similarity to duct alterations in BLEL [18]. Parotid specimens with HIV-associated LEC were therefore also included in this study.

Materials and methods

Surgical parotid specimens from cases of BLEL (*n*=12) and HIV-associated LEC (*n*=8) and specimens of normal parotid parenchyma (*n*=8) and of palatine tonsils (*n*=8) were retrieved from the files of the Institute of Pathology of the Ludwig Maximilians University of Munich (from the years 1988–1995). Nine of the 12 patients with histomorphologically verified BLEL were female, their ages ranging from 42 to 73 years (average 61 years). Bilateral swelling of parotid glands was seen in 8 patients, and a sicca syndrome was found in 9 patients. ANA and/or SS-A/B antibodies were demonstrated in 7 patients. Associated rheumatoid arthritis was diagnosed in 4 patients, progressive systemic sclerosis in 1 patient. The clinical data were incomplete in 3 patients. Altogether, in 9 of the 12 cases these data implied a clinical diagnosis of Sjögren's syndrome. Cases with associated MALT-type non-Hodgkin's lymphoma were excluded. Four specimens with mild to moderate dilatation of a few duct lesions, manifest as characteristic alterations of BLEL, were included. Parotid specimens with multifocal cystic duct dilatation and only limited periductal lymphocytic infiltration, representing so-called chronic sialectatic sialadenitis [33], were excluded. Comprehensive clinical data for the patients with HIV-associated LEC have recently been presented elsewhere by our group [18]. Specimens of palatine tonsils (from patients aged 14–32 years) did not show acute inflammation, increased fibrosis or squamous cell metaplasia of the reticulated crypt epithelium.

Each specimen was fixed in 4% buffered formaldehyde, embedded in paraffin wax and cut into 4-µm-thick serial sections. A panel of commercially available monoclonal mouse antibodies was applied with special reference to CK subtypes (details see Table 1). Modifications of the avidin–biotin complex method (ABC; [17]), the alkaline phosphatase anti-alkaline phosphatase method

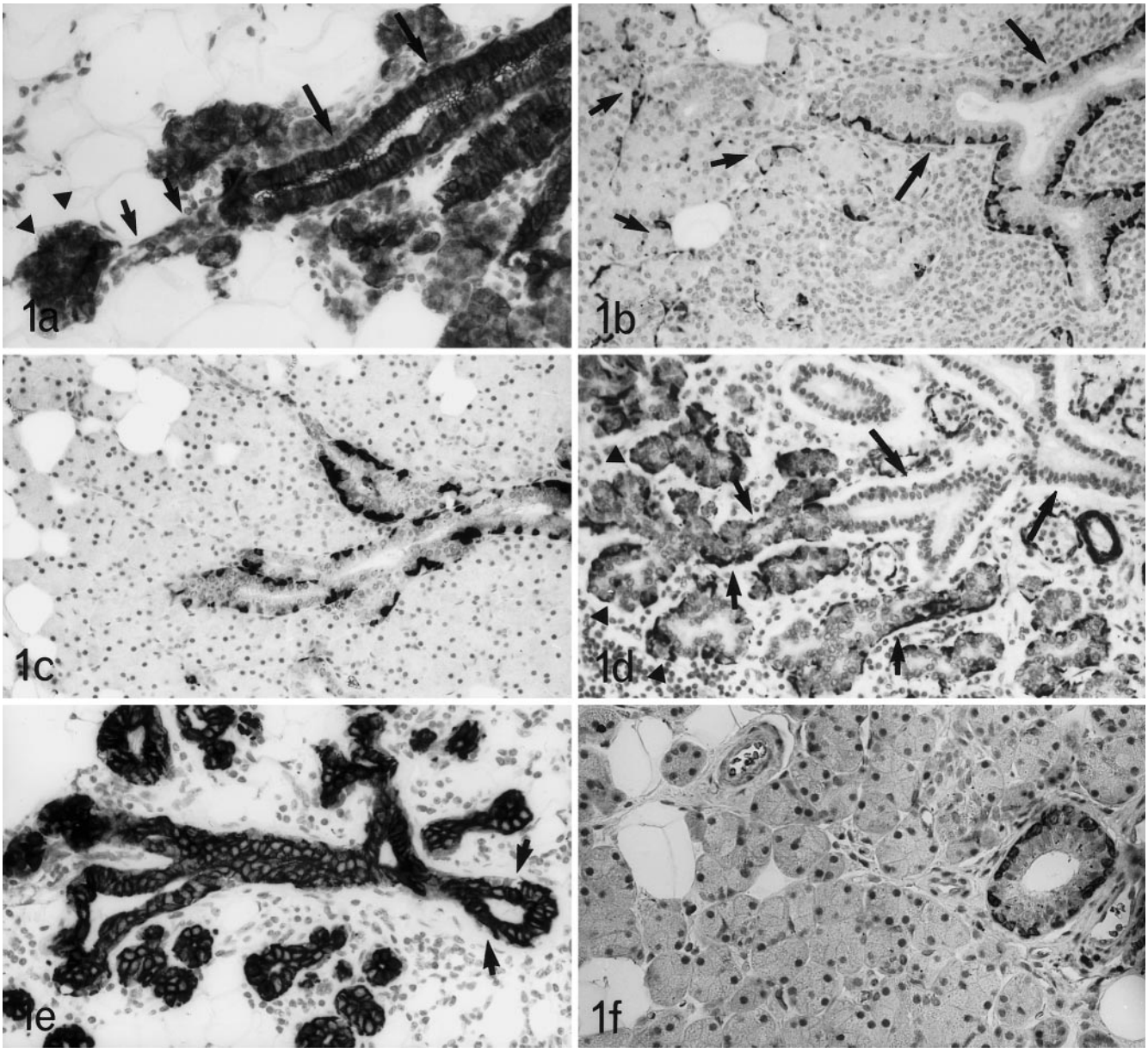
(APAAP; [6]) and the labelled streptavidin–biotin staining method (LSAB) were used. The extent of cytoplasmic immunoreactivity was semi-quantitatively evaluated by the following grading system: no expression - ; weak expression + ; moderate expression ++ ; strong expression +++ (Table 2). Immunohistochemical double-staining in the same section was performed to demonstrate antibodies to pan-keratin and the proliferation-associated antigen Ki-67 (MIB-1).

Results

The cellular composition of normal salivary duct, salivary duct lesion and tonsillar epithelium were analysed with regard to the immunoreactivity of different CK antibodies (broad-spectrum pan-keratin, CK subtypes 10, 13, 14, 18, 19, Ks8.12, α-actin, Ki-67, *Bcl*-2).

In the peripheral part of the normal duct system acini and intercalated ducts display a single-layered, cuboidal epithelium. Serous acinar cells expressed simple epithelial-type CK 18 exclusively, whereas intercalated duct cells also expressed CK 19 (Fig. 1e). Myoepithelial cells, surrounding the peripheral duct segment like a net, were stained by CKs 19 and 14 (Fig. 1b) and also by α smooth

Fig. 1a–f Immunohistochemical characterization of the intralobular salivary duct in longitudinal sections. All ×90 **a** The salivary duct consists of acinus (*arrowheads*), intercalated duct (*small arrows*) and striated duct (*large arrows*; broad-spectrum pan-keratin). **b** Basal-type CK 14 labels both basal cells of striated ducts (*large arrows*) and basket-type myoepithelial cells within the parenchyma (*small arrows*). **c** Whereas CK Ks8.12 exclusively stains basal cells of striated ducts, **d** α-actin is selectively expressed in contractile filaments of myoepithelial cells, surrounding acini (*arrowheads*) and intercalated ducts (*small arrows*). Striated ducts (*large arrows*) are mainly free of myoepithelial cells. **e** All luminal cell types – acinar cells, intercalated duct cells and oxyphilic cells of striated ducts – are strongly stained by CK 18, whereas basal cells (*arrows*) and myoepithelial cells are negative. **f** The proto-oncogene *Bcl*-2 is expressed exclusively in basal cells of striated ducts



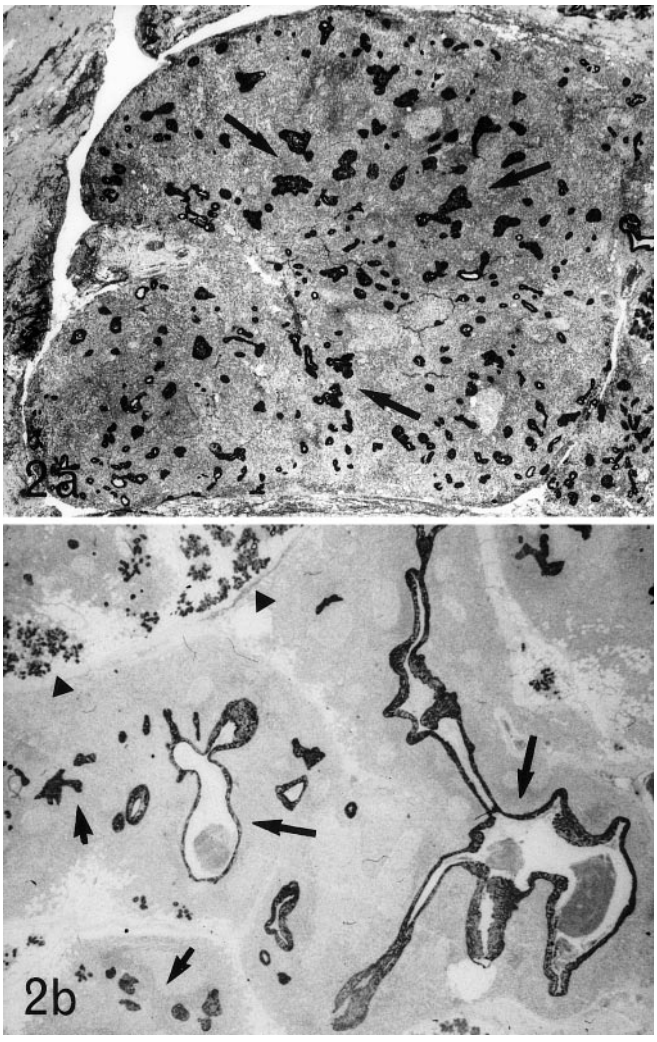


Fig. 2a, b Topographical distribution of lymphoepithelial duct lesions within salivary lobules. Pan-keratin stain (**a** ×13, **b** ×20). **a** Salivary lobule with the characteristic histomorphological triad of benign lymphoepithelial lesion (BLEL): intense lymphocytic infiltration, parenchymal atrophy and numerous cross sections of the generalized lesion of the central branching duct system (*arrows*). The peripheral rim of the lobule exhibits few duct lesions. **b** One of four specimens of BLEL, demonstrating mild to moderate dilatation of a few duct lesions (*large arrows*) without progression to large macroscopic cysts. Adjacent duct lesions without dilatation (*small arrows*) and parenchymal remnants (*arrowheads*) are seen

muscle actin, which labelled contractile microfilaments (Fig. 1d; Table 2).

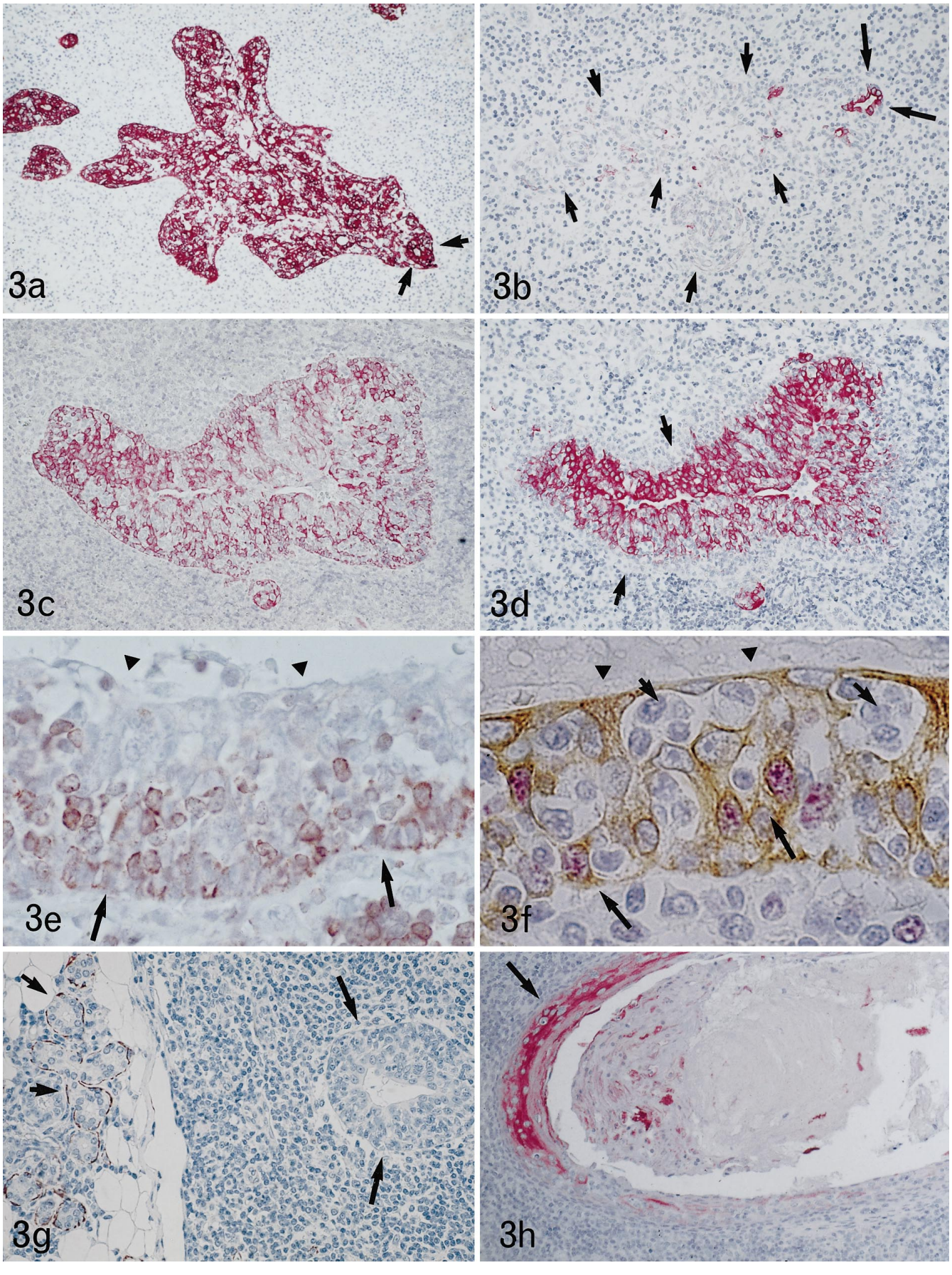
The central part of the intralobular duct system, represented by striated ducts, shows a bi-layered epithelium. The luminal layer of columnar, oxyphilic cells was stained intensely by CKs 19 and 18 (Fig. 1e), whereas in basally located cells there was strong expression of CKs 19, 14 and Ks8.12 (Fig. 1b, c). Striated ducts rarely demonstrated α actin-positive myoepithelial cells in the peripheral part (Fig. 1d). Stratified epithelial-type CKs 13 and 10 were not expressed in the cells of the normal duct (Table 2). Staining for the proto-oncogene *Bcl*-2 was seen exclusively in basal cells of striated ducts (Fig. 1f). Nuclear positivity for the proliferation-associated antigen Ki-67 was rarely found in acinar cells, intercalated duct cells and basal cells; it was not seen in oxyphilic cells and myoepithelial cells (not shown).

Duct lesions are evenly distributed in salivary lobules of BLEL, where they can be attributed to the branching system of striated ducts. They are rarely encountered in the peripheral rim of lobules, where few intercalated ducts and acini are preserved (Fig. 2a). In contrast to normal striated ducts, all duct lesions were characterized by an increase in the number of epithelial cells. Whereas the basal cell layer was generally preserved, suprabasal layers were reticulated and interspersed by an intense lymphocytic cell population. These suprabasal cells were irregularly shaped and showed a loss of cell polarity. In about half of the fully developed lesions no lumen was identifiable. In other islands the residual lumen was lined by remnants of oxyphilic luminal cells, stained by simple-epithelial-type CK 18 (Fig. 3a, b). In 4 cases a mild to moderate luminal dilatation was found in up to 10% of all duct lesions (Fig. 2b).

In contrast to the normal striated duct, suprabasal cell layers in advanced lesions exhibited a strong reactivity for stratified epithelial-type CKs 14, 13 and Ks8.12 (Fig. 3c, d). A few lesions also showed a faint expression of CK 10. All cells of the basal cell layer expressed Bcl-2, strongly, while cells of the middle layers showed only weak, and those of the luminal layer no, expression of *Bcl*-2 (Fig. 3e). In the basal and middle layers of the duct lesion numerous Ki-67-positive, proliferating epithelial cells were seen (Fig. 3f). α-actin expressing myoepithelial cells were not normally encountered in fully developed lesions (Fig. 3g).

As we have previously demonstrated in detail [18], all HIV-associated specimens showed a combination of ductal cysts of varying size and of duct lesions, similar to

Fig. 3a–h Immunohistochemical characterization of the lymphoepithelial duct lesion (**a–g** cases of BLEL, **h** HIV-associated LEC). **a** Typical branching lymphoepithelial island exhibits a multi-layered, reticulated epithelium; a duct lumen is only occasionally preserved (*arrows*; broad-spectrum pan-keratin). ×75 **b** The lesion (outlined by *small arrows*) is preponderantly negative for CK 18; only the preserved duct lumen is lined by remnants of CK 18-positive oxyphilic cells (*large arrows*). ×112 **c** All cell layers of duct lesions are intensely stained by stratified epithelial type CK 14 (as well as by CK Ks8.12, not shown). ×112 **d** In a serial section gain in expression of mucosa-type CK 13 is seen in all cell layers except the basal layer (*arrows*). ×112 **e** The proto-oncogene *Bcl*-2 presumably exerts an anti-apoptotic effect on regenerative basal cells (*arrows*) and a few suprabasal epithelial cells, whereas luminal cells during maturation show loss of expression of *Bcl*-2 (duct lumen: *arrowheads*). ×230 **f** Parallel, increased epithelial proliferation is demonstrated in basal and suprabasal cells: double staining against the proliferation-associated antigen Ki-67 (*red*; *large arrows*) and pan-keratin (*brown*). Numerous lymphocytes (*small arrows*) are enclosed in the reticulated epithelium (duct lumen: *arrowheads*). ×230 **g** α-Actin selectively stains myoepithelial cells within parenchymal remnants (*small arrows*); duct lesions generally prove to be devoid of α-actin-positive cells (*large arrows*). ×145 **h** Some large HIV-associated ductal cysts focally demonstrate further transition into full-blown squamous metaplasia, characterized by additional gain of expression of epidermis-type CK 10 (*arrow*). ×112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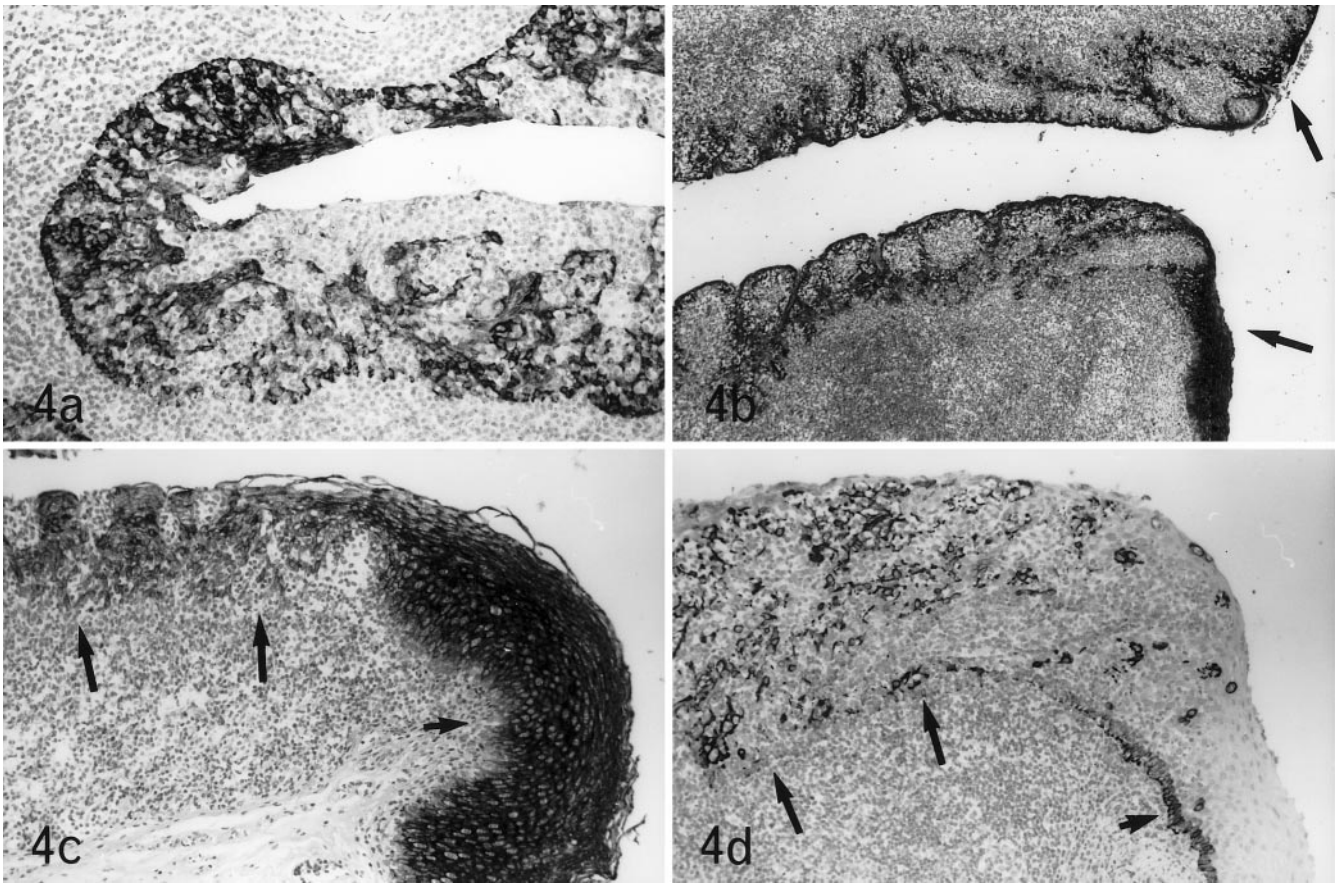

Fig. 4a–d Immunohistochemical characterization of the crypt and surface epithelium of palatine tonsils. **a** Tonsillar crypts physiologically demonstrate a multi-layered, reticulated epithelium with numerous intraepithelial antigen-presenting lymphocytes. CK Ks8.12 is expressed in all epithelial layers. ×65 **b** The reticulated crypt epithelium extends towards the tonsillar surface, where a noncornified, oropharyngeal-type squamous epithelium predominates (*arrows* pan-keratin). ×28 **c**, **d** In a higher magnification the transition of the reticulated crypt epithelium (*large arrows*) into squamous surface epithelium (*small arrow*) is shown. Mucosa-type CK 13 (**c**) is expressed in suprabasal layers of both types of epithelia, whereas CK 19 (**d**) stains all layers of crypt epithelium, but only the basal layer of surface epithelium. ×65

that seen in BLEL. The immunoreactivity of the epithelial cytoskeleton proved to be basically equivalent in duct/cyst lesions of HIV-associated specimens and of BLEL. However, in some of the HIV-associated large ductal cysts a further transition of the reticulated epithelium into a nonkeratinizing squamous epithelium was seen, lacking lymphocytic infiltration and additionally expressing epidermis-type CK 10 in suprabasal layers (Fig. 3h; Table 2).

The tonsillar surface displays a noncornified squamous epithelium equivalent to oropharyngeal mucosa in general. Here the basal cell layer expressed CKs 19, 14 and Ks8.12. Suprabasal layers were strongly labelled by mucosa-type CKs 13 and Ks8.12, were slightly positive for CK 14 and were negative for CK 19.

However, tonsillar crypts show reticulation of the stratified squamous epithelium, interspersed by an intense lymphocytic cell population. The basal cell layer was strongly stained by CKs 19, 14 and Ks8.12. Suprabasal cell layers were intensely labelled by CKs 19 and Ks8.12 and moderately by CKs 14 and 13. Both crypt and surface epithelia were negative for epidermis-type CK 10 and for alpha actin (Fig. 4a–d; Table 2).

Discussion

Characteristic duct alterations are a histomorphological hallmark of Sjögren-type sialadenitis. A proliferation of ductal (basal) cells [18, 20, 21, 28, 32, 38] and proliferation of both myoepithelial and ductal cells (so-called epimyoepithelial islands [1, 4, 5, 8, 10, 12, 14, 19, 34]) have both been invoked in the pathogenesis. This controversy derives from the disputed role of abluminal cells in striated ducts. Some authors regarded these basally located cells as an independent cell population (basal cells [3, 11, 13, 15, 28, 38]), while others included them with myoepithelial cells [4, 10, 12].

Topographically, a short overlap of basal and myoepithelial cells can be found in the distal segment of striated ducts. However, the two cell types are separate anatomically, as basal cells are located in the central part and myoepithelial cells in the peripheral part of the duct [3, 9, 13, 28, 38]. The intense staining of both cell types for CKs 19 and 14 probably reflects a common function in the mechanical support of different parts of the duct [3,

Table 3 Arguments for a morphological and functional distinction between basal cells and myoepithelial cells in the normal salivary duct (analysis of this study and the literature)

	Basal cell	Myoepithelial cell
Localization in the duct system [13, 14, 15, 28] (present study)	Striated and excretory ducts	Acini and intercalated ducts (rarely distal segment of striated ducts)
Cell morphology [9, 13, 14] (present study)	Triangular	Triangular plus basket-type cell processes
Expression of α-actin [9, 13, 14, 15, 28] (present study)	–	+
Expression of CK Ks8.12 [9, 13], (present study)	+	–
Proliferative capacity (Ki-67) [11, 38] (present study)	+	– (?)
Expression of *Bcl-2* [29] (present study)	+	–
Function ([13, 15, 23, 25]; present study)	Mechanical support of central part of duct Pluripotent cell function for ductal regeneration, metaplasia (and tumorigenesis?)	Mechanical support of acinus and peripheral part of duct Propulsion of saliva through contractile microfilaments

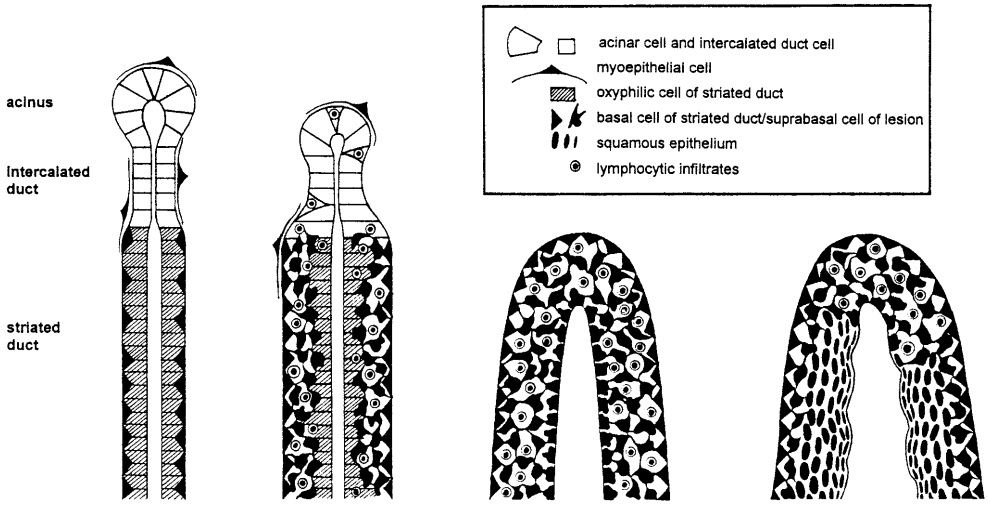

Fig. 5 Stepwise development of the lymphoepithelial duct lesion through a basal cell hyperplasia of striated ducts. Acini and intercalated ducts – including myoepithelial cells – undergo progressive atrophy in parallel. In HIV-associated lesions in a further step a multifocal cystic duct dilatation develops, with occasional further maturation into squamous cell metaplasia, indicated on the *right*

13, 15, 22, 24]. However, the rarely used stratified epithelial-type CK Ks8.12, which selectively stains basal cells, allows precise characterization [9, 13], and α-actin labels the contractile microfilaments of myoepithelial cells exclusively [9, 14, 15, 21, 28]. Triggered by appropriate vegetative stimuli, these contractile microfilaments provoke intermittent propulsion of saliva [13, 14], exhibiting the characteristic functional specialization of myoepithelial cells.

While we were not able to demonstrate proliferative activity in myoepithelial cells, basal cells demonstrated low Ki-67-positivity in the regular duct and markedly higher positivity in the duct lesion. This finding, together with the exclusive protein expression of *Bcl*-2 [29], underlines the postulated role of basal cells as a regenerative epithelial cell pool [11, 15, 22, 28]. These findings are in good agreement with those in the literature [3, 11, 13, 15, 28, 38], identifying basal cells in striated ducts, with specific morphological characteristics and distinct from basket-type myoepithelial cells (Table 3).

Our analysis of different developmental stages of BLEL (Fig. 5) indicated that duct lesions develop by reactive hyperplasia of basal cells of striated ducts, presumably triggered by a chronic autoimmune process. While acini and intercalated ducts, including myoepithelial cells, undergo progressive atrophy, basal cells are preserved, possibly due to an anti-apoptotic effect of *Bcl*-2 [29]. These proliferating basal cells no longer differentiate into oxyphilic cells, but the enhanced ductal regeneration is manifest as aberrant differentiation into a stratified and reticulated epithelium with abundant lymphocytic infiltrate. The gain of stratified epithelial-type CKs 14, 13 and Ks8.12 in suprabasal layers is a profound alteration to the CK profile compared with the normal striated duct. CKs 13 and Ks8.12 are the hallmark proteins for oropharyngeal-type squamous mucosa [22, 24, 25]. The gain of these CKs correlates to the ultrastructural equivalent of abundant tonofilament bundles in duct lesions [2, 5, 20, 21, 32, 38], indicating increased mechanical stability. The postulated development of duct lesions from myoepithelial cells has been based on staining with basal-type CK 14, but CK 14 proved not to be useful, because it reacts both with basal and myoepithelial cells [9, 13, 15, 24]. We did not find development or transforma-

tion of duct lesions from myoepithelial cells, confirming results of earlier immunohistochemical [21, 28, 32] and ultrastructural [20, 21, 32, 38] studies. Therefore, no rationale exists for labelling suprabasal cells of lesions as "modified myoepithelial cells" [10].

The crypts of palatine tonsils demonstrate a similar reticulated epithelium with lymphocytic infiltrates [26, 30, 31]. This reticulation was long regarded as a pathologic alteration following chronic tonsillitis [31], but it has recently been identified as a physiological adaptation favouring intense immunological communication between antigens of the oral cavity and specialized intraepithelial lymphocytes [26, 30, 31]. In addition to striking phenotypic similarity, our study exhibited an almost identical staining pattern of CK subtypes in duct lesions and crypt epithelium. Whereas the reticulation of crypt epithelium is a morphological prerequisite for the immunological function of tonsils, the development of a similar epithelium in BLEL is a pathologic process severely impairing the physiological function of production, modification and transportation of saliva. Ultimately it destroys the duct.

Does this duct lesion represent epithelial metaplasia [2, 8, 20]? In the duct lesions of BLEL basal cell hyperplasia develops without maturation into full-blown oropharyngeal-type squamous metaplasia. However, loss of differentiated oxyphilic cells, stratification of epithelium, loss of cell polarity and profound alteration of the CK profile are all findings that justify the designation of this lesion as a distinct type of duct metaplasia.

Four of our 12 specimens of BLEL exhibited mild to moderate dilatation of residual duct lumina without transformation into large cysts. In the literature sporadic duct dilatation is a well-documented feature of BLEL [8, 19, 34]. Lesions with luminal dilatation proved to be especially useful in the evaluation of immunoreactivity, because of an optimal topographical localization of the different cell layers. Cases of BLEL with luminal dilatation have to be distinguished from chronic sialectatic sialadenitis, which is characterized by pronounced and multifocal ductal dilatation, periductal fibrosis and only limited lymphocytic infiltration [33, 34]. Our group has recently provided evidence [18], that HIV-associated lymphoepithelial cysts represent an end-stage development of a cystic lymphoepithelial lesion with striking phenotypic similarity to BLEL [7, 37]. This study demonstrates that the pathogenesis of duct lesions is basically equivalent in both diseases. In large ductal cysts the additional transition of the reticulated epithelium into fully developed squamous metaplasia is presumably triggered mechanically by the long-standing pressure from the entrapped cyst fluid. This further progress within this distinct type of salivary duct metaplasia is characterized by additional gain of CK 10, which is the hallmark protein of epidermis, an epithelium with exceptional high degree of mechanical stability [22, 24].

Our findings provide evidence for a reactive basal cell hyperplasia of striated ducts with aberrant differentiation into a stratified and reticulated epithelium with profoundly altered function in BLEL. Both the phenotype and alterations to the CK profile in the duct lesions imitate the lymphoepithelial crypt epithelium of the palatine tonsils, and certain criteria for ductal metaplasia are fulfilled. Rather than epi-myoepithelial lesion, we regard the designations lymphoepithelial lesion and lymphoepithelial metaplasia as the most appropriate.

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