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HIV-related parotid lymphoepithelial cysts

Immunohistochemistry and 3-D reconstruction of surgical and autopsy material with special reference to formal pathogenesis

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Abstract Whether lymphoepithelial cysts in the parotid glands in HIV-infected patients develop from pre-existing salivary gland inclusions in intraparotid lymph nodes or from a lymphoepithelial lesion of salivary parenchyma is unclear. To examine their pathogenesis we performed a histological and immunohistochemical study of salivary specimens from 100 AIDS patients in different disease stages. There is a continuous morphological spectrum of changes within the salivary parenchyma, starting with lymphoid stroma infiltration and evolving to characteristic lymphoepithelial duct lesions with a immunohistochemically proven basal cell proliferation and to fully developed ductal cysts. Involvement of myoepithelial cells – postulated in comparable Sjögren-associated duct lesions – is excluded immunohistochemically. Computer-assisted 3-D reconstructions confirm an association of the cysts with the intralobular duct system.

Our study disproves the prevailing hypothesis, which suggests that the lymphoid cell compartment of HIV-associated lymphoepithelial cysts stems from pre-existing intraparotid lymph nodes. The results demonstrate that a secondary lymphatic infiltration of salivary parenchyma provokes a lymphoepithelial lesion of striated ducts with basal cell hyperplasia. The frequent progression to a multifocal cystic lymphoepithelial lesion may be supported by ductal compression through a high degree of lymphofollicular hyperplasia in early disease.

Key words HIV · Parotid gland · Lymphoepithelial cyst · Lymphoepithelial lesion · Sjögren disease

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Introduction

Sporadic lymphoepithelial cysts (LEC) of the parotid gland are a rare entity in the salivary glands (0.5% in the Hamburg Salivary Glands Register [32]). The term was introduced by Bernier and Bhaskar in 1958 [1]. Until 10 years ago LEC were reported almost exclusively as single, unilateral lesions; salivary inclusions in intraparotid lymph nodes or branchial cleft remnants were regarded as the possible origin [1, 32].

In 1985 Ryan et al. [29] described an HIV-associated lymphadenopathy of intraparotid lymph nodes. Bilateral, multicystic lesions in HIV-infected patients were reported for the first time in 1987 by Morris et al. [25, 26]. Since then, an increasing number of authors have presented histopathological studies on HIV-related LECs. Corresponding to the first description by Bernier and Bhaskar [1], the majority favoured an origin from intraparotid lymph nodes, attributing the cystic lesions and epithelial islands to pre-existing salivary gland inclusions [3, 6, 14, 15, 22, 24, 25, 28, 33, 34, 38]. Some authors described a Sjögren-like lymphoepithelial lesion of the parotid parenchyma, defined as intraglandular lymphoid hyperplasia in association with characteristic alteration of ductal epithelium [8, 21, 37]. Several authors presented parotid cysts in combination with a lymphoepithelial lesion, favouring a development of HIV-associated LECs from salivary parenchyma [9, 23, 35, 36].

The appropriate therapeutic approach is still controversial [9, 24, 33, 35]; generally only large cysts are resected and in order not to jeopardize the facial nerve they are often enucleated. The fact that the adjacent salivary tissue is not acquired makes morphological study of the pathogenesis of this disease difficult. Nevertheless, our surgical specimens included a few obtained from lateral parotidectomies, demonstrating preserved architecture of the salivary parenchyma with small cysts. As surgical specimens obviously represent selected material with mostly fully developed cysts, we also included salivary gland material obtained from AIDS autopsies with the aim of detecting precursor and follow-up lesions. On this

material we performed histological and immunohistochemical testing and also computer-assisted 3-D reconstructions to analyse the complex structure of the cysts and their formal pathogenesis.

Materials and methods

Histological investigations were performed in 16 surgical parotid specimens from 12 HIV-positive patients (bilateral in 4 patients) with the diagnosis LEC. Two of the patients were female. Their ages ranged from 27 to 71 years, with an average of 46 years. The patients had stages B and C disease according to the revised Center for Disease Control classification [5]. Preoperative sonography had indicated bilateral cystic lesions in 8 of the 12 patients. All patients underwent operation between 1987 and 1994 in the Clinic for Ear, Nose and Throat Diseases of the Ludwig Maximilian University, Munich, for exclusion of malignancy or for cosmetic reasons, or both. Five lateral parotidectomies and 11 enucleations of large cysts only were performed (Table 1).

In addition, 88 autopsy specimens from AIDS patients (all in CDC stage C [5]), performed between 1987 and 1994 at the Institute of Pathology of the Ludwig Maximilian University, Munich were analysed. The age at time of death was 41 years on average (2 months to 76 years). There were 2 female patients, and 6 were children (2 months to 16 years). In all, 88 autopsy specimens from the parotid glands were examined; specimens from the submandibular glands ($n = 69$), the sublingual glands ($n = 16$) and the lacrimal glands ($n = 14$) were also examined (Table 2).

Each specimen was fixed in 4% buffered formaldehyde, embedded in paraffin wax, cut into 4-µm-thick sections and stained with haematoxylin-eosin (HE). All surgical specimens and informative post-mortem specimens were also stained with Giemsa, periodic acid–Schiff and elastin-van Gieson. Immunohistochemistry was performed using polyclonal antibodies directed against pan-keratin (Histoprime, Wiesbaden, Germany, E 020) and CD3 pan-T (Dako, A 452) as well as monoclonal antibodies directed against alpha smooth muscle actin (Boehringer, Mannheim, Germany, NT 1148 818), cytokeratin 14 (Serotec, Wiesbaden, MCA 890), CD20/L26 pan-B (Dako, M 755), Mac 387 (Dako, M 747), Ki67/MIB 1 (Dianova, Hamburg, Germany, dia 505), CD 35 (DAKO, Ber-MAC-DRC, M 846), CMV (Dako, M 757) and p24 HIV antigen (Dako, M 857). Modifications of both the ABC [19] and the APAAP techniques [7] were used. Immunohistochemical double staining in the same sections was performed to show up antibodies to pan-keratin and Ki67. In situ hybridization studies were performed on formalin-fixed, paraffin-embedded tissue using standard procedures [2, 17] with a commercially available EBV DNA hybridization kit (PathoGene no. 32873, Enzo Biochem).

From each of 4 surgical specimens, 25–80 serial sections 20 µm each apart were prepared and stained for pan-keratin. Suitable cystic lesions from 2 of these cases were selected for computer-assisted 3-D reconstructions, which were performed using the VIDEOPLAN software (Zeiss/Kontron, Eching, Germany).

The degree of lymphoid infiltration of salivary parenchyma was scored in three grades: grade I, mild infiltration; grade II,

Table 1 Details of patients with cystic and noncystic HIV-associated parotid lymphoepithelial lesions (*CDC* Center for Disease Control)

Patient no.	Sex	Age	CDC stage (1993)	Mode of HIV infection	Diameter of Cysts (cm)	Presence of regular salivary parenchyma
Operative specimens						
1	M	61	C	Homosexual	0.5	+
2 Right	M	31	B	Unknown	1.5	+
Left					1.0	+
3	M	58	C	Blood products	(torn)	+
4 Right	M	40	B	Heterosexual	2.0	–
Left					3.0	–
5	M	27	B	Homosexual	3.5	–
6	F	35	B	i.v. Drug abuse	2.5	–
7 Right	M	49	B	Homosexual	1.5	–
Left					1.5	–
8	M	43	B	Heterosexual	3.0	–
9	F	71	C	Unknown	0.8	+
10 Right	M	59	B	Homosexual	1.0	+
Left					1.0	+
11	M	38	B	Homosexual	2.0	–
12	M	51	B	Homosexual	3.5	+
Post-mortem specimens						
13	M	46	C	Unknown	0.3	+
14	M	48	C	Homosexual	0.6	+
15	M	4	C	Diaplacentar	No cyst	+
16	M	7	C	Diaplacentar	No cyst	+
17	M	43	C	Homosexual	0.3	+

Table 2 Degree of lymphoid infiltration and lymphoepithelial duct lesions in different types of salivary glands (AIDS autopsy cases)

Localization	No. of patients	Degree of lymphoid infiltration[a]			Presence of lymphoepithelial duct lesions	Presence of cystic lesions
		I	II	III		
Parotid gland	88	30%	6%	6%	5 cases (6%)	3 cases (3%)
Submandibular gland	69	38%	7%	2%	1 case	–
Sublingual gland	16	19%	6%	–	1 case	–
Lacrimal gland	14	50%	7%	–	–	–

[a] See legend to Fig. 1

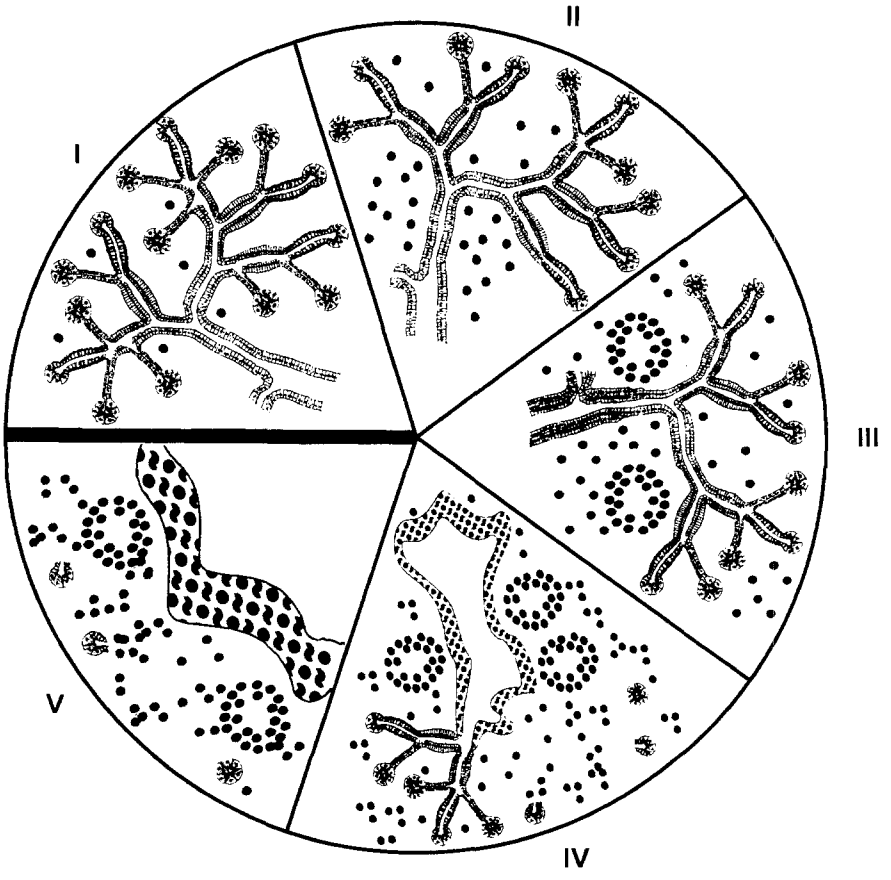

Fig. 1 Stepwise development of cystic lymphoepithelial lesion from salivary lobules. *I* Regular salivary parenchyma with mild lymphoid infiltration (grade 1); *II* moderate lymphoid infiltration and initial parenchymal atrophy in the centre of lobules (grade 2); *III* high degree of lymphofollicular hyperplasia and parenchymal atrophy (grade 3), lymphoepithelial hyperplasia of striated ducts; *IV* cystic dilatation of duct lesions; *V* large cystic lesion, only remnants of salivary parenchyma preserved

moderate infiltration and parenchymal atrophy; grade III, extensive infiltration with a high degree of parenchymal atrophy and presence of lymphoepithelial duct lesions (Fig. 1). The term "salivary lymphoepithelial lesion" was applied only to specimens demonstrating characteristic duct lesions (grade III).

Results

Surgical specimens

All 16 operative parotid specimens (representing 11 cyst enucleations and 5 lateral parotidectomies) exhibited lymphofollicular hyperplasia and the remnants of glandular parenchyma of varying degree (Figs. 1, 2). There was a continuous spectrum of cysts, ranging from small cysts each in the centre of a preserved salivary lobule (up to 0.5 cm diameter; Fig. 2b,c) to large spherical cystic lesions (up to 3.5 cm in diameter; Fig. 2d). The degree of intraglandular lymphatic infiltration and lymphofollicular hyperplasia correlated positively with the size of cysts and negatively with the amount of preserved salivary parenchyma. No correlation with CDC stages B or C was seen. Bilateral specimens regularly demonstrated comparable findings.

Computer-assisted 3-D reconstructions revealed complex cystic structures, projecting numerous branches to the periphery, communicating with scarcely preserved intercalated ducts and salivary acini (Figs. 2c, 3). All isolated epithelial components in routine single sections (Figs. 2c, 4b) were identified in reconstructions as parts of a ramified 3-D system, corresponding to the branching pattern of intralobular salivary ducts (Fig. 3). In addition, seemingly multiple cysts within a single lobule (Fig. 2d) were shown in 3-D reconstructions to belong to a single, bizarre-shaped cystic lesion. In fully developed cases hyperplastic secondary follicles were associated with intense distortion of cystic and ductal structures (Figs. 2d, 3).

The lymphoid infiltration of salivary parenchyma was most marked in the centre of lobules (Figs. 2b,c, 4a). Intercalated ducts and salivary acini were greatly diminished by this infiltration in fully developed lesions (Figs. 2d, 4a). Striated ducts, characterized by luminal oxyphilic cells and few basal cells, demonstrated infiltration by inflammatory cells, especially B lymphocytes, and to a minor degree by T lymphocytes and macrophages (Fig. 4a,b). These affected striated ducts exhibited a progressive increase of basal cell-like epithelial cells stained immunohistochemically with cytokeratin 14, and a parallel decrease, or loss, of cytokeratin 14-negative luminal oxyphylic cells (Figs. 4a,b, 5a). Intense proliferation of this prevailing cell type was confirmed by double staining with pan-keratin and the proliferation-associated antigen Ki67 (MIB 1; Fig. 6), whereas residual oxyphilic cells were regularly negative for Ki67. Participation of myoepithelial cells of acini and intercalated ducts, stained with alpha smooth muscle actin, was not seen (Fig. 5b). In a few large cysts parts of the wall were composed of a non-cornified, squamous

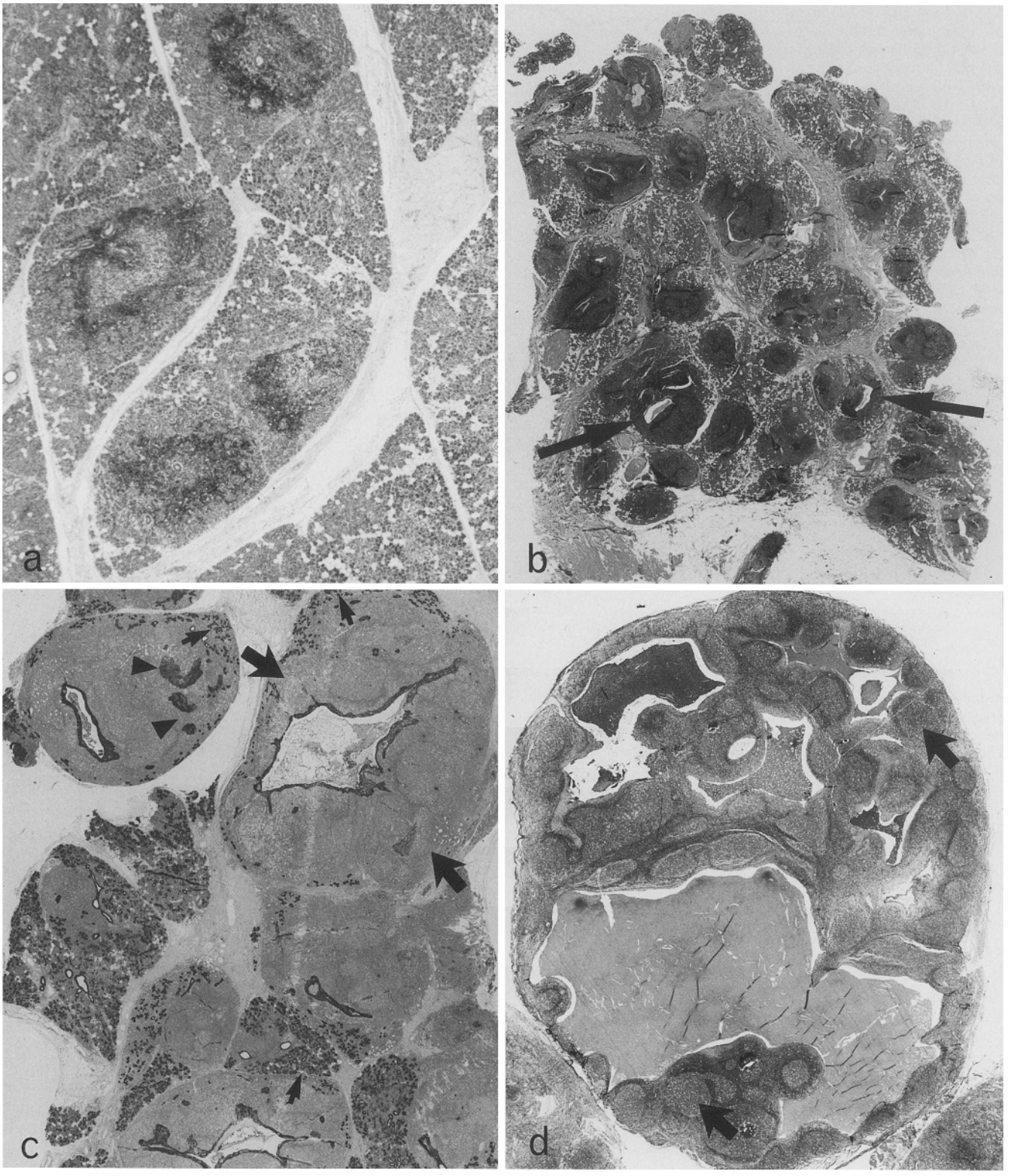

Fig. 2 **a–d** Stepwise development of cystic lymphoepithelial lesion from salivary lobules. **a** ×20, **b–d** ×8. **a** Early lesion with moderate lymphoid infiltration in the centre of all salivary lobules (autopsy specimen) T cell CD3 stain. **b** Advanced lesion with intense lymphoid infiltration and formation of small cysts (*arrows*) in the centre of lobules (lateral parotidectomy). HE. **c** The lobulated salivary gland architecture is still recognizable, remnants of salivary parenchyma are preserved in the periphery (*small arrows*), and medium-sized cysts and "lymphoepithelial islands" (*arrowheads*) are found near the centre of lobules. The *large arrows* point to the lobule used for 3-D reconstruction in Fig. 3 (lateral parotidectomy). Pan-keratin stain. **d** Fully developed, enucleated LEC with several, seemingly isolated, cystic components; lymphofollicular hyperplasia with large secondary follicles (*arrows*). PAS

Fig. 3 Computer-assisted 3-D reconstruction of a medium-sized cyst (*red*) projecting numerous ducts to the boundary of the lobule (*white*) and with adjacent hyperplastic secondary follicles (*green*; 42 serial sections)

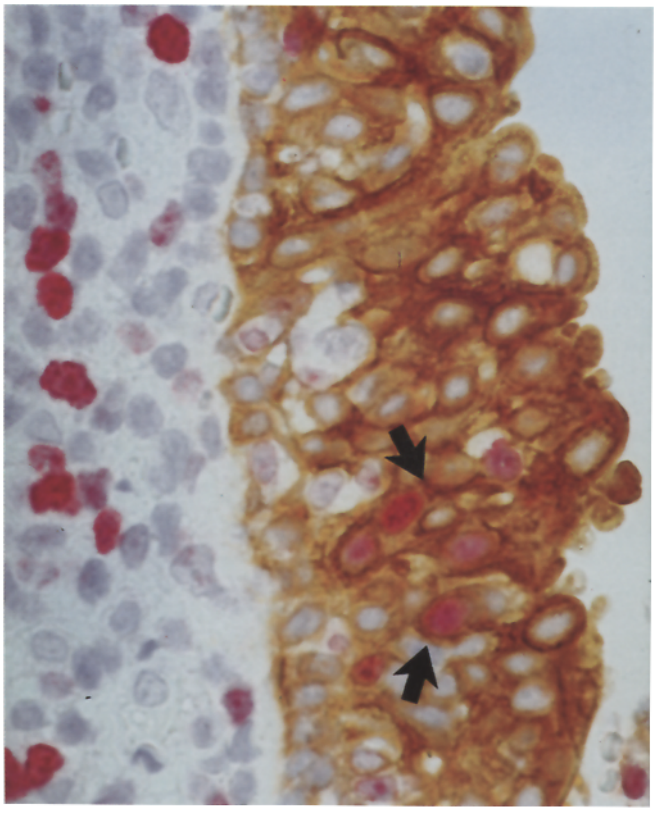

Fig. 6 Evidence of intense proliferation of basal cells: basal cells cytoplasmatically stained with pan-keratin (*brown*), the nuclei of proliferating basal cells (*arrows*) and lymphocytes stained red with Ki67/MIB 1 (surgical specimen). ×230

epithelium, lacking relevant lymphoid infiltration (not shown).

HIV p24 antigen was demonstrated only in follicular dendritic cells of secondary follicles, and not in the duct lesions (not shown). Active replication of cytomegalovirus (CMV) was excluded immunohistochemically in all 16 specimens. In addition, in situ hybridization for Epstein-Barr virus genome (EBV) was negative in all surgical parotid specimens. Intraparotid lymph nodes were identifiable in 4 of the 16 operative specimens. In 2 of these nodes salivary inclusions were demonstrated; lymphoepithelial lesions or cysts were not seen to be associated with these lymph node inclusions (Fig. 7).

Post-mortem specimens

In the parotid specimens obtained at 88 autopsies performed on AIDS patients, intense intraglandular lymphoid infiltration with characteristic duct lesions was seen in 5 cases; cystic lesions were found in 3 cases (Fig. 2a, Tables 1, 2). All the cysts were small (diameter up to 0.6 cm), demonstrating a flattened epithelium. As seen in Table 2, the degree of lymphoepithelial alteration proved to be most intense in the parotid gland, moderate in the submandibular gland, and mild in the sublingual and lacrimal gland; cystic lesions were seen exclusively in parotid glands. However, the degree of alteration correlates very closely in different salivary glands of the same patient. The degree of lymphoid infiltration was generally far less intense in autopsy specimens than in surgical specimens (Fig. 1).

Extensive examination of parotid glands in several sections revealed intraglandular lymph nodes in about 80% of cases. Lymphoepithelial lesions associated with

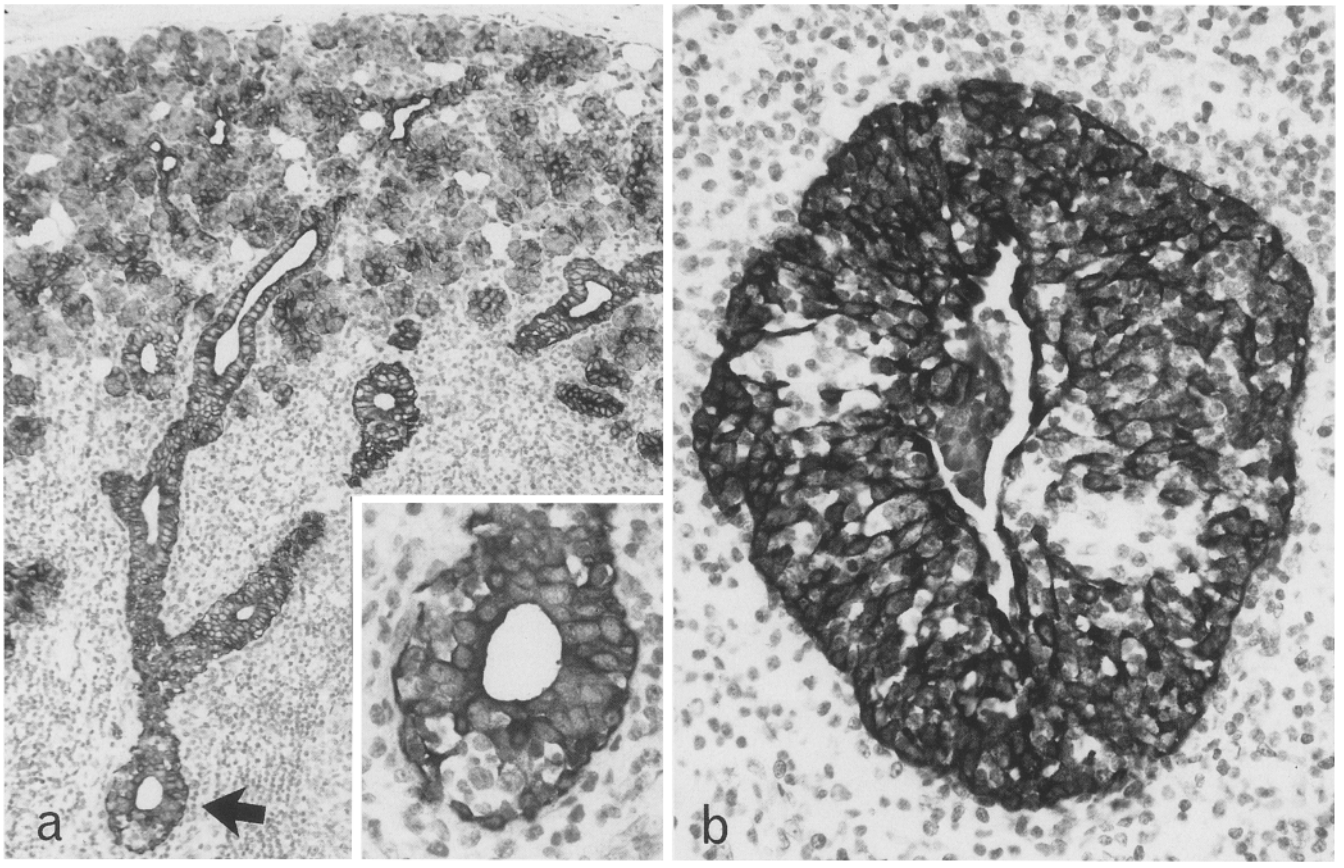

Fig. 4a, b Stepwise development of lymphoepithelial duct lesion (surgical specimen). Pan-keratin stain. **a** Intraglandular lymphofollicular hyperplasia with ductal infiltration and initial lymphoepithelial alteration of a central part of a striated duct (*arrow, inset*); parenchyma preserved at the periphery. ×112, *inset* ×300. **b** So-called lymphoepithelial island: cross section of a striated duct with high degree of lymphoepithelial hyperplasia. ×180

salivary inclusions in lymph nodes were not found. In 47 of the 88 autopsies CMV infection was shown in different organs; a mostly mild involvement of the salivary glands was seen by light microscopy and immunohistochemistry in 28 cases (32% of all autopsies). Nevertheless, in all 5 parotid specimens with lymphoepithelial lesions CMV manifestation was excluded and in situ hybridization for EBV DNA was negative in these cases. HIV p24-antigen was demonstrated in residual follicular dentritic cells of secondary follicles.

Discussion

Usually only fully developed, large parotid cysts are resected in HIV-infected patients; furthermore these cysts are mostly enucleated. These facts make the morphological study of the pathogenesis of HIV-associated LEC difficult. Most authors have favoured a development from pre-existing salivary gland inclusions in intraparotid lymph nodes [3, 6, 14, 15, 22, 24, 26, 28, 33, 34, 38]. Other investigations have described a Sjögren-like lymphoepithelial lesion of parotid parenchyma without relation to cysts [8, 21, 37] or concomitant with cysts [9, 23, 35, 36]. Nevertheless, neither hypothesis has yet been substantiated.

In the present study a thorough examination of surgical and autopsy specimens revealed a continuous morphological spectrum of noncystic and cystic lymphoepithelial lesions, sequentially deriving from parotid salivary lobules (Figs. 1, 2): in a few precursor lesions the multilobular gland architecture was well preserved and the lymphoid infiltration restricted to the centre of lobules; cysts were either absent or still small (Fig. 2a–c). The majority of enucleated, fully developed cysts demonstrated high-grade lymphofollicular hyperplasia devoid of regular salivary parenchyma (Fig. 2d). However, the demonstration of remnants of acini and ducts suggests that fully developed LECs represent an advanced stage of cystic lymphoepithelial alteration of salivary parenchyma (Figs. 2c, 4a,b). The uniform alteration of adjacent lobules and of the four bilateral specimens, furthermore, indicates a generalized lymphoepithelial lesion of parotid parenchyma.

This hypothesis is also supported by 3-D reconstructions of large cystic lesions revealing an architecture corresponding to the branching duct system of salivary lobules (Figs. 2c, 3). Apparently multiple cystic lesions within one salivary lobule in routine sections (Fig. 2d) merge into a single continuous cystic complex in 3-D reconstructions (Fig. 3). This bizarre distortion of large ductal cysts seems to be the result of a high-grade expansion of the lymphofollicular hyperplasia (Fig. 2d).

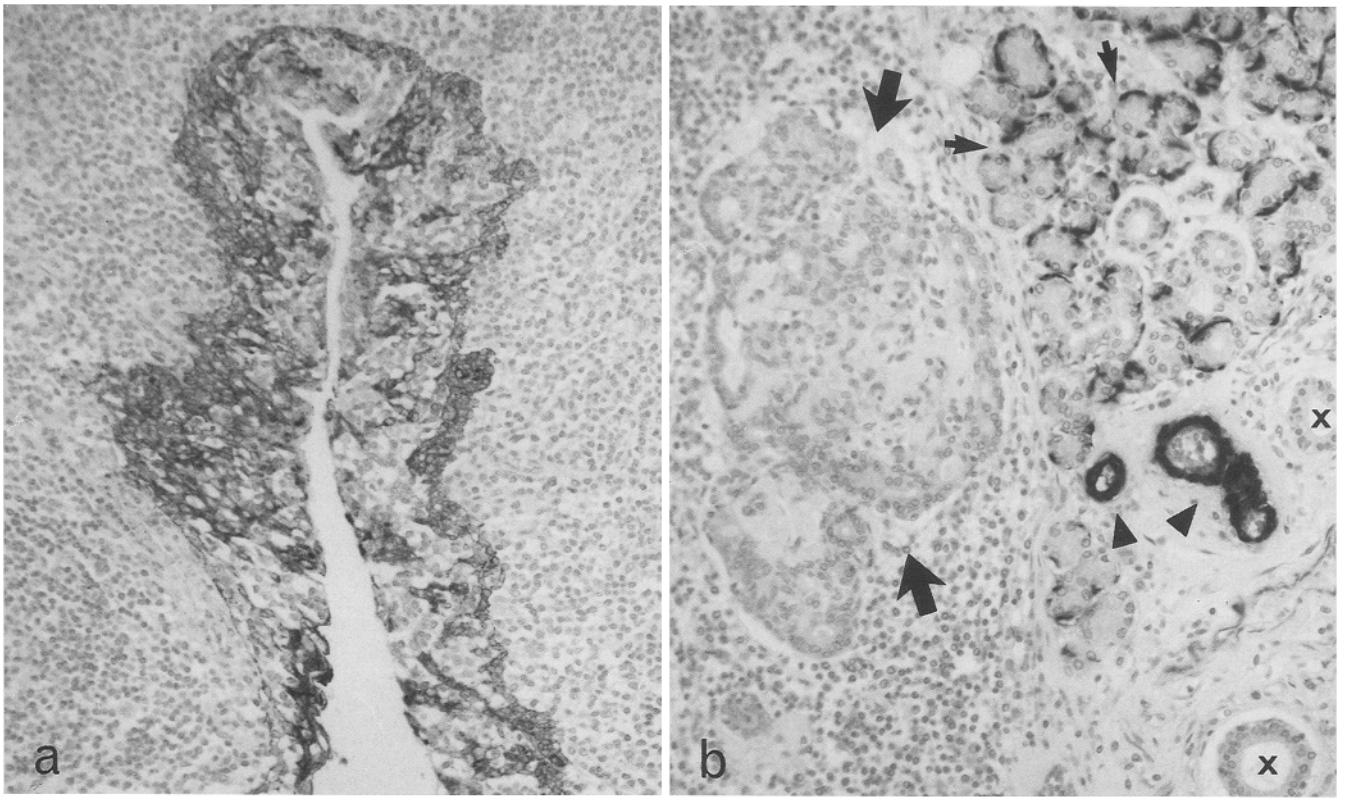

Fig. 5a, b Evidence for a predominance of basal cells in HIV-related lymphoepithelial duct lesions (surgical specimen). **a** Almost all epithelial cells of advanced lesions stained for cytokeratin 14. ×36. **b** Myoepithelial cells (*small arrows*) and blood vessels (*arrowheads*) are stained for alpha smooth muscle actin; striated ducts (*X*) and lymphoepithelial lesion (*large arrows*) are alpha actin-negative. ×45

Whereas surgical specimens generally demonstrated intense lymphatic hyperplasia and mostly advanced cystic lesions, the affected autopsy parotid specimens showed comparatively mild alterations: lymphoepithelial duct lesions with at most moderate lymphoid infiltration were seen in 6%, and associated small ductal cysts in half of these cases (3%; Fig. 2a). As the surgical cases obviously represent selected material, these figures from autopsies might indicate the actual prevalence of this salivary gland lesion in HIV-infected patients.

Intense work-up of parotid glands in multiple sections often reveals intraglandular lymph nodes. Owing to simultaneous embryological development, salivary gland inclusions in these lymph nodes are reported to be frequent [1, 18, 29, 32]. In our material these inclusions did not show lymphoepithelial duct lesions or cysts (Fig. 7), further calling in question the current hypothesis that HIV-associated lymphoepithelial cysts develop from lymph node inclusions.

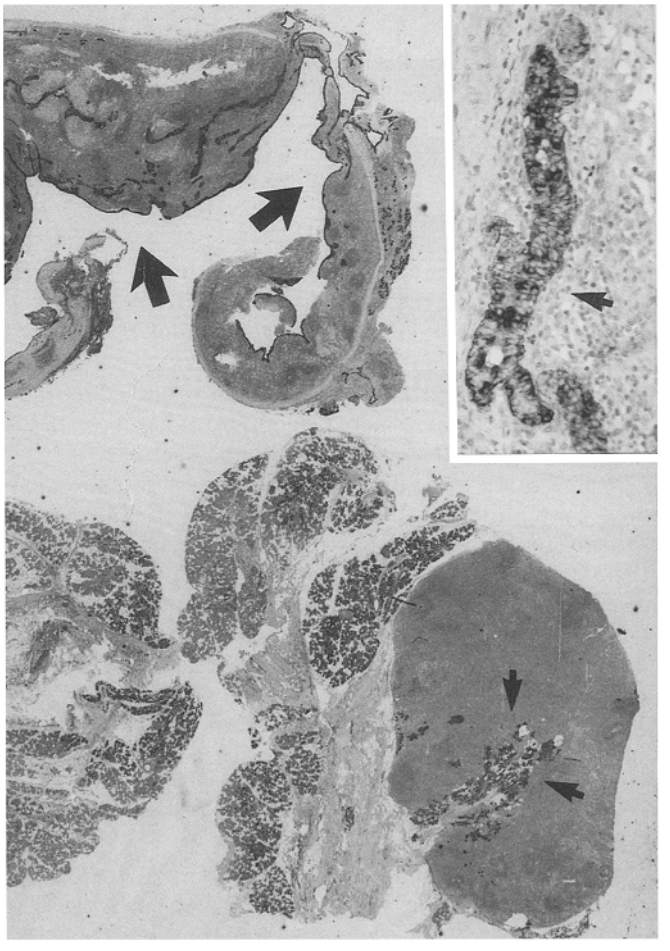

Fig. 7 Cystic lymphoepithelial lesion (*large arrows*; artifically torn) and regular salivary parenchyma, adjacent intraparotid lymphnode with inclusion of salivary parenchyma (*small arrows*; *inset*) lacking lymphoepithelial alteration (surgical specimen). Pan-keratin stain, ×6, *inset* ×110

Table 3 Epidemiological, clinical and histomorphological data on different types of parotid lymphoepithelial cysts

	HIV-related lymphoepithelial cysts[a, b]	Sjögren's disease[b]	Sporadic lymphoepithelial cysts[b]
Frequency of cysts	Up to 100%	3%	100%
Quantity of cysts	Mostly multiple	Sometimes multiple	Mostly singular
Size of cysts	1–4 cm	0.5–1 cm	1–2 cm
Cyst epithelium	Lymphoepithelial, sometimes squamous	Lymphoepithelial	Lymphoepithelial, sometimes squamous
Presence of lymphoepithelial islands	+++	+++	–
Formal pathogenesis	Ductal cysts within salivary lymphoepithelial lesion	Ductal cysts within salivary lymphoepithelial lesion	Presumably epithelial lymph node inclusions (?)
Serological findings	HIV positivity	Rheuma factor, SS-A/B antibodies	–
Sex predilection	Predominantly males (due to AIDS risk groups)	Predominantly females	–
Age predilection	20–50	40–70	60–80

[a] Results of presented study
[b] According to literature [1, 10, 12, 14, 16, 18, 20, 27, 31, 32]

Our study reveals morphological similarities of HIV-associated cystic lymphoepithelial lesions with conventional Sjögren's syndrome (synonym: benign lymphoepithelial lesion), demonstrating secondary intraglandular lymphofollicular hyperplasia associated with progressive loss of salivary parenchyma and the development of lymphoepithelial duct lesions (Table 3). In Sjögren-associated duct lesions subtyping of cytokeratins has revealed an increase of cytokeratin 14-positive epithelial cells. Since cytokeratin 14 stains both basal cells of striated/excretory ducts and myoepithelial cells [11, 13], involvement of myoepithelial cells has been postulated by some but not all, authors (epimyoepithelial islands/sialadenitis) [4, 10, 12, 27, 31]. In HIV-associated lesions investigations with cytokeratin subtypes have not been reported so far. Our immunohistochemical study of HIV-associated duct lesions identified a basal cell hyperplasia of striated ducts; involvement of myoepithelial cells has to be excluded because alpha smooth muscle actin cannot be detected immunohistochemically in these cells (Figs. 5, 6). The physiological presence of basal cells in striated ducts and their absence in intercalated ducts presumably explains why these lesions develop from striated ducts.

What are the reasons for the frequent and often enormous cystic dilatation of the duct lesions in HIV-associated cases? The loose and irregular basal cell hyperplasia seems to be one essential condition that enables the intense cystic dilatation of the otherwise narrow and tense striated ducts. Nevertheless, whereas in conventional Sjögren disease only about 3% of parotid specimens showed cyst formation (Salivary Gland Register of the U.S. Armed Forces Institute of Pathology) [10]), all of our HIV-associated surgical specimens demonstrated cystic lesions. As the lymphofollicular hyperplasia in HIV-associated lesions generally exceeds the lymphoid infiltration seen in Sjögren's lesions [21, 23, 37], this high degree of lymphoid hyperplasia in early disease stages might represent an additional factor in cyst formation by compression of excretory ducts. However, comparable large cysts were not found in our autopsy cases; the small size of the cysts in these may be the result of reduced lymphoid infiltration and hence reduced ductal obstruction caused by a final generalized depletion of lymphoid tissue in AIDS patients.

Whereas our autopsy findings demonstrated a minor lymphoid infiltration in the other salivary glands as well, the maximum alteration is regularly encountered in parotid glands [1, 10, 16]. This fact presumably explains why almost all surgical specimens, including all our cases, are from parotid glands [9, 23, 28, 29]. It has been repeatedly reported that squamous epithelium can be found in LEC [3, 4, 9, 14, 15, 20, 28, 33]. We found this type of epithelium only in large cysts. This suggests a further step towards squamous metaplasia of the lymphoepithelial duct lesions, presumably not connected with the primary pathogenesis but secondary to a long-standing high pressure from the entrapped cyst fluid.

Our finding of parotid lymphoepithelial lesions in 6% of AIDS autopsies surpasses by far the low prevalence of conventional Sjögen's syndrome in the general population (primary Sjögren's syndrome in about 0.1% of females owing to anti-SS-B antibody [16]). Sjögren's syndrome is thought to be a cytokine-mediated autoimmune reaction against salivary gland structures; genetic factors (HLA-DR 3) may predispose; viruses (especially EBV) are discussed as a cofactor in the pathogenesis [10, 16, 21]. Concerning HIV-associated lesions Itescu reported a "diffuse infiltrating CD8 lymphocytosis syndrome" with salivary and pulmonary involvement, associated with HLA-DR 5 [21]. Whether infectious co-factors play a pathogenetic role is unclear. Like others [3, 9, 14, 23, 30], we demonstrated HIV p24-antigen only in follicular dentritic cells, and not in duct lesions, and we excluded a positive correlation of CMV and EBV to salivary lymphoepithelial lesions. For a detailed comparison of epidemiological, clinical and histomorphological findings in HIV-associated lymphoepithelial cysts, Sjögren's disease and sporadic lymphoepithelial cysts, see Table 3.

In summary, our observations from different disease stages including autopsy material cast some doubt on the prevailing pathogenetic hypothesis that HIV-associated lymphoepithelial cysts derive from pre-existing salivary gland inclusions in intraparotid lymph nodes. Rather, we suggest that a secondary lymphoid infiltration of parotid lobules triggers a lymphoepithelial duct lesion of striated ducts, characterized immunohistochemically as a basal cell hyperplasia. The subsequent development to a multifocal and bilateral cystic lymphoepithelial lesion is presumably enhanced by duct compression through high-grade lymphofollicular hyperplasia in early disease stages. Further studies are needed to elucidate the aetiology of the secondary lymphoid infiltration of salivary parenchyma.

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References

1. Bernier JL, Bhaskar SN (1958) Lymphoepithelial lesions of salivary glands. Cancer 6:1156–1179
2. Brigati DJ, Myerson D, Leary JJ, Spalholz B, Travis SZ, Fong CKY, Hsiung GI (1983) Detection of viral genomes in cultured cells and paraffin-embedded tissue sections using biotin-labeled hybridization probes. Virology 126:32–50
3. Bruner JM, Cleary KR, Smith FB, Batsakis JG (1989) Immunocytochemical identification of HIV (p24) antigen in parotid lymphoid lesions. J Laryngol Otol 103:1063–1066
4. Caselitz J, Osborn M, Wustrow J, Seifer G, Weber K (1986) Immunohistochemical investigations on the epimyoepithelial islands in lymphoepithelial lesions. Lab Invest 55:427–432
5. Center For Disease Control (1993) Revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. MMWR Morb Mortal Wkly Rep 41:1–19
6. Cleary KR, Batsakis JG (1990) Lymphoepithelial cysts of the parotid region: a 'new face' on an old lesion. Ann Otol Rhinol Laryngol 99:162–164
7. Cordell JL, Falini B, Erber WN (1984) Immunoenzymatic labeling of monoclonal antibodies using immune complexes of alkaline phosphatase and monoclonal anti-alkaline phosphatase (APAAP)complexes. J Histochem Cytochem 32:219–229
8. Couderc L-J, D'Agay M-F, Danon F, Harzie M, Brocheriou C (1987) Sicca complex and infection with human immunodeficiency virus. Arch Intern Med 147:898–901
9. D'Agay M-F, Roquancourt A de, Peuchmaur M, Janier M, Brocheriou C (1990) Cystic benign lymphoepithelial lesion of the salivary glands in HIV-positive patients. Virchows Arch [A] 417:353–356
10. Daniels TE (1992) Benign lymphoepithelial lesion and Sjögren's syndrome. In: Ellis GL, Auclair PL, Gnepp DR (eds) Surgical pathology of the salivary glands. Saunders, Philadelphia, pp 83–106
11. Dardick I, Parks WR, Little J, Brown DL (1988) Characterization of cytoskeletal proteins in basal cells of human parotid salivary gland ducts. Virchows Arch [A] 412:525–532
12. Donath K, Seifert G (1972) Ultrastruktur und Pathogenese der myoepithelialen Sialadenitis. Virchow Arch [A] 356:315–329
13. Draeger A, Nathrath WBJ, Lane EB, Sundström BE, Stigbrand TI (1981) Cytokeratins, smooth muscle actin and vimentin in human normal salivary gland and pleomorphic adenomas. APMIS 99:405–415
14. Elliott JN, Oertel YC (1989) Lymphoepithelial cysts of the salivary glands. Am J Clin Pathol 93:39–43
15. Finfer MD, Schinella RA, Rothstein SG, Persky MS (1988) Cystic parotid lesions in patients at risk for the acquired immundodeficiency syndrome. Arch Otolaryngol Head Neck Surg 114:1290–1294
16. Fox RJ, Kang Ho-Il (1992) Pathogenesis of Sjögren's syndrome. Rheum Dis Clin North Amer 18:517–537
17. Gall JG, Pardue ML (1971) Nucleid acid hybridization in cytological preparations. Methods Enzymol 38:470–480
18. Godwin JT (1952) Benign lymphoepithelial lesion of parotid gland; report of 11 cases. Cancer 5:1089–1103
19. Hsu SM, Raine L, Fanger H (1981) Use of avidin–biotin peroxidase complex (ABC) in immunoperoxidase techniques: a comparison between ABC and unlabeled antibody (PAP) procedures. J Histochem Cytochem 29:577–584
20. Isaacson PG (1994) Malignant lymphomas of the salivary gland. In: Isaacson PG, Norton AJ (eds) Extranodal lymphomas. Churchill Livingstone, Edinburgh, pp67–83
21. Itescu S, Brancato LJ, Buxbaum J, Gregersen PK, Risk CC, Croxson TS, Solomon GE, Winchester R (1990) A diffuse infiltrative CD8 lymphocytosis syndrome in human immunodeficiency virus (HIV) infection: a host immune response associated with HLA-DR5. Ann Internal Med 112:3–10
22. Kornstein MJ, Parker GA, Mills AS (1988) Immune histology of the benign lymphoepithelial lesion in AIDS-related lymphadenopathy. Hum Pathol 19:1359–1361
23. Labouyrie E, Merlio JPH, Beylot-Barry M, Delord B, Vergier B, Brossard G, Lacoste D (1993) Human immunodeficiency virus type 1 replication within cystic lymphoepithelial lesion of the salivary gland. Am J Clin Pathol 100:41–46
24. Mandel L, Reich R (1992) HIV parotid gland lymphoepithelial cysts. Oral Surg Oral Med Oral Pathol 74:273–278
25. Morris MR (1988) Unusual lymphadenopathies or cystic lesions and the parotid gland. Otol Head Neck 98:268
26. Morris MR, Moore DW, Shearer GL (1987) Bilateral multiple lymphoepithelial cysts of the parotid gland. Otol Head Neck 97:87–90
27. Palmer RM, Eveson JW, Gusterson BA (1986) "Epimyoepithelial" islands in lymphoepithelial lesions. Virchows Arch [A] 408:603–609
28. Poletti A, Manconi R, Volpe R, Carbone A (1988) Study of AIDS-related lymphadenopathy in the intraparotid and perisubmaxillary gland lymph nodes. J Oral Pathol 17:164–167
29. Ryan JR, Ioachim HL, Marmer J, Lebeau JM (1985) Acquired immune deficiency syndrome-related lymphadenopathies presenting in the salivary gland lymph nodes. Arch Otolaryngol 111:554–556
30. Schiodt M, Greenspan D, Daniels TE (1989) Parotid gland enlargement and xerostomia associated with labial sialadenitis in HIV-infected patients. J Autoimmun 2:415–425
31. Seifert G (1995) Ätiologie und Differentialdiagnose der Sialadenitis. Laryngorhinootologie 74:274–281
32. Seifert G, Waller D (1982) Klassifikation der Parotiszysten - Differentialdiagnose der Speichelgangszysten und lymphoepithelialen Zysten. Laryngol Rhinol Otol 61:78–86
33. Shaha A, DiMaio T, Webber C, Thelmo W, Jaffe BM (1993) Benign lymphoepithelial lesions of the parotid. Am J Surg 166:403–406
34. Smith FB, Rajdeo H, Panesar N, Bhuta K, Stahl R (1988) Benign lymphoepithelial lesion of the parotid gland in intravenous drug users. Arch Pathol Lab Med 112:742–745
35. Sperling NM, Pi-Tang Lin, Lucente FE (1990) Cystic parotid masses in HIV infection. Head Neck 12:337–341
36. Tunkel DE, Loury MC, Fox CH, Goins MA, Johns ME (1989) Bilateral parotid enlargement in HIV-seropositive patients. Laryngoscope 99:590–595
37. Ulirsch RC, Jaffe ES (1987) Sjögre's syndrome-like illness associated with the acquired immunodeficiency syndrome-related complex. Hum Pathol 18:1064–1068
38. Werning JT (1992) Infectious and systemic diseases. In: Ellis GL, Auclair PL, Gnepp DR (eds) Surgical pathology of the salivary glands. Saunders, Philadelphia, pp 39–59