Virchows Arch. A Path. Anat. and Histol. 388, 13–38 (1980)

Virchows Archiv A

Histologic Subclassification of the Cystadenolymphoma of the Parotid Gland*

Analysis of 275 Cases

G. Seifert, H.G. Bull, and K. Donath

Institute of Pathology, University of Hamburg and Tumor Center Hamburg, Martinistraße 52, D-2000 Hamburg 20, Federal Republic of Germany

Summary. Cystadenolymphomas (CAL) of the parotid gland are variable in their epithelial differentiation and the ratio of the epithelial tumor component to lymphoid stroma. Two hundred and seventy five cases of CAL from the files of the Salivary Glands Register of the Institute of Pathology, University of Hamburg (1965–1979) were analysed. Their pathogenesis from parenchyma included in regional lymph nodes is discussed. The following subclassification was established.

1. Depending on to the ratio of epithelial tumor component to lymphoid stroma, three subtypes were distinguished. Subtype 1, "typical CAL" with an epithelial tumor component of 50%, amounted to 77% of all cases of CAL studied. Oncocytic differentiation and focal metaplasia to goblet cells or squamous epithelium was also found. 13.5% of CAL were classified as subtype 2, "stroma-poor CAL" with an epithelial tumor component of 70 to 80%. The tumor structure was similar to that of an oncocytoma in places. Two per cent of the CAL were in subtype 3, "stroma-rich CAL" with an epithelial tumor component of only 20 to 30%. Subtype 3 was found solely in men. The average age at presentation (61 years) was slightly lower than that of all the cases studied (65 years).

2. In 7.5% of the cases large areas of squamous cell metaplasia and regressive changes was found within a CAL. These cases were classified as subtype 4 ("metaplastic CAL"). The average age was 67 years. The case histories showed that 20% of these metaplastic CAL had previously been irradiated.

3. Bilateral CAL was found in 7.5% of the cases. In 4% multifocal CAL occurred in the parotid gland unilaterally. Recurrences were observed in 2% of all CAL.

4. Carcinoma in CAL is rare (we found two cases in our own material). In 50% of all cases reported radiotherapy was mentioned in the case histories.

* Dedicated to Prof. Dr. W. Sandritter, Freiburg/Br., on the occasion of his 60th birthday

Offprint requests to: Prof. Dr. G. Seifert

0340-1227/80/0388/0013/$05.20

5. Malignant tumors coincident with CAL were recorded in 3% of the cases.

6. The lymphoid stroma showed reaction patterns similar to those of the regional lymph nodes. These included granulomatous changes (foreign body granuloma with cholesterol deposits, tuberculosis) and tumor metastases. In the neighborhood of oncocytic tumor epithelium focal accumulations of plasma cells forming IgA and IgG were found.

Metaplasia to squamous epithelium is believed to be caused by circulatory disturbances, irradiation, and other noxae. In the differential diagnosis of the stroma-poor subtype 2, oncocytoma and cystic sialadenoma must be excluded, and in the differential diagnosis of subtype 4 (the metaplastic CAL), sebaceous adenoma, mucepidermoid tumor, squamous cell carcinoma, lymphoepithelioma, and other non-tumorous lesions of the parotid gland (lymphoepithelial cysts, myoepithelial parotitis) must be ruled out. Our findings suggest that CAL develops from parenchyma included in parotid lymph nodes with the oncocytic ductal epithelium representing the neoplastic component.

Key words: Cystadenolymphoma – Subclassification – Pathogenesis – Differential diagnsosis – Stromal reactions.

In the WHO classification of tumors of the salivary glands (Thackray and Sobin 1972), the cystadenolymphoma (CAL, Warthin's tumor) belongs to the group of monomorphic adenomas. It is frequently encountered in salivary glands (12.5% of all salivary gland tumors and 70% of all monomorphic adenomas are CAL). CAL has several characteristics: a preferential occurrence in the parotid, predilection for men and highest incidence in the 6th to 7th decade; it is a benign, well encapsulated tumor of greyish brown cut surface with small cysts, bilateral or multiple occurrence in about 10% of the cases, predominantly oncocytic epithelial differentiation, and organoid lymphoid stroma (Pape 1963; Evans and Cruickshank 1970; Thackray and Lucas 1974; Seifert and Donath 1976a, b; Matteson et al. 1976).

A retrospective analysis of 275 cases of CAL which had been recorded in the Salivary Glands Register of the Institute of Pathology, University of Hamburg, in the period from 1965 to 1979, revealed a number of findings which form the basis of the subclassification of CAL put forward in this study. The main criteria of the subclassification were: ratio of epithelial tumor component to lymphoid stroma, specific epithelial differentation and reaction patterns of the lymphoid stroma. From this subclassification further information was gained regarding the pathogenesis of CAL, from parenchyma included in regional lymph nodes. Criteria for the differential diagnostic exclusion of other tumors of the parotid gland (oncocytoma, mucoepidermoid tumor, squamous cell carcinoma) and lymphoepithelial cysts were also obtained.

Material and Methods

The 275 cases of CAL which had been examined in the years 1965 to 1979 were evaluated according to a uniform diagnostic system (Bull 1979). This included clinical data (age, sex, location, previous

Table 1. Age and sex distribution of 275 cases of cystadenolymphomas of the parotid gland

Age (years)	Sex		Total number *n*
	m.	f.	
0–10	–	–	–
11–20	–	–	–
21–30	2	1	3
31–40	3	2	5
41–50	14	5	19
51–60	52	12	64
61–70	87	24	111
71–80	40	21	61
more than 80	6	2	8
unknown	3	1	4
Sum	207	68	275

Table 2. Subclassification of 275 cases of cystadenolymphomas (CAL) of the parotid gland

Subtype	Sex		Total number	
	m.	f.	*n*	%
1 Typical CAL	160	51	211	77
2 Stroma-poor CAL	28	9	37	13.5
3 Stroma-rich CAL	6	–	6	2
4 Metaplastic CAL	13	8	21	7.5
Sum	207	68	275	100

radiotherapy, recurrences), macroscopic findings (tumor size, formation of a capsule, adjacent parotid tissue), epithelial differentiation (oncocytes, squamous epithelium, goblet cells, sebaceous epithelium), histological architecture (papillae, macro- and microcysts, solid sheets of cells), secretory pattern of epithelial cells, structure of lymphoid stroma (amount, formation of lymph follicles, cellular differentation, granuloma, etc.) and the ratio of epithelial tumor component to lymphoid stroma. For histological evaluation paraffin-embedded sections were stained with: haematoxylin-eosin, PAS or astra blue. In addition, semi-thin sections embedded in resin were examined and the indirect peroxidase method of Taylor and Burns (1974) was applied to demonstrate plasma cells forming immunoglobulins. The age and sex distribution of our cases is shown in Table 1. The highest incidence was in the 7th decade. CAL was found three times more often in men than in women.

Subclassification of Cystadenolymphomas

From the ratio of epithelial tumor component to lymphoid stroma three subtypes were distinguished: subtype 1 ("typical CAL"), subtype 2 ("stroma-poor CAL"), subtype 3 ("stroma-rich CAL"). Subtype 4 was characterized by large areas of epithelial metaplasia and defined as "metaplastic CAL". The percentages of the individual subtypes found in the total number of cases studied and the age and sex distributions are shown in Table 2.

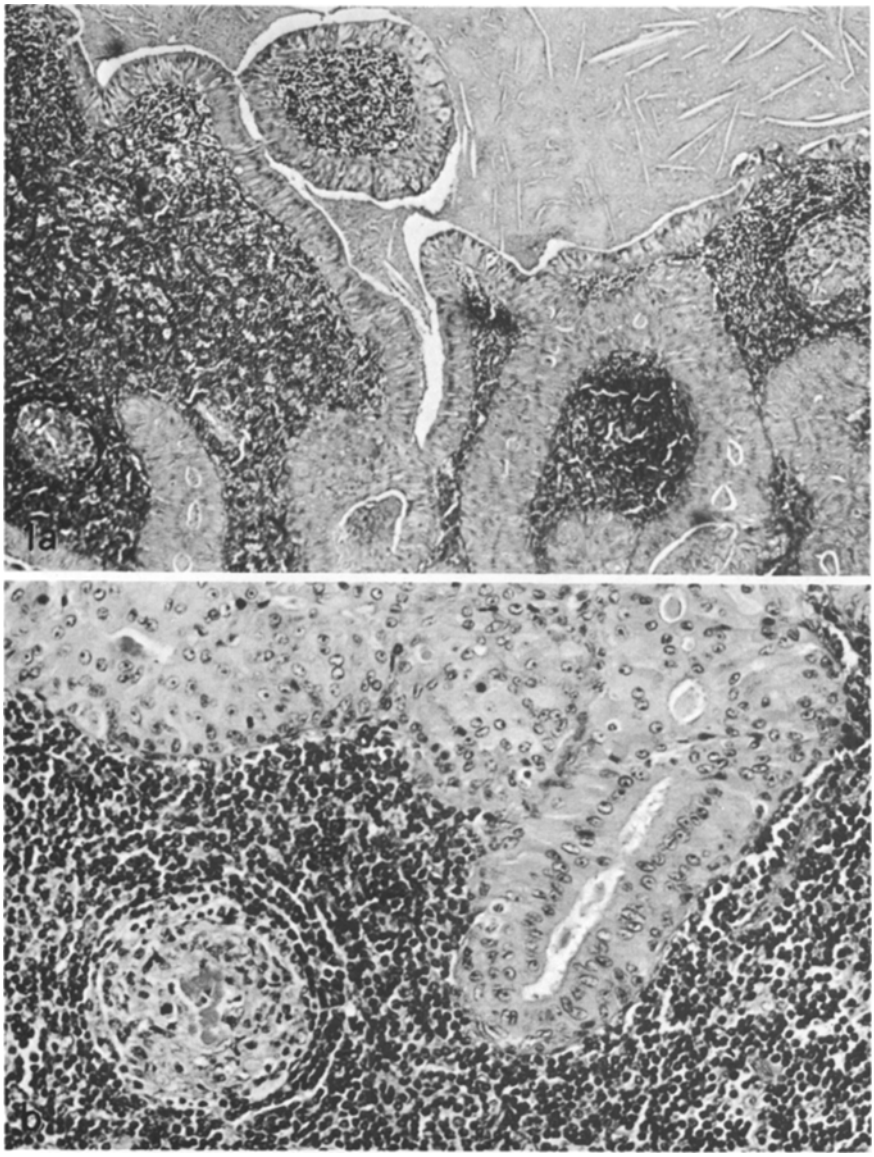

Fig. 1a and b. Cystadenolymphoma, subtype 1 (J-No. 18917/78): **a** Cystic and papillar arrangement of the oncocytic epithelial component, surrounded by a lymphoid stroma. **b** Lymphoid stroma with a lymph follicle. Haematoxylin-eosin. **a** ×63, **b** ×160

Subtype 1 ("Typical CAL")

Subtype 1 amounted to 77% of all our CAL cases. The ratio of epithelial tumor component to lymphoid stroma was 1:1 (Fig. 1).

The epithelial cells were arranged in two rows and possessed acidophilic,

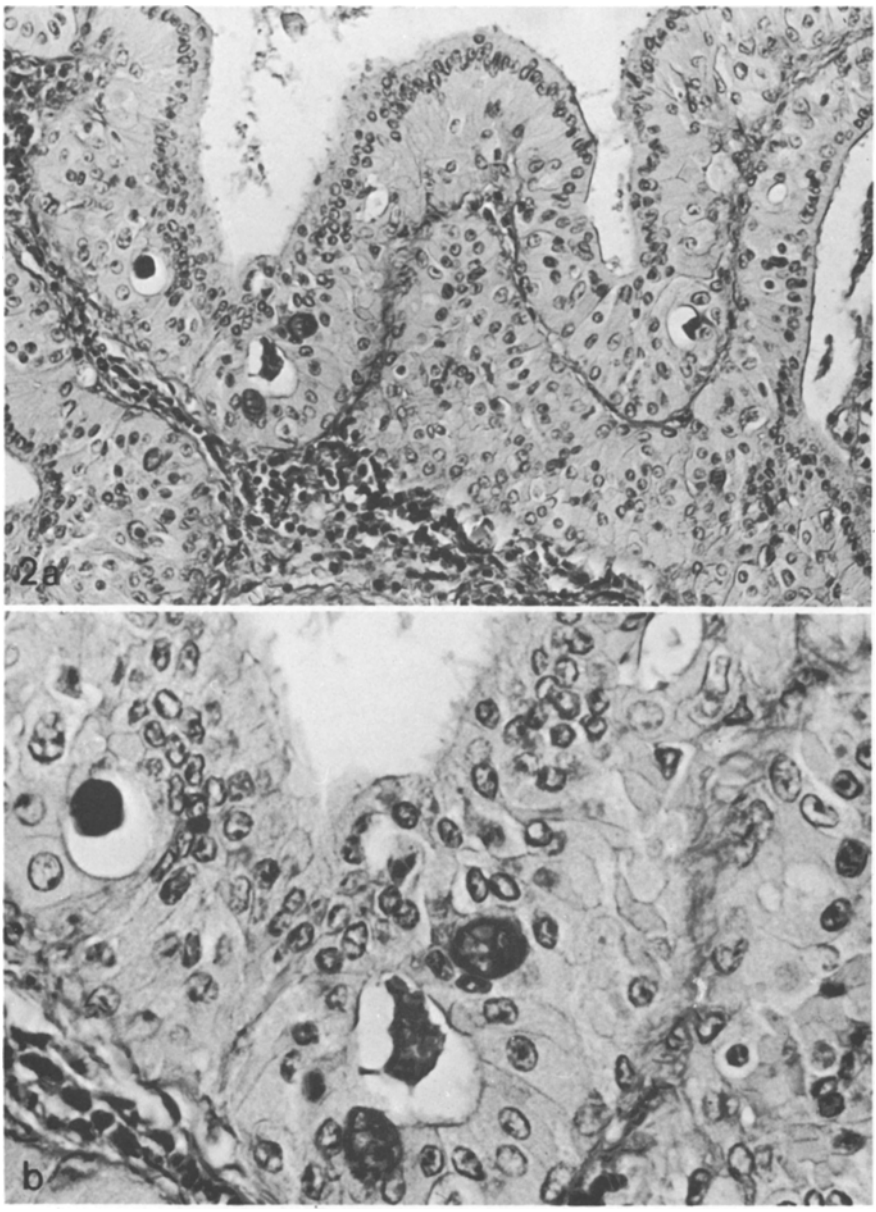

Fig. 2a and b. Cystadenolymphoma, subtype 1 (J-No. 998/77): goblet cell metaplasia with scattered mucus-producing cells between the oncocytic cells. PAS reaction. **a** ×160, **b** ×400

oncocytic cytoplasm. They formed papillary projections into the lumina of micro- and macrocysts. The cysts contained an acidophilic secretion, occasionally desquamated epithelial cells, lymphocytes, macrophages and crystalloid precipitations. In the basal row, the epithelial cells were cuboidal or pyramidal in shape,

while the apical row consisted of tall cylindrical epithelial cells. Signs of apocrine secretion were frequently noted.

45% of the cases of subtype 1 CAL showed an exclusively oncocytic differentiation of the epithelium. In 23% of the cases, scattered groups of goblet cells were seen (Fig. 2), in 11% islands of squamous epithelial cells, and in 21% foci of both goblet cell and squamous cell metaplasia were found. In about one third of the cases, focal epithelial proliferations without a lymphoid stroma component were observed in the epithelium. In two cases these epithelial proliferations formed oncocytic microadenomas.

The lymphoid stroma consisted of lymphoreticular tissue in which lymph follicles were enclosed. The cellular composition of the lymphoid stroma was that of normal lymph node tissue (predominantly lymphocytes and centroblasts, some plasma cells, mast cells, and macrophages). In the lymph follicles clearly activated germinal centers reacting positive to a PAS stain were sometimes observed, thus demonstrating immunological activity.

With the indirect immuno-peroxidase method, focal accumulations of plasma cells producing IgA and IgG were demonstrable in the lymphoid stroma directly adjacent to the oncocytic epithelial component. The number of plasma cells forming IgA or IgG was almost identical. In the center of large areas of lymphoid stroma, groups of plasma cells were also observed. Here, slightly more IgG than IgA was produced and small amounts of IgM were also found (Fig. 3).

Subtype 2 ("Stroma-Poor CAL")

The epithelial component of this tumor was 70 to 80% of the total (Fig. 4). 13.5% of the cases studied were classified as subtype 2. There were no significant differences between subtype 1 and subtype 2 in age or sex distribution.

The epithelial component had a distinct tendency to proliferate by forming nests of tubular cells. In 71% of the cases, isolated areas of goblet cell or squamous epithelial cell metaplasia were found. In the poorly developed lymphoid stroma lymph follicles with poorly activated germinal centers were also noted occasionally.

In individual tumor areas the tumor structure was largely identical with that of the classic oncocytoma, but differed in that examination of the entire tumor disclosed the existence of several tumor foci with a distinctive lymphoid stromal component.

Subtype 3 ("Stroma-Rich CAL")

The epithelial tumor component of this subtype amounted to only 20 to 30%. 70 to 80% of the tumor mass was formed by lymphoid stroma (Fig. 5). Only 2% of all examined CAL cases fell into this subtype. In two thirds of the cases, isolated areas of goblet cell and squamous cell metaplasia were noted. The lymphoid stroma contained numerous lymph follicles with activated germinal centers. Subtype 3 was found solely in men. The average age of 61 years was slightly lower than the 65 years of the total CAL cases.

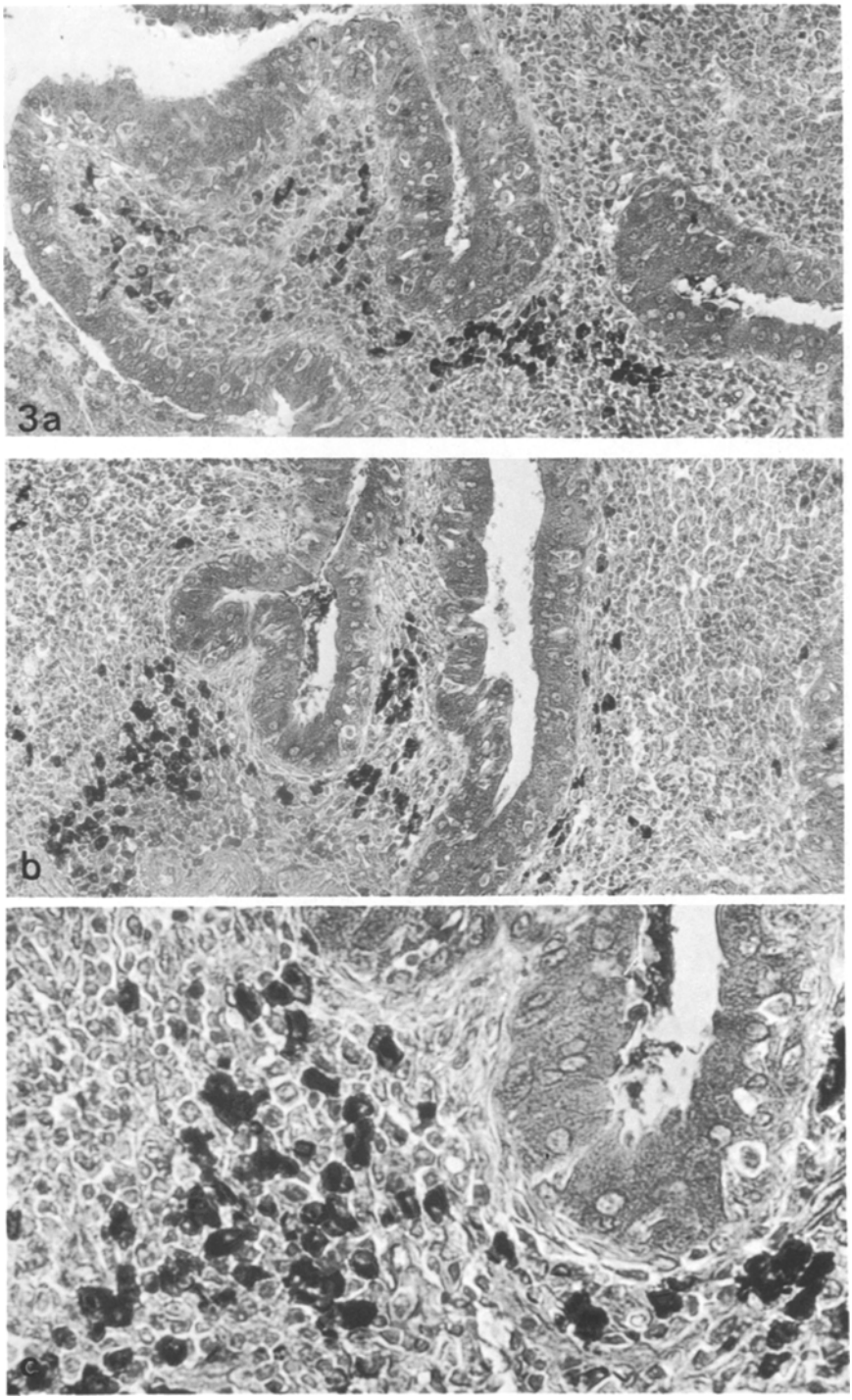

Fig. 3a–c. Cystadenolymphoma, subtype I (J-No. 18917/78): **a** Groups of IgA containing plasma cells adjacent to the oncocytic cells. **b** Groups of IgG containing plasma cells. **c** Part of b with IgG containing plasma cells. Indirect immunoperoxidase technique. **a** and **b** $\times 100$, **c** $\times 400$

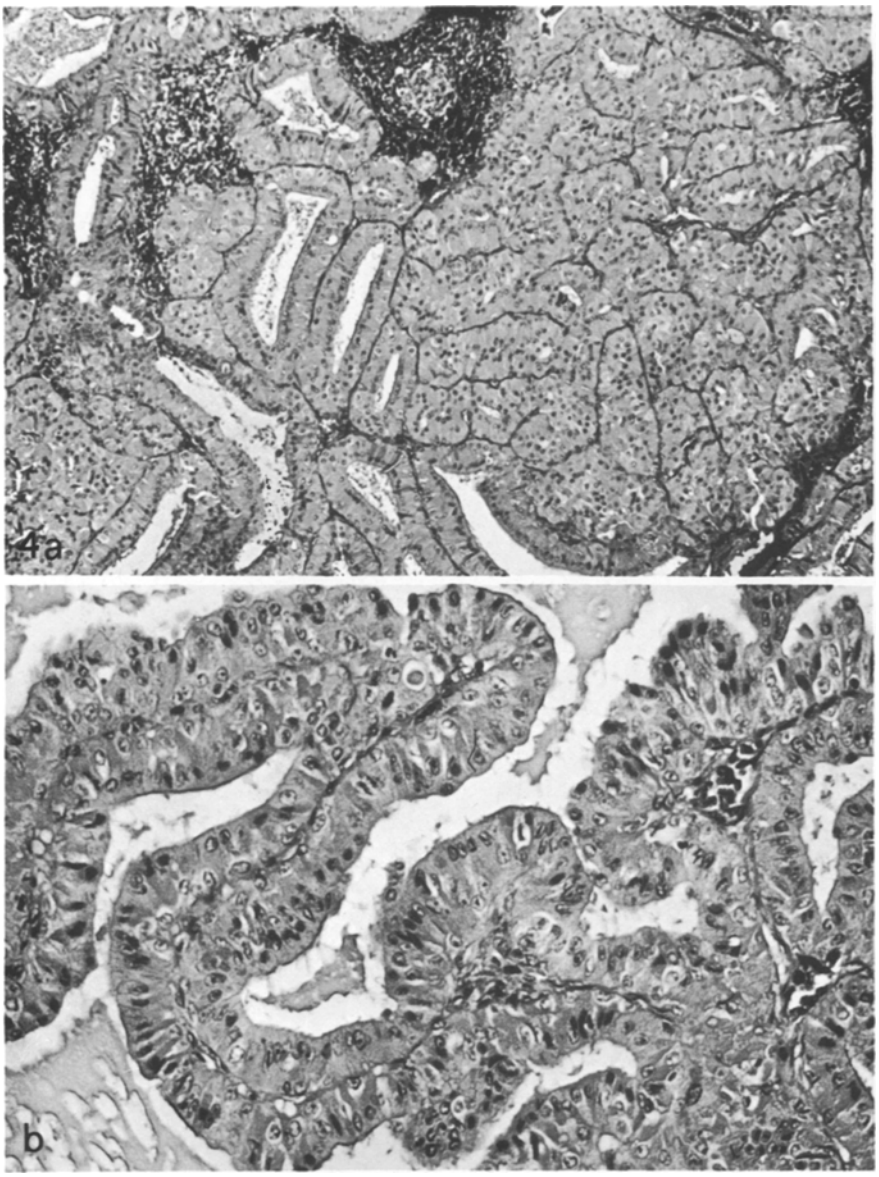

Fig. 4a and b. Stroma-poor cystadenolymphoma, subtype 2 (J-No. 26166/77): **a** Preponderance of the epithelial component; small stromal component. **b** Distinct proliferation of the oncocytic cells. Haematoxylin-eosin. **a** ×63, **b** ×160

Subtype 4 ("Metaplastic CAL")

In 7.5% of the CAL cases, subtype 4 was diagnosed. This was characterized by large areas of epithelial cell metaplasia and often by regressive changes. Only some foci of typical oncocytic epithelium were observed (Fig. 6) or oncocy-

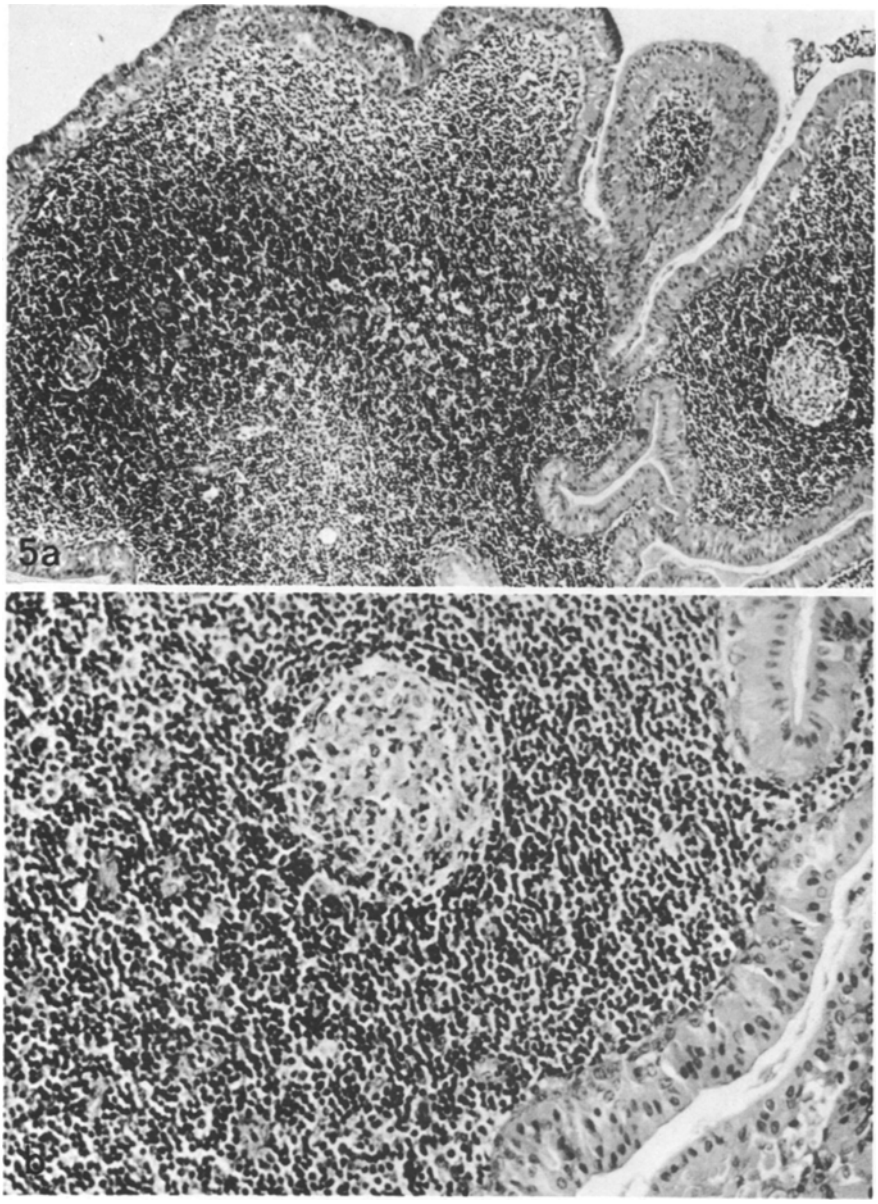

Fig. 5a and b. Stroma-rich cystadenolymphoma, subtype 3 (J-No. 6406/77): **a** Preponderance of the lymphoid stromal component. **b** Stromal component with a lymph follicle. Haematoxylin-eosin. **a** ×63, **b** ×160

tic epithelium was totally absent. Rather, the tumor cell groups adjacent to micro- and macrocysts consisted of several layers of squamous epithelium (Fig. 7). Within these groups of squamous cells, isolated goblet cells were found. The composition and amount of the lymphoid stroma were similar to that

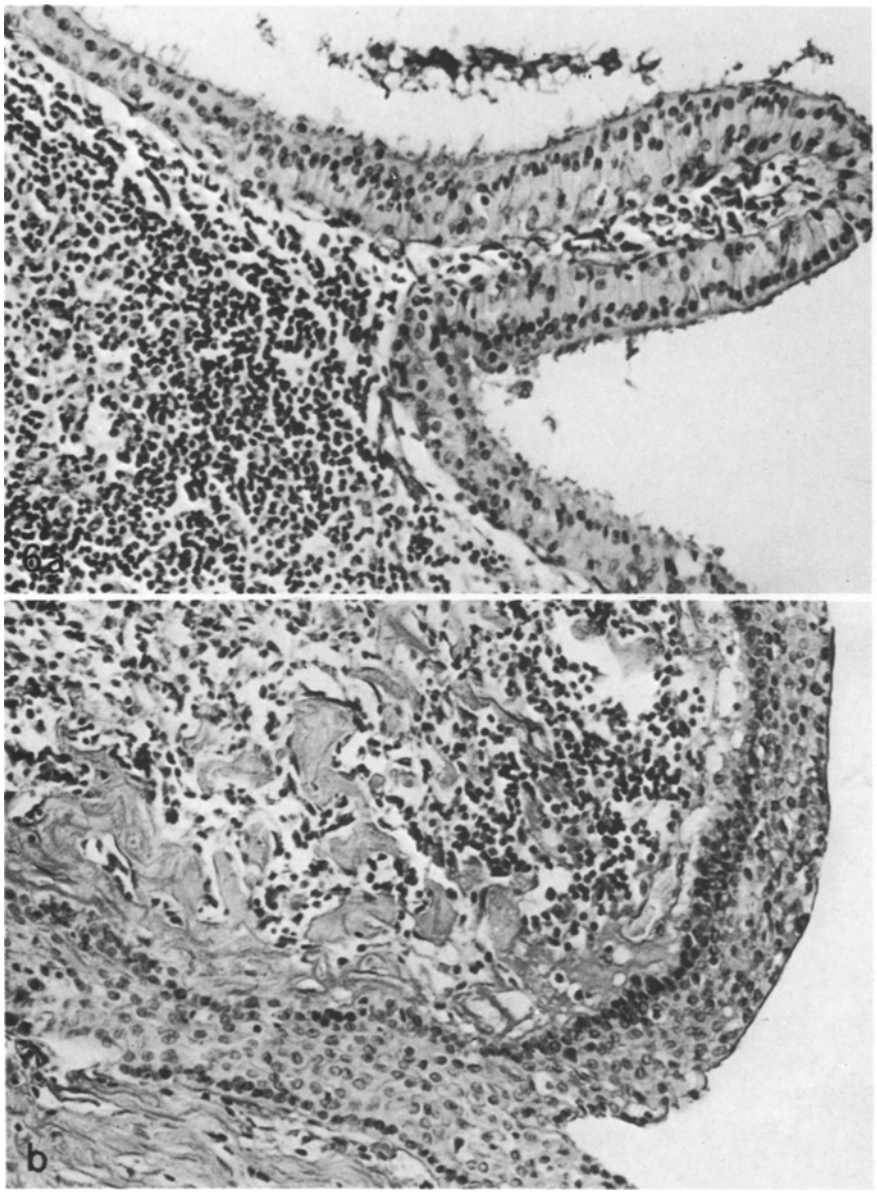

Fig. 6a and b. Metaplastic cystadenolymphoma, subtype 4 (J-No. 8157/65): **a** Rests of typical cystadenolymphoma. **b** Squamous cell metaplasia; regressive alterations of the lymphoid stromal component. PAS reaction. **a** and **b** × 160

of subtype 1. In 70% of the cases severe regressive changes with areas of hyalinisation or even liquefaction and parenchymal necrosis were noted. The average age of 67 years was slightly the total study (65 y). The incidence of metaplastic

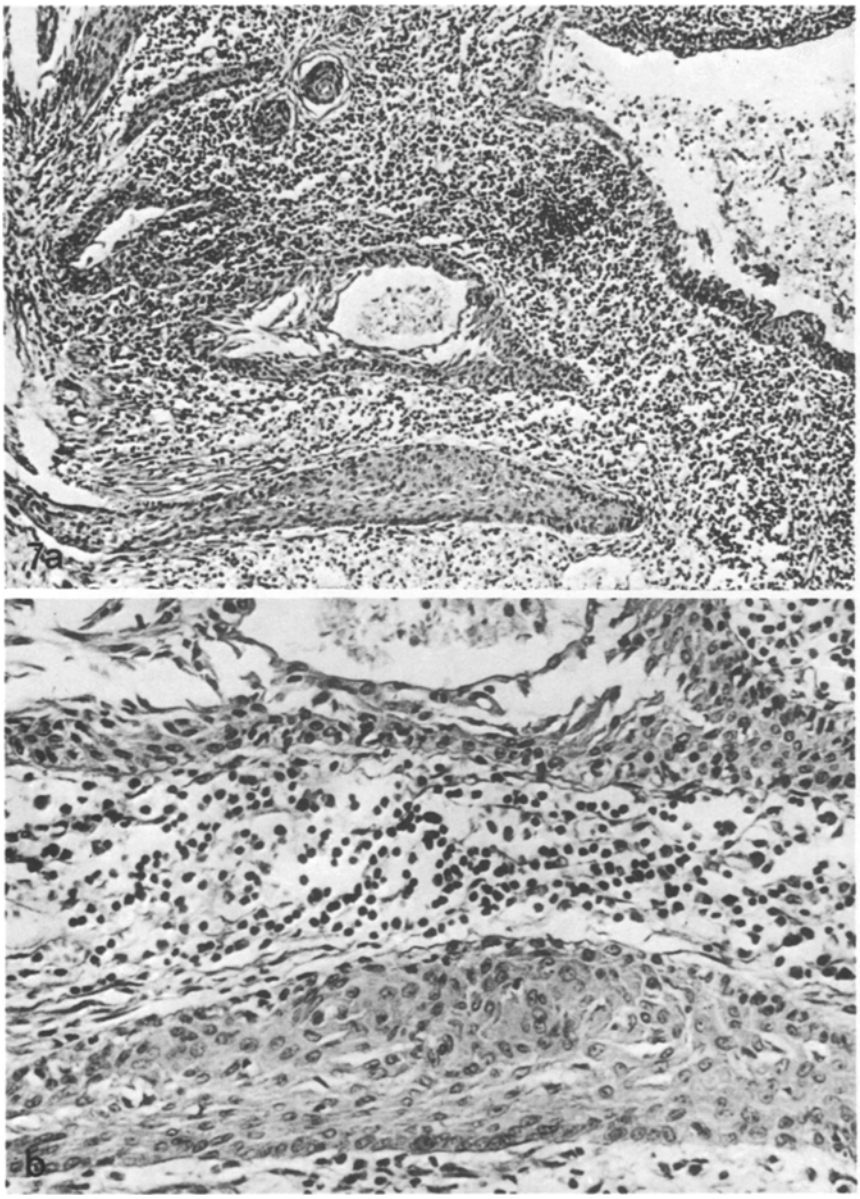

Fig. 7a and b. Metaplastic cystadenolymphoma, subtype 4 (J-No. 14010/72): Complete squamous cell metaplasia of the epithelial component; lymphoid stroma without lymph follicles. Astrablue staining. **a** ×63, **b** ×160

CAL in females (male:female=3:2) was higher than the incidence of all CAL together in females (male:female=3:1). The case histories revealed that 20% of the tumors had previously been irradiated, another 20% had possibly undergone radiotherapy, although no precise data were available in these later cases.

Table 3. Carcinomas in pre-existing cystadenolymphomas (according to Seifert et al. 1977).

Authors	Age (years)	Sex		Type of carcinoma	Radiation therapy	Recidives	Metastases
		m.	f.				
Lederman (1943)	66	+	–	Epidermoid carcinoma	+	–	Ly[a]
Ruebner and Bramhall (1960)	67	+	–	Undifferentiated carcinoma	–	+	Ly
De la Pava et al. (1965)	72	+	–	Epidermoid carcinoma	+	–	Ly
Little and Rickles (1965)	78	+	–	Adenocarcinoma	+	–	Ly
Doebroessy et al. (1972)	49	–	+	Undifferentiated carcinoma	+	+	Ly
Kessler et al. (1977)	63	+	–	Adenocarcinoma	–	–	Ly, Lung, Liver, Skin
Own case Seifert et al. (1977)	54	–	+	Adenocarcinoma	–	–	–
Own case Fleischer et al. (1980)	73	–	+	Cystadenocarcinoma	–	–	–

[a] Ly=Lymph nodes

Bilateral and Multifocal CAL

Bilateral CAL occurred in 7.5% of the cases. When compared with women, the incidence of bilateral CAL in men (male:female=6.3:1) was clearly higher than the incidence of all CAL in men (3:1). 75% of the bilateral CAL cases were of subtype 1, 17.5% subtype 2, and 7.5% subtype 3. In a single case three recurrences were recorded.

The diagnosis of *multifocal CAL* was established in those cases where multiple adenoma nodules had developed. These were clearly separated from each other by parotid tissue free of tumor. 4% of all our cases were multifocal CAL. The majority (75%) were classified as stroma-poor subtype 2 CAL.

Recurrences occurred in 2% of all CAL cases.

Carcinoma in CAL

In line with the definition of "carcinoma in pleomorphic adenoma", malignant lesions were considered "carcinoma in CAL" if the malignant tumor had developed within a CAL which had previously existed for some time. In our files there were two patients with adenocarcinoma in a CAL (Seifert et al. 1977; Fleischer et al. 1980). Our own cases and the findings described in the literature are summarized in Table 3. Histologically, the carcinomas were adenocarcino-

Table 4. Malignant second tumours in cystadenolymphomas of the parotid gland

Age (years)	Sex		Type of second tumor	Remarks
	m.	f.		
71	+	–	Carcinoma in a pleomorphic adenoma of the parotid gland	Subtype 1
71	+	–	Epidermoid carcinoma of the parotid gland	Subtype 1
87	+	–	Epidermoid carcinoma of the auricle	Subtype 1
40	+	–	Epidermoid carcinoma of the lower lip	Subtype 1 Radiation?
63	+	–	Epidermoid carcinoma of the larynx	Subtype 1 Radiation +
65	+	–	Epidermoid carcinoma of the lung	Bilateral CAL Subtype 1
71	+	–	Basalioma of the cheek	Subtype 1 Radiation +
77	+	–	Basalioma of the dorsum of the nose	Subtype 1 Radiation +
71	+	–	Malignant centrocytic lymphoma of the parotid gland	Chronic myoepithelial parotitis, CAL of 0.5 cm diameter (secondary finding)

mas, squamous cell carcinomas, or undifferentiated carcinomas. In 50% of the cases, the carcinoma had developed following radiotherapy. According to the above definition, metastases in the lymphoid stroma of CAL or malignant tumors coincident with CAL may not be classified as "carcinoma in CAL".

Tumors Associated with CAL

This category included all cases of CAL in which a syn- or metachronic tumor was noted, either within the parotid gland but clearly separated from the CAL or in another organ. In 3% of all our cases malignant tumors occurred simultaneously with CAL. Our own findings are shown in Table 4. There were two carcinomas of the parotid gland (1 carcinoma in a pleomorphic adenoma, 1 squamous cell carcinoma), three cases of carcinoma of the head and neck region (auricle, lower lip, larynx) and one carcinoma of the bronchus. In two cases basal cell carcinoma of the face was associated with CAL. A highly differentiated malignant centrocytic lymphoma of the parotid gland with a pre-existing chronic myoepithelial parotitis (immuno-sialadenitis) was found in one of our patients. According to the case histories, several of these patients had previously received radiotherapy to the maxillofacial region.

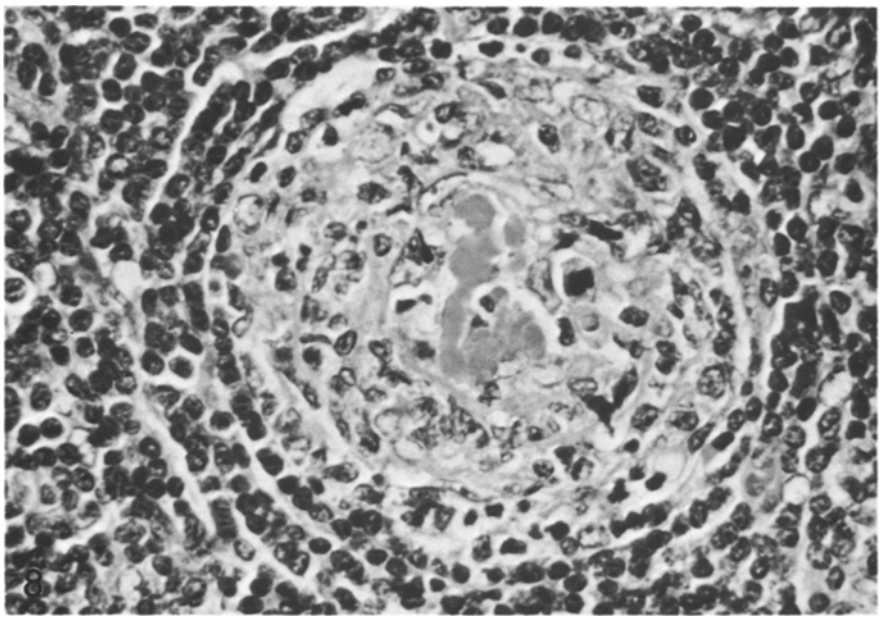

Fig. 8. Cystadenolymphoma, subtype 1 (J-No. 18917/78): Lymphoid stroma with an activated lymph follicle (zonal arrangement of lymphocytes; central hyaline precipitation). Haematoxylin-eosin. ×400

Table 5. Alterations of the lymphoid stroma of cystadenolymphomas of the parotid gland.

Age (years)	Sex		Stromal alterations	Remarks
	m.	f.		
77	+	–	Giant cell granulomas with cholesterine crystals	Subtype 1 Basalioma of the dorsum of the nose
63	+	–	Giant cell granulomas with cholesterine crystals	Two CAL Subtype 4 with granulomas, Subtype 1 without granulomas
81	+	–	Giant cell granulomas of foreign body type	Subtype 1 operation long time ago
58	+	–	Productive- exsudative tuberculosis	Subtype 1 Additionally, tuberculosis of cervical lymph nodes
83	+	–	Malignant follicular centrocytic-centroblastic lymphoma	Subtype 1 Lymphomas of other cervical lymph nodes
61	+	–	Metastases of an undifferentiated carcinoma	Subtype 1 Primary tumor Origin unknown

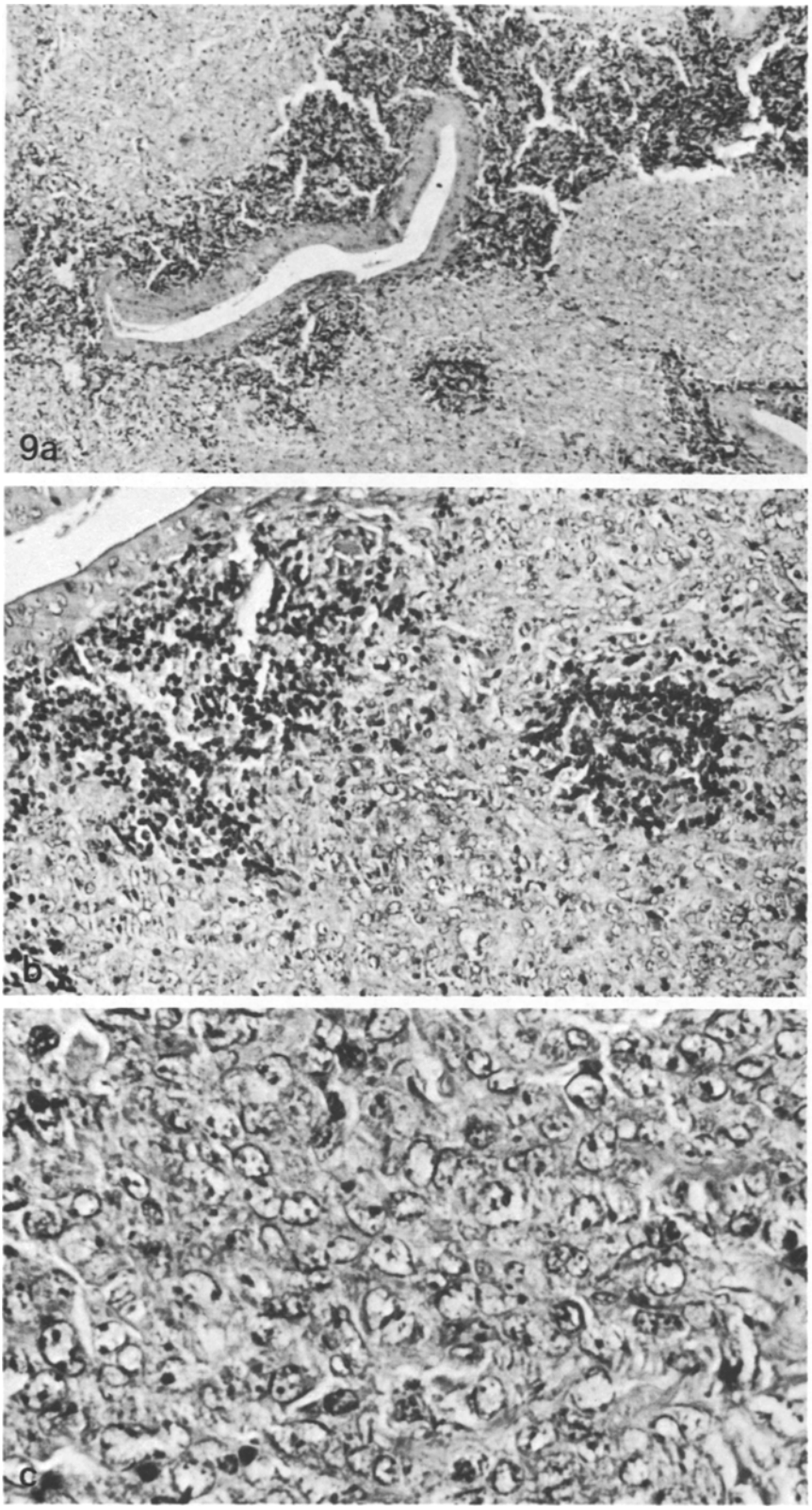

Fig. 9a–c. Cystadenolymphoma with metastases of an *undifferent* carcinoma in the stromal component (J-No. 21727/76): **a** and **b** Clear cellular tumor cell infiltration of the lymphoid stromal component (with dark lymphocytes around the epithelial component). **c** Higher magnification of tumor cell groups in the lymphoid stroma. Haematoxylin-eosin. **a** ×63, **b** ×160, **c** ×400

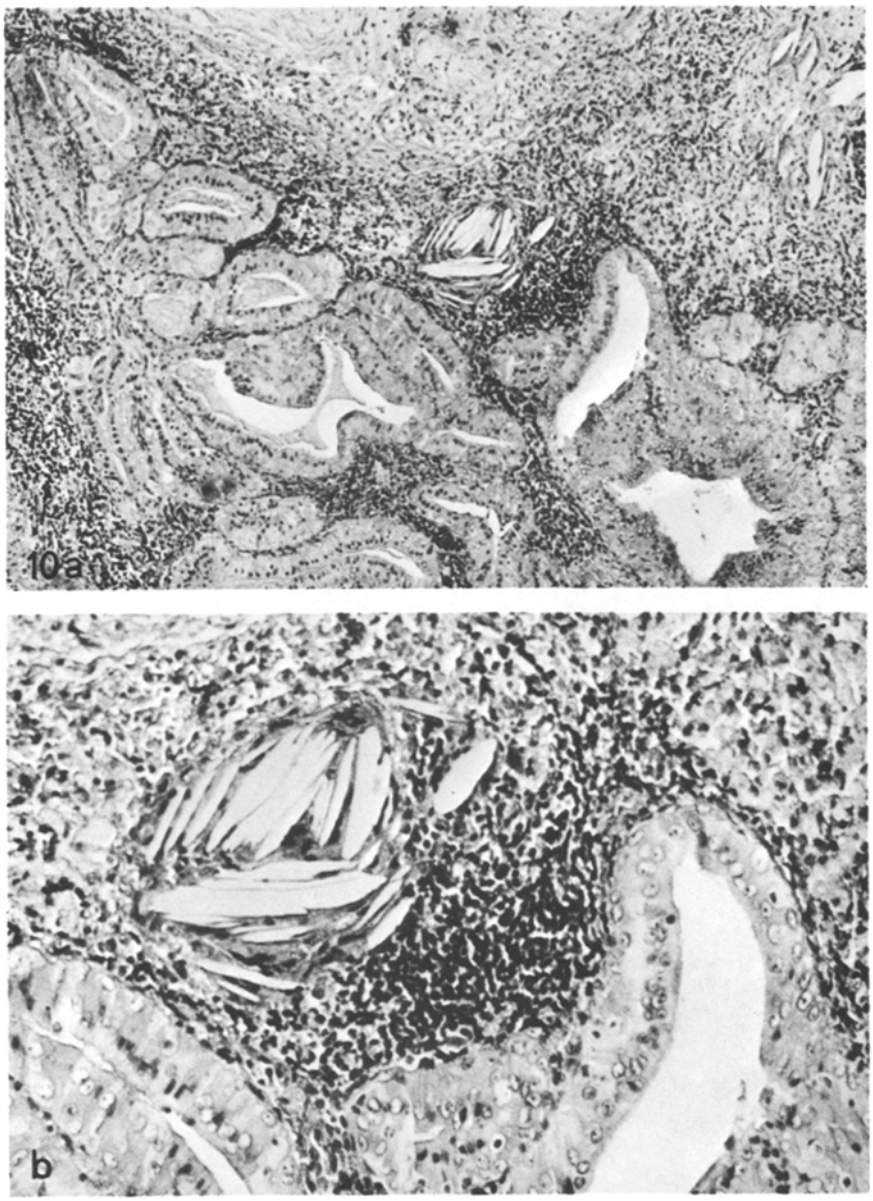

Fig. 10a and b. Cystadenolymphoma, subtype 1 (J-No. 12268/78): **a** Giant cell granuloma with cholesterine crystals in the neighborhood of the epithelial component. **b** Higher magnification of the focus with giant cell granuloma. Haematoxylin-eosin. **a** ×160, **b** ×400

Changes of Lymphoid Stroma in CAL

In addition to the variable amounts of lymphoid stroma and the stromal reactions (Fig. 8) resembling the changes found in regional lymph nodes (activated

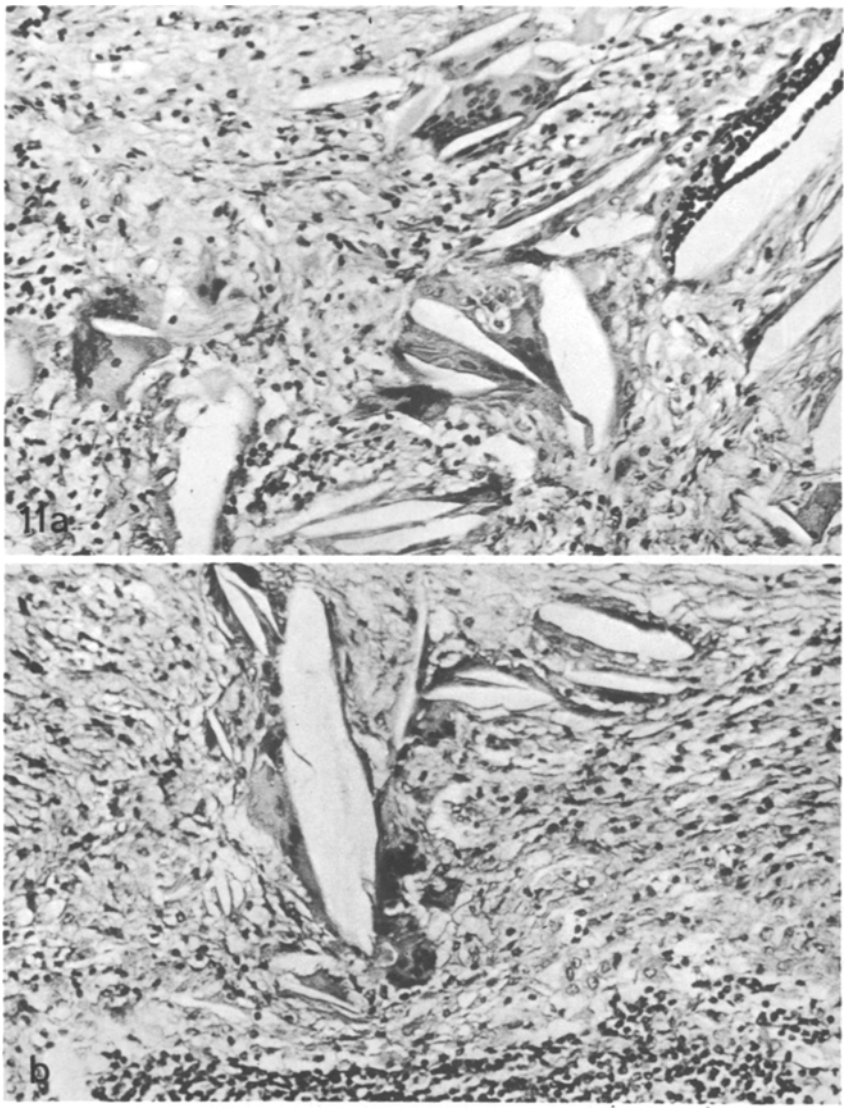

Fig. 11 a and b. Cystadenolymphoma, subtype 4 (J-No. 34467/78): Multiple giant cells with cholesterine crystals; lympho-and histiocytic cellular infiltration of the surrounding tissue. Haematoxylin-eosin. **a** and **b** × 160

follicles, precipitation of immunoglobulins, hyalinisation, tissue liquefaction) several extraordinary alterations of the lymphoid stroma were observed in our cases. Our findings are summarized in Table 5. The inflammatory granulomatous tissue reactions and the occurrence of metastases (Fig. 9) showed that the lymphoid stroma of CAL reacted exactly like the regional lymph nodes of the parotid gland and in the neck. The histological structure of the granulomatous changes (foreign body giant cells, histiocytes, macrophages, xanthoma cells,

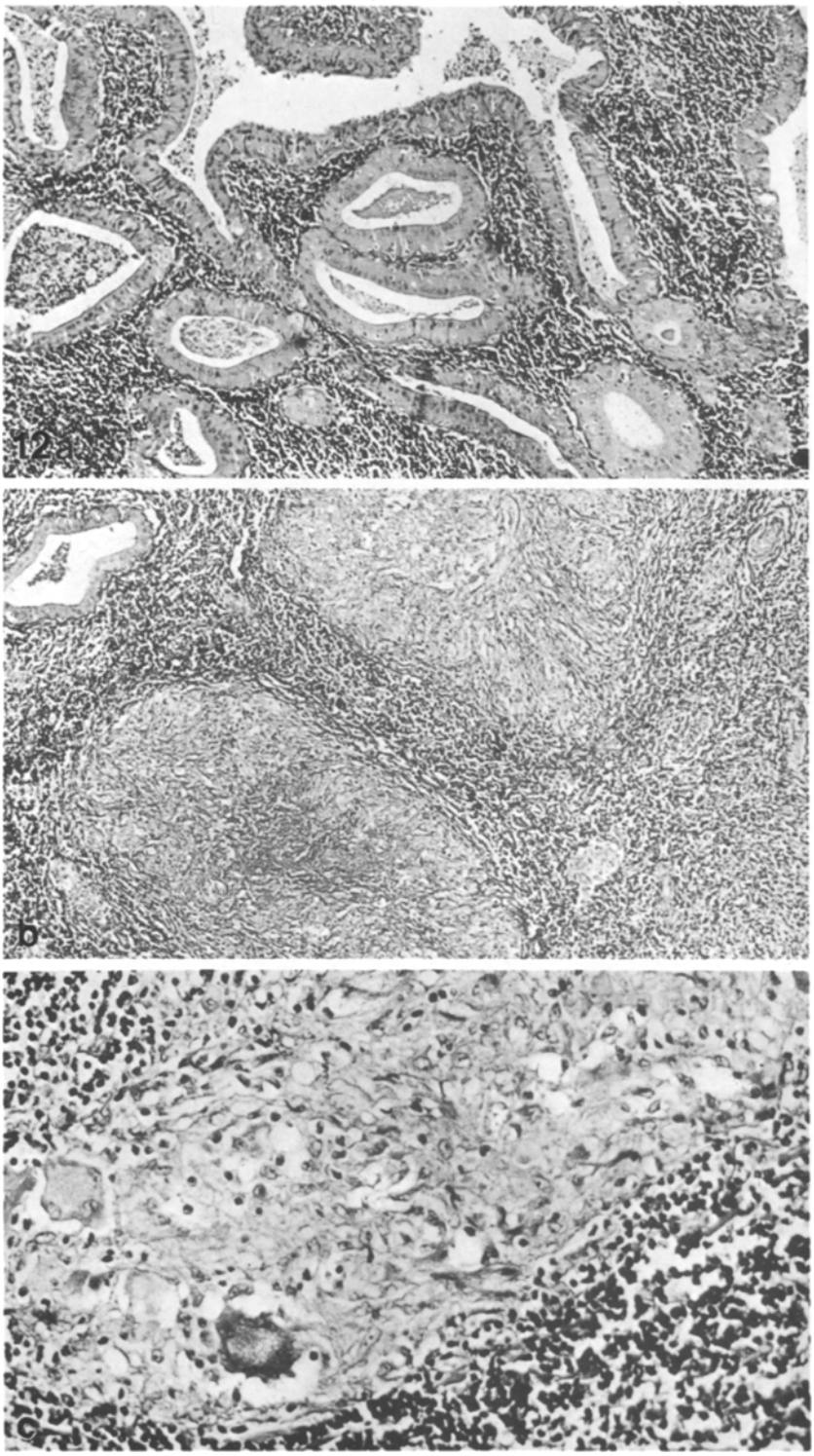

Fig. 12a–c. Cystadenolymphoma, subtype 1 with tuberculous granulomas in the stromal component (J-No. 3249/79): **a** Rest of cystadenolymphoma. **b** Two tuberculous granulomas in the stromal component. **c** Higher magnification of a granuloma with epitheloid cells and giant cells of Langhans type. Haematoxylin-eosin. **a** and **b** ×63, **c** ×160

cholesterol deposits; Figs. 10, 11) indicated a stromal reaction which was either the result of exudation of saliva into the lymphoid stroma or due to previous operations. In one case we noted a productive exudative tuberculosis of a cervical lymph node. Microscopic findings in the lymphoid stroma of the CAL were identical (Fig. 12). In another case a malignant lymphoma (a highly differentiated follicular centrocytic lymphoma) was found in the lymphoid stroma of the CAL and in other cervical lymph nodes. This finding supports the theory that the lymphoid stroma of CAL reacts in the same manner as the regional lymph nodes.

Discussion

According to the *subclassification of CAL,* 90% of the cases fell under subtype 1 (epithelial component 50% of the tumor mass) and subtype 2 (epithelial component 70 to 80% of the tumor mass). Common to both these subtypes were the age and sex distribution, the presence of foci of goblet cell and squamous cell metaplasia and the structure of the lymphoid stroma. In one third of the subtype 1 cases focal epithelial proliferation, without a lymphoid stroma, was found. Subtype 2 was characterized by a distinct proliferative tendency of the epithelium and for these reasons we believe that subtype 2 has developed from subtype 1 by further adenomatous growth. Apparently, adenomatous proliferation has reduced the lymphoid stroma component. In the stroma-rich subtype 3 which amounted to only 2% of all CAL (epithelial tumor component 20 to 30% only), the average age of 61 years was 4 years lower than that of subtypes 1 and 2. Subtype 3 is therefore thought to be an early form of CAL which in its further clinical course, develops into subtype 1 or subtype 2. This theory is supported by the fact that no regressive changes within the substance of the tumor were found in subtype 3. With subtype 4 – metaplastic CAL amounting to 7.5% of all CAL – the average age was 67 years. This increase (2 years compared with subtypes 1 and 2) may indicate an longer duration of the tumor. Squamous epithelial cell metaplasia and the regressive stromal changes characteristic of metaplastic CAL, suggest that metabolic and vascular noxae originally caused the transformation of the tumor structure. In 20% of the cases metaplastic CAL had previously been irradiated. In another 20% previous radiotherapy was assumed, although no precise data were available. Metaplastic CAL was more frequent in females (male:female=62:38) than all CAL taken together (male:female=75:25). This finding will need further explanation in view of the probable pathogenesis of metaplastic CAL.

Metaplasia to goblet cells and squamous epithelial cells in CAL is not surprising in view of the development of the human parotid gland. From the 20th week of pregnancy, *goblet cells* are found in the salivary duct system of the embryonal parotid (Donath et al. 1978). Later on in life, focal accumulations of goblet cells are observed in the duct system of the parotid gland (Seifert 1964, 1966). The number of goblet cells increases notably in sialadenitis caused by irradiation (Seifert and Geier 1971). In mucoepidermoid tumors, which are believed to develop from the salivary duct system, the variable amounts of

mucus-forming goblet cells present in the tumor is particularly characteristics. In routine examinations of the parotid gland, *metaplasia to squamous epithelial cells* is found as regularly as accumulations of goblet cells and is comparable to similar processes in other organs (bronchial system, prostate, cervix uteri). In general, only focal squamous cell metaplasia is found in CAL (Jensen and Husted 1970). The almost complete trasnformation of oncocytic tumor epithelium into groups of squamous epithelial cells in metaplastic CAL can best be compared to changes taking place in infarctions of the salivary glands (Donath 1979) which are also known as "necrotizing sialometaplasia" in the Anglo-American literature. Here zones of ischaemic tissue in the region of arterial vessels of salivary glands are largely or completely occluded by thrombosis, arteriitis, arteriosclerosis or postoperative ligature. Metaplasia of the ductal epithelium to squamous epithelium is initiated by hyperplasia of the reserve cells of the duct system. During this process goblet cells are also formed.

The theory that CAL develops from displaced ducts included within intra- or periglandular parotid lymph nodes is supported by numerous arguments (Pape 1963; Kleinsasser et al. 1966). Parenchymal tissue enclosed in lymph nodes of the parotid is a regular finding in children. In the further course of life, the glandular acini within the lymph nodes undergo partial involution while the ducts remain intact and show focal oncocytic metaplasia (Seifert 1966). CAL arises predominantly at the lower cervical pole of the parotid and sometimes seems to be located outside the parotid tissue in the adjacent soft tissue. Histologically, however, it is always possible to prove a connection between tumor tissue and the margin of the parotid gland. Further arguments in support of our theory concerning the *pathogenesis of CAL* are the hypothetical development of the various subtypes outlined above (subtype 3 as stroma-rich preliminary stage of subtypes 1 and 2, development of subtype 2 from subtype 1 by further adenomatous epithelial proliferation), bilateral occurrence of CAL at the lower parotid pole in 7.5% (Thackray and Lucas 1974: 5%; Smith and Fesmire 1969; Jensen and Husted 1970; Avka 1970; Lumerman et al. 1975), multifocal occurrence of mostly subtype 2 CAL in 2% of the cases, recurrences in 2% of the cases, and the particular behavior of the lymphoid stroma in CAL. In the literature several cases of CAL in the region of the submandibular gland (Kurreja and Jain 1971; Thackray and Lucas 1974) and in the region of the tonsils (Fahmy 1973) have been reported. However, they are not incompatible with the supposition that CAL develops within lymph nodes, since lymphatic tissue is also present in these regions.

The structure of the *lymphoid stroma* of CAL is similar to that of the regional lymph nodes. This applies to the cellular composition as well as the reaction patterns observed in the lymphoid stroma of CAL. B-lymphocytes prevail in the lymphoid stroma (Cossman et al. 1977). Like in other lymphoid organs, the distribution of immunocytes is polyclonal. Plasma cells forming IgG and IgA, were demonstrable (v. Gumberz 1980). This pattern of distribution indicates an immunological reaction by the lymphoid stroma in the neighborhood of oncocytic tumor cell proliferation and excludes a reaction to local inflammation. The neoplastic potential of the oncocytic ductal epithelium in CAL is also indicated by the fact that, particularly in the regions of papillary

proliferation, carcino-embryonal antigen may be found (Korsrud and Brandtzaeg 1979). Allegra's hypothesis (1971) – that CAL is an immunological disease of a retarded hypersensitive type, similar to Hashimoto's struma and that the entire lymphoid stroma is an immunological reaction to the oncocytic cell proliferation, could not be supported. The lymphoid stroma is considered to be lymphoreticular tissue analogous to lymph node and shows an immunological reaction only in the neighborhood of oncocytic tumor cells. Interpretation of these changes as a local immunological reaction is supported by the fact that in our case of an adenocarcinoma in a pre-existing CAL an unusually heavy infiltration by plasma cells was observed. These had produced immunoglobulins. especially IgA and IgG and also some IgM (Fleischer et al. 1980).

The macrophages found in the lymphoid stroma contain ceroid pigment which is thought to be an undegradable final product of lysosomal degradation of mitochondria (Bucher and David 1977). The liquefactions, cicatrisations, or granulomas sometimes noted in the stroma are identical with analogous findings made in lymph nodes (Patey and Thackray 1970). As a reaction to secretory products discharged into the stroma, foreign body granulomas with giant cells and cholesterol crystals may develop (Thackray and Lucas 1974). Also the occurrence of tuberculosis (Bucciarelli 1969) or any other infectious allergic granulomatosis as well as metastases or malignant lymphomas in the lymphoid stroma of CAL support the theory that the lymphoid stroma is comparable to regional lymph node tissue. As a consequence, it is possible to define CAL as a "monomorphic adenoma", since the mainly oncocytic epithelial tumor component constitutes the tumor parenchyma proper.

The *development of carcinoma in CAL* is very rare. In addition to our two cases (Seifert et al. 1977; Fleischer et al. 1980), six other instances have been reported in the literature. Histologically, the tumors were either adenocarcinomas, squamous cell carcinomas or undifferentiated carcinomas. Carcinogenesis due to previous radiotherapy is possible in individual cases. Carcinoma in CAL must be differentiated from metastases within the lymphoid stroma of benign CAL and malignant tumors occurring simultaneously with CAL.

Association of CAL with other tumors has been reported repeatedly. Tumors occurring simultaneously with CAL were either pleomorphic adenomas (Astacio 1974), mucoepidermoid tumors (Gadient and Kalfayan 1975; Lumeran et al. 1975) or bilateral parotid carcinomas (Assor 1974). CAL was also found in association with a mucoepidermoid tumor of the parotid and carcinomas of the thyroid gland and the mandible (Jannaccone 1975). In 3% of all our cases, CAL was coincident with malignant tumors, the majority of which were located in the head and neck region (2 carcinomas of the parotid, 2 basal cell carcinomas, 1 malignant lymphoma, and 1 carcinoma each of the auricle, lower lip and larynx). The case histories revealed that several of these patients had previously received radiotherapy to the face. However, so far there has been no overall explanation for the simultaneous occurrence of CAL and malignant tumors.

The subclassification of CAL plays an important role in the *differential diagnosis* of CAL when compared with other parotid tumors or non-tumorous lesions of the parotid. The typical subtype 1 CAL does not present any problems in differential diagnosis. The *stroma-poor subtype 2* has some morphological

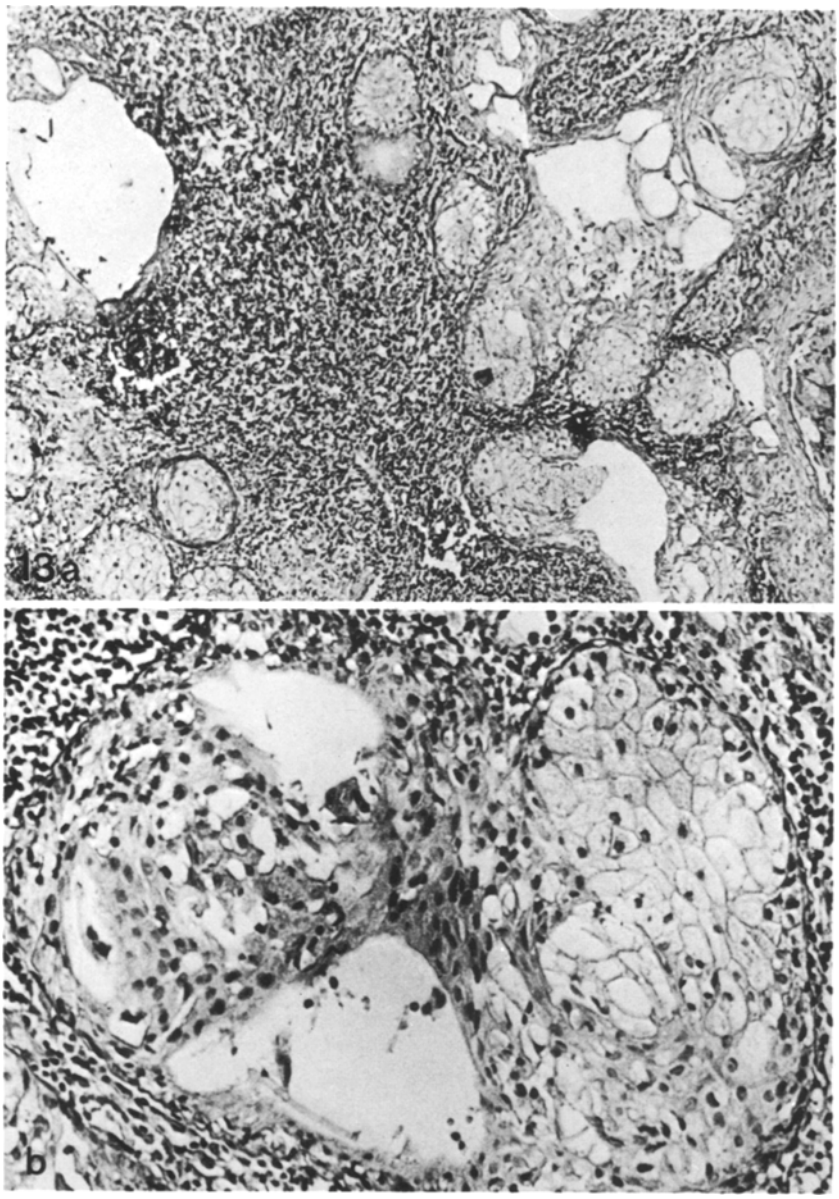

Fig. 13a and b. Sebaceous lymphadenoma (J-No. 26691/78): sebaceous gland cell groups and microcysts, surrounded by a lymphoid stromal component. **a** Haematoxylin-eosin, ×63. **b** PAS reaction. ×160

similarities with the oncocytoma and the cystic adenoma of the salivary ducts. However, the *oncocytoma* can be distinguished from subtype 2 CAL by two characteristics: different epithelial differentiation (polygonal, mostly solid or trabecular groups of ductal epithelium with a broader rim of cytoplasm than the tumor cells of CAL; Kleinsasser et al. 1966) and more or less total absence

of a lymphoid stroma component. In the *cystic adenoma of the salivary ducts* (Seifert and Schulz 1979) similar oncocytic epithelial patterns showing cysts and papillae like those in CAL are found, but no lymphoid stroma component is seen. Metaplastic CAL of subtype 4 must be distinguished from sebaceous adenoma, mucoepidermoid tumors and squamous cell carcinoma. The *sebaceous lymphadenoma* (Fig. 13) is characterized by epidermoid cystic cell groups in which sebaceous cells are enclosed and a lymphoid stroma resembling that of CAL (Kleinsasser 1964; Schmid and Albrich 1973; Seifert and Schulz 1979; Tschen and McGavran 1979). As regards its pathogenesis, it is assumed that sebaceous lymphadenoma also develops from parenchyma enclosed in parotid lymph nodes. Similarities with the *mucoepidermoid tumor* may exist if a metaplastic CAL is associated with sheets of goblet cells. A few cases, presenting difficulties in differential diagnosis and leading to misinterpretations after cytological examination have been reported in the literature (Lindberg and Akermann 1976; Zajicek et al. 1976). The same is true of false diagnoses after cytologic examination of metaplastic CAL, in particular its classification as *squamous cell carcinoma* (Lindberg and Akermann 1976). After radiotherapy to the CAL region, epithelial dysplasia may be associated with squamous cell metaplasia.

A special problem in differential diagnosis is the distinction of CAL (metaplastic type 4) from *lymphoepithelial tumors* (Schmincke 1921; Doerr 1956). The "peribranchial blastema" (Doerr 1956) comprises all ectodermal derivates of the branchial intestine and is characterized by a distinct relationship between lymphatic tissue and epithelial cells. The lymphoepitheliomas are typical of the lymphatic pharyngeal ring. The existence of typical lymphoepitheliomas of the salivary glands is dubious. In the Salivary Glands Register we have not observed a case of lymphoepithelioma and consider the reports in the literature to be misinterpretations. The cases of Skorpil (1939) must be classified as chronic myoepithelial parotitis. Von Albertini (1974) interprets the observations of Skorpil as "solid adenolymphoma" and denies the occurrence of lymphoepithelioma of the salivary glands, but his classification of "solid adenolymphoma" (Figs. 93, 94) is erroneous. These cases show the typical changes of chronic myoepithelial parotitis. The term "acinic adenolymphoma" of Geiler (1957) is another misinterpretation; these cases are metastases of acinic cell tumours in the regional lymph nodes (Seifert et al. 1977). The tumour cells are arranged in an alveolar pattern and embedded in lymph nodes.

Another point of problem is the fact that a distinct *interaction* must be postulated between the *onkocytic epithelial cells* and the *lymphoid stromal component*. New aspects of the interpretation of this phenomenon result from the evidence of a special secretory immune system of the salivary glands (Hurlimann 1971). The periductal plasma cells produce IgA, the epithelial cells of the striated ducts produce the secretory component. At the same time the onkocytic tumour component of CAL is derived from the striated ducts. This finding may be a basis for the explanation of the onkocytic cell proliferations at greater ages, since this may be a time of disturbances of the immune system.

Non-tumorous lesions of the parotid to be distinguished from CAL include parotid cysts and chronic myoepithelial parotitis. In surgical pathology, *parotid cysts* are found in 2 to 6% of the cases (Eneroth 1964; Richardson et al. 1978). Acquired retention cysts of the salivary duct system are often lined by metaplastic epithelium and separated from the remaining glandular parenchyma by connective tissue with an inflammatory infiltrate. Oncocytic differentiation, papillae or typical lymphoid stroma are missing. Congenital parotid cysts are believed to have developed from the first branchial arch ("branchiogenic parotid cysts") or are interpreted as "lymphoepithelial cysts" (Bernier and Bhaskar 1958). These parotid cysts can be distinguished from metaplastic CAL by the following criteria: predominance of macrocysts, no signs of secretion, broad sheets of

lymphoid stroma (like in stroma-rich CAL of subtype 3), occurrence in a younger age group, no predilection for men.

Chronic myoepithelial parotitis (Seifert 1979) is an inflammatory lesion characterized by extensive destruction of glandular acini, distinct lymphocytic infiltration and the development of isolated groups of myoepithelial cells. Further characteristics are: high incidence in women during their menopause, bilateral occurrence, recurrences and syntropia with Sjögren's syndrome. Foci of ductal ectasia with secretory bodies or microliths are found. However, because of its tumorous nature, this inflammation is often confused with CAL (Cruickshank 1965). We also want to refer, though not discuss in further detail, to the fact that it is often combined with malignant lymphomas (Seifert 1980).

References

Albertini A von (1974) Histologische Geschwulstdiagnostik, 2nd ed. Stuttgart: Thieme

Allegra SR (1971) Warthin's tumor: a hypersensitivity disease? Ultrastructural, light, and immunofluorescent study. Hum Pathol 2:403–420

Assor D (1974) Bilateral carcinoma of the parotid, one cancer arising in a Warthin's tumor. Am J Clin Pathol 61:270–274

Astacio JN (1974) Papillary cystadenoma lymphomatosum associated with pleomorphic adenoma of the parotid gland. Oral Surg 38:91–95

Bernier JL, Bhaskar SN (1958) Lymphoepithelial lesions in salivary glands; classification and histogenesis. Cancer 11:1156–1179

Bucciarelli E (1969) Adenolinfoma e tubercolosi clicicamente primitiva della parotide. Lav Anat Pat Perugia 29:139–146

Buchner A, David R (1977) Pigmented cells in adenolymphoma (Warthin's tumor). J Oral Pathol 6:106–112

Bull H-G (1979) Pathomorphologische Subklassifikation der papillären Cystadenolymphome der Parotis. Analyse von 204 Fällen. Diss Hamburg

Cossman J, Deegan MJ, Batsakis JG (1977) Warthin's tumor. B-lymphocytes within the lymphoid infiltrate. Arch Pathol Lab Med 101:354–356

Cruickshank AH (1965) Benign lymphoepithelial lesion to be distinguished from adenolymphoma. J Clin Pathol 18:391–400

Doebroessy L, Ronay P, Molnar L (1972) Malignant papillary cystadenoma lymphomatosum. Oncology 26:457–465

Doerr W (1956) Über die lymphoepithelialen Geschwülste Schmincke-Regaud. Ärztl Wochenschr 11:169–182

Donath K (1979) Pathohistologie des Parotisinfarktes. – Necrotizing sialometaplasia. Laryngol Rhinol 58:70–76

Donath K, Dietrich H, Seifert G (1979) Entwicklung und ultrastrukturelle Cytodifferenzierung der Parotis des Menschen. Virchows Arch A Path Anat and Histol 378:297–314

Eneroth C-M (1964) Histological and clinical aspects of parotid tumours. Acta Oto-Laryngol Suppl 191

Evans RW, Cruickshank AH (1970) Epithelial tumours of the salivary glands. Philadelphia-London-Toronto: Saunders

Fahmy S (1973) Adenolymphoma of the tonsillar fossa. J Laryngol 87:675–679

Fleischer I, Caselitz J, Löning Th, Seifert G (1980) Histological and immunocytochemical examinations of the stromal reaction in carcinomas of the parotid gland. – Analysis of 52 cases. Cancer Res Clin Oncol 96:193–209

Gadient StE, Kalfayan B (1975) Mucoepidermoid carcinoma arising within a Warthin's tumor. Oral Surg 40:391–398

Gumberz Ch v (1980) Über das Vorkommen Immunglobulin-produzierender Plasmazellen bei chronischer Parotitis, malignen Lymphomen und Cystadenolymphomen der Parotis. Diss Hamburg

Hurlimann J (1971) Immunoglobulin synthesis and transport by human salivary glands. Curr Top Pathol 55:69–108
Iannaccone Ph (1975) Multiple primary tumors. Four distinct head and neck tumors. Arch Pathol (Chicago) 99:270–272
Jensen PSt, Husted E (1970) Cystadenolymphoma (Warthin's Tumor) of the parotid gland. Scand J Plast Reconstr Surg 4:114–121
Kavka SJ (1970) Bilateral simultaneous Warthin's tumors. Arch Otolaryngol 91:302–303
Kessler E, Koznizky IL, Schindel J (1977) Malignant Warthin's tumor. Oral Surg 43:111–115
Kleinsasser O (1964) Über das Sebaceolymphom der Parotis. Monatsschr Ohrenheilk 98:318–325
Kleinsasser O, Klein HJ, Steinbach E, Hübner G (1966) Onkozytäre adenomartige Hyperplasien, Adenolymphome und Onkozytome der Speicheldrüsen. Arch klin exp Ohr-, Nas- Kehlk-Heilk 186:317–336
Korsrud FR, Brandtzaeg P (1979) Immunohistochemical studies on the epithelial and lymphoid components of Warthin's tumour. Acta Otolaryngol Suppl 360:221–224
Kurreja HK, Jain HK (1971) Adenolymphoma of submandibular salivary gland. J Laryng 85:1201–1203
Lederman M (1943) Adenolymphoma of the parotid salivary gland. Br J Radiol 16:383–385
Lindberg LG, Akerman M (1976) Aspiration cytology of salivary gland tumors: Diagnostic experience from six years of routine laboratory work. Laryngoscope 86:584–594
Little JW, Rickles NH (1965) Malignant papillary cystadenoma lymphomatosum. Report of a case, with a review of the literature. Cancer (Philad) 18:851–856
Lumerman H, Freedman P, Caracciolo P, Remigio PS (1975) Synchronous malignant mucoepidermoid tumor of the parotid gland and Warthin's tumor in adjacent lymph node. Oral Surg 39:953–958
Matteson StR, Cutler LS, Herman PA (1976) Warthin's tumor. Report of a case and survey of 205 salivary neoplasms. Oral Surg 41:129–134
Pape H-D (1963) Das papilläre Zystenadenolymphom. Ein Bericht über 20 Fälle. Stoma (Heidelberg) 15:189–207
Patey DH, Thackray AC (1970) Infected adenolymphoma: a new parotid syndrome. Br J Surg 57:569–572
Pava S de la, Knutson GH, Mukhtar F, Pickren JW (1965) Squamous cell carcinoma arising in Warthin's tumor of the parotid gland. First case report. Cancer (Philad) 18:790–794
Richardson GS, Clairmont AA, Erickson ER (1978) Cystic lesions of the parotid gland. Plast Reconstr Surg 61:364–370
Ruebner B, Bramhall JL (1960) Malignant papillary cystadenoma lymphomatosum. Arch Path (Chicago) 69:110–117
Schmid KO, Albrich W (1973) Die Bedeutung von Talgzellen und Talgdrüsen für Parotisgeschwülste. Virchows Arch Arch Abt A Path Anat 359:239–253
Schmincke A (1921) Über lymphoepitheliale Geschwülste. Beitr path Anat 68:161–170
Seifert G (1964) Die Sekretionsstörungen (Dyschylien) der Speicheldrüsen. Ergeb Pathol 44:103–188
Seifert G (1966) Mundhöhle, Mundspeicheldrüsen, Tonsillen und Rachen. In Doerr W, Uehlinger E (eds) Spezielle pathologische Anatomie, vol 1. Berlin-Heidelberg-New York: Springer
Seifert G (1979) Wangenschwellungen bei Speicheldrüsenentzündungen. Pathologisch-anatomische Differentialdiagnose der Sialadenitis. HNO (Berlin) 27:119–128
Seifert G (1980) Lymphoid lesions of the oral cavity. Path Res Pract 167:179–203
Seifert G, Donath K (1976a) Die Morphologie der Speicheldrüsenerkrankungen. Arch Oto-Rhino-Laryngol 213:111–208
Seifert G, Donath K (1976b) Classification of the pathohistology of diseases of the salivary glands. Review of 2,600 cases in the salivary glands register. Beitr Pathol 159:1–32
Seifert G, Geier W (1971) Zur Pathologie der Strahlen-Sialadenitis. Z Laryngol Rhinol 50:376–388
Seifert G, Heckmayr M, Donath K (1977) Carcinome in papillären Cystadenolymphomen der Parotis. Definition und Differentialdiagnose. Z Krebsforsch 90:25–36
Seifert G, Schulz C-P (1979) Das monomorphe Speichelgangadenom. Klassifikation und Analyse von 79 Fällen. Virchows Arch A Path Anat and Histol 383:77–99
Skorpil F (1939) Über die Lymphoepitheliome (Schmincke) der Speicheldrüsen. Frankf Z Pathol 53:450–466
Smith JF, Fesmire FM (1969) The benign papillary cystadenoma lymphomatosum. Oral Surg 27:95–102

Taylor CR, Burns J (1974) The demonstration of plasma cells and other immunoglobulin-containing cells in formalin-fixed, paraffin-embedded tissues using peroxidase-labelled antibody. J Clin Pathol 27:14–20

Thackray AC, Lucas RB (1974) Tumors of the major salivary glands. Atlas of tumor pathology, second series, fasc 10. Washington: Armed Forces Institute of Pathology

Thackray AC, Sobin LH (1972) Histological typing of salivary gland tumors. Geneva: World Health Organization

Tschen JA, McGavran MH (1979) Sebaceous lymphadenoma. – Ultrastructural observations and lipid analysis. Cancer 44:1388–1392

Zajicek J, Eneroth CM, Jakobsson P (1976) Aspiration biopsy of salivary gland tumors. VI. Morphologic studies on smears and histologic sections from mucoepidermoid carcinoma. Acta Cytologica 20:35–41

Accepted April 29, 1980