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Immunoglobulin-Containing Plasma Cells in Chronic Parotitis and Malignant Lymphomas of the Parotid Gland

Comparing Immunocytochemical Observations of Frequency and Localization

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Summary. IgA-containing plasma cells in the periductal gland tissue are part of the special secretory immune system of the salivary glands. The reaction of Ig-containing plasma cells (localization, frequency, specific Ig-content) was analyzed by the indirect immunoperoxidase method in chronic recurrent parotitis (9 cases), chronic myoepithelial parotitis (benign lymphoepithelial lesion, Sjögren's syndrome; 8 cases), and malignant lymphoma associated with chronic myoepithelial parotitis (11 cases). The following results were obtained:

1. In chronic recurrent parotitis, parallel to the increase in IgA in the salivary secretion, a marked multiplication of IgA-containing plasma cells was found in the inflammatory infiltrate and the remaining non-inflamed periductal parenchyma of the parotid gland. In the marginal zone of inflammation, a slight increase of IgG-containing plasma cells was also observed.

2. In chronic myoepithelial parotitis, the total plasma cellular infiltration was slightly less distinct than in chronic recurrent parotitis. The most remarkable increase in Ig-containing plasma cells developed in the marginal zones – away from the myoepithelial cellular islands – as well as in the area of ductular proliferations, and was characterized by a strong increase of IgG-containing plasma cells. At the same time, a slight increase of IgM-containing plasma cells was observed. No plasma cells were found in the myoepithelial cellular islands.

3. In the malignant lymphomas associated with myoepithelial parotitis, which were mainly highly differentiated lymphomas (immunocytomas, centrocytic-centroblastic lymphomas) and rarely poorly differentiated immunoblastic lymphomas, there was a distinct decrease of IgG-containing plasma cells when compared with the numbers in this group without lymphoma.

The differing degrees of prevalence and Ig-content of the plasma cells partly describe the change taking place in the local secretory immune system

* Prof. Dr. med. Dr. med. h.c. Carl Krauspe dedicated on the occasion of his 85th birthday

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of the parotid gland. The possible relationships between chronic recurrent parotitis and auto-immune myoepithelial parotitis on one hand and the stages of transition (prelymphoma) to malignant lymphoma on the other, are discussed.

Key words: Immunoglobulin containing plasma cells – Indirect immunoperoxidase technique – Chronic recurrent parotitis – Chronic myoepithelial parotitis – Sjögren's syndrome – Malignant lymphomas in Sjögren's syndrome.

The salivary glands have two functional mechanisms in defence against infections. Lysozymes and salivary mucins represent non-specific factors. The specific immunoreaction is performed by a special secretory immune system (Hurlimann 1971; Brandtzaeg 1976; Seifert and Donath 1976; Seifert 1979). This system consists of IgA-forming plasma cells in the neighbourhood of the salivary ducts and the secretory component (SC), which is formed in the golgi-area of the striated ducts. By being coupled to IgA this is passed on as an IgA-SC-complex (Tourville et al. 1969).

In chronic parotitis two different courses can be distinguished clinically and morphologically: the chronic recurrent parotitis promoted by bacterial infection and secretory disturbances, and chronic myoepithelial parotitis, the pathogenesis of which is related to auto-immunological reactions (Haubrich 1976; Becker et al 1978; Seifert 1979). Recently, attention has been repeatedly drawn to the formation of malignant lymphomas on the basis of a myoepithelial parotitis – Sjögren's syndrome – (Heckmayr et al. 1976; Seifert and Burkhardt 1979; Lennert et al. 1979). The development of malignant lymphomas associated with immune parotitis is related to disturbances of the local immune system.

The indirect immunoperoxidase technique (Taylor and Burns 1974) offers the possibility of investigating the presence and localization of immunoglobulin-containing plasma cells in paraffin-embedded material and the ability to make comparative statements about the pattern of distribution found in different human parotid diseases. This paper will make a comparative analysis of frequency, localization, and the special immune contents of plasma cells in chronic recurrent parotitis, chronic myoepithelial parotitis, and malignant lymphomas associated with chronic myoepithelial parotitis. In this way we will investigate the various components of the special secretory immune system of the parotid gland and its various reactions.

Material and Methods

Out of the material available at the salivary glands register of the Institute of Pathology of the University of Hamburg 9 cases of chronic recurrent parotitis, 8 cases of myoepithelial parotitis, and 11 cases of malignant lymphomas associated with chronic myoepithelial parotitis were analyzed. All cases were interpreted in accordance with a uniform diagram (v. Gumberz 1980).

As a matter of routine, the tissue material was fixed in formalin and embedded in paraffin. 3 μ thick serial sections were produced from the paraffin blocks and stained with haematoxylin-eosin, astrablue, and the PAS reaction. In addition, the sections were treated using the indirect immunoperoxidase technique as indicated by Taylor (Taylor and Burns 1974; Taylor and Mason 1974; Burns

Table 1. Frequency of Ig-containing plasma cells (four grades of intensity; s. text)

Grade	Number of Ig-containing plasma cells[a]
0	0
1	1–25
2	26–60
3	61–100
4	More than 100

[a] Occurrence of four visual fields with a magnification of ×400

1975; Pinkus and Said 1977; Taylor 1978; Sternberger 1979). This method was employed in a modified form (Löning et al. 1977):

1. Blocking of endogenous peroxidase.
2. Incubation with normal goat serum.
3. Incubation with specific rabbit anti-human-immunoglobulin:
   a) with rabbit normal serum (1:15);
   b) with anti-IgA (1:40);
   c) with anti-IgG (1:10);
   d) with anti-IgM (1:10);
   e) with anti-secretory component (1:20).
4. Incubation with goat anti-rabbit-immunoglobulin.
5. Incubation with rabbit horse-radish-peroxidase-antiperoxidase-complex.
6. Staining with diaminobenzidine (DAB).
7. HE counter-staining.

The specific rabbit anti-human-immunoglobulin and the goat anti-rabbit-immunoglobulin were supplied by "Immunological Laboratories", Netherlands, the PAP-complex by "Medak", Hamburg.

In each case, the specificity of the staining was controlled by sections overcoated with rabbit normal serum.

The stained plasma cells, separated according to Ig-classes, were quantitatively estimated in different morphological zones. For this purpose, the stained plasma cells of four visual fields per zone were counted and added up "light"-microscopically (enlargement: 400×). According to the total, the intensity degrees were classified in four steps (Table 1), considering only clearly identifiable stained plasma cells.

The malignant lymphomas were classified in accordance with the Kiel classification (Lennert 1978).

Results

Chronic Recurrent Parotitis (Table 2)

Chronic recurrent parotitis is characterized by a periductal and intralobular cell infiltration of different intensity, focal duct ectasia, formation of lymph follicles, interstitial fibrosis, and atrophy of the secreting part of the glandular tissue. The cell infiltrates consist mainly of lymphocytes and plasma cells, with some histiocytes and single leukocytes.

In the immunohistological examinations four zones were distinguished (Table 2): intact remaining glandular tissue without inflammatory infiltration, marginal areas of the inflammatory focus, interstitital infiltrates, and periductal inflammatory zones. The division into degrees of inflammation was made according to the system shown in Table 1.

Table 2. Localization and frequency of Ig-containing plasma cells in chronic recurrent parotitis ($n=9$ cases)

Case No.	Parenchyma without inflammation			Margin of inflammation			Inflammatory infiltration					
							interstitial tissue			periductal tissue		
	A	G	M	A	G	M	A	G	M	A	G	M
20654/77	4	0	0	4	3	0	4	3	0	4	3	1
23556/77	1	0	0	4	3	0	0	0	0	1	1	0
25386/77	3	0	0	4	2	0	1	0	0	2	0	0
25491/77	2	0	0	3	1	0	0	0	0	0	0	0
29972/77	2	0	0	2	1	0	0	0	0	0	1	0
32721/77	3	0	0	2	1	0	2	1	0	3	1	0
34866/77	3	0	0	4	2	0	4	2	0	4	2	0
1919/78	3	0	0	4	3	0	4	3	0	4	3	0
24792/78	2	0	0	4	2	0	1	1	0	3	2	0

Grade 0–4 s. Table 1
A = IgA; G = IgG; M = IgM

An increase of periductal plasma cells with exclusively IgA-content and a staining intensity of mostly 2–3 (Fig. 1) was observed in the non-inflamed glandular tissue remaining. In the marginal area of the inflammatory foci, plasma cellular infiltration with IgA-continued to increase (degree 4 in two-thirds of the cases). In addition, also plasma cells with IgG-content were now discernible, though less intensely stained than in IgA-containing plasma cells. Within the area of inflammation itself, the plasma cell infiltrations with IgA-content were more pronounced in the periductal zones than in the remaining interstitial intralobular tissue, the same applying to the plasma cell accumulations with IgG-content. With the exception of one case, it was not possible to prove the presence of plasma cells with IgM-content. Where there was very intensive lymphocytic periductal cell infiltration, a decline in the number of plasma cells was observed.

Chronic Myoepithelial Parotitis (Table 3)

Chronic myoepithelial parotitis is characterized especially by the formation of myoepithelial cellular islands, a variably intense reduction of glandular acini, focal duct proliferation, and a mainly lymphocytic interstitial cell infiltration. In five cases, the myoepithelial cellular islands showed remaining lumina, intact basal membranes and lymphocytic penetration, and in two cases a hyaline transformation associated with the destruction of the basal membranes. One case was characterized by an early form of myoepithelial parotitis with the lobular structure still partly intact.

When carrying out the immunohistological examinations, two further zones (border and centre of the myoepithelial cellular islands) were distinguished in

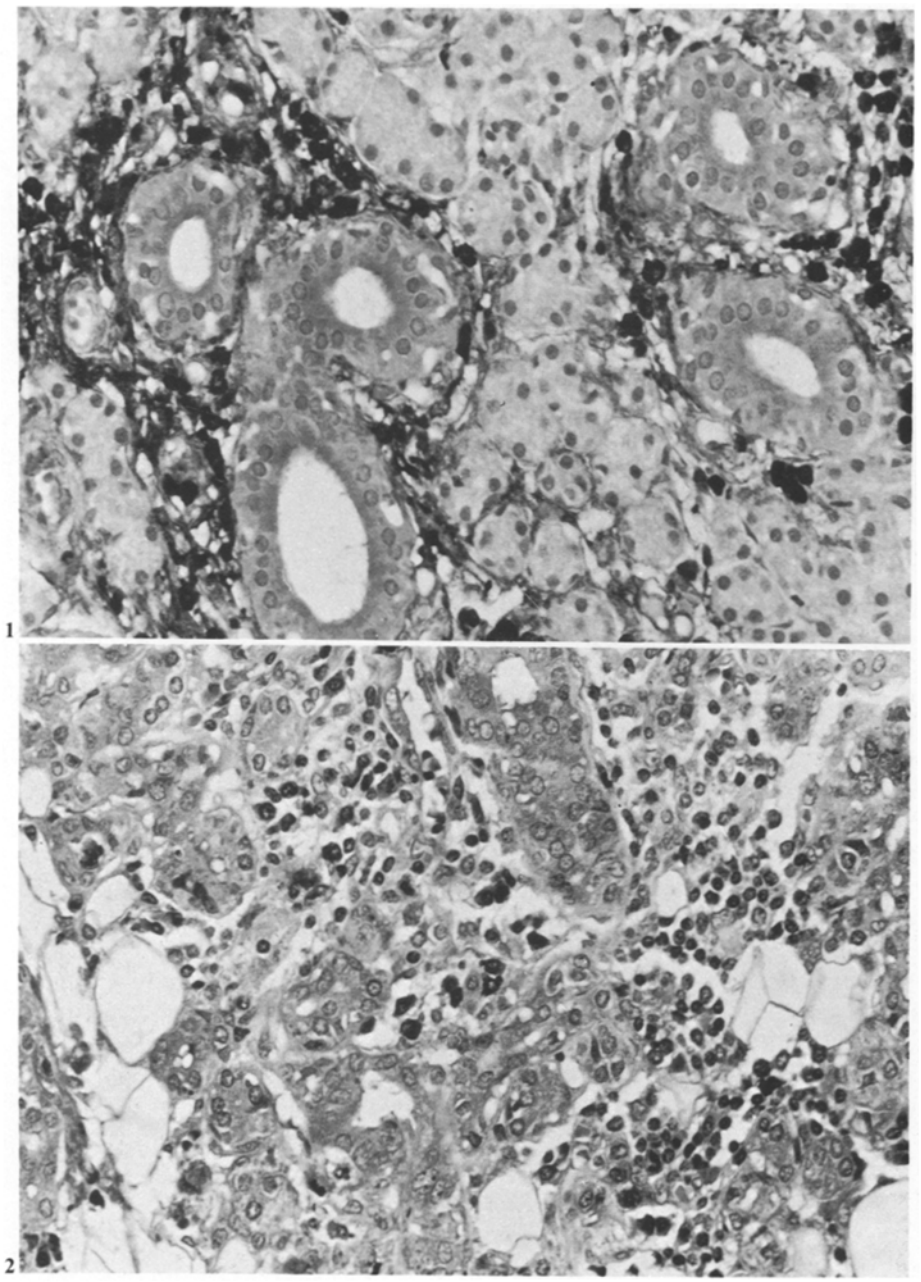

Fig. 1. Chronic recurrent parotitis (J.-No. 1919/78): distinct infiltration of IgA-containing plasma cells (grade 3) on the outside of the inflammatory area of the parotid gland. Indirect immunoperoxidase technique (IgA). ×400

Fig. 2. Chronic recurrent parotitis (J.-No. 20654/77): periductal infiltration of IgA-containing plasma cells (grade 4). Indirect immunoperoxidase technique (IgA). ×400

Table 3. Localization and frequency of Ig-containing plasma cells in chronic myoepithelial parotitis ($n=8$ cases)

Case No.	Parenchyma without inflammation			Margin of inflammation			Inflammatory infiltration											
							Interstitial tissue			Margin of ductal proliferations			Margin of m.i.			Center of m.i.		
	A	G	M	A	G	M	A	G	M	A	G	M	A	G	M	A	G	M
6163/77	2	0	0	4	4	2	1	3	1	–	–	–	1	2	1	0	0	0
11506/77	1	0	0	3	4	1	1	1	1	2	4	0	1	1	0	0	0	0
29761/77	1	0	0	1	1	0	1	0	0	–	–	–	1	1	0	0	0	0
2815/78	1	0	0	3	2	0	1	0	0	1	2	0	2	1	0	0	0	0
3104/78	–	–	–	3	3	1	1	1	1	1	1	1	0	1	1	0	1	0
21490/78	2	0	0	3	4	2	1	1	1	2	4	1	2	1	1	0	0	0
22239/78	1	0	0	2	2	0	1	1	0	–	–	–	1	1	0	0	0	0
25459/78	1	0	0	2	3	1	1	1	1	1	2	1	1	1	1	0	0	0

Grade 0–4 s. Table 1
A = IgA; G = IgG; M = IgM; m.i. = myoepithelial islands

addition to the four zones of the chronic recurrent parotitis. The different degrees of the inflammatory infiltrate were outlined in accordance with the method in Table 1. In the remaining non-inflamed glandular tissue, an increase of plasma cells with IgA-content (degree 1–2) was observed though less intensely by than in chronic recurrent parotitis (degree 2–3). The plasma cellular infiltrate increased distinctly in the marginal area of the inflammation (degree 2–3, rarely 4). The increase of plasma cells with IgG-content was striking, in three cases even surmounting the number of IgA-containing plasma cells. So was the increase of IgM-containing plasma cells (degree 1–2 in five cases). In the inflamed area itself, plasma cells with Ig-content were reduced when compared with the marginal zone of the inflammatory infiltrate. The most marked infiltration was observed in the periductal sections of the duct (Figs. 3, 4) and a distinct increase of IgG-containing plasma cells up to degree 4 was also registered (Figs. 5, 6). Little IgM was found in the plasma cells (degree 1). In the vicinity of the myoepithelial islands, there was generally only a slight plasma cell infiltration observable (mostly degree 1) with a mixture of IgA-, IgG-, and IgM-containing plasma cells. Within the myoepithelial cellular islands, practically no Ig-containing plasma cells could be identified.

Malignant Lymphomas in Chronic Myoepithelial Parotitis (Table 5)

In 11 cases malignant lymphomas developed where myoepithelial parotitis already existed. In more than two-thirds of the cases woman of an average age of 69 years were afflicted. All cases were extranodal non-Hodgkin's lymphomas presenting in the parotid gland. The patients showed the typical clinical symptoms of a Sjögren's syndrome. The classification of the malignant lymphomas

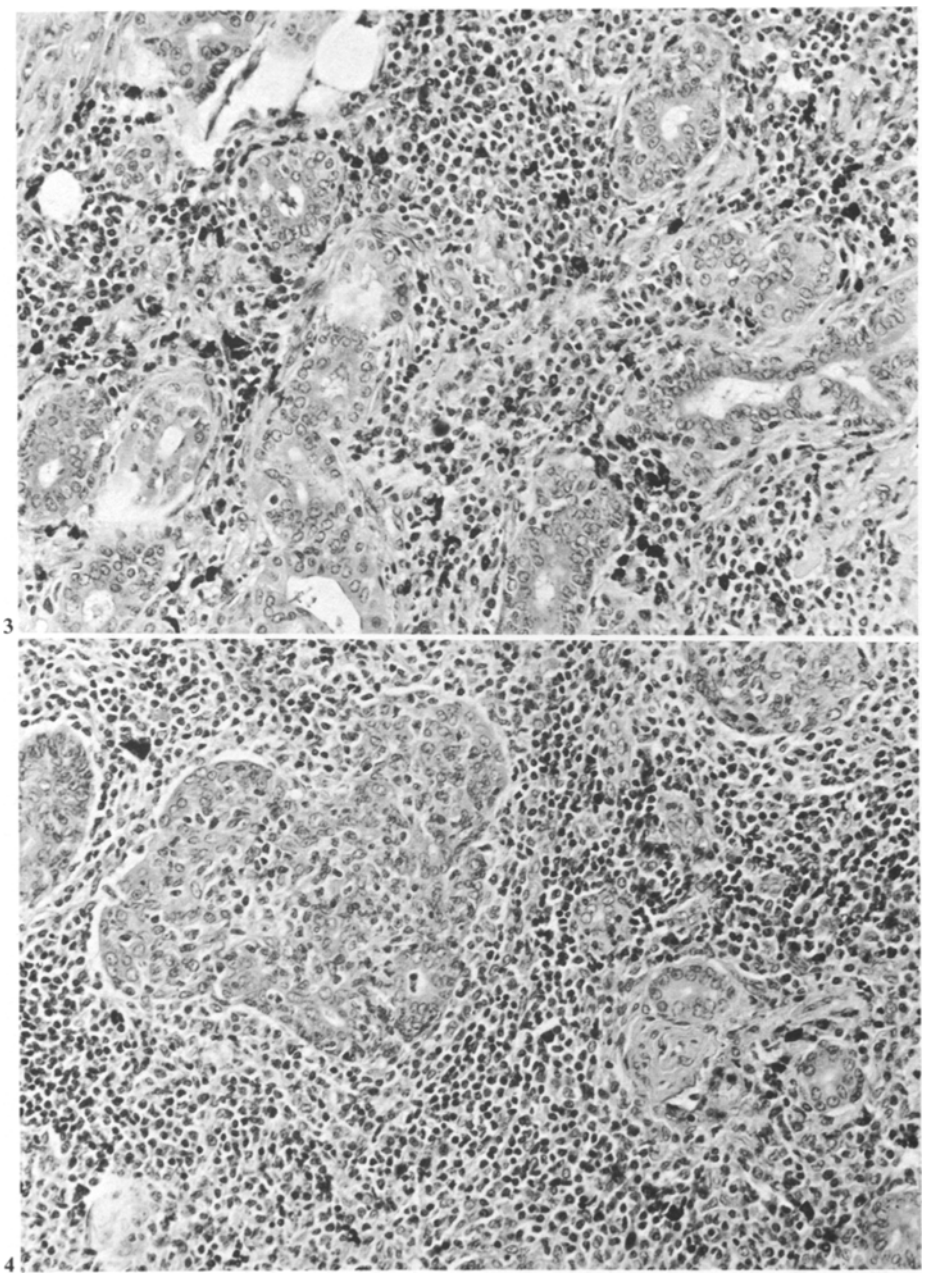

Fig. 3. Chronic myoepithelial parotitis (J.-No. 21490/78): IgA-containing plasma cells (grade 2) in the direct neighbourhood of ductular proliferations. Indirect immunoperoxidase technique (IgA). ×250

Fig. 4. Chronic myoepithelial parotitis (J.-No. 21490/78): IgA-containing plasma cells (grade 2) in the area of ductal rudiments and proliferations (right side). Myoepithelial island (left side) without plasma cell infiltration. Immunoperoxidase technique (IgA). ×250

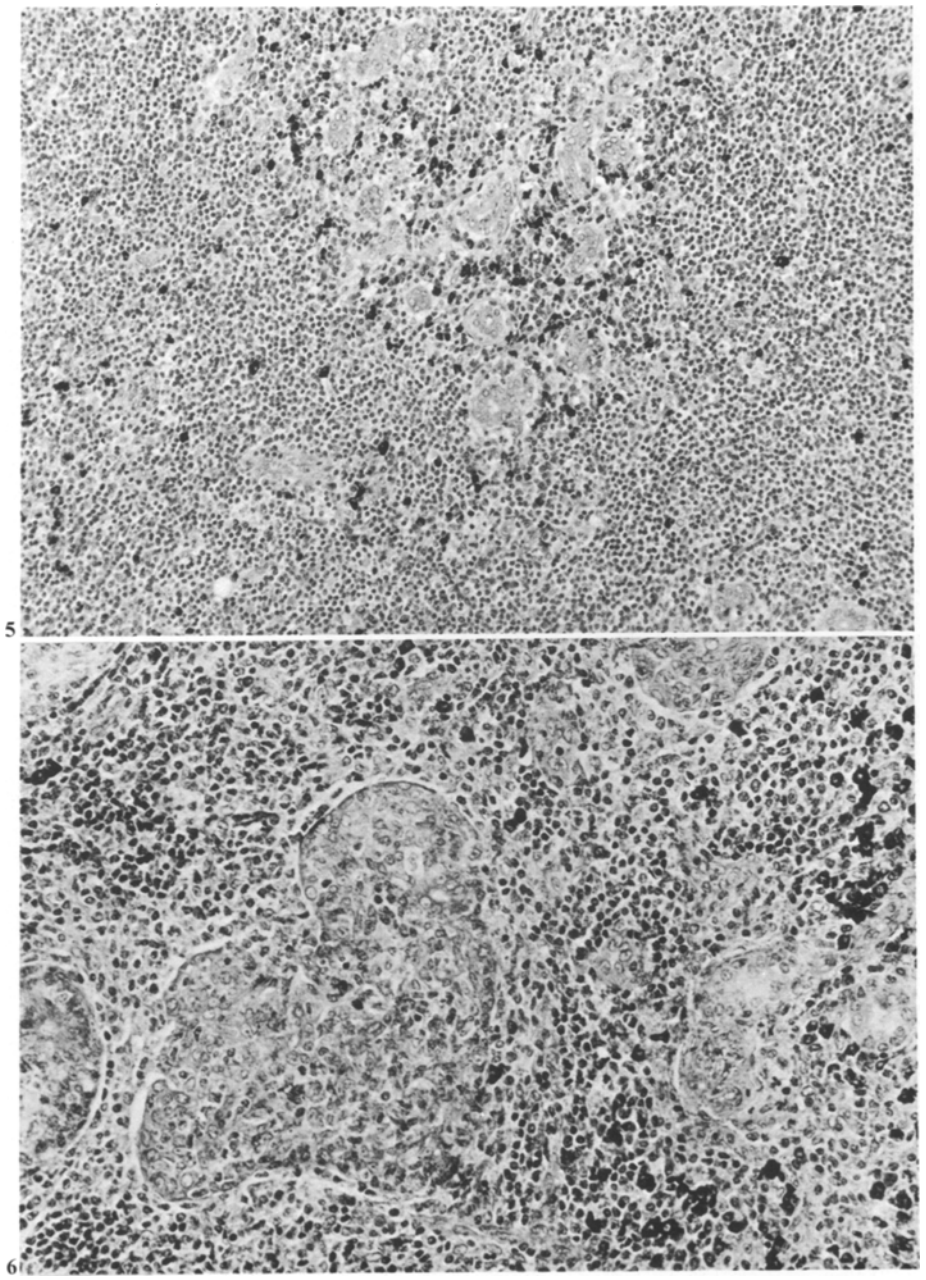

Fig. 5. Chronic myoepithelial parotitis (J.-No. 21490/78): IgG-containing plasma cells (grade 4) in the neighbourhood of ductular proliferations. Indirect immunoperoxidase technique (IgG). ×160

Fig. 6. Chronic myoepithelial parotitis (J.-No. 21490/78): IgG-containing plasma cells (grade 4) in the area of ductal rudiments and proliferations (right side); no plasma cells in a myoepithelial island (left side). Indirect immunoperoxidase technique (IgG). ×250

Table 4. Classification of malignant lymphomas in chronic myoepithelial parotitis ($n=11$ cases). Kiel classification (Lennert 1978)

Case No.	Age (years)	Sex		Diagnosis
		m	f	
25366/76	46	+		Diffuse centroblastic lymphoma
34323/76	72		+	Lymphoplasmocytic lymphoma (Immunocytoma)
34372/76	68		+	Immunoblastic lymphoma
6690/77	70	+		Lymphoplasmocytic lymphoma (Immunocytoma)
1938/78	71	+		Centrocytic lymphoma (Centrocytoma)
3466/78	67		+	Lymphoplasmocytic polymorphcellular lymphoma (Immunocytoma)
4950/78	58		+	Lymphoplasmocytic polymorphcellular lymphoma (Immunocytoma)
12402/78	?		+	Immunoblastic lymphoma
13068/78	78		+	Diffuse centrocytic lymphoma
26109/78	87		+	Lymphoplasmocytic lymphoma (Immunocytoma)
28031/78	73		+	Lymphoplasmocytic lymphoma (Immunocytoma)

Table 5. Localization and frequency of Ig-containing plasma cells in malignant lymphomas in myoepithelial parotitis ($n=11$ cases)

Case No.	Parenchyma without inflammation			Margin of inflammation			Inflammatory infiltration										
							Interstitial tissue			Margin of ductal proliferation			Margin of i.m.			Center of i.m.	Lymphoma
	A	G	M	A	G	M	A	G	M	A	G	M	A	G	M	Ig	Ig
25366/76	–	–	–	–	–	–	1	2	0	–	–	–	0	0	0	0	0
34323/76	–	–	–	3	3	0	3	4	0	4	3	0	1	1	0	0	0
34372/76	1	0	0	1	1	0	0	0	0	1	–	–	1	0	0	0	0
6690/77	1	0	0	1	1	0	1	1	1	–	–	–	1	0	0	0	0
1938/78	1	0	0	1	1	0	1	1	0	–	–	–	1	1	0	0	0
3466/78	–	–	–	3	3	0	0	1	0	–	–	–	1	0	0	0	0
4950/78	1	0	0	1	1	0	1	0	0	–	–	–	1	0	0	0	0
12402/78	–	–	–	1	1	0	0	0	0	–	–	–	0	0	0	0	0
13068/78	1	0	0	3	2	1	1	1	1	4	3	0	1	1	1	0	0
26109/78	–	–	–	–	–	–	1	1	0	–	–	–	1	0	0	0	0
28031/78	–	–	–	2	1	0	0	0	0	–	–	–	0	0	0	0	0

Grade 0–4 s. Table 1
A = IgA; G = IgG; M = IgM; m.i. = myoepithelial islands

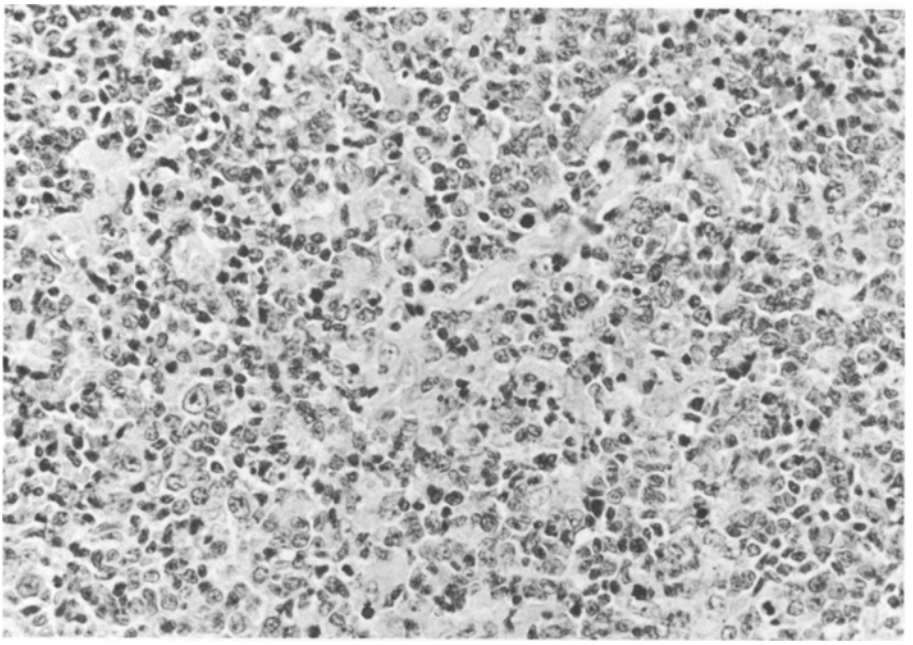

Fig. 7. Malignant lymphoma (immunocytoma) in myoepithelial parotitis (J.-No. 34323/76): Lymphoma with lymphoplasmacytoid differentation. No Ig-containing plasma cells. Indirect immunoperoxidase technique (IgG). ×400

was made in accordance with the Kiel classification (Lennert 1978). The largest number were highly differentiated lymphomas with a low malignancy (6 immunocytomas, 3 tumors of the germinal centers), only two cases of poorly differentiated immunoblastic lymphomas were found. The tumor infiltrates of the malignant lymphomas had lead to a far-reaching penetration of the glandular tissue and, in the majority of cases, to the inclusion of the adjacent soft tissue into the lymphoma. The remains of the previously existing myoepithelial parotitis were characterized by myoepithelial cellular islands, showing in a part distinct hyaline transformation.

During the immunohistological examination, the same glandular areas were distinguished as in cases of myoepithelial parotitis. The lymphoma tissue only contained tumor cells (Table 5).

In the remaining tissue of the parotid gland, only a few scattered plasma cells with IgA-content (degree 1) were found; there were no cells with IgG-content. In the marginal zones of the inflammation, IgA and IgG-containing plasma cells were found, however, of less marked staining intensity (mostly degree 1–2) than in chronic myoepithelial parotitis without lymphoma development. Within the inflammatory infiltrate, a sparse plasma cell accumulation (mostly degree 1) with changing content of IgA or IgG and hardly any of IgM, was discernible. Only in two cases was a rather focal arrangement of plasma cells (degree 3–4) found with abundant content of IgA and IgG. By the method employed, no plasma cells with Ig-content were discernible within the myoepithelial islands and the lymphomas themselves.

Discussion

In chronic recurrent parotitis the IgA-content of the saliva increases markedly (Brandtzaeg 1976). This sialochemical statement correlates with the pronounced increase in IgA-containing plasma cells in the inflamed area of the parotid gland (degree 4 in two-thirds of the cases) as well as in the noninflamed marginal areas (degree 2–3). The greatest extent was found in the periductal tissue zones, this being the place of primary antigen-antibody-reaction in ascending bacterial inflammatory processes. Apart from a local activation of lymphoid cells caused by antigen, an additional derivation of the cells from the circulating pool of lymphocytes must also be considered (Talal et al. 1970 and 1974), especially with regard to IgG-containing plasma cells, although their number is generally inferior to those containing IgA. The degree of Ig-containing plasma cells and the gravity of the glandular destruction in chronic inflammation were not correlated. Ig-containing plasma cells were found mainly in areas where intact glandular tissue still existed. Where the parenchyma was widely destroyed and the lymphocytic infiltration was very dense, the number of Ig-containing plasma cells was rather reduced.

In chronic myoepithelial parotitis, representing either a local immunoparotitis (benign lymphoepithelial lesion) or the partial picture of a Sjögren's syndrome, auto-immunological processes directed against salivary duct epithelium are of outstanding significance. In the course of the inflammation, the B-cell component in the area of small salivary glands (labial glands) recedes and is increasingly replaced by T-cell compartiments (Greenspan et al. 1974; Talal et al. 1974; Tannenbaum et al. 1975). The antibodies against salivary duct epithelium existing in the serum of patients with Sjögren's syndrome (Bertram and Halberg 1965) are found especially when combined with rheumatoid arthritis (MacSween et al. 1967).

The antibodies were mostly localized in the IgG-fraction, less in the IgM-fraction and insignificantly in the IgA-fraction (Feltkamp and van Rossum 1968). Immunohistologically, the antigen-antibody-reaction was localized in the salivary duct epithelium (Tarpley et al. 1974). Our immunohistological findings agree with these observations. The greatest extent of plasmacellular infiltration was found in the marginal area of the myoepithelial zone of inflammation (degree 2–3, rarely also 4). This corresponded with an increasing Ig-content, the IgG-content augmenting more strongly than the IgA-content, and with a pronounced increase of IgM-containing plasma cells being registered. The IgG-containing plasma cells also increased very distinctly (degree 4) in the area of ductular proliferation foci, whereas only a slight plasma cell infiltration (degree 1) existed in the direct vicinity of the myoepithelial cellular islands and no plasma cells with Ig-content were observed within the islands themselves. The further destructive inflammatory process was characterized by a stage by stage course (Donath and Seifert 1972). In the beginning, islands with remaining duct lumina and inclusion of duct epithelium were found; later only islands of myoepithelial cells and lymphocytic infiltration were seen and finally hyaline-transformed islands with declining lymphocytic penetration remained. This seems to indicate that, after destruction of the ductal structures, no antigen-determinants remain to feed the auto-aggression process.

The key agent leading to the changed antigen determination of the duct epithelium and thus releasing the auto-antigen immunoreaction, is unknown. Batsakis et al. (1975) discuss a developmental spectrum from chronic recurrent parotitis via local benign lympho-epithelial lesion to generalized Sjögren's syndrome. In a previous paper (Seifert and Donath 1977), we also established the hypothesis that relations exist between chronic recurrent sialadenitits and immunosialadenitis, more convincingly since, in the intermediate stages, the existence of isolated myoepithelial cellular islands can be demonstrated. Findings in experimental immunosialadenitis and spontaneous autoimmuno-sialadenitis in inbred mice (Seifert and Donath 1967; Seifert 1979; Seifert and Burkhardt 1979; Seifert 1980) seem to indicate the same direction.

Malignant lymphomas of the parotid gland developing on the basis of a preexistent immunoparotitis have been described repeatedly (Anderson and Talal 1972; Hyman and Wolff 1976; Heckmayr et al. 1976; Seifert and Donath 1976; Seifert 1979 and 1980; Lennert et al. 1979). Between the primary immunoparotitis and the formation of malignant lymphoma there is generally an interval of ten or more years. The clinical change from an immunological inflammatory process to malignant lymphoma may be signalized by a transition from hyper- to hypogamma globulinemia (Tatal and Bunim 1964; Bloch 1976). The majority of lymphomas are relatively highly differentiated B-cell-tumors of the immunocytoma-type (lympho-plasmacytoid lymphomas) or tumors of the germinal centers (centrocytic-centroblastic lymphomas), more rarely of poorly differentiated immuno-blastical lymphomas (Lennert 1978; Lennert et al. 1979). Special B-cell-lymphomas distinguish themselves by monoclonal Ig-formation (Lennert 1978). Intracytoplasmatic monoclonal IgM (with kappa light chains) have been identified in lymphomas combined with Sjögren's syndrome (Zulman et al. 1978). In the prelymphomas the existence of monoclonal IgM kappa was interpreted as a marker and an early symptom of neoplasia (Faguet et al. 1978; Lennert et al. 1979). The change from polyclonal lympoid cells in chronic immunoreaction to neoplastic single clone formation in the lymphoma can be based upon different mechanisms (overstimulation and exhaustion, mutation, loss of suppressor-T-lymphocytes and others). In our material, comparing with the chronic myoepithelial parotitis without lymphoma formation, we found a pronounced decrease of Ig-containing plasma cells (degree 1–2). In the remaining myoepithelial islands as well as in the lymphomas themselves, no Ig-containing plasma cells were discernible.

Altogether, our examinations show differences in the frequency of plasma cell infiltration and its Ig-content in the three different pathological processes of the parotid gland. The highest percentage of IgA-containing plasma cells was found in chronic recurrent parotitis, especially in the marginal zones of the inflammation and in still intact glandular structures. In chronic myoepithelial parotitis a distinct increase of IgG-containing plasma cells was observed, especially in the area of ductular proliferation. With the progression of the inflammatory process combined with the destruction or hyaline transformation of the myoepithelial cellular islands, a decrease of plasma cell infiltration with Ig-content was observed. The greatest extent of plasma cell reduction was found in malignant lymphomas developing on the basis of a previously existing myo-

epithelial parotitis. These changes of plasma cell infiltration with Ig-content demonstrate changes of the local secretory salivary gland immunosystem and transitions from pseudolymphoma to the formation of malignant lymphoma. The fact that only B-cell-lymphomas were observed and that they mainly were highly differentiated immunocytomas or centrocytic-centroblastic lymphomas seems to emphasize the correctness of this hypothesis.

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