Med. J. Kagoshima Univ., Vol. 47, Suppl. 2. 77~84, November, 1995

Invited Paper

Comparison of Silver-Binding Nucleolar Organizer Regions (AgNORs) between Myoepithelial Sialadenitis and Low-Grade B-Cell Lymphoma of Salivary Gland

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Summary

We quantified nucleolar organizer regions demonstrable by silver staining technique (AgNORs) in six cases of myoepithelial sialadenitis (MESA) and 16 low-grade B-cell lymphomas (mucosa-associated lymphoid tissue (MALT) 11, centrocytic 2, centroblastic-centrocytic 3). These salivary gland lesions were histologically and immunohistochemically defined as MESA or low-grade B-cell lymphoma. There was no significant difference in AgNOR counts per nucleus between MESA and low-grade B-cell lymphoma. The pooled mean AgNOR number in MESA was significantly higher than that in MALT lymphoma, and significantly lower than those in centrocytic lymphoma and centroblastic-centrocytic lymphoma. The AgNOR numbers in the cellular component of MESA were also analyzed. The follicle center centroblasts of MESA exhibited a significantly higher pooled mean AgNOR number than other kinds of lymphoid cells in MESA. Furthermore, AgNOR numbers of salivary gland lymphomas were compared with those of cellular elements in MESA. There was a statistically significant increased AgNOR number of neoplastic centroblasts in centroblastic-centrocytic lymphoma when compared with follicular centroblasts in MESA. The pooled mean AgNOR number in centrocytic lymphoma was significantly higher than that in MALT lymphoma, mantle zone and interfollicular lymphocytes in MESA. However, there was no significant difference between centrocytic lymphoma versus follicular centrocyte in MESA and between centrocytic lymphoma versus centroblastic-centrocytic lymphoma. The pooled mean number of AgNOR in MALT lymphoma was statistically lower than that in follicular centrocytes in MESA. However, there was no significant difference in AgNOR numbers between MALT lymphoma and interfollicular or mantle zone lymphocytes of MESA. Therefore, we propose the MALT lymphoma may represent a mucosal counterpart of mantle zone lymphocyte-or interfollicular lymphocyte-related low-grade B-cell lymphomas.

Key words: Nucleolar organizer regions, myoepithelial sialadenitis, low-grade B-cell lymphoma of salivary gland.

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Introduction

Myoepithelial sialadenitis (MESA), which is also called immunosialadenitis, is a morphological feature of Sjögren's syndrome, but it may also be found in patients without the clinical picture of Sjögren's syndrome and lead to development of lymphoma[1-3]. The association between MESA and primary B-cell lymphoma of the salivary gland is well recognized[4,5], especially, the relationship of mucosa-associated lymphoid tissue (MALT) lymphoma to MESA is noted[6,7]. Nevertheless, there is controversy about the differential diagnosis between the two conditions. Recent authors have questioned the validity of distinguishing between MESA and primary salivary gland lymphoma and it has become apparent that traditional morphological criteria, particularly the presence of germinal centers, are unreliable[7]. In a previous study of primary

salivary gland lymphoma, which included cases of "pseudolymphoma", Takahashi et al[7]. demonstrated light chain restriction in all cases. In the course of their study these authors characterized the B-cell mucosa-associated lymphoid tissue (MALT) lymphomas of the salivary gland as indolent tumors that usually remain localized for a long time. In low-grade B-cell lymphoma of the salivary gland, MALT lymphoma has been reported as the frequent histologic subtype[7,8]. Unusual histologic appearance of MALT lymphoma may lead to misdiagnosis, usually as a benign lesion, pseudolymphoma, or so-called MESA[7].

Silver-stained nucleolar organizer regions (AgNORs) contain loops of DNA (rDNA) encoded for ribosomal RNA (rRNA) production and associated with nucleoli. AgNORs estimation has been shown to aid in the distinction between certain benign and malignant tumors, and between low- and high-grade tumors[9-12] and may help as an indication of cell proliferation[13-15]. In a few previous studies of non-Hodgkin's lymphomas and reactive follicular hyperplasia of lymph node, a significantly increased mean AgNOR number was found in high-grade lymphomas when compared with low-grade lymphomas[10], whereas mean AgNOR number of reactive follicular hyperplasia was greater than that in follicular lymphoma[16].

In this study using a silver staining technique, nucleolar organizer region-associated proteins have been studied in paraffin sections of 6 cases of MESA and 16 cases of low-grade B-cell lymphoma in salivary gland. The main aims of this study were: firstly, to assess the reliability of AgNOR staining method in distinguishing between MESA and low-grade B-cell lymphoma; secondly, to establish whether the mean number of AgNORs can be used as a marker of classification between MALT lymphoma and MESA; and thirdly, to determine if there is any relationship between the mean AgNOR count in lymphoma cells of low-grade B-cell lymphoma and that in the histogenetically related cellular components of MESA.

Material and Methods

1. Tissues

Histology

Sixteen operatively resected primary salivary gland low-grade B-cell lymphomas were gathered from the files of the Department of Pathology, Nagasaki University Hospital and its affiliated hospitals between 1962 and 1984. In addition, six cases of MESA were also examined. Surgical specimens were routinely fixed in formalin and processed in paraffin. Hematoxylin and eosin, Giemsa and periodic acid-Schiff stained paraffin sections of resected tissues of major salivary glands were examined, and classified according to the updated Kiel system[17] by one (H. T.) of the authors. These comprised the following Kiel subtypes of low-grade B-cell lymphomas: MALT (11), centrocytic (two), centroblastic-centrocytic (three).

Immunohistochemistry

Immunoperoxidase staining was performed on paraffin tissue sections in 22 cases of MESA and low-grade lymphomas, and thereafter the immunological phenotype of all cases was determined. Paraffin sections cut at 3 μm were stained by the use of the avidin-biotin complex technique as described previously[18]. The antibodies chosen included those reported to detect markers of B-cell (immunoglobulins, L26, KiB3, LN1, LN2) and T-cell (UCHL1, MT1, DFT1), as well as the HLA-DR antigen marker LN3, BerH2 (activated lymphoid cells) and Leu-7 (natural killer cells). Antibodies detecting cathepsin D, lysozyme and alpha-1-antitrypsin were used as markers of histiocytic origin, in addition to KP1 and LN5. Antibody to epithelial membrane antigen (EMA) was used to detect tumors of epithelial origin. Primary antibodies used in the present study were purchased from Dako Ltd. (Copenhagen, Denmark), Pathol. Inst. Univ. Kiel (Germany), Techniclone Int. (CA, USA), and Becton-Dickinson (CA, USA). In all cases of non-Hodgkin's lymphomas, the specimens were characterized by means of the demonstration of monotypic immunoglobulin and B-cell markers (L26, KiB3, LN1 and/or LN2), and were all of established B-cell lineage. Conversely, stains with T-cell marker (UCHL1) and histiocytic markers (cathepsin D, lysozyme, alpha-1-antitrypsin, KP1 and LN5) were totally negative. Lymphoid cells in six cases showed a polytypic immunoglobulin pattern and these cases belonged to MESA.

2. AgNOR staining method

Sections were cut at 3 μm from routinely processed paraffin blocks, dewaxed in xylene, and hydrated through graded methanol into deionized distilled water. Thereafter a one-step silver nitrate staing was performed. The staining solution was freshly prepared by dissolving 2% gelatin in deionized distilled water adding formic acid to a final concentration of 1%. This solution was mixed with 2 volumes of 5% aqueous silver nitrate to obtain the final working solution. The paraffin sections were immersed in an AgNOR staining solution for 40 min under darkroom conditions at room temperature. Gold-enhancement was performed by covering the sections with 0.2% aqueous gold chloride for 10 min, followed by 1:5-diluted photographic fixing solution for 5 min in order to prevent discoloration of the AgNOR dots. The sections were washed with deionized distilled water prior to counterstaining with Mayer's hematoxylin, dehydrated through alcohols to xylene and mounted with synthetic medium. All of the sections for examination were stained at the same time and with same solution.

3. Counting Procedure and statistical analysis

Counting was done by using a × 100 oil immersion objective to a total magnification of × 1000 by one and the same person (H. T.) of the authors. In MESA, AgNORs were counted in 200 cells of follicular centroblasts, follicular centrocytes, mantle zone lymphocytes, and interfollicular lymphocytes, respectively. In every case of salivary gland lymphomas, AgNOR dots were counted in at least 200 nuclei. The nuclei for the study were selected randomly, and a counting grid was employed to ensure that there was no duplication of counting. All separate silver stained dots in the nucleoli and nucleoplasm were counted as AgNORs and polycyclic structures were counted as one[19]. Focussing was adjusted for each nucleus to include all the AgNORs in all possible focal planes in the counts. The comparison was made between follicular centroblasts in MESA and neoplastic centroblasts in centroblastic-centrocytic lymphoma; among follicular centrocytes in MESA, neoplastic cells of MALT lymphoma, and neoplastic centrocytes in centroblastic-centrocytic lymphoma and centrocytic lymphoma; among mantle zone lymphocytes and interfollicular lymphocytes in MESA, and neoplastic cells of MALT lymphoma; and between MESA and low-grade B-cell lymphoma, in order to examine the correlation of AgNORs with hyperplastic and neoplastic changes of lymphoid cells. The mean number of AgNORs per nucleus was calculated and all the data were statistically assessed. The mean values for all groups were compared using the Student's t-test.

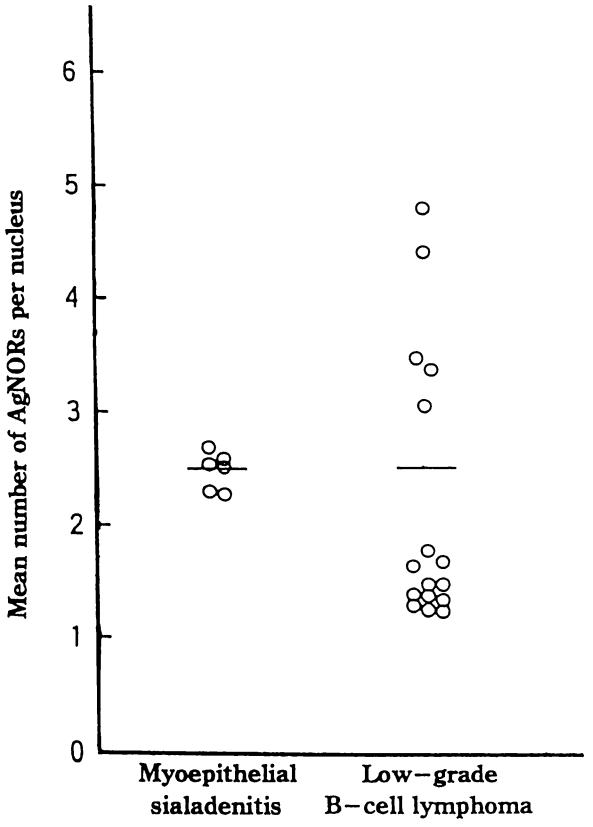

Fig. 1. Scattergram showing the mean numbers of AgNORs in low-grade B-cell lymphoma of salivary gland and myoepithelial sialadenitis. Horizontal bars indicate mean in both groups.

Results

1. AgNOR counts

AgNORs were seen as small, well defined black silver-stained intranuclear structures, sometimes in aggregates within the nucleolus, in all of the salivary glands examined in this study. They exhibited somewhat varying size and configuration, and occurred in all kinds of cells investigated. There appeared to be a somewhat greater variation in size and configuration of the AgNORs in malignant than in reactive lymphoid cells. The pooled mean number of AgNORs in MESA and low-grade B-cell lymphoma are summarized in Table 1 and a scattergram (Fig. 1).

Myoepithelial Sialadenitis (MESA)

In six cases of MESA, the pooled mean number of AgNORs ranged between 2.27 and 2.69 (mean, 2.48 ± 0.17) (Table 1). The pooled mean number of AgNORs were determined from the following cell types; mantle zone lymphocytes (mean, 1.37 ± 0.10) (Fig. 2), interfollicular lymphocytes (mean, 1.42 ± 0.11) (Fig. 3), follicular centrocytes (mean, 2.62 ± 0.21) (Fig. 4), and follicular centroblasts (mean, 4.53 ± 0.65) (Fig. 4). Analysis of pooled means showed a significant difference between the AgNOR numbers derived from follicular centroblasts and follicular centrocytes ($p < 0.01$). There was also a significant difference between pooled mean AgNOR numbers from follicular centrocytes and mantle zone and interfollicular lymphocytes ($p < 0.01$), but not between the latter two cell types.

Low-grade B-cell Lymphoma

In 16 cases of low-grade B-cell lymphomas, the pooled mean number of AgNORs was 2.19 ± 1.21. The group of MALT lymphoma contained the lowest mean number of AgNORs (mean, 1.44 ± 0.18) among three types of low-grade B-cell lymphomas investigated (Fig.5). The pooled mean number of AgNORs in centrocytic lymphoma (mean, 3.22 ± 0.23) (Fig. 6) was found to be significantly higher than that in MALT lymphoma ($p < 0.05$). The highest value in low-grade B-cell lymphoma was found in centroblastic-centrocytic lymphoma (mean, 4.23 ± 0.67) (Fig. 7). The pooled mean number of AgNORs in this lymphoma was significantly higher than that in MALT lymphoma ($p < 0.05$). However, there was no significant difference when compared with centrocytic lymphoma.

Table. 1. Distribution of AgNORs in low-grade B-cell lymphoma of salivary gland and myoepithelial sialadenitis

Histologic and cell types	No.	Pooled mean	S.D.	Range
MESA	6	2.48	0.17	2.27-2.69
Centroblast	6	4.53	0.65	3.23-5.47
Centrocyte	6	2.62	0.21	2.47-2.91
Mantle zone lymphocyte	6	1.37	0.10	1.25-1.54
Interfollicular lymphocyte	6	1.42	0.11	1.22-1.52
Low-grade B-cell lymphoma	16	2.19	1.21	1.24-4.80
Centroblastic-centrocytic	3	4.23	0.67	3.49-4.80
Centrocytic	2	3.22	0.23	3.06-3.39
Mucosa-associated lymphoid tissue	11	1.44	0.18	1.24-1.77

2. Comparison of the AgNORs among cellular components in MESA and low-grade B-cell lymphoma

The results of AgNOR numbers in low-grade B-cell lymphomas in comparison with that in the cells constituting the MESA were summarized in Table 2 and Fig. 8. When treating MESA as one group, the pooled mean number of AgNORs was non-significantly higher than that in low-grade B-cell lymphomas. MESA exhibited a significantly higher pooled mean AgNOR number than the MALT lymphoma ($p < 0.01$), whereas lower pooled mean AgNOR number

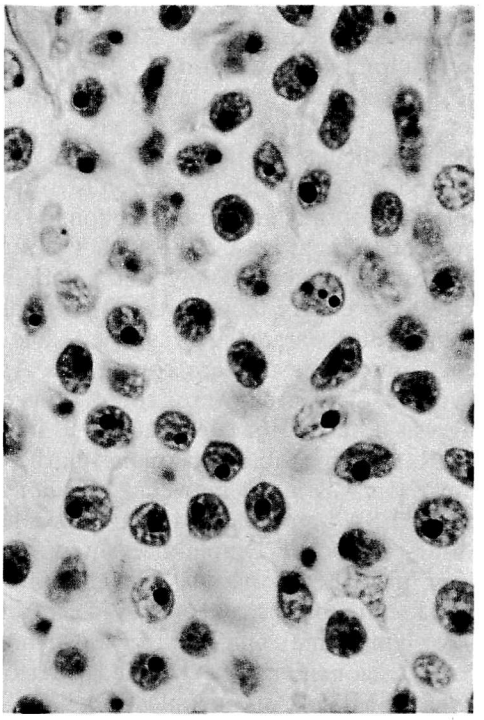

Fig. 3. Interfollicular lymphocytes in reactive lymphoid hyperplasia. Almost all nuclei contain one to three AgNOR dots. Silver colloid staining, original magnification × 500.

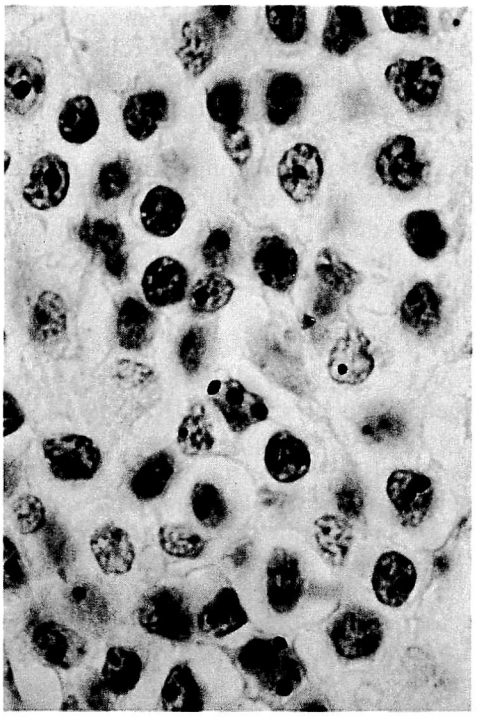

Fig. 2. Mantle zone lymphocytes in reactive lymphoid hyperplasia. The nuclei contain one to four AgNOR dots. Silver colloid staining, original magnification × 500.

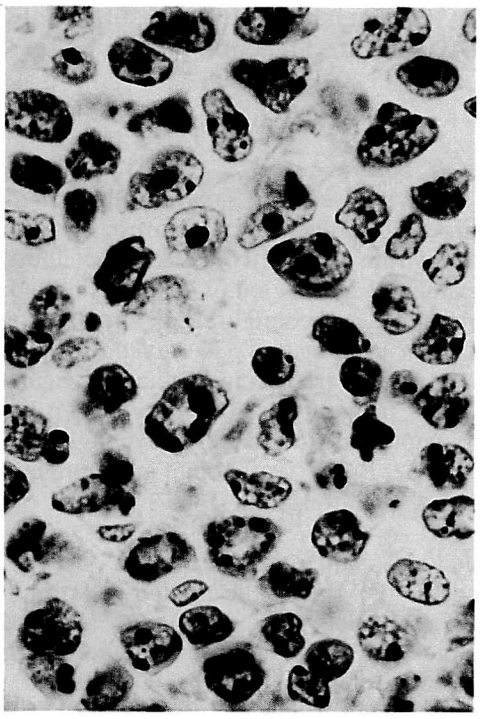

Fig. 4. Follicular centroblasts and centrocytes in reactive lymphoid hyperplasia. Centroblasts containing three to nine AgNOR dots in nuclei and centrocytes showing two to six dots per nucleus. Silver colloid staining, original magnification × 500.

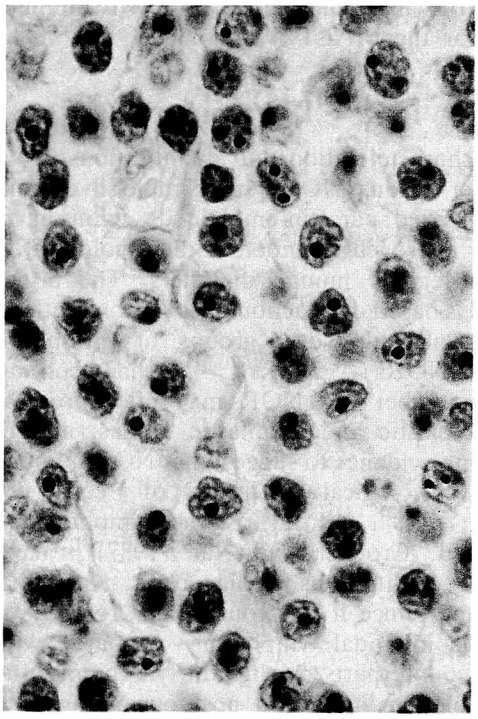

Fig. 5. MALT lymphoma.Most neoplastic cells contain one to four AgNOR dots. Silver colloid staining, original magnification × 500.

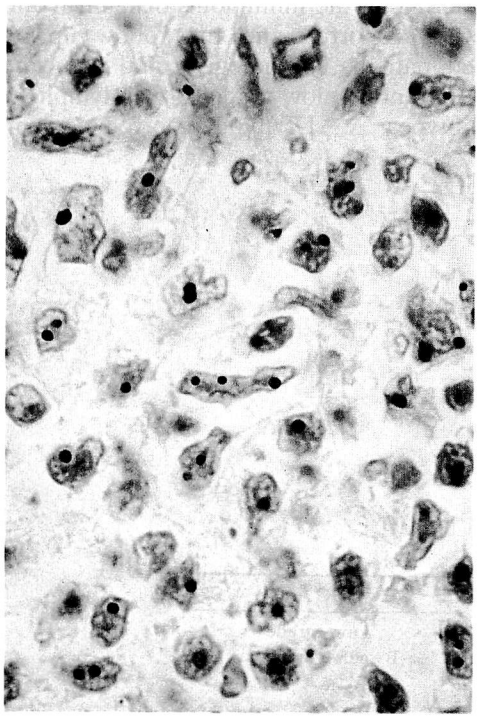

Fig. 6. Centrocytic lymphoma. The cleaved medium-sized nuclei contain one to seven AgNOR dots. Silver colloid staining, original magnification × 500.

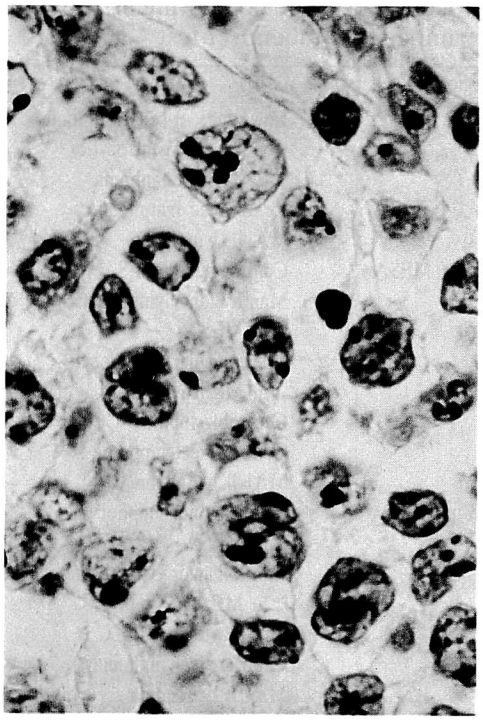

Fig. 7. Centroblastic-centrocytic lymphoma. The nuclei of neoplastic centroblasts and centrocytes present the highest number of AgNORs among low-grade B-cell lymphomas investigated. Silver colloid staining, original magnification × 500.

than the centrocytic lymphoma and centroblastic-centrocytic lymphoma.

In MESA, the highest value of pooled mean AgNOR numbers was identified in follicular centroblasts. Among low-grade B-cell lymphomas, the highest value of AgNORs was found in centroblastic element of centroblastic-centrocytic lymphoma. There was no statistically significant difference between the neoplastic centroblasts of centroblastic-centrocytic lymphoma and the follicular centroblasts of MESA in mean AgNOR score. The mean number of AgNORs per nucleus in centrocytic lymphoma was lower than that in follicular centroblasts of MESA ($p < 0.01$) and higher than those in mantle zone and interfollicular lymphocytes of MESA ($p < 0.01$). However, the difference among centrocytic lymphoma, neoplastic centrocytes of centroblastic-centrocytic lymphoma and follicular centrocytes of MESA did not reach a statistically significant level. The pooled mean number of AgNORs in neoplastic cells of MALT lymphomas did not reach a statistically significant level when compared with mantle zone lymphocytes and interfollicular lymphocytes in MESA. Moreover, the neoplastic cells of MALT lymphomas showed a significantly lower pooled mean AgNOR number than that of the follicular centrocytes in MESA ($p < 0.01$). In comparison with follicular centroblasts in MESA, a significant decrease

Table 2. Comparison of pooled mean AgNORs using unpaired Student's *t*-test

Histologic and cell types	Comparison	*P*-value
MESA	Low-grade B-cell lymphoma	N. S.
	Centroblastic-centrocytic (CB-CC) lymphoma	$p<0.01$
	Centrocytic lymphoma	$p<0.01$
	MALT lymphoma	$p<0.01$
Centroblast in MESA	Centrocyte in MESA	$p<0.01$
	Mantle zone lymphocyte in MESA	$p<0.01$
	Interfollicular lymphocyte in MESA	$p<0.01$
	Centroblast in CB-CC	N. S.
	Centrocytic lymphoma	$p<0.01$
	MALT lymphoma	$p<0.01$
Centrocyte in MESA	Mantle zone lymphocyte in MESA	$p<0.01$
	Interfollicular lymphocyte in MESA	$p<0.01$
	Centrocyte in CB-CC	N. S.
	Centrocytic lymphoma	N. S.
	MALT lymphoma	$p<0.01$
Mantle zone lymphocyte in MESA	Interfollicular lymphocyte in MESA	N. S.
	MALT lymphoma	N. S.
Interfollicular lymphocyte in MESA	MALT lymphoma	N. S.
CB-CC	Centrocytic lymphoma	N. S.
	MALT lymphoma	$p<0.05$
Centroblast in CB-CC	Centrocyte in CB-CC	N. S.
Centrocyte in CB-CC	Centrocytic lymphoma	N. S.
Centrocytic lymphoma	MALT lymphoma	$p<0.05$

($p < 0.01$) in pooled mean AgNOR numbers was found for the MALT lymphomas.

Discussion

The characterization and quantitation of nucleolar organizer regions (NORs) by a simple silver staining on formalin-fixed, paraffin-embedded sections have added another approach to understanding biological features of a variety of human disorders. The argyrophilic method is based on reaction of silver ions with carboxyl groups and sulphydryl groups of phosphoproteins bound to NORs (AgNORs)[20,21]. It had been suggested that the number of AgNORs may reflect processes such as hyperplastic and neoplastic tissues, and there is increasing evidence to suggest that NOR numbers are a useful histological marker of cell proliferation[10-12,15,22,23]. As far as the lymphoid tissue is concerned, Crocker and Nar (1987)[10] have used AgNOR counting as a diagnostic discriminant for malignancy since it was found that AgNORs may be increased in nodal lymphomas compared with their benign counterparts. Malignant lymphoma of salivary gland holds an important position among extranodal lymphomas[24]. There are many clinicopathological studies on salivary gland non-Hodgkin's lymphomas, however, there are only a few which stressed a close relationship between salivary gland non-Hodgkin's lymphoma and benign lymphoid lesions (MESA).

Considering all the immunohistochemical and histological data reported and the follow up of these diagnosed patients, pathologists and clinicians have divided extranodal low-grade B-cell lymphoma into three subtypes, MALT type, centrocytic lymphoma

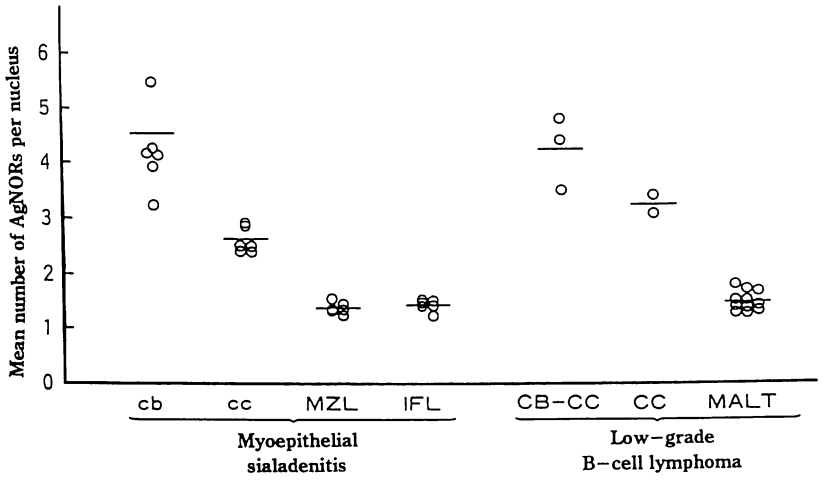

Fig. 8. Scattergram representing the mean numbers of AgNORs in low-grade B-cell lymphoma of salivary gland and in cell types of myoepithelial sialadenitis. Horizontal bars show mean in each group. cb, centroblast, cc, centrocyte; MZL, mantle zone lymphocyte; IFL, interfollicular lymphocyte; CB-CC, centroblastic-centrocytic lymphoma; CC, centrocytic lymphoma; MALT, mucosa-associated lymphoid tissue lymphoma.

and centroblastic-centrocytic lymphoma. This categorization of extranodal low-grade B-cell lymphoma is not straightforward as a grey area exists between these subtypes, which in some cases can be resolved by immunohistochemistry. Newer techniques and approaches are required to achieve satisfying results for classifying extranodal low-grade B-cell lymphoma. We therefore stained a variety of low-grade B-cell lymphoma of salivary gland with the AgNOR technique to see if some conclusive answer could be obtained. Since obvious distinction could be made between MALT and centroblastic-centrocytic or centrocytic lymphomas on the basis of NOR numbers, it appears that quantification of AgNORs might also be of importance in the grading of three subtypes.

As referred to the histological differentiation between MESA and MALT lymphoma is occasionally problematic. In order to assist the separation of MALT lymphoma from MESA, a variety of morphological and immunohistochemical methods have been reported[4,7]. Low-grade B-cell lymphomas arising from gastrointestinal-associated lymphoid tissue have recently been reported to show the features of MALT lymphoma[4,7]. In a previous study of primary salivary gland lymphoma which included cases of MESA, Takahashi et al. (1992)[7] demonstrated light chain restriction in all cases. Although the histogenesis of these MALT lymphomas is not fully understood, ample evidence favors derivation from a B-cell subcohort native to mucosal linings. In addition, a relationship has been proposed to the B-cells of the marginal zone and/or of lymph follicles[25,26].

In the present study, the AgNOR numbers differed among low-grade B-cell lymphomas, and MALT lymphomas had the lowest mean values of AgNORs. As described in "Material and Methods" of this study, 11 MALT lymphomas showed monotypic immunoreactivity for immunoglobulin of neoplastic cells. Interestingly, the present study demonstrated that the pooled mean AgNOR numbers per nucleus in histopathologically and immunohistochemically verified MALT lymphoma were significantly lower than those in the overall lymphoid cells of MESA. This low value of MALT lymphoma is in agreement with clinical follow-up studies revealing that some MALT lymphomas grow very slowly or may be stationary for several years[4,8]. Recently, Cronin et at. (1989)[16] and Weiss et al. (1987)[27] have reported than reactive follicular hyperplasia shows greater proliferative activity than follicular lymphoma. Most follicular lymphomas are low-grade lymphomas, possibly low cell proliferation, whereas hyperplastic follicles are highly active units, as can be seen in any reactive lymph node immunostained with monoclonal antibody Ki67. This raises the possibility that increased number of AgNORs may reflect cell proliferation rather than biological malignancy.

A relationship between AgNOR numbers in neoplastic cell of low-grade B-cell lymphomas and those in reactive counterparts of MESA was analyzed. In centroblasts of centroblastic-centrocytic lymphomas, in general, the mean AgNOR numbers were higher than in their corresponding non-tumorous cell types. It is now obvious that centrocytic lymphomas are not derived from the follicular centrocytes, but rather from the mantle zone lymphocytes[17]. Hence we used AgNOR numbers for the reactive mantle zone lymphocytes and neoplastic centrocytes for statistical evaluation. The corresponding value of 3.22 in centrocytic lymphoma is significantly higher than that of 1.37 in mantle zone lymphocytes of MESA. Although there are still some uncertainties as to the histogenesis of the MALT lymphomas, a relationship has been proposed to the B-cells of marginal zone and/or germinal centers[25,26]. Therefore, it seems adequate for the present purpose to compare the data for MALT lymphomas with those for mantle zone lymphocytes, interfollicular lymphocytes and follicular centrocytes in MESA. No apparent difference was observed between MALT lymphoma and mantle zone lymphocytes or interfollicular lymphocytes in MESA. On the other hand, AgNOR numbers in MALT lymphomas were lower than that in follicular centrocytes of MESA. The observations in this study suggest that MALT lymphoma was not significantly different from the AgNOR reading of non-tumorous counterpart.

Our findings indicated that AgNOR numbers in MESA progressively increased from mantle zone and interfollicular lymphocytes to follicular centrocytes and follicular centroblasts. Furthermore, the AgNOR numbers in non-Hodgkin's B-cell lymphoma exhibited progressive increases from MALT lymphoma to centrocytic lymphoma or centroblastic-centrocytic lymphoma. Our results are in disagreement with a previous study by Crocker and Nar (1987)[10], in which no significant differences were found in AgNOR numbers between mantle zone and interfollicular lymphocytes and follicular centrocytes of reactive lymphadenitis. Futhermore, in node-based low-grade lymphoma, they described a considerable overlap in AgNOR numbers among immunocytoma, centrocytic lymphoma and centroblastic-centrocytic lymphoma. This discrepancy between our results and data of Crocker and Nar (1987)[10] may be due to the different organ, or different method of AgNOR counting, since in our study we took into consideration all of the separable AgNOR in the nucleus and therefore counted a higher number of AgNOR in follicular centrocytes and follicular centroblasts of MESA and neoplastic cells of non-Hodgkin's lymphomas.

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