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Epithelial HLA-DR expression and T lymphocyte subsets in salivary glands in Sjögren's syndrome

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SUMMARY

Salivary glands obtained at biopsy from patients with Sjögren's syndrome and controls were studied with regard to phenotype of infiltrating and residing cells, by means of a double immunoenzymatic staining technique. The infiltrating lymphocytes, which were sparse or absent in the control group in contrast to their abundant presence in the Sjögren patients, consisted in both groups mainly of T lymphocytes, the majority of which were T helper cells. In the controls, the glandular epithelial cells were HLA-DR$^-$ whereas in the Sjögren patients HLA-DR$^+$ epithelial cells were found, mainly confined to areas, where the epithelial cells were seen in close proximity to the perifery of dense lymphocytic infiltrates. The data are in accordance with recent findings of HLA-DR expressing residing cells in the target organs of various chronic inflammatory diseases and might indicate the induction of HLA-DR expression in nonlymphocytic cells of target organs in which a cellular infiltration dominated by cells of the T helper phenotype is found.

Keywords HLA-DR expression epithelium Sjögren's syndrome salivary glands

INTRODUCTION

Sjögren's syndrome (SS) is a chronic inflammatory disease, in which exocrine glands, mainly salivary and lacrimal glands, become heavily infiltrated with lymphocytes leading to, among other symptoms, decreased production of saliva and tears, i.e. the 'sicca complex'. In about half of the cases an underlying connective tissue disease is present, most often rheumatoid arthritis, but also systemic lupus erythematosus, progressive systemic sclerosis and other connective tissue diseases (CTD) (i.e. secondary Sjögren's syndrome, 2°SS). In cases where no CTD is present, the syndrome exists as a distinct entity (primary Sjögren's syndrome, 1°SS). In both 1°SS and 2°SS multiple autoantibodies, such as rheumatoid factor, antinuclear antibodies, anti-SSA and anti-SSB, are found. Increased occurrence of extraglandular manifestations and a markedly increased frequency of the histocompatibility alleles HLA-B8/DR3 in patients with 1°SS support the view that 1° & 2°SS are clinically and immunogenetically separate entities, (Moutsopoulos *et al.*, 1980).

Previous studies have shown that the gene products of the major histocompatibility complex (MHC), known as class II antigens, among others HLA-DR in the human system, play a vital immunoregulatory role, e.g. by interaction with T lymphocytes (Benacerraf, 1981). Class II antigens are expressed not only on the cell surface of immunocompetent cells, but also on the surface of non-lymphoid cells (Wiman *et al.*, 1978). The recent finding of epithelial expression of

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class II antigens in the target organs of various inflammatory and autoimmune diseases (Hanafusa *et al.*, 1983; Scheynius & Tjernlund, 1984; Olsson *et al.*, 1985), raises the possibility of HLA-DR expression of non-lymphoid cells being induced by the action of products derived from activated lymphocytes (Steeg *et al.*, 1982).

Characterization of the antigenic expression and spatial relationship of the infiltrating and residing cells in the target organ might assist a further understanding of the pathogenetic mechanisms leading to glandular involvement in SS. In this study, we investigated minor salivary glands from patients with 1°SS, 2°SS, and controls.

MATERIALS AND METHODS

Patients. Fifteen patients and four control subjects were studied. (For details regarding individual patients, see Table 1.). All patients had focal lymphocytic infiltrates in minor salivary glands, grades three or four according to Table 2. (Chisholm & Mason, 1968); xerostomia with chew-stimulated whole salivary secretion rate $<0{\cdot}7$ ml/min (Heintze, Birkhed & Björn, 1983); decreased tear production with Schirmer's test $<5{\cdot}5$ mm/5 min and filamentary keratitis seen by staining with Rose-Bengal $>3\frac{1}{2}$-points according to van Bijsterveld (van Bijsterveld, 1969). Seven

Table 1. Clinical characteristics of patients with Sjögren's syndrome and controls

Clinical group, patients	Age (years) & Sex	Disease duration Sjögren's syndrome (years)	Concomitant Connective Tissue Disease/duration (years)	Antirheumatic treatment
Sjögren's syndrome				
Primary				
1	63 F	9	—	—
2	45 F	15	—	chlorquinephosphate 160 mg/day
3	38 F	1	—	—
4	71F	5	—	—
5	29 F	23	—	—
6	38 F	26	—	—
7	45 F	3	—	—
Secondary				
8	64 F	3	RA/10	—
9	70 F	1	RA/1	—
10	70 M	36	RA/40	—
11	75 F	3	RA/25	Prednisolone 5 mg/day
12	53 F	0·5	RA/1	Prednisolone12 mg/day
13	55 F	2	PM/2	—
14	77 F	5	Scl/18	—
15	40 F	5	SLE/6	—
Controls				
16	45 F	—	—	—
17	24 F	—	—	—
18	46 M	—	—	—
19	45 F	—	—	—

RA rheumatoid arthritis, definite or classical according to the ARA criteria (Ropes *et al.*, 1958), PM Polymoysitis, Scl Scleroderma, SLE Systemic Lupus Erythematosus according to revised ARA criteria (Tan *et al.*, 1982).

Table 2. Grading of lymphocytic infiltrate in labial salivary gland tissue, according to Chisholm and Mason (Chisholm & Mason, 1968)

Grade	Lymphocytes per 4 mm^2 of salivary gland tissue
0	Absent
1	Slight infiltrate
2	Moderate infiltrate or less than one focus*
3	One focus*
4	More than one focus*

* Focus = an aggregate of 50 or more lymphocytes and histiocytes.

patients fulfilling these criteria were diagnosed as 1°SS. Eight patients fulfilling the criteria and having a co-existing CTD were regarded as 2°SS. Four control subjects were biopsied as a part of evaluation for xerostomia, none of them fulfilled any of the above criteria, nor did they present any symptoms or signs suggestive of SS and they all had normal inflammatory parameters (ESR, haptoglobin, CRP, immunoglobulins) in their sera. All control glandular specimen showed lymphocytic infiltrates grades zero or one.

Biopsy from the lower lip salivary glands were performed as earlier described (Greenspan *et al.*, 1974). The biopsy material was immediately placed in transport medium (Histocon, Histolab Bethlehem Ltd., Gothenburg, Sweden) at 4°C and within one hour snap frozen and stored at −70°C. Sections 4 μm thick were cut in a cryostat at −20°C.

Immunohistochemical staining procedure. The frozen tissue sections were examined by means of a sensitive double immunoenzymatic technique allowing the simultaneous recognition of cells reacting with mouse monoclonal antibodies and rabbit antiserum (Klareskog *et al.*, 1982). The primary antibodies used are summarized in Table 3. The rabbit antiserum to HLA-DR antigens has been described earlier (Klareskog *et al.*, 1978). The mouse monoclonals Anti-HLA-DR, Anti-Leu 1, Anti-Leu 2a and Anti-Leu 3a were provided by Becton-Dickinson Corp. (Sunnyvale, CA, USA). OKM 1 and OKT 9 were purchased from Ortho (Raritan, NJ, USA). Anti-μ-heavy chain (Anti-IgMμ) anti-γ-heavy chain (Anti-IgG–γ) antibodies were from Seward (London, UK). The

Table 3. Combinations of monoclonal antibodies and antiserum used in a double immunoenzymatic technique to determine epithelial HLA-DR expression and cell phenotypes in minor salivary glands in Sjögren's syndrome.

Rabbit antibodies	Monoclonal mouse antibodies	Specificity of mouse monoclonals
Normal rabbit serum	Anti-HLA-DR	A class II antigen of the MHC
Rabbit anti-HLA-DR	Anti-Leu 1	All peripheral T lymphocytes
Rabbit anti-HLA-DR	Anti-Leu 2a	Suppressor/cytotoxic T lymphocytes
Rabbit anti-HLA-DR	Anti-Leu 3a	Helper T lymphocytes
Rabbit anti-HLA-DR	OKM 1	Monocytes/macrophages, granulocytes
Rabbit anti-HLA-DR	Anti-γ-heavy chain	IgG expressing B lymphocytes and plasma cells
Rabbit anti-HLA-DR	Anti-μ-heavy chain	IgM expressing B lymphocytes and plasma cells
Rabbit anti-HLA-DR	OKT 9	Transferrin receptor denoting proliferating cells

secondary antibodies swine-anti-rabbit and sheep-antimouse were delivered from Dakopatts (Glostrup, Denmark) and Cappel (Malvern PA, USA) respectively. Mouse-anti-peroxidase antibodies were kindly given to us by Dr Mason, Oxford, UK. The rabbit-anti-alkaline phosphatase serum used, was produced in our own laboratory and had similar characteristics to the serum described earlier (Mason & Sammons, 1978). Alkaline phosphatase type VIII, horseradish peroxidase, 3-amino-9-ethyl-carbazol, naphtol-AS-MX buffer and Fast Blue reagents were all purchased from Sigma (St Louis, MO, USA), levamisole (Levopericol) was obtained from Leo (Helsingborg, Sweden). Control incubations omitting the primary antibodies or using normal rabbit serum were all negative. Sections for routine histopathologic examination and grading of lymphocytic infiltration were stained with hematoxylin and eosin.

Quantitation of cells. The sections were read blindly and the infiltrating cells were regarded positive for peroxidase when stained brown, and positive for alkaline phosphatase when stained deep blue. The total amount and arrangement of infiltrating cells were graded on a 0 to 4 scale, (Chisholm & Mason, 1968) Table 2. The number of positively stained cells out of the total number of infiltrating cells was estimated and subdivided in the following five classes: 0–5%, 5–25%, 25–50%, 50–75% and 75–100%. The periductal lymphocytic infiltrates were estimated separately from the scattered lymphocytes seen in the surrounding glandular tissue.

RESULTS

Control specimens. The control specimens showed a normal salivary gland tissue structure with epithelial ducts and acini in a loose connective tissue stroma, in which some scattered lymphocytes were seen. As the results with rabbit anti-HLA-DR serum and monoclonal Anti-HLA-DR corresponded well, these will not be regarded separately in the subsequent discussion. All the control ductal epithelial were OKT 9^+, whereas only a few of the acinar epithelial cells showed this staining.

In all the control specimens, irregular, OKM 1^-, dendritic cells with a cytoplasmic HLA-DR expression were seen evenly distributed in the tissue between acini, ducts and vessels (Fig. 1). The dendritic cells constituted 5–25% of the non-epithelial cells in the normal glandular tissue. Less than

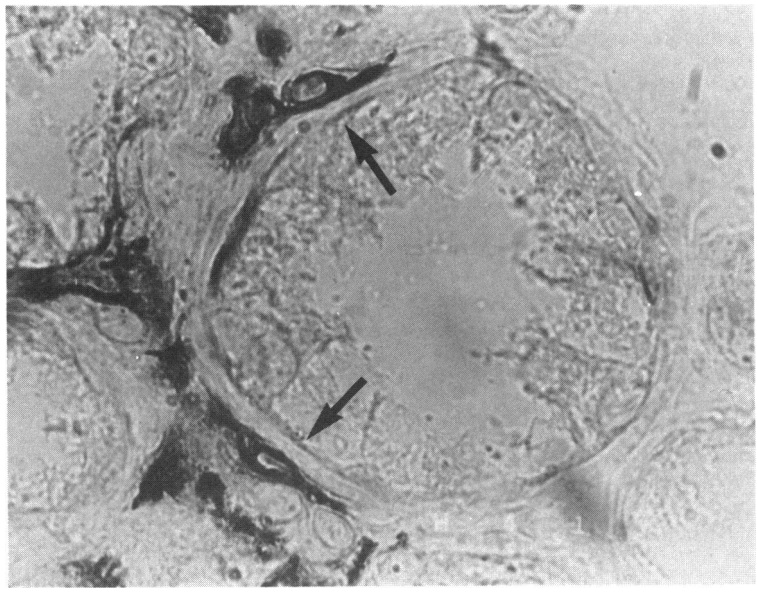

Fig. 1. Minor salivary gland tissue stained by use of monoclonal Anti-HLA-DR, showing HLA-DR$^+$ dendritic cells (arrows) in a normal control specimen. × 1,000.

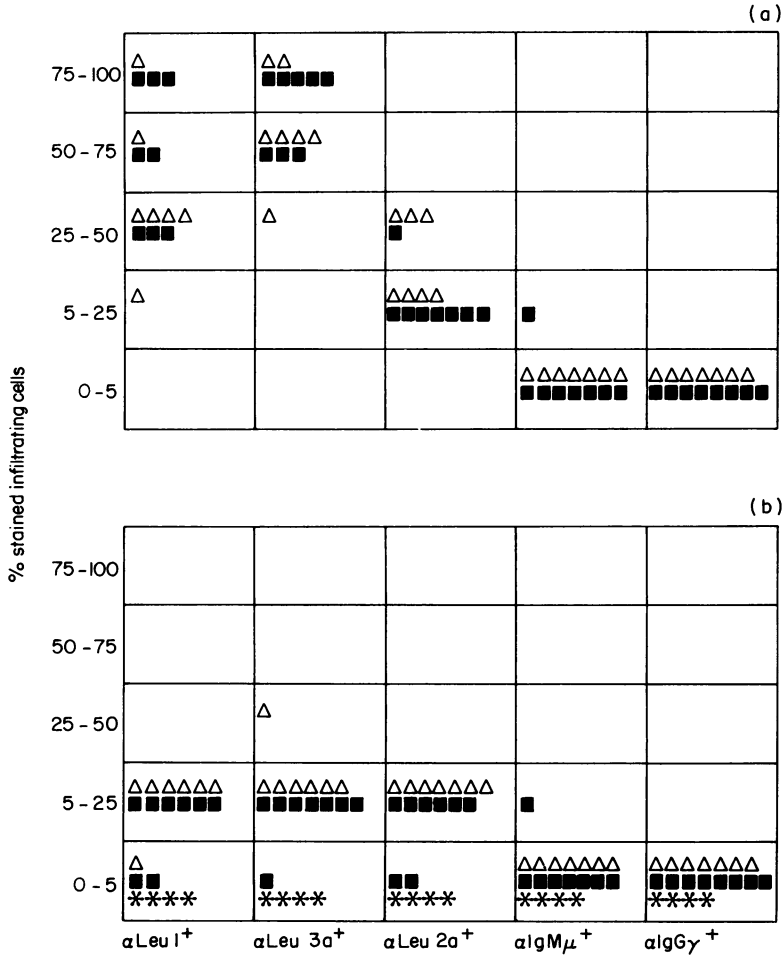

Fig. 2. Relative number of lymphocytes of different subsets infiltrating minor salivary glands in Sjögren's syndrome and controls, expressed as percent stained cells out of total number infiltrating cells, (a) within focal periductal lymphocytic infiltrates, and (b) outside infiltrates. (△) primary Sjögren's syndrome specimen; (■) secondary Sjögren's syndrome; (✳) normal control.

5% of the non-epithelial cells were OKM 1$^+$, anti-HLA-DR$^+$ monocytes/ macrophages, also evenly distributed in the tissue. The remaining non-epithelial cells were made up by stromal cells as observed in light microscopy.

The few scattered lymphocytes seen were mainly of the Anti-Leu 1$^+$ phenotype (Fig. 2), most of them in close proximity to the salivary ducts. Abundant IgM$^+$ extracellular material was observed, though hardly any IgG$^+$ or IgM$^+$ cells were seen.

Patient specimens. In the glandular tissue of 1°SS and 2°SS dense, focal periductal lymphocytic aggregates were seen. In the surrounding normal looking glandular tissue, widespread, but not focally arranged, infiltrating lymphocytes were also found. About half of the ductal epithelial cells close to the lymphocytic infiltrations were HLA-DR$^+$ (Fig. 3). A large part of the acinar epithelial cells close to lymphocytic infiltrates were also HLA-DR$^+$. In contrast, the salivary duct, located centrally in the lymphocytic infiltrates, as well as the ducts and acini at some distance to the infiltrates, were HLA-DR$^-$.

All ductal epithelial cells of 2°SS were OKT 9$^+$, whereas in 1°SS the frequency of OKT 9$^+$ ductal epithelial cells varied. The acinar epithelial cells were occasionally OKT 9$^+$ in both 1°SS and 2°SS. The OKT 9$^+$ staining was unrelated to the proximity of the lymphocytic cells.

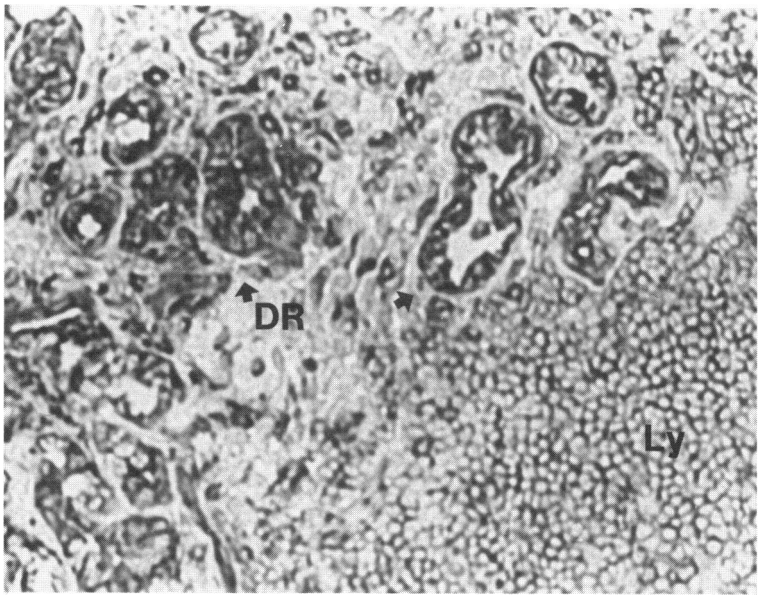

Fig. 3. HLA-DR expressing ductal and acinar epithelial cells close to a lymphocytic infiltrate in minor salivary gland tissue from a patient with Sjögren's syndrome. × 250.

In the dense periductal lymphocytic infiltrates, Anti-Leu 3a$^+$ cells outnumbered lymphocytes of other phenotypes, see Fig. 2. Anti-leu 2a$^+$ cells were hardly ever found close to the duct in the periductal infiltrates. Up to 25% of the periductal and tissue infiltrating lymphocytes expressed HLA-DR. Despite the sparse number of Ig$^+$ cells, an intense staining for extracellular IgG and IgM was found in the whole sections.

Less than 5% of the cells in the periductal infiltrates were OKM 1$^+$, HLA-DR$^+$ monocytes/macrophages. Due to the density of the cellular infiltration, it was not possible to discern any spatial relationship between HLA-DR expressing OKM 1$^+$ monocytes/macrophages and any certain subset of T cells.

Sparse numbers of OKM 1$^+$, HLA-DR$^+$ monocytes/macrophages, less than 10 cells per section, were seen outside the infiltrates. Hardly any granulocytes were seen irrespectively of location in the glandular tissue sections from patients with 1°SS and 2°SS. Outside the periductal infiltrates, and seemingly unrelated to the infiltrating lymphocytes, were HLA-DR$^+$, OKM 1$^-$ dendritic cells, with a distribution that corresponded to what was seen in the control specimens.

DISCUSSION

The presently used immunohistochemical double staining technique, which permits phenotypic characterization and spatial analysis of infiltrating and residing cells of the target organ, has proved specific and reproducible when extensively applied on various tissue specimens, especially from patients with inflammatory diseases (Klareskog *et al.*, 1982; Scheynius & Tjernlund, 1984; Jansson, Karlsson & Forsum, 1984). In the present study, distinct differences were found between salivary gland tissues of patients and controls, not only concerning infiltration of lymphocytes, required for the diagnosis of SS (Daniels, 1984) but also regarding epithelial expression of HLA-DR antigen of cells in close proximity to dense lymphocytic infiltrates.

The lymphocytic infiltrates were mainly composed of Anti-Leu 3a$^+$ cells in 1° as well as 2°SS. These findings are in accordance with earlier reports using different techniques (Talal *et al.*, 1974; Adamson *et al.*, 1983; Isenberg *et al.*, 1984).

Since the sum of anti-Leu $2a^+$ and anti-Leu $3a^+$ cells in some singular specimens was higher than the number of Anti-Leu 1^+ cells, the possibility exists, that the Anti-Leu 3a antibody reacted not only with T helper cells, but also with some non-lymphocytic cells, as has been suggested and extensively discussed in a previous report (Lindblad *et al.*, 1983), or alternatively, the Anti-Leu 1 antibody does not define all the peripheral T lymphocytes (Ljunghall, Lööf & Forsum, 1982).

The finding of very few Ig^+ cells and plasma cells are in contrast to some earlier studies, in which a dominance of B cells was suggested (Chused *et al.*, 1974; Lane *et al.*, 1983); but in accordance with others (Talal *et al.*, 1974; Adamson *et al.*, 1983). The discrepancy may be due to technical factors or may reflect sampling differences. The presence of high amount of extracellular Ig-staining material, despite the seemingly absence of B cells and plasma cells, has been reported in salivary glands of 2°SS (Isenberg *et al.*, 1984), and has previously been found in other inflammatory lesions such as the rheumatoid nodules (Hedfors *et al.*, 1983) and synovial membrane (Lindblad *et al.*, 1983). Thus the relationship between the presence of B cells and the finding of extracellular Ig-staining material in these states remains unclear.

The HLA-DR expression of epithelial cells seen adjacent to the focal lymphocytic infiltrates in the Sjögren's syndrome salivary glands, but not in controls, has not been reported earlier. A similar spatial arrangement between lymphocytic infiltrates dominated by T helper cells and HLA-DR expression of residing cells, normally not expressing class II antigens, has, however, recently been reported in various inflammatory and autoimmune states (Tjernlund, 1978; Hanafusa *et al.*, 1983; Jansson *et al.*, 1984; Scheynius & Tjernlund, 1984; Olsson *et al.*, 1984), and may as such constitute a general phenomenon seen in various immunopathological conditions. Mere activation or cellular proliferation as the cause of class II antigens expression is not likely, as the strong OKT 9^+ staining of the ducts, seen in both patients and controls, was unrelated to the HLA-DR expression.

Sjögren's syndrome has been considered as a slowly developing chronic autoimmune disease with unknown initiating factor or factors. As the diagnosis of the disease is founded on the presence of lymphocytes infiltrating the glands, no conclusion can be drawn with regard to the sequence, in which the various events occur, i.e. whether the infiltrating lymphocytes induce the expression of class II antigens of the epithelial cells by the action of close contact with passive absorption, or the secretion of specific activating factors working at short distance, or alternatively, the once activated HLA-DR expressing epithelial cells attract the lymphocytes. Increasing evidence indicates, however, that a variety of stimuli can induce or modulate class II antigen expression, *in vivo* and *in vitro*, of cells normally not expressing the antigen, where the induction of the 'aberrant' class II antigens includes hormonal stimuli (Klareskog, Forsum & Peterson, 1980), lectins (Pujol-Borrell *et al.*, 1983), and γ-interferon (Steeg *et al.*, 1982).

No conclusive differences were found between samples from patients with 1°SS and 2°SS. Whether this indicates a common tissue reaction unrelated to differences in clinical manifestations, or is due to tissue sampling relatively late in the disease process, deserves further investigation. The lack of difference may also partly be explained by the widespread use of non-steroidal anti-inflammatory drugs with cyclooxygenase inhibiting activity in the SS patient group, thereby potentially interfering with cellular interaction and HLA-DR expression (Synder, Beller & Unanue, 1982).

In conclusion, the HLA-DR expression of residing cells in the presence of lymphocytic infiltrates of mainly T helper cell phenotype, as seen in Sjögren's syndrome and recently reported in other chronic diseases with lymphocytic infiltration, may be a common denominator of various pathological autoimmune states. An elucidation of the functional properties of the antigen expressing cells might assist an understanding of initiating and perpetuating mechanisms in these diseases.

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