

Histopathological findings in salivary glands of Sjögren's syndrome

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Introduction

There is substantial circumstantial evidence that the glandular pathology in Sjögren's syndrome (SS) is immunologically mediated and antigenically driven, with several potential salivary gland autoantigens described in the literature (e.g. 1,2,3). The inflammatory infiltrate consists primarily of activated T-cells, accompanied by altered expression of different molecules characteristic of antigen-driven immune reactions. Abnormal lymphoproliferation and immunological hyperactivity may also predispose for the 40X increased risk to develop non-Hodgkin malignant lymphoma (4).

Diagnostically, SS presents clinically significant criteria problems. There are no universally accepted classification criteria. Several different tests with different sensitivity and specificity are currently applied to individuals tentatively suffering from SS, for example the Copenhagen criteria (5). The presence of a focal, periductal mononuclear cell infiltrate in lower lip salivary gland (LSG) biopsies is generally regarded as the single best criterion for the objective diagnosis of the salivary gland component (6) even though this test alone is insufficient to satisfy the complete diagnostic criteria of the disease. The likelihood that an individual suffering from SS will have a positive LSG biopsy test is usually regarded as high, i.e. the sensitivity of this test is high. Conversely, the specificity of this test is not 100%; i.e. patients who do not have the disease do not necessarily present a negative test. Consequently, the findings to be described below may occasionally also appear in patients suffering from conditions unrelated to SS. Therefore, this test can not be relied upon diagnostically to the exclusion of other examinations, such as testing of other functional parameters of the salivary glands (sialometry, scintigraphy) combined with functional tests of the lacrimal glands.

Salivary gland histopathology in Sjögren's syndrome

Sjögren's syndrome (SS) may produce bilateral parotid swelling. Such glands usually show benign lymphoepithelial lesions characterised by a heavy lymphocytic infiltrate and destruction of the acini. The ductal and surrounding myoepithelial cells become hyperplastic, forming "epimyoeplithelial islands", changes rarely or never seen in the minor salivary glands (cf 7). Clinicians tend however to avoid biopsies of parotid glands because of potential surgical risks of facial nerve damage, fistula and scarring. Also, data suggest that major glands commonly have lymphocytic foci with no history of disease (reviewed in 8), in contrast to lower lip glands in which such foci are regarded as a significant change in SS. Consequently, biopsies of the lower lip salivary glands (LSG) have evolved into a useful test, included as an integral part of all currently advocated tests including the Copenhagen criteria (5).

Taking a LSG biopsy is a rather simple procedure. At least five lobules should be harvested due to variation in the degree of lymphocytic involvement between as well as within glands (7,9). In such biopsies, focal aggregates of more than 50 lymphocytes are significant and when more than one such focus is present per 4 mm² of glandular parenchymal surface appearing in the microscopic section of the biopsy, a diagnosis of focal or autoimmune sialadenitis (AS) is supported (10). This is presently regarded as the basic microscopic finding in LSG biopsies of SS and the severity correlates with the presence of keratoconjunctivitis sicca and circulating autoantibodies (9). A confirmed diagnosis of AS satisfies one of three objective criteria; two of which must be positive in order to completely satisfy the Copenhagen criteria of the oral component of SS (5). In our Malmö department, some 30% of the 2578 LSG biopsies submitted in the period 1988-98 from tentative

cases of SS fulfilled the histopathologic criteria of AS, based on a diagnostic threshold at greater than 1 focus/4mm².

In AS of LSG, infiltrating lymphocytes are mainly T-cells, with few B-cells (11) and similar findings are seen in lacrimal glands (12). The infiltrates characteristically appear focally (not diffusely) at salivary ducts corresponding to intralobular excretory ducts. Ducts more closely associated with the acini and corresponding to intercalated or striated ducts of major glands are poorly developed or absent in minor glands. The lymphocytic infiltrates do not initially develop in direct association with the secretory acinar component of the minor gland parenchyma. It may also be of significance that the excretory ducts are accompanied by thin-walled blood vessels, forming a ductal/vascular (d/v) complex. In SS, Greenspan et al (7) noted that minor lymphocytic accumulations were related to these blood vessels, the ducts seemingly becoming “engulfed” following expansion of the infiltrates and these authors even hypothesised that the initial lesion in SS might involve the small blood vessels themselves. In contrast, the concept of “autoimmune epithelitis” has been proposed to reflect a primary role by the ductal epithelium, thought to be major attractants of the lymphocytes (13). Cuello et al (14) argue along the same line based on chemokine expression by the ductal epithelial cells in SS but not in normal glands.

A large proportion of the T-cells in fully developed foci have an activated, primed or “memory” phenotype (e.g. 15,16), of interest since CD45R0+ (“memory type”) T-cells adhere better to endothelial cells than CD45R0-cells (17). Indirectly, these findings suggest a mechanism by which T-cells activated outside the glands may enter into the glands as a consequence of their activated state. Experimental data in rodents show that this may occur (18). In contrast, Aziz et al (19) interpreted their HLA-DR and ICAM-1 data as supportive of a local activation of the lymphocytes in the microenvironment of the glands.

The B-cell component or immunoglobulin-secreting plasma cells may be significant in LSG of SS. Plasmacytic infiltrates throughout the glands and not associated with the lymphocytic foci seem to show an increase in IgM and a decrease in IgA-secreting cells (20). The diagnostic significance of these findings is presently unclear.

Exactly how the infiltrates may interfere with function resulting in reduced salivary secretion is unknown. Acini but not the ducts are the principal source of salivary fluid (21). A simple blockage of saliva transportation through the ducts can be excluded, since this would result in salivary retention phenomena, notably absent in AS. Therefore, reduced or lack of acinar production of fluid must be the immediate cause of hyposalivation. A common histopathologic observation in AS of LSG is, however, that acini surrounding the lymphocytic foci look remarkably unaffected, casting doubt upon “destructive autoaggression” as the sole causative event. The normal-looking acini may also explain why some researchers recently suggested that reduced salivation may be due to autoantibodies in SS interfering with signalling receptors involved in the para-sympathetic (muscarinic) stimulation thought to be the main regulator of fluid secretion (22).

Primary fluid secretion in SS is critically dependent upon a local, vascularly derived interstitial fluid component. A combined action of multiple different membrane transport systems (Na⁺, K⁺, Ca⁺, HCO₃⁻, Cl⁻) acting upon the acinar epithelium results in an osmotic gradient for NaCl causing a transepithelial (=transacinar cell, whereas ductal cells are impermeable to water) movement of water from the interstitium to acinar lumina (21). Therefore, anything interfering with the supply of interstitial fluid may also interfere with acinar fluid production, even though acinar cells may still be functioning normally. It is possible that a gradually enlarging lymphocytic infiltration at the ductal/vascular complex may also interfere with the continuous supply of interstitial fluid, which acinar cells normally depend upon for production of primary salivary fluid.

AS confers a degree of specificity to the histopathologic change in LSG of SS. The focal pattern may reflect a sequential, time-course mechanism of recruitment of lymphocytes (6). Obviously, it

may also reflect a specific interaction between lymphocytic and endothelial cells suggestive of specific properties or changes of the d/v compartment, related to the mechanisms of lymphocyte infiltration. These are areas of ongoing research, particularly regarding the role of adhesion molecules such as ICAM-1, constitutively expressed on the endothelial cells (19). Inflammatory cytokines may activate different endothelial adhesion molecules at the site of periductal foci (15) and this may represent an important mechanism for perpetuation of the inflammatory process. Initially accumulated T-cells may induce endothelial VCAM-1 expression thereby facilitating a later accumulation of B-cells (16). However, only little VCAM-1 endothelial expression but more of ELAM-1 in addition to ICAM-1 has also been demonstrated (19).

At present, it is difficult to obtain a clear picture of the cytokine and adhesion molecule profile in LSG biopsies of SS (6). Data suggest that the periductal clusters are characterised by 80% T-cells, mainly CD4+/CD45RO+ primed, “memory-type“ T-cells, expressing adhesion molecules LFA-1 or VLA-4 adjacent to venules with upregulated ICAM-1, ELAM-1 and/or VCAM-1 (23). The very earliest changes preceding the appearance of periductal foci are poorly understood and the natural course of the foci is virtually unknown. It has been suggested that they are potentially reversible (24). They may gradually increase in size at the expense of the acinar component. Occasionally, a very atrophic microscopic picture is found in LSG biopsies of tentative SS cases, with replacement of the parenchymatous component by fibrous connective tissue. Such atrophy is however only rarely accompanied by focal lymphocytic infiltrates and therefore does not strictly fulfil the criteria of AS. Speculatively, this may represent an end-stage of a longstanding but now down-regulated AS. Further studies are required to solve this as well as the other problems referred to above, related to the pathogenic events of the LSG changes in Sjögren’s syndrome.

References

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