The importance of minor salivary gland biopsy in prediction of lymphoma in Sjögren’s syndrome: should we be obtaining more information about prognosis from minor salivary gland samples?

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Theander,1 in this issue, provides an important contribution with the article ‘Lymphoid organization in labial salivary gland biopsies is a possible predictor for the development of malignant lymphoma in primary Sjögren’s syndrome’. It has been known for many years that ectopic germinal centres are present in minor salivary gland biopsies of a sub-population of patients with Sjögren’s syndrome (SS). The frequency of SS patients with an ectopic germinal centre in the minor salivary gland biopsy has ranged from 10% to 25%.2–4 Previous studies by Jonsson and his research group have described the clinical and laboratory characteristics of SS patients with ectopic germinal centres in their minor salivary gland biopsies.5–9 Other groups have also used histology, immunohistology and gene profiling to characterise the ectopic germinal centre in SS.10–14 In the current paper, the frequency of ectopic germinal centres was somewhat lower than in previous publications. The goal has been to determine the risk of B cells undergoing transition from benign lymphoproliferation to overt malignancy.15

The current study1 extends those studies by emphasising the increased risk of lymphoma in SS patients whose minor salivary gland biopsy contains an ectopic germinal centre. This is not a new concept, because an association between ectopic germinal centre formation and lymphoma development in primary SS was initially proposed in 1999.16 Despite the important prognostic information to be gained from a more detailed analysis of the minor salivary gland biopsy, most rheumatologists in the USA do not obtain biopsies, and oral pathologists do not routinely examine them critically for the presence of ectopic germinal centres. At present, the minor salivary gland biopsy is used in the USA predominantly either in the research setting or as an ‘obligation’ to fulfil SS criteria in the patient lacking antibody to SS-A or SS-B. The current article emphasises the need for rheumatologists to obtain minor salivary gland biopsies as a method to predict the risk of lymphoma and for the pathologist to read the biopsy with attention to ectopic germinal centres as well as focus score.

In addition to routine histology, the detection of ectopic germinal centres may be improved by the use immunohistochemistry to detect both particular subsets of B cells and dendritic cells. Monoclonal antibodies have also been used to evaluate the types of cells in the lip biopsy, although generally on a research basis for over 25 years. However, we have not established uniform guidelines for oral pathologists to use histological stains or immunohistochemistry to evaluate B cells and dendritic cells in minor salivary gland biopsies.

The importance of this article is that it challenges us to ‘move on’ from the current method of evaluation of the minor salivary gland biopsy using routine histology simply to ‘count lymphocytes’ and calculate focus scores. The key take-home message of this article would include, at a minimum, the reporting of lymphoid organisation/germinal centre-like structures in the lip biopsy by pathologists. In view of the importance of the detection of ectopic germinal centres in minor salivary gland biopsies, we should strongly advocate for guidelines to pathologists that identify germinal centres and their associated lymphoid/dendritic cells. It would appear that many talented and perhaps overworked pathologists are not aware of the rudimentary methods to evaluate and grade minor salivary gland biopsies from SS patients. All too often, rheumatologists receive the rather useless report ‘no evidence of cancer’ and not even the report of a calculated focus score. As we establish patient registries to improve prognosis and guide therapies, minor salivary gland samples must be collected, processed and evaluated in a uniform manner to allow comparison of results from different cohorts of patients.

In other medical specialties, biopsies of lymph nodes or breast tumours routinely employ ‘special immunohistological stains’ for prognosis and establishment of therapy. This paper raises the question of whether we are getting maximal information from minor salivary gland biopsies in rheumatology. The strong association of germinal centre-like structures with a higher risk of lymphoma provides an important clinical incentive for rheumatologists to demand a more detailed report of the minor salivary gland biopsy. In addition, the added knowledge of the pathogenesis derived from understanding of these ‘extraglandular’ lymphoid infiltrates will help us move forward with novel treatments by identifying subsets of SS patients.18

From a critical point of view, the article by Theander1 in this issue does have the significant limitations of a retrospective study, ascertainment bias of a tertiary institution, a relatively small number of patients and the lack of associations that would be expected from other published studies for lymphoma risk in SS. The incidence of lymphoma in SS patients has been estimated to be 5–10% of patients (or higher with long-term follow-up),19–20 representing an increased risk that has ranged from six to 44-fold.21–25 Some predictors have been repeatedly documented from large patient cohorts, namely hypocomplementaemia, persistent or recurrent salivary gland swelling and cutaneous vasculitis or palpable purpura with hazard ratios for low complement factor 4 (C4) levels of up to 9.5 by Theander et al.26 These results confirmed the importance of low C4 levels and palpable purpura at first presentation as markers of high risk for lymphoma in primary SS.23 The current study by Theander1 did detect an association...
with low C4 levels but not with palpable purpura. The lack of association of ecto-
germinal centres, lymphoma and other expected risk factors is most likely
due to the limited number of lymphomas (n=7) included in the study. Also, it is
important to note that the other classic risk factors, including cryoglobulin, sus-
tained parotid enlargement and a history of palpable purpura, were not assessed
in all patients of the cohort in the present
study. Therefore, the ability to draw
strong conclusions about relative risk of a
single variable such as germinal centres is
very much limited by ascertainment bias
of which tests are ordered. The only way
to avoid this bias is to examine a cohort
prospectively in which all patients have
all the tests.

A clear explanation of why germinal
centre-like structures in the biopsy
should indicate or even facilitate lym-
phocyte and dendritic cells are generated—germinal centre-like structures may
represent an incidental finding. However,
a ‘simple’ but reasonable hypothesis
might be that lymphocytes and dendritic
cells are generated (or mature) with the
expression of particular homing recep-
tors that see cognate ‘ligands’ expressed
on a subset of high endothelial venules
in characteristic tissues. For example,
mucosal lymphocyte homing receptors for B cells were well described over 20
years ago in mucosal lymphomas, with a
more recent description of specific
homing receptors on high endothelial
venules for T cells and dendritic cells.
These homing receptors have been asso-
ciated with the development of extran-
adal lymphomas.27–30

Indeed, it is reasonable to propose that various subsets of SS patients generate
lymphoid and dendritic cells with char-
acteristic homing receptors. The ability
of homing receptors for cells capable of forming germinal centres would predis-
pose to lymphoma, because the proximity
of particular dendritic and lymphoid
elements in the tissue will lead to mutual
expansion and eventual neoplastic trans-
formation of B cells. Also, autoantibody
expressed by B cells in germinal centres
may play an important role in the per-
petuation of immune stimulation by T cells and dendritic cells in response to
immune complex and further perpetua-
tion of stimulatory cytokine release.31–34

The lip biopsy can thus be viewed as a
consistent and safe source of tissue to
make prognostic and therapeutic deci-
sions, as well as the elucidation of the
interface between immune stimulation and
lymphoproliferation.

In summary, this paper emphasises
that the detection of germinal centre-
like structures in a minor salivary gland
biopsy is important in clinical decision-
making. For the rheumatologist, we must
obtain the biopsy more frequently as part of
the database for prognostic purposes.
Furthermore, it is time to set specific
guidelines to instruct pathologists in a
standardised method of routine micros-
copy, special histological stains and per-
haps immunohistology to detect ectopic
germinal centres. Then we will be able
to correlate these histological data with
prognosis and response to therapy. Now
that we have emerging therapies for
the depletion of particular lymphocyte
subsets and modulation of cytokines, in-
cluding B-cell factors and T-regulator
cells, we must learn to identify subsets of
SS patients, and the most obvious method
will be based on better extrac-
tion of information from minor salivary
gland tissue biopsies.

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