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?

Robert I Fox

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 subpopulation 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 immunohistology 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 basis¹⁷ for over 25 years. However, we have not established uniform guidelines for oral pathologists to use histological stains or immunohistology 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

Correspondence to: Robert I Fox, Rheumatology Clinic, Scripps Memorial Hospital-XIMED Medical Group, Suite #910, 9850 Genesee Avenue, La Jolla, CA 92037, USA; robertfoxmd@mac.com
with low C4 levels but not with palpable purpura. The lack of association of ecto-
pic 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 germi-
nal centre-like structures in the biopsy
should indicate or even facilitate lymph-
oma development has not been provided—germinal centre-like structures may
represent an incidental fi nding. 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-
odal 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 proxim-
ity 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.
Furthemore, 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,
including 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.

Competing interests None.
Provenance and peer review Commissioned; externally peer reviewed.
Accepted 6 June 2011

Ann Rheum Dis 2011;70:1351–1353
doi:10.1136/ard.2011.152751

REFERENCES
1. Theander E. Lymphoid organisation in labial salivary gland biopsies is a possible predictor
for the development of malignant lymphoma in primary Sjögren’s syndrome. Ann Rheum Dis
2011;70:1363–8.
2. Greenspan JS, Daniels TE, Talal N, et al. The histopathology of Sjögren’s syndrome in labial
infiltrates in primary Sjögren’s syndrome using monoclonal antibodies. J Immunol 1983;130:
203–8.
marker of morbidity and mortality in patients with primary Sjögren’s syndrome. Rheumatology
and autoantibody production in the target organ of patients with Sjögren’s syndrome. Arthritis Rheum
TNF-family members APRIL and BAFF and lymphoid organization in primary Sjögren’s syndrome.
7. Jonsson MV, Skarstein K, Jonsson R, et al. Serological implications of germinal center-
9. Jonsson MV, Skarstein K. Follicular dendritic cells
confirm lymphoid organization in the minor salivary
clonal proliferation of B cells within the
target tissue of an autoimmune disease.
The salivary glands of patients with Sjögren’s syndrome.
expression profling of minor salivary glands clearly
distinguishes primary Sjögren’s syndrome patients
from healthy control subjects. Arthritis Rheum
2005;52:1534–44.
syndrome: indications for disturbed selection
and differentiation in ectopic lymphoid tissue.
Identiﬁcation of transitional type II B cells in
the salivary glands of patients with Sjögren’s syndrome.
Immunohistochemistry of the B-cell component in
lower lip salivary glands of Sjögren’s syndrome
and healthy subjects. Scand J Immunol
Role of B cells in Sjögren’s syndrome — from
benign lymphoproliferation to overt malignancy.
Front Biosci 2007;12:2159–70.
Malignant lymphoma in primary Sjögren’s syndrome:
A multicenter, retrospective, clinical study by the
European Concerted Action on Sjögren’s Syndrome.
17. Fox RI, Cardstens SA, Fong S, et al. Use of
monoclonal antibodies to analyze peripheral
blood and salivary gland lymphocyte subsets
in Sjögren’s syndrome. Arthritis Rheum
Topology of innervation of salivary glands by
protein gene product 9.5 and synaptophysin
immunoreactive nerves in patients with Sjögren’s
of lymphoma development in primary Sjögren’s
20. Theander E, Manthorpe R, Jacobsson LT.
Mortality and causes of death in primary
21. Kassan S, Talal N. Sjögren’s syndrome with
systemic lupus erythematosus/mixed connective
tissue disease. In: Talal N, Moutopoulos HM,
Kassan SS, eds. Sjögren’s Syndrome: Clinical and
Immunological Aspects. Berlin: Springer Verlag,
Autoimmune and chronic inflammatory disorders and
risk of non-Hodgkin lymphoma by subtype.
23. Ioannidis JP, Vassiliou VA, Moutopoulos HM.
Long-term risk of mortality and lymphoproliferative
disease and predictive classification of
primary Sjögren’s syndrome. Arthritis Rheum
24. Brito-Zeron P, Ramos-Casals M, Nardi N,
et al. Circulating monoclonal immunoglobulins in
Sjögren syndrome: prevalence and clinical
significance in 237 patients. Medicine (Baltimore)
25. Brito-Zeron P, Ramos-Casals M, Bove A,
et al. Predicting adverse outcomes in primary
Sjögren’s syndrome: identification of
prognostic factors. Rheumatology (Oxford)


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?

Robert I Fox

Ann Rheum Dis 2011 70: 1351-1353
doi: 10.1136/ard.2011.152751

Updated information and services can be found at:
http://ard.bmj.com/content/70/8/1351

These include:

References
This article cites 33 articles, 12 of which you can access for free at:
http://ard.bmj.com/content/70/8/1351#BIBL

Email alerting service
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Topic Collections
Articles on similar topics can be found in the following collections
Pathology (444)
Clinical diagnostic tests (1282)
Radiology (1113)
Surgical diagnostic tests (431)
Immunology (including allergy) (5144)

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/