Is lymphocytic sialadenitis IgG4-related?

Sirs,

IgG4-related disease is a systemic fibroinflammatory condition characterised by a dense IgG4-positive lymphoplasmocytic infiltrate in involved organs. Salivary gland is one of the most common sites of the disease and minor lip salivary glands involvement has been described (1).

The objective of our study was to determine the prevalence of IgG4-related disease among patients with lymphocytic sialadenitis on labial salivary gland biopsy (LSGB). We performed IgG4 immunostaining on all consecutive LSGB showing lymphocytic sialadenitis realised over a one-year period. The diagnoses based on such a systematic strategy were analysed.

Three hundred and fifty patients had a LSGB in the University Hospital Centre of Bichat, Paris, France between 1st January 2012, and 31st December 2012. Among them, 79 patients (23%) had a lymphocytic sialadenitis according to Chisholm classification (Chisholm ≥3) (2).

The female/male sex ratio was 3.2/1. Mean age was 55.5±15.7 years old (range: 23–86). Twenty-one (26.6%) reported active or past tobacco use.

Labial biopsies were performed for suspicious of Sjögren's syndrome (68/79, 86.1%), sarcoidosis (7/79, 8.9%) or amyloidosis (4/79, 5%). Sjögren's syndrome (SS) was suspected because of sicca symptoms (48/68, 70.6%), arthralgia (12/68, 17.6%), lung disease (3/68, 4.4%), neurological symptoms (3/68, 4.4%) or salivary gland enlargement (2/68, 2.9%).

Only one (1/79, 1.3%) LSGB showed histopathological features of IgG4-related disease including a dense lymphoplasmocytic infiltration with a ratio of IgG4/IgG+ plasma cells of more than 40%. There was mild and not storiform fibrosis. This patient displayed obvious features of IgG4-related disease, including enlarged parotid glands, autoimmune pancreatitis, sclerosing cholangitis, retroperitoneal fibrosis, and elevated serum IgG4 (1500 mg/dl).

The main diagnosis associated with lymphocytic sialadenitis in our cohort was SS (29/79, 36.7%) as detailed in Table I. Despite a low level of IgG4+ immunostaining in 12 cases, pathological criteria for IgG4-related disease were missing in all cases. This observation appeared consistent with previous report (3).

In 15 cases (19%), no diagnosis could be elicited despite extensive screening (*i.e.* autoimmune diseases, pre-existing lymphoma, past head and neck radiation treatment, hepatitis C infection, acquired immunodeficiency disease, and sarcoidosis). IgG4 immunostaining was negative in all but one case showing less than 3% of IgG4+ plasma cells.

Our retrospective systematic study confirms that autoimmune disorders – mostly SS – are the leading cause of lymphocytic sialadenitis. Nevertheless, since around 2/3 of the patients did not have SS, lymphocytic sialadenitis is not specific for SS. In our hands, lymphocytic sialadenitis was never IgG4-related in patients with a defined autoimmune disorder.

Consistent with previous report (4), no final diagnosis could be obtained despite extensive workup in 19% of the patients with lymphocytic sialadenitis. Disappointingly, IgG4 staining was also always negative in the patients with unexplained lymphocytic sialadenitis.

Dense IgG4+ lymphoplasmocytic tissue infiltration consistent with IgG4-related disease was observed in one patient only (1.2%), who otherwise displayed cardinal features of IgG4-related disease. Hence, minor lip salivary glands can be involved in IgG4-related disease. Lip biopsy, because it is simple and safe, can be useful for a definite diagnosis when IgG4-related disease is suspected.

Our study has limitations since it is a monocentric retrospective analysis of a small number of patients. In addition, the diagnosis value of the IgG4 immunostaining would have been likely higher if we had restricted the analysis to lymphocytic sialadenitis with a noticeable plasma cell component. Eventually, serum IgG4 levels were not measured (5).

In conclusion, the prevalence of IgG4-related disease among patients with lymphocytic sialadenitis on LSGB is very low. IgG4 immunostaining has a poor diagnostic yield and should not be systematically performed in lymphocytic sialadenitis. On the other hand, LSGB, by being simple and safe, can be useful for a definite diagnosis when IgG4-related disease is suspected.

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Table I. Diagnosis associated with lymphocytic sialadenitis.

	n. (%) of patients
Sjögren's syndrome*	29 (36.7)
Primary	16
Secondary¥	13
Autoimmune diseases	17 (21.5)
RA	6
SLE	3
Myositis	3
MCTD	2
Scleroderma	1
ANCA vasculitis	1
Hashimoto thyroiditis	1
Idiopathic pulmonary fibrosis	5 (6.3)
Sarcoidosis	3 (3.8)
B-cell lymphoma	3 (3.8)
CLL	1
MGUS	1
NHL	1
Hepatitis C infection	2 (2.5)
IgG4-related disease§	1 (1.3)
Miscellaneous♦	4
No diagnosis	15 (19)

RA: rheumatoid arthritis; SLE: systemic lupus erythematosus; MCTD: mixed connective tissue disease; CLL: chronic lymphocytic leukaemia; MGUS: monoclonal gammopathy of undetermined significance; NHL: non-Hodgkin's lymphoma.
* According to the 2002 revised European criteria (6).
¥ Secondary Sjögren's syndrome was associated with RA (n=4), Hashimoto thyroiditis (n=4), SLE (n=2), MCTD (n=2) or autoimmune hepatitis (n=1).
§ According to international criteria (7).
♦ Miscellaneous referred to unclassified arthritis (n=1), idiopathic uveitis (n=1), multiple sclerosis (n=1) and tuberculosis (n=1).

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