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Diagnostic Value of Minor Salivary Gland Biopsy: A Retrospective Study

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ABSTRACT

Objective: Minor salivary gland biopsy is an adjunctive diagnostic method which is widely used and its diagnostic value is still controversial. It is mainly used in sarcoidosis and Sjögren's Syndrome. This study aims to identify the contribution of histopathological diagnosis to clinical diagnosis and to supply information to literature.

Methods: Minor salivary gland biopsy was carried out on the patients with early diagnosis of sarcoidosis or Sjögren's Syndrome who were referred from the hospital clinics of Istanbul University Faculty of Medicine, to the Oral and Maxillofacial Surgery Department of the Faculty of Dentistry. 100 patients between the ages of 18-65 were performed lower lip MSGB, then patients were called, the questions were asked and the answers were evaluated.

Results: The presence of dry mouth was statistically higher in patients with Sjögren's Syndrome than histopathologically normal patient and sarcoidosis patients. In patients with Sjögren's syndrome, the presence of dry eyes was found to be statistically significantly higher than the others. A statistically significant difference of clinical diagnosis distribution was observed between the patients with normal histopathological findings and patients with mild inflammation infiltration, granulomatous sialadenitis and lymphocytic sialadenitis.

Conclusion: Minor salivary gland biopsy is an easy and trusted method for establishing sarcoidosis and Sjögren's Syndrome diagnosis and follow-up. Studies reveal that as more knowledge about disease immunology is collected and more sensitive techniques for interpretation of saliva and other serological markers are developed, less invasive or noninvasive techniques will come into question. Contemporarily, it will continue to be one of the main diagnostic tests for adjunctive diagnostic of multisystemic chronic diseases.

Keywords: minor salivary glands, biopsy, sarcoidosis, amiloidosis, Sjogren's Syndrome

1. INTRODUCTION

Minor salivary gland biopsy (MSGB) is an adjunctive diagnostic method which is widely used in internal medicine, rheumatology, thoracic medicine and ophthalmology. The MSGB technique was first used in 1966 for the diagnosis of Sjögren's Syndrome; but with Chisholm and Mason's publication in 1968, it began to be used routinely (1). After that publication, MSGB has been included in almost all classification criteria due to identification of lymphocytic infiltration of the salivary glands. With the introduction of the American European Consensus standards in 2002, the value of MSGB has risen (2,3).

The main diseases that may require minor salivary gland biopsy are sarcoidosis, Sjögren's Syndrome, amyloidosis and other infiltrative diseases. Despite the simplicity of the technique, MSGB is not preferred in daily practice because it is considered as an invasive technique and has variable complication rates according to the technique that is used (4). Although it is a controversial technique, it is among the diagnostic criteria of certain diseases. Our purpose in this article is to contribute to defining the role of MSGB in future diagnostic criteria.

2. METHODS

Between 01.06.2017 and 01.06.2018, lower lip MSGBs were conducted on 100 patients between 18-65 years old with early diagnosis of sarcoidosis or Sjögren's Syndrome referred from the hospital clinics of Istanbul University Faculty of Medicine to the Oral and Maxillofacial Surgery Department of the Faculty of Dentistry. Evaluation of MSGB findings is done by expert histopathologists in the Department of Pathology, Istanbul Medicine Faculty, Istanbul University. The stitches were removed after 7 days, and a retrospective analysis was made with a pre-prepared survey. This project

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has been reviewed and approved by the Ethical Committee of Istanbul University, Faculty of Dentistry (2017/13).

2.1. Operation Procedure

Prior to the MSGB procedure, the patient's lower lip is palpated for the appropriate incision area. In order to prevent damage to the structure of the samples to be taken, local anesthesia is performed as a ring blockage. The lip ruled out and, an incision (approximately 1 cm) is made superficially on the mucosa in order not to damage the deep tissues, including nerves and muscles. Since it is important to collect enough salivary glands for diagnosis, five minor salivary glands are taken and kept in 10% formaldehyde solution.

2.2 Histopathologic Evaluation

The common findings in MSGBs focal lymphocytic sialoadenitis, with a focus score >1, defined as the number of lymphocytic foci (which are adjacent to normal-appearing acini and contain >50 lymphocytes) per 4 mm^2 of glandular tissue.

2.3. Statistical Evaluation

In this study, statistical analysis was done by NCSS (Number Cruncher Statistical System) 2007 Statistical Software (Utah, USA) package program. In addition to descriptive statistical methods (mean, standard deviation), one-way analysis of variance between groups, Tukey multiple comparison test for sub-group comparisons, independent t-test for comparison of dual groups, and chi-square test for comparison of qualitative data were used. The results were evaluated at $p<0.05$ level.

3. RESULTS

There was no statistically significant difference between the mean age and sex of patients with normal histopathological diagnosis and with sarcoidosis and Sjögren's Syndrome ($p>0.05$). There was no statistically significant difference between the patients with normal histopathological diagnosis and patients with sarcoidosis and Sjögren's Syndrome in terms of allergy, smoking, presence of rheumatic disease, presence of nodules in the lung, incision design, and presence of oral aphthae ($p>0.05$).

The presence of dry mouth in the group with histopathologic diagnosis of Sjögren's Syndrome was statistically higher than groups with normal histopathology and sarcoidosis ($p=0.036$) and the presence of dry eyes in the group with histopathologic diagnosis of Sjögren's Syndrome was statistically higher than groups with normal histopathology and sarcoidosis ($p=0.0001$) (Figure 1). Mild inflammatory infiltration was found in patients with normal histopathological diagnosis and lymphocytic sialenitis was significantly higher in the Sjögren's Syndrome group.

Histopathological results of the minor salivary glands were classified as normal, mild inflammatory infiltration, granulomatous sialadenitis and lymphocytic sialadenitis. There was no statistically significant difference between the mean age and gender distribution of these patients ($p>0.05$). No statistically significant difference was observed between patients with normal histopathology, mild inflammatory infiltration, granulomatous sialadenitis and lymphocytic sialadenitis in terms of allergy, smoking, dry mouth, dry eyes, rheumatism, presence of nodules in the lung, presence of oral aphthae and incision distribution ($p> 0,05$).

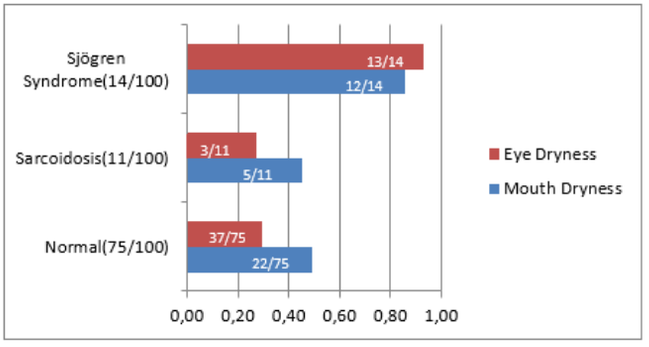

Figure 1. *Eye and Mouth Dryness Ratio in Patient Groups*

The histopathological diagnosis of minor salivary gland biopsies revealed that 11% of the patients had sarcoidosis, 14% had Sjögren's syndrome and 75% had normal histopathological results (Figure 2).

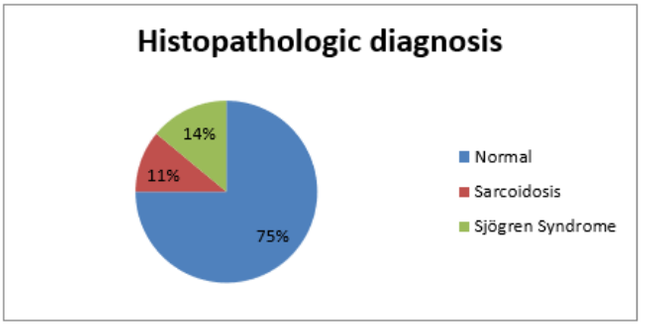

Figure 2. *Histopathologic Diagnosis of Patient Groups*

It was asked if the patients were under regular control and 50% of the patients with Sjögren's Syndrome were under regular control, significantly higher than other two groups (Figure 3).

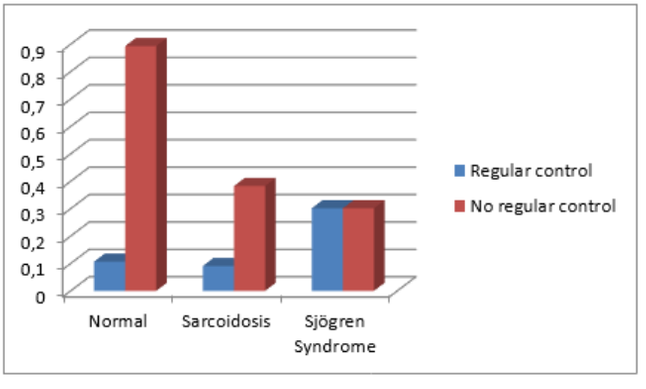

Figure 3. *Percentage of Patients with and without Regular Control*

4. DISCUSSION

The MSGB technique was first used in 1966 for the diagnosis of Sjögren's Syndrome; but with Chisholm and Mason's publication in 1968, it began to be used routinely in diagnosis of various other connective tissue diseases including rheumatoid arthritis, osteoarthritis, Reiter's disease, psoriatic arthritis, scleroderma (1).

Before Chisholm and Mason's publication, some authors advocated that biopsies should be taken from the major salivary glands; however, because of the buccal fat and the buccal muscle deep dissection, biopsies from the parotid gland may cause complications such as sialocele and facial nerve injury due to trauma (5-7). Besides that, in one study, based on the US-European Union diagnostic criteria (AECG) for diagnosis of Sjögren's Syndrome, both lip biopsy and parotid biopsy were performed simultaneously from 35 patients and the same specificity and sensitivity values were obtained in both procedures (8). According to these studies, MSGB is more advantageous in terms of both reducing the risk of complications and ease of applications. The only long-term complication reported was continuous numbness of the lower lip in 0-6% of patients (8-10).

One of the reported major disadvantages of the technique is that it may be difficult to obtain sufficient number of minor salivary gland tissue to establish a histopathological diagnosis. Although this technique is referred to as lip biopsy, it does not include mucosal tissue for diagnosis. Instead, approximately 5 minor salivary gland tissues are required (7). In this study, no patient had insufficient number of salivary glands.

Caporali et al. stated that MSGB can be performed easily and provides sufficient material for histopathological studies and it is safe. Moreover, mentioned in same study, only one patient had long-term paresthesia. It is underlined that this technique is acceptable for patients and the possibility of re-performation during the follow-up period is a huge advantage (11). In our study, paresthesia was not observed during the post biopsy controls.

Some studies report problems with histopathological evaluation of MSGB. Vivino et al. reported false positivity in almost half of the initial diagnosis of 60 MSGBs. It is highlighted that these variabilities can be minimized with the exact use of Chisholm criteria (12). Bamba et al. questioned the contribution of MSGB to the diagnosis and its necessity and concluded that MSGB is an invasive method which can cause false negativities and false positivities (13). Since it is included in Consensus Criteria (AECG), it continues to be used in the diagnosis of Sjögren's Syndrome. It has been reported be helpful diagnosis in patients with nonspecific clinical findings, extraglandular involvement and autoantibody negativity (14). In this study there were no false negative or positive histological results in any case. All diagnoses matched with other clinical findings.

The fact that this technique is invasive has led to the search for alternative methods that can replace it. Efforts have been made to improve the accuracy of diagnostic criteria using new methods such as ultrasonography and B cell subpopulations (15-18). Two studies have suggested that serological markers have better results than lip biopsies (19,20). Bamba et al. also stated that 53% of samples are accompanied by normal anti-SSA and anti-SSB antibody levels but a positive lip biopsy and according to that MSGB is not an excellent marker. Nevertheless, considering both the symptoms of the disease and the serology will produce a more accurate clinical picture (13). One of the limitations of our study was that we only evaluated the biopsy results and the answers given to the questions in the questionnaire. As the biopsy unit, there was no chance to obtain serological and immunological markers in our study. We suggest it would be useful to examine serologic and immunological markers in multidisciplinary studies, as well.

Although it has not yet been accepted among the diagnostic criteria, salivary gland scintigraphy is another alternative test which has been evaluated as a less invasive method in recent years. In a study conducted by Aquilera et al., 61 healthy volunteers, 66 patients with Sjögren's Syndrome and 18 patients with a diagnosis of fibromyalgia were performed both a minor salivary gland biopsy and a salivary gland scintigraphy. As a result, it was reported that salivary gland scintigraphy, which is evaluated at normal limits, would not clarify the diagnosis of Sjögren's Syndrome, mild changes in saliva flow should be evaluated as nonspecific, but moderate and severe changes support the diagnosis of Sjögren's Syndrome. Therefore, it was concluded that salivary gland scintigraphy cannot replace minor salivary gland biopsy (21).

Again, the ultrasound scoring system, which was claimed as a non-invasive diagnostic method, was compared with scintigraphy and biopsy on 107 patients and 28 healthy people in a study group of by Milic et al. and the specificity and sensitivity of scintigraphy was measured as 90% and 87%, respectively (22).

Another method recommended instead of salivary gland scintigraphy in the differential diagnosis of Sjögren's Syndrome is magnetic resonance (MR) sialography. Tonami et al. performed minor salivary gland biopsy, MR sialography and salivary gland scintigraphy in 130 patients with suspected Sjögren's Syndrome. MR sialography and salivary gland scintigraphy results of 80 patients, whose small salivary gland biopsy findings proved Sjögren's Syndrome histopathologically, have been compared. As scintigraphy for Sjögren's Syndrome shows high sensitivity, MR sialography has been reported to have high specificity, in addition it has also been reported that minor salivary gland biopsy is the main diagnostic method (23).

Molecular basis of autoimmune diseases has been investigated in recent years. Salivary gland biopsy materials are also evaluated in terms of many criteria such as DNA microarray, IL-22 producing cell level, presence of monocyte chemotactic protein-1 receptor, IL-17, IL-23 and the expression of their receptors (24-27). Another reason why MSGB is indispensable is that besides the routine histopathological evaluation, it

makes possible to determine the presence and number of ectopic germinal centers, which is an important criterion for lymphoma (28). Beside, Jonsson et al. reported that the presence and absence of germinal center-like structures could be used to determine the serologic profiles of patients and thus to identify subgroups that would help predict their prognosis (29). Studies have shown that lymphocytic evaluation of lymphocytic infiltration, which can be used as a positive finding for Sjögren's Syndrome, is related to the diagnosis (2,11,30). Our study supports this information ($p = 0.0001$).

5. CONCLUSION

As more information is collected about the immunology of Sjögren's Syndrome, amyloidosis and sarcoidosis, and more sensitive techniques are developed for the interpretation of histopathological, serological and immunological markers, less invasive or noninvasive methods will be preferred. Today, MSGB continues to be one of the tests used as an adjunctive diagnostic method in the diagnosis and treatment of chronic and multi systemic diseases such as Sjögren's Syndrome, amyloidosis and sarcoidosis.

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