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REVIEW PAPER

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Labial salivary gland biopsy in the diagnosis of Sjögren's syndrome

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ABSTRACT

Introduction. Labial salivary gland biopsy is used for diagnosis of Sjögren's syndrome (SS) and lymphoma accompanying SS.

Aim. The aim of this study was to present the main techniques used for taking labial salivary gland biopsies in the diagnosis of SS with respect to their advantages, histologic criteria, validation, complications, and their usefulness for diagnostic procedures, monitoring disease progression, and treatment evaluation.

Material and methods. This study is based on analysis of literature.

Results. The microscopic confirmation of SS is based on the presence of focal lymphocytic sialadenitis (FLS) with a focus score ≥1 per 4 mm^2 of glandular tissue. A lymphocytic focus is defined as a dense aggregate of 50 or more lymphocytes adjacent to normal-appearing mucous acini in salivary gland lobules that lacked ductal dilatation. Other histopathological features of SS are lymphoepithelial lesions and a relative decrease of <70% IgA + plasma cells. Labial salivary gland biopsy is characterized by high specificity, a positive predictive value, and an average sensitivity of 79% in SS.

Conclusion. It can be also valuable in diagnosing B-cell mucosa-associated lymphoid tissue (MALT) lymphomas but it is not recommended for the monitoring of SS progression and the effectiveness of the treatment. Persistent lower lip hypoesthesia is the most severe complication of labial salivary gland biopsy.

Keywords. biopsy, labial glands, salivary glands, Sjögren's syndrome

Introduction

Labial minor salivary gland biopsy (LSGB) is used for the diagnosis of systemic disorders, such as amyloidosis, sarcoidosis, Sjögren's syndrome (SS), lymphoma accompanying SS, and other connective tissue disorders, and also to confirm neonatal haemochromatosis.[1] The final classification criteria of SS, which was approved by the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) in 2016, is based on the weighted sum of 5 items: anti-SSA/Ro antibody positivity and focal lymphocytic sialadenitis (FLS) with a focus score of 1 foci/4 mm^2, each scoring 3; an abnormal ocular staining score of 5 (or a van Bijsterveld score of 4), a Schirmer's test result of 5 mm/5 minutes, and an unstimulated salivary flow rate of 0.1 ml/minute, each scoring 1. Individuals with signs and/or symptoms suggestive of SS who have a total score of 4 for the above items meet the criteria for primary SS.[2,3] Although LSGB is considered a minor procedure, its results may have a significant impact on the diagnosis

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of SS, and the lack of uniformity in methodology and potential adverse effects have hindered its application. There is no standardized technique that yields adequate tissue for analysis and minimizes adverse effects.

Aim

The aim of this study was to summarize the main techniques used for taking labial salivary gland biopsies in the diagnostic workup of SS with respect to their advantages, histologic criteria, validation, complications, and their usefulness for diagnostic procedures, monitoring disease progression, and treatment evaluation.

Histologic criteria for diagnosis of SS on labial salivary gland biopsies

SS is an autoimmune disease characterized by chronic T-and B-cell infiltration of the salivary glands or lachrymal glands, leading to exocrine gland dysfunction with symptoms and signs of dry mouth and keratoconjunctivitis sicca.[4-11] Patients may present with variable combinations of systemic extra-glandular manifestations such as peripheral neuropathy, arthralgia and lung disease. SS is often difficult to diagnose, as the clinical and laboratory manifestations vary widely. None of the laboratory markers are both sensitive and specific. However, several sets of classification criteria have been developed over the last few decades. All these sets combine clinical findings, serological tests, and a histological evaluation of salivary gland involvement. In all previous classifications, both objective and subjective tests were included in diagnosis of SS.[4-14] The current classification is based only on an objective clinical, serological and histopathological test. LSGB is an objective test of SS and plays a significant role in the diagnostic process. In fact, the presence of either anti-SSA/SSB seropositivity or a positive lip biopsy is a requirement for an individual to be classified as having SS. The microscopic confirmation of SS is based on the presence of focal lymphocytic sialadenitis (FLS) with a focus score ≥1 per 4 mm^2 of glandular tissue.

According to the revised American-European Consensus Group's (AECG) classification criteria and the ACR classification criteria for SS, a labial salivary gland biopsy is considered positive if minor salivary glands demonstrate FLS, with a focus score of 1 or more, as evaluated by an expert histopathologist. A lymphocytic focus is defined as a dense aggregate of 50 or more lymphocytes adjacent to normal-appearing mucous acini in salivary gland lobules that lacked ductal dilatation.[2,3,15,16] FLS is applied to specimens that show the presence of 1 or more foci of lymphocytes located in periductal and perivascular locations. The foci can contain plasma cells, but these must be a minority constituent of the inflammatory infiltrate. The focus score can be calculated for those specimens showing the histopathologic appearance of FLS. The number of lymphocytic foci is then determined for all the gland lobules in a single tissue section. The focus score is then calculated as the number of foci per square millimeter of glandular tissue multiplied by four, which then yields foci/4mm^2. A focus score of 1 equates to 1 focus/4 mm^2. To determine the focus, a calibrated eyepiece grid or image analysis software with a closed polygon tool is used. FLS has to be distinguished from nonspecific chronic sialadenitis. The symptoms of non-specific sialadenitis are mild to moderate acinar atrophy, interstitial fibrosis, and ductal dilatation, with lymphocytes and macrophages often scattered in the parenchyma, but not forming dense aggregates of 50 or more lymphocytes immediately adjacent to normal-appearing acini.[15] In addition to the focus score (FS), two scoring systems for salivary glands are in use for the diagnosis and classification of SS. These systems are based on the presence of foci. Grading according to Tarpley's system involves destruction of acinar tissue and fibrosis.[17] Grading according to the Chisholm and Mason system is based on the presence of infiltrates from slight to one or more foci.[18] There are also other histopathological features in the labial glands that are associated with SS and therefore might be indicative of this disease. Lymphoepithelial lesions (LELs) are striated ducts, which are infiltrated by lymphocytes with concurrent hyperplasia of the epithelial cells. They are found both in parotid and labial glands, and are more representative of parotid glands than labial glands. Besides LELs, the salivary gland of SS patients also presents a relative decrease in IgA^+ plasma cells. Several studies showed that a relative decrease of <70% IgA^+ plasma cells was more sensitive and more disease specific than the FS. Both features can help assess the salivary gland biopsies for the diagnosis of SS, especially when the FS in the biopsy is <1.[19] The tissue specimens should be immediately placed in a wide-mouthed container, coded, and fixed in a generous amount of 10% formalin buffered saline for 24h. There is no standardization of labial salivary gland biopsies in SS, but Fox noticed several points of importance in LSGB.[19] The first issue refers to a sufficient amount of glandular tissue. A reasonable compromise is four glands, although a minimum sized evaluable surface area (8mm^2) may be achieved with 2-3 glands. The largest possible area to be sampled would give the best results, but a larger operative field increases the surgical risk. On the other hand, some glands may be atrophic or damaged, and the volume of the material obtained through the biopsy should be sufficient to overcome this artefact and achieve a valid result. It is more recommended to evaluate multiple different lobules than to concentrate on a single abnormal lobule, which may not be typical of the entire gland. In routine management, H&E staining is used in order to determine these structures. For clinical trials, addi-

tional staining with CD21 as well as CD20 and CD3 is required. CD21 is a marker of follicular dendritic cells. Germinal centers should be reported and pathologists are advised to use caution in order to avoid overestimating germinal centers by relying solely on CD21.[20,21] Furthermore, the distribution of the inflammatory cells in the gland may be uneven. Considering this uneven distribution, a single tissue section may result in underdiagnosis. While increasing the number of sections has the potential to reduce this problem, the optimal number of sections has yet to be determined. Some research suggests taking labial salivary glands at different depths from the same incision. FS can change significantly at different tissue depths within the minor salivary glands. Multiple sections for LSGB increase the diagnostic value and are more representative than a single section.[22]

Indications for LSGB and its usefulness in SS

LSGB is characterized by quite high specificity, a positive predictive value, and an average sensitivity of 79% in SS.[23] In other studies, the sensitivity and specificity are reported at 86.7% and 97.4%, respectively.[24] The sensitivity and specificity of labial salivary gland biopsies vary in the literature. Data from different studies are often difficult to compare, because different sets of criteria for diagnosing SS have been used and the outcome of the labial biopsy is a strong determinant for the final diagnosis. In the normal population, labial biopsy resulted in 6% to 9% false-positive diagnoses; 18% to 40% of the patients with a clinical diagnosis of SS have a negative labial biopsy, resulting in a sensitivity of 60% to 82% and a specificity of 91% to 94%.[25] In some cases, a positive histologic confirmation in LSGB does not correspond with serologic positivity for SSA or SSB. Thus, clinicians avoid performing LSGB in most patients with positive SSA/SSB serology.[26,27] On the other hand, clinical presentation of sicca symptoms and positive serology reliably predicted the results of a lip biopsy.[26] Taking both symptoms and serology into consideration is more likely to yield an accurate clinical picture than either one alone. Several studies have questioned the utility based on the invasiveness of the procedure and the high rate of pathologic misinterpretation.[25] Moreover, patients with a typical presentation of SS do not derive any additional benefit from a lip biopsy. A positive serologic result and a positive ocular test make the taking of a LSGB redundant and only in case of a negative serologic outcome or a negative result in the ocular test is a LSGB is indicated.[28] These divergent results are reported mainly in the initial stages of SS or in patients with low focus score.[26] Lack of adequate tissue can also lead to misdiagnosis or lack of diagnosis. Moreover, a possible cause of these divergent results between clinical and serological symptoms and LSGB could be the fact of taking immunosuppressive medications and steroids. There is a stronger correlation between the lip biopsy and clinical presentation of sicca with positive serology, suggesting that corticosteroids may have a tendency to confound biopsy results. The use of high-dose corticosteroids can not only relieve a patient's symptoms of SS, but also decrease the lymphocytic infiltrate of a second minor salivary gland biopsy. To avoid the confusion of false negatives, clinicians should be wary of performing a lip biopsy in patients on immunosuppression with clear criterion for SS.[25] High specificity and sensitivity make LSGB particularly useful for patients with inconclusive clinical findings, incipient forms of the syndrome, SS with negative anti-Ro/la serology, and extra-glandular involvement.[25] Moreover, LSGB can be valuable in diagnosing B-cell mucosa-associated lymphoid tissue (MALT) lymphomas, which very rarely accompany SS. 4% to 7% of patients with SS develop malignant B cell lymphoma, 48% to 75% of which are of the MALT type. These B-cell lymphomas are more frequently located in the parotid glands than in labial glands.[29] Furthermore, LSGB may be a very useful in diagnosis of SS in children. Histopathological evidence of typical FLS is also considered by some pediatric rheumatologists to be the gold standard in the diagnosis of childhood SS.[30] Unfortunately, LGB is not recommended for monitoring disease progression and treatment evaluation.

Anatomical implications and complications

Minor salivary glands are widely distributed in the labial, buccal, and palatal mucosa of the oral cavity. Microscopic findings involving lymphocytic infiltration surrounding the excretory ducts in combination with the destruction of acinar tissue are representative for all minor salivary glands and are pathognomonic changes for SS. Lip salivary glands are largely used for assisting the diagnosis of SS, because they are easily accessible and lie above the muscle layer. They are separated from the oral mucous membrane by a thin layer of fibrous connective tissue. Orientation and identification of glandular tissue is easiest. The risk of excessive postoperative bleeding is decreased because the arterial supply to the lip lies deep.

One of the most severe complications of LSGB is sensitive nerve injury. This localized sensory alternation can be described as an anesthesia, a reduced or partial loss of sensation, a transitory numbness or a hypoesthesia. These sensations can last for a few months or can be permanent. Persistent lip numbness occurs in up to 6% of biopsies performed in the lower lip.[3] The branches of the mental nerve in the lower lip are closely associated with the salivary glands and this anatomical relationship increases the risk of postoperative sensory sensations. Additionally, the branch of the mental nerve usually divides into 2 sub-branches: a horizontal and a vertical, which have an ascending course toward the vermillion

border and are in close relation to the labial salivary glands. Incisional biopsies shorter than 2 cm performed with a scalpel have reported complications ranging from 0% to 9.3%, whereas those using larger incisions (2–3 cm) have described complications in the range of 3.7–31%. Transient disorders of lip sensitivity are found to occur in up to 11.7% of procedures. Persistent lower lip hypoesthesia is reported in about 3.4–4% of cases.[23] Larger incisional biopsies and punch biopsies are associated with a higher risk of both transient and persistent lower lip numbness. Other possible complications of LSGB are less severe, usually transient or temporary, and are associated with localized postoperative inflammation or improper healing. The symptoms of postoperative inflammations are local pain and swelling. Blood vessel injuries result in external hematoma. The possible delayed complications are the formation of granulomas, internal scarring and cheloid formation. Some patients can report burning or tingling sensations, and functional deficits during the immediate postbiopsy period such as eating, sleeping or speech difficulties.[15]

Surgical technique and approaches

Labial gland biopsy can be a excisional or incisional technique. The most recommended site is normal–appearing mucosa of the lower lip. A wide range of surgical approaches have been described for harvesting a few accessory glands from the lower lip using different instruments such as a scalpel, a punch or cup forceps. The use of a forceps with a fenestrated active end to stabilize the lip has also been suggested.[3] The excisional biopsy is carried out by excising an ellipse of oral mucous membrane down to the muscle layer. Ideally, 6 to 8 minor glands must be harvested and sent for histopathologic examination. The wound should be closed with 4-0 silk sutures, which are removed after 4 to 5 days. The modification of this method is the technique with a mucosal excision of 3.0 × 0.75 cm. Another recommended technique is a 1.0 to 1.5 cm wedge-shaped excision of the mucosa between the midline and commissure. The incisional biopsy is described as a 1.5–2.0 cm linear incision of mucosa, parallel to the vermillion border and lateral to the midline. Gorson and Ropper reported a 1-cm vertical incision just behind the wet line through the mucosa and submucosa.[31] It is usually that case that the lateral lip compartments are advocated for biopsy, because of the glandular-free zone in the center of the lower lip. Berquin et al., described an oblique incision, starting 1.5 cm from the midline and proceeding latero-inferiorly to avoid the central glandular-free zone.[32] According to Saruhanoğlu et al., the vertical incision technique is associated with less pain, less swelling, less scar formation and less difficulty in eating when compared with the horizontal incision technique.[33] There is insufficient evidence to support the superiority of one technique over the others and the shape and the size of the incision can be considered a matter of preference.[34] The incision shape includes elliptical, circular, linear, horizontal, vertical, and wedge shapes and the incision length varies from a few millimeters to 2 cm.

Another recommended modification using loupe operation glasses to precisely excise the salivary glands without disturbing the direct underlying sensible nerves. The alternative technique to scalpel biopsy is the minor salivary gland punch biopsy. This biopsy can be performed by a single operator, and it is less expensive than classical scalpel biopsy. This technique consists of obtaining the biopsy from the buccal side of the lower lip, which is stabilized by the patient him/herself using a 4-5 mm punch, which permits the retrieval of a cylinder of tissue up to 8 mm in length.[5] The punch biopsy is suggested because of the absence of risk to the patient and because of its simplicity. However, according to Varela-Centelles et al., punch biopsies did not provide enough material for diagnosis of Sjögren's syndrome. Moreover, the findings of this study strongly discouraged the punch technique for minor salivary gland lip biopsy and provided information on the superiority of the linear incisional biopsy in terms of neural damage.[23]

Based on our own clinical experience, I suggest a 1.0 to 1.5 cm linear, horizontal incision of mucosa parallel to the vermillion border and lateral to the midline with the tip of a 15 scalpel. The lower lip should be retracted and everted under tension to expose the inner surface and allow visualization of the minor salivary glands just to the depth of the mucosa. Local anesthesia injected submucosally with 0.5 to 1.0 ml of 1% lidocaine with 1:200000 epinephrine is sufficient. The anesthesia hydro-dissects and lifts the mucosa away from the salivary glands, provides delivery of local anesthetic directly to sensory nerve fibers and temporarily displaces small vessels deep in the glands to promote hemostasis and visualization during the dissection. In this technique both margins of incision should be gently crafted to access the submucosal layer. This stage of procedure can be performed using blunt-tipped iris scissors by spreading in a plane perpendicular to the mucosal incision and parallel to the direction of the sensory nerve fibers. In my opinion this technique is fast, simple and leaves a small scar. The linear incision secures a good adherence of wound margins and proper and fast healing. Unfortunately, this method is not effective in small amounts of salivary glands. It is difficult to find the sufficient amount of labial glands. Moreover, it may be difficult to harvest a sufficient number of labial salivary glands in atrophic mucosa of patients with long-standing SS. Furthermore, the recommended method is a 1 cm lenticular incision of mucosa, lateral to the midline, and removal of the mucosa to uncover the submucosal layer and obtain a few adjacent salivary glands.

This technique ensures good visibility into the operating field to avoid blood vessels and nerve injures. This incision provides adequate glandular tissue for diagnosis. The wound should be closed by a few non-resorbable, single, interrupted stitches. One very important issue is to harvest only labial salivary glands without muscular or other tissues. It is the most valuable specimen for histopathological examination, because it only includes glandular tissue. Additionally, this technique decreases the risk of nerve damage and postoperative pain and assures successful healing. Sensory nerve fibers are almost always visible just below the plane of dissection and care should be taken to identify and preserve them. The next very important issue is not to puncture the labial glands in order to reduce the risk of mucocele formation. It is even better to remove all visible labial salivary glands from the operating field before suturing in order not to damage the glands or their ducts. Patients should also avoid taking steroids before the biopsy. The factors potentially contributing to a false-negative rate include the use of oral steroids that may result in immunosuppression and confound histopathologic results.[15]

Alternative salivary gland biopsies in SS

The selection of the best surgical approach in terms of related morbidity is hampered by the absence of comparative studies and the proliferation of descriptive papers that do not state negative outcomes associated with the technique used. Moreover, reports describing the percentage of surgical complications have limited validity due to the lack of standardizations when defining and categorizing the complications in accordance with their severity.

The main alternative types of salivary gland biopsies in SS are parotid gland biopsy and sublingual gland biopsy. Parotid gland biopsy allows the clinician to monitor the disease progression and to assess the effect of an intervention treatment in SS. Parotid tissue can be harvested easily, repeated biopsies from the same parotid gland are possible, and the histopathologic results can be compared with other diagnostic results derived from the same gland, such as secretory function, sialographic appearance and ultrasonography. Furthermore, parotid biopsy is better in the identification of lymphomas.[25] The main possible complications are facial nerve damage, Frey's syndrome and development of sialoceles and salivary fistulae. A temporary change in sensation in the skin area of the incision is also a well-documented complication after parotid biopsy. Some patients might also develop preauricular hypothesia, although this is usually temporary. Furthermore, in SS, the salivary gland tissue is replaced by fatty tissue, and the risk of harvesting fatty tissue is thereby increased if done by inexperienced physicians.[35,36] Parotid biopsy is particularly recommended in pediatric patients in whom SS is suspected and who have a negative minor salivary gland biopsy result. Incisional biopsy of the parotid gland overcomes most of the disadvantages of labial biopsy. When evaluating the parotid and labial biopsy, sensitivity and specificity are comparable, estimated to be 78% and 86%, respectively.[25,37] Comparative studies suggest that both procedures – sublingual and parotid biopsy – retain a diagnostic potential comparable to that of lip biopsy and may be associated with lower postoperative morbidity. A comparison of sublingual gland biopsy with labial gland biopsy is better than that of labial gland biopsy, whereas the specificity of the latter is greater than that of the former. Sublingual gland biopsy is a relatively safe procedure, although the postoperative complications of sublingual salivary gland biopsy include ligaturing the Wharton duct, resulting from the placement of sutures, bleeding and swelling in the floor of the mouth. Damage to the lingual nerve related to this biopsy technique has never been reported in the literature. No specialized histopathologic criteria have been established for the diagnosis of SS after a sublingual gland biopsy, and researchers merely used the criteria for labial gland biopsies.[25,38-40]

Conclusions

Labial salivary gland biopsy is an integral part of diagnosis of Sjögren's syndrome, but it has a limited value for monitoring of the disease progression and for an assessment of effectiveness of the treatment. The standardization of the surgical technique and the histopathological examination can increase the diagnostic value of the biopsy.

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