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Original article

Clinicopathologic Utility of Minor Salivary Gland Biopsy in Suspected Sjögren syndrome: Experience from a Single Center in Libya

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Abstract
Sjögren syndrome (SS) is a chronic systemic autoimmune disease characterized by lymphocytic infiltration and progressive dysfunction of exocrine glands, primarily affecting salivary and lacrimal glands. Diagnosis remains challenging because of overlapping sicca symptoms, variable serologic findings, and diverse clinical presentations. Minor salivary gland biopsy (MSGB) remains an important component of the 2016 ACR/EULAR classification criteria as it provides direct histopathological evidence of focal lymphocytic sialadenitis and helps support the diagnosis, especially in patients with non-specific clinical manifestations or negative serological findings. To evaluate the clinicopathologic utility of minor salivary gland biopsy in patients with suspected Sjögren syndrome at Al Hilal University Hospital, Misrata, Libya. This retrospective single-center case series was conducted at Al Hilal University Hospital, Misrata, Libya, between October 2025 and April 2026. Patients who underwent labial minor salivary gland biopsy for suspected Sjögren syndrome were included. Clinical presentation, serological findings, and histopathological features were reviewed from available medical records. Histopathological examination focused on the presence of focal lymphocytic sialadenitis, focus score assessment, acinar atrophy, stromal fibrosis, and ductal epithelial changes. Six patients were included in this series, with ages ranging from 48 to 85 years (median age: 64 years). Most patients were female (5/6, 83.3%). Dry mouth was reported in all cases, while dry eyes were present in five patients. Two patients showed positive autoimmune serology, including ANA and/or anti-Ro antibodies, whereas the remaining patients were seronegative despite clinical suspicion of Sjögren syndrome. Biopsy findings consistent with Sjögren syndrome, defined by focal lymphocytic sialadenitis with a focus score ≥1 focus/4 mm², were identified in four cases (67%). The main microscopic findings included dense periductal lymphocytic infiltrates, acinar atrophy, and mild stromal fibrosis. The remaining two biopsies showed only mild chronic inflammatory changes without definite diagnostic lymphocytic foci and were interpreted as non-specific chronic sialadenitis. One patient showed systemic autoimmune involvement with chronic renal impairment, positive ANA and anti-Ro antibodies, and renal biopsy findings consistent with chronic diffuse lupus nephritis associated with marked chronic tubulointerstitial nephritis, suggesting possible secondary Sjögren syndrome overlap associated with systemic lupus erythematosus. Minor salivary gland biopsy continues to play an important role in the evaluation of patients with suspected Sjögren syndrome, particularly in cases with negative serology or unclear clinical findings. In our experience, histopathological examination provided valuable diagnostic information and helped support disease classification when clinical and serological findings alone were insufficient. Close collaboration between pathologists and rheumatologists remains essential for accurate diagnosis and appropriate patient management, especially in resource-limited settings.

Keywords. *Sjögren syndrome, Minor Salivary Gland Biopsy, Focal Lymphocytic Sialadenitis, Seronegative Sjögren syndrome, Sicca Symptoms, Autoimmune Sialadenitis, Histopathology, Focus Score.*

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Introduction

Sjögren syndrome (SS) is a chronic autoimmune disease that primarily affects the salivary and lacrimal glands, leading to symptoms of dry mouth and dry eyes [1-3]. Although glandular involvement is the most recognized feature, the disease may also affect other organs, including the kidneys, lungs, nervous system, and musculoskeletal system [4]. SS is seen more commonly in middle-aged women, although the clinical presentation and severity can vary considerably between patients [5]. Diagnosing SS can be difficult because sicca symptoms are not specific and may also be seen with aging, medication use, diabetes mellitus, and other inflammatory or autoimmune conditions [2]. In addition, commonly used serological markers such as anti-Ro/SSA and anti-La/SSB antibodies are not detected in all patients, particularly in

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early or seronegative disease [6]. Minor salivary gland biopsy (MSGB) remains an important component of the 2016 ACR/EULAR classification criteria, as it provides direct histopathological evidence of salivary gland involvement and can be especially helpful in patients with inconclusive clinical or serological findings [3]. The characteristic histopathological finding is focal lymphocytic sialadenitis with a focus score of ≥1 focus per 4 mm² [7]. Previous studies have highlighted the diagnostic value of MSGB, particularly in seronegative and clinically challenging cases where histopathological assessment may help support disease classification and improve diagnostic confidence [8,9]. More recent reports have also emphasized its usefulness in patients with atypical or extra-glandular manifestations of SS [10]. Despite the recognized importance of MSGB, data from North African populations remain limited. Therefore, this study aimed to evaluate the clinicopathologic utility and histopathological findings of minor salivary gland biopsy in patients investigated for suspected Sjögren syndrome at Al Hilal University Hospital, Misrata, Libya.

Methods

Study Design

This study was designed as a retrospective single-center clinicopathologic case series conducted at Al Hilal University Hospital, Misrata, Libya.

Study Period

The study included cases diagnosed between October 2025 and April 2026.

Patient Selection

Patients were included if they had a clinical suspicion of Sjögren syndrome and underwent minor salivary gland biopsy during the study period. Only cases with adequate histopathological material and available clinical and serological data were included in the analysis.

Data Collection

Clinical information and laboratory findings were reviewed from available medical records. Demographic data, presenting symptoms, autoimmune serology, and evidence of systemic involvement were documented when available.

Histopathological Evaluation

All hematoxylin and eosin (H&E)-stained slides were reviewed. Histopathological assessment focused on the presence of focal lymphocytic sialadenitis, focus score evaluation, periductal lymphocytic aggregates, acinar atrophy, stromal fibrosis, ductal epithelial changes, and chronic inflammatory infiltrates. Biopsy adequacy required structurally preserved salivary gland parenchyma measuring at least 4 mm². Biopsy adequacy and focus score assessment were performed using routine light microscopic estimation of glandular surface area. A focus score of ≥1 focus per 4 mm² was considered supportive of Sjögren syndrome according to established classification criteria [3]. Cases were evaluated in correlation with the 2016 ACR/EULAR classification criteria, in which a focus score of ≥1 focus/4 mm² contributes 3 points toward disease classification. Diffuse chronic inflammatory infiltrates associated with marked fibrosis, severe acinar atrophy, or nonspecific chronic sialadenitis were not included in the diagnostic focus score assessment.

Results

Demographic and Clinical Findings

Six patients were included in this series, with ages ranging from 48 to 85 years (median age: 64 years). Five of six patients were female. All patients presented with xerostomia, while xerophthalmia was reported in five cases. Two patients showed positive autoimmune serology, including ANA and/or anti-Ro antibodies, whereas the remaining patients were seronegative despite clinical suspicion of Sjögren syndrome. Additional clinical manifestations included arthralgia and evidence of systemic autoimmune involvement. One patient showed systemic autoimmune involvement with chronic renal impairment, positive ANA and anti-Ro antibodies, and renal biopsy findings consistent with chronic diffuse lupus nephritis associated with marked chronic tubulointerstitial nephritis, suggesting possible secondary Sjögren syndrome overlap associated with systemic lupus erythematosus.

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Table 1. Clinicopathologic Characteristics of Included Cases

Case	Age/Sex	Clinical Features	Serology	Focus Score (/4 mm²)	Histopathological Findings	Final Interpretation
1	52/F	Xerostomia, xerophthalmia	ANA+	FS = 1	Focal lymphocytic sialadenitis with mild acinar atrophy and focal lymphoid aggregates	Sjögren syndrome
2	68/F	Xerostomia, arthralgia	Negative	FS >1	Focal lymphocytic sialadenitis with dense multifocal periductal lymphoid aggregates and acinar atrophy	Sjögren syndrome
3	75/F	Sicca symptoms, renal impairment	ANA+, anti-Ro+	FS >1	Marked focal lymphocytic sialadenitis with multifocal lymphoid aggregates, acinar atrophy, and stromal fibrosis	Sjögren syndrome with possible secondary overlap (SLE-associated)
4	48/F	Xerostomia	Negative	FS >1	Focal lymphocytic sialadenitis with focal periductal lymphoid aggregates adjacent to salivary ducts	Sjögren syndrome
5	85/M	Dry mouth	Negative	FS <1	Mild chronic inflammation without definite focal lymphoid aggregates or acinar atrophy	Non-specific chronic sialadenitis
6	60/F	Xerostomia	Negative	FS <1	Minimal scattered chronic inflammatory infiltrate with preserved glandular architecture and no definite focal lymphocytic sialadenitis	Non-specific chronic sialadenitis

Table 2. Comparison of the Present Study with Selected Published Studies on Minor Salivary Gland Biopsy in Sjögren Syndrome

Study	*Country*	*Study Type*	*Number of Cases*	*Main Findings*	*Seronegative Cases*	*Systemic/Renal Involvement*
Daniels et al. [7]	USA	Clinicopathologic study	Large cohort	Established the diagnostic role of MSGB in SS	Not specifically emphasized	Limited
Goel et al. [8]	USA	Retrospective study	47 cases	High diagnostic utility of MSGB in anti-SSA-negative patients	Yes	Not emphasized
Romala et al. [9]	India	Case report	1 case	Biopsy confirmed seronegative SS	Yes	No
Piperi et al. [10]	Greece	Case series	Pediatric cases	Diagnostic value of MSGB in clinically challenging presentations	Partial	Limited
Mahadoon and Mathunny [16]	India	Case series and literature review	Multiple cases	Importance of clinicopathologic correlation and focus score assessment	Yes	Limited
Present study	Libya	Single-center case series	6 cases	Diagnostic utility of MSGB in suspected SS with clinicopathologic correlation	Yes	Yes

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Histopathological Findings

Histopathological findings consistent with Sjögren syndrome were identified in four biopsies (67%). These cases showed focal lymphocytic sialadenitis with dense lymphocytic aggregates centered mainly around the salivary ducts. The inflammatory infiltrates were composed predominantly of mature lymphocytes and were associated with varying degrees of glandular damage. Additional microscopic findings included acinar atrophy, mild to moderate stromal fibrosis, duct-centered chronic inflammation, and focal distortion of the normal glandular architecture. The remaining two biopsies showed only mild chronic inflammatory infiltrates without definite lymphocytic foci. Overall, the glandular architecture was largely preserved, and these cases were interpreted as non-specific chronic sialadenitis.

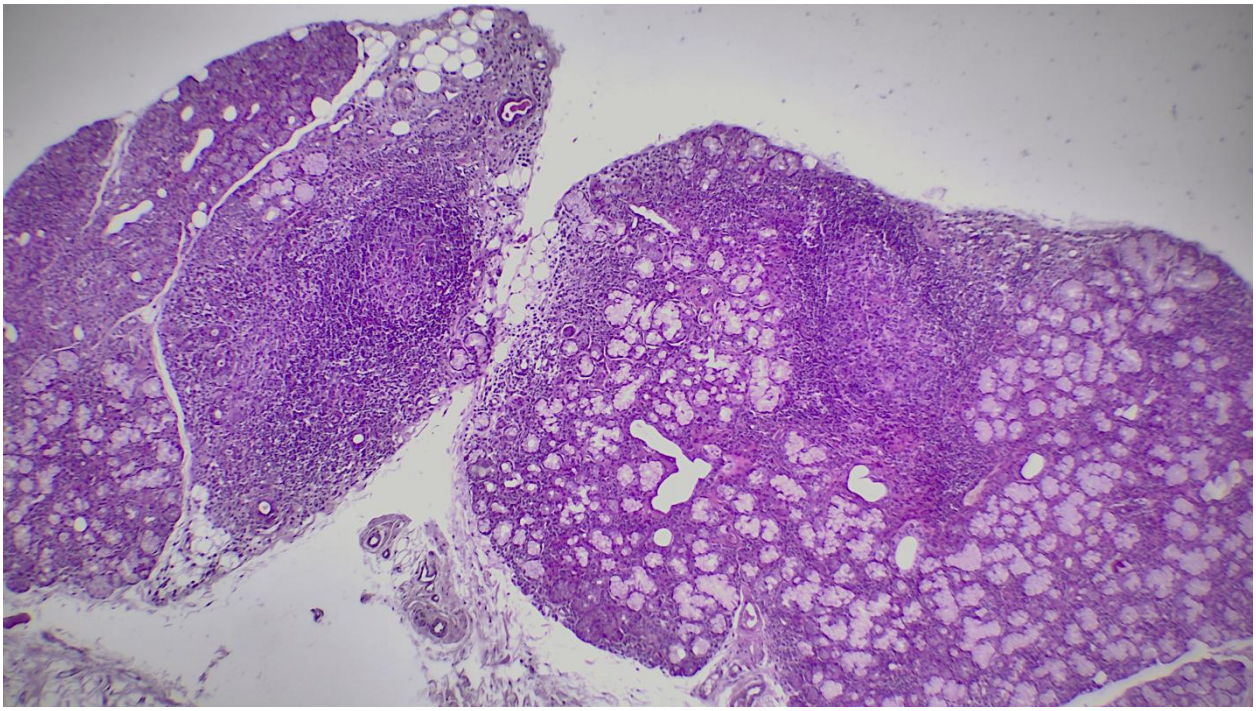

Figure 1. Low-power photomicrograph of focal lymphocytic sialadenitis in minor salivary gland tissue, demonstrating dense periductal lymphocytic aggregates and associated acinar atrophy (H&E stain).

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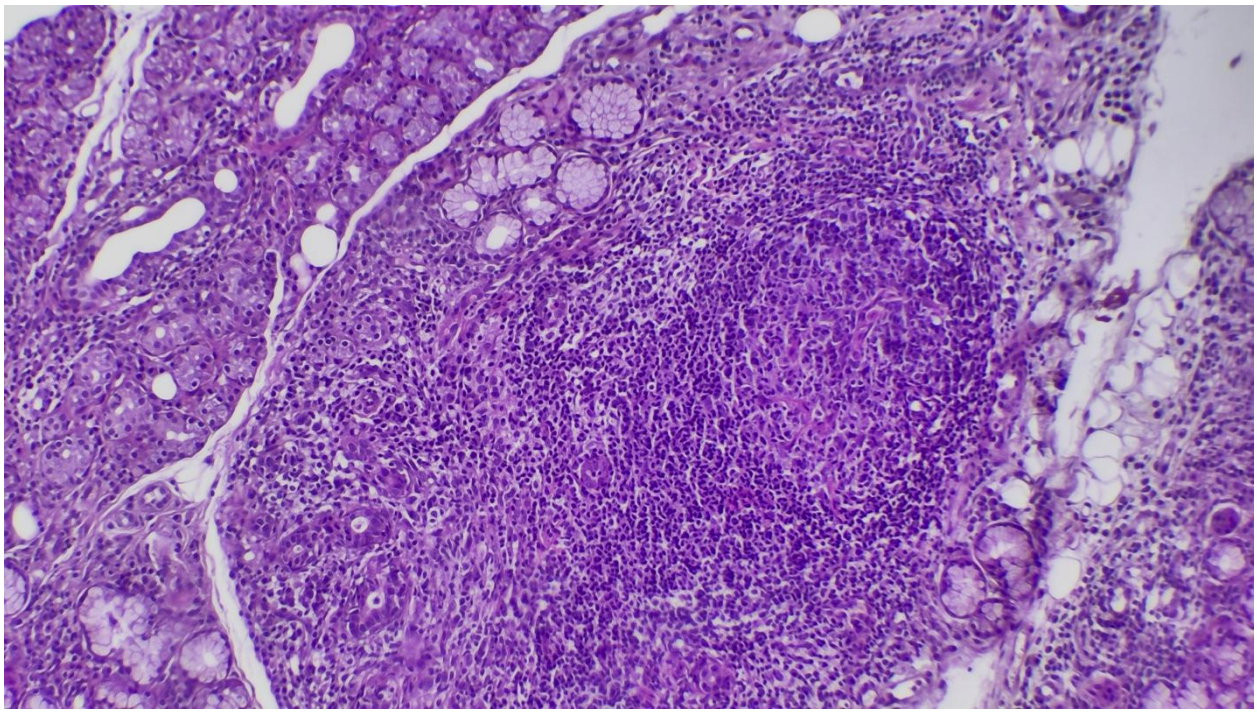

Figure 2. High-power photomicrograph showing focal lymphocytic sialadenitis with associated mild atrophy of the salivary acini (H&E stain)

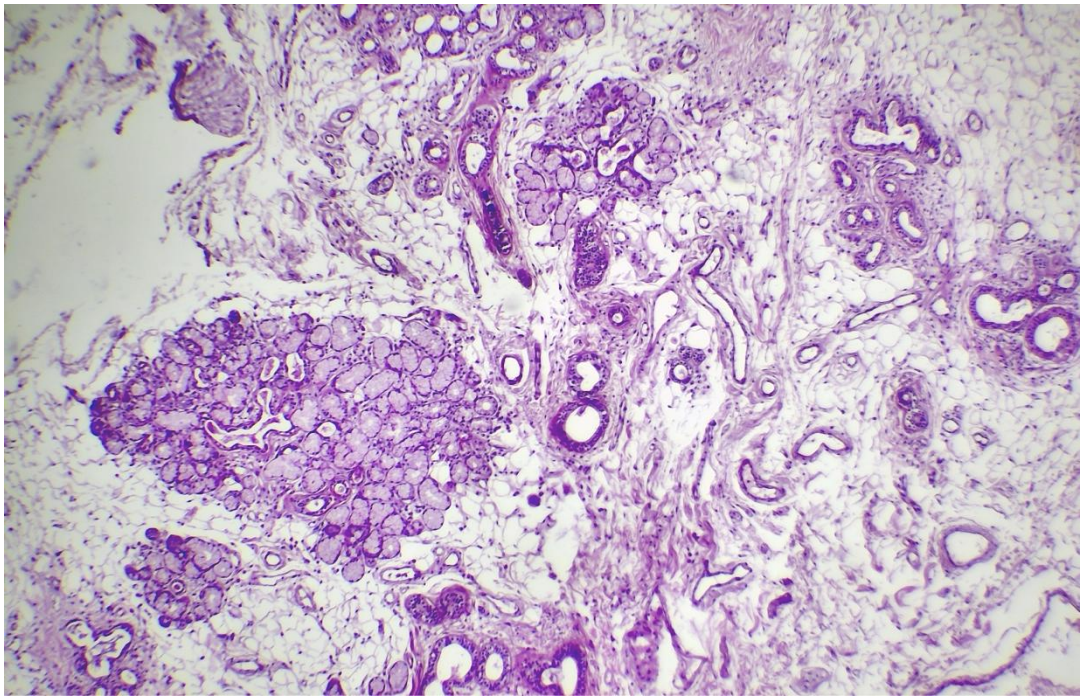

Figure 3. Minor salivary gland tissue showing chronic lymphocytic sialadenitis with associated acinar atrophy, stromal fibrosis, and relative preservation of the lobular architecture (H&E stain)

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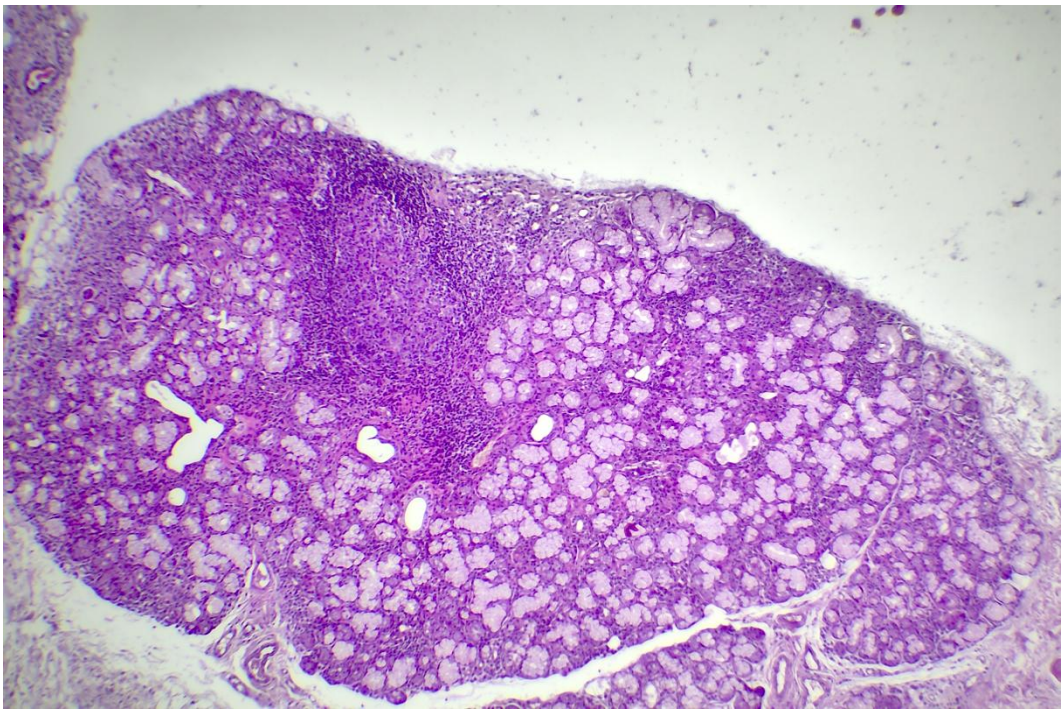

Figure 4. Minor salivary gland biopsy demonstrating focal lymphocytic sialadenitis with a dense lymphocytic focus adjacent to salivary gland acini, compatible with focus score assessment (H&E stain).

Discussion

The present study highlights the practical value of minor salivary gland biopsy in the evaluation of patients with suspected Sjögren syndrome at a tertiary referral center in Libya. In our series, histopathological findings supportive of Sjögren syndrome were identified in 67% of cases, reinforcing the important role of tissue-based diagnosis, particularly in patients with clinically suspicious disease. Previous studies have shown that minor salivary gland biopsy is especially useful in patients with negative or inconclusive serology, where histopathological examination may provide objective evidence supporting the diagnosis [8,9]. In the current series, several patients were seronegative despite having clinical features suggestive of Sjögren syndrome, and biopsy findings played an important role in disease classification. The female predominance observed in this study is in keeping with the well-recognized epidemiology of Sjögren syndrome, which predominantly affects middle-aged women [5]. The age range of our patients was also similar to that reported in previous international studies [11]. On microscopic examination, focal lymphocytic sialadenitis remained the main diagnostic finding in positive cases, as illustrated in Figure 1 and Figure 4. Dense periductal lymphocytic aggregates were frequently associated with acinar atrophy, stromal fibrosis, and varying degrees of chronic duct-centered inflammation. These findings are consistent with the characteristic histopathological features described in the literature [7]. Comparison with previously published studies demonstrates that our findings are generally consistent with the reported diagnostic value of minor salivary gland biopsy, particularly in clinically suspected seronegative cases, as summarized in Table 2.

Recent reports continue to highlight the importance of minor salivary gland biopsy in seronegative Sjögren syndrome, particularly in patients with persistent sicca symptoms despite negative autoimmune serology. Romala et al. described a patient with severe xerostomia and negative anti-SSA/SSB antibodies in whom the diagnosis was ultimately supported by labial salivary gland biopsy and focus score assessment [9]. Similar findings were observed in our series, where histopathological examination provided important diagnostic support in clinically suspected cases with inconclusive serological findings. Mahadoon and Mathunny also highlighted the importance of integrating clinical, serological, and histopathological findings when evaluating suspected Sjögren syndrome [16]. Their findings support our experience that biopsy interpretation should not be considered in isolation, but rather as part of an overall clinicopathologic assessment. In addition to the classic glandular manifestations, Sjögren syndrome may also involve several extra-glandular organs, including the kidneys. Renal involvement has been reported in approximately 5–10% of patients with primary Sjögren syndrome and is most commonly associated with chronic tubulointerstitial nephritis, although

glomerular lesions and overlap autoimmune diseases may also occur [4,12]. Previous studies have shown that renal manifestations may contribute significantly to morbidity and may occasionally represent one of the presenting features of systemic disease. In our series, one patient showed chronic renal impairment associated with positive ANA and anti-Ro antibodies. Renal biopsy findings were consistent with chronic diffuse lupus nephritis accompanied by marked chronic tubulointerstitial nephritis, suggesting possible secondary Sjögren syndrome overlap. These findings further highlight the importance of careful systemic evaluation in patients presenting with suspected SS, particularly in the extra-glandular manifestations. Minor salivary gland biopsy is generally considered a safe and minimally invasive procedure, with most patients experiencing only minor and temporary discomfort [13]. However, interpretation of biopsy findings can sometimes be challenging, particularly in small specimens, seronegative cases, or biopsies showing only mild chronic inflammatory changes. In such situations, close clinicopathologic correlation remains important to help distinguish true focal lymphocytic sialadenitis from non-specific chronic sialadenitis [14]. The limitations of this study include the small sample size, retrospective single-center design, and limited availability of complete serological and follow-up data in some patients. In addition, focus score assessment was performed using routine light microscopic estimation without digital morphometric analysis. Overall, the findings of this single-center series support the continued value of minor salivary gland biopsy in everyday diagnostic practice, especially in clinically suspected seronegative cases where histopathological examination may provide important diagnostic support. Our experience also highlights the importance of close collaboration between rheumatologists and pathologists in achieving accurate diagnosis and appropriate disease classification in patients with suspected Sjögren syndrome [15].

Recommendations

Minor salivary gland biopsy should be considered in patients with persistent sicca symptoms, particularly when serological findings are negative or inconclusive. Histopathological findings must always be interpreted in conjunction with clinical and serological data to enhance diagnostic accuracy and reduce the risk of overdiagnosis. Careful focus score assessment and standardized histopathological evaluation are essential to minimize interobserver variability in biopsy interpretation. Close collaboration between rheumatologists and pathologists remains critical for accurate diagnosis and appropriate disease classification. Patients diagnosed with Sjögren syndrome should also be systematically evaluated for possible extra-glandular manifestations, including renal involvement, to ensure comprehensive disease management. From a research perspective, larger multicenter studies from Libya and North Africa are needed to better characterize the clinicopathologic spectrum of Sjögren syndrome in the region. Future investigations incorporating salivary gland ultrasonography, immunohistochemistry, and molecular markers hold promise for improving diagnostic evaluation and refining disease stratification.

Conclusion

Minor salivary gland biopsy remains a valuable diagnostic tool in patients with suspected Sjögren syndrome, particularly in seronegative or clinically challenging cases. In our series, histopathological evaluation provided important diagnostic support and contributed to more confident disease classification. The findings of this single-center Libyan case series also highlight the importance of close collaboration between rheumatologists and pathologists in the evaluation of suspected Sjögren syndrome and reinforce the continued role of tissue-based diagnosis in routine clinical practice. Further multicenter studies from Libya and North Africa are needed to better characterize the clinicopathologic spectrum of Sjögren syndrome within the region.

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