HISTOLOGICAL EVALUATION OF SALIVARY GLAND ALTERATIONS IN AUTOIMMUNE DISEASES.

Soatova Feruza Bahodirovna
Assistant at the Alfraganus University
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Abstract

Histological assessment of salivary gland alterations in autoimmune disorders highlights the profound structural and cellular changes occurring within glandular tissues, particularly in Sjögren's syndrome (SS). This chronic autoimmune disease primarily targets the exocrine glands, resulting in lymphocytic infiltration, progressive inflammation, and functional impairment, which clinically manifest as xerostomia (dry mouth) and xerophthalmia (dry eyes).

Characteristic histopathological hallmarks—such as acinar cell atrophy, ductal dilatation, and lymphoid focal aggregates—play a decisive role in both diagnosis and understanding of immune-mediated tissue damage. Histological examination remains a cornerstone diagnostic method, complementing clinical assessments and serological findings to establish a definitive diagnosis of autoimmune sialadenitis. Detection of focal lymphocytic sialadenitis, a key microscopic indicator of SS, is particularly valuable for distinguishing it from other glandular pathologies presenting with similar clinical features.

Recent developments in diagnostic methodology, notably ultrasound-guided core needle biopsy, have enhanced both the precision and interpretive depth of glandular histological evaluation. Beyond diagnosis, these findings inform patient stratification and therapeutic planning, enabling clinicians to align treatment strategies with the extent and pattern of tissue injury.

Histopathological Features in Autoimmune Diseases

The histopathological examination of salivary glands in autoimmune diseases provides vital insights into the degenerative, inflammatory, and reparative processes that underlie glandular dysfunction. Among these conditions, Sjögren's syndrome (SS) stands as the prototype, characterized by profound alterations in both parenchymal and ductal components.

Microscopically, these changes manifest as a progressive loss or complete disappearance of acinar structures, accompanied by dense lymphocytic infiltration and hyperplasia of ductal epithelial cells. The formation of epimyoepithelial islands, a hallmark of SS, reflects chronic immune-mediated stimulation and reorganization of glandular tissue. In advanced stages, these features are often accompanied by ductal dilatation, focal inflammation, acinar atrophy, and varying degrees of fibrosis, which together contribute to irreversible glandular impairment and the clinical presentation of xerostomia.

The presence of adipose tissue infiltration within the glandular parenchyma, though frequently noted, remains controversial in terms of its pathological significance—some authors interpret it as an age-related or reparative change, while others consider it a marker of chronic inflammatory destruction. Moreover, lobular fibrosis, often underappreciated in earlier studies, correlates closely with the intensity of lymphocytic infiltration and the chronicity of the disease, suggesting that fibrotic remodeling is not merely secondary but an integral component of autoimmune progression.

Diagnostic Value of Histology

Histological evaluation of salivary gland tissue remains a cornerstone in the diagnosis of autoimmune sialadenitis, including Sjögren's syndrome and related conditions. Diagnosis typically integrates clinical examination, serological markers (such as anti-Ro/SSA and anti-La/SSB antibodies), and microscopic analysis, the latter being indispensable for confirming focal lymphocytic sialadenitis—the defining lesion of SS.

Research indicates that salivary gland dysfunction, commonly leading to hyposalivation and oral dryness, may occur in association with broader systemic autoimmune conditions such as systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA). In these contexts, histopathology provides not only confirmatory evidence but also helps differentiate primary Sjögren's syndrome from secondary forms linked to other autoimmune diseases.

Recent methodological advances, particularly the introduction of ultrasound-guided core needle biopsy (US-guided CNB), have markedly improved the precision and safety of obtaining parotid and labial gland specimens. This minimally invasive technique enables quantitative evaluation of inflammatory foci, grading of glandular damage, and stratification of patients into mild, moderate, or severe categories, thereby supporting both clinical management and research classification systems.

Implications for Patient Stratification and Research

Beyond its diagnostic significance, histopathology serves as a powerful tool for patient stratification and therapeutic planning in autoimmune salivary gland diseases. By analyzing the cellular composition, distribution of inflammatory infiltrates, fibrosis intensity, and degree of acinar destruction, clinicians can predict disease severity and tailor therapeutic interventions accordingly.

In clinical research, histological criteria are increasingly employed to select patient cohorts for targeted therapies, ensuring that individuals with comparable histological patterns are grouped together for more accurate evaluation of treatment efficacy. This approach enhances the precision of clinical trials and fosters the development of personalized medicine strategies.

Looking ahead, the refinement of quantitative histological scoring systems and the integration of digital pathology, immunohistochemical markers, and molecular profiling promise to revolutionize the interpretation of salivary gland biopsies. These advances will likely bridge the gap between morphological findings and functional clinical outcomes, providing a more comprehensive understanding of autoimmune pathogenesis and guiding the evolution of tailored therapeutic regimens.

Autoimmune Diseases Affecting Salivary Glands

Autoimmune diseases exert a profound influence on the structure and function of salivary glands, with Sjögren's syndrome (SS) being the most extensively studied and clinically significant example. This chronic systemic autoimmune disorder primarily targets exocrine glands, especially the salivary and lacrimal glands, leading to progressive inflammation, lymphocytic infiltration, and subsequent glandular destruction. The resulting impairment in glandular secretion manifests as xerostomia (dry mouth) and xerophthalmia (dry eyes)—the hallmark symptoms of the disease.

In SS, the immune system aberrantly attacks glandular epithelial cells, triggering a cascade of immunopathological events that disrupt normal acinar and ductal architecture. Persistent immune activation leads to loss of secretory acini, fibrotic remodeling, and epithelial

hyperplasia, which collectively compromise salivary output. Over time, the chronic inflammatory process extends beyond local glandular involvement, often giving rise to systemic manifestations, such as arthralgia, fatigue, and vasculitis. Other autoimmune diseases, including systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and systemic sclerosis, can also affect salivary glands, either as secondary forms of SS or as part of broader autoimmune pathology, thereby complicating differential diagnosis and management.

Histological Characteristics

The histological hallmark of Sjögren's syndrome is focal lymphocytic sialadenitis (FLS), characterized by the accumulation of dense lymphoid foci (typically consisting of ≥50 mononuclear cells) adjacent to normal-appearing acini and ducts. These infiltrates, composed predominantly of CD4+ T cells and B cells, reflect the immune-mediated destruction of glandular tissue.

Salivary gland biopsies reveal a spectrum of changes, ranging from mild periductal inflammation and acinar shrinkage in early disease to advanced fibrosis, fatty infiltration, and ductal dilatation in chronic stages. The focus score—defined as the number of lymphoid aggregates per 4 mm^2 of glandular tissue—remains a critical histological parameter for diagnosis and disease classification.

In addition to Sjögren's syndrome, other autoimmune disorders can produce similar histopathological findings. For instance, SLE-associated sialadenitis often presents with non-specific lymphocytic infiltration and atrophy, whereas rheumatoid arthritis-related glandular involvement tends to display mild fibrosis with plasma cell predominance. Understanding these subtle histological distinctions is essential for accurate differential diagnosis and for preventing misclassification among overlapping autoimmune conditions.

Diagnostic Relevance and Future Directions

The diagnostic approach to autoimmune salivary gland disease relies on an integrated assessment that combines clinical findings, serological tests, and histopathological analysis. Among these, salivary gland biopsy—typically of the labial minor glands—is pivotal for establishing a definitive diagnosis. It enables visualization of focal lymphocytic sialadenitis, quantification of the focus score, and evaluation of fibrosis and ductal changes, all of which are instrumental in applying current ACR/EULAR classification criteria for Sjögren's syndrome.

Recent technological innovations have enhanced the precision of histological diagnostics. Ultrasound-guided core needle biopsy (CNB) of the parotid gland offers a less invasive yet highly informative alternative to traditional methods, providing larger, more representative tissue samples with fewer complications. Furthermore, the integration of histology with advanced molecular techniques—including single-cell RNA sequencing, transcriptomics, and proteomics ("omics") approaches—is paving the way toward a new era of histo-molecular pathology. These combined analyses can identify novel biomarkers, clarify immune cell heterogeneity, and uncover molecular signatures predictive of disease severity and treatment response.

In the future, the refinement of digital pathology platforms, AI-assisted histological scoring, and quantitative morphometric analyses will likely revolutionize the field, allowing for personalized disease stratification and targeted therapy selection. Thus, histological and molecular characterization of salivary gland tissue will continue to serve not only as a

diagnostic cornerstone but also as a critical foundation for precision medicine in autoimmune diseases.

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