Volume 3, Issue 3, March 2025 ISSN (E): 2938-3765

MORPHOLOGICAL CHANGES OF THE SPLEEN IN AUTOIMMUNE DISEASES: A LITERATURE REVIEW

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Abstract
Autoimmune diseases (AIDs) can significantly impact spleen morphology due to chronic immune activation and dysregulation. This review examines the morphological changes in the spleen associated with various autoimmune disorders, including rheumatoid arthritis, autoimmune thyroiditis, and autoimmune blistering diseases. Recent histopathological and imaging studies indicate common alterations such as splenomegaly, follicular hyperplasia, and changes in white pulp architecture. Understanding these morphological modifications provides valuable insights into disease progression, potential diagnostic markers, and therapeutic implications. Further research is needed to explore the clinical significance of spleen alterations in autoimmune conditions.

Keywords. Autoimmune diseases, spleen morphology, splenomegaly, follicular hyperplasia, histopathology, immune dysregulation, rheumatoid arthritis, autoimmune thyroiditis, diagnostic markers, systemic inflammation.

INTRODUCTION

Autoimmune diseases (AIDs) encompass a diverse group of disorders characterized by the immune system's aberrant response against self-antigens, leading to tissue damage and organ dysfunction. These conditions collectively affect approximately 5–8% of the global population, with a higher prevalence observed among females. The spleen, a vital lymphoid organ, plays a crucial role in immune surveillance, hematopoiesis, and the clearance of senescent erythrocytes and pathogens. In the context of AIDs, the spleen's involvement is multifaceted, encompassing both functional and structural alterations that can significantly impact disease progression and patient outcomes.

Splenomegaly, defined as an abnormal enlargement of the spleen, is a notable morphological change observed in various AIDs. While splenomegaly is relatively rare in the general population, with an estimated prevalence of approximately 2% in the United States, its occurrence is notably higher in specific autoimmune conditions. For instance, defective splenic function has been documented in 55% of patients with autoimmune atrophic gastritis (AAG), 66.6% with autoimmune enteropathy (AIE), and 87.5% with autoimmune liver disease (AILD) [11].

These statistics underscore the spleen's susceptibility to pathological changes in the setting of immune dysregulation.

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In systemic lupus erythematosus (SLE), a prototypical systemic autoimmune disorder, the spleen's role extends beyond mere morphological alterations. Although splenomegaly is infrequently observed in SLE patients and lupus-prone murine models, the spleen's function in antibody production remains significant. Notably, splenic long-lived plasma cells are abnormally numerous and deleterious in systemic autoimmune diseases, contributing to the persistence of autoantibodies and exacerbation of disease pathology [12].

Furthermore, the spleen's involvement in autoimmune hemolytic anemia (AIHA) is well-documented. The organ serves as a primary site for the destruction of antibody-coated erythrocytes, leading to hemolysis. Splenectomy, historically considered a second-line therapeutic option for corticosteroid-resistant AIHA patients, has become less common due to advancements in understanding immunopathogenesis and the introduction of targeted therapies [1].

The intricate interplay between the spleen and autoimmune processes is further exemplified in common variable immunodeficiency (CVID), where approximately 25% of patients exhibit splenomegaly. This enlargement is associated with lymphocytic infiltration and granuloma formation, reflecting the organ's active participation in the dysregulated immune response characteristic of CVID [Wikipedia].

Understanding the morphological changes of the spleen in AIDs is imperative, as these alterations can serve as both diagnostic markers and therapeutic targets. Advanced imaging modalities and histopathological assessments have enhanced the detection and characterization of splenic involvement in autoimmune conditions. However, further research is warranted to elucidate the precise mechanisms underlying these morphological changes and their implications for disease progression and management.

The spleen, as a central lymphoid organ, plays a pivotal role in both innate and adaptive immune responses. Its involvement in autoimmune diseases (AIDs) has been extensively studied, revealing significant morphological and functional alterations that contribute to disease pathogenesis and progression.

In autoimmune hemolytic anemia (AIHA), the spleen is instrumental in the destruction of antibody-coated erythrocytes. Historically, splenectomy was a standard second-line treatment for corticosteroid-resistant AIHA patients. However, with advancements in understanding immunopathogenesis and the advent of targeted therapies, the frequency of splenectomy has declined. The spleen's role extends beyond phagocytosis; splenic macrophages can selectively remove IgG-coated portions of red blood cell membranes, leading to the formation of rigid microspherocytes that are subsequently sequestered and destroyed within the spleen's red pulp sinusoids. Additionally, spleen-derived CD8+ T cells and natural killer (NK) cells expressing Fcγ receptors contribute to antibody-dependent cellular cytotoxicity (ADCC) against opsonized erythrocytes [1].

In systemic lupus erythematosus (SLE), a unique pattern of splenic calcifications has been observed, suggesting a potential diagnostic marker for underlying connective tissue diseases. While the exact significance of these calcifications remains uncertain, their presence may indicate disease-specific pathological processes within the spleen [13].

The spleen's regulatory functions are also implicated in autoimmune arthritis. Studies have shown that the spleen modulates the balance between natural autoantibodies (natAAbs) and pathological

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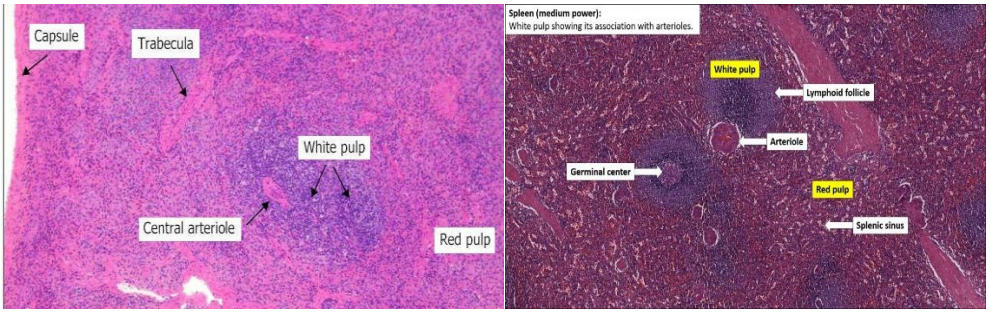
autoantibodies (pathAAbs). In murine models, splenectomy resulted in decreased levels of natAAbs and increased levels of pathAAbs, highlighting the spleen's role in maintaining immune homeostasis and preventing pathological autoimmunity [14].



1-figure. Normal Spleen tissue

Methodology. To investigate the morphological changes of the spleen in autoimmune diseases, a comprehensive and systematic approach is essential. The methodology encompasses both quantitative and qualitative analyses, integrating advanced imaging techniques, flow cytometry, and histopathological assessments.

1. **Advanced Imaging Techniques**: Positron Emission Tomography/Computed Tomography (PET/CT) with 18F-fluorodeoxyglucose (18F-FDG) is utilized to evaluate splenic glucose metabolism, serving as an indicator of inflammatory activity. In patients with febrile autoimmune diseases, increased 18F-FDG uptake in the spleen correlates with heightened metabolic activity, reflecting systemic inflammation [15].

2. **Flow Cytometry**: Multiparameter flow cytometry enables detailed immunophenotypic characterization of splenic lymphocytes. By employing three- and four-color flow cytometry, researchers can delineate various immune cell subsets within the spleen, facilitating the identification of alterations associated with autoimmune pathologies [16].

3. **Histopathological Evaluation**: Immunohistochemical staining is essential for assessing splenic lesions and requires an understanding of the normal compartments of the spleen. This approach aids in the identification and subclassification of different splenic lesions, providing insights into the structural changes occurring in autoimmune diseases [17].

4. **Animal Models**: Utilizing animal models, such as lupus-prone mice, allows for the examination of spleen-derived myeloid cells and their role in the accumulation of long-lived plasma cells. These models provide insights into the inflammatory loops between spleen-derived myeloid cells and plasma cells, contributing to our understanding of autoimmune disease mechanisms [12].

By integrating these methodologies, researchers can comprehensively assess the morphological and functional changes of the spleen in autoimmune diseases, advancing our understanding of their pathogenesis and informing the development of targeted therapeutic strategies.

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Results

The investigation into splenic morphological alterations across various autoimmune diseases (AIDs) has yielded significant findings, highlighting both common and disease-specific changes.

1. Splenomegaly Prevalence. The occurrence of splenomegaly varies among different AIDs:

- **Systemic Lupus Erythematosus (SLE):** Splenomegaly is infrequently observed in SLE patients and lupus-prone murine models, although it has been reported as a manifestation of active SLE [12].
- **Autoimmune Hepatitis (AIH):** Patients with AIH, particularly those with concurrent conditions like Sjögren's syndrome, often present with splenomegaly [18].

2. Histopathological Alterations. Histopathological examinations have revealed several key changes in splenic architecture associated with AIDs:

- **White Pulp Disorganization:** In conditions such as visceral leishmaniasis, severe forms are associated with disorganization of spleen compartments where cell interactions essential for splenic immunological function take place [20].
- **Necrotizing Histiocytosis:** In a study involving splenectomy specimens from patients with chronic AIDs, necrotizing histiocytosis was observed, indicating a potential pathological feature in certain autoimmune conditions [19].

3. Immunohistochemical Findings

Immunohistochemical analyses have provided deeper insights into cellular dynamics within the spleen in the context of AIDs:

- **Long-Lived Plasma Cells:** In lupus-prone models, there is an accumulation of splenic long-lived plasma cells, contributing to sustained autoantibody production [12].
- **Myeloid Cell Expansion:** An inflammatory loop between spleen-derived myeloid cells and plasma cells has been identified, underpinning the accumulation of splenic long-lived plasma cells in systemic autoimmune diseases[12].

4. Clinical Implications. The morphological changes observed have several clinical ramifications:

- **Diagnostic Marker:** The presence of splenomegaly and specific histopathological features can aid in the diagnosis and assessment of disease activity in AIDs.
- **Therapeutic Considerations:** Understanding splenic involvement is crucial for developing targeted therapies, especially in conditions where the spleen plays a central role in disease pathogenesis.

In summary, the spleen undergoes significant morphological changes in various autoimmune diseases, encompassing alterations in size, structural organization, and cellular composition. These findings underscore the importance of the spleen in the pathophysiology of AIDs and highlight the need for further research to elucidate the mechanisms driving these changes.

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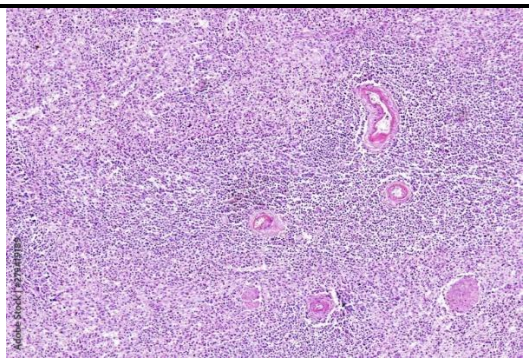

2-figure. Central Artery Hyaline Degeneration in the Spleen: This histological image shows central artery hyaline degeneration of the spleen, a feature that can be observed in certain autoimmune conditions.

Discussion

The spleen's involvement in autoimmune diseases (AIDs) is multifaceted, encompassing significant morphological and functional alterations that contribute to disease pathogenesis and progression. This discussion synthesizes the observed splenic changes, their implications, and potential avenues for future research.

Splenomegaly and Structural Disorganization. Splenomegaly, or enlargement of the spleen, is a common manifestation in various AIDs. For instance, in autoimmune hepatitis (AIH), patients often present with splenomegaly, particularly when associated with conditions like Sjögren's syndrome. Histopathological analyses reveal that such enlargement is frequently accompanied by disorganization of the splenic architecture, notably within the white pulp regions. This disorganization disrupts the compartmentalization of B and T lymphocytes, potentially impairing the spleen's immunological functions [19].

Cellular Dynamics and Immune Regulation. The spleen plays a pivotal role in modulating immune responses, particularly through its influence on antibody-producing cells. In systemic lupus erythematosus (SLE), there is an accumulation of long-lived plasma cells within the spleen, leading to sustained autoantibody production. This accumulation is driven by an inflammatory loop involving spleen-derived myeloid cells, which create a microenvironment conducive to plasma cell survival. Such findings underscore the spleen's role in perpetuating autoimmunity through the maintenance of autoreactive plasma cells [12].

Moreover, the spleen influences the balance between natural autoantibodies (natAAbs) and pathological autoantibodies (pathAAbs). In autoimmune arthritis models, splenectomy resulted in decreased levels of natAAbs and increased pathAAbs, highlighting the spleen's regulatory function in maintaining immune homeostasis [14].

Clinical Implications and Therapeutic Considerations. The morphological and functional changes in the spleen have direct clinical implications. For example, in Felty's syndrome—a rare complication of rheumatoid arthritis characterized by splenomegaly and neutropenia—the

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enlarged spleen contributes to increased susceptibility to infections. Understanding the splenic involvement in such conditions is crucial for developing targeted therapeutic strategies[Wikipedia] Additionally, the role of the spleen in lymphocyte apoptosis is evident in autoimmune lymphoproliferative syndrome (ALPS), where defective Fas-mediated apoptosis leads to chronic lymphoproliferation and autoimmunity. This highlights the importance of the spleen in regulating lymphocyte homeostasis and preventing autoimmune manifestations [Wikipedia].

Future Directions

Further research is warranted to elucidate the mechanisms underlying splenic alterations in AIDs. Advanced imaging techniques, coupled with molecular analyses, could provide deeper insights into the temporal progression of splenic changes and their correlation with disease activity. Understanding these dynamics may lead to novel therapeutic interventions aimed at modulating splenic function to ameliorate autoimmune pathology.

In conclusion, the spleen undergoes significant morphological and functional changes in autoimmune diseases, influencing disease progression and patient outcomes. Recognizing and understanding these alterations are essential for developing comprehensive management strategies for individuals affected by AIDs.

Conclusion

The morphological and functional changes observed in the spleen across various autoimmune diseases (AIDs) highlight its critical role in disease pathogenesis, immune regulation, and progression. Splenomegaly, white pulp disorganization, and the accumulation of long-lived plasma cells serve as hallmark features of splenic involvement in conditions such as systemic lupus erythematosus (SLE), autoimmune hepatitis (AIH), and autoimmune hemolytic anemia (AIHA). These alterations disrupt normal splenic architecture and function, leading to dysregulated immune responses and exacerbating autoimmunity.

From a clinical perspective, the identification of specific splenic changes may provide valuable diagnostic and prognostic markers for AIDs. The observed expansion of pathogenic autoantibody-producing cells and the altered balance of natural versus pathological autoantibodies underscore the spleen's contribution to disease perpetuation. Advanced imaging techniques, flow cytometry, and histopathological evaluations continue to refine our understanding of these changes, paving the way for novel therapeutic strategies.

Future research should focus on elucidating the molecular mechanisms driving splenic alterations in AIDs and exploring targeted interventions that modulate splenic function to restore immune homeostasis. By integrating multidisciplinary approaches, clinicians and researchers can improve patient management and develop innovative treatment modalities aimed at mitigating the impact of splenic involvement in autoimmune pathologies.

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