

## MORPHOLOGICAL CHANGES OF THE SPLEEN DURING THE USE OF IMMUNOSUPPRESSIVE DRUGS

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**Abstract:** Immunosuppressive drugs are widely used in modern clinical practice for organ and tissue transplantation, autoimmune diseases, oncohematological disorders, and severe inflammatory conditions. Their primary effect is the suppression of various components of the immune response, which inevitably leads to structural and functional alterations in immune organs. The spleen, as the largest peripheral lymphoid organ, is particularly sensitive to immunosuppression. This review presents a comprehensive analysis of macroscopic, microscopic, and ultrastructural changes of the spleen associated with the use of different classes of immunosuppressive agents, as well as the underlying pathogenetic mechanisms and their clinical significance.

**Key words:** spleen, immunosuppressive drugs, immunosuppression, white pulp, red pulp, lymphoid atrophy, apoptosis.

### Introduction

The spleen is a major peripheral organ of the immune system and plays a crucial role in immune surveillance of blood-borne antigens, humoral and cellular immune responses, phagocytosis of senescent blood cells, blood reservoir function, and hematopoiesis during embryonic life. Morphologically, the spleen consists of white pulp and red pulp, each responsible for specific immunological and hematological functions.

White pulp contains periarteriolar lymphoid sheaths (PALS) rich in T lymphocytes, lymphoid follicles representing B-cell zones with germinal centers, and the marginal zone, which is essential for antigen presentation and initiation of immune responses. Red pulp is composed of venous sinusoids and splenic cords (cords of Billroth) that are responsible for blood filtration and macrophage-mediated phagocytosis.

Immunosuppressive therapy interferes with lymphocyte proliferation, differentiation, and activation, leading to marked morphological alterations in the spleen. Understanding these changes is important for both pathological diagnostics and clinical assessment of the adverse effects of long-term immunosuppression.

### Classification and Mechanisms of Action of Immunosuppressive Drugs

Immunosuppressive agents are classified into several major groups based on their mechanisms of action:

#### 1. Glucocorticoids (prednisolone, dexamethasone):

- inhibit transcription of pro-inflammatory cytokines;
- induce apoptosis of T and B lymphocytes;
- suppress migration and activation of immune cells.

#### 2. Cytotoxic (antiproliferative) agents (azathioprine, cyclophosphamide, methotrexate):

- inhibit DNA and RNA synthesis;
- suppress proliferation of rapidly dividing cells, including lymphocytes.

#### 3. Calcineurin inhibitors (cyclosporine, tacrolimus):



- block T-cell activation;
- inhibit interleukin-2 production.

**4.mTOR inhibitors** (sirolimus, everolimus):

interfere with cell cycle progression of lymphocytes;  
prevent clonal expansion of immune cells.

**5.Biological agents and monoclonal antibodies:**

- selectively target specific immune cell populations or cytokines.

Differences in pharmacological mechanisms result in both common and drug-specific morphological changes in the spleen.

**Macroscopic Changes of the Spleen**

Long-term or intensive immunosuppressive therapy is commonly associated with splenic atrophy. The main macroscopic features include:

- reduction in spleen weight and size;
- thinning and flattening of the splenic capsule;
- soft or, in cases of fibrosis, firm consistency;
- pale gray or grayish-red appearance on cut surface;
- poor visualization or complete loss of the follicular pattern.

In certain clinical conditions, especially when immunosuppression is accompanied by infectious complications or portal hypertension, moderate splenomegaly with signs of congestive hyperemia may be observed.

**Microscopic Changes of the Spleen**

**Changes in the White Pulp**

The white pulp is the most vulnerable component of the spleen during immunosuppressive therapy. Typical histological findings include:

- marked atrophy of lymphoid follicles;
- significant reduction in T- and B-lymphocyte populations;
- disappearance or severe reduction of germinal centers;
- thinning, fragmentation, or complete loss of periarteriolar lymphoid sheaths (PALS);
- depletion of the marginal zone.

Cytotoxic agents and glucocorticoids frequently induce extensive lymphocyte apoptosis, characterized by nuclear pyknosis, karyorrhexis, and formation of apoptotic bodies that are subsequently phagocytosed by macrophages.

**Changes in the Red Pulp**

Alterations in the red pulp are usually less pronounced but remain clinically relevant:

- dilation of venous sinusoids;
- decreased number and functional activity of macrophages;
- disruption of the normal architecture of the splenic cords;
- focal degenerative changes in reticuloendothelial cells.

Prolonged immunosuppression may lead to stromal remodeling and interstitial or perivascular fibrosis, further impairing splenic filtration function.

**Ultrastructural Changes**



Electron microscopic examination reveals profound subcellular alterations, including:

- mitochondrial swelling and degeneration in lymphocytes;
- reduction of rough endoplasmic reticulum;
- chromatin condensation along the nuclear membrane;
- loss of intercellular contacts and immune synapses.

These ultrastructural changes reflect severe suppression of metabolic and functional activity of immune cells.

### **Pathogenesis of Morphological Alterations**

The development of splenic morphological changes during immunosuppression is based on several interrelated mechanisms:

- inhibition of lymphocyte proliferation;
- activation of programmed cell death (apoptosis);
- suppression of cytokine and growth factor synthesis;
- impairment of antigen presentation and cell-to-cell interactions;
- microcirculatory disturbances and tissue hypoxia.

Together, these processes result in structural remodeling of the spleen and a significant decline in its immunological competence.

### **Clinical and Diagnostic Significance**

Morphological alterations of the spleen associated with immunosuppressive therapy are clinically significant and correlate with:

- increased susceptibility to bacterial, viral, and fungal infections;
- reduced efficacy of vaccination;
- elevated risk of secondary lymphoproliferative and malignant disorders;
- impairment of hematological and filtration functions of the spleen.

For pathologists, recognition of these characteristic changes may serve as a morphological indicator of prolonged or excessive immunosuppression.

### **Conclusion**

Immunosuppressive drugs induce characteristic and predictable morphological changes in the spleen, predominantly manifested by atrophy of the white pulp, depletion of lymphoid cell populations, and disruption of normal splenic architecture. The severity and pattern of these changes depend on the type of immunosuppressive agent, dosage, duration of therapy, and individual patient factors. A thorough understanding of these morphological effects is essential for pathological evaluation, clinical risk assessment, and optimization of immunosuppressive treatment strategies.

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