

INFLAMMATION AND IMMUNE-MEDIATED DISEASES IN COMPANION ANIMALS: PATHOLOGICAL MECHANISMS, DIAGNOSTIC APPROACHES AND EMERGING PERSPECTIVES

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ABSTRACT

Inflammation is a crucial defense mechanism against infection, tissue damage, and other harmful stimuli. However, persistent or dysregulated inflammation can lead to tissue damage and immune-mediated disease. Significant inflammatory and immune-mediated disorders in dogs and cats include immune-mediated hemolytic anemia (IMHA), immune-mediated thrombocytopenia, immune-mediated polyarthritis, chronic inflammatory enteropathies, dermatological conditions, renal disease, and inflammatory disorders of the nervous system. These conditions include complex interactions between innate and adaptive immunity, cytokines, genetic susceptibility, environmental factors, and the microbiome. Histopathology is an essential diagnostic method even if immunohistochemistry, molecular diagnostics, and inflammatory biomarkers provide additional information. Emerging technologies like digital pathology, artificial intelligence, spatial biology, and multi-omics may improve future treatment strategies and disease characterization.

KEYWORDS: Artificial intelligence; Canine and feline diseases; Cytokines; Histopathology; Immune-mediated disorders; Inflammation; Multi-omics; Spatial biology; Veterinary pathology.

1. INTRODUCTION

Inflammation is a coordinated biological reaction that includes immune cells, blood vessels, cytokines, chemokines, and other mediators. Acute inflammation is mostly related with neutrophil recruitment, but chronic inflammation typically involves macrophages, lymphocytes, tissue injury, fibrosis, and healing. Immune-mediated illnesses occur when immune responses become overactive or directed to inappropriate targets. Dogs and cats naturally acquire various inflammatory and immune-mediated diseases, making them excellent models for veterinary and comparative immunopathology.

2. Immunological Basis of Inflammation

The initial line of defence is innate immunity, which uses pattern-recognition receptors such as Toll-like and NOD-like receptors. When activated, these cells produce inflammatory mediators including TNF- α , IL-1, IL-6, chemokines, and interferons.

Adaptive immunity is mediated by antigen-specific T and B cells. CD4⁺ T cells can differentiate into Th1, Th2, Th17, and regulatory T-cell subsets, whereas CD8⁺ lymphocytes can kill target cells. B and plasma cells generate antibodies. Abnormal modulation of these reactions can lead to autoantibody production and tissue damage.

3. Major Inflammatory Mediators

Neutrophils play a significant role in acute inflammation by performing phagocytosis, degranulation, producing reactive oxygen species, and forming extracellular traps. Macrophages are involved in inflammation, the elimination of damaged cells, tissue healing, and fibrosis. Lymphocytes and plasma cells are typically found in chronic inflammatory lesions.

Inflammatory mediators include TNF- α , IL-1 β , IL-6, IL-17, interferon- γ , and TGF- β . Chemokines control the recruitment and location of inflammatory cells.

4. Mechanisms of Immune-Mediated Injury

Immune-mediated tissue damage can arise through many hypersensitivity mechanisms.

- Type I reactions involve IgE and are often linked to allergies.
 - Type II: Antibodies cause cell damage, including erythrocytes and platelets.
 - Type III: is characterized by immune-complex deposition and complement activation, which can contribute to renal and vascular disorders.
 - Type IV: T-cell-mediated tissue damage linked to several chronic inflammatory diseases.
- In naturally occurring diseases, multiple mechanisms may be involved.

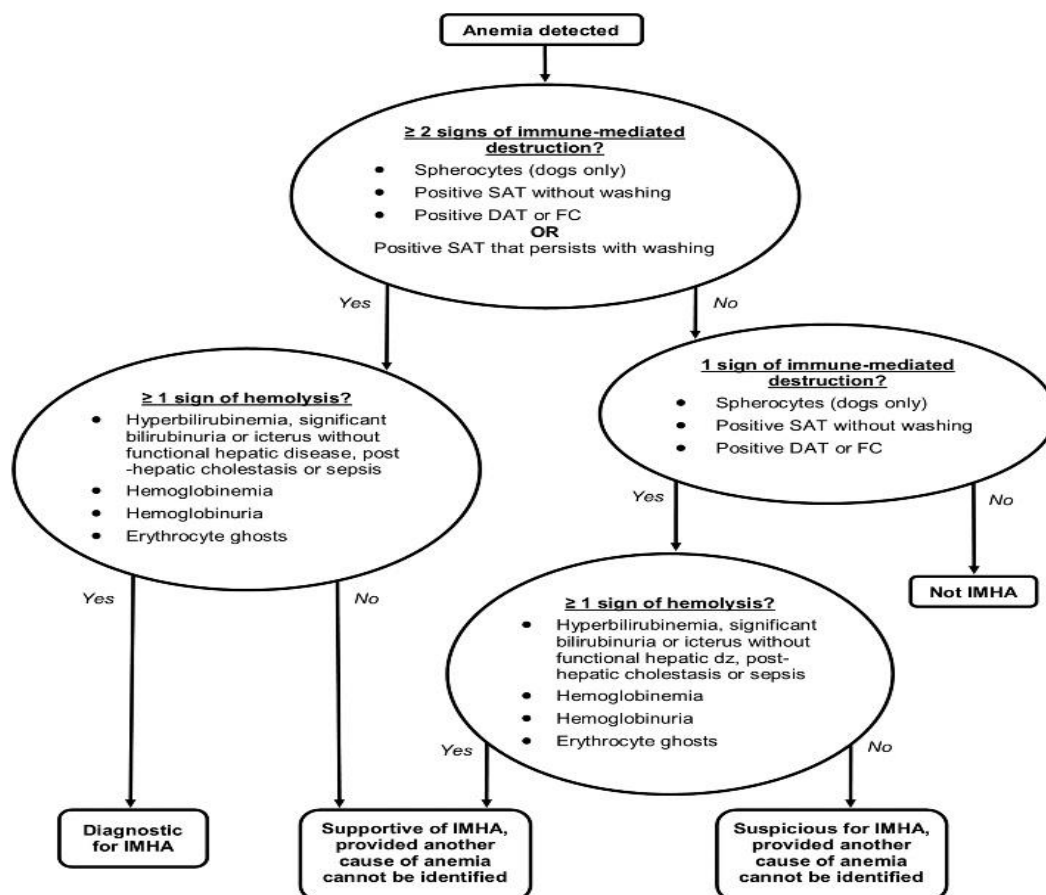
5. Major Immune-Mediated Diseases

5.1 Immune-Mediated Hemolytic Anemia (IMHA)

Immune-mediated hemolytic anemia is characterized by immune-mediated destruction of erythrocytes. Red cells may be removed by macrophages through extravascular hemolysis, while complement activation can contribute to intravascular hemolysis.

Diagnosis of autoimmune hemolytic anemia (AIHA) recommend the direct antiglobulin test (DAT) in patients with hemolysis, but also emphasize that the test is neither specific nor 100% sensitive for AIHA. The diagnostic tests

described below therefore should be interpreted in combination with the results of other diagnostic tests and response to immunosuppression. SAT- saline agglutination test; DAT- direct antiglobulin test; FC-flow cytometry



5.2 Immune-Mediated Thrombocytopenia

When a blood artery wall is broken, platelets become activated and link together to form a "platelet plug" that stops bleeding. As a result, when platelet levels are significantly reduced or the platelets are unable to function correctly, the patient is at danger of uncontrolled bleeding. When thrombocytopenia becomes severe, various clinical symptoms may emerge. The patient may appear lethargic. Examining the skin or gums may reveal small, pinpoint bleeding areas known as petechiation. Larger bleeding regions known as ecchymoses (bruises) may also occur. Sometimes there are nose bleeds, blood in the urine, or blood in the stool (which is often black and sticky). Prolonged bleeding following a traumatic experience may also indicate a coagulation disorder.

5.3 Immune-Mediated Polyarthritis

Immune-mediated polyarthritis is a significant inflammatory joint condition in dogs. It can be erosive or non-erosive, and it can develop as a primary disease or as a result of systemic conditions. Synovial fluid testing, imaging, clinical symptoms, and the elimination of infectious causes are critical for diagnosis.

6. Immune-Mediated Dermatological Diseases

Canine atopic dermatitis is a complicated inflammatory illness characterized by genetic predisposition, epidermal barrier failure, allergens, immunological dysregulation, and alterations in the cutaneous microbiota. Histological lesions may include epidermal hyperplasia, hyperkeratosis, spongiosis, and mixed inflammatory infiltrates.

Pemphigus syndromes are autoimmune illnesses characterized by antibodies against epidermal adhesion proteins. Acantholysis and intraepidermal vesicle development are typical histological findings. Cutaneous lupus syndromes can cause interface dermatitis, basal-cell degeneration, apoptotic keratinocytes, and inflammatory infiltration.

7. Gastrointestinal and Hepatobiliary Disease

Chronic inflammatory enteropathies result from interactions between intestinal immunology, epithelial barrier function, nutrition, microbiota, and environmental variables. Histopathology may reveal lymphoplasmacytic, eosinophilic, neutrophilic, or mixed inflammation along with epithelial damage and architectural alterations. The intestinal microbiota helps to regulate the immune system, and dysbiosis has been linked to gastrointestinal, allergy, and inflammatory illnesses in dogs and cats. However, it is unclear if dysbiosis causes or contributes to disease. Chronic hepatobiliary illnesses can affect lymphocytes, plasma cells, macrophages, hepatocellular damage, and fibrosis. Standardized examination of liver samples improves diagnostic consistency and disease grading.

8. Immune-Mediated Renal and Neurological Diseases

Immune-complex glomerular illness can compromise the glomerular filtration barrier. Light microscopy, immunofluorescence or immunohistochemistry, electron microscopy, urinalysis, and proteinuria assessment may all be required to make the diagnosis.

Important neurological inflammatory disorders include steroid-responsive meningitis-arteritis and meningoencephalitis of unclear origin. Meningeal and perivascular inflammation, gliosis, necrosis, and tissue damage are among the possible histopathological findings. Before identifying sterile immune-mediated illness, it is important to rule out infectious causes.

9. Role of Histopathology and Immunohistochemistry

Histopathology remains central to veterinary immunopathology. Important features include:

1. Distribution of lesions
2. Predominant inflammatory cell population
3. Degree of tissue injury
4. Necrosis or apoptosis
5. Vascular involvement
6. Fibrosis and tissue remodeling
7. Microorganisms or foreign material
8. Chronicity and tissue architecture

Immunohistochemistry can further characterize inflammatory-cell populations. Common markers include **CD3** for T lymphocytes, **CD20/CD79a** for B lymphocytes, **Iba1/CD204/CD68** for macrophages, and **Ki-67** for cellular proliferation.

10. Biomarkers and Microbiome

Inflammatory biomarkers can help in illness assessment and monitoring. C-reactive protein is commonly utilized in dogs, whereas serum amyloid A is a key inflammatory measure in cats. Interpretation should take into account species, disease kind, disease stage, and concurrent circumstances.

The microbiome is becoming recognized as a key regulator of immunological homeostasis. Microbial composition can affect epithelial integrity, immunological signaling, and inflammatory responses.

11. Genetic and Environmental Factors

Immune-mediated illnesses are regulated by interactions between genetic susceptibility and environmental variables. Breed predisposition, nutrition, infections, drugs, allergies, stress, and changes in the microbiome can all contribute to illness development.

12. Future Perspectives

Future veterinary immunopathology is likely to increasingly use:

- **Digital pathology** for quantitative lesion assessment
- **Artificial intelligence** for histological image analysis
- **Spatial biology** for localization of immune-cell populations
- **Multi-omics** for integrated molecular characterization
- **Targeted immunomodulatory therapies** for more precise treatment

These technologies may improve disease classification, biomarker discovery, and individualized management.

13. Challenges

Many immune-mediated disorders lack a single reliable diagnostic test. Infectious, inflammatory, and neoplastic disorders might have similar pathology characteristics. Species variations, a scarcity of validated biomarkers, and the absence of uniform pathological rating systems remain significant problems.

14. CONCLUSION

Inflammatory and immune-mediated diseases are important disorders of dogs and cats and can affect almost every organ system. Their pathogenesis involves interactions between innate and adaptive immunity, inflammatory mediators, genetics, environmental factors, and the microbiome. Histopathology remains fundamental for diagnosis, while immunohistochemistry, biomarkers, molecular techniques, digital pathology, artificial intelligence, spatial technologies, and multi-omics provide new opportunities for improved disease characterization. Future research should emphasize validated biomarkers, standardized pathological scoring systems, longitudinal studies, and integration of pathological, molecular, and clinical data.

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