Immunosuppression and Infection: Two Peas in a Pred

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Objectives

(1) Review mechanisms of immunosuppression in canine and feline patients.

(2) Identify common presentations for infections associated with immunosuppression.

(3) Discuss an approach for diagnosing atypical infections.

Reference: Tizard *Veterinary Immunology* Chapter 39, 40 and 41

Introduction

Immunosuppression or immunodeficiency is often clinically noted when patients present with recurrent, chronic or atypical infections. Veterinary practitioners need the skills to recognize, diagnose and treat these infections especially as our patients live longer and more patients receive immunosuppressive therapies to treat concurrent disease.

Primary Immunodeficiencies of Dogs

A result of limited genetic diversity in some breeds of dogs has led to the development of numerous inherited canine immunodeficiencies. Only a few have been well-studied and characterized including: Severe Combined immunodeficiencies (SCID) in JRT and Cardigan Welsh Corgis, IgM deficiency of Dobermans, IgA deficiency of GSD and Shar-Peis, IgG (?) deficiency in CKCS (*Pneumocystis* infection).

Secondary Immunodeficiencies of Dogs and Cats

Viral Infections

Viral infections can predispose animals to other infections both by priming tissues for secondary infection and by directly affecting the immune system. Important examples include:

- Canine Distemper Virus
    - Can replicate in several cell types by has a predilection for lymphocytes (CD150 receptor on B and T-Cells).
    - Initial invasion of the tonsils leads to the virus spreading to the spleen, thymus, lymph nodes and mucosal lymphoid tissue. Cellular destruction

can lead to thymic strophy and lymphocyte depletion in the secondary lymphoid tissues.

- Inihibits IL-1 and IL-2 production.
- Documented *Pneumocystis* infection secondary to CDV.

- Feline Leukemia Virus
  - Retrovirus (can integrate into genome for permanent infection). Approximately 70% of cats that exposed become infected.
  - Immunosuppression often leads to cancer in many permanently infected animals.
  - Lymphoid depletion also predispose to infections such as FIP, mycoplasmosis, toxoplasmosis and fungal infections.
- Feline Immunodeficiency Virus
  - Retrovirus (lentivirus) similar to HIV in people.
  - Approximately 10-30% are also co-infected with FIV.
  - This virus infects CD4+ and CD8+ T-cells and B cells
  - Further immunosuppression occurs when IL-2 is suppressed and Th2 (Helper T-cell) response is further suppressed.
  - Virus also progresses to affect macrophage lines as well.

Malnutrition

Severe nutritional deficiencies reduce T cell function and impairs cell-mediated response. Severe starvation has very little effect on B cell function. In recent years, adipose tissue has been identified in playing an important role in innate and adaptive immunity. Adipose tissue of obese animals is rich in classically activated (M1) macrophages which are associated with pro-inflammatory states. Lean adipose tissue in contrast, contains small numbers of alternatively activated (M2) macrophages which suppress inflammation. Malnourished individuals are thought to be more susceptible to bacterial pneumonia. Overnutrition may predispose animals to viral infections which may have to do with cell replication that viruses are dependent on.

Age and Immunity

Aging has been linked to reduced activity of neutrophils (respiratory burst and chemotaxis), macrophage (phagocytosis, respiratory burst, chemotaxis, cytokine production, MHC expression), Dendritic cells (NO production, B cell stimulation, overall numbers), NK cells (cytokine production, response to cytokines, numbers, killing activity) and T cells (proliferation and overall numbers). It is important to note though that in general younger animals may show less resistance then elderly animals.

Extreme Exercise

Well-documented decrease in immunoglobulin production of canine athletes (sled dogs) following races that may remain low for up to 4 months.

Iatrogenic Immunosuppression

Coticosteroids: The most widely used immunosuppressants in companion animal vet medicine. The administration leads to excessive cellular production of IfKB which is an antagonist to the transcription factor NfKB. This transcription factor is critical in the expression of several key inflammatory pathways. It has been well established that therapy predisposes to UTI/ bacteriuria.

Cyclosporine: A calcineurin inhibitor that dampens the Th1 response by blocking IL-2 and IFN-y. Also has indirect suppressive effects on macrophages, B cells, NK cells, neutrophils and eosinophils. There are many case series and case reports associated with infections especially opportunistic invasive fungal infections.

Splenectomy: This is removal of the largest collection of lymphoid tissue from the body. Tick-borne infections such as *Babesia* and *Ehrlichia* may recrudesce following splenectomy.

Common Presentations

In general infections in immunocompromised patients are slow to respond to appropriate therapy and may persist regardless. Cytology and histopathology can be used to guide culture selection or conversation with a clinical microbiologist. Routinely aerobic, anaerobic, fungal and mycobacterial cultures should be considered in atypical presentations.

Urinary Tract Infection

UTI is common with the administration of glucocorticoids, as well as, systemic diseases such as diabetes mellitus and Cushing's disease. It can be difficult to differentiate between bacteriuria. Bacterial culture is recommended in all cases of immunocompromised animals due to need for targeted antimicrobial therapy and potential for atypical bacteria.

Dermatophytosis

Evidence of folliculitis in any immunocompromised animal should be evaluated for dermatophyte (ringworm) infection. This is particularly true for cats. Culture is still considered gold-standard but new PCR tests may be helpful in diagnosis. All dermatophytes should be treated in animals with immunosuppression. *Demodex* and *Staphylococcus* folliculitis should be considered as differential diagnoses.

Wounds

Immunocompromised animals with contaminated wounds should be treated with prophylactic antibiotics (i.e amoxicillin-clavulanate). It is not uncommon to see infections associated with iatrogenic wounds in these patients as well (i.e. e-tubes, surgical sites).

Saprophytic Bacterial Infections

Immunocompromised animals are likely more susceptible to organisms that can be found in the environment. Aerobic and anaerobic culture should be considered in these patients. Examples of bacteria associated with immunosuppression include *Nocardia* spp, *Mycobacterium* spp., and *Burkholderia cepecia.*

Opportunistic Fungal Infections

Aspergillus and *Candida* may be associated with infection in immunosuppressed animals. It is important to note that any fungal agent can cause disease in immunocompromised patients when "in the wrong place at the wrong time." GSD appear to be particularly susceptible to systemic fungal infections (i.e. *Aspergillus*). Fluconazole is considered first line for Candida infection and itraconazole for *Aspergillus* and other molds. Identification is critical for definitive therapy and susceptibility testing is typically performed at reference laboratories.

Therapeutic Approach

Therapy can be difficult in patients with immunosuppression/compromise. Aggressive antimicrobial therapy AND treatment of the underlying cause may be necessary. In general whenever possible bactericidal/fungicidal drugs over "static" ones. Surgical intervention may also be necessary to debulk wounds but healing may be delayed. Finally, therapeutic intervention will often require prolonged therapy and close monitoring.