“PARALELNS AND DIVERGENCE”: VETERINARY DERMATOLOGY AND THE HUMAN COUNTERPART

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I have no actual or potential conflict of interest in relation to this program/presentation.
Dermatology for Animals?

- Common diseases we treat and parallels
  - Atopic Dermatitis and Cutaneous Adverse Food Reactions
  - Immune mediated diseases: Pemphigus Complex, Uveodermatologic Syndrome, Vasculitis
  - Neoplasia: Squamous cell carcinoma, Cutaneous T cell Lymphoma
  - Miscellaneous “fun” stuff
Zoonotic Aspect

- What can our patients give your patients?
  - Methicillin resistant staphylococcus
  - Dermatophyte
  - Sarcoptes
  - Allergen dander contribution😊
Canine Atopic Dermatitis

- The most common dermatologic disease we treat in all species
- Canine atopic dermatitis increasingly common disease
  - Pruritus
  - Secondary pyoderma
  - Secondary Malassezia
  - Otitis
  - Pododermatitis
Clinical Signs
Palmar aspect of carpi
Periocular and Perioral
Canine Atopic Dermatitis

- Comparable counterpart to human AD
- Pruritus, erythema
  - Conjunctivitis, rhinitis not typical
- Pruritus frustrating for pet owners
- Secondary skin infections
  - Secondary pyoderma
    - Resistant Staph Pseudintermedius increasingly common
  - Malassezia dermatitis
- Typically progressively worsens with age
Classic Collarettes
Hypothesis of Canine AD

- Genetic mutations associated with impaired epidermal barrier
  - Filaggrin, ceramides
  - Alterations in microbiome
  - Breed predisposition
- Development of allergen specific IgE
- Th2 mediated response in acute phase
  - IL4, IL6, IL13, IL31
- Th1 shift in more chronic stages
Atopic Dermatitis - Pathophysiology

- **Gene mutations**
  - Downregulation cornified envelope
    - Filaggrin mutations
      - Decreased filaggrin expression
      - Decreased ceramides
      - Loss of function mutation
      - Increased transepidermal water loss
Atopic Dermatitis - Pathophysiology

- Gene mutations
  - Barrier Function Alterations
    - Disorganized lipid lamellae
    - Widened intercellular spaces
    - Release of lamellar bodies

- Altered microbiome
Atopic Dermatitis - Pathophysiology

- Histamine
  - Levels similar or lower in dogs with AD compared to normal counterpart
    - Antihistamines have minimal therapeutic benefit in canine patients

- Leukotrienes
  - No differences noted in AD dogs versus normal dogs
Atopic Dermatitis - Pathophysiology

- Immunologic Abberations
  - Total IgE’s not significantly different between normal and atopic dogs as seen in human medicine
  - Acute lesions
    - CD4+, TH2 lymphocytes, eosinophils, and release of IL4 and IL13
      - Increased survival and maturation of eosinophils
  - Chronic lesions
    - Macrophages, TH1 cytokines IL2, IL12, IFN gamma
Canine AD – Secondary Infections

- Contribute to pruritus
- **Staphylococcus pseudintermedius**
  - High prevalence in AD canine patients
    - Altered barrier function and cornified envelope
    - Altered microbiome
      - Lower microbial diversity in AD
- **Malassezia pachydermatis**
  - Greater IgE response in AD canines versus normal
Human AD

- Extensive human literature on staph and role of superantigens in the pathophysiology

- Immunologic mechanisms by which staph precipitate AD
  - Epithelial presentation to TH2 cells
  - TH2 response and IgE production
  - Treg subversion
  - Expansion and migration of skin homing T cells
  - Modulation of chemokines
  - IgE super-antigen production
Secondary Staphylococcal pyoderma

- Normal dogs do not develop skin infections
- Primary disease must be sought
  - Hypersensitivity disorders most common cause
  - Systemic disease
    - Cushing’s
    - Hypothyroid
- Which came first lesions or pruritus?
  - Itch that rashes or rash that itches?
Canine Staphylococcus

- Staph pseudintermedius predominant canine strain
- S. aureus strains diagnosed in companion animals typically the same strains that cause disease in humans.
  - “Humanosis” of MRSA
- Pet owners and veterinary personnel may carry S. pseudintermedius (considerations in epidemiology)
- Other important Staphylococci
  - S. schleiferi (coag + species and coag – species)
  - S. lugdunensis
MRSA and MRSP

- Owners share their MRSA
- Dogs share their MRSP
- Disease causing ability depends on immune status of whom they are sharing with
- Decontamination procedures of households
  - Pet bedding a source
- Antibiotic resistance can cut both ways
Diagnosis of Canine AD

- History, clinical signs, and exclusion of other pruritic diseases
  - Food allergy
  - Parasite hypersensitivity
  - Dermatophytosis

- Criteria
  - Hanifin and Rajka – adapted Willemse Criteria, modified over the years
    - Onset
    - Glucocorticoid responsiveness
    - Pinnae, paws, and cheilitis
Treatment Options for K9 AD

- **Supportive**
  - Avoidance, bathing, antihistamines, fish oil
- **Glucocorticoid therapy**
- **Cyclosporine therapy**
  - Calcineurin inhibitor thus decrease TH2 cytokines
- **Allergen immunotherapy**
  - Induction of IgG
  - Induction of T regulatory cells, IL10
- **Oclacitinib (Apoquel®)**
  - Janus Kinase Inhibitor
- **Canine Atopic Dermatitis Immunotherapeutic**
  - Anti-IL31 monoclonal antibody therapy
Allergen Immunotherapy for K9 AD

- Intradermal allergen testing gold standard
  - Percutaneous testing in pilot study (felines)
- 75% of patients symptoms improve by 50% or more
- Allergen immunotherapy initiated
  - Subcutaneous q1-2 weeks
  - Non-aqueous sublingual daily
  - Multiple allergens included in extracts
    - Potency of allergen 2,000PNU to 20,000PNU
    - Allergen monotherapy not generally utilized
Allergen Immunotherapy for K9 AD

- **Pollens**
  - Trees, weeds, grasses

- **Dusts and mites**
  - Dust mites - *D. farinae, D. pteronyssus*
  - Storage mites - *Tyrophagus*
  - House dust

- **Danders**
  - Human, cat, cattle, sheep, mouse epithelia

- **Molds**

- **Insect hypersensitivity**
Intradermal allergy testing
Oclacitinib (Apoquel®)

- Janus Kinase Inhibitor
  - Developed by Zoetis for Canine AD
  - Janus Kinases activate intracellular signal transducers and activators of transcription (STAT)
    - Activates biologic response and cytokine production
Ligand - Receptor - JAK - Function

**Receptors sharing γ-chain**
- IL-2, IL-4

**Type 1 IFNR**
- IFN-α/β/κ/ω/ε

**IL-10R family**
- IL-10

**Receptors sharing gp130 subunit**
- IL-6, IL-13, IL-31, G-CSF

**Type II IFNR**
- IFN-γ

**IL-12R family sharing p40 subunit**
- IL-12

**Hormone receptor family**
- GMS/CSF, EPO

**IL-3R family**
- IL-5

**JAK1**
- Tyk2

**JAK3**
- Tyk2

**JAK1**
- JAK2

**Tyk2**

**FUNCTION**

- Growth & maturation of lymphoid cells
- Differentiation & homeostasis of T cells, NK
- B cell class switching
- Inflammation

- Antiviral
- Inflammation
- Anti-tumor

- Naive T cell differentiation
- T cell homeostasis
- Inflammation
- Granulopoiesis

- Antiviral
- Inflammation

- Innate immunity
- Differentiation & proliferation of Th17
- Inflammation

- Erythropoiesis
- Myelopoiesis
- Megakaryocyte & platelet production
- Growth
- Mammary development
Apoquel® Oclacitinib

- Primarily Janus Kinase 1 (JAK1) inhibitor
  - Decrease IL2, IL6, IL13
  - Decrease in “Itch cytokine” IL31
- Mild JAK3 activity
- Minimal JAK2 activity
  - Hematopoiesis
- Effective in 85% of patients with AD
  - Excellent safety profile at prescribed dosage protocol and at this stage of usage


Canine Atopic Dermatitis
Immunotherapeutic

- Based on the model of IL31 = Itch in atopic dogs
- IL31 levels significantly higher in AD dogs compared to normal counterpart
- Caninized monoclonal antibody to bind IL31
- Injection available on conditional licensing
- Provided control of pruritus for up to 4 weeks
- Safety profile unparalleled
Food Allergy

- Type I Immunologic mechanism best studied in humans
- Type I, III, IV implicated in veterinary patients
- Incidence reported 1% to 10% of all allergic skin diseases occurring in veterinary patients
- GI disease
- Dermatologic disease
  - 20% can have concurrent GI symptoms
Food Allergy

- Can mimic atopic dermatitis
- Clinical variability
  - Any age
  - Non-seasonal
- Pruritus most common complaint
  - Some pets only recurrent otitis
  - Ears, rears
  - Poor response to glucocorticoids
Food Allergens

- Allergen immunogenicity depends on stimulation of IgE production and histamine release of mast cells after bridging of the allergen between two IgE molecules on the surface of the mast cell membrane.

- In humans food allergens almost exclusively 10-70kDa molecular weight
  - No such data available in canine patients
  - Hydrolyzed diets variable size hydrolysate
    - 1kDa to 1000kDa
Food Allergens

- Most common allergens
  - Beef, chicken, dairy, soy, wheat

- Diagnosis based on response to strict elimination dietary trial
  - Challenge diet to confirm*

- Blood allergy testing not a sensitive tool for diagnosis
  - High false positive and negative
  - IgE measurement – Type I reaction only
Sarcoptes

- Geographic variations in incidence
  - High prevalence Colorado/Utah
  - Variability in other areas of the country

- Initially mimics atopic dermatitis
  - Initial response to steroids
  - Chronic disease becomes refractory to steroid therapy and fails to respond to cyclosporine
  - Intense pruritus
    - Ear margins, elbows, hocks, ventrum
Sarcoptes

- Transmission via fox, coyotes, dogs
  - Does not require direct contact
  - Survives off host for 4 to 21 days at ideal temps (50-59F)
  - Humans and other animals can be transient carriers

- Mites can be difficult to recover in skin scrapings
Sarcoptes Household

- All in contact animals treated
- Humans/Owners often affected in chronic cases
  - Factors that increase human transient carrier state
    - Dog sleeps with owners
    - Duration of infestation of the dog
    - Immune status of the human owner
    - Immune status of the pet
  - Papular pruritic rash torso, inner aspect of arms
    - Typically do not require treatment
      - Immunocompromised individual may require treatment
Other Parasites

- Cheyletiella
- Demodex
- Lice
- Fleas
- Ticks
- Bird mites
Dermatophytosis

- Highly variable clinical presentation
  - Pruritus and mild seborrhea sicca
  - Marked alopecia and pruritus
  - Acantholysis
  - Nodular to kerion

- Diagnosis via
  - DTM remains most sensitive tool
    - Poor confidence in referral practitioners interpretation of DTM
    - Failure to treat appropriately common
Dermatophytosis
Dermatophytosis
Dermatophytosis
Dermatophytosis
Environmental Concerns

- Arthrospores from infected pets can remain in the environment for 12-24 months
- Environmental cleaning
- Isolation of pet
How not to diagnose dermatophytosis
Immune Mediated Diseases

- Less common than hypersensitivity disorders
- Focus for today
  - Pemphigus Foliaceus
  - Dermatomyositis
- Fun topics for another day
  - Vasculitis
    - Primary versus secondary
  - “Lupoid” diseases
    - Discoid lupus, Lupoid onychodystrophy, mucocutaneous, systemic
  - Sterile panniculitis
  - Erythema multiforme, Sweet’s syndrome, TEN
Pemphigus Complex

- **Pemphigus Foliaceus**
  - Most common disease we treat after hypersensitivity disorders

- **Pemphigus vulgaris**
  - Much less common in animals than in man
Pemphigus Targets

- Pemphigus foliaceus
  - Similar clinically to human counterpart
  - Human autoantibody target desmoglein-1
  - Veterinary autoantibody target desmocollin-1

- Pemphigus vulgaris
  - Autoantibody to desmoglein-3 paralleled
  - Clinical presentation similar
Dermatomyositis

- Cause humans and canines is unknown
  - Familial history variable in humans
  - Common in collies and Shetland sheepdogs
  - Breeding studies in collies support autosomal dominant with variable expressivity

- Clinical similarities
  - Face/periocular, areas of mechanical trauma
  - Myositis typically months after skin lesions and correlates with skin lesion severity
Dermatomyositis
Non-inflammatory alopecia

- Endocrine disease
  - Cushings
  - Atypical Cushings
  - Hypothyroid
  - Alopecia X
  - Seasonal Flank Alopecias

- Owner topical hormone replacement
  - Can affect pet even with barrier precautions
Owner utilizing topical estrogen prescribed as birth control
Infectious Disease

- Atypical bacterial infections
  - Actinomyctes, Nocardia
  - Post-grooming Pseudomonas furunculosis

- Atypical systemic fungal infections
  - Sporotrichosis
  - Coccidiomycosis, Cryptococcosis, Blastomycosis, Histoplasmosis

- Viral disease
  - Herpes, papilloma
Post Grooming Furunculosis

**Veterinary**
- Pseudomonas contaminated shampoo
- Malaise, febrile, painful
- Systemic fluoroquinolone treatment

**Human Parallel**
- "Hot tub folliculitis"
- Lesions develop days after exposure
- Malaise, low grade fever
- +/- systemic treatment
Pseudomonas Folliculitis

Veterinary

Human
Sporotrichosis
Otic Disease

- Chronic otitis externa
- Otitis media
- Otic foreign bodies
- Otic masses
Neoplasia

- Melanoma
  - Human tyrosinase DNA vaccine utilized for treatment of canine melanoma
    - Each dose contains plasmid DNA that expresses the gene coding for human tyrosinase
    - Upon injection, the DNA is taken up by muscle cells which then express the human tyrosinase protein
    - Stimulates an immune response effective against canine melanoma cells which express tyrosinase

- Epitheliotrophic lymphoma

- Solar induced
  - Actinic keratoses
  - Hemangioma/hemangiosarcoma
  - Squamous cell carcinoma
Actinic keratoses
Squamous cell carcinoma
Hemangiomas
Epitheliotrophic lymphoma
Miscellaneous

- Thermal burns
  - Dorsal thermal necrosis
- Topical steroid overuse
- Delusional parasitosis of pet owner
Thermal Burn
Pathophysiology Thermal Burns

- Not well understood
- Multifactorial
  - Hydration and health status
  - Neurosensory input
  - Duration of exposure and direct sunlight
  - Color of the dog
- Human parallel
  - Women post breast reconstruction
Topical steroid overuse

- Atrophy
- Telangectasia
- Milia
- Comedones
- Spay scar atrophy and slight gapping
Delusional Parasitosis

- Clients bring jars, bags, samples of hair, clippings
  - “Matchbox” sign
  - Report seeing bugs, fibers
- Perform complete parasite treatment trial for the household
  - Treat all in contact animals
  - Exclude true possibility of parasite
Thank you! Questions?


Development of a model of IL-31 induced pruritus in beagle dogs


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- Skin biopsies from pruritic and non-pruritic lesions in cases of human and mouse atopic dermatitis (AD)
  - Up-regulation in interleukin-31 mRNA levels implicating a contributory role of this cytokine in the development of pruritus.

- Using recombinant canine IL-31 (cIL-31 or IL-31), we have developed an anti-pruritic screening model in dogs using exogenous IL-31 to induce episodes of pruritus in the presence/absence of test article treatments.
  - IL-31 produced significant pruritus compared to mock protein or saline injections.

- The model was validated by demonstrating that administered prednisolone significantly decreased IL-31 induced pruritus. Additionally, the janus kinase inhibitor, oclacitinib, reduced IL-31 induced pruritus in the dog. This data indicate that IL-31 produces pruritus in the dog and this can be used as a basis for a model to identify antipruritic compounds.