Common immune-mediated skin conditions in veterinary dermatology

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Learning Outcomes

- Understand the pathogenesis of pemphigus foliaceus
- Identify the common presentations of canine and feline pemphigus foliaceus
- Formulate an approach to the diagnosis of pemphigus foliaceus
- Review medical management options for pemphigus foliaceus in cats and dogs
- Identify key clinical signs and breed predispositions for sebaceous adenitis in dogs
- Understand the diagnostic workup for a dog with sebaceous adenitis
- Identify clinical features of both the juvenile and adult-onset of sterile granulomatous dermatitis and lymphadenitis (juvenile cellulitis)
- Review treatment options for sterile granulomatous dermatitis and lymphadenitis (juvenile cellulitis)

Overview

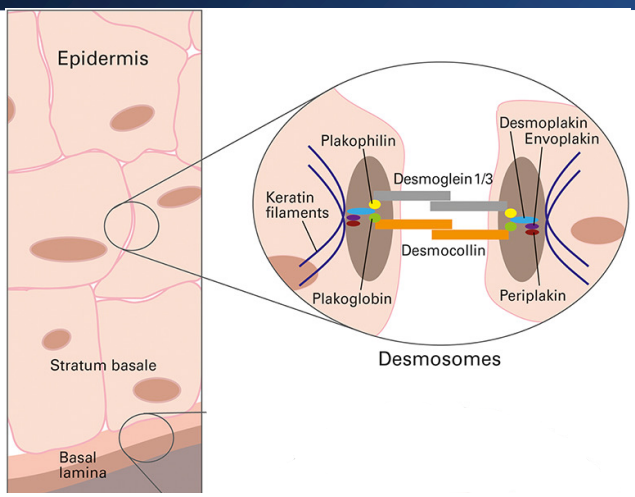
- Pemphigus Foliaceus
  - Normal cell adhesion
  - Pathogenesis
  - Canine pemphigus foliaceus
  - Feline pemphigus foliaceus
  - Diagnosis
  - Treatment
- Granulomatous Sebaceous Adenitis
  - Pathogenesis
  - Canine Sebaceous Adenitis
    - Clinical Features
    - Diagnosis
    - Treatment
  - Feline Sebaceous Adenitis
    - Clinical Features
    - Diagnosis
    - Treatment
- Juvenile Cellulitis
  - Clinical Features
  - Diagnosis
  - Treatment

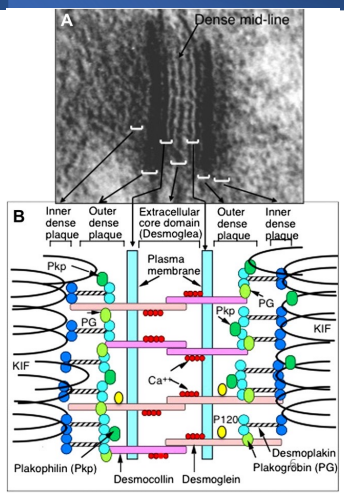
Pemphigus Foliaceus

What are the pemphigus diseases?

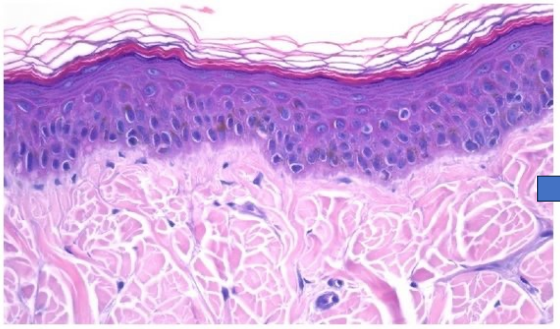
- Autoimmune skin diseases affecting cats, dogs, horses, goats and people
- An IgG-mediated cellular response causing antibody attack against desmosomes and other protein structures within the skin
- Characterized by acantholysis
  - Breakdown of epidermal desmosomal connections between keratinocytes

Normal cell adhesion molecules

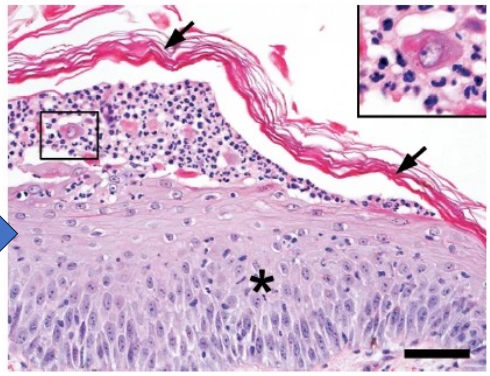




Cell adhesion molecule loss



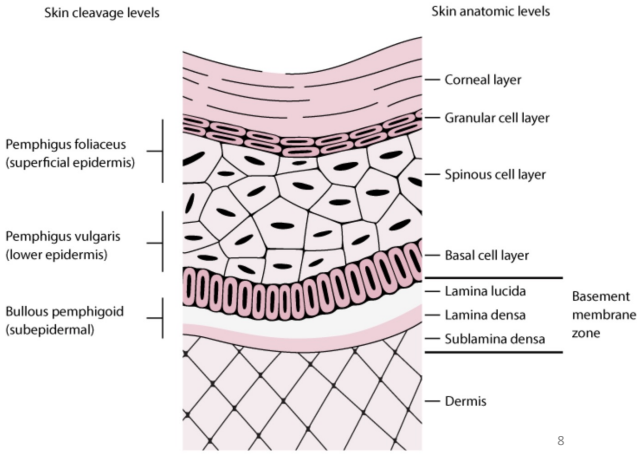
Normal canine skin



Canine skin with pemphigus foliaceus and acantholysis

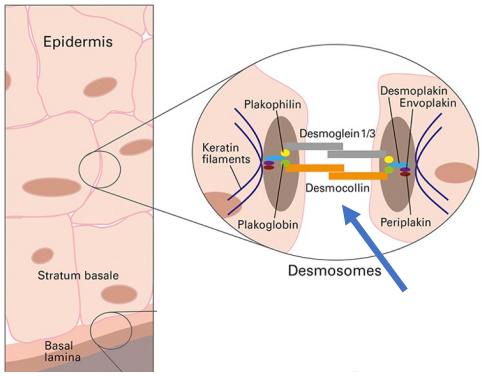
Variations of Diseases with Cell Adhesion Loss

- Each auto-immune target will determine what cell layer is affected
- Different diseases develop as a result with variable severity and distribution on the body



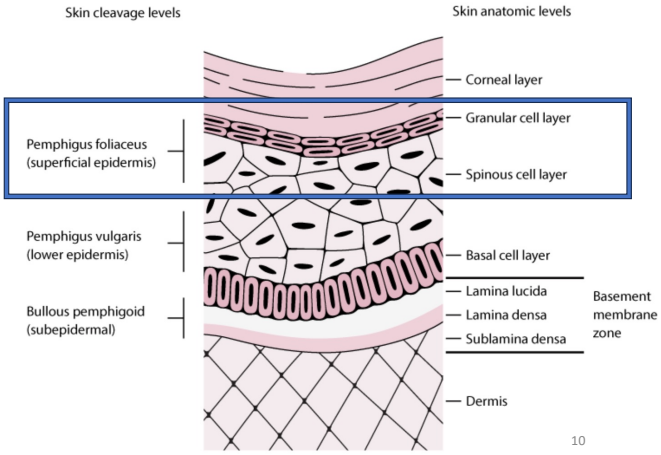
Pathogenesis

- Desmocollin-1 identified as the major autoimmune target in canine pemphigus foliaceus
- Unknown if previous drug exposure plays a roll
- Ultraviolet light exposure likely contributes

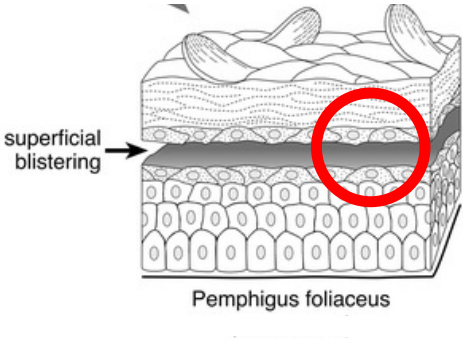


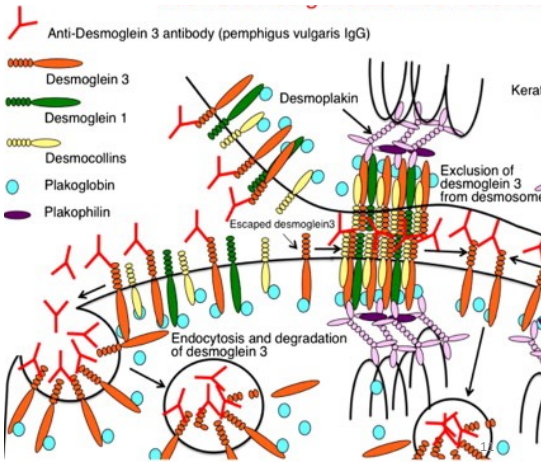
Pathogenesis

- Desmocollin-1 has higher expression in the upper epidermal layers (stratum granulosum)
- Mainly affects the granular layer of the epidermis



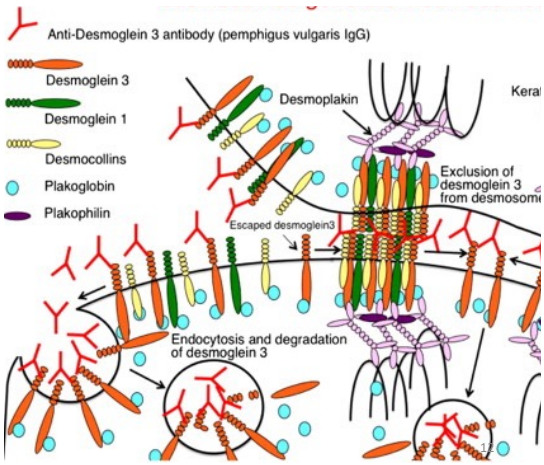
How does IgG cause adhesion loss?





How do immune cells cause adhesion loss?

- Multiple hypotheses:
  1. Anti Dsg-3 antibody steric hinderance interferes with adhesion
  2. Pemphigus IgG induced intracellular signaling may lead to desmosomal dissociation
  3. Intracellular adhesion dependent on cholinergic mechanisms may be affected



Canine Pemphigus Foliaceus

Canine Pemphigus Foliaceus

- Genetic predisposition
- Middle age to older dogs most commonly affected, but any age
- Unknown if breed predilection
  - Akitas and chow chows possibly over-represented

Table 1

Most Common Dog Breeds Diagnosed With Pemphigus Foliaceus

Breed	No. of Dogs
Mixed-breed dog	40
Akita	10
Labrador retriever	9
Cocker spaniel	5
German shepherd dog	3
Chinese shar pei	3
Chow chow	2
Boston terrier	2
Shih tzu	2
Australian cattle dog	2

Distribution

- Often bilaterally symmetrical
- Footpads often affected
  - Fissures, crusts
- Mucosal lesions not typically a feature

Table 2

Locations of Dermatological Lesions in Dogs With Pemphigus Foliaceus

Site	No. of Dogs (%)
Trunk	53 (58%)
Inner pinnae	46 (51%)
Dorsal muzzle	37 (41%)
Foot pads	32 (35%)
Periocular area	26 (29%)
Outer pinnae	23 (25%)
Planum nasale	23 (25%)
Interdigital area	10 (11%)
Lips	9 (10%)
Perianal area	5 (5%)
Mucous membranes	2 (2%)

Clinical Signs

- Large pustules
- Yellow crusts
- Erosion
- Papules
- Variable pruritus
- Alopecia
- Nasal depigmentation (later on in course of disease)

- Systemic signs
  - Depressed
  - Anorexia
  - Febrile

- May be rapid onset (1-2 weeks)

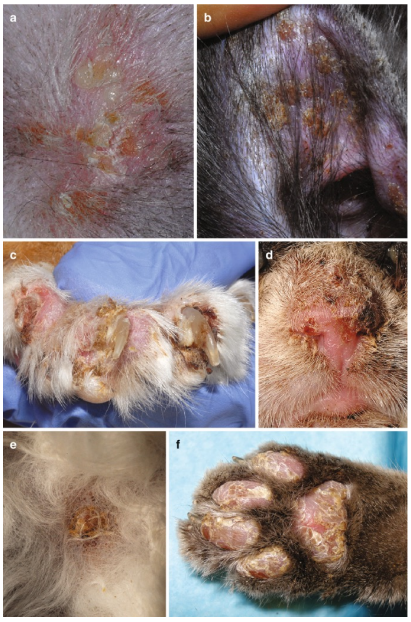
Clinical Signs



Clinical Signs- Dogs



Feline Pemphigus Foliaceus

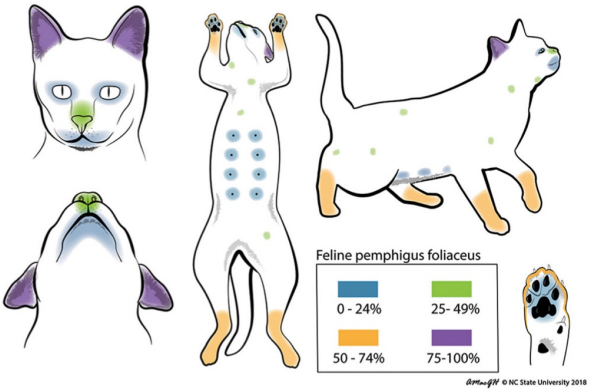


Feline Pemphigus Foliaceus

- The most common autoimmune disease of the skin in cats
- Less common disease than canine pemphigus foliaceus
- No breed, age or sex predispositions
  - Median age 5 years

Distribution

- Focal crusting is the most common feature in many cats
- Head, face and ears affected most
- Can be bilaterally symmetrical
- Involvement of the claw folds may be only clinic sign
  - Often affects claws bilaterally or all the claws
  - Usually purulent discharge



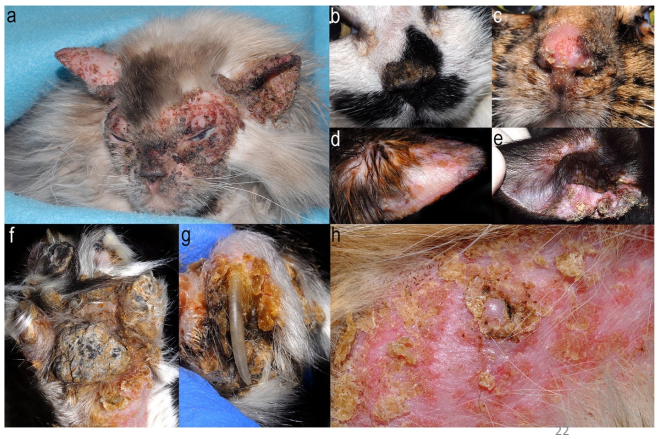
Clinical Signs

Dermatological signs

- Pustules
- Crusts
- Erosions
- Pruritus (majority of cases)
- Purulent discharge from claw beds
- Otitis externa

Systemic signs

- Lethargy
- Fever



Clinical Signs



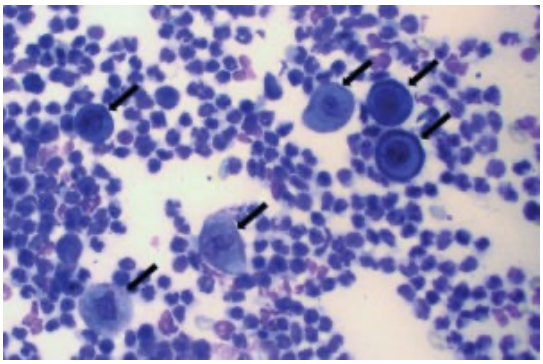
Making a diagnosis of Pemphigus Foliaceus

Making a diagnosis of Pemphigus Foliaceus

- Start with cytology
  - Look for evidence of acantholytic cells
- Rule out ringworm (dermatophytosis)
- Biopsy, if possible
  - Make sure you include the crust or pustule!
  - Can be difficult if no easily accessible biopsy site available

Cytology

- Impression smears recommended
- Look for evidence of acantholytic keratinocytes
  - Large, basophilic staining skin cells
  - Can be single cells or in clusters
  - Can be seen on 10x magnification
- Quantify secondary infections



Acantholytic Keratinocytes

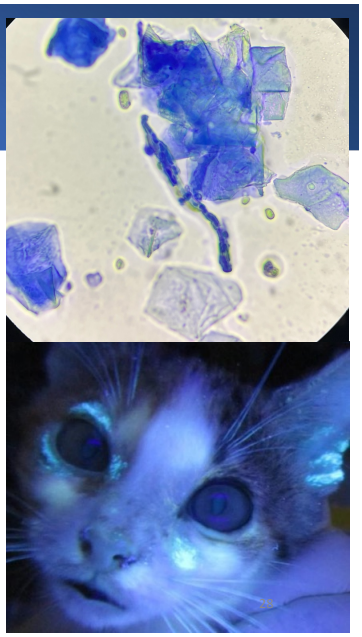
- Three main causes:
  1. Pemphigus
  2. *Trichophyton* (dermatophytosis) infection
  3. Severe *Staphylococcus* infections

Which cat has pemphigus and which has ringworm?

Ruling Out Ringworm

Point of Care Options

- Cytology
  - Tape strip most rewarding
- Wood's lamp does not rule out *Trichophyton* infections
  - Does not fluoresce
  - Fluorescence with *Microsporum canis*



Ruling Out Ringworm

Laboratory Tests

- Ringworm PCR is fast
  - Turn around time usually within 5 days
  - This is my diagnostic of choice over culture

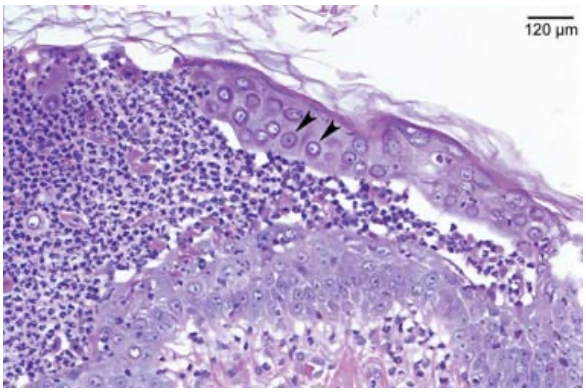
- Ringworm culture
  - Personally, I only do if I am more suspicious of ringworm
  - Can take 3 weeks to come back
    - Delays treatment of either disease
  - Send to a reference laboratory

Biopsy

- Always biopsy if this option is available
- 6mm punch biopsy recommended
- Need to include the crusts or pustules!

Histopathology

- Characteristic description
  - Subcorneal pustules with acantholytic cells (arrow heads) admixed with neutrophils and eosinophils
  - Hair follicles may be involved
- Recommend adding on silver (fungal) stains such as GMS/PAS stain to rule out dermatophytosis



Treatment

- Treat concurrent secondary infections
  - Bacterial culture, if present
  - I tend to avoid beta lactam and sulfa antibiotics, if possible.
- Treat until clinical remission
  - Ideally recheck cytology
  - Both antifungals and antibiotics, if indicated
    - Typically a prolonged course

Treatment- Dogs

- Glucocorticoids
  - First line monotherapy
  - Immunosuppressive dose:
    - Prednisone 2mg/kg PO SID or equivalent then taper
- Azathioprine
  - Good second line in severe cases
  - Bone marrow suppression and hepatotoxicity
- Atopica (modified cyclosporine)
  - Can be useful as adjunct therapy
  - Not sufficient for monotherapy
- Doxycycline/tetracycline and niacinamide
  - Not preferable as lower efficacy

Treatment- Dogs

Table 4

Drugs That Achieved Final Control of Pemphigus Foliaceus in 80 Dogs

Drugs	No. of Dogs
Prednisolone (0.1 to 4 mg/kg/d PO*) and azathioprine (0.4 to 3 mg/kg/d PO)	24
Dexamethasone (0.09 to 0.1 mg/kg/d PO) and azathioprine (0.8 to 2 mg/kg/d PO)	2
Methylprednisolone (0.1 to 0.4 mg/kg/d PO) and azathioprine (1 to 2.2 mg/kg/d PO)	4
Triamcinolone (0.08 mg/kg/d PO) and azathioprine (1 mg/kg/d PO)	1
Prednisolone (0.1 to 4 mg/kg/d PO)	22
Methylprednisolone (0.1 mg/kg/d PO)	1
Triamcinolone (0.07 mg/kg/d PO)	1
Azathioprine (0.4 to 3 mg/kg/d PO)	9
Tetracycline† or doxycycline (3 to 18 mg/kg/d PO) and niacinamide†	8
Prednisolone (0.3 to 1.25 mg/kg/d PO) and aurothioglucose (0.07 to 0.15 mg/kg)‡	2
Essential fatty acids§ PO	2
Prednisolone (1 mg/kg/d) and cyclosporine (3 mg/kg/d PO)	1
Aurothioglucose‡ (0.15 mg/kg)	1
Methylprednisolone (0.2 mg/kg/d PO), tetracycline, and niacinamide† PO	1
Tacrolimus (0.1% topically)	1

* PO=per os
† Tetracycline and niacinamide were each given at 250 mg PO q 8 h in dogs <15 kg and at 500 mg PO q 8 h in dogs >15 kg

Treatment

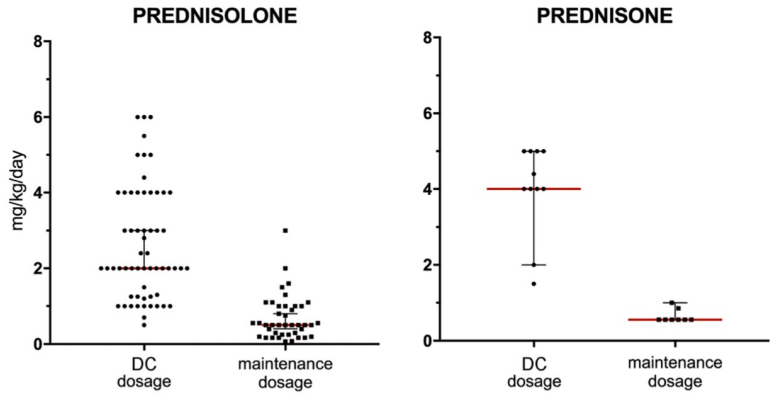


Fig. 5 The maintenance dosages of oral glucocorticoids were significantly lower than those needed to induce disease control. A dot plot graph depicting daily dosages of individual cases; the horizontal red line indicates the median dosage and the vertical lines indicate 95% confidence interval (*p* values < 0.0001 for both prednisolone and prednisone dosages; Mann-Whitney test)

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Treatment- Cats

- Glucocorticoids
  - First line monotherapy
  - Immunosuppressive dose:
    - Prednisolone: Minimum 2mg/kg PO SID or equivalent then taper
  - Use tablet forms rather than compounded/transdermal products
    - May lead to treatment failure
- Atopica (modified cyclosporine)
  - Can be useful as adjunct therapy
  - Not sufficient for monotherapy
- Chlorambucil
  - Not as monotherapy; typically in combination with glucocorticoids

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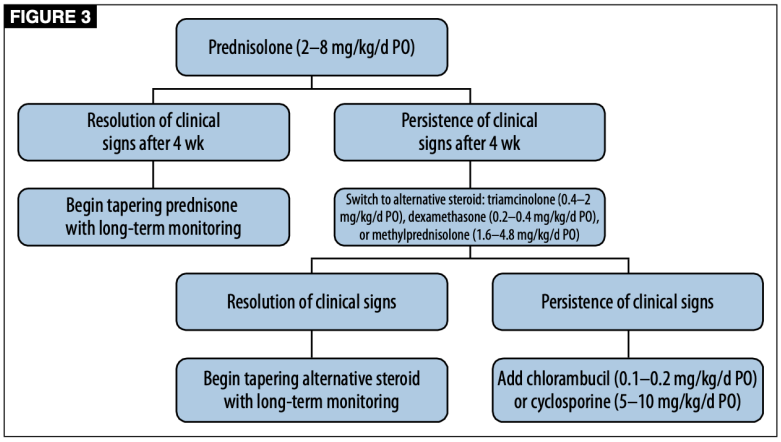
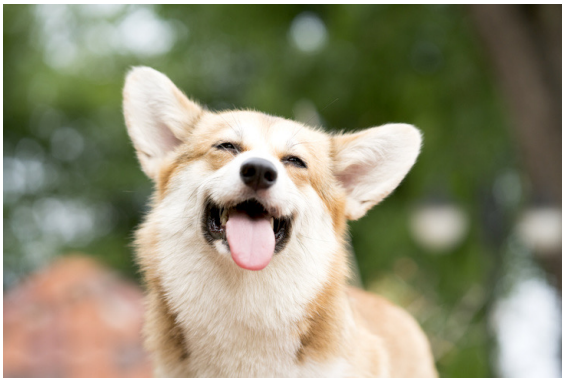
Treatment- Cats



Therapeutic options for pemphigus foliaceus.[2,6,8]

Prognosis

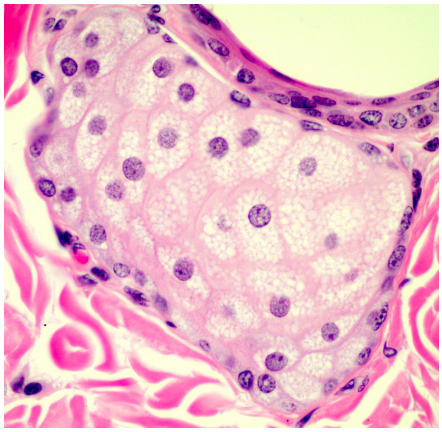
- Dogs
  - Satisfactory response in 93% of cases
  - ~50% complete remission
  - Immunosuppression required indefinitely
- Cats
  - Mean time to disease control 28 days
  - 40/44 of cats achieved control in one study



Granulomatous Sebaceous Adenitis

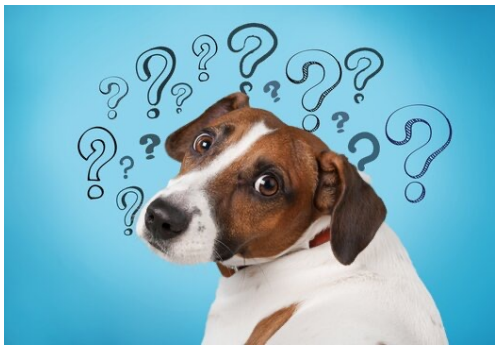
Granulomatous Sebaceous Adenitis

- Characterized by destruction and loss of sebaceous glands in the dermis
- Can be secondary to variety of diseases
  - Feline acne
  - Demodicosis
  - Juvenile cellulitis
  - Leishmaniosis
  - Sterile granuloma disorders
  - Uveodermatologic syndrome



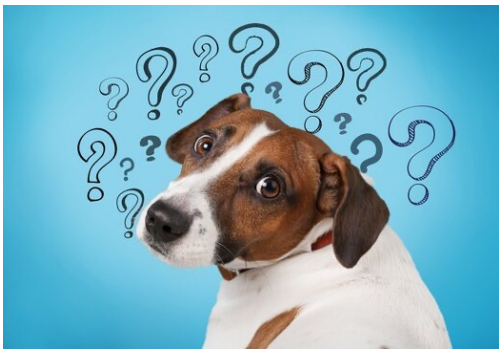
Granulomatous Sebaceous Adenitis

- Possibly more than one etiology
  - Multiple presentations of the disease
- Strong breed predispositions suggests a genetic basis
  - Autosomal recessive mode of inheritance in standard poodles and akitas
- Believed due to cell mediated immunologic reaction directed at sebaceous glands
- Mainly thought to be mediated by T cells and dendritic cells, but not confirmed as could be secondary inflammation
- Possible faulty lipid metabolism or storage



Granulomatous Sebaceous Adenitis

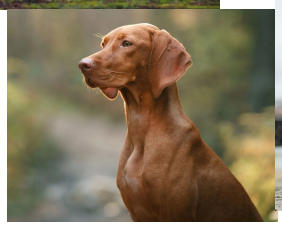
- Possible keratinization abnormality with subsequent obstruction of sebaceous ducts
- Early changes may have peri-isthmus fibrosis, with lymphocytes and macrophages around sebaceous duct
- Ductal disease results in a blockage of sebaceous gland



Granulomatous Sebaceous Adenitis

- Strong breed predispositions
  - Standard Poodles
  - Vizslas
  - Akitas
  - German Shepherd
  - Samoyeds
  - Springer Spaniels
  - Lhasa Apso
  - Havanese
- Possible increased frequency
  - Beagles
  - Chow chows
  - Daxys
  - Min Pinschers
  - Retrievers





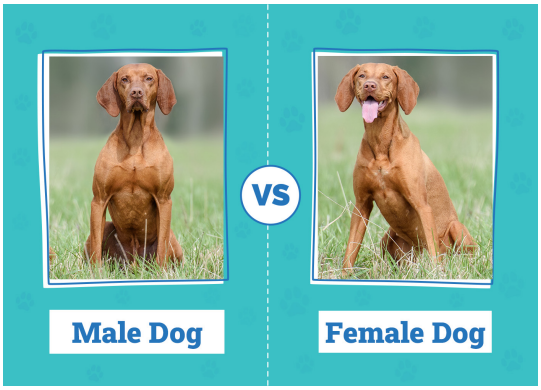

Granulomatous Sebaceous Adenitis

Table 1: Breed distribution in the study of 104 dogs with sebaceous adenitis

Breeds	No. of Dogs	Breeds, continued	No. of Dogs	Breeds, continued	No. of Dogs
springer spaniel	25	standard schnauzer	2	Newfoundland	1
standard poodle	21	eurasier	2	Old English sheepdog	1
akita	10	St Bernhard	2	Chinese crested dog	1
lhasa apso	6	havanese	1	rottweiler	1
chow-chow	3	boxer	1	samoyed	1
flatcoated retriever	3	briard	1	vizla	1
Bernese mountain dog	2	collie	1	Welsh springer spaniel	1
hovawart	2	coton de tuléar	1	mixed breeds	11
Labrador retriever	2	golden retriever	1	Total	104

Granulomatous Sebaceous Adenitis

- Males over-represented
  - 62% in poodles
  - 67% Havanese
  - 68% in springer spaniels
- Affects young to middle age dogs
- Many different forms:
  - Severe and progressive
  - Wax and wane
  - Localized and self limiting



Granulomatous Sebaceous Adenitis

- Can vary based on breed
- Can be separated into long-coated and short-coated presentations
- Lesions tend to start dorsally on cervical or hear region
- Pinnae usually affected
- Develops into generalize appearance over time
- Legs and paws tend to be spared
- Poodles tend to generalize more rapidly than other breeds
- Variable pruritus

Granulomatous Sebaceous Adenitis

- **Long-coated** (poodle, GSD, akita, samoyed)
  - Early
    - Lighter/darker hair colour
    - Straightening of curved hairs
  - Progression
    - Follicular casting
    - Dull, brittle hair
    - Alopecia
    - Scale
    - Matted hair
  - Secondary bacterial folliculitis/furunculosis
    - Akitas more than others
  - Otitis externa
    - Dry ear canals on sampling
    - More occurrence in border collies, springer spaniels

Granulomatous Sebaceous Adenitis

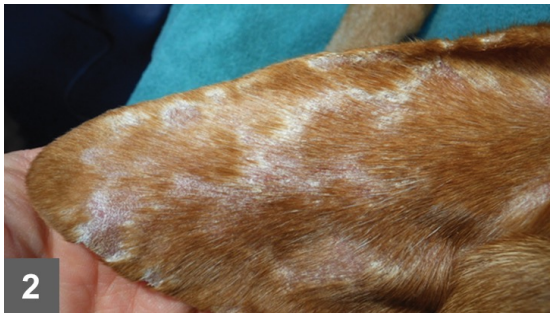
- **Long-coated** (poodle, GSD, akita, samoyed)

Granulomatous Sebaceous Adenitis

- **Short Coated** (Daxy, Viszla, Min Pin, beagle)
  - Annular areas of scale and alopecia which enlarge peripherally
    - Become polycyclic (multiple rings)
  - Moth eaten appearance
    - Not associated with folliculitis
  - Scale
  - Follicular casting variable
  - Pyoderma rare
  - Pinnal ulceration (rare- Vizslas)

Granulomatous Sebaceous Adenitis

- **Short Coated** (Daxy, Viszla, Min Pin, beagle)

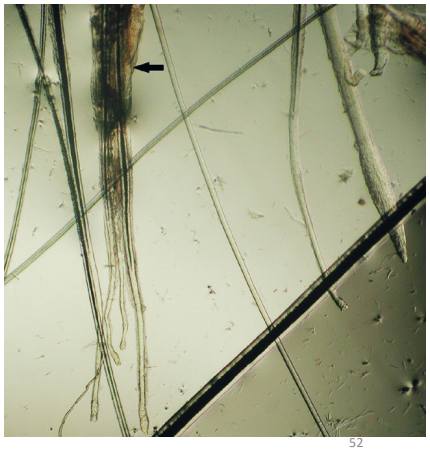


Differential Diagnoses

- Demodicosis
- Dermatophytosis
- Keratinization defects
  - Primary Seborrhea (cocker spaniels, springer spaniels, Westies, basset hounds)
  - Vit A responsive dermatosis (cocker spaniels)
  - Ichthyosis (breed dispositions)
- Follicular dysplasia
  - Canine flank alopecia

Granulomatous Sebaceous Adenitis

- Rule out other causes of sebaceous adenitis
  - Skin scrapes
  - Fungal culture
- Trichogram
  - Follicular casting suggestive of SA, seborrhea, Vit A-responsive, demodicosis and follicular dysplasia
- Biopsy

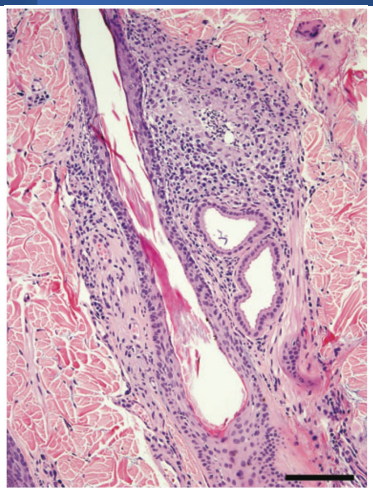


Granulomatous Sebaceous Adenitis

- Variable in intensity

Long coated

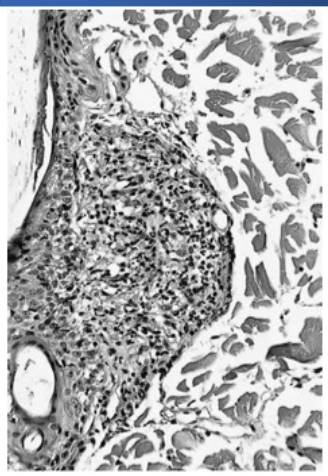
- Mild to moderate acanthosis
- Moderate to severe hyperkeratosis
- Follicular plugging
- Keratin ensheaths hair shafts
- Variable granulomatous to pyogranulomatous sebaceous adenitis
  - Sebocytes may not be visible within granuloma
- Diffusely absent sebaceous glands in progressive disease
- mild isthmus peri-follicular inflammation where previous glands were



Granulomatous Sebaceous Adenitis

Short coated/nodular form (Vizsla, etc)

- Discrete, large nodular granulomatous to pyogranulomatous periadnexal inflammation centered at previous sebaceous glands
  - May extend into subcutis
- Inflammation more prominent and consistent through all stages of disease
- Perifollicular fibrosis



Granulomatous Sebaceous Adenitis

- Systemic and topical therapy have been shown to be better in combination
- No one treatment consistently effective
- Some dogs will have cyclic patterns
- Rare spontaneous remission
- Treat secondary infections

Granulomatous Sebaceous Adenitis

- Keratolytic shampoos
  - Salicylic acid
  - Ethyl lactate
  - Douxo Seb (Ophytrium)
- Emollient rinses
- Oil treatment
  - Baby oil soak
  - Alpha Keri oil
- 50-75% propylene glycol in water once daily as spray

Granulomatous Sebaceous Adenitis

- Cyclosporine A
  - 5mg/kg/day
  - Only treatment to show increased in sebaceous glands with clinical improvement

- Synthetic retinoids
  - Isotretinoin
    - 0.8-3.5mg/kg/day
    - 1mg/kg SID/BID in Plumbs
      - I start BID
      - Can taper if improvement
      - WARN OWNER ABOUT BIRTH DEFECTS
  - Etretinate
    - 0.7-1.8mg/kg/day

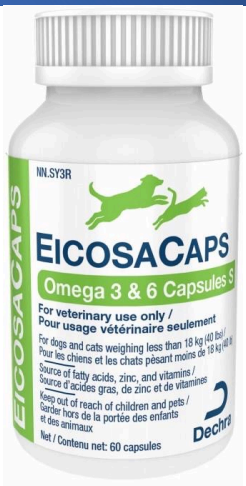
Granulomatous Sebaceous Adenitis

- Glucocorticoids
  - Commonly unresponsive to steroids

- Apoquel
  - Case report only
  - Used in combination with low dose steroid
  - 0.65mg/kg SID

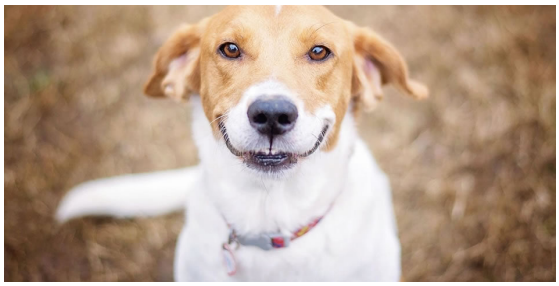
Granulomatous Sebaceous Adenitis

- Omega 3/6 fatty acid supplementation
  - Can increase circulating cyclosporine levels
  - EPA 180mg/4.5kg weight
- Vitamin A
  - Adjunct therapy
  - Mean dose 1037 IU/kg SID in study
  - 10,000-30,000 IU SID (as per Small Animal Derm)
  - Improvement in 3 months
  - Can cause KCS
- Tetracycline/niacinamide
  - Tetra 250-500mg/dog q8h
  - Niacinamide 250-500mg/dog q8h



Granulomatous Sebaceous Adenitis

- Good in most cases
- Can result in euthanasia if improperly managed and clients not informed on treatment
  - 14/44 dogs in one study
- Slow improvement (months)
  - Must inform owners this takes time to recover



Granulomatous Sebaceous Adenitis in Cats

Granulomatous Sebaceous Adenitis

- Multifocal annular areas of scale, crust, follicular casts and alopecia
- Begin on head, pinnae and neck
- Spread caudally on body

Granulomatous Sebaceous Adenitis

- Cyclosporine
  - Case report at 5mg/kg (not 7mg/kg) SID
- Dermascent Essential-6 Spot On/Atop7
  - Case report for partial efficacy
  - After failure to respond to Omega 6 FAs
- Topical treatments
  - Godspeed
  - Make reasonable recommendations for owner

Juvenile Cellulitis

Juvenile Cellulitis

Also known as….

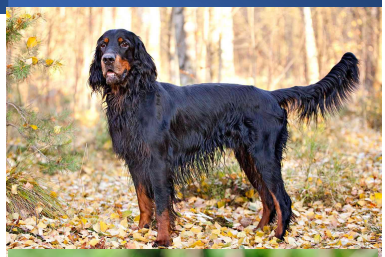
- Puppy strangles
- Juvenile pyoderma
- Juvenile granulomatous dermatitis and lymphadenitis
- Sterile granulomatous dermatitis and lymphadenitis

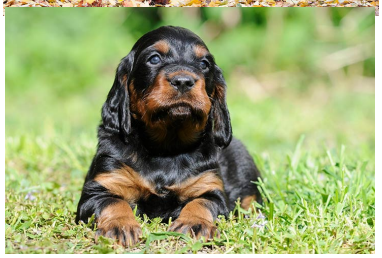
Juvenile Cellulitis

- Uncommon granulomatous and pustular disorder of the face, pinnae and submandibular lymph nodes
- Commonly a disease of puppies, but some cases in older dogs
- Unknown cause
- Heritability suspected due to breed predispositions
- Immune dysfunction suspected
  - Sterile
  - Responds to glucocorticoids
- Possible vaccine association

Juvenile Cellulitis

- Puppies aged 3 weeks to 4 months most commonly affected
- Multiple puppies in the same family may be similarly affected
- Rarely, in older dogs
- Golden retrievers, dachshunds and Gordon setters appear to be predisposed; possibly English cockers, Labs and Lhasa apso
- No sex predilection





Juvenile Cellulitis

- Usually bilaterally symmetrical lesions
- Acute swollen face, especially eyelids, lips and muzzle
- Submandibular lymph node enlargement
- Papules, pustules develop within 24-48h
- Progress to fistulae and crusts
- Marked purulent otitis externa
- Thickened and edematous pinnae
  - Pustules on the concave pinnae
- Skin abscess

Juvenile Cellulitis

Juvenile Cellulitis

- Swollen prepuce or rectal mucosa
- Possible concurrent sterile pyogranulomatous panniculitis
  - Firm to fluctuant subcutaneous nodules
  - May be painful
  - Fistulation possible
  - Painful, but not pruritic

Systemic Symptoms

Young dogs

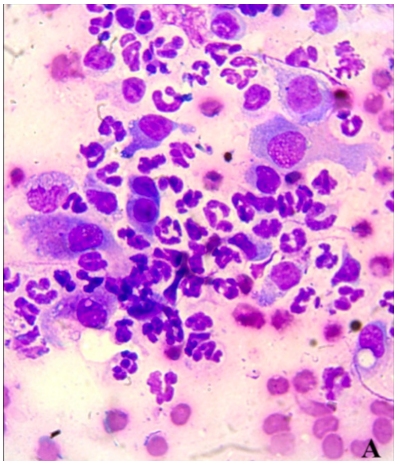
- Lethargy
- Depression
- No pyrexia or anorexia

Older dogs

- Lameness
- Arthritis
- Paresis or neurological signs
- Pyrexia

Diagnosis

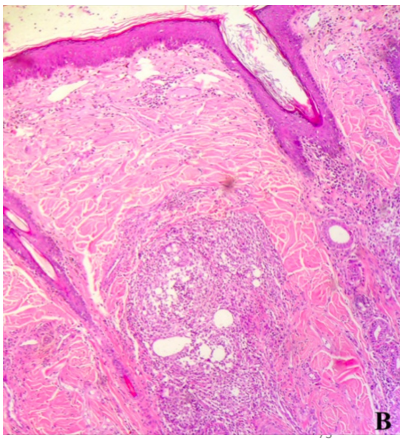
- Cytology
  - Pyogranulomatous inflammation
  - No micro-organisms unless secondary infection
- Culture
  - Sterile
- Trichogram/deep skin scrape
  - Rule out demodicosis
- Biopsy



Diagnosis

Histology

- Epidermis normal, acanthotic or ulcerated
- Discrete granulomas and pyogranulomas in early lesions consisting of large epithelioid macrophages and neutrophil cores in the dermis
- Sebaceous and epitrichial glands may be obliterated
- Suppurative changes to superficial dermis and rupture of hair follicles extending into panniculus in late lesions
- Chronic lesions may be scarred in the subcutis



Treatment

- Can spontaneously regress in some dogs but early and aggressive therapy recommended due to possible scarring
- Oral glucocorticoids at immunosuppressive doses recommended until disease in remission
  - Possible better response to dexamethasone (0.2mg/kg SID)
- Griseofulvin 14.2-34mg/kg q12h effective in 6/6 cases within 3 weeks
- Wet soaks with aluminum acetate or magnesium sulfate
- Antibiotics if secondary infections
- Treat for Demodex (Isoxazolines preferred)

Juvenile Cellulitis

- Mean duration of treatment ~60 days
- Median time to remission 28 days
- Reoccurrence possible (11/30 dogs in 1 study) but thought to be uncommon in textbooks

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