Pemphigus in Dogs and Cats

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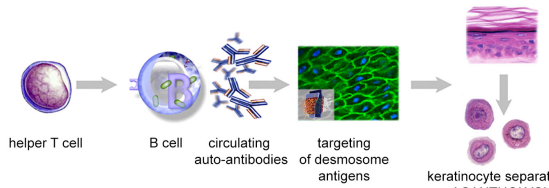
Think and Do

1

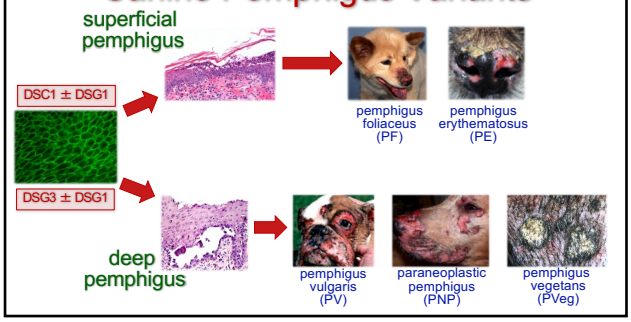
What are Pemphigus?

pemphigus: a group of autoimmune blistering skin diseases caused by auto-antibodies targeting keratinocyte desmosome proteins and resulting in cell-cell separation (acantholysis)



2

Canine Pemphigus Variants



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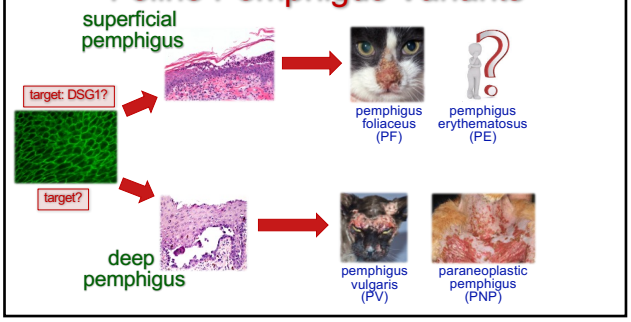
Feline Pemphigus Variants



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Superficial Pemphigus: Pemphigus Foliaceus (PF) Pemphigus Erythematosus (PE)

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Canine Pemphigus Foliaceus
Incidence and Prevalence

- Cornell University VTH (1975-1984):
  - 26/9,750 dogs with skin diseases
  - incidence: ~ 3 per year per 1,000 dogs
- MSU histopathology laboratory (1997):
  - 1% of surgical skin biopsies
- University of Florida VTH (1978-1981):
  - 26/84 dogs with autoimmune skin diseases (31%)

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Canine Pemphigus Foliaceus
Signalment

– gender distribution:
- Ihrke, 1985: F:M ratio = 24:13 = 1.9
- Scott, 1987: F:M ratio = 12:14 = 0.9
- Gomez, 2004: F:M ratio = 13:20 = 0.4
- Mueller, 2006: F:M ratio = 45:46 = 1.0
- Carlotti, 2009: F:M ratio = 24:20 = 1.2

equal representation of male and female dogs

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Canine Pemphigus Foliaceus
Signalment

– age of onset:
- Ihrke, 1985: range: <1-12 yrs; mean = 4.2
- Scott, 1987: range: <1-12 yrs; mean = 6.0
- Gomez, 2004: range: <1-12 yrs; mean = ?
- Mueller, 2006: range: <1-16 yrs; mean = 6.5
- Carlotti, 2009: range: 1-13 yrs; mean = 6.7

wide range of ages of disease onset

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Canine Pemphigus Foliaceus
Breed Predisposition: Chows

- OR = 12** (U Penn, 1986-1991)
- OR = 16 (Dunstan, 1997)
- OR = 31*** (NCSU, 1995-2002)
- OR = 12*** (UCD, 1999-2004)
- OR = 7*** (Duclos, 1995-2003)

☞ overall odds ratio (95% CI): 13 (8 - 21)

two-sided Chi^2: * P < 0.05; ** P < 0.01; *** P < 0.001; NS: not significant

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Canine Pemphigus Foliaceus
Breed Predisposition: Chows

– line predisposition:
- common ancestors
- vertical transmission
- littermates affected

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Canine Pemphigus Foliaceus
Breed Predisposition: Akitas

- OR = 29 (Ihrke, 1985)
- OR = 3^{NS} (Scott, 1987)
- OR = 38*** (Upenn, 1986-1991)
- OR = 23 (MSU, 1997)
- OR = 10*** (UCD, 1999-2004)
- OR = 7^{NS} (NCSU, 1995-2002)

two-sided Chi^2: * P < 0.05; ** P < 0.01; *** P < 0.001; NS: not significant

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Canine Pemphigus Foliaceus
Association with Sun Exposure?

– higher disease activity in summer months
(Rosenkrantz, 1993)

– higher clinical scores in summer and lower scores in winter in 10/12 (83%) dogs
(Iwasaki, *AAVD & ACVD* 2003)

– UVB induction of acantholysis in normal skin of a dog with PF
(Iwasaki, *AAVD & ACVD* 1997)

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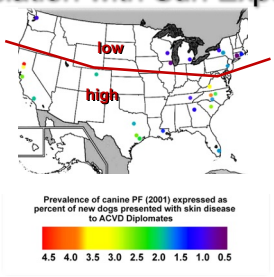
Canine Pemphigus Foliaceus
Association with Sun Exposure?



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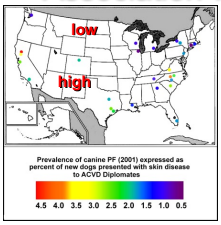
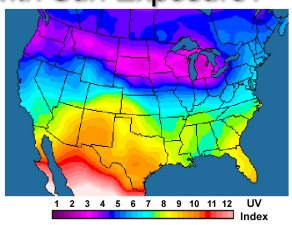
Canine Pemphigus Foliaceus
Association with Sun Exposure?





Is UV irradiation a trigger?
Are there arthropod-borne (infectious) triggers?

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Canine Pemphigus Foliaceus
Association with Sun Exposure?

acute flare 24 hours following prolonged sun exposure

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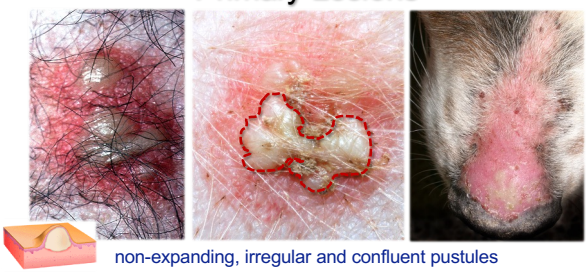
Canine Pemphigus Foliaceus
Primary Lesions



non-expanding, irregular and confluent pustules

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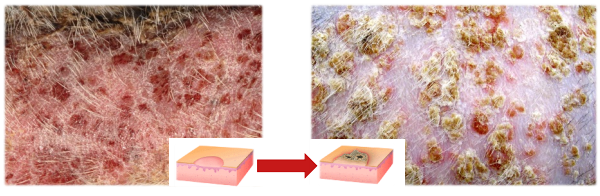
Canine Pemphigus Foliaceus
Secondary Lesions



small, often-confluent, erosions and (multi-layered) crusts,
rare, small, non-expanding collarettes

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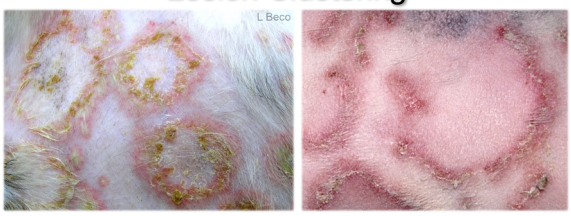
Canine Pemphigus Foliaceus
Lesion Clustering



annular-to-polycyclic arrangement of primary lesions
clear center and non-expanding lesions ≠ staphylococcal epidermal collarettes

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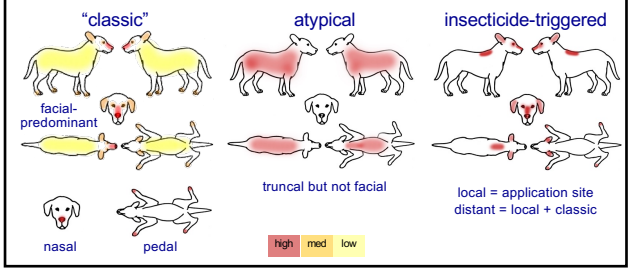
Canine Pemphigus Foliaceus
Different Phenotypes



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Canine Pemphigus Foliaceus
"Classic" Variant

facial-predominant, bilaterally-symmetrical distribution

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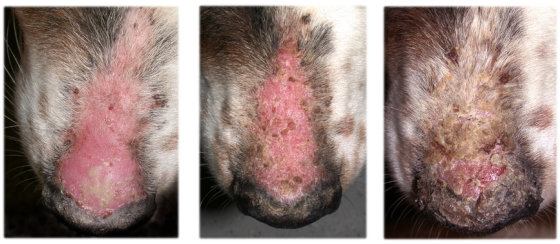
Canine Pemphigus Foliaceus
"Classic" Variant



facial-predominant, bilaterally-symmetrical distribution

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Canine Pemphigus Foliaceus
"Classic" Variant

facial-predominant, bilaterally-symmetrical distribution

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Canine Pemphigus Foliaceus
"Classic" Variant

secondary infection and sepsis — after 12 days of antibiotics

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Canine Pemphigus Foliaceus
Nasal-Predominant (Classic) Variant

(pustules), erosions and crusts predominating on the nasal planum

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Canine Pemphigus Foliaceus
Pedal-Predominant (Classic) Variant

(pustules), erosions and crusts predominating on the footpads

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Canine Pemphigus Foliaceus
Generalized (Classic) Variant

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Canine Pemphigus Foliaceus
Generalized (Classic) Variant

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Canine Pemphigus Foliaceus
Generalized (Classic) Variant

Development of a secondary telogen effluvium? Effect of glucocorticoids?

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Canine Pemphigus Foliaceus
Generalized (Classic) Variant

Development of a secondary telogen effluvium?

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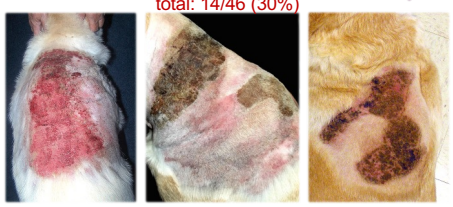
Insecticide-Triggered Contact PF
Lesions Localized to the Application Site

- Promeris: 8/22 (36%)
- Certifect: 6/21 (29%)
- Vectra 3D: 0/3 (0%)

total: 14/46 (30%)



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Insecticide-Triggered Contact PF
Lesions Distant from the Application Site

- Promeris: 14/22 (64%)
- Certifect: 15/21 (71%)
- Vectra 3D: 3/3 (100%)

total: 32/46 (70%)

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Canine Pemphigus Foliaceus
Atypical Variant

truncal-predominant distribution, without or with minimal facial/pedal lesions

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Some Canine Pemphigus Foliaceus Mimics

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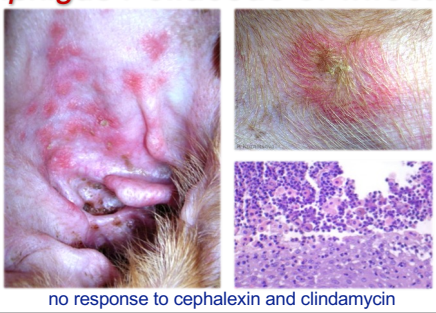
Pemphigus Foliaceus or Infection?



no response to cephalexin and clindamycin

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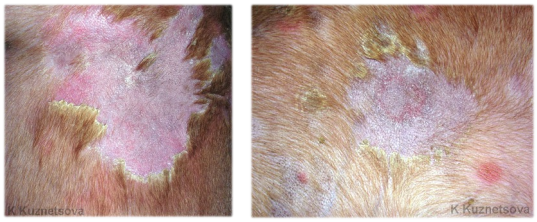
Pemphigus Foliaceus or Infection?



exfoliative superficial pyoderma (ESP)
due to multi-antibiotic-resistant *Staphylococcus*
→ full response to topical fusidic acid

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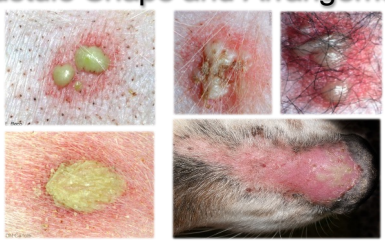
Pemphigus Foliaceus or Infection?
Pustule Shape and Arrangement



round, slowly expanding
= impetigo

irregular, confluent
= pemphigus foliaceus

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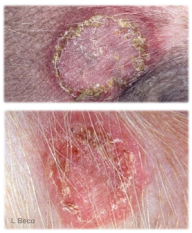
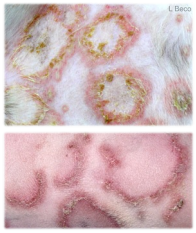
Pemphigus Foliaceus or Infection?
Lesion Configuration


expanding + inflamed center
= exfoliative pyoderma


clustering + normal center
= pemphigus foliaceus

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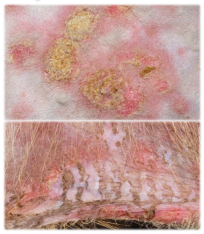
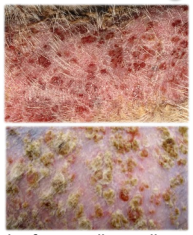
Pemphigus Foliaceus or Infection?
Epidermal Collarettes and Scaling


expanding collarettes + scaling
= exfoliative pyoderma


lack of expanding collarettes
= pemphigus foliaceus

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Pemphigus Foliaceus or Infection?
Rapidly-Expanding Alopecia + Scaling


pemphigus foliaceus
+
telogen effluvium


pemphigus foliaceus
+
exfoliative superficial pyoderma

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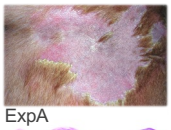
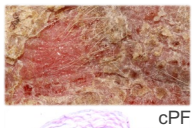
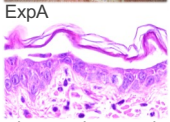
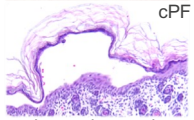
Pemphigus Foliaceus or Infection?
Absence or Presence of Erosions


ExpA


cPF


subcorneal separation
= exfoliative pyoderma


subgranular erosions
= pemphigus foliaceus

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Pemphigus Foliaceus or Infection?


Beagle crossbred, FS, 6 years

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Pemphigus Foliaceus or Infection?

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Pemphigus Foliaceus or Infection?

after one week of oral cephalexin

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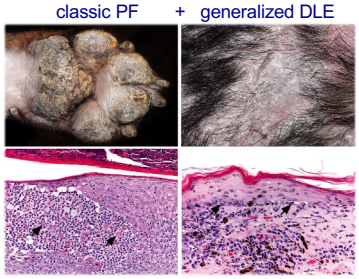
Cutaneous Poly-Autoimmunity

classic PF + generalized DLE



(Levy, Vet Dermatol 2020)

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Canine Pemphigus Foliaceus
Autoimmune Co-Morbidities

– Tufts University, 2002 to 2016: 90 dogs with PF
- concurrent autoimmune disease: 17 (19%)
  - autoimmune polyarthropathy: 4/17 (24%)
  - keratoconjunctivitis sicca: 4/17 (24%)
  - immune-mediated thrombocytopenia: 3/17 (18%)

common presence of poly-autoimmunity
(Falk, NAVDF 2017)

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Canine Pemphigus Foliaceus
Systemic Signs

pruritus: 22% pain (esp. pedal): 35% fever and lethargy: 45%

(Ihrke, JAVMA 1985, Scott; Comp Cont Ed 1987; Mueller, JAAHA 2006)

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Feline Pemphigus Foliaceus
Signalment (186 Cats)

– no confirmed breed predisposition
– female:male ratio: 1.4
– age of disease onset: 0.3-16 y (median: 7 y)

(Bizikova, BMC Vet Res 2019)

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Feline Pemphigus Foliaceus
Lesion Type

pustules erosions crusts

(Bizikova, BMC Vet Res 2019)

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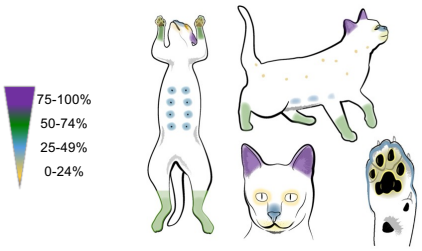
Feline Pemphigus Foliaceus
Lesion Distribution



(Bizikova, BMC Vet Res 2019)

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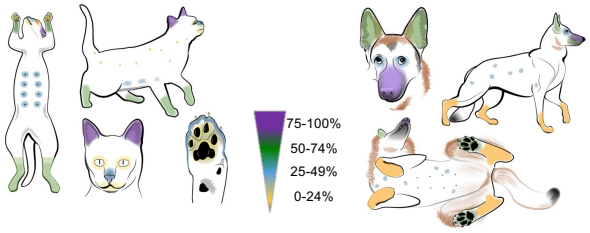
Canine vs. Feline Pemphigus Foliaceus
Lesion Distribution



(Bizikova, BMC Vet Res 2019)

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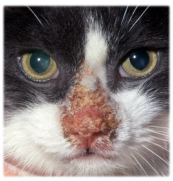
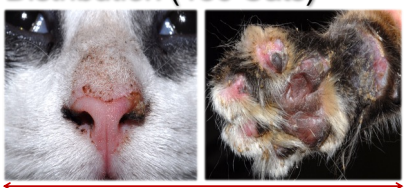
Feline Pemphigus Foliaceus
Lesion Distribution (186 Cats)



"localized"
(1 region)
19%



"generalized"
(>1 region)
81%

(Bizikova, BMC Vet Res 2019)

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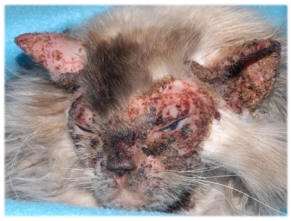
Feline Pemphigus Foliaceus
Lesion Distribution (186 Cats)



facial involvement: 85%

(Bizikova, BMC Vet Res 2019)

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Feline Pemphigus Foliaceus
Lesion Distribution (186 Cats)

pinnae: 85%

nose: 85%

(Bizikova, BMC Vet Res 2019)

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Feline Pemphigus Foliaceus
Lesion Distribution (186 Cats)

pads: 22%

(Bizikova, BMC Vet Res 2019)

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Feline Pemphigus Foliaceus
Lesion Distribution (186 Cats)

paronychia (around claws): 56%
(only: 11%)
(Bizikova, BMC Vet Res 2019)

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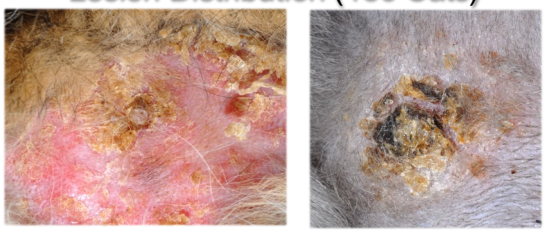
Feline Pemphigus Foliaceus
Lesion Distribution (186 Cats)



areola/periareolar: 10%
(Bizikova, BMC Vet Res 2019)

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Feline Pemphigus Foliaceus
Systemic Signs

pruritus: 64%

fever: 27%

lethargy: 50%

concurrent thymoma: 4 cats

(Bizikova, BMC Vet Res 2019)

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Some Feline Pemphigus Foliaceus Mimics

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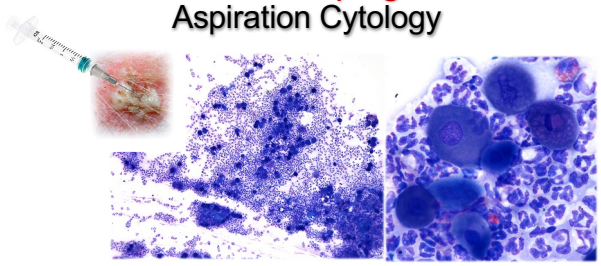
Canine & Feline Pemphigus Foliaceus
Aspiration Cytology



neutrophils, acantholytic keratinocytes, no intracellular bacteria
= similar to the vaginal smear of a bitch in diestrus

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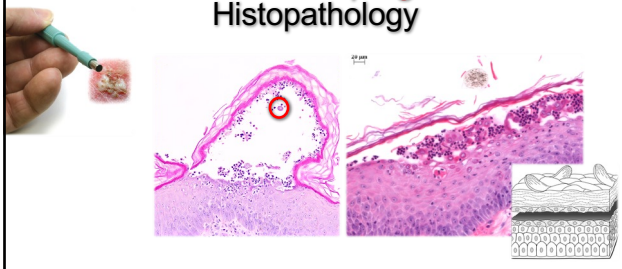
Canine & Feline Pemphigus Foliaceus
Histopathology



subcorneal pustules with acantholytic keratinocytes

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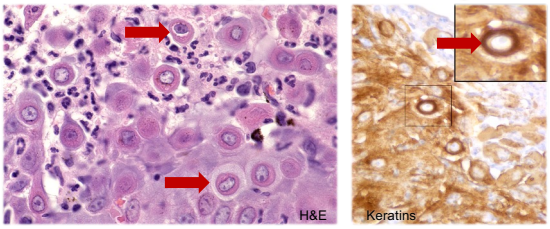
Canine Pemphigus Foliaceus
Histopathology " *Keratin Ring*"



condensation of keratin filaments after separation from desmosomes

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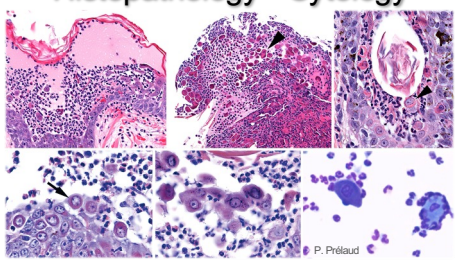
Canine Insecticide-Triggered PF
Histopathology - Cytology



microscopic lesions identical to those of spontaneous PF

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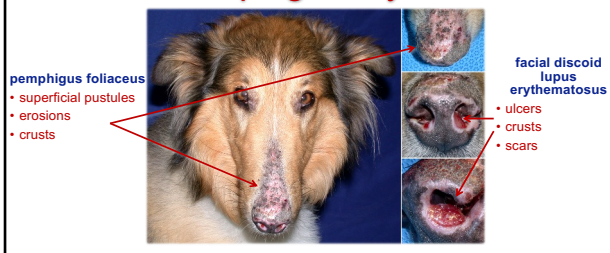
Canine Pemphigus Erythematosus



PE = PF + DLE

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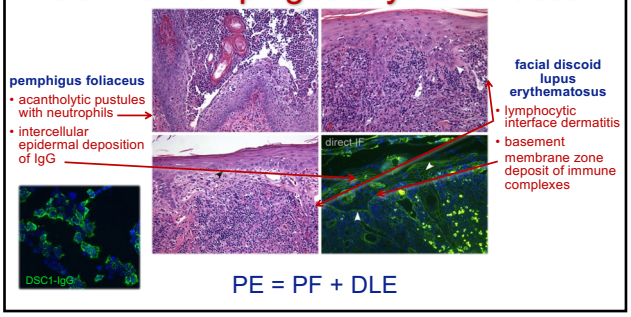
Canine Pemphigus Erythematosus



PE = PF + DLE

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Treament of Superficial Pemphigus
"Traditional Therapy"

1) start glucocorticoids at baseline

2) begin the taper of glucocorticoids when partial remission and no new lesions

3) add a lymphocyte immunosuppressant if no complete remission within 1-2 months

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Canine Pemphigus Foliaceus
Response to "Traditional Therapy"

April 7 D0 | April 19 D12 | May 2 D25 | August 18 D110

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Canine Pemphigus Foliaceus
Prognosis and Outcome

–University of Pennsylvania (1994-2000):

- 43 dogs diagnosed with PF
- 26/43 (60%) dogs died during study period
- 92% of death occurred during first year of treatment
- 11/26 (69%) dogs were euthanized due to poor quality of life, lack or treatment efficacy or adverse effects of treatment

(Gomez, J Amer Vet Med Assoc 2004)

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Canine Pemphigus Foliaceus
Prognosis and Outcome

–NC State University (1994-2003):

- 39 dogs diagnosed with PF
- 14/36 (39%) dogs died during study period
- death or euthanasia due to presumed or confirmed adverse effects of immunosuppression with glucocorticoids ± azathioprine

(Olivry, unpublished 2004)

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Canine Pemphigus Foliaceus
Prognosis and Outcome

–specialty practices (US, AU; 1994-2002):

- 91 dogs diagnosed with PF
- rate of complete remission: ~50%
- time to complete remission: 1.5 to 29 months
  - with glucorticoids alone: mean = 7 months
  - with glucocorticoids + azathioprine: mean = 12 months

(Mueller, J Amer Anim Hosp Assoc 2006)

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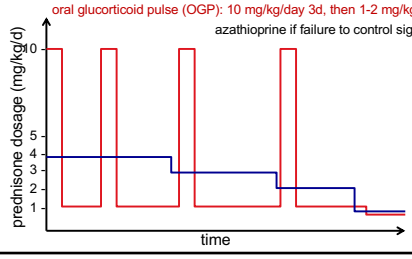
Pulse versus Traditional Therapy
General Principles

traditional glucocorticoid therapy (TGT): 4 mg/kg/d then tapered
oral glucorticoid pulse (OGP): 10 mg/kg/day 3d, then 1-2 mg/kg/d
azathioprine if failure to control signs



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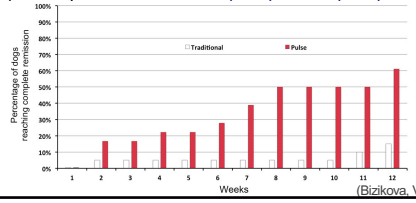
Pulse versus Traditional Therapy
3-Month Outcome

	Traditional	Pulse	P
✓ number of dogs:	20	18	
✓ # (%) of complete remission:	3 (15%)	11 (61%)	0.006



(Bizikova, Vet Dermatol 2015)

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Pulse versus Traditional Therapy
3-Month Outcome

	Traditional	Pulse	P
✓ number of dogs:	20	18	
✓ number (%) of CR:	3 (15%)	11 (61%)	0.006
✓ median time to CR (wks):	9.1	6.9	0.435
✓ number (%) with adjuvant:	12 (60%)	7 (39%)	0.330
✓ number (%) severe ADEs:	2 (10%)	2 (11%)	1.000

CR = complete remission

(Bizikova, Vet Dermatol 2015)

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Canine Pemphigus Foliaceus
Oral Glucocorticoid Pulses

before | 10 days after first pulse

(Bizikova, Vet Dermatol 2015)

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Pulse versus Traditional Therapy
Adverse Drug Events

– oral glucocorticoid pulses:
- diarrhea: 2 dogs (11%)
- melena: 1 dog (5%)
- aggressivity: 2 dogs (11%)

– traditional glucocorticoid therapy:
- azathioprine-induced cytopenias: 1 dog (5%)
- sudden death: 1 dog (5%)

(Bizikova, Vet Dermatol 2015)

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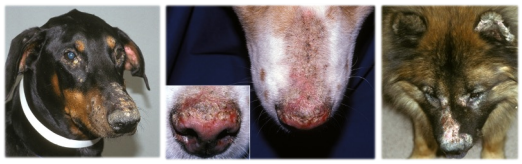
Canine Pemphigus Foliaceus
Prognosis and Outcome

– long-term (> 1 year) remission off medication:
- 6/51 (12%) dogs with spontaneous PF



(Olivry, Vet Dermatol 2004)

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Canine Insecticide-Triggered PF
Prognosis and Outcome (45 Dogs)

– spontaneous remission: 0 (0%)

– complete remission: 37 (82%)
- "localized" variant: 13/14 (93%)
- "distant" variant: 24/31 (77%)

– time to complete remission: weeks to 1 year

– probability of discontinuing treatment: 30 (67%)
- "localized" variant: 10/14 (71%)
- "distant" variant: 20/31 (65%)

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Feline Pemphigus Foliaceus
Prognosis and Outcome (158 Cats)

– spontaneous remission: 2/146 (< 1%)

– complete remission: 146/158 (92%)

– time to complete remission: median = 21 days

– probability to discontinue treatment: 22/131 (17%)

(Bizikova, BMC Vet Res 2019)

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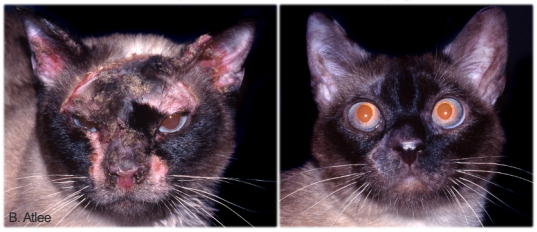
Feline Pemphigus Foliaceus
Response to Therapy



after 2 months of chlorambucil

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Pemphigus Foliaceus
Comparative Prognosis and Outcome



– spontaneous CR:	< 1%	0%	<1%
– % CR:	~50%	82%	92%
– time to CR (median):	12 m	variable	21 d
– % stop treatment:	12%	67%	17%

(Mueller, JAAHA 2006; Olivry, unpublished; Bizikova, BMC Vet Res 2019)

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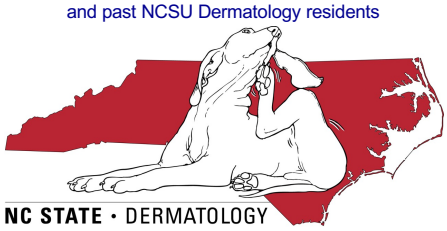

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