Transforming Lives

COMMON IMMUNE MEDIATED DERM DISEASE

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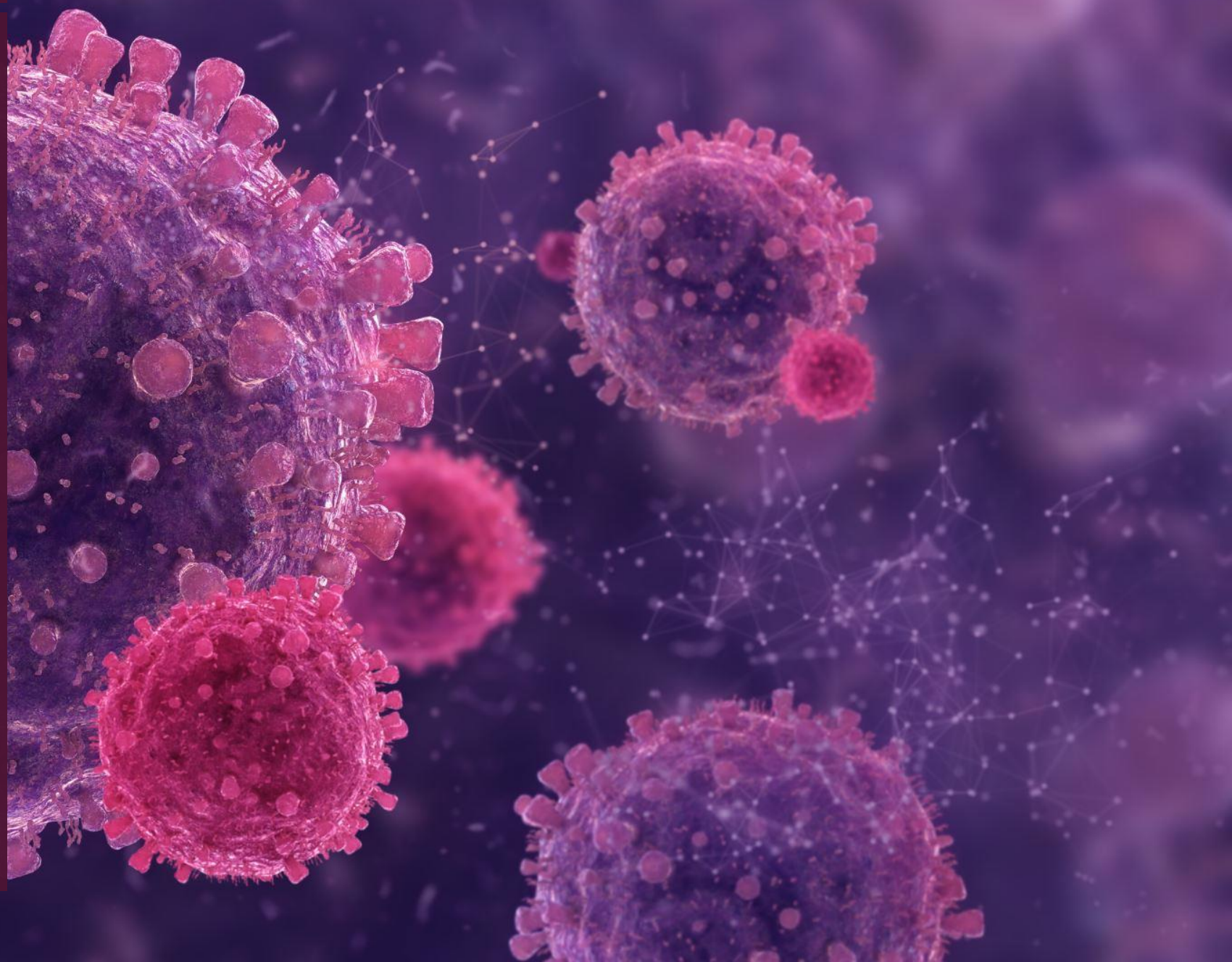
ASSISTANT PROFESSOR DERMATOLOGY



Welcome to the 10th World Congress of Veterinary Dermatology

July 25-29, 2024 / Boston, Massachusetts, USA

OVERVIEW

- Review 3 common immune mediated/auto immune diseases
- Review clinical signs, pathogenesis, diagnosis, treatment
- Discuss biopsy techniques

WHAT IS AN IMMUNE MEDIATED DISEASE?

Immune mediated and auto immune used interchangeably

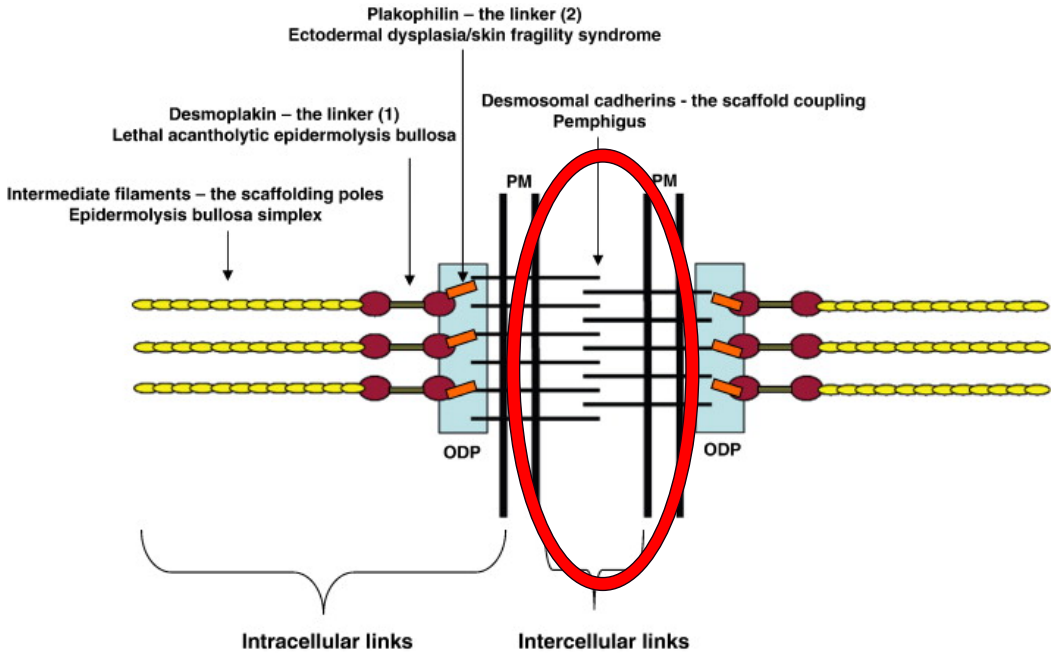
Immune mediated characterized by common inflammatory pathways leading to inflammation

Auto immune disease - antibody causing disease identified

Dysregulation of normal immune response

Lack definitive etiology

PEMPHIGUS FOLIACEUS



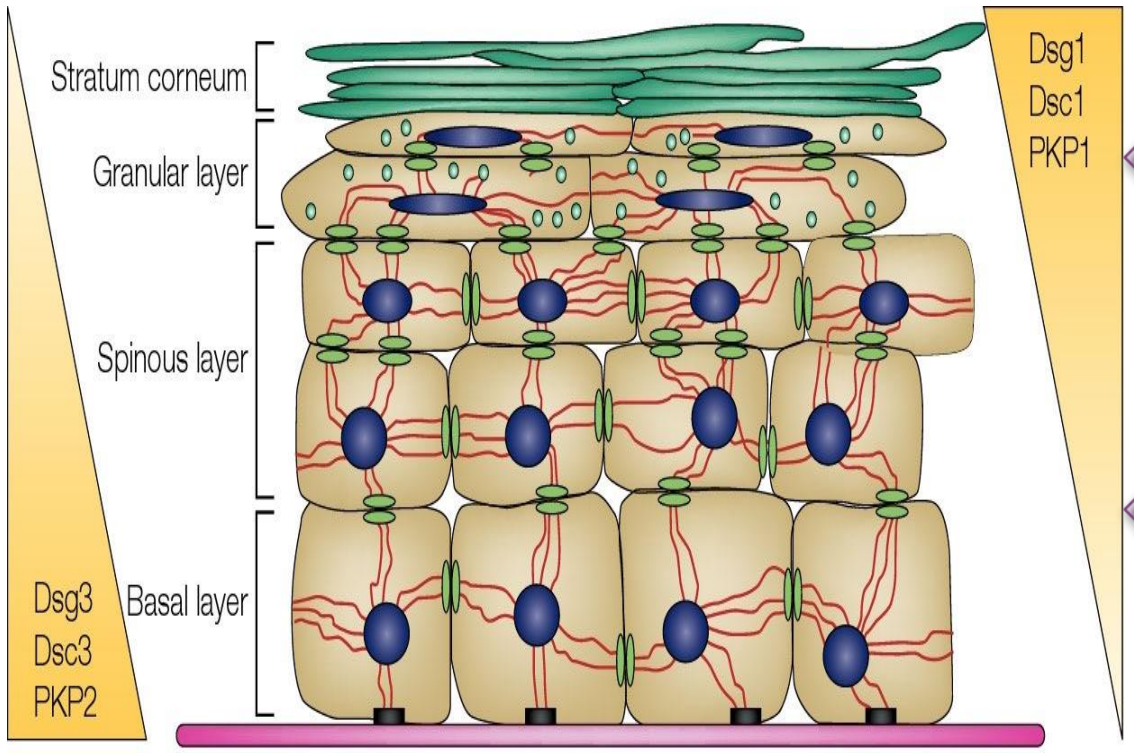
- Most common auto-immune skin disease
- Acantholysis of desmosome
- Type II hypersensitivity reaction
  - Antibody dep. cell mediated cytotoxicity

PEMPHIGUS FOLIACEUS

- Facial vs. generalized
  - Anti-Desmocolin-1 &/or anti-Desmoglein-1 IgG
  - Control: healthy, other skin disease
- Anti-DSC1 IgG in 100% (classic) & 53% (atypical)
- Anti-DSG1 IgG + in two atypical (7%), also anti-DSC1 IgG +
- Triggers: adverse drug reaction, chronic skin disease, neoplasia, vaccines

Bizikova P, Mamo L. Abstract NAVDF 2019.

CLINICAL SIGNS



PF = Lesion formed underneath *stratum corneum* or inside *stratum granulosum*

Pemphigus vulgaris (PV)
Lesion formed just above the basal cell layer

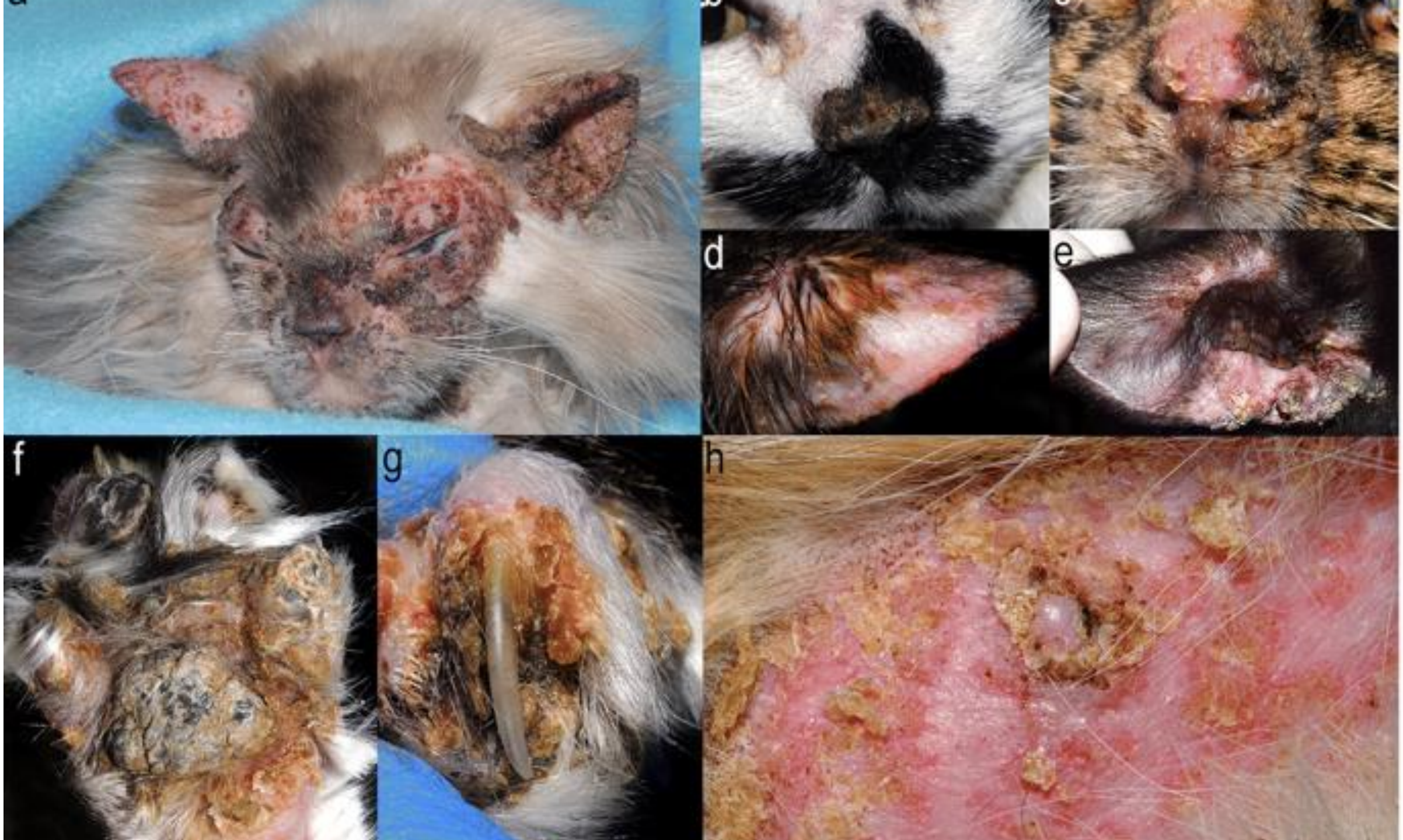
PEMPHIGUS FOLIACEUS IN CATS

- SPF, healthy cats, allergic cats, PF
- Antikeratinocyte IgG
  - 77% of PF
  - 19% allergic cats
  - 1 healthy cat
  - Confirms antikeratinocyte IgG
  - Molecular target unknown

Levy B, Mamo L, Bizikova P. Abstract NAVDF 2019.

PEMPHIGUS FOLIACEUS

- Both dogs and cats
  - No sex predilection
  - Age of onset
    - 6 years (mean)
  - Susceptible breeds
    - Akitas, Chow-chows, Retrievers, Setters, Dachshunds, Dobermans, Newfoundlands, Bearded Collies, Schipperkes
    - Siamese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Research article | Open Access | Published: 09 January 2019

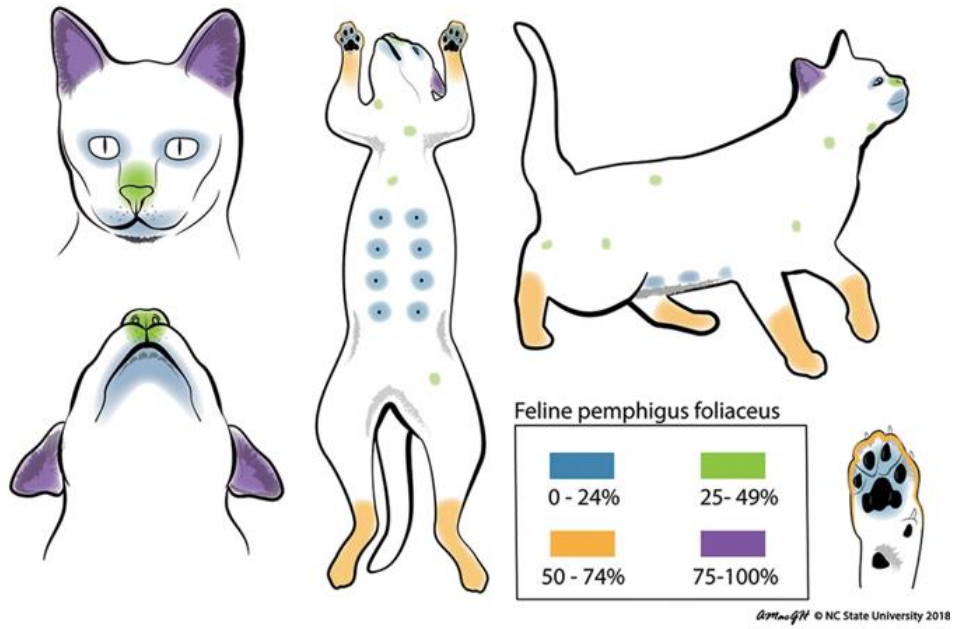
Feline pemphigus foliaceus: original case series and a comprehensive literature review

Petra Bizikova & Amanda Burrows

BMC Veterinary Research 15, Article number: 22 (2019) | Download Citation

2446 Accesses | 1 Altmetric | Metrics »

- Mean 6 yrs
- Female cats marginally over-represented
- No specific triggers, vaccination preceded in 2 cats
  - Itraconazole, cimetidine, topical mixture, abx, methimazole
- Systemic signs 63% (lethargy, febrile)
- Pruritus in 32/35

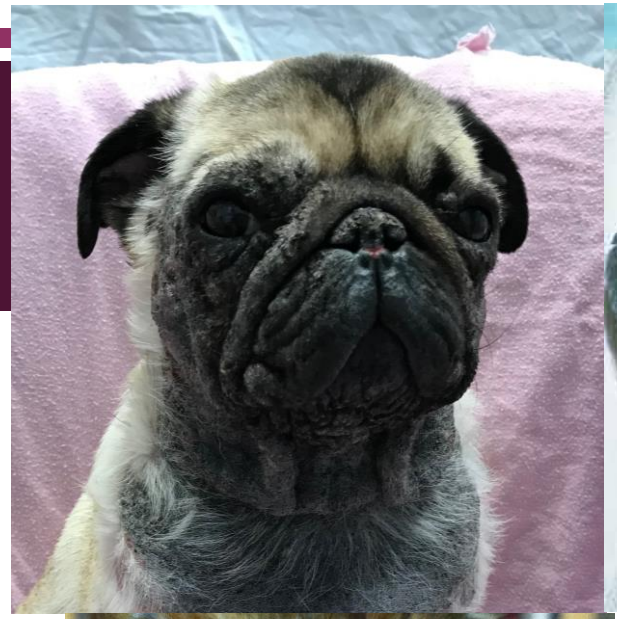


GENERALIZED PF

- Entire body
- General malaise
- Poor appetite
- Weight loss
- +/- Pyrexia
- +/- Pruritus
- Wax and wane
- NO mucosal involvement

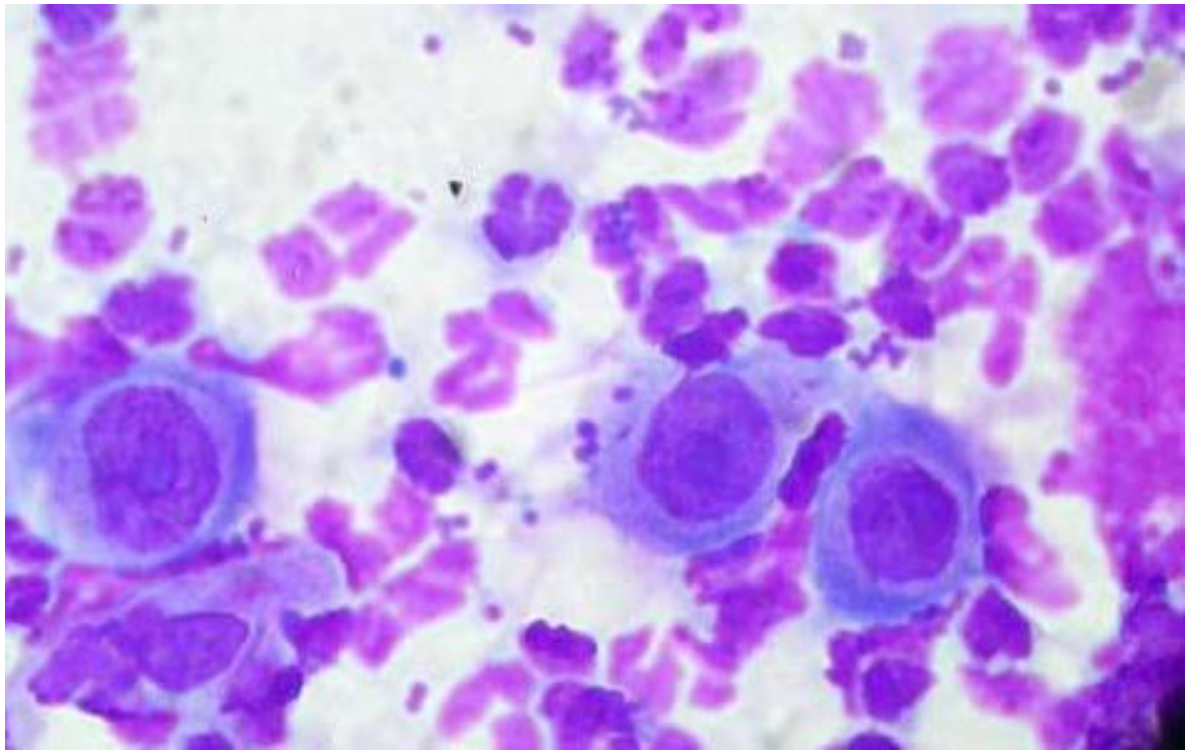
DIFFERENTIAL DIAGNOSES

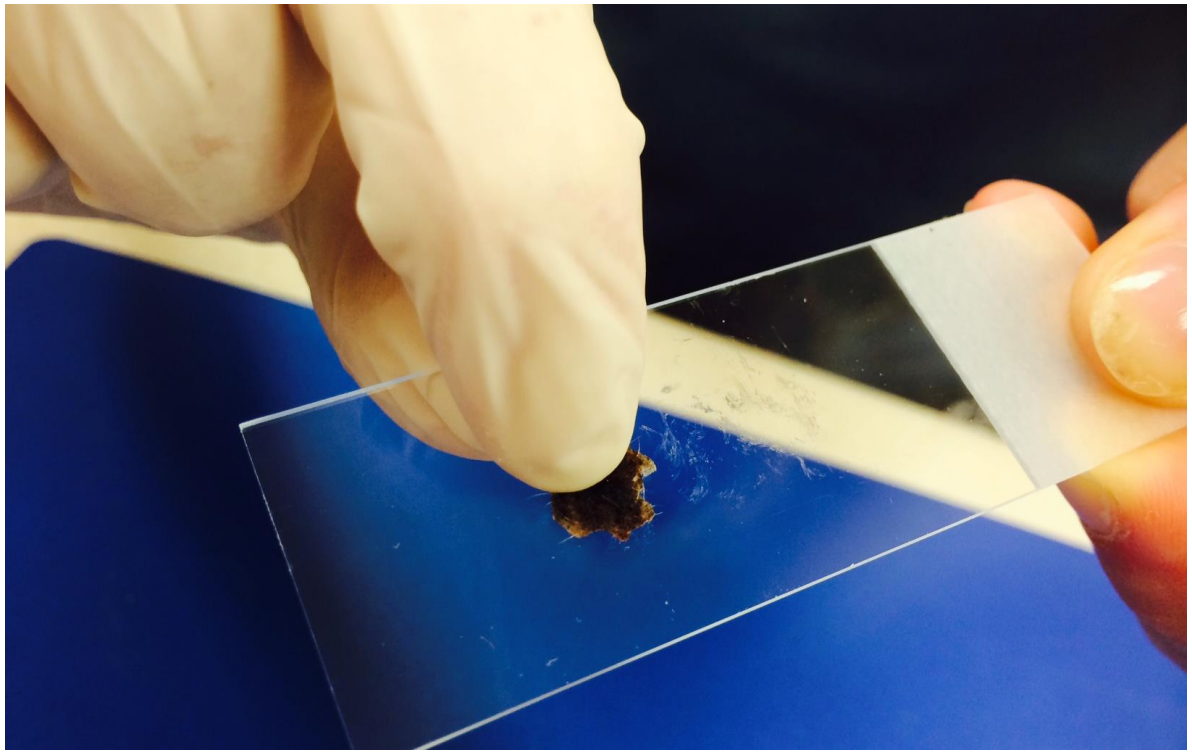
- Demodicosis
- Dermatophytosis
- Bacterial pyoderma
- Zinc responsive dermatosis
- Superficial necrolytic dermatitis
- DLE, SLE
- Neoplasia (CTCL)
- Distemper?



DIFFERENTIAL DIAGNOSES

- Bacteria and demodex need follicles!





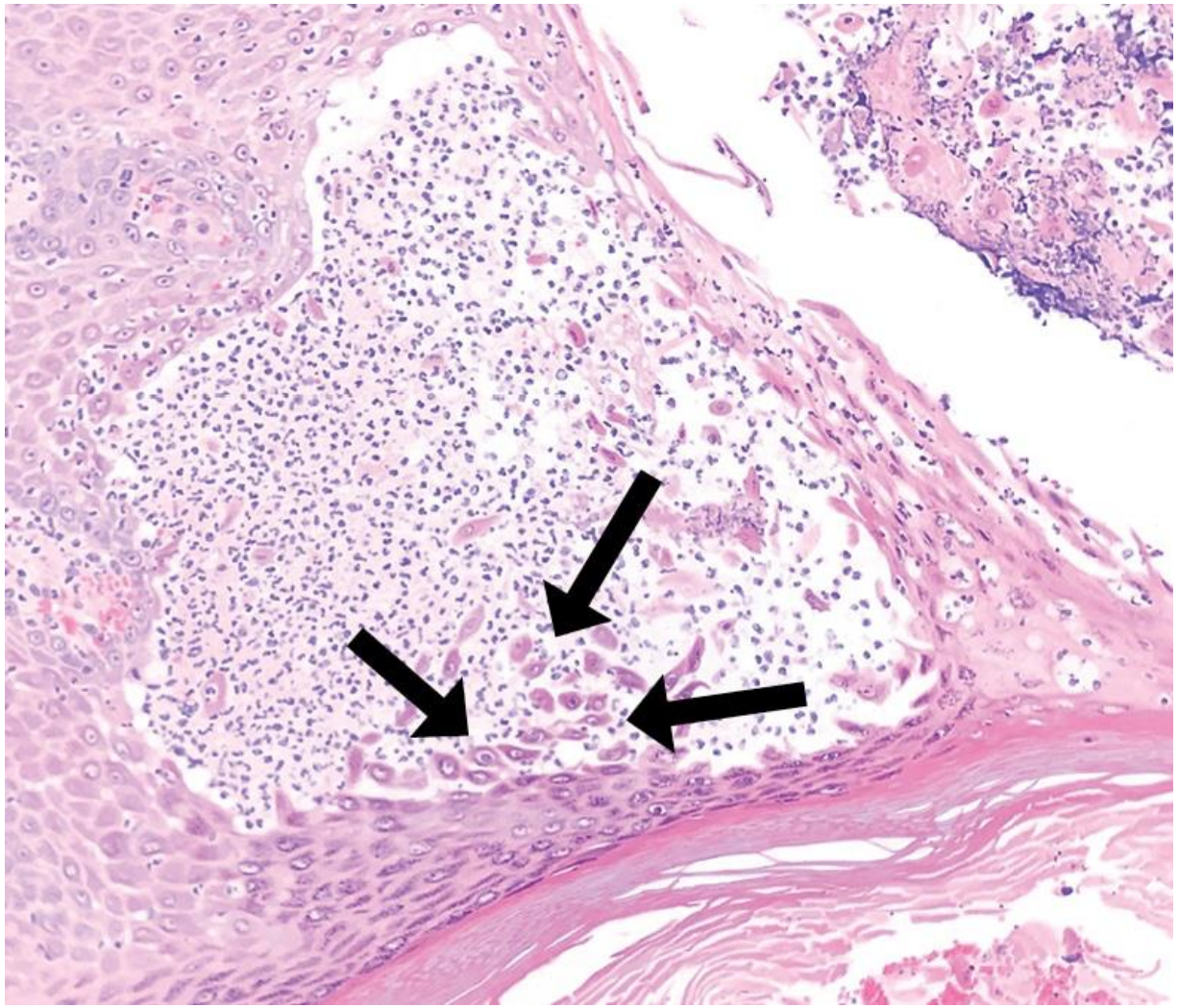
DIAGNOSTIC WORK-UP

Acantholytic cells

Trichophyton mentagrophytes, Staphylococcus species

DIAGNOSTIC WORK-UP

- Deep skin scraping
- Fungal culture
- Biopsy
  - Intra/subcorneal or intragranular pustules
  - Fresh neutrophils, eosinophils
  - Bloodwork



Today's Veterinary Practice

TREATMENT

- Treat Secondary infection
- Baseline bloodwork
  - Q 2 weeks for monitoring
  - Complete blood count, biochemical profile +/- U/A
  - FeLV/FIV testing

TREATMENT

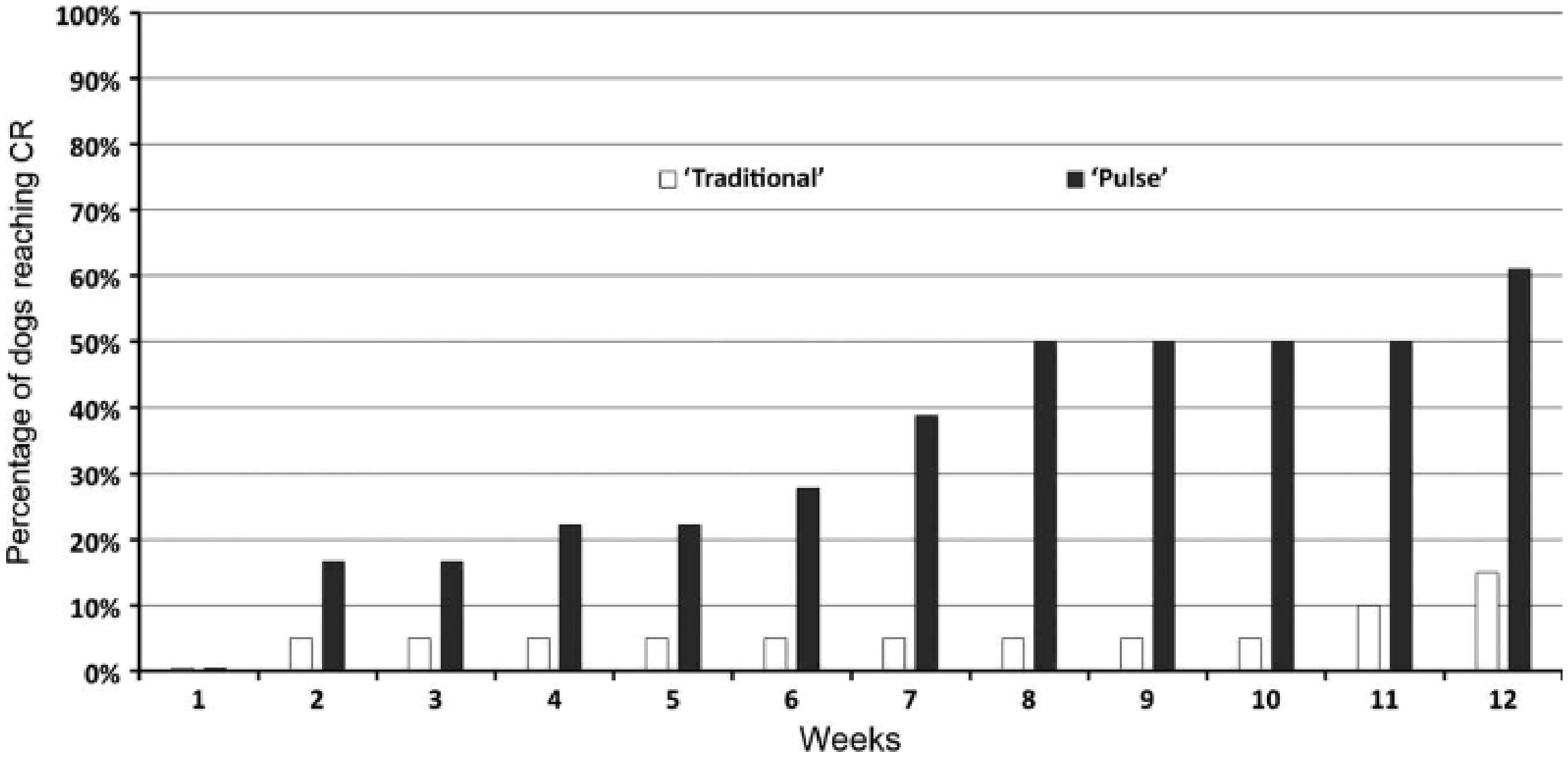
- Induce remission with glucocorticoids
- Prednisone (dogs), Prednisolone (cats)
  - 2.2mg/kg/d PO -> dogs
  - 4.4 mg/kg/d -> cats
  - Taper GRADUALLY pending response
- Dexamethasone
  - 0.2-0.4 mg/kg/day PO (dogs)
  - Taper GRADUALLY pending response

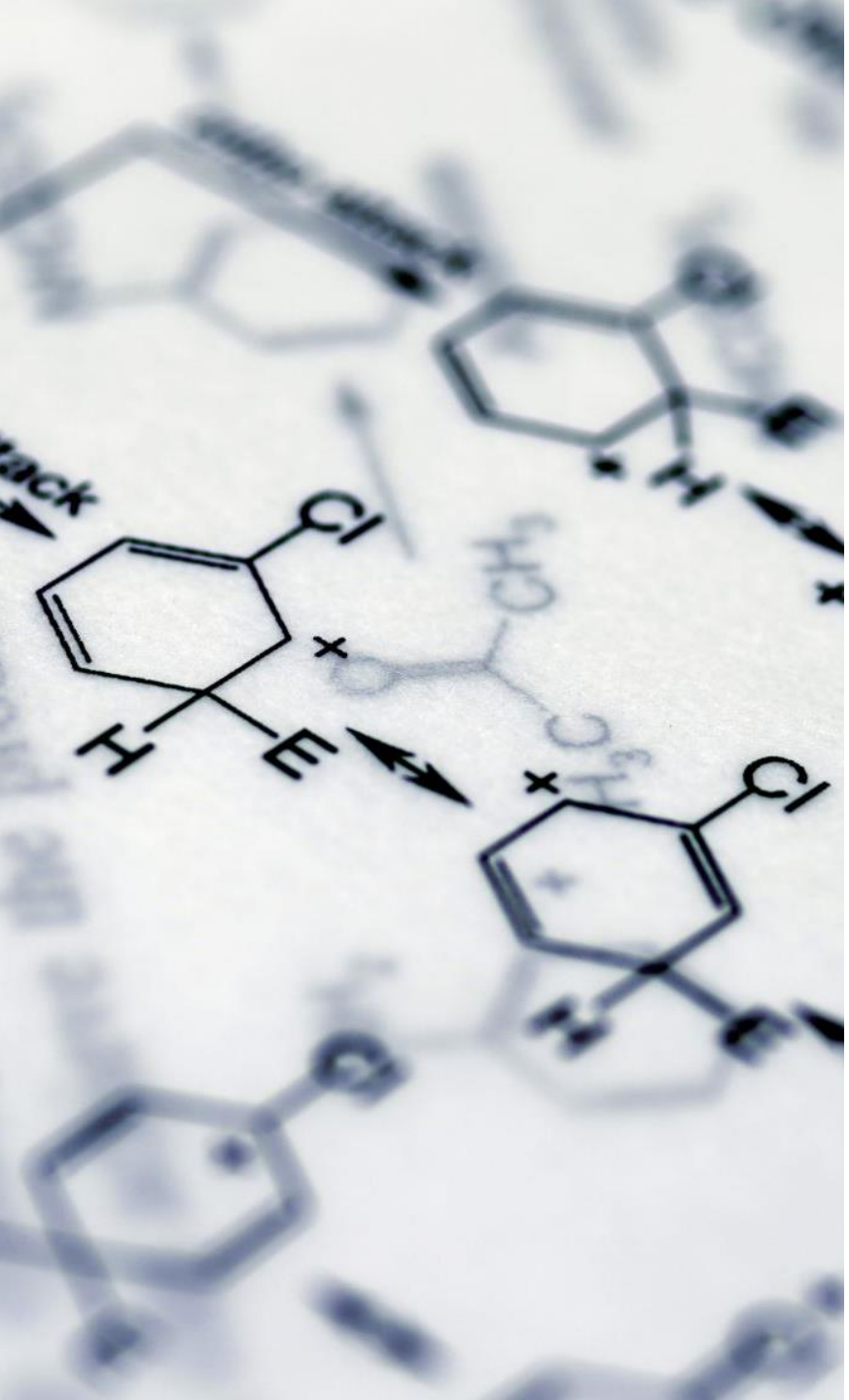
Vet Dermatol 2015; **26**: 354–e77 DOI: 10.1111/vde.12241

Oral glucocorticoid pulse therapy for induction of treatment of canine pemphigus foliaceus – a comparative study

Petra Bizikova*† and Thierry Olivry*†

- 20 Traditional (2 mg/kg/day)
- 18 Pulse (10 mg/kg daily for 3 days, <2 mg/kg/day)
  - Pulses could be repeated (not more than once weekly)
- If after 4 weeks, new lesions, addition of immunosuppressant
- 61% pulse vs 15% traditional = remission in 12 weeks
  - 39% pulse vs 60% traditional = extra therapy
- Dose higher in traditional group (3.2 mg/kg mean)
- No stat diff for time to remission, adjuvant treatment or ADR


100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Percentage of dogs reaching CR
'Traditional'
'Pulse'
1
2
3
4
5
6
7
8
9
10
11
12
Weeks



AZATHIOPRINE

- Antagonist of purine metabolism
  - Inhibition of DNA, RNA and protein synthesis
  - Cytotoxic to T cells
  - 1.5 – 2.5 mg/kg PO q 24 hrs
- Lag time of 4-8 weeks
- Maintenance of q 48-72 hrs
- Side effects:
  - Myelosuppression (lymphopenia, anemia, leukopenia)
  - Increased risk of infection, GI upset, pancreatitis
  - Hepatotoxicity

AZATHIOPRINE

- NOT cats
  - TPMT (thiopurine methyltransferase) enzyme
    - Profound neutropenia and thrombocytopenia
  - High in Malamutes
- Complete blood count
  - q 2-3 wks for 2 months then q 3 months
- Serum biochemistry profile
  - q 2-3 wks for 1-3 months then pending dosing
- Then reduce both to q 6 months

CHLORAMBUCIL

- Alkylating agent
  - Interferes with cross-linking of DNA
- 0.1-0.2 mg/kg PO q24hrs (dogs)
  - 8-12 week lag phase
  - Then taper to lowest dose q 48 hrs
  - Same monitoring as azathioprine
    - Myelosuppression and hepatotoxicity
    - Not as common as azathioprine
    - GI upset, anorexia, increased susceptibility to infections

MYCOPHENOLATE MOFETIL

- Inhibits gaunine synthesis
  - T and B cells are dependent upon gaunine
- Success rates of 50%
- Dosage: 15-39 mg/kg q 12-24 hrs
- Lag time
- Side effects: vomiting, diarrhea, bone marrow suppression and increased susceptibility to opportunistic infections
- CBC q 2-3 weeks for first 1-2 months
- Biochemistry prior to use, after 2-4 weeks and then pending response

Ackerman AL, May ER, Frank LA. Vet Dermatol 2017:28(2);195-e44.

CYCLOSPORINE

- Off-label use
- Calcineurin inhibitor
  - Decreases IL-2 production & activation of T cells
  - Decreases cytokine production
- 5-30 mg/kg q 24 hrs for 30-60 days then taper
- Screen cats for toxo (IgG/IgM), FeLV/FIV
- GI upset, secondary infections, gingival hyperplasia, papillomatosis, hepatotoxicity and nephrotoxicity at higher doses

OCLACITINIB

Received: 15 January 2023 | Accepted: 26 August 2023
DOI: 10.1111/vde.13203
ORIGINAL ARTICLE
Veterinary Dermatology

The use of oclacitinib compared to azathioprine in the management of canine pemphigus foliaceus: A retrospective analysis

Andrea Hernandez-Bures[1] | Wille A. Bidot[2] | Craig E. Griffin[3] | Wayne S. Rosenkrantz[1]

- Off-label use
- 30 dogs -> OC or AZA + GC
  - Induction
    - Partial remission: imp by greater or equal 50% (poor <50%)
  - Maintenance
    - Remission maintained with OC/AZA + GC at same or tapered
- No significant diff in ability to induce remission (AZA 13 & OC 11 PR or CR)
- No difference between GC sparing effect (AZA 77.9% red, OC 64.4%)
- 1/15 in AZA and 3/15 in OC had 100% reduction of GC dose
- No major BW abnormalities in OC group

OTHER OPTIONS

- Topical Hydrocortisone aceponate
- Pentoxifylline
- Topical tacrolimus
- Bruton's tyrosine kinase inhibitor

PROGNOSIS

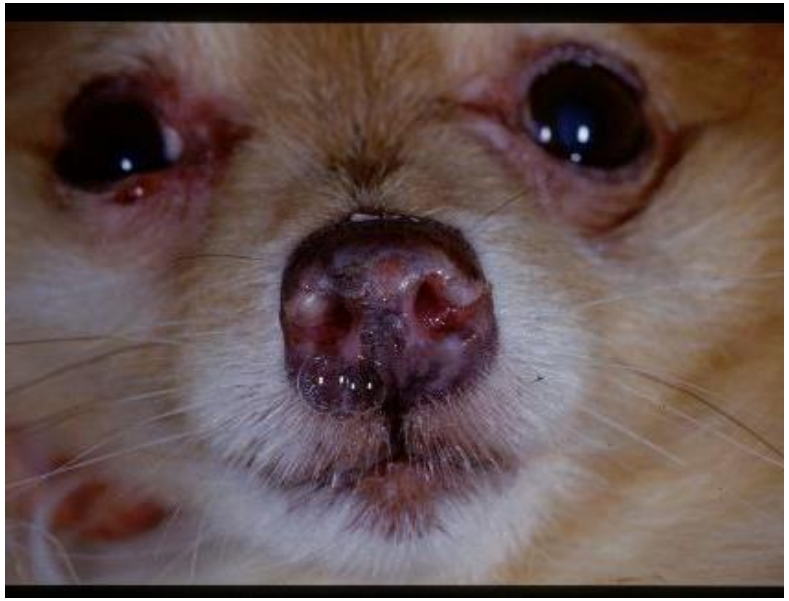
- Prognosis fair to good
  - 71% survival rate
  - Retrospective fatality rate was 60.5%
    - Txt 10+ months correlated with survival
- One study showed average time to remission 9 months
- Euthanasia
  - Finances
  - No response
  - Side effects

Gomez S, Morris DO, Rosenbaum MR, et al. J Am Vet Med Assoc. 2004;224(8):1312-1316.

CATS WITH PF

- Glucocorticoid monotherapy induced remission in majority
  - 2.8 mg/kg/day (lower)
  - Injectable steroids not recommended
- Negative impact on QofL

Jordan TJM, Affolter VA, Outerbridge CA et al. Vet Dermatol 2019:30;209-217.



DISCOID LUPUS ERYTHEMATOSUS

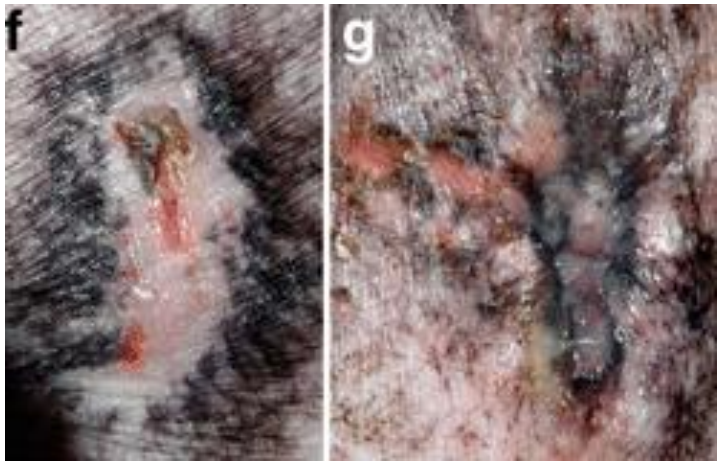
- First documented in 2 dogs in 1979
- Localized (facial) vs generalized
- 31% GSD in largest 4 studies
  - Akita, husky, collie, Shetland sheepdog
- Rarely in cats
- No sex predilection
- Young to middle age
  - Median age 7 yrs

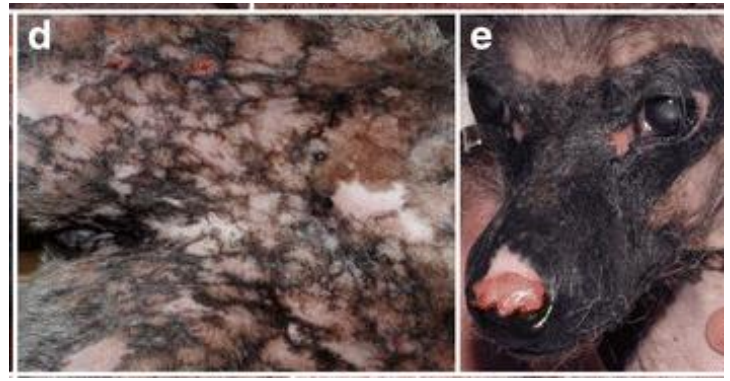
Olivry T, Linder KE, Banovic F. BMC Veterinary Research:2018;14:132

DISCOID LUPUS ERYTHEMATOSUS

- Immune complex deposition at BM
  - Dogs positive for IgG
- Nasal planum
- Periocular region, pinnae, muzzle, lips
  - Paw pads rarely affected
- Depigmentation, erythema
- Chronicity = erosions, ulcers, crusting
- Deep nasal ulcers = epistaxis

GENERALIZED DLE





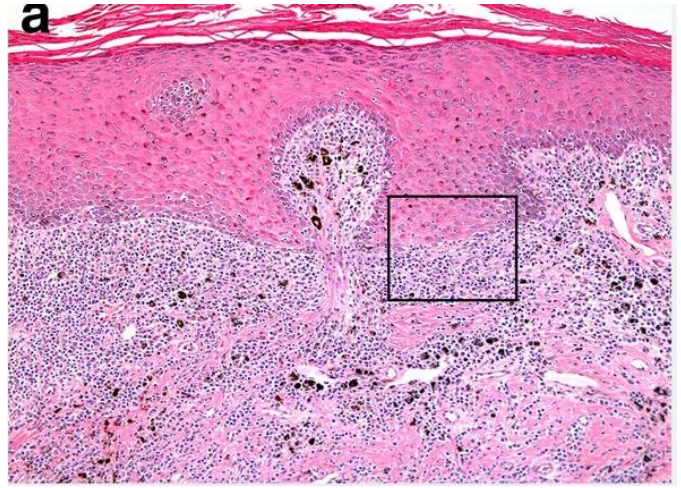
- Generalized plaques - depigmentation, erythema, scaling, alopecia, ulcers
- Neck, dorsum, lateral thorax
  - 40% MC
- Reticulated hyperpigmentation visible on abdomen & thorax in two
- Pruritus and pain
- Ddx: Ischemic dermatopathy, old dog EM

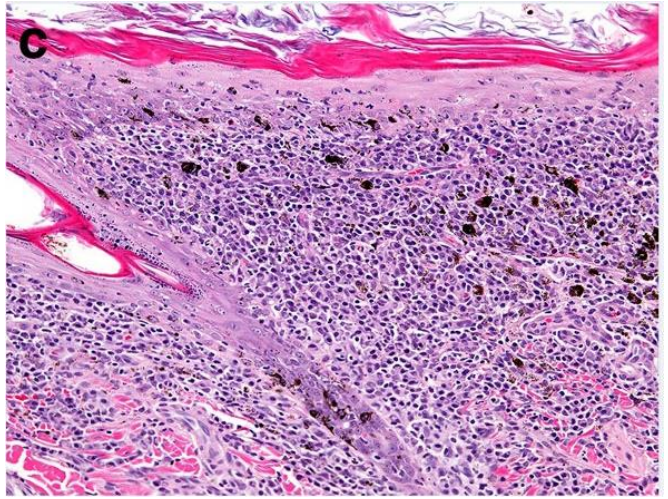
DIFFERENTIAL DIAGNOSES

- Mucocutaneous pyoderma
- Uveodermatologic syndrome
- Cutaneous T cell epitheliotropic lymphoma
- Pemphigus complex (PE)
- Discoid Lupus Erythematosus
- Systemic Lupus Erythematosus
- Superficial necrolytic dermatitis
- Infectious (lower on list)
  - Demodicosis, Dermatophytosis

DIAGNOSTIC WORK-UP

- Cytology
- Deep skin scraping
- Fungal culture
- Biopsy
  - Lymphoplasmacytic interface dermatitis
  - Hydropic degeneration of basal cells
  - Pigmentary incontinence
- Canine DLE and mucocutaneous pyoderma (MCP) similar
  - Bloodwork





DIAGNOSTIC TESTING

- Direct immunofluorescence reveals immunoglobulin deposits at the dermoepidermal junction
- ANA generally negative
- Tests for other circulating autoantibodies generally negative
- Skin cytology = unrewarding

TREATMENT

- Avoid sunlight
- Topical tacrolimus monotherapy
  - q12 hours for 4-6 weeks to achieve remission, then tapered
- Few potential side effects

TETRACYCLINE/NIACINAMIDE

- 70% response
- Tetracycline
  - Inhibits neutrophil chemotaxis, degranulation, phagocytosis
  - Inhibits lymphocyte transformation, proliferation
- Niacinamide (Vasodilator)
  - Stabilizes leukocytes from releasing proteases
  - Protects mast cells from activation
  - Prevents release of chemotactic factors
  - Blocks IgE mediated mast cells degranulation

White SD, Rosychuk RAW, Reinke SI, Paradis M. J Am Vet Med Assoc. 1992;200:1497–500.

TETRACYCLINE/NIACINAMIDE

- Dosing:
  - 250 mg of each <10 Kg
  - 500 mg of each >10 Kg
  - Q 8 hrs until resolved -> 90-120 days
  - Taper to twice daily
- Side effects
  - GI upset, anorexia, lethargy
  - Hepatotoxicity or hindlimb weakness
  - Not in dogs with neuropathies (seizures)
  - NIACIN: vasodilation, hypotension, tachycardia, and GI

PROGNOSIS

- Good prognosis
- SCC development from chronic DLE
- No reports of progression to SLE

Scott DW, Miller WH. Vet Dermatol. 1995;6:99–104.

SYMMETRIC LUPOID ONYCHODYSTROPHY

- Cause and pathogenesis unknown
- Young to middle age
- No sex predilection
- German shepherd, Gordon setter, Rottweiler
  - Dog Leukocyte Antigen (DLA) class II alleles documented indicating possible genetic predisposition
    - Part of MHC
    - DLA involved in regulation of antigens
      - Increased risk of disease development

Wilbe M, Ziener ML, Aronsson A, et al. PLoS ONE 2010;5:e12332.

DIFFERENTIAL DIAGNOSES

- Symmetric Lupoid Onychodystrophy
- Trauma
- Dermatophytosis
- Neoplasia
- Infection

DIAGNOSTIC WORK UP

- Cytology of nailbed
- Radiographs
- CBC and biochemistry and thyroid panel
- Biopsy to confirm SLO
  - Hydropic and lichenoid interface dermatitis
- Most dermatologists diagnose SLO based on clinical signs

TREATMENT

- Treat secondary infections
- Claw trim q 2-3 weeks
- Pain control
- GA to remove loose claws - pain relief +/- bandaging
- Improvement in 3-4 months then taper
  - SLOW taper every 6-8 weeks (0.7 to 2.1 mm/wk)
  - Assess growth at nail base
- Tetracycline/niacinamide (as for DLE)
- Cyclosporine as for PF (my opinion: lower dose needed)

TREATMENT

- Cyclosporine and fish oil equally effective when dog fed diet high in omega-3
  - Fish oil group 14/18 normal claws (mean)
  - Cyclosporine group 15/18 normal claws (mean)
- My opinion: Steroids for pain control, immediate anti-inflammatory action for first 4 weeks
- Type of fatty acid not important

Ziener ML, Nødtvedt A. Acta Veterinaria Scandinavica. 2014;56:66.

SLO, HYPOTHYROIDISM AND FOOD ALLERGIES

- 30 dogs 17% hypothyroidism
- Antithyroid antibodies?
- Same DLA haplotype protective for hypothyroidism in Gordon setters?
- 1 dog with confirmed CAFR

Mueller RS, Rosychuk RA, Jonas LD. J Am Anim Hosp Assoc. 2003;39:139–150.

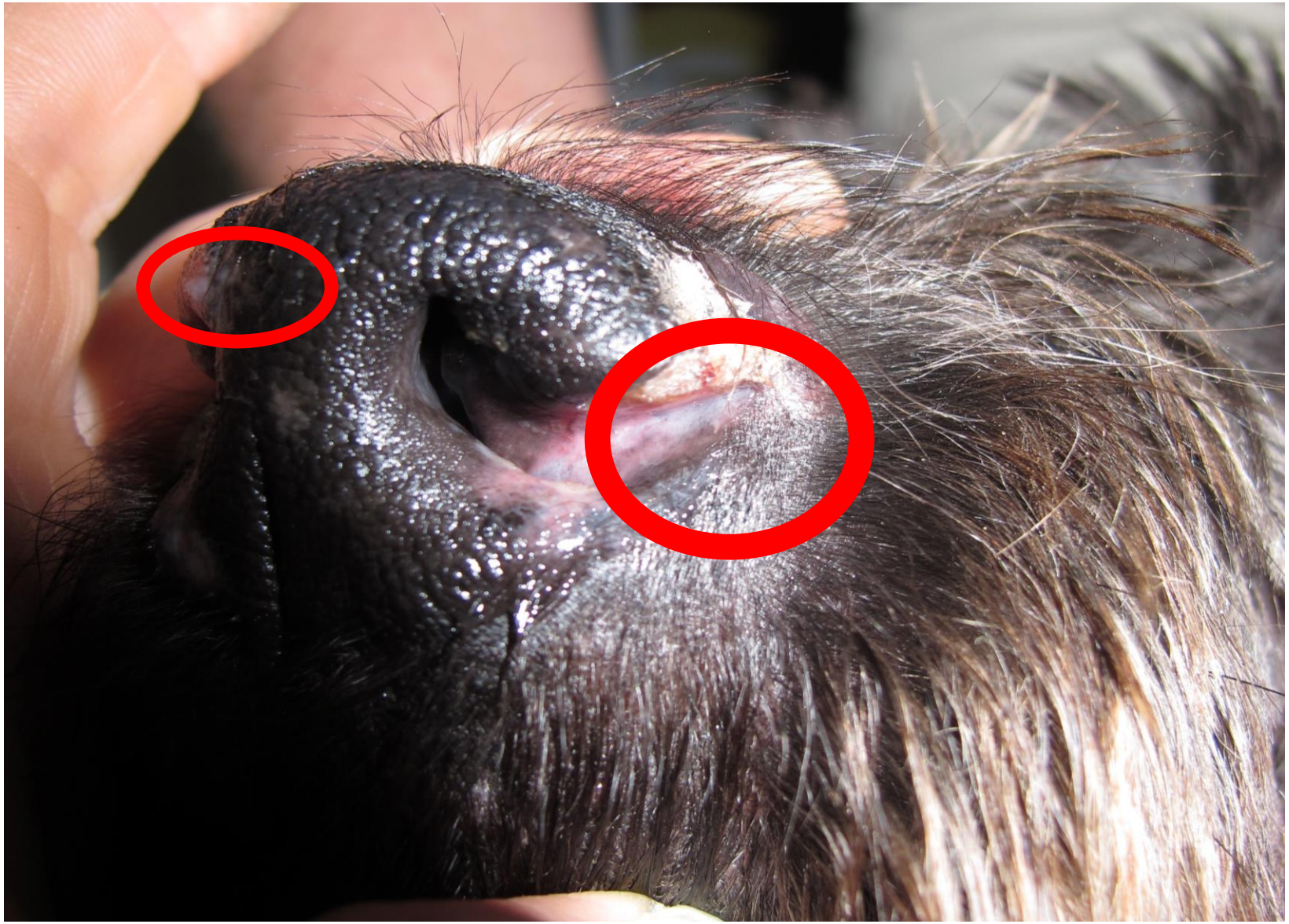
ART OF THE SKIN BIOPSY

- Think of Ddx
- Primary lesions ideally
  - Waxing and waning
- JUST abnormal
- Multiple samples
  - Include crust
- Footpad: Edge
- No sterile preparation

SITE SELECTION

- Study by Mauldin *et al*
- Draw straight line at biopsy site
  - Parallel to direction of hair growth
- Midpoint will be sample area
- Consistently able to view hair follicle from os to bulb
- No ulcers

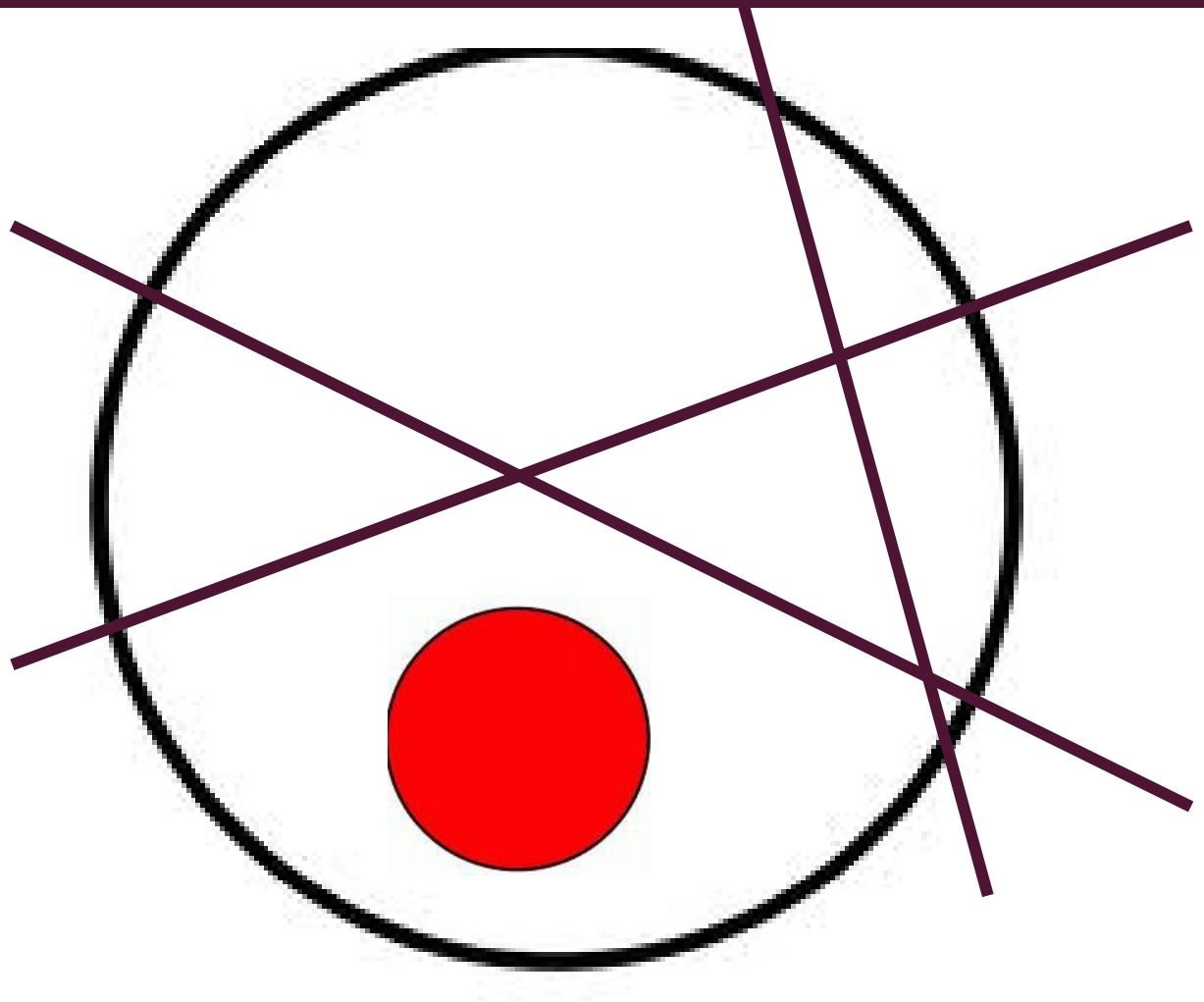
Mauldin E, Castle S, Davenport GM *et al*. *Vet Med* 2002: April; 286-288.



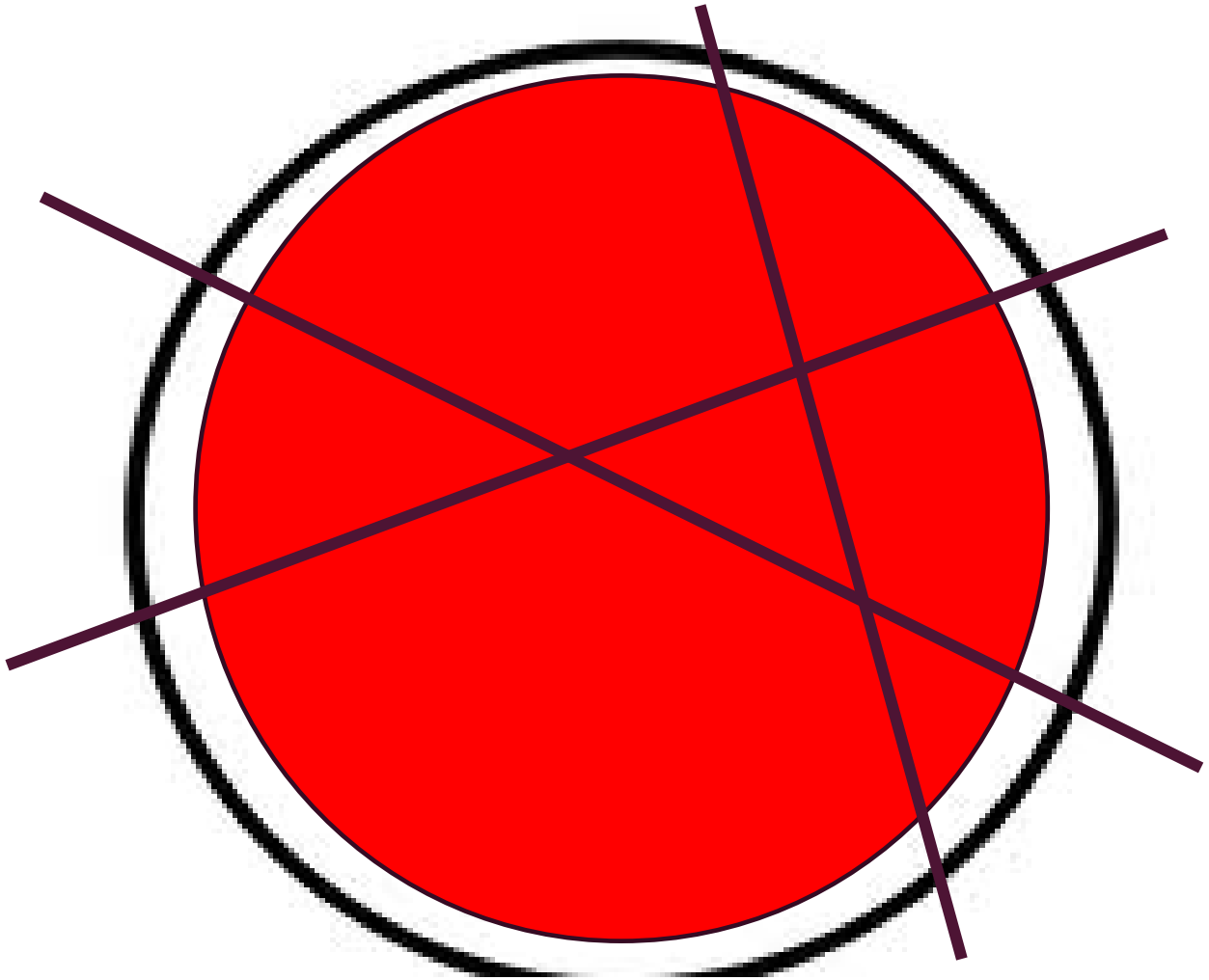
ANESTHESIA

- Local vs general
- Selection of punch
  - Covers lesion
  - Smaller for certain location
  - Generalized
    - Go big or go home!

BIOPSY PUNCH SIZE

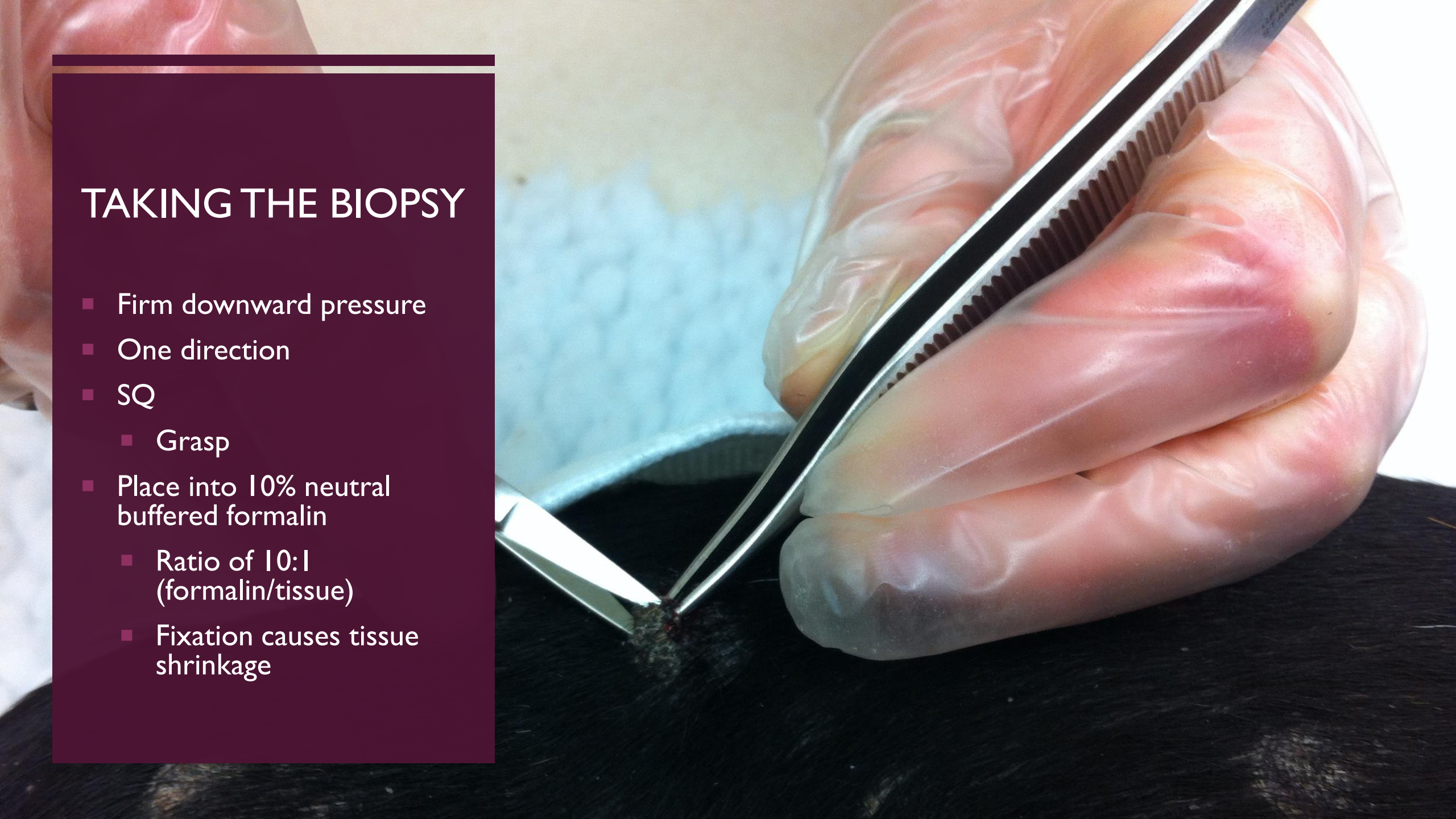


BIOPSY PUNCH SIZE



TAKING THE BIOPSY

- Firm downward pressure
- One direction
- SQ
  - Grasp
- Place into 10% neutral buffered formalin
  - Ratio of 10:1 (formalin/tissue)
  - Fixation causes tissue shrinkage



SUBMISSION

Avoid freezing

- 95% ethyl alcohol as 10% fixative volume
- 12 hours fixation before cold exposure

>1cm in diameter → section

Veterinary dermatopathologist or pathologist with interest in skin

Differential list, history, photos, response to medications

Special stains for infectious disease

Diagnosing The Avengers: Penn dermatologists explore medical conditions of Marvel universe

by Jules Lipoff and Misha Rosenbach, For the Inquirer, Updated: April 30, 2019

Hulk/Bruce Banner

Mark Ruffalo as Hulk.

Risky behavior: exposure to gamma radiation.

Current signs of disease: green skin, dissociative identity disorder (previously known as multiple personality disorder).

Radiation can have many affects on the body; in the skin especially, it can cause radiation dermatitis and increase the risk of skin cancers.

The Hulk's green skin can be caused by extensive green tattoos and medication-related discoloration. Patients with chromhidrosis may develop green sweat. The bacteria *Pseudomonas* is known for causing green nails. Leukemia spreading into the skin can also sometimes appear green (with lesions called chloromas).

Gamora also has green skin, so these must all be considerations for her health as well.

Groot

COURTESY OF THE FRANKLIN INSTITUTE
Groot is voiced by Vin Diesel.

Risky behavior: is a tree.

Though Groot's exact species of tree has not been clearly defined, he is at risk for many common tree diseases that other Avengers can ignore. For instance, oak wilt kills thousands of oak trees each year. It is a fungus that can move through roots or insects (watch out, Ant-Man) and causes leaf discoloration and death. Other tree diseases with scary names include: apple scab, needle blight, lethal yellow, and thousand canker disease.

Groot should regularly seek a checkup with a botany specialist.

CASE TIME

INTERACTIVE ☺

WINSTON, 3 YR OLD, MN, PUG

- AVC Derm 1.5 yrs prior
  - Diagnosed with AD
- Apoquel for 9 months
  - More pruritic
  - More lesions
  - Non-responsive to antibiotics
  - Non-responsive to food change

WINSTON, 3 YR OLD, MN, PUG

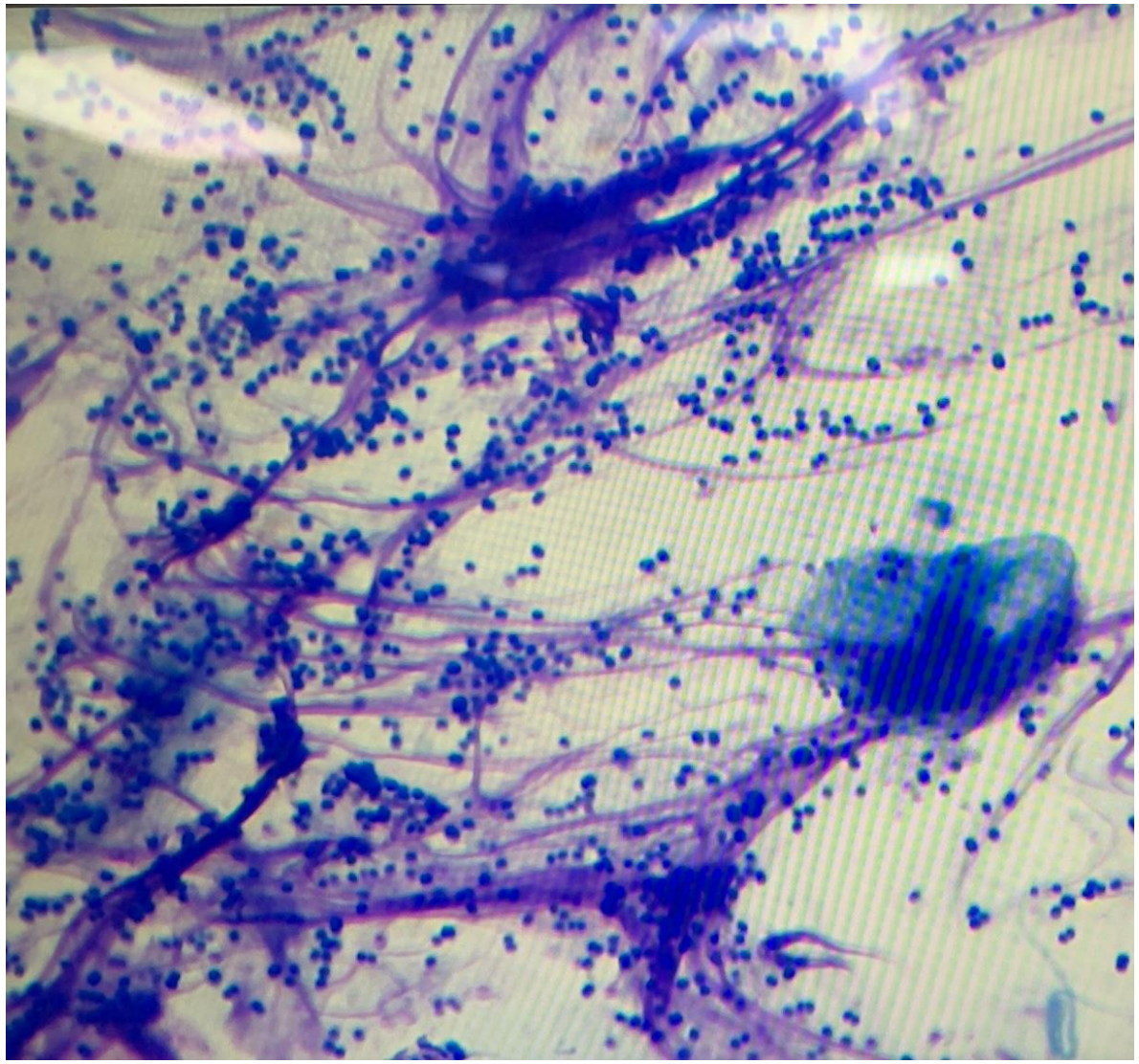
- Lethargy
- No GI
- Other dog in house unaffected
- Fish based grain inclusive diet + treats
- Receives selamectin monthly
- No PU/PD
- No known health issues

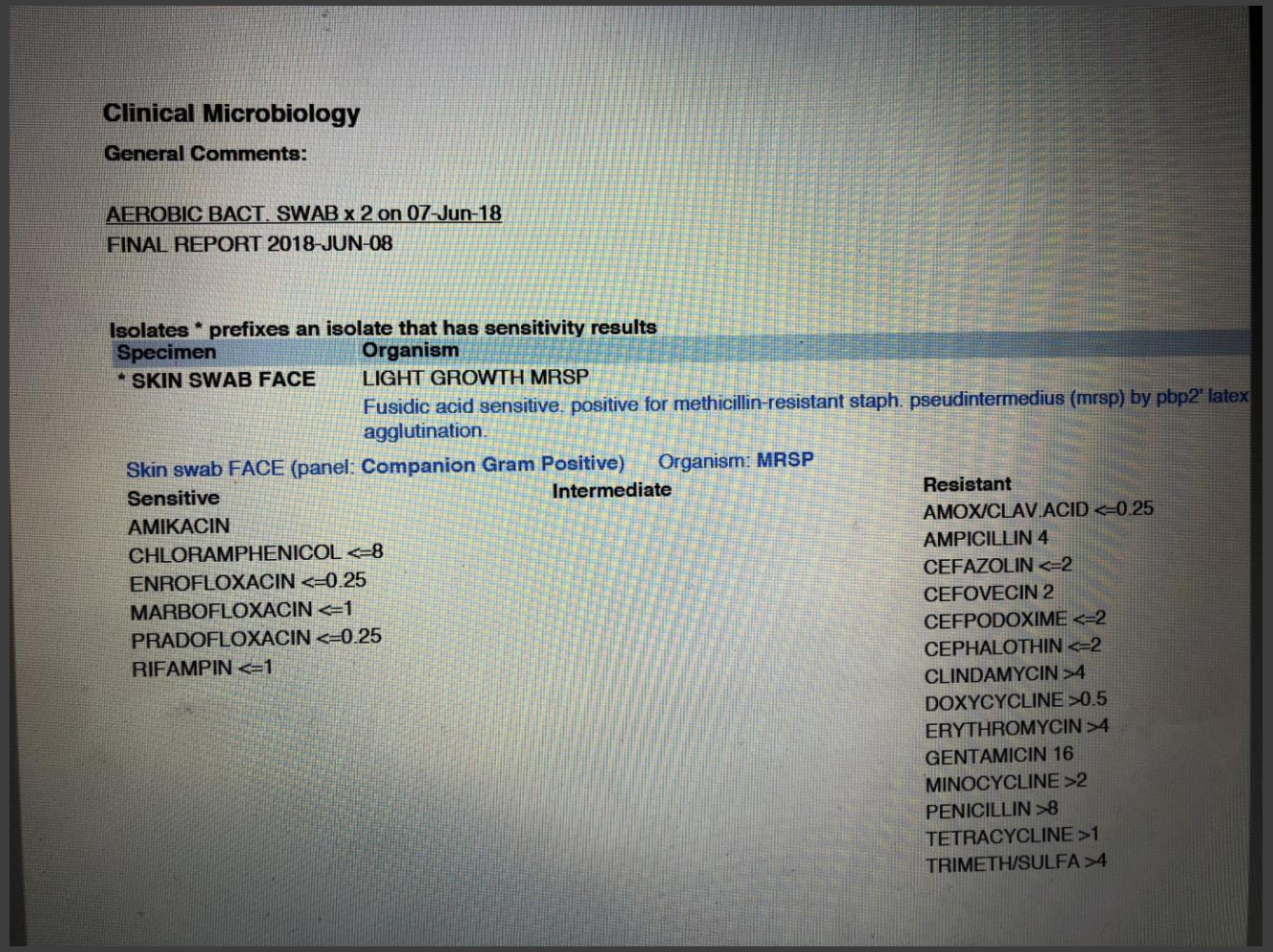
DIFFERENTIALS

- What could this be?
- Allergy flare
- Cutaneous adverse food reaction
- Infection
- Parasite
- Cutaneous T Cell lymphoma
- Endocrine disease
- Dermatophytosis
- Immune mediated disease

WHAT NOW?

- Minimum database
- Cytology + Skin scraping + Wood's lamp





Clinical Microbiology

General Comments:

AEROBIC BACT. SWAB x 2 on 07-Jun-18
FINAL REPORT 2018-JUN-08

Isolates * prefixes an isolate that has sensitivity results

Specimen	Organism
* SKIN SWAB FACE	LIGHT GROWTH MRSP
	Fusidic acid sensitive. positive for methicillin-resistant staph. pseudintermedius (mrsp) by pbp2' latex agglutination.

Skin swab FACE (panel: **Companion Gram Positive**) Organism: **MRSP**

Sensitive	Intermediate	Resistant
AMIKACIN		AMOX/CLAV.ACID <=0.25
CHLORAMPHENICOL <=8		AMPICILLIN 4
ENROFLOXACIN <=0.25		CEFAZOLIN <=2
MARBOFLOXACIN <=1		CEFOVECIN 2
PRADOFLOXACIN <=0.25		CEFPODOXIME <=2
RIFAMPIN <=1		CEPHALOTHIN <=2
		CLINDAMYCIN >4
		DOXYCYCLINE >0.5
		ERYTHROMYCIN >4
		GENTAMICIN 16
		MINOCYCLINE >2
		PENICILLIN >8
		TETRACYCLINE >1
		TRIMETH/SULFA >4

HOW TO TREAT

WHY DEMODICOSIS??

- No immunosuppressive medication
- Endocrine?
- Neoplasia?
- Allergic skin disease?

Bloodwork unremarkable
+
History of allergic skin disease

TREATMENT PLAN

- Isoxazoline
  - Until 2 negative scrapings 4 weeks apart
- Topical antimicrobial treatment
  - 4 weeks then REPEAT cytology
- Start cyclosporine

LIVING HIS BEST LIFE

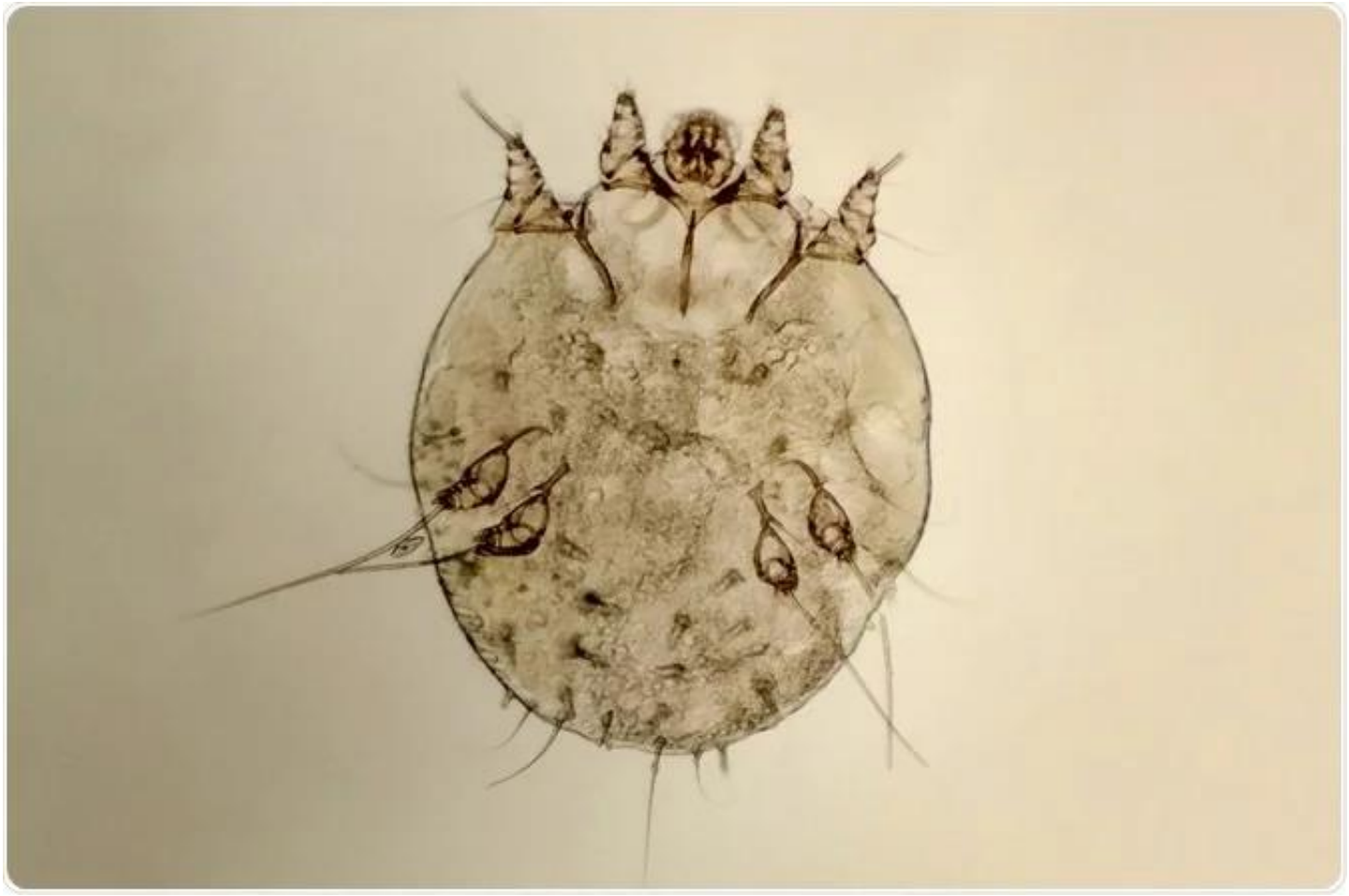
MILO
5 YR, MN, MIXED BREED

MILO

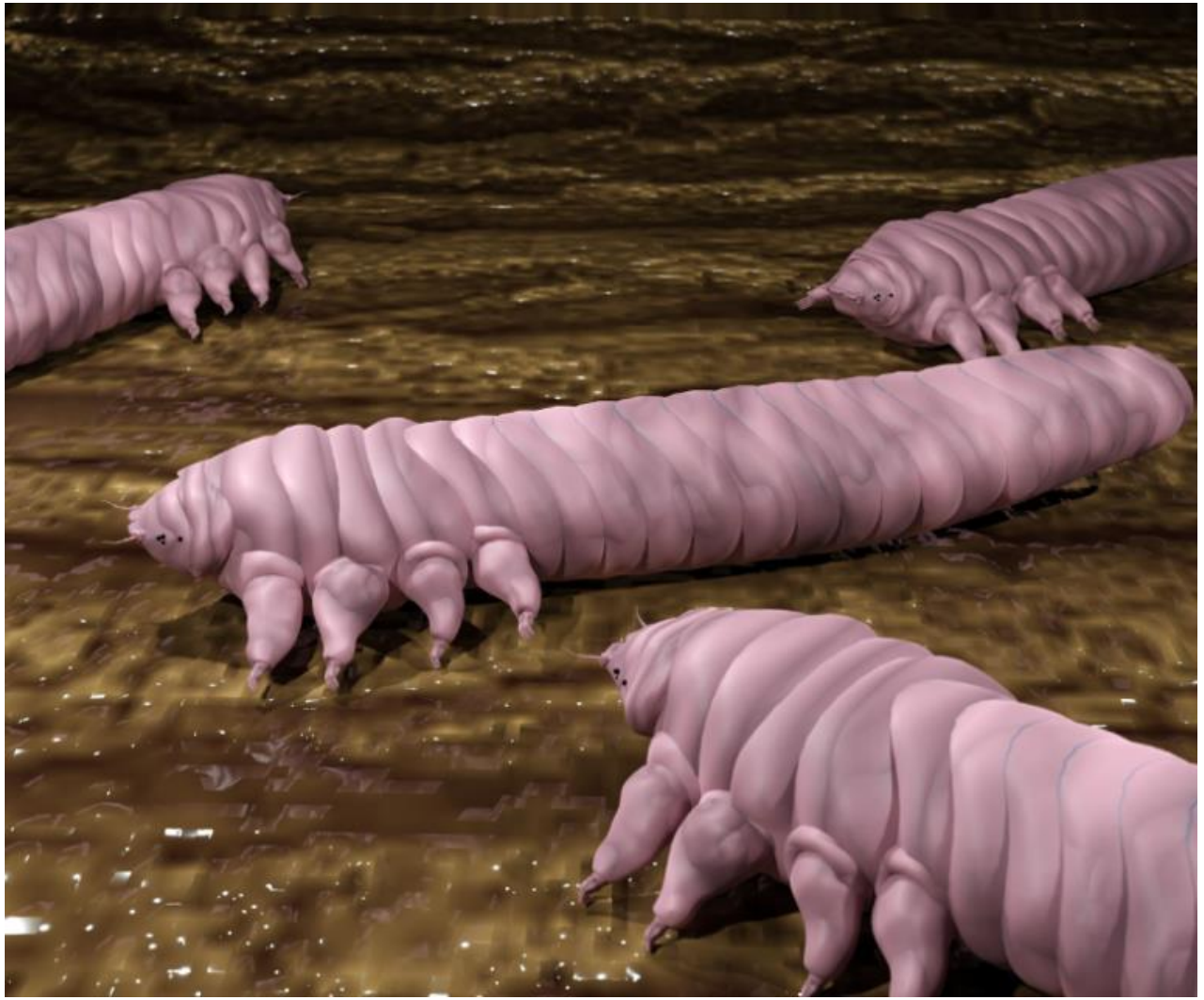
- Intensely pruritic for 12 months
- No prior history of skin disease
- Otherwise healthy
- Family vet
  - Multiple diet trials (great compliance) – no response
  - Cytology at every visit – infections treated appropriately
  - Fungal culture negative
  - Skin scrapes negative

MILO

- Apoquel – no response
- Cytopoint – no response
- Atopica – no response
- Steroids – no response
- Considering immunosuppression with azathioprine



WHAT WOULD YOU DO?



NEVER FORGET PARASITES!

FIDGIT, 12 YR, MN, DSH

- Convenia for URI
- 7 days later “flaky” skin

CUTANEOUS ADVERSE DRUG REACTION

- Histopathology consistent
- Condition worsened

TREATMENT

- Started oral glucocorticoids
- Treated secondary infection
- Once medication ”gone” -> signs resolve with time

6 MONTHS LATER

EXFOLIATIVE DERMATITIS

- Paraneoplastic syndrome
- Thymoma
- Diagnostic imaging not consistent

4 MONTHS LATER

- “Stable” but needed prednisolone

3 MONTHS LATER

- Presented to Internal Medicine
- Changes in stool
- Mild ocular discharge
- Cough
- Ct scan

THANK YOU