



AMERICAN COLLEGE OF
ACVD
VETERINARY DERMATOLOGY

Cutaneous Manifestations of Systemic Disease

Catherine Outerbridge DVM , MVSc
Diplomate ACVIM (Small Animal Medicine)
Diplomate ACVD
University of California , Davis , CA , USA

UCDAVIS

Catherine Outerbridge

I have the following disclosures* related to my presentation:

Employee: University of California, Davis
School of Veterinary Medicine and
William Pritchard Veterinary Medical Teaching Hospital

Grants/Research contracts: PRINCIPIA BIOPHARMA

Consulting: ELANCO
ZOETIS

Investments: none

I will discuss results of clinical trial for the following agents that are currently NOT approved for use in animals.

none

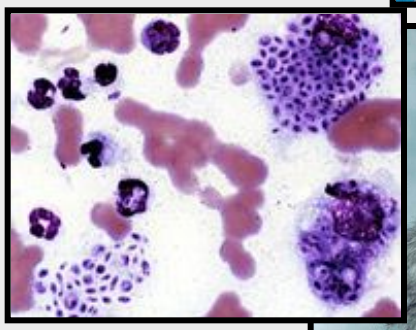
*Disclosures include spouse and immediate family where relevant.

Cutaneous Manifestations of Systemic Disease…

- Cutaneous changes associated with
  - Hormonal / endocrine disturbances
  - Paraneoplastic / metastatic changes
  - Nutritional or metabolic perturbations
  - Systemic infectious disease
  - Vasculitis
  - Auto-immune systemic disease

Cutaneous Manifestations of Systemic Disease

- Recognizable markers of underlying systemic disease
- Skin can provide vital diagnostic information
- Skin lesions indicate systemic disease because of common pathogenesis



The Skin & Systemic Disease

- Role in homeostasis & defense
- Appearance & integrity influenced by
  - Hormonal levels & interactions
  - Nutritional status
  - Perfusion & vascular integrity
  - Systemic organ function

Courtesy of SD White

DO skin lesions warrant evaluation for systemic disease??

1. Yes, skin biopsy for possible SLE
2. Yes, Evaluate for liver disease
3. No, Check for exposure to photosensitizing plants : contact or ingestion
4. No, stop smearing stuff on the horse

Skin lesions warrant evaluation for systemic disease??

2. Yes, Evaluate for liver disease

- Type III systemic photosensitivity: (Secondary photosensitivity)
- Ingested chlorophyll in gut → phylloerythrin
  - absorbed into portal circulation; liver removes & excretes in bile
  - Phylloerythrin ⬆ as liver function ⬇
  - Hepatic toxins: plants containing pyrrolizidine alkaloids: Common groundsel, Salvation Jane

Cutaneous Manifestations of Systemic Disease…

- Cutaneous changes associated with
  - Hormonal / endocrine disturbances

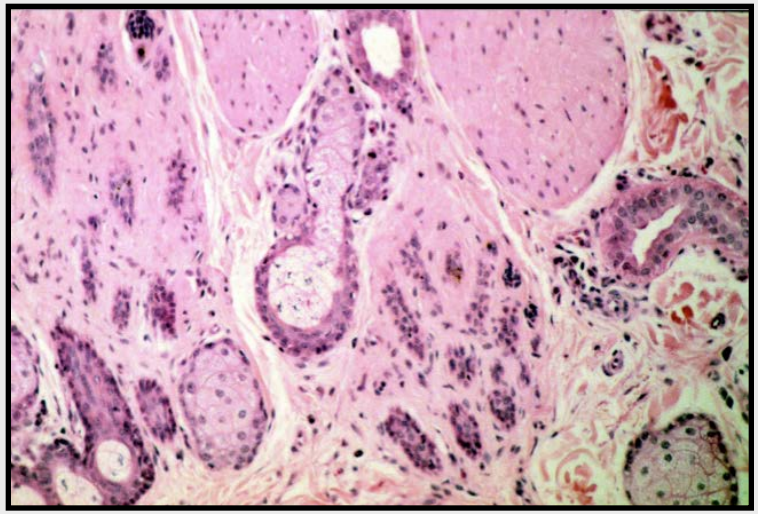
Hormonal Disturbances

- Most common endocrinopathies with dermatologic manifestations
  - Canine hypothyroidism
  - Hyperadrenocorticism
- Diagnosis based on clinical suspicion w/ confirmation via provocative testing of gland function
- Hyperestrogenism : numerous causes

Skin Changes in Hypothyroidism

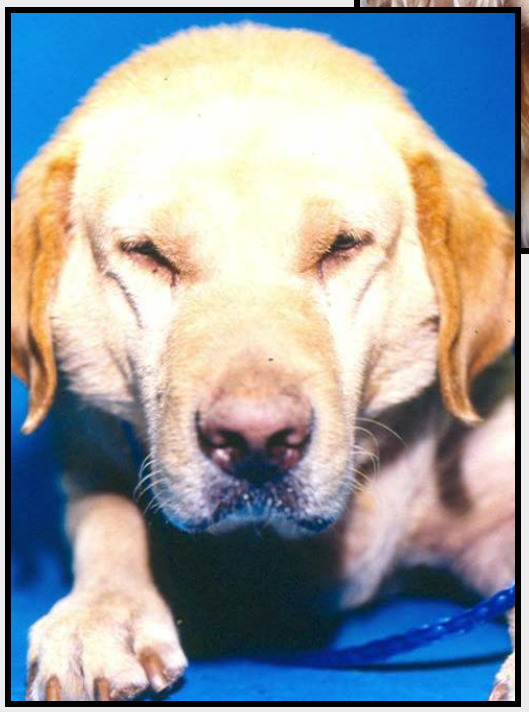
- Sebaceous gland & follicular atrophy :
  - **Symmetric alopecia, dull / dry hair coat**
- Failure to initiate anagen :
  - **Alopecia, often in areas of wear**
- Disturbances in cornification :
  - **Scaling**

Predominance non haired telogen follicles



Skin Changes in Hypothyroidism

- Hyperpigmentation
- Glycosaminoglycans ↑ in dermis
  - **myxedema**
  - **“tragic look”**
- Predisposes to
  - Recurrent pyoderma
  - Otitis externa



Pinnal margin scaling in a hypothyroid dog

Alopecia over the dorsal muzzle in a hypothyroid dog

Unusual alopecic pattern in a hypothyroid Rhodesian Ridgeback

A

Which dog is hypothyroid?

1) A
2) B
3) Both
4) Neither, these dogs have follicular dysplasia
5) Can't tell, would do T4

B

A

Which dog is hypothyroid?

1) A
2) B
3) Both
4) Neither, these dogs have follicular dysplasia
5) Can't tell, would do T4

B


Photo courtesy of Dr. Stephen White

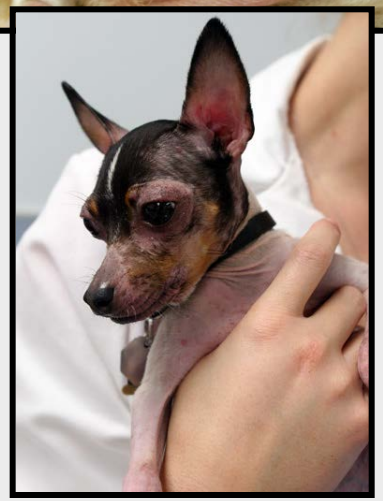
Endocrine Skin Changes in HAC

- Epidermal & dermal atrophy
  - **Thin, hypotonic skin, easy bruising, visible dermal vasculature, phlebectasia**
- Increased telogen follicles & pilosebaceous atrophy
  - **Alopecia, comedones**

Endocrine Skin Changes in HAC

- Suppressed keratinocyte & fibroblast proliferation
  - **Cornification disturbances, poor wound healing**

- ⬇collagen synthesis
  - **Poor wound healing, ⬇ elasticity**



- Increased risk of infections : pyoderma, fungal infections, demodex

Calcinosis Cutis

- Dystrophic calcification
- Hypercortisolemia : dogs & chinchillas

- Erythematous papules coalesce & form gritty plaques, ulcerations, crusts
- Histology : mineralization of dermal collagen

Calcinosis Cutis

Veterinary Dermatology

Vet Dermatol 2013; **24**: 355–e79 DOI: 10.1111/vde.12026

Calcinosis cutis in dogs: histopathological and clinical analysis of 46 cases

Katherine A. Doerr*, Catherine A. Outerbridge†, Stephen D. White†, Philip H. Kass‡, Ryoji Shiraki§, Andrea T. Lam¶ and Verena K. Affolter**

- Predisposed breeds: Labradors, Rottweillers, boxers & Staffordshire terriers
- Majority iatrogenic hypercortisolemia or spontaneous HAC , 5 had renal disease
- Mineral is apatite

Calcinosis cutis

6 months later

This Boxer has……..

1) Endocrine alopecia

2) Cyclical flank alopecia

3) Telogen effluvium

4) Dermatophytosis

This Boxer has……..

1) Endocrine alopecia

2) Cyclical flank alopecia

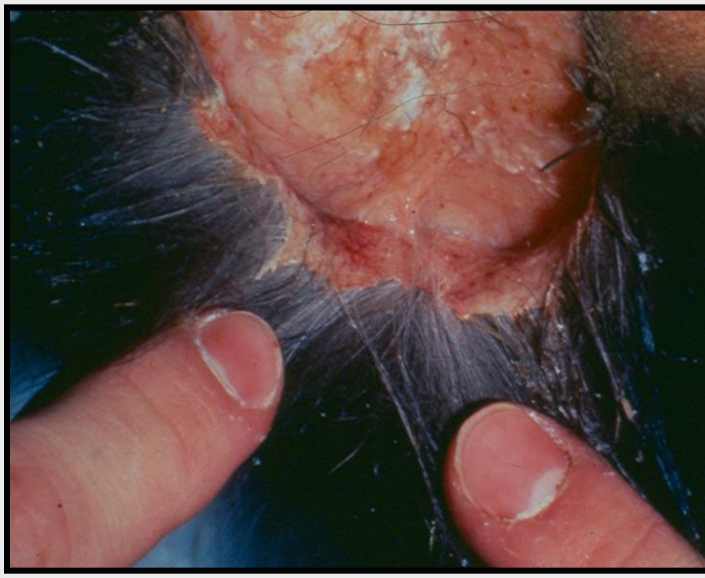
3) Telogen effluvium

4) Dermatophytosis

Not all alopecia is due to endocrine disease

Feline Acquired Skin Fragility

- Thin fragile skin , tears easily
- Hypercortisolemia
  - Pituitary dependent HAC , adrenal tumor , iatrogenic from corticosteroid administration
- ↑ progestational compounds



Courtesy Dr. R Rosychuk

Feline Acquired Skin Fragility

Courtesy of Verena Affolter

Hyperestrogenism

- Excess estrogen can inhibit anagen initiation ➡ alopecia
- Can occur w/
  - testicular tumors
  - cystic ovaries or granulosa cell tumors
  - estrogen supplementation for urinary incontinence
  - second hand exposure to human topical estrogens

Hyperestrogenism

- Excess estrogen can inhibit anagen initiation ➡ alopecia
- Can occur w/
  - **testicular tumors**
  - cystic ovaries or granulosa cell tumors
  - estrogen supplementation for urinary incontinence
  - second hand exposure to human topical estrogens

Testicular Tumor- Associated Skin Disease

- Uncommon male endocrine skin disease: testicular neoplasia, often cryptorchid testes
- If functional Sertoli-cell testicular tumor, estrogenic substances ➔ feminization + highly characteristic skin lesions
- Seminomas & interstitial cell testicular tumors can cause identical skin lesions

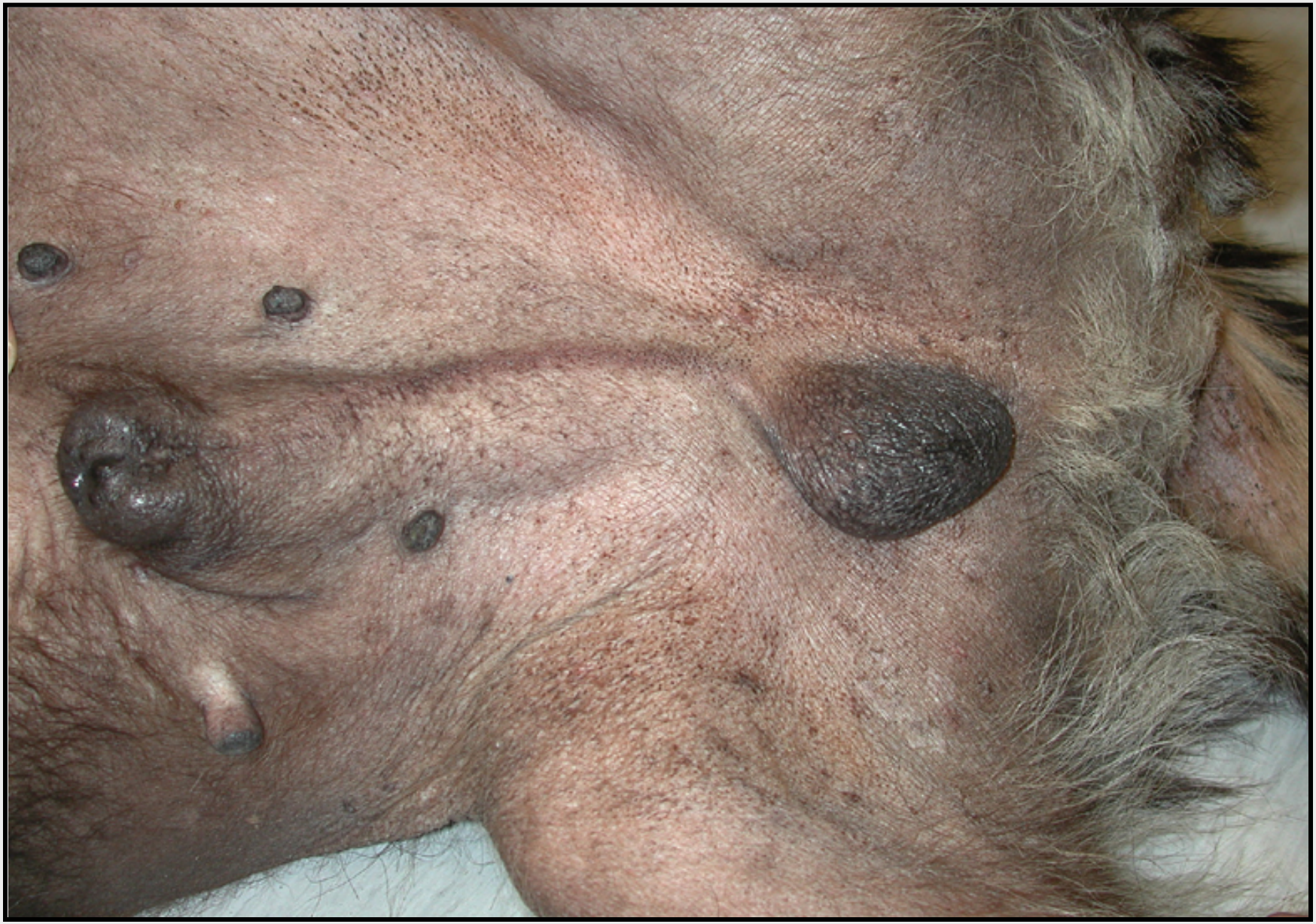
Canine Sertoli Cell Tumor-Associated Skin Disease

- Bilateral symmetrical alopecia begins in perineal & genital region → ventrum & caudal thighs
- Linear preputial erythema or hyperpigmentation
- Macular melanosis
- Prognosis good, metastasis rare

Photo courtesy of Dr. D. Spann

Sertoli Cell Tumor-Associated Skin Disease

Sertoli Cell Tumor-Associated Skin Disease



Sertoli Cell Tumor-Associated Skin Disease

Photos courtesy of Dr P Ihrke

What is a unique cutaneous sign of sex hormone imbalance seen only with canine testicular neoplasia ?

1. Ventral & caudal thigh alopecia w/ macular hyperpigmentation
2. Linear preputial erythema and/or hyperpigmentation
3. Feminization with gynecomastia
4. Dull, dry, brittle hair coat that epilates easily

What is a unique cutaneous sign of sex hormone imbalance seen only with canine testicular neoplasia ?

1. Ventral & caudal thigh alopecia w/ macular hyperpigmentation
2. Linear preputial erythema and/or hyperpigmentation
3. Feminization with gynecomastia
4. Dull, dry, brittle hair coat that epilates easily

Clues to the Diagnosis

- Male dog
- Palpable testicular mass or cryptorchid
- Linear preputial erythema or hyperpigmentation
- Perineal, caudal thigh & ventral alopecia w/ macular hyperpigmentation
- Feminization

Cutaneous Manifestations of Systemic Disease…

- Associated with
  - Hormonal / endocrine disturbances
  - Paraneoplastic / metastatic changes

Paraneoplastic Syndromes :

- Cutaneous clinical signs develop distantly from the tumor site
- Skin lesions caused by presence of tumor but NOT skin infiltration by neoplastic cells

- Pathomechanisms:
  - Humoral factors released by tumor
    - Hormones, cytokines, growth factors
  - Immune response targeting tumor may cross react with normal tissue

Paraneoplastic Syndromes Yes? – No? - Maybe…

- Classification - ‘Fair’ to use term *paraneoplastic* if cancer simply produced more of the substance that the organ normally produces?

- ‘Paraneoplastic’? Hyperadrenocorticism, Sertoli cell tumor-associated skin disease?

Paraneoplastic Syndromes : Establishing Suspicion or Proof

- Removal of 1^0 tumor causes resolution or temporary regression of syndrome
- Proven cases with similar clinical & histopathologic findings

Paraneoplastic Skin Diseases

- Canine Sertoli cell / testicular neoplasia
- Feline paraneoplastic alopecia
- Feline thymoma-associated exfoliative dermatitis
- Canine nodular dermatofibrosis
- Canine paraneoplastic pemphigus
- Canine superficial necrolytic dermatitis/ metabolic epidermal necrosis (small % w/ glucagonoma)

Paraneoplastic Skin Diseases

- Canine Sertoli cell / testicular neoplasia
- Feline paraneoplastic alopecia
- Feline thymoma-associated exfoliative dermatitis
- Canine nodular dermatofibrosis
- Canine paraneoplastic pemphigus
- Canine superficial necrolytic dermatitis/ metabolic epidermal necrosis (small % w/ glucagonoma)

Paraneoplastic Syndromes:

- Critically useful markers when…….
- Paraneoplastic skin lesions develop ***before*** other clinical signs occur
- Skin lesions are highly ***characteristic*** for a specific type of tumor

15 year old MC DSH: history of inflammatory bowel disease with worsening diarrhea and weight loss

1 month ago acutely developed, over 2 to 3 days, hair loss.

What would you do for Norman?

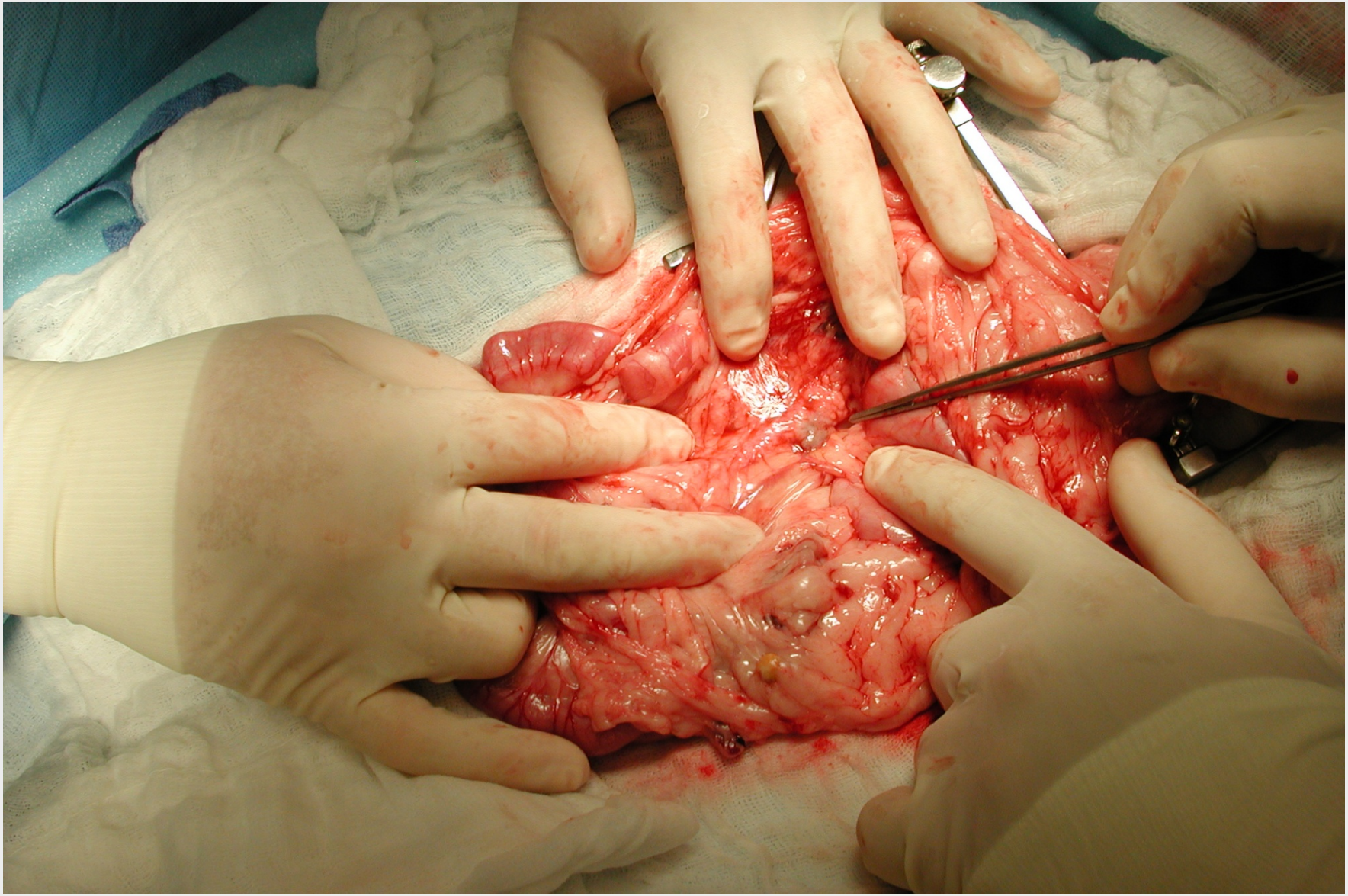
1. Derm data base: cytology, skin scrapings, wood's lamp, +/- fungal culture
2. Stop the owner from smearing topical corticosteroids…
3. Call a surgeon, this cat needs an abdominal exploratory
4. Call a radiologist, this cat needs an abdominal ultrasound

What would you do for Norman?

1. Derm data base: cytology, skin scrapings, wood's lamp, +/- fungal culture
2. Stop the owner from smearing topical corticosteroids…
3. Call a surgeon, this cat needs an abdominal exploratory
4. Call a radiologist, this cat needs an abdominal ultrasound

Clinical Findings

- Cytology: numerous *Malassezia* organisms
- Abdominal ultrasound: pancreatic mass
- Surgery



Paraneoplastic Skin Diseases

- Canine Sertoli cell / testicular neoplasia
- Feline paraneoplastic alopecia
- Feline thymoma-associated exfoliative dermatitis
- Canine nodular dermatofibrosis
- Canine paraneoplastic pemphigus
- Canine superficial necrolytic dermatitis/ metabolic epidermal necrosis (small % w/ glucagonoma)

Feline Paraneoplastic Alopecia

- Rare, cutaneous marker for underlying visceral neoplasia
  – Pancreatic adenocarcinoma
- Characteristic clinical appearance
  - Ventral alopecia w/ shiny skin
  - Hair epilates easily
  - Rapid onset (days to weeks)
  - Dry, fissured, peeling paw pads
  - ↑ Grooming (pruritus?), secondary *Malassezia* common

Feline Paraneoplastic Alopecia

Feline Paraneoplastic Alopecia

Feline Paraneoplastic Alopecia

Photo courtesy of Stephen White

Feline Paraneoplastic Alopecia

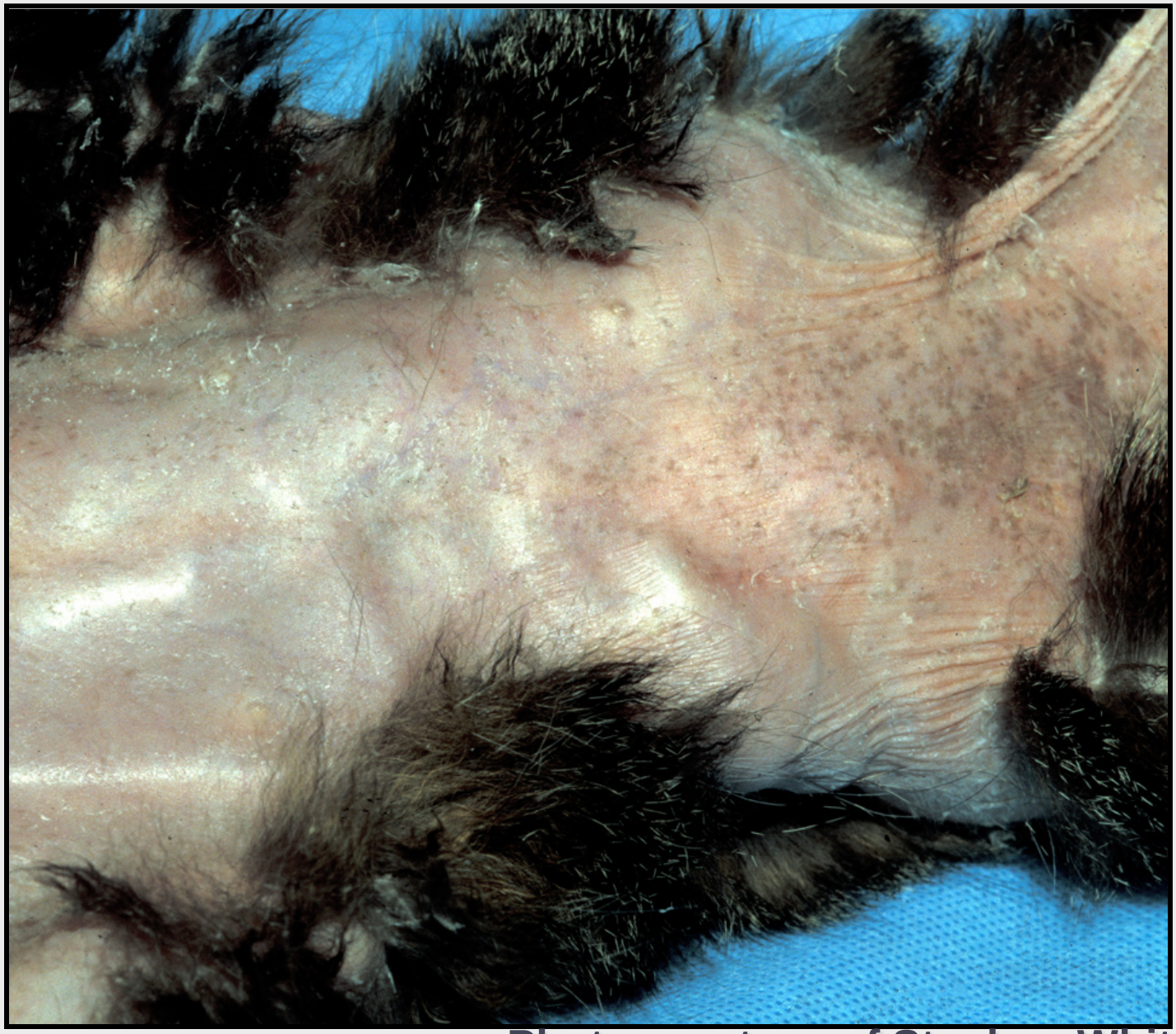
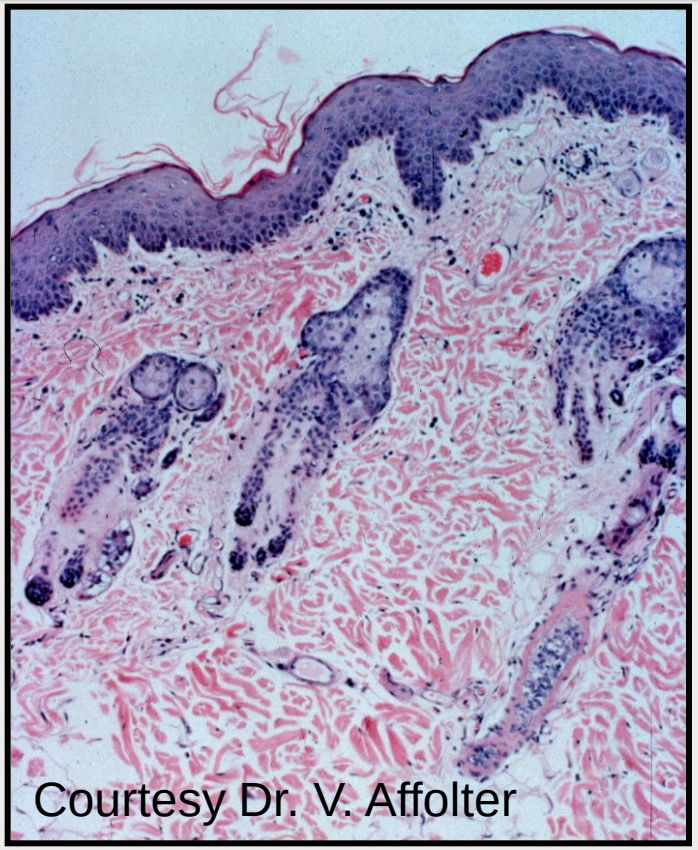


Photo courtesy of Stephen White

Feline Paraneoplastic Alopecia pawpads

Feline Paraneoplastic Alopecia

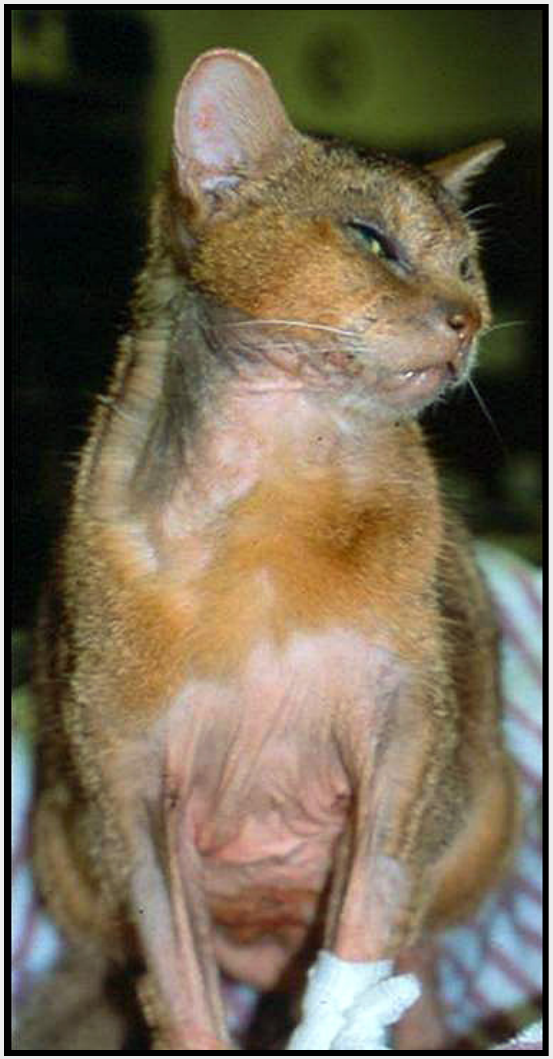
- Systemic - lethargy, inappetence, weight loss
- Exocrine pancreatic AC, often w/ liver metastases
- Skin histology: severe atrophy & miniaturization of hair follicles, epidermal hyperplasia


Courtesy Dr. V. Affolter

- Removal of tumor may give symptomatic relief until recurrence w/ metastases

Clues to the Diagnosis

- Older cat , often unwell



Clues to the Diagnosis

- Older cat , often unwell
- Acute onset marked ventral alopecia w/ very shiny appearance to skin

Clues to the Diagnosis

- Older cat , often unwell
- Acute onset marked ventral alopecia w/ very shiny appearance to skin
- Foot pad lesions
- Abdominal ultrasound
  - Pancreatic or hepatic pathology
- Skin biopsy

Paraneoplastic Skin Diseases

- Canine Sertoli cell / testicular neoplasia
- Feline paraneoplastic alopecia
- Feline thymoma-associated exfoliative dermatitis
- Canine nodular dermatofibrosis
- Canine paraneoplastic pemphigus
- Canine superficial necrolytic dermatitis/ metabolic epidermal necrosis (small % w/ glucagonoma)

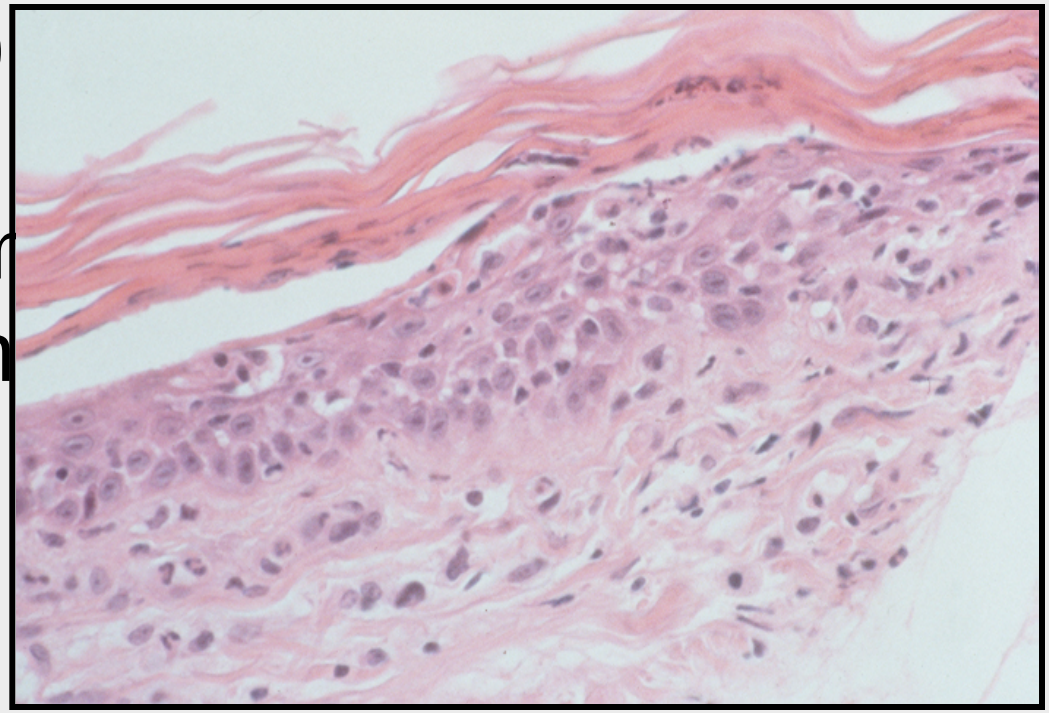
Feline Thymoma-Associated Exfoliative Dermatitis

- Rare, marker for underlying thymoma,
- Non- pruritic, erythematous scaling
- Dramatic exfoliation, alopecia, sheets of scale, begins head & neck → generalizes

Photos Courtesy of Dr. A Simon

Feline Thymoma-Associated Exfoliative Dermatitis

- Systemic signs (if present)- Coughing, dyspnea, lethargy, anorexia
- Skin histopathology: CD3 + ve, interface dermatitis (EM like) & mural folliculitis
- Removal of thymom dermatitis confirmin syndrome



Feline Thymoma-Associated Exfoliative Dermatitis

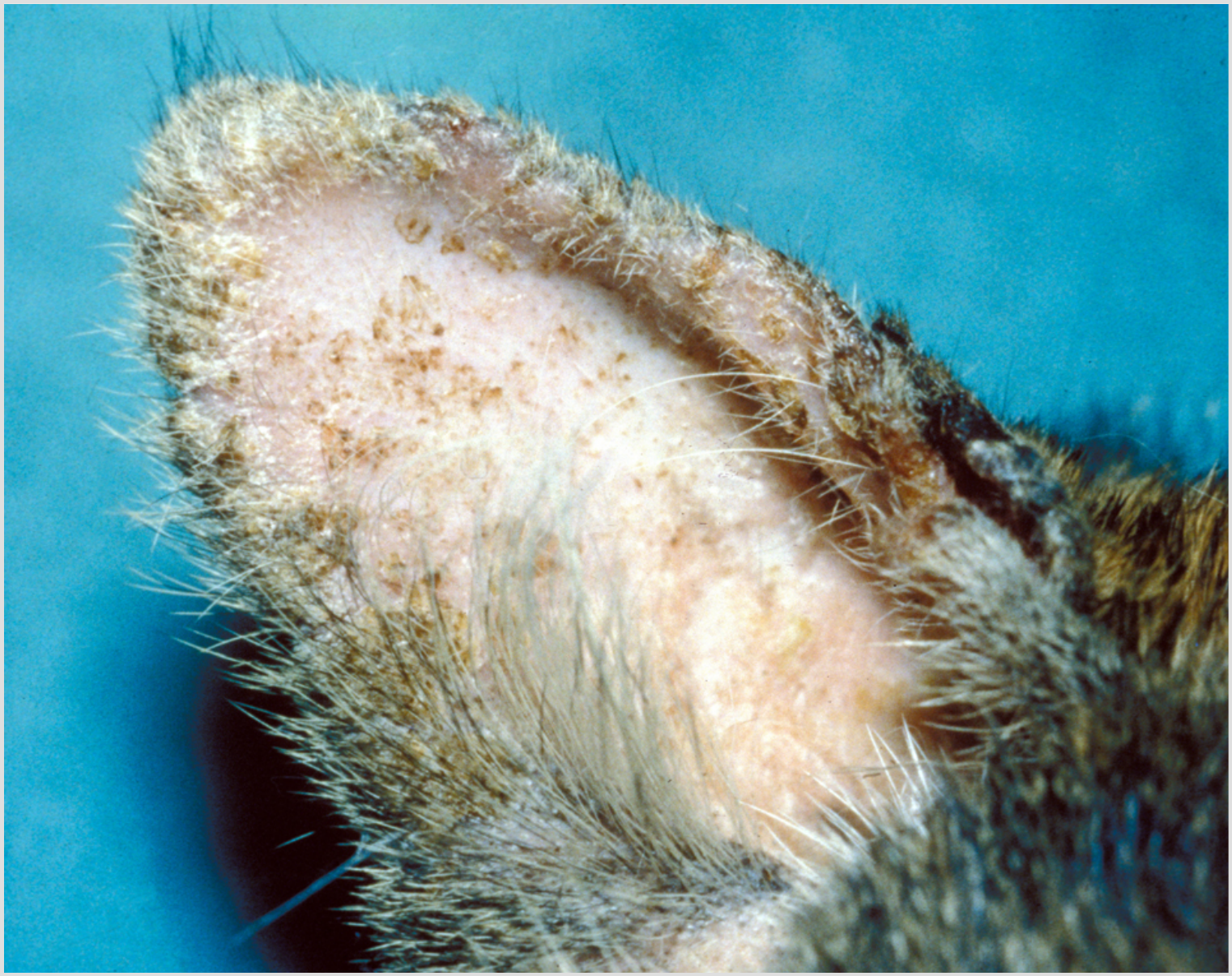
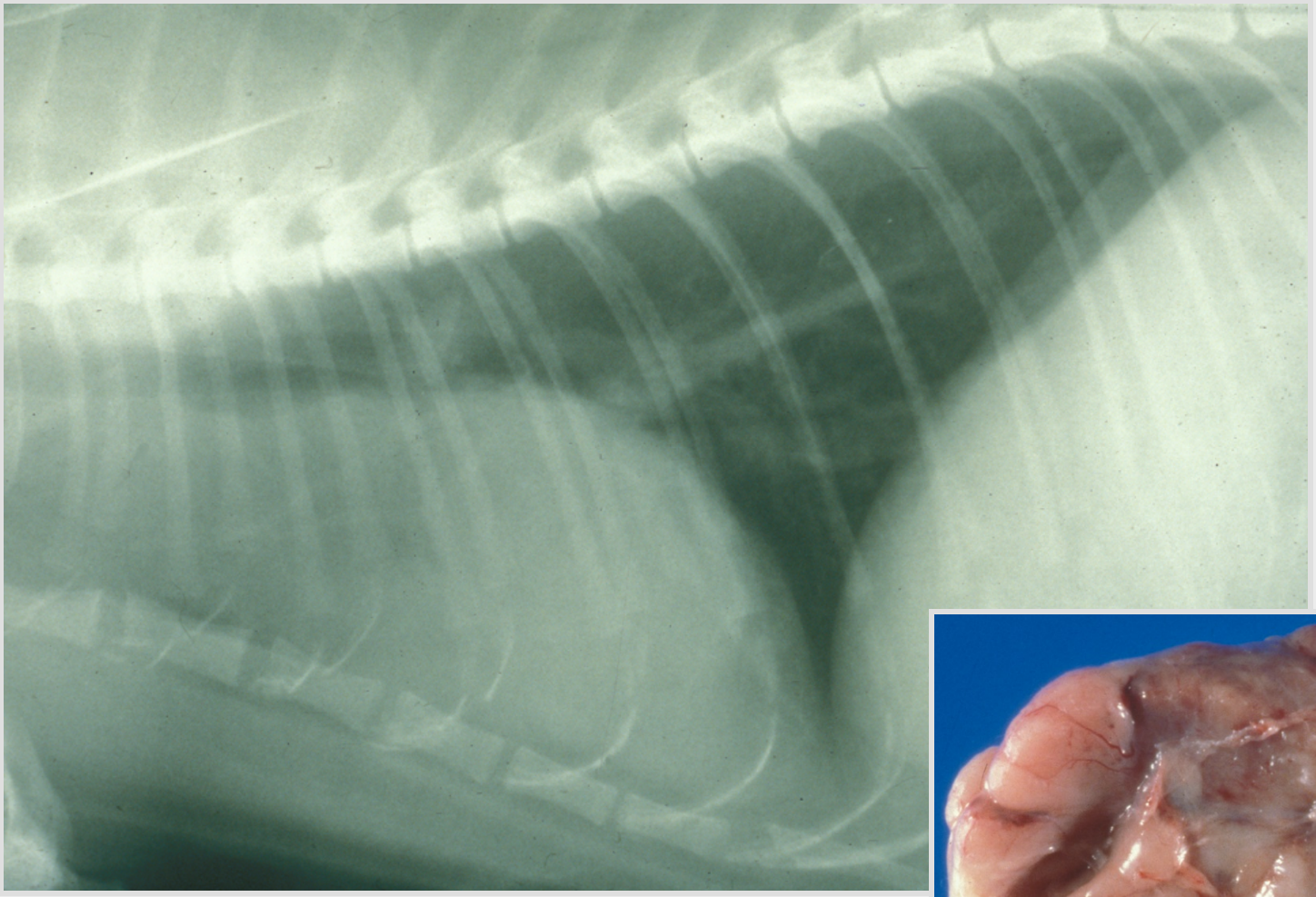


Photo courtesy of Thierry Olivry



Feline Thymoma –
Photo courtesy of Thierry Olivry

Post thymectomy

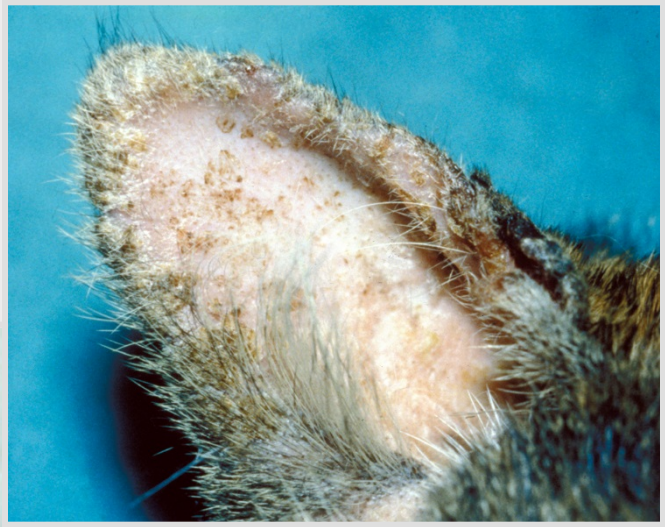


Photo Courtesy of Thierry Olivry

Which morphologic description fits best with exfoliative dermatitis ?

1. Interface dermatitis with lymphocyte exocytosis
2. Mural folliculitis with degenerative mucinotic changes
3. Interface dermatitis & interface mural folliculitis
4. Sheets of stratum corneum lifting of the epidermis

Which morphologic description fits best with exfoliative dermatitis ?

1. Interface dermatitis with lymphocyte exocytosis

2. Mural folliculitis with degenerative mucinotic changes

3. Interface dermatitis & interface mural folliculitis

4. Sheets of stratum corneum lifting of the epidermis

Clues to the Diagnosis

- Older cat
- Scaling, exfoliative skin lesions
- Thoracic films
- Skin biopsy :
  - Interface dermatitis & mural folliculitis

- Similar clinical & histologic findings w/ out thymoma present

Veterinary Dermatology

Vet Dermatol 2015; **26**: 40–e13 DOI: 10.1111/vde.12169

Nonthymoma-associated exfoliative dermatitis in 18 cats

Monika Linek*, Silvia Rüfenacht†, Chiara Brachelente‡, Claudia von Tscharner‡, Claude Favrot§, Sylvia Wilhelm†, Claudia Nett¶, Ralf S. Mueller, Ursula Mayer†† and Monika Welle‡**

- 18 cats , 12/18 were systemically not well
- Generalized (77%) or multifocal (23%) marked exfoliation
- Thymoma excluded via imaging or necropsy
- Treated w/ immunosuppressive corticosteroids or cyclosporine

Paraneoplastic Skin Diseases

- Canine Sertoli cell / testicular neoplasia
- Feline paraneoplastic alopecia
- Feline thymoma-associated exfoliative dermatitis
- Canine nodular dermatofibrosis
- Canine paraneoplastic pemphigus
- Canine superficial necrolytic dermatitis/ metabolic epidermal necrosis (small % w/ glucagonoma)

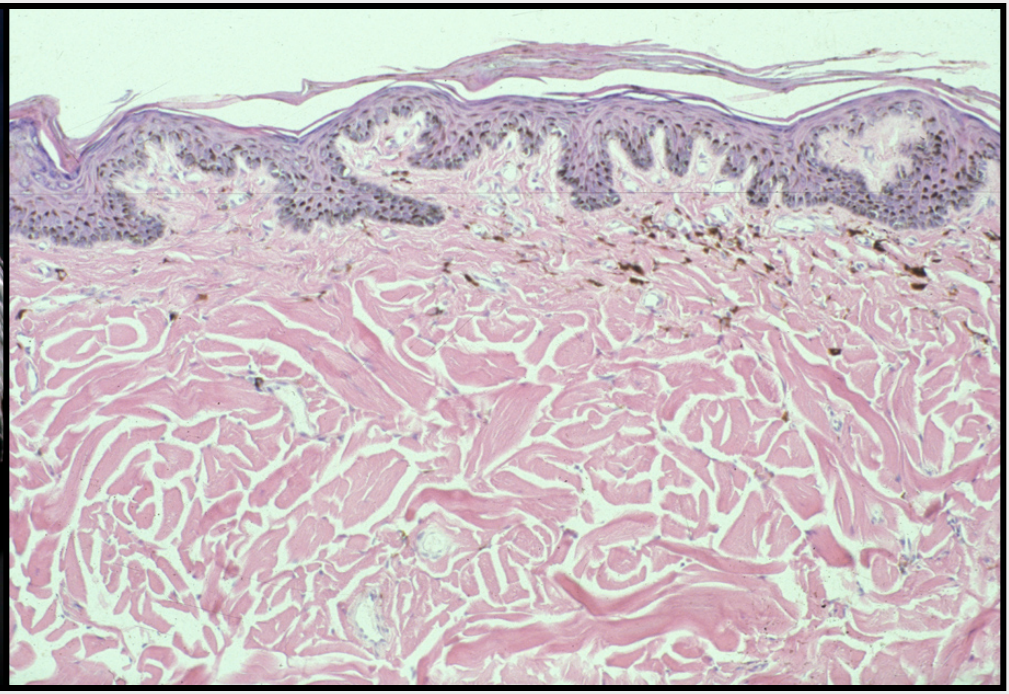
Canine Nodular Dermatofibrosis
Renal Cystadenocarcinoma Nodular Dermatofibrosis (RCND)

- Rare cutaneous marker of – Renal cystadenocarcinoma & cystadenomas
- Multiple firm, well circumscribed, dermal nodules on distal extremities & head
- Ulcerate as enlarge, may cause lameness

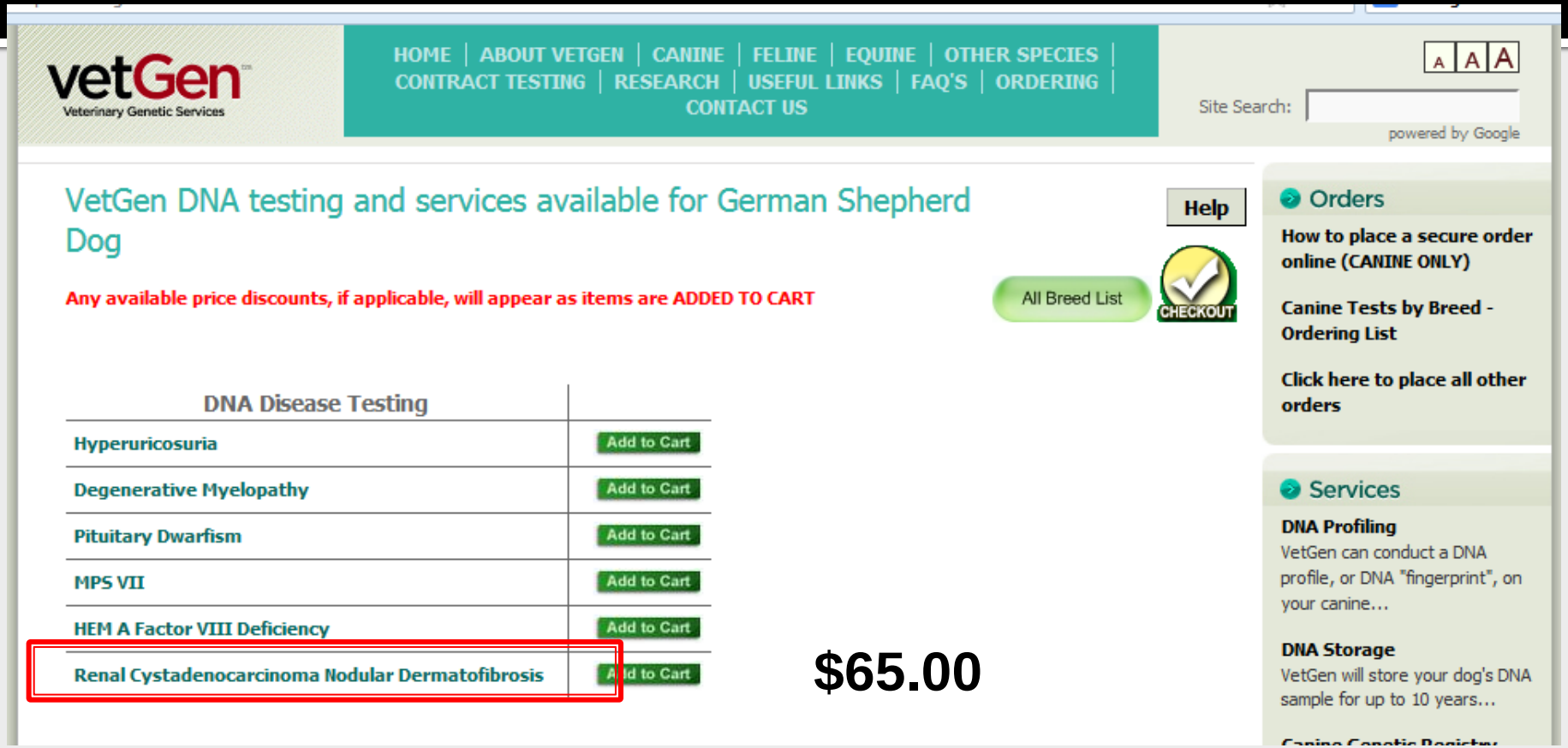
Photos courtesy of Jan Declercq

Canine Nodular Dermatofibrosis RCND

- Nodules of dense mature collagen
- Marked predilection for German Shepherd Dogs & related cross-breeds
  - Autosomal dominant inheritance



RCND Gene testing



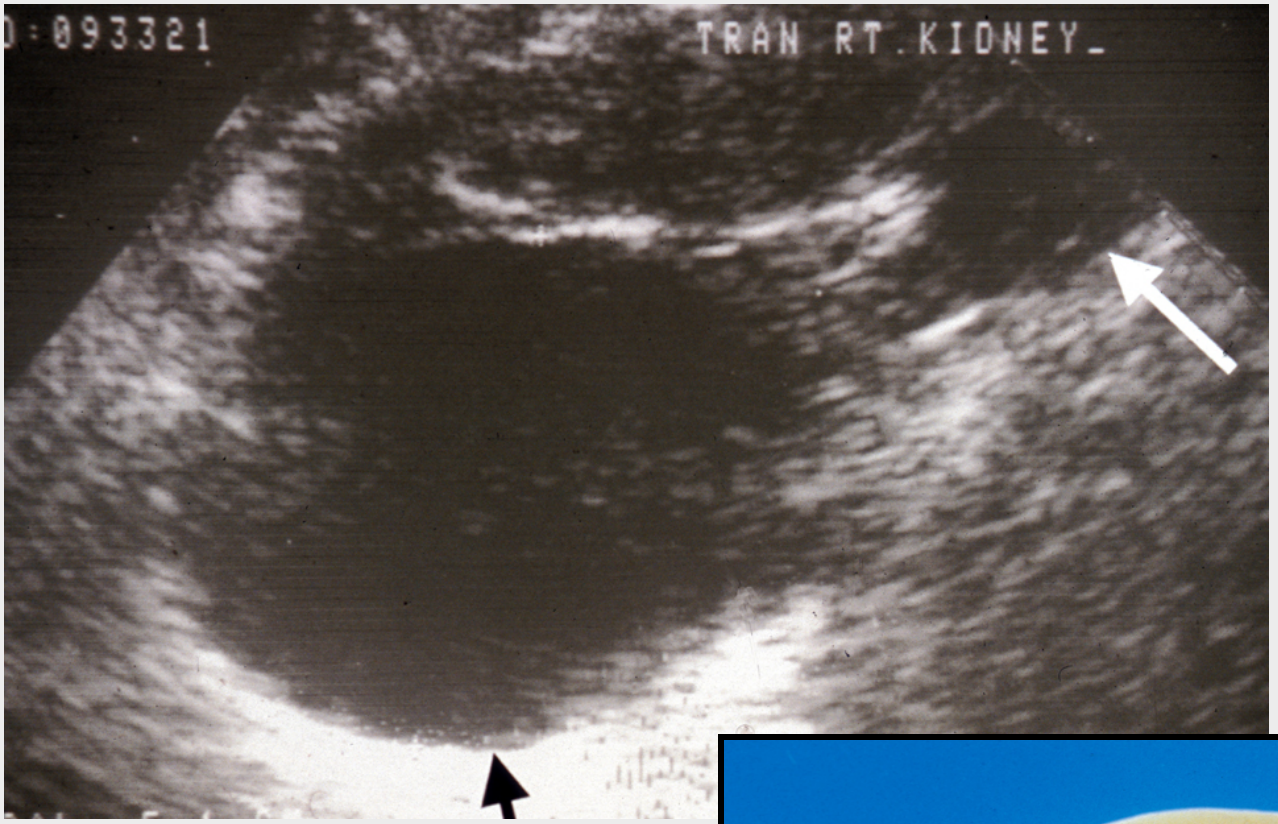
Autosomal dominant : folliculin gene (FLCN) mutation

Folliculin may act as a tumor suppressor

Canine Nodular Dermatofibrosis RCND

- Renal lesions (cysts, cystadenomas & cystadenocarcinomas) often multifocal & bilateral – can be metastatic

- Intact females may develop uterine leiomyomas
- Dx: biopsy lesion & renal ultrasound
- Long term prognosis guarded : lesions slowly progressive median survival times > 2yrs



Photos courtesy of Stephen White

Clues to the Diagnosis

- German Shep w/ dermal nodules
- Skin biopsy of nodular lesions
  - Dense collagenous hyperplasia
- Gene testing
- Ultrasound of kidneys
- Serial monitoring
  - May live years

Courtesy Dr. S.D. White

Paraneoplastic Skin Diseases

- Canine Sertoli cell / testicular neoplasia
- Feline paraneoplastic alopecia
- Feline thymoma-associated exfoliative dermatitis
- Canine nodular dermatofibrosis
- Canine paraneoplastic pemphigus
- Canine superficial necrolytic dermatitis/ metabolic epidermal necrosis (small % w/ glucagonoma)

Canine Paraneoplastic Pemphigus (PNP)

- Very rare, severe mucocutaneous, blistering auto-immune disease resembling pemphigus vulgaris

- Canine PNP reported with…..
  - thymic lymphoma & splenic sarcoma
  - Drug reactions??

Paraneoplastic Pemphigus

- Severe oral ulcerations w/ polymorphous skin lesions
- Skin Bx: lesions of PV, PF & EM→ look for internal neoplasia
- Auto-antibodies against cell adhesion molecules (envoplakin, periplakin, desmoglein 1 & 3)
- Prognosis very poor, deteriorate rapidly

Courtesy Of Dr. T. Olivry

PNP - Photos courtesy of Peter Lemmens, Jan Declercq,
Sherry Myers & Heather Weaver

Paraneoplastic Skin Diseases

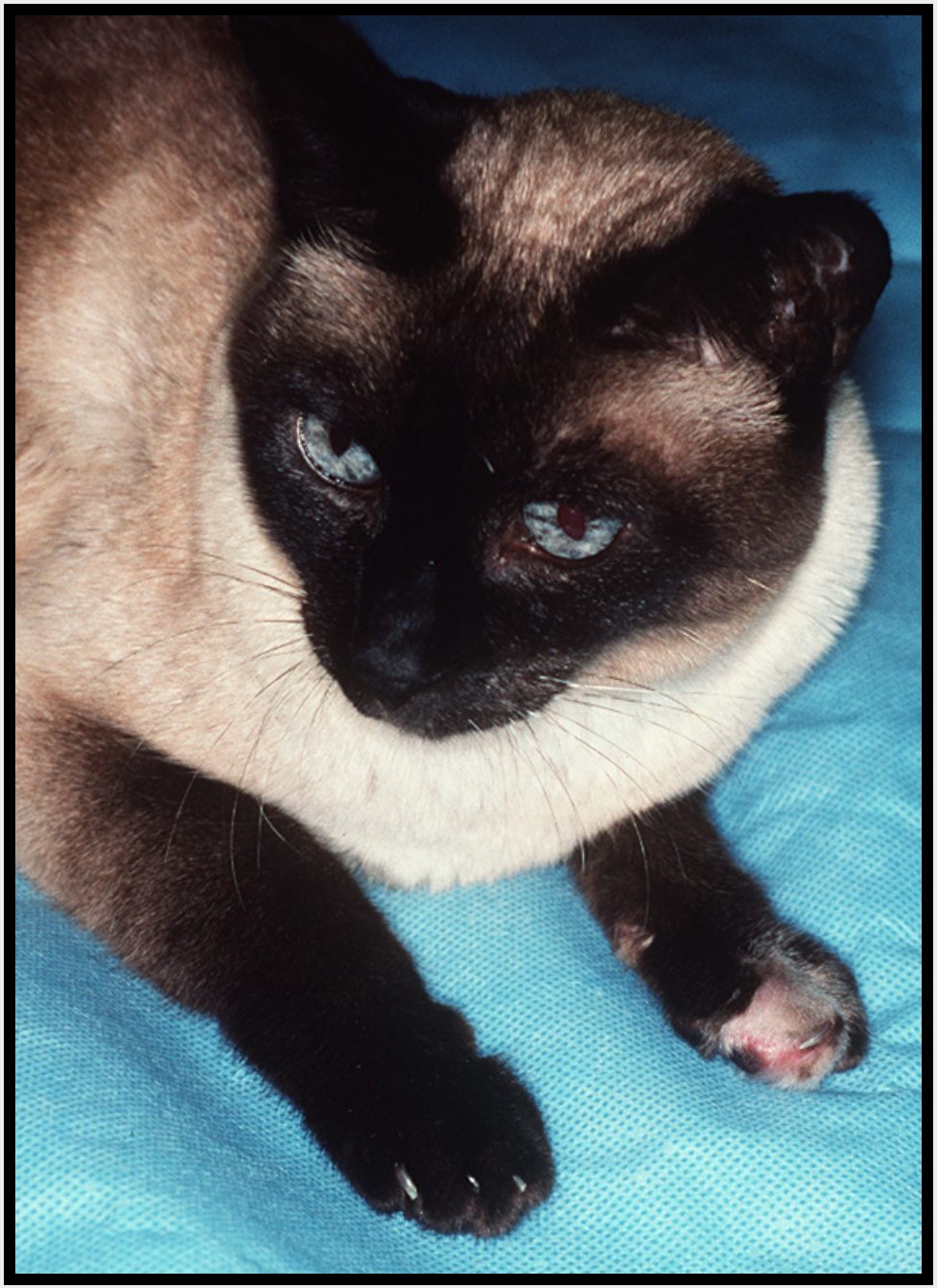
- Canine Sertoli cell / testicular neoplasia
- Feline paraneoplastic alopecia
- Feline thymoma-associated exfoliative dermatitis
- Canine nodular dermatofibrosis
- Canine paraneoplastic pemphigus
- Canine superficial necrolytic dermatitis/ metabolic epidermal necrosis (small % w/ glucagonoma)

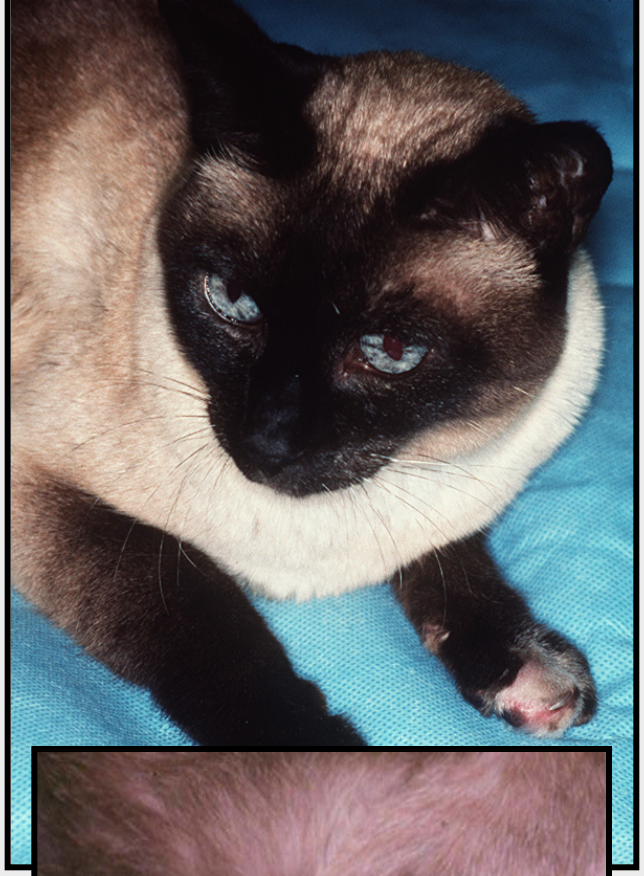
Paraneoplastic Skin Diseases

- Consider if unusual clinical & histopathologic patterns, especially in older animals
- Probably other paraneoplastic skin diseases yet to be diagnosed & described
- Can mimic adverse drug reactions
- Message?

Paraneoplastic Skin Diseases

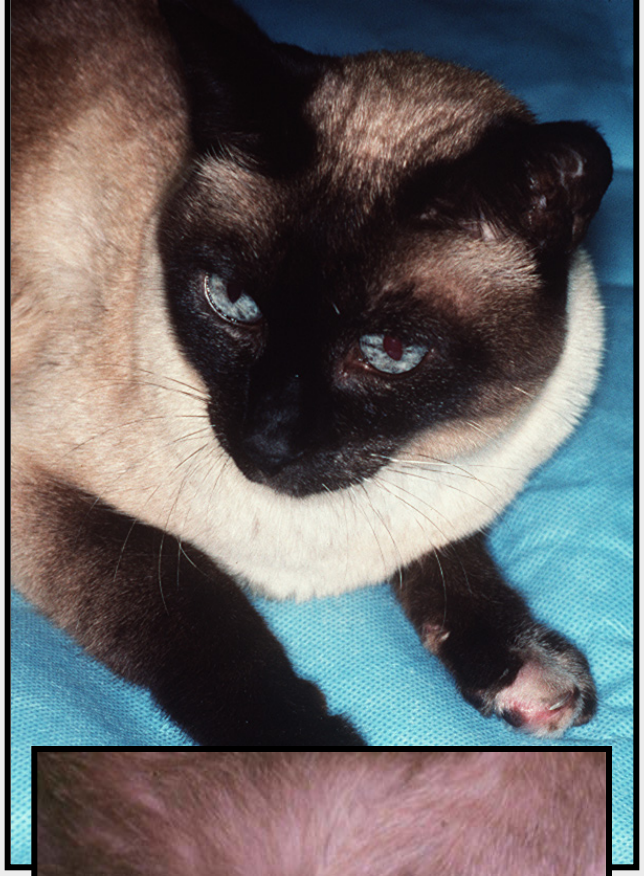
- Consider if unusual clinical & histopathologic patterns, especially in older animals
- Probably other paraneoplastic skin diseases yet to be diagnosed & described
- Can mimic adverse drug reactions
- Message? Look for them!





Could this be manifestation of underlying systemic disease?

1. **Yes, I would biopsy**
2. **No, I would treat for plasma cell pododermatitis w/ doxycycline**
3. **Yes, I would get a chest Xray**
4. **Yes, I would get samples for culture**



Could this be manifestation of underlying systemic disease?

1. **Yes, I would biopsy**
2. **No, I would treat for plasma cell pododermatitis w/ doxycycline**
3. **Yes, I would get a chest Xray**
4. **Yes, I would get samples for culture**

Metastatic Disease

- Number of tumors can metastasize to skin
- Primary pulmonary carcinoma in cats metastasizes to digits

Cutaneous Manifestations of Systemic Disease…

- Associated with
  - Hormonal / endocrine disturbances
  - Paraneoplastic / metastatic changes
  - Nutritional or metabolic perturbations
    - Zinc responsive dermatosis
    - Generic dog food
    - Lethal acrodermatitis
    - SND
    - Xanthoma

Zinc-Responsive Dermatosis

- Syndrome I : Siberian husky , Alaskan malamute & others
- Genetic defect in GI absorption of Zn ?
- Syndrome II : Growing puppies diet deficient in Zn or w/ excess phytates or minerals (Ca^{+2})

Courtesy Dr. S.D. White

Clues to the Diagnosis

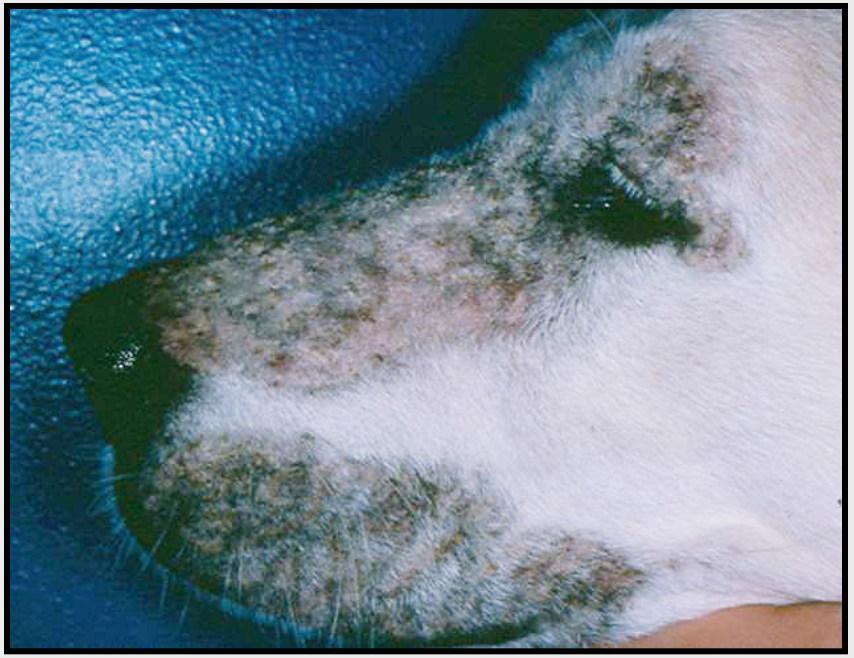
- Signalment, but can be non-arctic breeds
- Lesions :
  - Peri-ocular & peri-oral lesions , also footpads
  - Adherent scale w/ erythema
- Skin biopsy :
  - Choose thick adherent scale or crust →Parakeratosis

Treatment

- Zn supplementation :
  2 - 4 mg / kg elemental Zn daily
- Different Zn salts
  similar efficacy
- Balanced diet
  resolves lesions
  in Type II

Generic Dog Food

- Associated w/ feeding poor quality dog food to young dogs
- Well demarcated , thick, crusted plaques : muzzle , pressure points , mucocutaneous areas
- Skin biopsy: Acanthosis, parakeratosis
- Treatment: Feed better quality diet



Courtesy Drs. Sousa & Ihrke

Lethal Acrodermatitis

- White Bull Terriers
- Inherited AR
- Defect in Zn absorption / metabolism ?
- ↓ Zn & Cu levels
- ↓ IgA levels

Lethal Acrodermatitis

- First weeks of life : stunted growth, crusting dermatitis, footpad lesions, arched hard palate, bronchopneumonia
- Histology of skin biopsy : severe parakeratosis

© Blackwell- Gross, Ihrke, Walder, Affolter: Skin Diseases of the Dog & Cat
Courtesy Dr. A.C. Mundell

Clues to the Diagnosis

- Young white bull terrier
- Villous hypertrophy & fissures of footpads
- Skin lesions distal extremities & muco-cutaneous junctions
- Arched hard palate
- Biopsy

- NO treatment : fatal bronchopneumonia

© Blackwell- Gross, Ihrke, Walder, Affolter: Skin Diseases of the Dog & Cat
Courtesy Dr. A.C. Mundell

Hepatocutaneous Syndrome / Superficial Necrolytic Dermatitis

- Uncommon disease w/ characteristic clinical presentation
  - poorly understood pathophysiology
- Synonyms :

  - Diabetic dermatopathy
  - Hepatocutaneous syndrome (HCS)
  - Superficial necrolytic dermatitis (SND)
  - Metabolic epidermal necrosis (MEN)
  - Canine necrolytic migratory erythema (cNME)

- Multiple disease processes result in similar histologic skin lesion : refer to skin disease as SND or MEN, or cNME if glucagonoma

Superficial Necrolytic Dermatitis

- Visually distinctive skin lesions associated w/ systemic metabolic disease
  - Characteristic, metabolic, vacuolar hepatopathy is most common
  - Glucagonoma : small % of affected dogs
    - Paraneoplastic SND/MEN or cNME
  - Anticonvulsant medications: phenobarb
  - Concurrent hypoaminoacidemia
  - May have concurrent diabetes mellitus

Superficial Necrolytic Dermatitis

- Older dogs : mean age 10 yrs
- Male dogs over-represented
- Smaller dogs
- Certain breeds predisposed ?

Survey of Breeds of Dogs Affected with SND / HCS Based on Reported Cases: 110 Compiled Cases

Mixed breed	**25**	**Bichon Frise**	**1**
Terrier mix	**6**	**Cairn terrier**	**1**
Shetland sheepdog	**11**	**Cavalier King Charles spaniel**	**1**
Cocker spaniel	**11**	**Golden retriever**	**1**
West Highland white terrier	**10**	**Keeshond**	**1**
Scottish terrier	**5**	**Labrador retriever**	**1**
Jack Russell terrier	**5**	**Maltese**	**1**
German Shepherd	**5**	**Miniature poodle**	**1**
Border Collie	**4**	**Old English Sheepdog**	**1**
Lhasa Apso	**3**	**Pomeranian**	**1**
Beagle	**3**	**Rough Collie**	**1**
Welsh Corgi	**3**	**Samoyed**	**1**
Schipperke	**2**	**Springer Spaniel**	**1**
American Eskimo	**1**	**Standard poodle**	**1**
Australian Shepherd	**1**	**Yorkshire terrier**	**1**

Survey of Breeds of Dogs Affected with SND / HCS Based on Reported Cases: 110 Compiled Cases

Mixed breed	25	Bichon Frise	1
Terrier mix	6	Cairn terrier	1
Shetland sheepdog	11	Cavalier King Charles spaniel	1
Cocker spaniel	11	Golden retriever	1
West Highland white terrier	10	Keeshond	1
Scottish terrier	5	Labrador retriever	1
Jack Russell terrier	5	Maltese	1
German Shepherd	5	Miniature poodle	1
Border Collie	4	Old English Sheepdog	1
Lhasa Apso	3	Pomeranian	1
Beagle	3	Rough Collie	1
Welsh Corgi	3	Samoyed	1
Schipperke	2	Springer Spaniel	1
American Eskimo	1	Standard poodle	1
Australian Shepherd	1	Yorkshire terrier	1





SND Feet - (Ekatrina Kuznetsova, Francesco Albanese, Bill Miller)

Superficial Necrolytic Dermatitis

- Visually distinctive skin lesions have characteristic distribution
- Foot pads hyperkeratotic w/ fissures
- Crusting & ulcerations over pressure points (↑ skin fragility) , muzzle , mucocutaneous areas (peri - oral , peri - ocular , urogenital regions)

Percentage of Reported Cases (110 dogs) Displaying Commonly Reported Clinical Findings in Dogs with SND / HCS

Clinical Findings	
Hyperkeratotic and fissured footpads	94 %
Peri-oral or peri-ocular skin lesions	62 %
Perianal or perineal skin lesions	33 %
Elbow skin lesions	30 %
Perivulvar or scrotal or preputial skin lesions	28 %

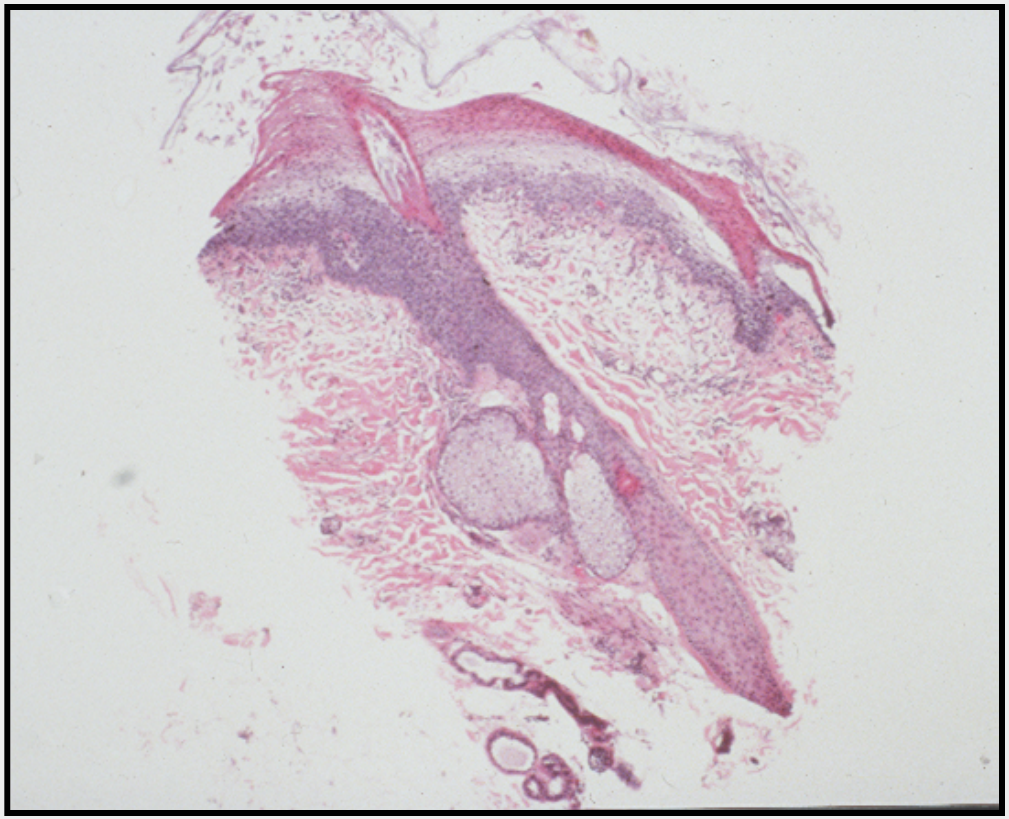





SND courtesy of Francesco Albanese

Superficial Necrolytic Dermatitis

- Characteristic histology:
  - Parakeratosis
  - Superficial epidermal edema
  - Basal cell hyperplasia
  - “Red , white & blue” lesion

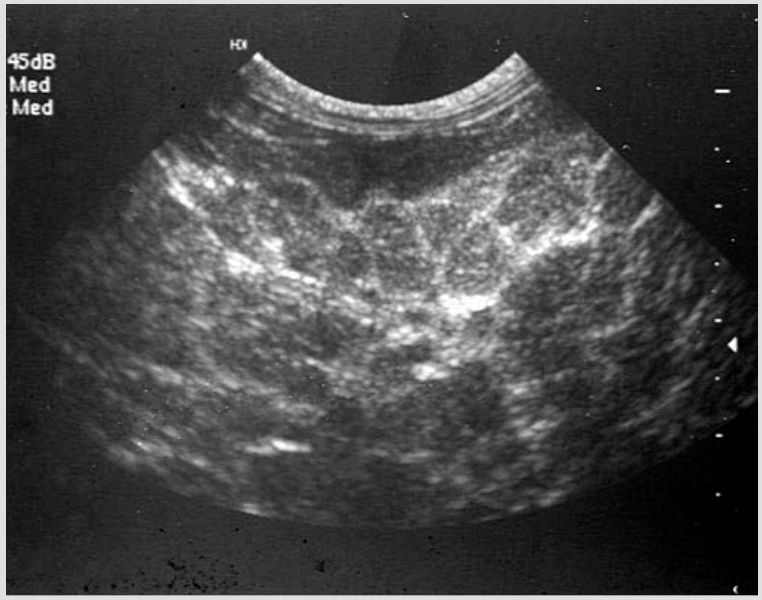


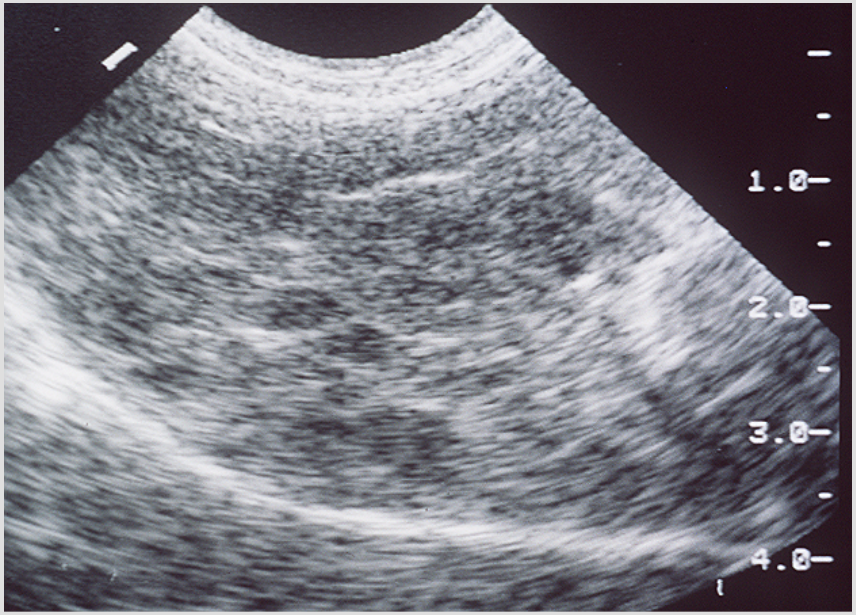
Percentage of Reported Cases (110 dogs) Displaying Commonly Reported Laboratory Findings in Dogs with SND / HCS

Laboratory Findings	
Elevated serum alkaline phosphatase (ALP)	98 %
Elevated serum alanine transferase (ALT)	71 %
Anemia	37 %
Hypoalbuminemia	33 %
Diabetes mellitus	33 %

Superficial Necrolytic Dermatitis

- **Ultrasound of liver: "Honeycomb" pattern may be present**

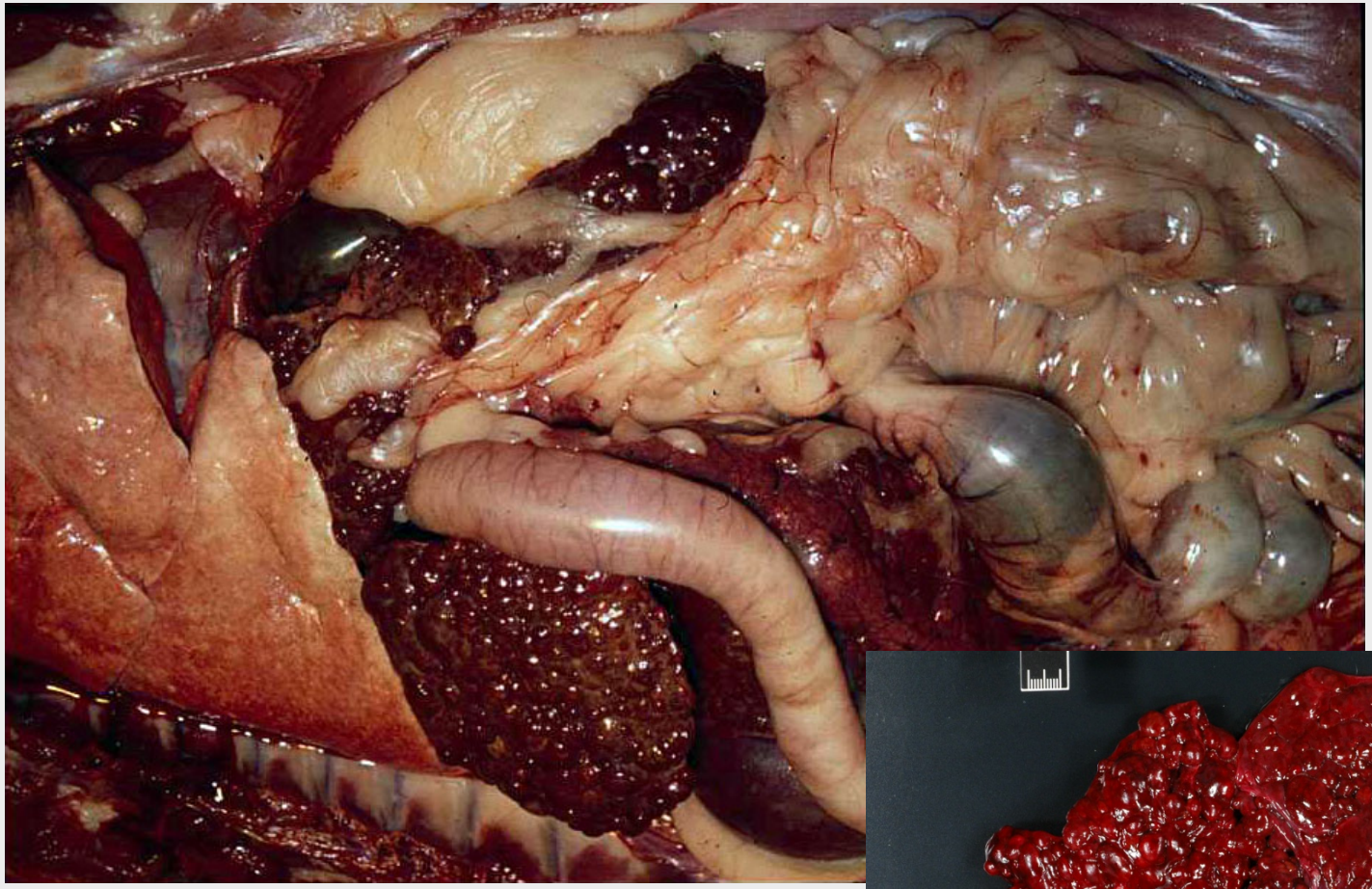


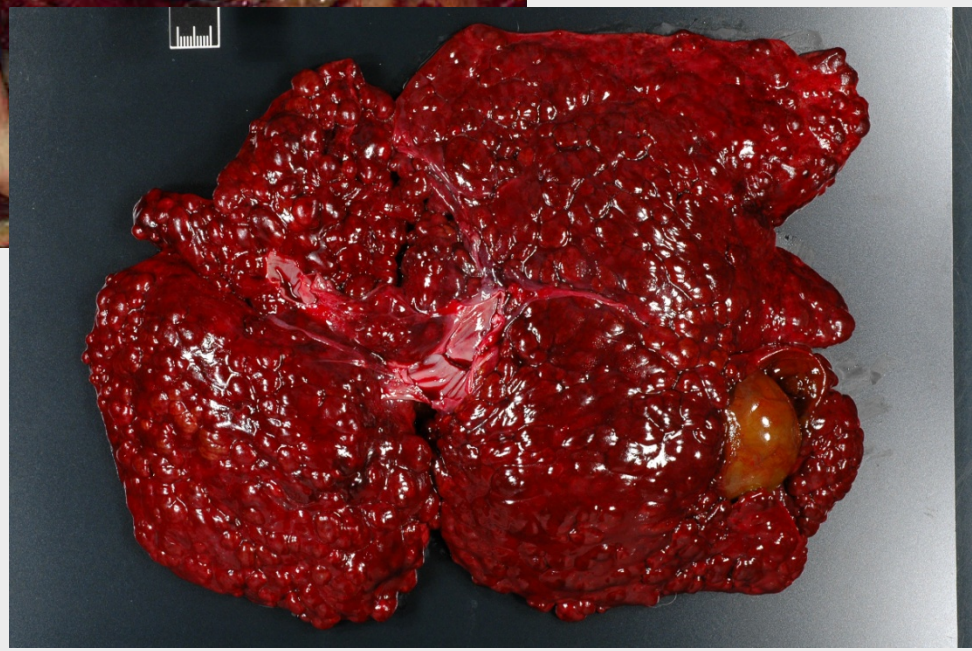


- **Pattern is absent if glucagonoma associated**
- **Pancreatic mass?**

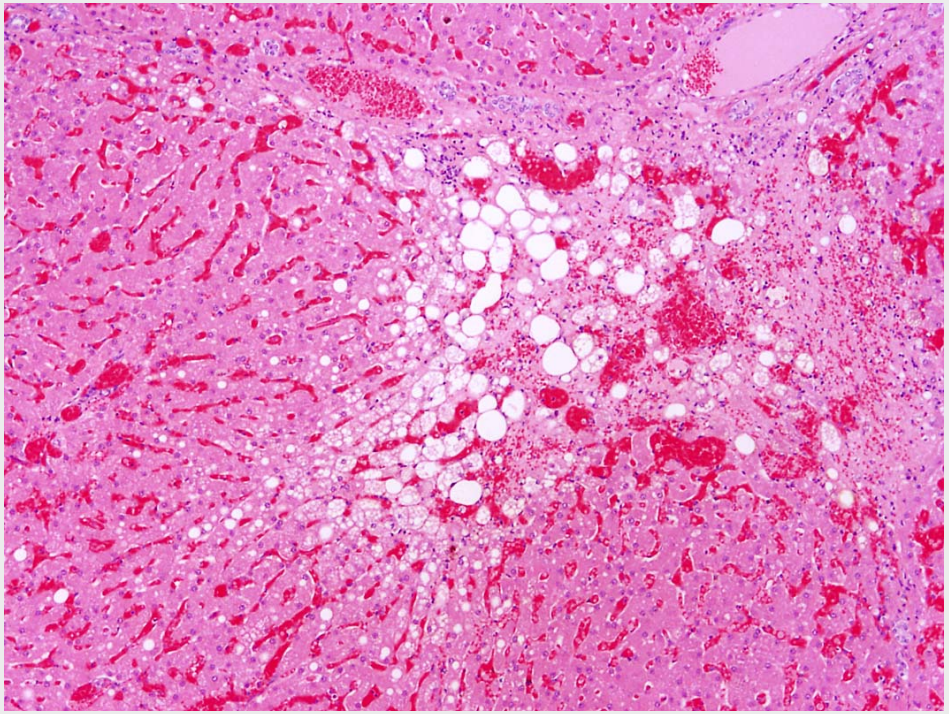
Superficial Necrolytic Dermatitis: cNME

- SND can be paraneoplastic → Canine Necrolytic Migratory Erythema
- Diagnose cNME:
  - Supportive clinical signs
  - Compatible skin histopathology w/ SND
  - Pancreatic or hepatic masses on ultrasound w/ absent “swiss cheese” hepatic pattern on ultrasound
  - Elevated glucagon +/- diabetes mellitus
- Prognosis poor, palliative therapy w/ somatostatin analogue octreotide

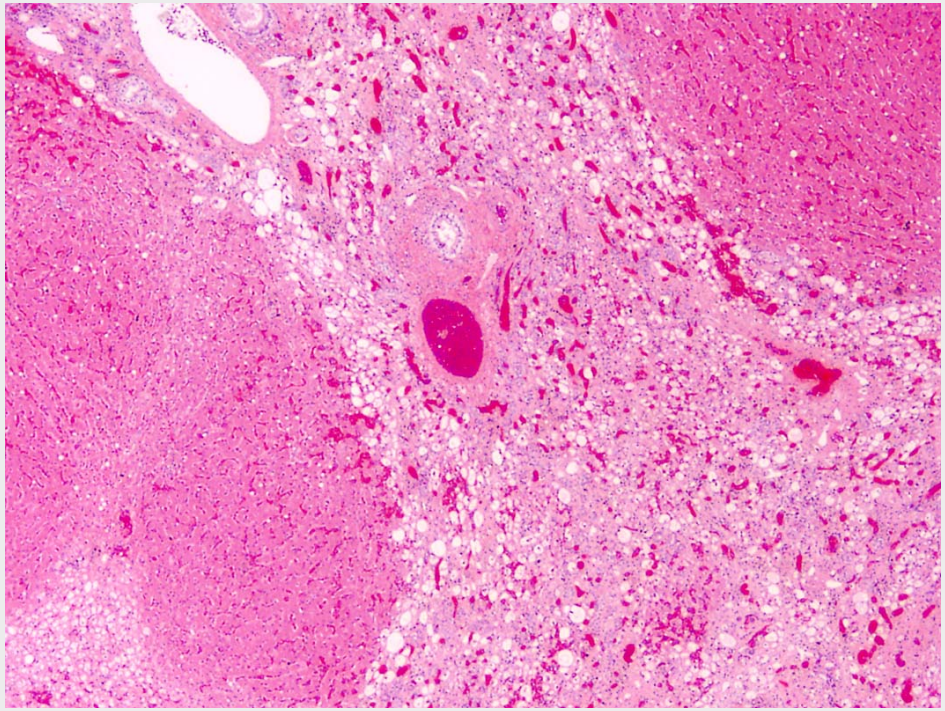




Vacuolation of hepatocytes



Collapsed parenchyma between hepatic tissue enhances nodular effect



Which foot pads makes you suspicious for SND ?

A

B

C

D

Which foot pads makes you suspicious for SND ?

PF

Vasculitis

ETCL

SND

Clues to the Diagnosis

- Signalment : older , certain breeds , males
- Typical lesions & distribution
  - Foot pads involved
- Systemically unwell ?
- Hepatic ultrasound &
  ↑ liver enzymes
- Skin biopsy
- Concurrent diabetes mellitus ?
- Hypoaminoacidemia

Treatment

- Poor Prognosis :
  - Mean survival time 3 months
  - Survival times > 8 months possible in some dogs with nutritional therapy
- Treatment :
  - Palliative nutritional therapy
  - Treat any secondary skin infections
  - Manage diabetes mellitus
  - Glucagonoma associated SND : surgery or octreotide

Nutritional Therapy

- Protein supplementation
  - Intravenous amino acid infusions
  - Oral hyperalimentation
    - High protein diet, protein or amino acid powder supplements, egg yolks
- Zinc supplementation
- Essential fatty acid (EFA) supplementation

SND Study :

Veterinary Dermatology 2002, **13**, 177–186

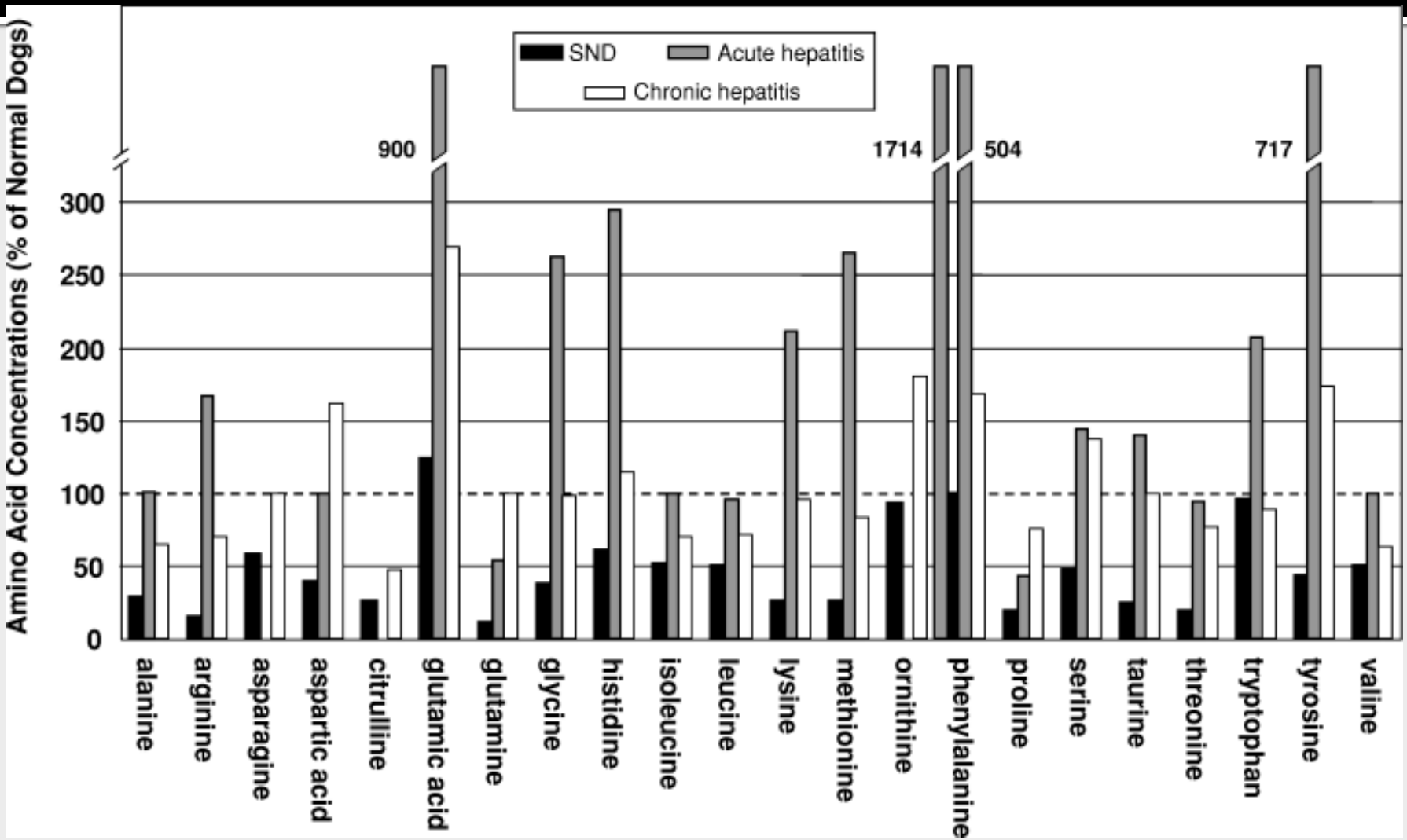
Plasma amino acid concentrations in 36 dogs with histologically confirmed superficial necrolytic dermatitis

CATHERINE A. OUTERBRIDGE, STANLEY L. MARKS and QUINTON R. ROGERS

From the Department of Medicine and Epidemiology (Outerbridge and Marks), and Department of Molecular Biosciences (Rogers), School of Veterinary Medicine, University of California, Davis, CA 95616

- Profound hypoaminoacidemia in all 36 dogs
- Majority of amino acids less than 60 % of normal plasma concentrations
- 9 / 22 amino acids less than 30 % of normal
- This degree of hypoaminoacidemia can not be attained with decreased intake

Plasma amino acid concentrations in 36 dogs with histologically confirmed superficial necrolytic dermatitis



Veterinary Dermatology Volume 13, Issue 4, pages 177-186,
12 AUG 2002 DOI: 10.1046/j.1365-3164.2002.00295.x

	Normal	SND	Acute Hepatitis	Chronic Hepatitis
Total Amino Acids (nmol / ml)	3229	895	4520	2710
BCAA : AAA ratio	3 - 4	2.5 - 2.8	< 1.0	1 - 2

Plasma amino acid panels, concentration of total amino acids & BCAA : AAA ratios in SND dogs significantly different from dogs w/ acute & chronic hepatitis

Hypothesize that the hypoaminoacidemia seen in SND reflects increased hepatic catabolism of AA

Intravenous AA infusions

- Unless other risk for hepatic encephalopathy exists or there is renal dysfunction SND dogs require significant protein supplementation
- AA infusions initially bypass portal circulation so peripheral tissues get AA
- No studies as to best protocol
- Typically use crystalline, amino acid solutions w/out electrolytes

Intravenous AA infusions

- Hyperosmolar & low pH solutions
  - Ideally use central vein & monitor for hyperosmolality & acidosis (monitor BUN & ammonia if warranted)
- Individual response is widely variable
  - During infusion dogs often seem brighter
  - Positive effects (↑energy, ↑ appetite & improved skin lesions) : last hours to weeks

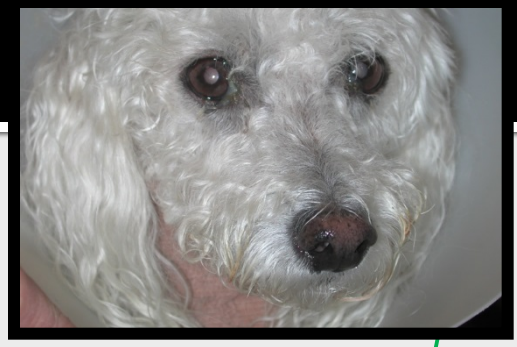
Intravenous AA infusions

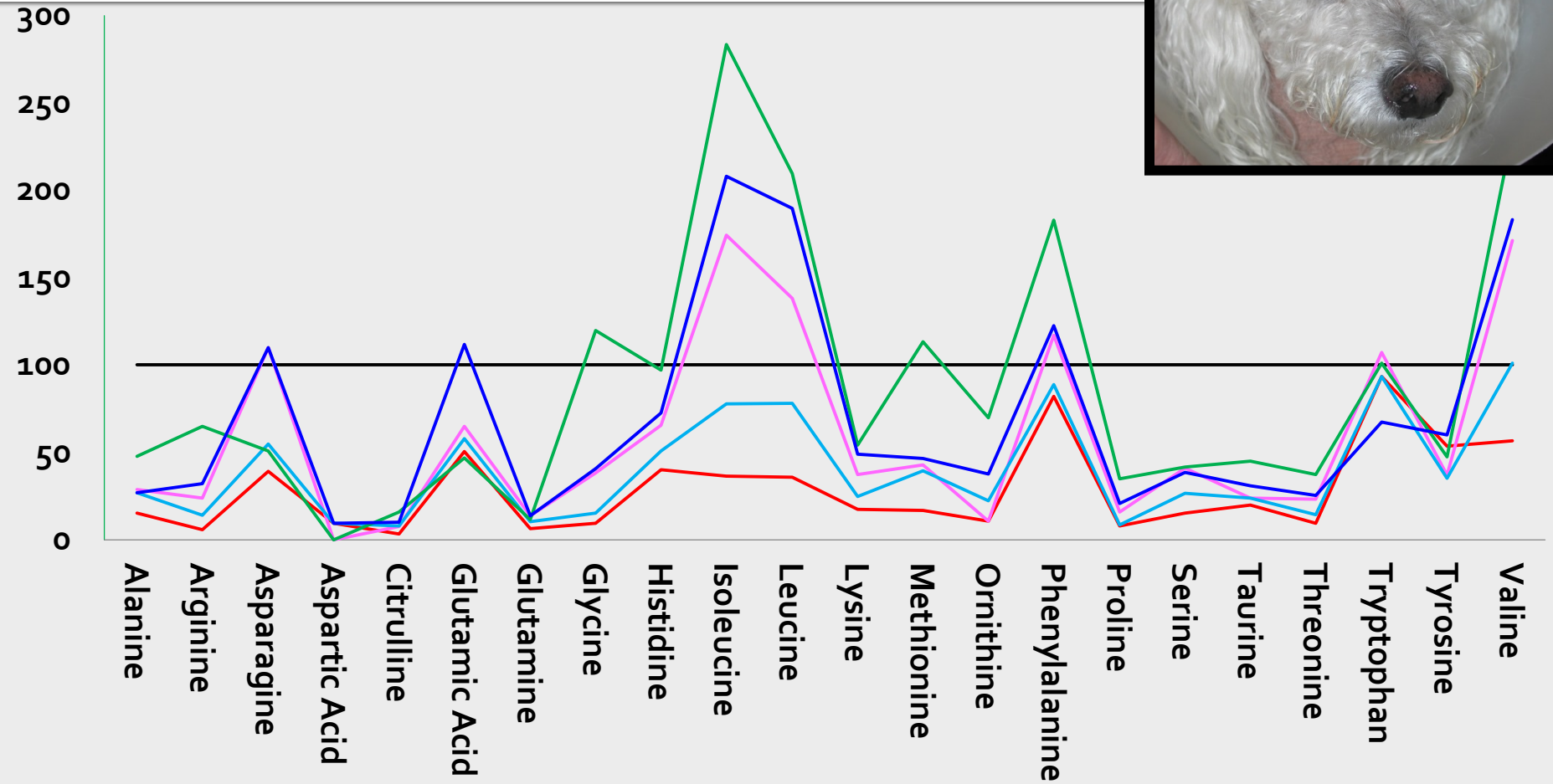
- Serial infusions are recommended
  - “fill er up” therapy infuse over day or days & repeat 2- 4 x / month or as needed
  - Infuse twice the quantity of AA provided by administering standard canine critically ill parenteral nutrition (2 x 18.4% protein on ME basis)

<u>Example 18 kg dog</u> : RER = 622 kcal /day

- **18. 4 % of RER = 115 kcal / day x 2 = 230 kcal /day**
- **If 8.5% AA solution supplies 0.34 kcals / ml need 677 mls / 24 hrs = 28 mls / hr**
- **Start at 14 mls / hr for 2 to 3 hours monitor for signs of hyperosmolality or acidosis if tolerating increase to 28 mls / hr**

Amino Acid Panels in a Dog Receiving AA infusions





Oral Supplementation

- Best oral nutritional approach is not known
- Highly digestible protein diet supplemented w/ protein or AA powder
- Literature reports feeding egg yolks
- Zinc and EFA supplementation

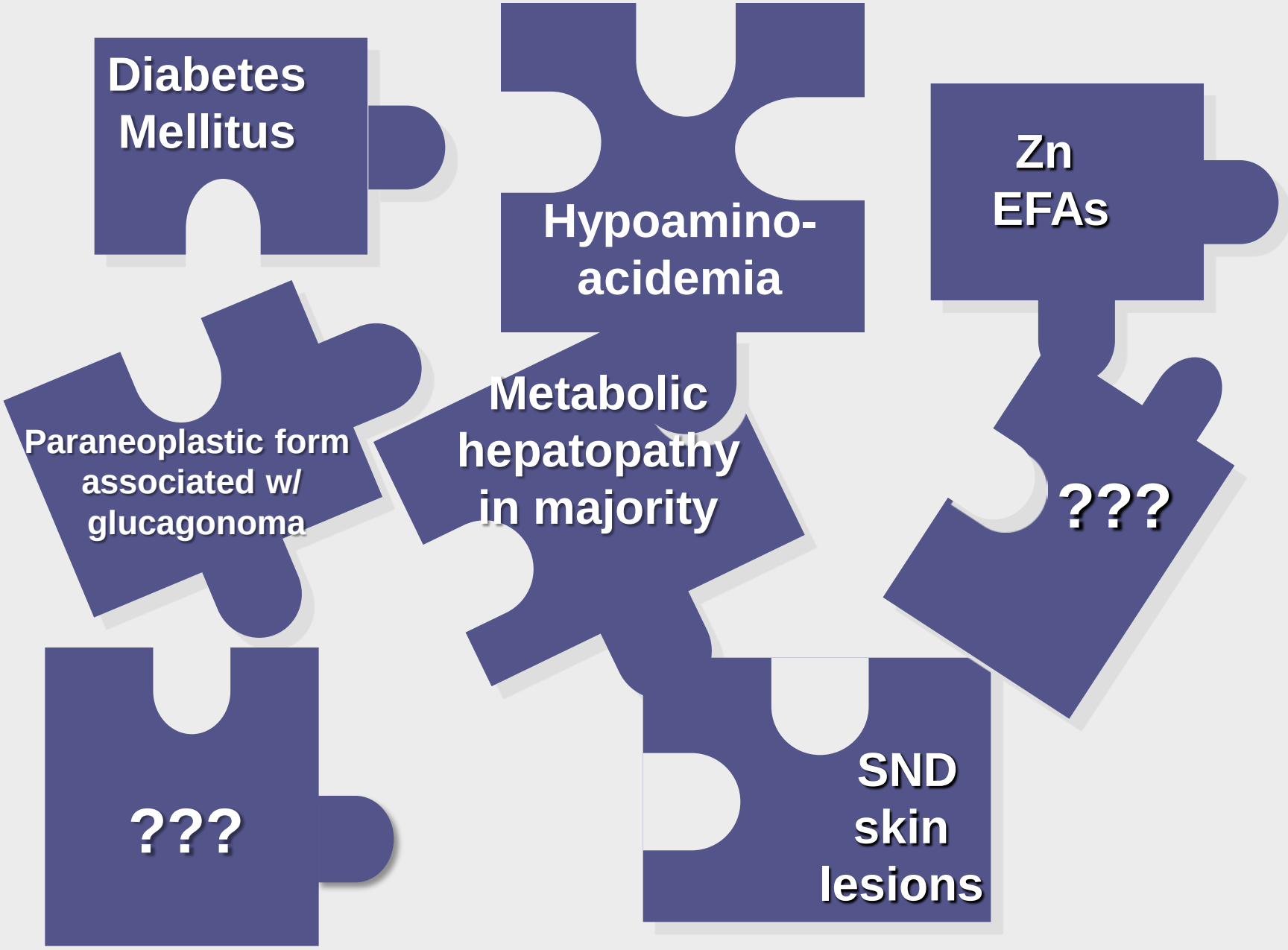
Oral Protein Hyperalimentation

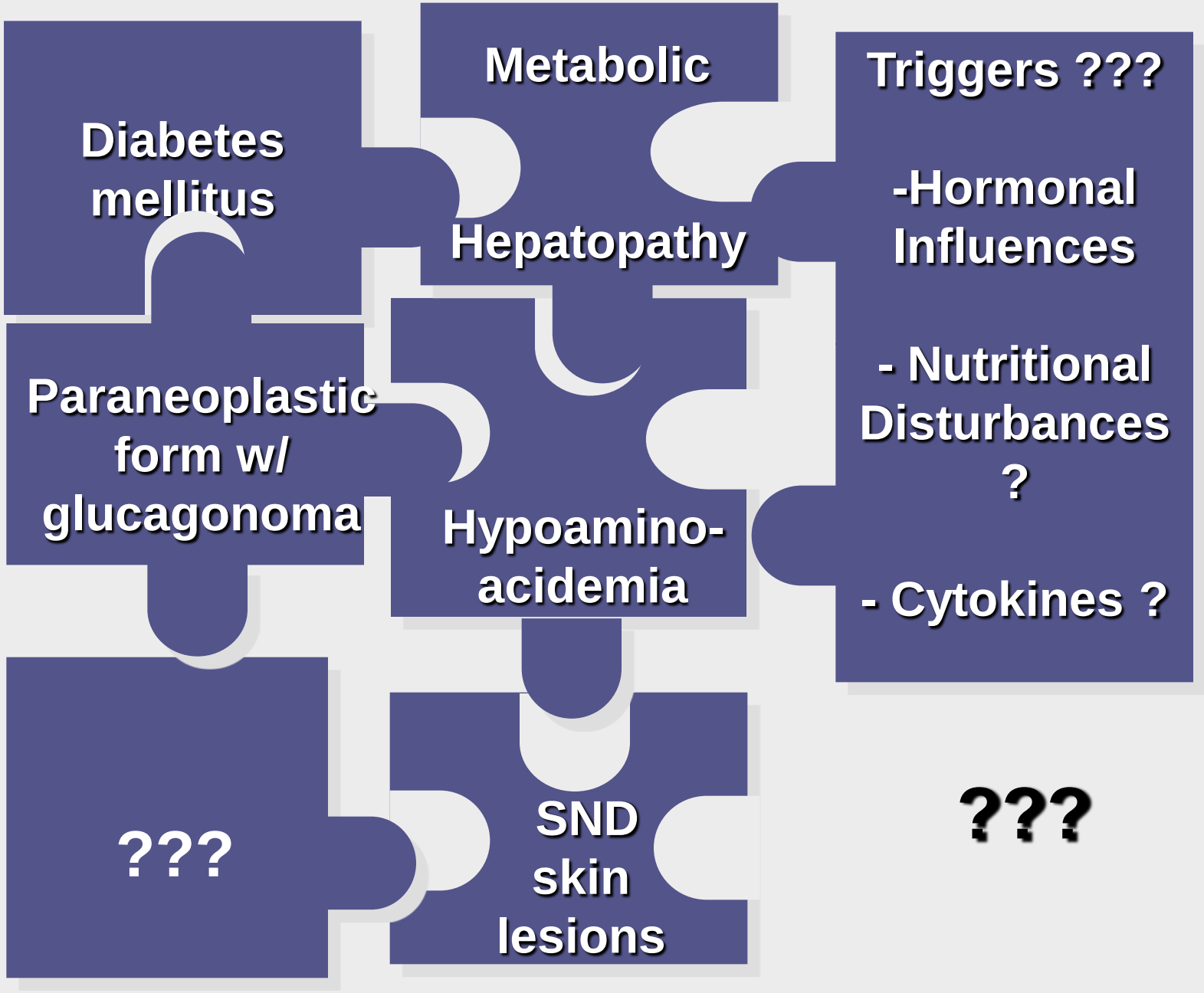
- Questionable efficacy
  - AA enter portal circulation after absorption & likely depleted before reaching peripheral tissues
  - Some dogs clinical response w/ oral hyperalimentation
- High digestibility, quality diet (> 25% protein)
- Protein supplement or AA powder
  - Any supplements added to base diet should not exceed 10% of daily caloric intake to avoid risk of diluting balanced base diet
- Egg yolks (recommended in # of sources)
  - Yolks have < 50% of protein in eggs
  - Source of EFAs (linoleic acid), Vit A, B vitamins, calcium
  - 55 cal /egg , feed 1 to 2 scrambled eggs/day ?

Zinc and EFA Supplementation

- Both are carried by albumin so ↓ albumin → to ↓ in zinc and EFAs in NME people & likely SND dogs

- Zinc is cofactor for linoleic acid synthesis
- In NME humans AA, zinc and EFA deficiencies have direct tissue effects & influence inflammatory mediators likely could also be occurring in SND dogs
- Zinc supplementation 2-4 mg/kg/day

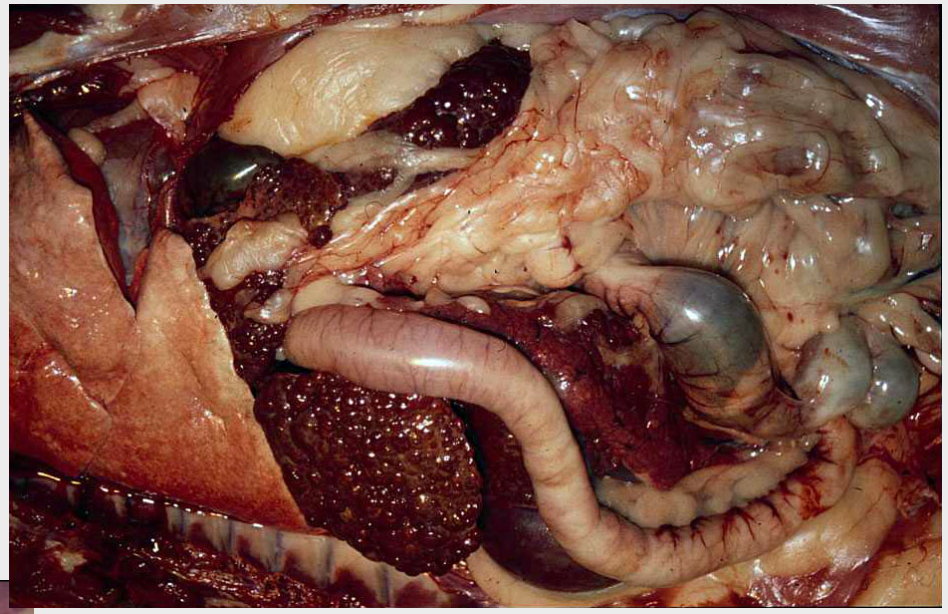

Diabetes Mellitus
Hypoamino-acidemia
Zn
EFAs
Paraneoplastic form associated w/ glucagonoma
Metabolic hepatopathy in majority
???
???
SND skin lesions


Diabetes mellitus
Metabolic
Hepatopathy
Triggers ???
-Hormonal Influences
- Nutritional Disturbances ?
- Cytokines ?
Paraneoplastic form w/ glucagonoma
Hypoamino-acidemia
???
SND skin lesions
???

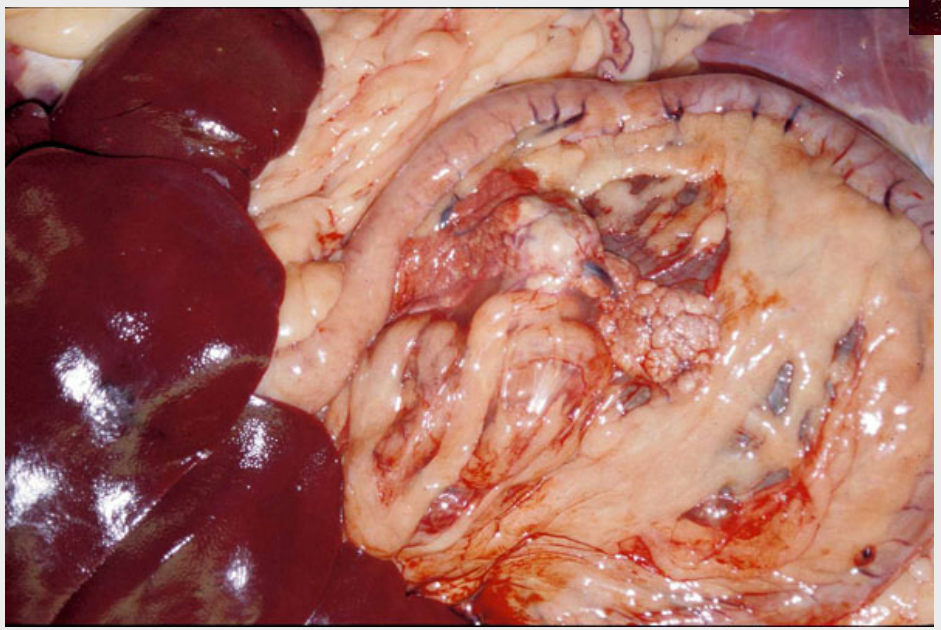
Which is the paraneoplastic form of SND ?

A

A



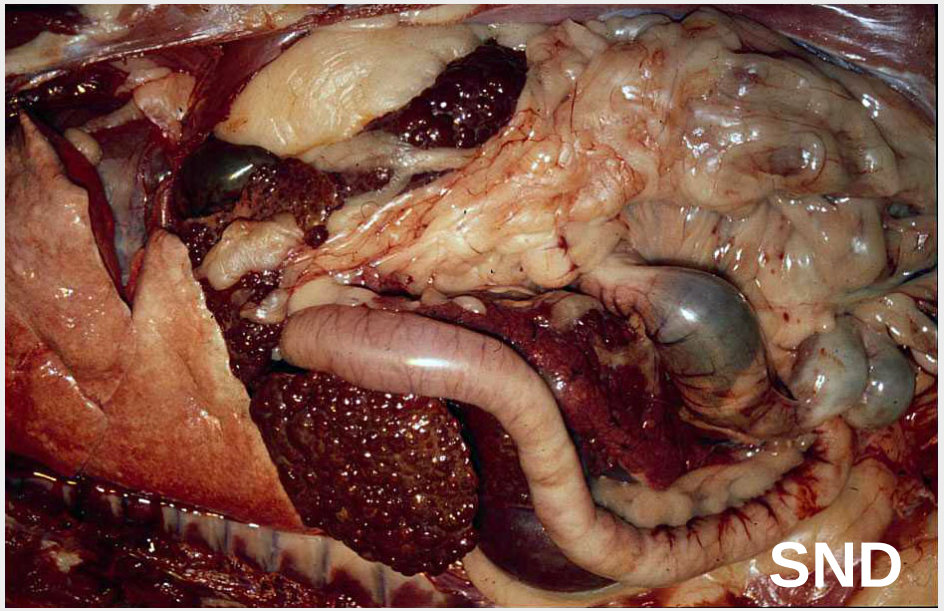
B

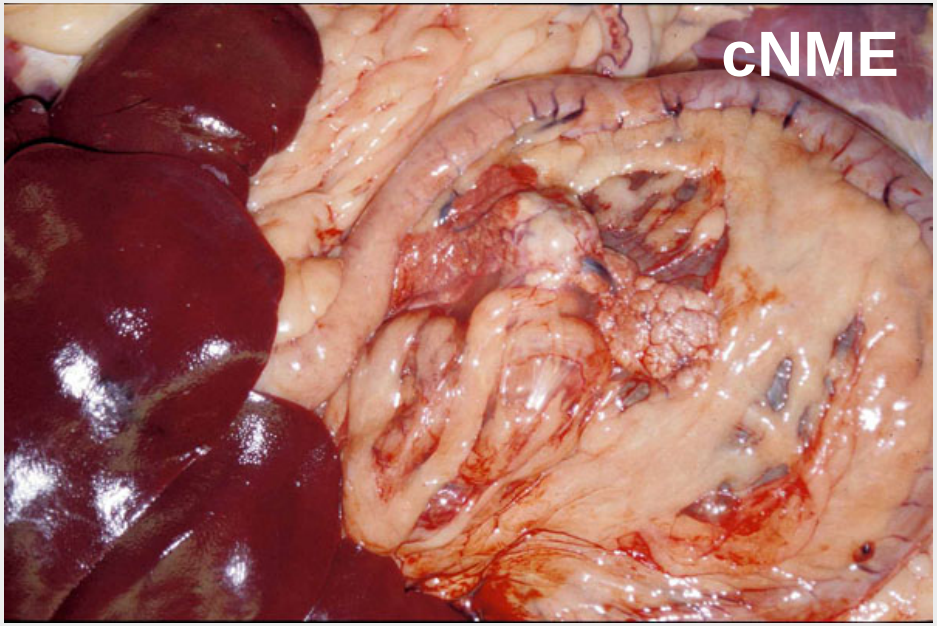


B

Which is the paraneoplastic form of SND ?

A





B

Cutaneous Xanthomas

- Pale yellow / white plaques , nodules , papules with erythematous borders
- Lesions over bony prominences on face, limbs , trunk & footpads
- ID underlying disturbance in lipid metabolism : diabetes mellitus or hereditary dislipoproteinemia

Cutaneous Xanthomas

Courtesy of Dr. S White

fed low fat diet

Cutaneous Manifestations of Systemic Disease…

- Associated with
  - Hormonal / endocrine disturbances
  - Paraneoplastic / metastatic changes
  - Nutritional or metabolic perturbations
  - Systemic infectious disease
    - Leishmaniasis, deep systemic mycosis, viral

Leishmaniasis

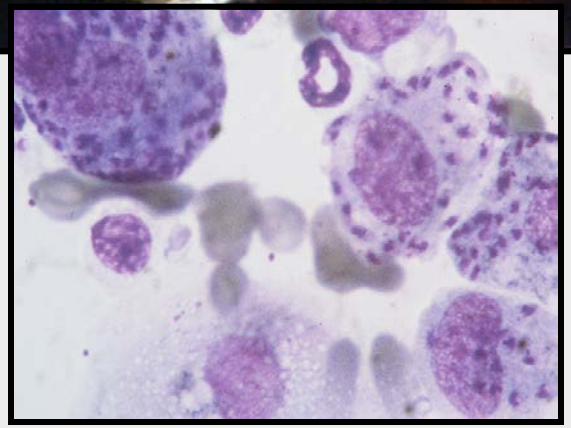
- Protozoal disease
  - Travel history ?
- Skin lesions common
  - Alopecia, erythema, marked scaling & ulcers
- Systemic signs
  - Weight loss, muscle atrophy lameness, GI signs, PU / PD, lymphadenopathy, renal failure , epistaxis , ocular involvement

Courtesy of Dr. SD White

Photos Courtesy of Dr. S D White

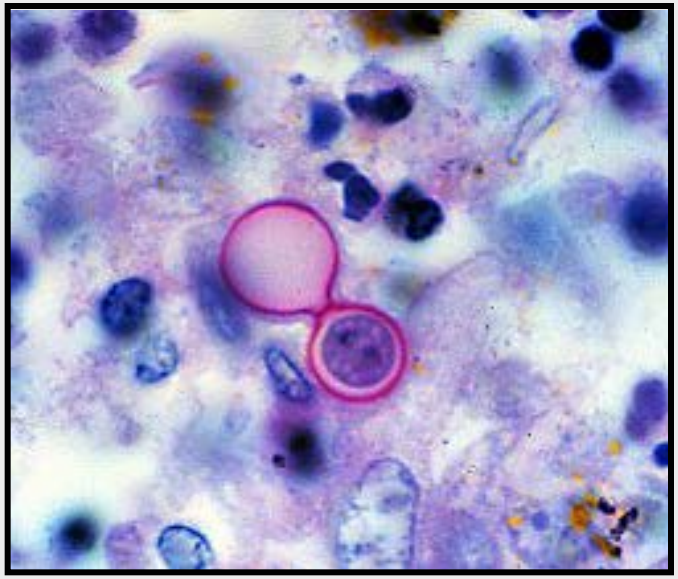
Leishmaniasis

- Diagnosis:
  - ID organism in FNA of lymph nodes, bone marrow, skin biopsy , culture, PCR or serum titres
- Treatment: allopurinol & antimonials

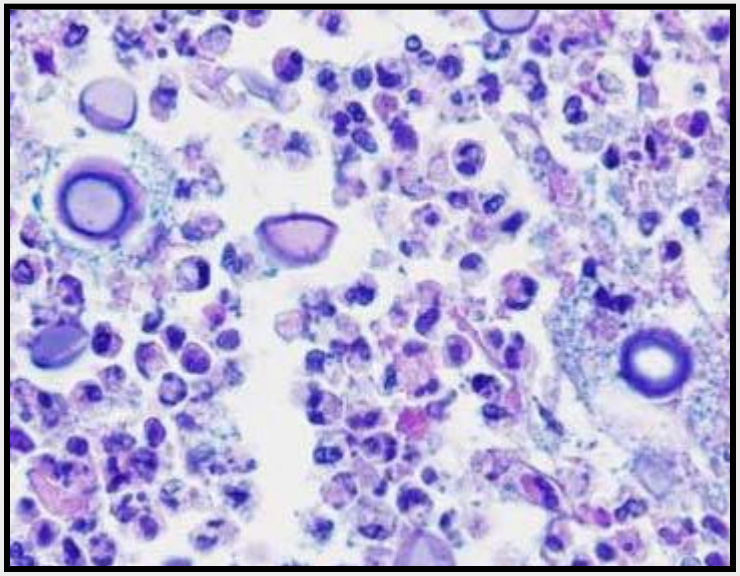


Fungal Diseases

- Deep systemic mycosis : ulcerative nodules / plaques
  - Blastomycosis , coccidioidomycosis, histoplasmosis , cryptococcosis



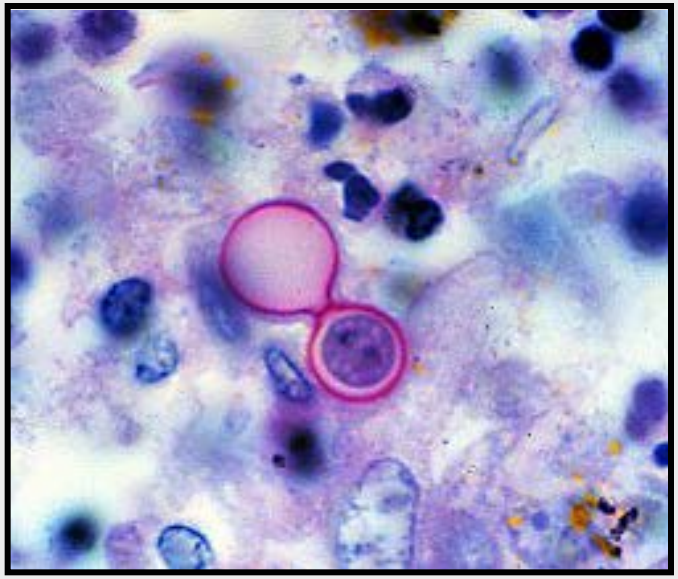
Blastomyces



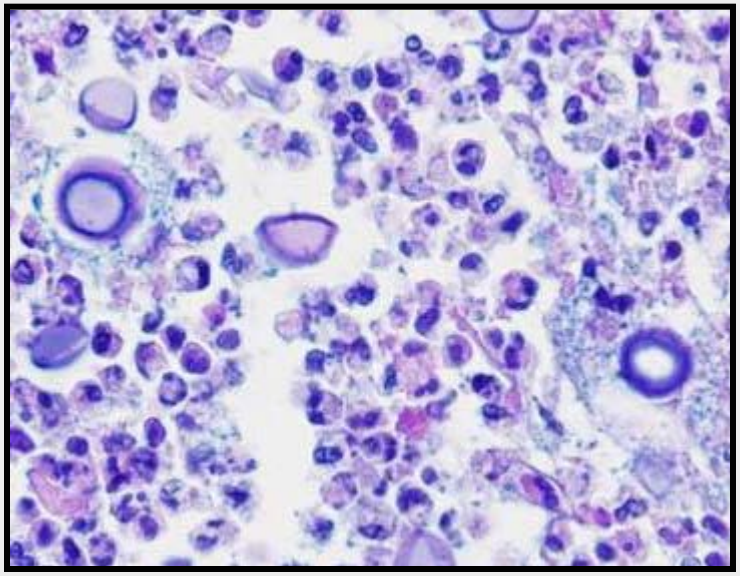
Cryptococcus

Fungal Diseases

- Deep systemic mycosis : ulcerative nodules / plaques
  - **Blastomycosis** , coccidioidomycosis, histoplasmosis , **cryptococcosis**



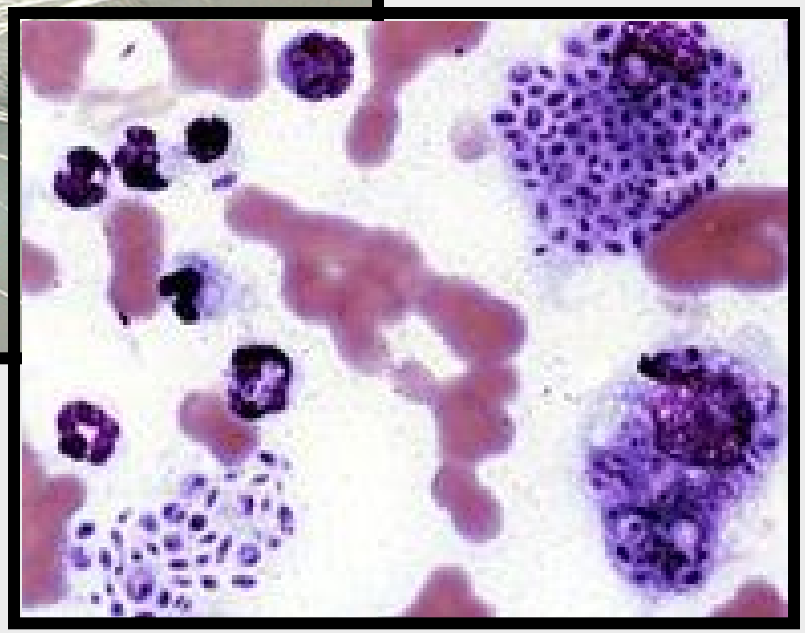
Blastomyces



Cryptococcus

Fungal Diseases

- Deep systemic mycosis : ulcerative nodules / plaques
  - **Blastomycosis** , coccidioidomycosis, histoplasmosis , **cryptococcosis**
- Nasal Aspergillosis : “Drainage board” effect : erosions
- Sporotrichosis : nodular , ulcerative
- Diagnosis demonstration of organism
  - cytology, biopsy, or culture



Clues to the Diagnosis

- Lesions are localized : nodules, draining tracts & ulcerative lesions
- History : Concurrent nasal OR respiratory signs?
- Histopathology: pyogranulomatous inflammation +/- organism visible
- Skin easily accessible tissue for culture !!

Treatment

- Appropriate antifungal therapy

Canine Distemper Virus (CDV)

- “Hard pad disease”
  - uncommon
- Diagnosis :
  - Other clinical signs of distemper
  - Skin biopsy with immunohistochemistry for CDV antigen

Courtesy Dr. C. Sedgewick

Feline Leukemia Virus

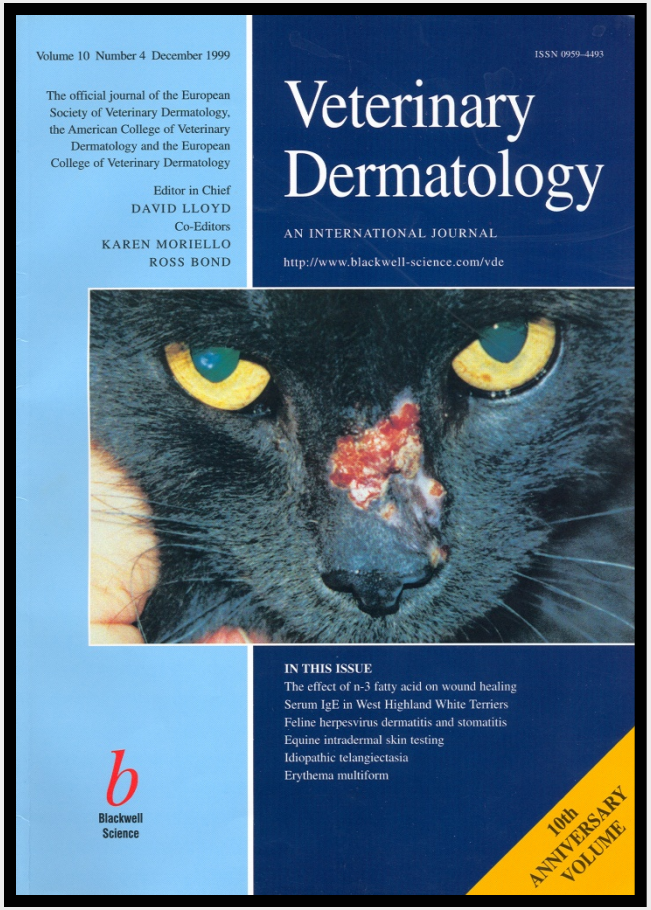
- Cutaneous horns

Feline Leukemia Virus

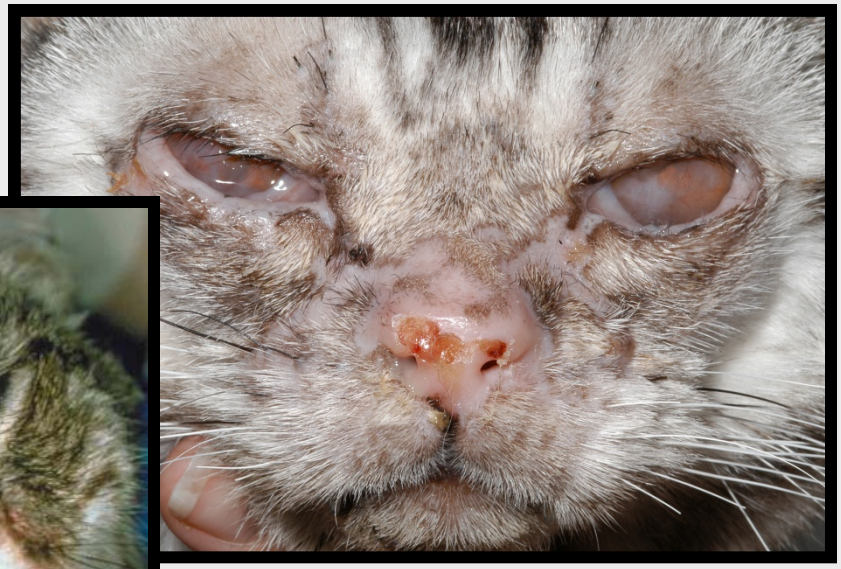
- Cutaneous horns
- Cats can be lame
- Diagnosis :
  - FeLV +ve
  - Skin biopsy
    + / - Immuno - histochemistry for viral antigen

Feline Herpesvirus Ulcerative Dermatitis

- "Ulcerative facial & nasal dermatitis and stomatitis in cats associated with feline herpesvirus 1" -*Vet Derm 1999 : Hargis AM et al*
- Eosinophilic , necrotic ulcerative facial lesions w/ visible intranuclear inclusion bodies



Many Faces of Feline Herpes Virus Ulcerative Dermatitis

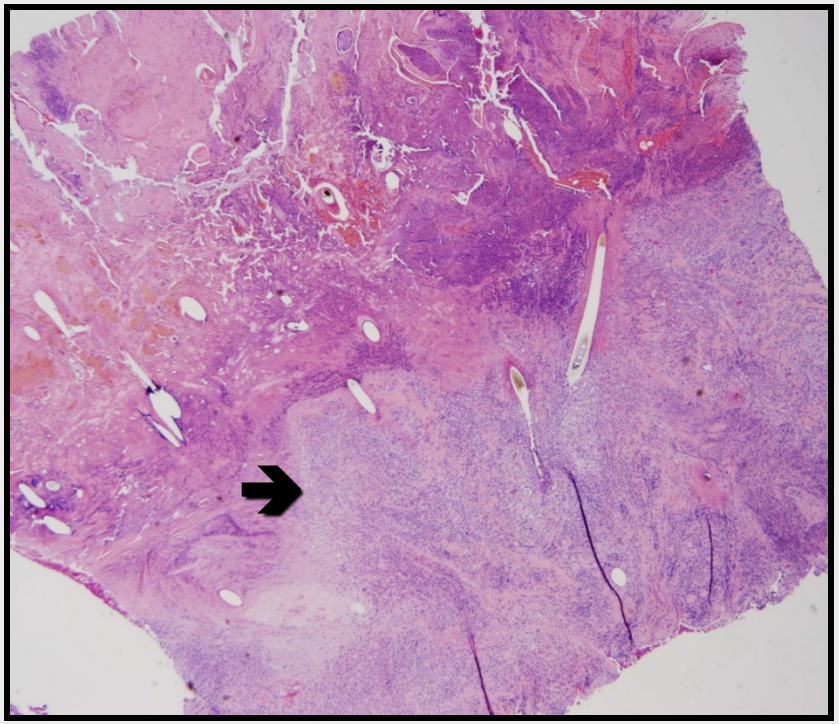


Clues to the Diagnosis

- History & response to therapies
- Dorsal muzzle lesion

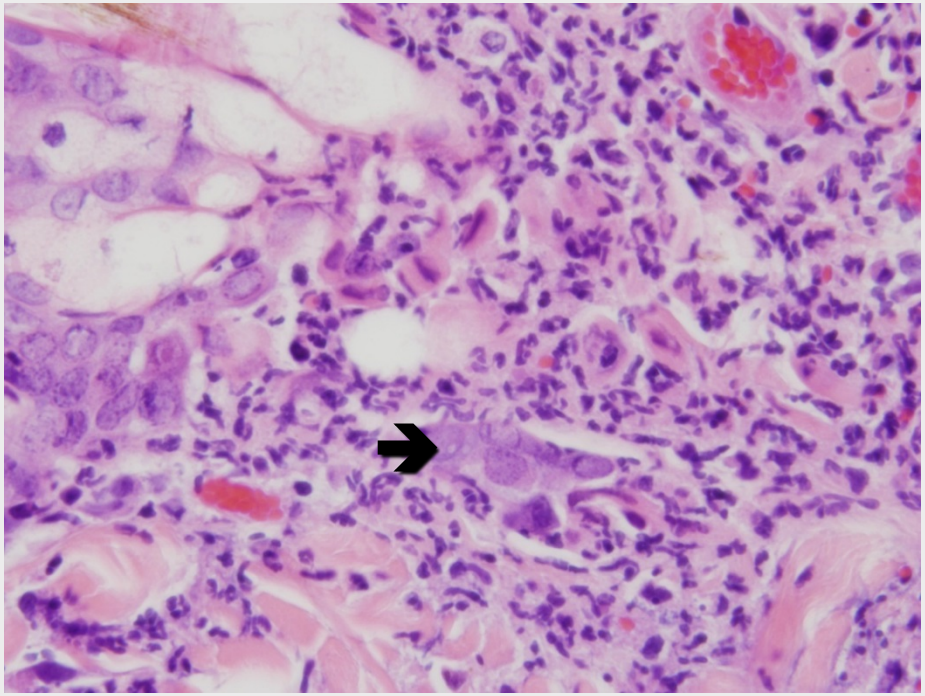
Clues to the Diagnosis

- History & response to therapies
- Dorsal muzzle lesion
- Histopathology : Ulcerative , necrosis w/ eosinophils



Clues to the Diagnosis

- History & response to therapies
- Dorsal muzzle lesion
- Histopathology : Ulcerative , necrosis w/ eosinophils
- Visible inclusions ?



Clues to the Diagnosis

- History & response to therapies
- Dorsal muzzle lesion
- Histopathology : Ulcerative , necrosis w/ eosinophils
- Visible inclusions ?
- PCR for FHV-1 in skin biopsy: sensitive & specific test

Treatment

- Alpha Interferon (IFN) : 1 million units / m^2 SQ three times a week
- Famcyclovir : 60 mg / kg q 8 hours
- Lysine : 500mg PO BID
- Treat secondary infections

3 months of SQ α- interferon

4 yr MC Cat : Most likely DDX?

1. **Clearly fungal disease get sample for culture**
2. **It is not fungal it is lesion related to FHV-1**
3. **I can’t tell it could be A or B need biopsy to help differentiate**
4. **It is a carcinoma in situ**

4 yr MC Cat : Most likely DDX?

1. **Clearly fungal disease get sample for culture**
2. **It is not fungal it is lesion related to FHV-1**
3. **I can't tell it could be A or B need biopsy to help differentiate**
4. **It is a carcinoma in situ**

Cutaneous Manifestations of Systemic Disease…

- Associated with
  - Hormonal / endocrine disturbances
  - Paraneoplastic / metastatic changes
  - Nutritional or metabolic perturbations
  - Systemic infectious disease
  - Vasculitis

Vasculitis

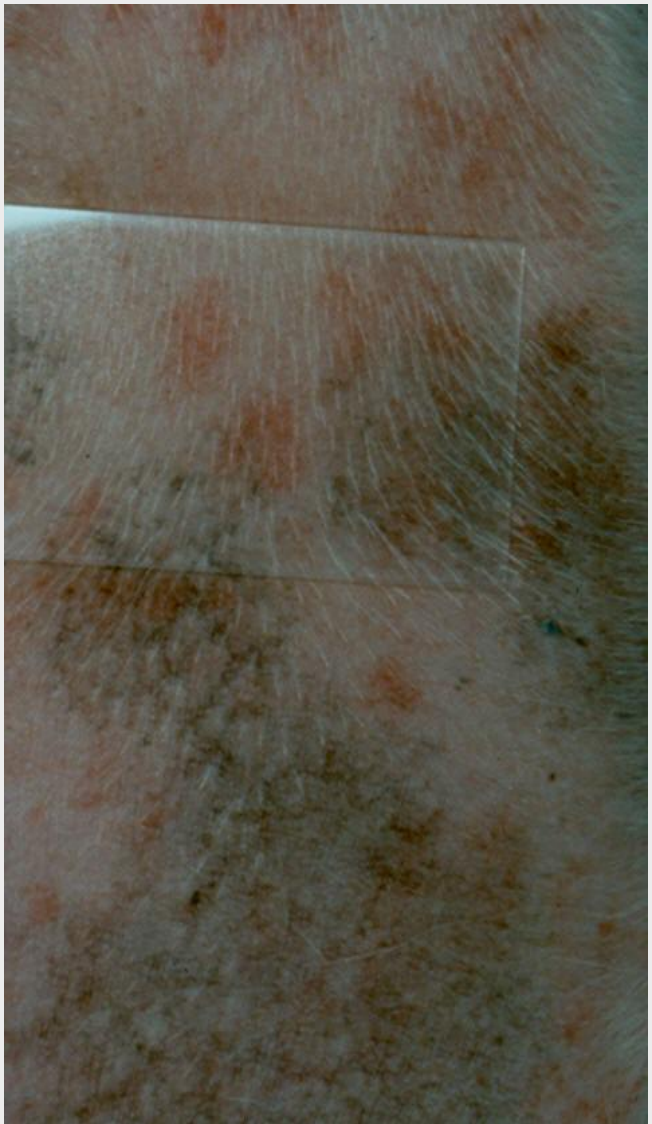
- Characterized by inflammation of & damage to blood vessels
- Nonimmunopathogenic mechanisms
  - Vascular wall invasion (tumor, bacteria)
  - Hemodynamic changes
- Immunopathogenic mechanisms
  - Deposition of immune complexes
  - Immunologic activity directed at vascular wall components

Vasculitis

- Characterized by inflammation of & damage to blood vessels
- Primary or sole manifestation of a disease OR secondary to another primary disease
- Confined to a single organ (eg : skin) or may simultaneously involve multiple organ systems

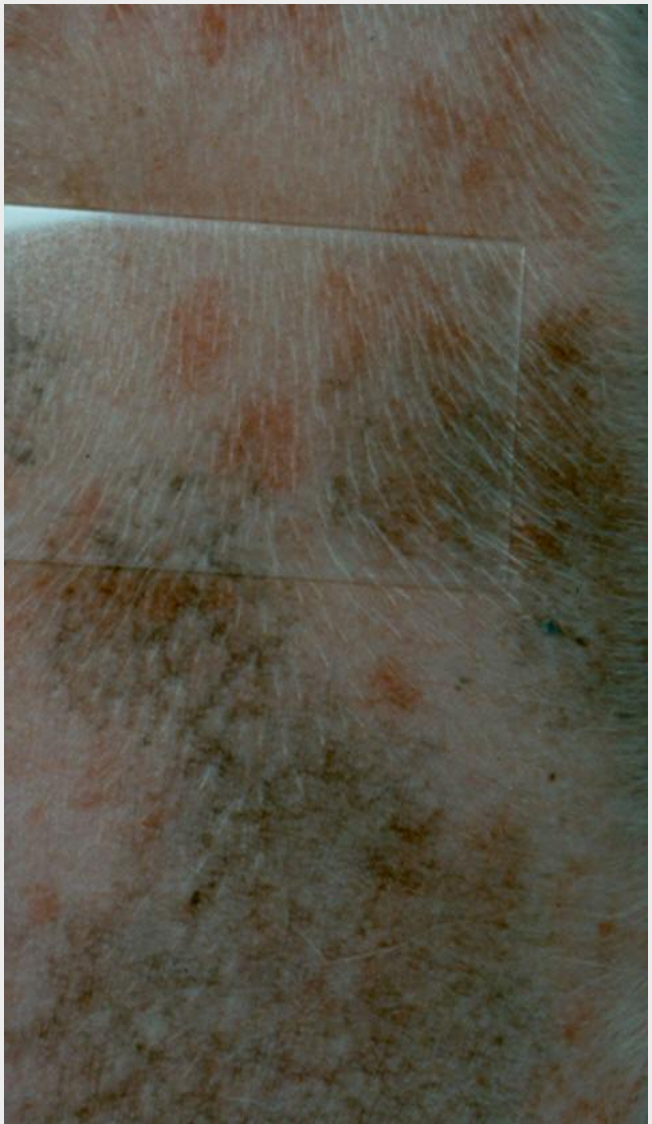
This technique allows you to……

1. Determine if there is vasculitis in the skin
2. Differentiate erythema from hemorrhage in the skin
3. Magnify the lesions



Diascopy allows you to……

1. Determine if there is vasculitis in the skin
2. Differentiate erythema from hemorrhage in the skin
3. Magnify the lesions

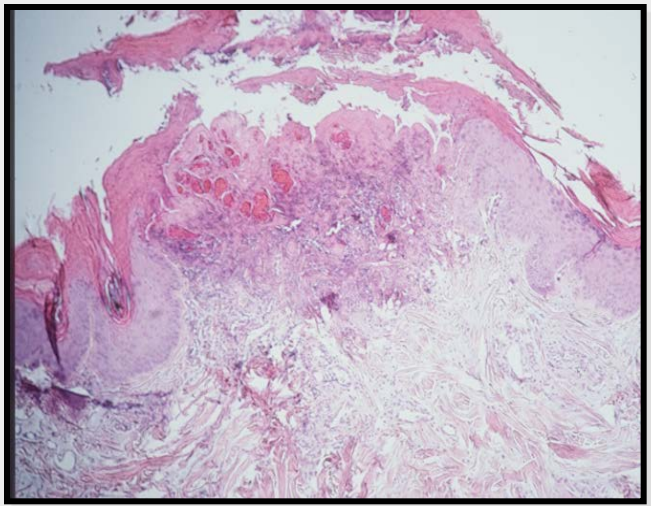


Vasculitis

- Foot pad lesions :
  discrete ulcers ,
  chronic lesions ➔pale
  central depressions

Vasculitis

- Foot pad lesions : discrete ulcers , chronic lesions → pale central depressions
- Concurrent lesions on tail tip or pinnal margins
- May be lesions elsewhere : erythema , hemorrhagic macules , necrosis & ulceration
- Biopsy: evidence of vasculitis



Classification of Etiologies

- Infectious vs non-infectious etiologies
- Infectious : bacterial , rickettsial , viral, parasitic , protozoal
- Non-infectious :
  - Exogenous (drug)
  - Endogenous (neoplasia)
  - Unknown etiology

INFECTIOUS VASCULITIS	EXAMPLES
Bacterial	Bacterial endocarditis, septicemia
Fungal	Disseminated fungal infections
Viral	FIP, herpes
Rickettsial	Ehrlichiosis, Rocky Mountain Spotted Fever
Parasitic	Dirofilariasis
Protozoal	Leishmaniasis, babesiosis, trypanasomiasis, toxoplasmosis

NON-INFECTIOUS VASCULITIS	
Exogenous antigen	Drugs, vaccines
Endogenous antigen	Neoplasia, immune-mediated systemic disease (SLE)
Unknown antigen	Classify histologically by cell type involved and type of vessel involved

Clues to Diagnosis

- Compatible lesions & path
- Screen for etiologies
  - Review drug & travel history
  - Evaluate for evidence of systemic involvement:
    - joint , muscle or neck pain, heart murmur, fundic exam
  - Evaluate for infectious etiologies : tick titers
  - Evaluate for other evidence of immune-mediated disease

Treatment

- Depends in part on cause of vasculitis
- Treat any underlying infectious disease
- If no infectious etiology
  - Glucocorticoids
  - Pentoxifylline
  - Focal lesions : topical tacrolimus

Cutaneous Manifestations of Systemic Disease…

- Associated with
  - Hormonal / endocrine disturbances
  - Paraneoplastic / metastatic changes
  - Nutritional or metabolic perturbations
  - Systemic infectious disease
  - Vasculitis
  - Auto-immune systemic disease

Autoimmune Skin Diseases

- Uncommon diseases
- Autoantibodies or lymphocytes target cutaneous proteins → skin lesions

- Require skin biopsy for diagnosis
- Autoimmune skin diseases w/ systemic involvement
  - Systemic lupus erythematosus
  - Erythema multiforme & Toxic epidermal necrolysis
  - Sterile nodular panniculitis

Systemic Lupus Erythematosus

- Multiple organ systems affected :
  - fever, polyarthritis, protein losing nephropathy, anemia, thrombocytopenia
  - skin lesions (~ 20 % of the time)
- Pleomorphic skin lesions : Erythema, scaling, depigmentation, crusting , ulceration
- Involve muzzle , nasal planum, pinnae , distal extremities, oral cavity & panniculus.

Systemic Lupus Erythematosus

- Systemic evaluation could include
  - CBC
  - Serum biochemistry
  - Urinalysis
  - Urine protein : creatinine ratio
  - Joint taps
  - ANA
  - Skin biopsy: interface dermatitis

Diagnostic Procedures RESULTS

Service	Request	Status	Date	Procedure	Img
Hematology/Cytology	14H12261	Final	19Aug14	7006 - Complete blood count	
Clinical Chemistry	14C15906	Final	19Aug14	7602 - Small Animal Panel 2	
Cardiology	27711	Consul	19Aug14	1292 - Cardiac Ultrasound	
Hematology/Cytology	14H12280	Final	19Aug14	7134 - Cytology	
SA Ultrasound	88037	Final	19Aug14	6900 - Sa Ultrasound Scan	
SA Ultrasound	88037	Final	19Aug14	6925 - Cystocent U/S Guided	
Clinical Chemistry	14C15966	Final	19Aug14	7450 - Urine Urinalysis	
Bacteriology/Mycology	14M08115	Final	19Aug14	8031 - Urine Aerobic C&s	✓
SA Radiography	184571	Final	19Aug14	6016 - X-Ray - Thorax	
Bacteriology/Mycology	14M08130	Final	20Aug14	8003 - 4DX Snap Test	✓
Bacteriology/Mycology	14M08147	Final	20Aug14	8047 - Aer/Anaer Bld C & S	✓
Hematology/Cytology	14H12358	Final	20Aug14	7101 - Joint fluid	
Hematology/Cytology	14H12358	Final	20Aug14	7102 - Fluid.joint.add.site	
Biopsy	14B2452	Final	20Aug14	9011 - Biopsy interpret	✓
Clinical Chemistry	14C16096	Final	21Aug14	7774 - Electrolyte.Ser.Plas	
Hematology/Cytology	14H12405	Final	21Aug14	7134 - Cytology	
Hematology/Cytology	14H12406	Reques	21Aug14	7134 - Cytology	
SA Ultrasound	88060	Reques	21Aug14	6922 - Level 2 Intervention	
Clinical Chemistry	14C16148	Final	22Aug14	7780 - Electrolyte/mineral	
Hematology/Cytology	14H12490	Final	23Aug14	7006 - Complete blood count	
Clinical Chemistry	14C16225	Final	23Aug14	7602 - Small Animal Panel 2	

Clues to the Diagnosis

- Diagnosis of immune-mediated disease in 2 or more organ systems, fever, +ve ANA
- Compatible skin pathology
- Prognosis depends on organ systems involved
- Treatment : Immuno-suppressive therapy :
  - corticosteroids, cyclosporine, azathioprine, chlorambucil

Courtesy Dr P Ihrke

Are there enough criteria to diagnose SLE ?

1) Not sure
2) I think so
3) No
4) Yes

Dxed with Immune mediated thrombocytopenia (ITP)
Cell poor interface dermatitis w/ lichenoid band on skin bx
Febrile
Non proteinuric Stage 2 kidney disease

Are there enough criteria to diagnose SLE ?

1) Not sure
2) I think so
3) No
4) Yes

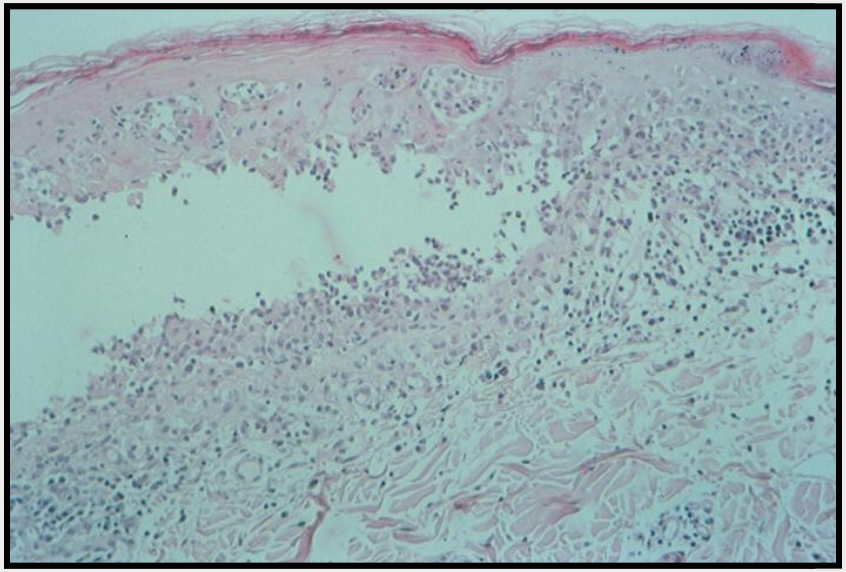
Dxed with Immune mediated thrombocytopenia (ITP)
Cell poor interface dermatitis w/ lichenoid band on skin bx
Febrile
Non proteinuric Stage 2 kidney disease -

Erythema Multiforme

- Acute onset of pleomorphic erythematous macules & papules , urticarial , target lesions , ulcers
- Lesions can be focal or generalized & may involve mucocutaneous junctions, oral cavity & pinnae
- Lesions often coalesce

Erythema Multiforme

- Minor and major variants: clinical designation based on % of body involvement
- EM major more closely linked to drugs ?
- Biopsy multiple lesions
  - Avoid areas of ulceration need intact epidermis
  - Histology : single cell necrosis, apoptotic keratinocytes w/ lymphocyte satellitosis
  - Confluent necrosis → ulceration



Erythema Multiforme SJS

Abstract Send to:

Vet Dermatol. 2014 Oct;25(5):406-e64. doi: 10.1111/vde.12142. Epub 2014 Jul 3.

Erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis: a comparative review.

Yager JA[1].

Author information

Abstract

BACKGROUND: Human erythema multiforme (EM) and Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) are separate conditions. There is no consensus on classification criteria for the eponymous diseases in animals.

RESULTS: Animal EM is very different from 90% of human EM, which is herpes virus associated (HAEM). Animals lack acrally distributed, typical raised targets. Unlike canine parvovirus 'EM', HAEM is not an active infection. Animal EM is often attributed to drugs, but this is rarely proved. Conversely, human and animal SJS/TEN are almost identical, life-threatening disorders of epidermal necrosis and detachment, typically triggered by drugs (occasionally by infectious agents). Both EM and SJS/TEN are mediated by cytotoxic lymphocyte responses against altered keratinocytes (infectious agents or drugs). Apoptosis results from direct cytotoxicity or through soluble mediators, namely Fas ligand, granzymes, perforin and granulysin. Diagnosis in humans is clinicopathological, with emphasis on clinical lesions; histopathology confirms the pathological process as interface (cytotoxic) dermatitis. Human EM is self-limiting; only recurrent and rare persistent cases require antiviral/immunosuppressive therapies. Drug-induced EM responds to drug withdrawal. Idiopathic canine EM (>40%) is usually chronic, refractory to treatment and may represent heterogeneous conditions. Early identification and removal of the causative drug and high-quality supportive care are critical in SJS/TEN. Mortality rate is nevertheless high.

CONCLUSIONS AND CLINICAL IMPORTANCE: (1) Histopathological lesions do not reliably differentiate EM, SJS and TEN. (2) A multicentre study to develop a consensus set of clinical criteria for EM and SJS/TEN in animals is overdue. (3) No adjunctive therapies, including intravenous immunoglobulin and ciclosporin, have met evidence-based standards.

Clues to the Diagnosis

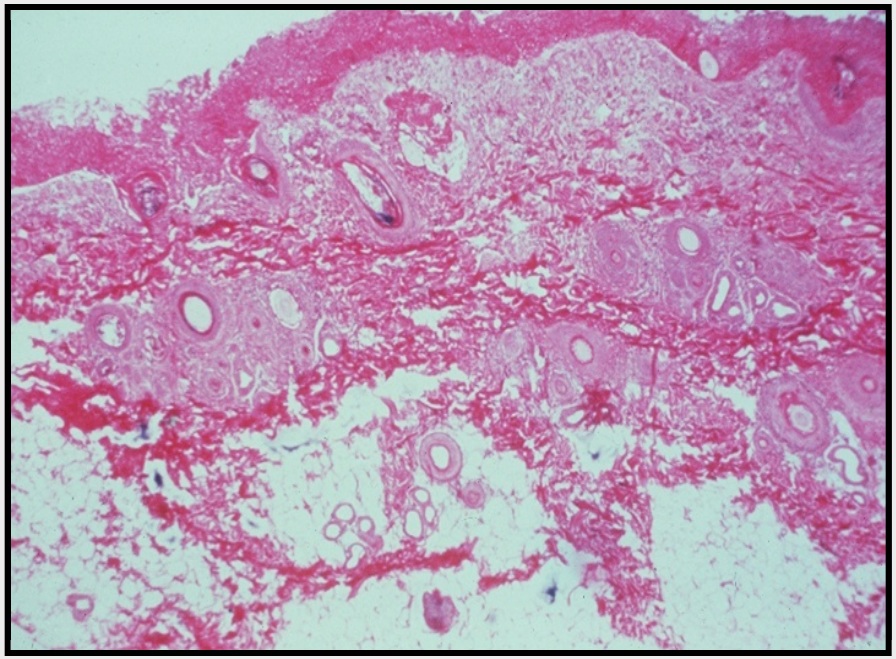
- Acute onset of lesions
- Varied lesions: erythematous macules or plaques, coalescing erosions, crusts
- Targetoid lesions very suggestive
- Oral cavity may be involved
- Biopsy
- Prognosis depends on severity & what are underlying triggers

Treatment

- Stop DRUGS!
- Underlying disease?
  - Infection?
- Supportive care : fluids, novel antibiotics
- Immuno-suppressive therapy ?

Toxic Epidermal Necrolysis

- Rare & often fatal ulcerative disease of skin & mucosal surfaces
- Highly linked to adverse drug reactions
- Widespread confluent erythema → epidermal necrosis & ulceration
  - + ve Nikolsky sign
- Biopsy: coagulative necrosis of epidermis



Sterile Nodular Panniculitis

- Ulcerated or draining nodular lesions +/- subcutaneous nodules
- Lesions often truncal
- Febrile episodes
- Can be associated w/ pancreatitis or immune mediated dz
  - SLE, polyarthritis

Clues to the Diagnosis

- History draining tracts poorly responsive to antibiotics
- Biopsy: nodular panniculitis
- Negative tissue cultures for infectious etiologies

- Treat w/ immunosuppressive therapy
  - Often corticosteroids

Cutaneous Disease is Not Always Skin Deep

- Certain skin lesions serve as recognizable markers of underlying systemic disease
- Skin lesions can be an indicator for systemic disease because of a shared common pathogenesis
- Skin can provide vital diagnostic information for systemic disease

Questions??

caouterbridge@ucdavis.edu