Joint Pathology Center
Veterinary Pathology Services

WEDNESDAY SLIDE CONFERENCE 2025-2026

Conference #9 — 22 October 2025

CASE I:

Signalment:
3 months-old, female, Piétrain x Large White, pig, *Sus scrofa domesticus*

History:
Two pigs were purchased from a commercial pig breeder and housed in a research facility where a planned necropsy was carried out as part of an experimental procedure. Both animals showed skin lesions unrelated to the experimental design.

Gross Pathology:
Multiple, 1-2 mm in diameter, non-raised, red to blue, irregular lesions were found diffusely distributed through the skin of the ventral and inguinal regions well as the head, nose and ears. Upon incision, lesions were localized at the dermal/subcutaneous junction.

Laboratory Results:
Cells lining cystic cavities immunohistochemically stained positive with pan-cytokeratin and negative with CD31. Immunohistochemistry with Ki67 and alpha-SMA revealed a low proliferative index in the apocrine epithelial cells and strong positivity for alpha-SMA in the basal area of the cystic lesions.

Microscopic Description:
Haired skin (dorsal nose, three sections):

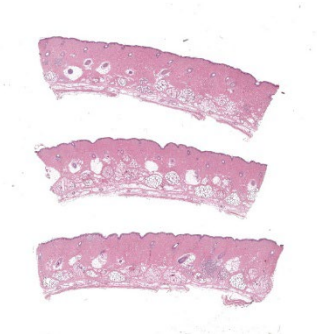

Figure 1-1: Haired skin, pig. Three sections of haired skin are submitted for examination. (HE, 7X)

Within the deep dermis and subcutis there are multiple well delineated clusters of variably distended apocrine glands with sinuous cystic cavities and partial tubular folding, which expand and replace dermal adipose tissue and muscle. Most of the clustered cysts are lined by a single layer of flattened columnar epithelial cells without apical blebbing. Adjacent smaller clusters of lesser distended glands exhibit one to several layers of more cuboidal epithelium. The outer layer of the cyst wall consists of thin layers of myoepithelial cells. Many gland lumina contain pale eosinophilic secretory products. Surrounding tissue and stroma comprise mild lymphoplasmacytic infiltrates.

Focally in the mid dermis and associated with a hair follicle there is a localized, well demarcated focus of moderate mixed cellular in-

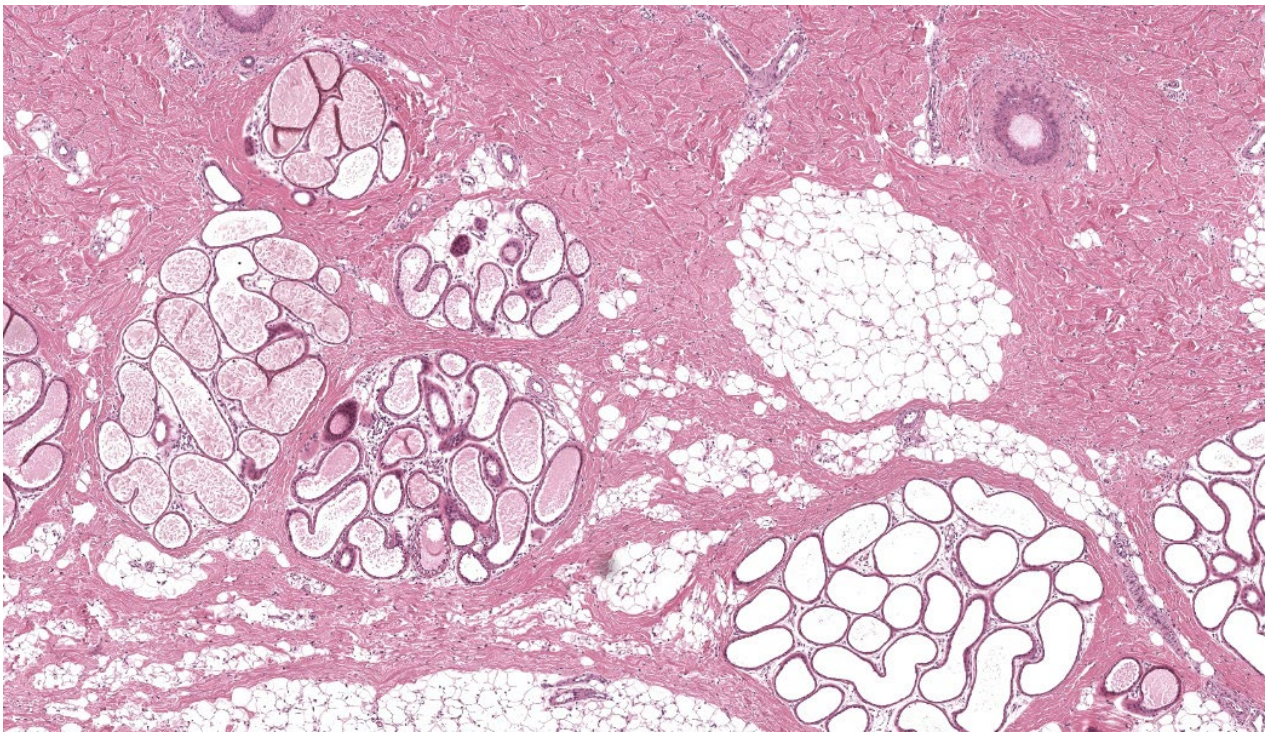

Figure 1-2: Haired skin, pig. Apocrine glands are diffusely and markedly dilated, some with retention of eosinophilic secretory product. (HE, 53X)

flammation composed of macrophages, neutrophils and lesser lymphocytes and plasma cells. These encase numerous distorted and/or ruptured apocrine glands, infiltrate their epithelium and are present within the lumen of remaining glandular structures (foreign body type reaction). Macrophages frequently contain cellular debris.

The remaining epidermis and dermis are unremarkable.

Contributor's Morphologic Diagnoses:
Skin: cystic distention of apocrine glands, diffuse, severe, with compression of adjacent muscle tissue consistent with cutaneous apocrine cystomatosis.

Skin: hidradenitis and dermatitis, focally extensive, moderate, chronic, mixed cellular with apocrine gland rupture (foreign body type reaction).

Contributor's Comment:
Cutaneous apocrine cystomatosis is an uncommon non-neoplastic condition, which has been first reported in three pigs from three different abattoirs in Spain in 2020.[6] There, the lesions appeared as brown, non-prominent nodules within the subcutaneous fat distributed over the entire dorsal region. Microscopically, the authors' findings correspond to results reported here. Ki67 immunohistochemistry showed only few glands with single cells of positive stained epithelium indicating a low proliferative index. In addition to the findings of Lopez-Figueroa et al. an inflammatory site was present in the case described here. This possibly occurs due to rupture of an adjacent dilated gland.

Cutaneous apocrine cystomatosis has also been reported in dogs and cats[4,9,10]. In dogs, it is mainly distributed over the head and neck

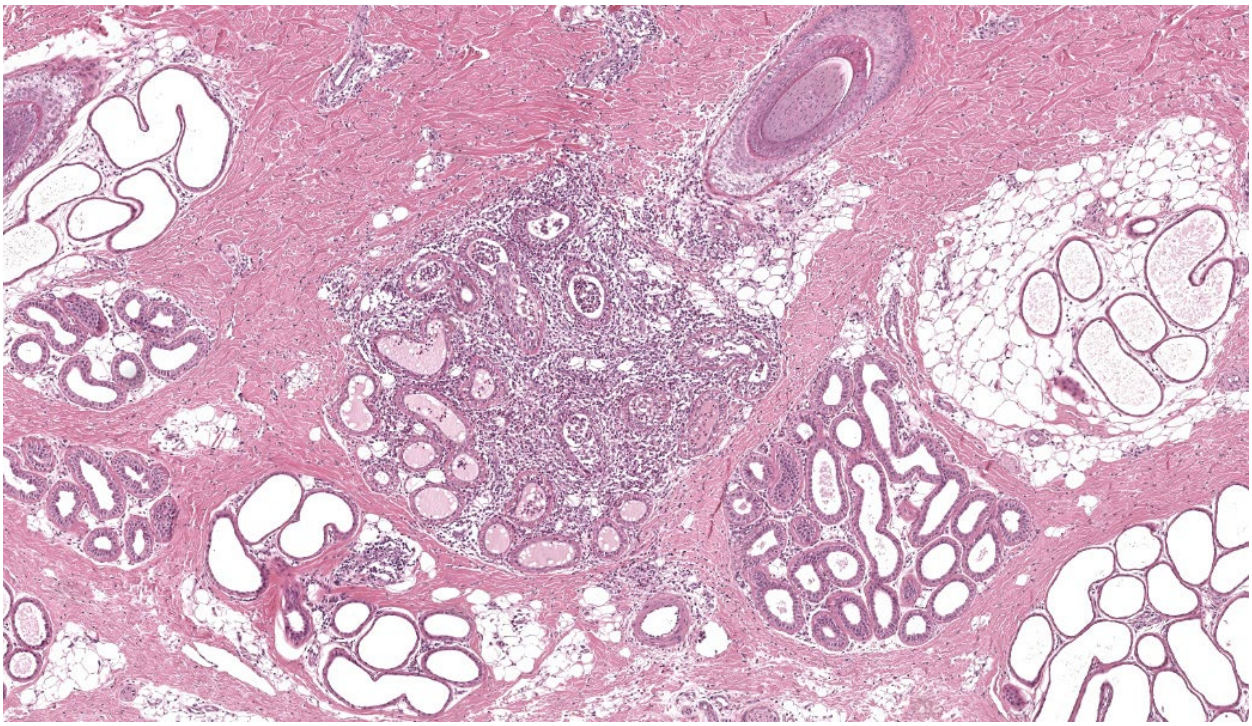

Figure 1-3. Haired skin, pig: Occasionally, rupture of dilated apocrine glands results in infiltration of moderate numbers of lymphocytes, plasma cells, macrophages, and neutrophils, which are often present within the lumina of dilated glands. (HE, 7X)

but was also described at the dorsal trunk and flanks as well as solitary at the cheeks. Microscopically, the lesions are described as multiple clusters of cystically dilated sweat glands, but, in contrast to the lesions in the pigs, show the same morphology as normal apocrine glands with a single layer of cuboidal to columnar epithelium with dome-shaped apical surface. In addition, the epithelial cells of the cyst wall in dogs show some pseudo-papillary projections protruding into the lumen. Inflammation and fibrosis in the surrounding tissue is rare and mild. In case of cyst rupture, moderate inflammation can occur comprising plasma cells, neutrophils and lymphocytes. Pale siderophages, which contain pigment from the iron content of apocrine secretions, may be found.

Feline ceruminous cystomatosis is the corresponding disorder described in cats.[4] The lesion develops from the ceruminous glands and occurs in the external ear and the inner pinna.[5] Microscopically, the cysts are lined by a single layer epithelium that varies from attenuated to cuboidal to columnar. In contrast to dogs and pigs, the surrounding dermis often shows mild fibrosis with detection of inflammatory cells like lymphocytes, neutrophils, mast cells and pigmented macrophages.

The etiology of cutaneous apocrine cystomatosis is uncertain. For dogs, a senile degenerative change has been discussed because affected animals were middle-aged or older. The average age in affected cats has been reported between 8 and 9.5 years, but animals as young as one year can be affected.[4] As all described cases in pigs were from abattoirs or, in our case, from experimental studies, and therefore

comparatively young (3 to 6 months), the disease in pigs seems to be unrelated to the aging process. A congenital origin is also discussed as normal apocrine glands are absent and no other alterations in the surrounding tissue are detectable.[6] Whether there is a genetic origin in dogs and cats is unknown.

In cats, there seems to be a breeding predisposition in Persian and Abyssinian cats with a slight male predominance, whereas in dogs and pigs no over-representation in certain breeds or sex predilection is described to date.[3]

The differential diagnosis of cutaneous apocrine cystomatosis includes apocrine hidrocystoma/cystadenoma, particularly described in cats, where it is predominantly located in the eyelid.[1,2] It is a benign neoplasm characterized by cysts with a single or multilayered cuboidal to columnar epithelium and true papillary projections into the cavity. These neoplasms usually show a higher proliferative index.

In humans, cutaneous apocrine cystomatosis has not been described. The related benign neoplasm is, corresponding to the differential diagnosis in animals, the apocrine hidrocystoma/cystadenoma, which includes a spectrum of benign cystic lesions of ductal sweat gland origin, with architecture ranging from simple cystic (hidrocystoma) to more complex (cystadenoma).[7]

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JPC Diagnoses:
Haired skin, apocrine glands: Dilation, chronic, diffuse, marked.

JPC Comment:
The JPC was fortunate enough to host Dr. Charles Bradley again this year for an excellent dermatopathology-focused conference that was preceded by his highly educational and forever crowd-pleasing "Approach to a Case Using Pattern Analysis" lecture. This first case was a great exercise in reminding the pathologist to not overinterpret histological findings. Participants are, rightfully so, primed to expect description-heavy cases in conferences. Every once in a while, though, a moderator selects a case that is on the leaner descriptive side to make this point: don't make a mountain out of a molehill and only describe what you see, not what you want to see. Participants did an excellent job adhering to this principle, and most were able to reach the correct diagnosis. The contributor in this case provided an excellent write-up of this lesion across species and it is well-worth the read.

Conference discussion for this case covered numerous topics, including the specific histologic findings that can assist the pathologist in

species identification based on skin. Dr. Bradley insists on this as part of his dermatopathology diagnostic process: look at the slide first, try to identify the species you have, and then check the case information. If they don't seem to match up, a call to the submitting clinician might be in order. For most porcine skin, the epidermis is thicker than other common species, usually 5-7 nucleated cells thick, and forms papillary, shallow rete pegs that project into and interdigitate with the superficial dermis.[8] This papillary epidermis is also a feature of human skin. Porcine skin is especially thick on the dorsum. Additionally, pig sebaceous glands are sparse and typically associated with hair follicles. Porcine hair follicles are, generally, large and far apart from one another.

Participants were asked to describe the difference between apocrine and eccrine glands and why they chose apocrine cystomatosis over eccrine cystomatosis. Histologically, apocrine and eccrine glands are indistinguishable, but location, which varies by species, can help with differentiation. In humans, eccrine glands are all over the body and responsible for sweat production, which aids in thermoregulation, whereas apocrine glands are restricted to the axilla and groin regions. In pigs, eccrine glands are restricted to the tip of the snout and to the carpal regions and serve no thermoregulatory function.[5] In dogs, eccrine glands are restricted to the paw pads and nose, and have limited sweating function.[5] Apocrine glands, however, are everywhere in pig skin and are, like the sebaceous glands, associated with hair follicles. The skin samples in this case were from the abdomen and dorsal nose, neither of which is an eccrine gland location in pigs. Differentiating between the two can be diagnostically important, especially in cases of neoplasia, as eccrine adenocarcinomas are considered more aggressive than apocrine adenocarcinomas.

There was brief discussion on the inflammatory component in this case. Mild inflammation of apocrine glands, known as hidradenitis, is a common background lesion in many species that is usually associated with folliculitis. In this case, the focus of inflammation was severe enough that it was unanimously thought by conference participants to be due to a ruptured apocrine gland secondary to dilation. There was a question posed to participants regarding possible other differentials based on gross images in other species, and included apocrine cystadenoma, basal cell adenoma, sebaceous adenoma, or melanocytic neoplasms. Of these, apocrine cystadenoma vs. apocrine cystomatosis was discussed most heavily for educational purposes, the main differences being that this lesion was diffuse throughout the skin, which is more common with cystomatosis, and there are no papillary projections into the lumens of affected glands. Papillary projections of epithelial cells into the cystic glandular lumen are a common finding in apocrine cystadenomas, but not in cystomatosis.[7] Wrapping up conference discussion of this case was a brief review of apocrine cystomatosis lesions in other species, which are discussed by the contributor in their comment.

Apocrine gland cystomatosis is also known as epitrichial sweat gland cystomatosis, apocrine cystic hyperplasia, and cystic hyperplasia of apocrine sweat glands (human and canine term).[6,10] When initially described in the medical literature, it was proposed that cyst formation might be due to the occlusion of excre-

tory ducts.[7,9] Later, it was suggested that apocrine cysts result from episodes of glandular hyperplasia followed by an involution phase and inability of the body to reabsorb the contents of the dilated glands.[7,9] More recently, though, single or multiple apocrine cysts have been described as either benign sweat gland tumors, as idiopathic, non-neoplastic, senile degenerative changes or, such as in this pig's case, as a congenital condition.[6,7,9]

References:

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CASE II:

Signalment:
12-year-old neutered male Pomeranian dog (*Canis lupus familiaris)*

History:
The patient has been presented for a specialistic dermatological examination due to the presence of blackish skin lesions scattered throughout the body, particularly severe in the abdomen, thigh, neck, and chest. Multifocal areas were characterized by severe alopecia. Licking of the groin area was reported. The patient has been treated with levothyroxine.

Gross Pathology:
Four skin biopsy punches from the abdomen, thigh, neck, and chest were received and processed.

Laboratory Results:
N/A

Microscopic Description:
Haired skin. All the biopsies are histologically similar. The superficial and mid dermis are obscured by a moderate to severe inflammatory infiltrate, often obscuring the dermo-epidermal junction. The inflammatory infiltrate is represented by a prevalence of lymphocytes and plasma cells, macrophages occasionally engulfing melanin (melanophages), and rare neutrophils. The epidermis is moderately thickened (irregular hyperplasia), with mild intercellular edema (spongiosis) and severe thickening of the stratum corneum by predominantly nucleated (parakeratotic hyperkeratosis) or less frequently non-nucleated keratin (orthokeratotic hyperkeratosis). Numerous apoptotic figures are observed throughout the epidermis, occasionally surrounded by lymphocytic satellitosis. Similar lesions are observed in the hair follicles. There is multifocal erosion or ulceration of the epidermis; the ulcerated areas are obscured by serocellular crusts.

Contributor's Morphologic Diagnoses:
MD: Haired skin. Lymphoplasmacytic interface dermatitis, diffuse moderate chronic, with epidermal hyperplasia, numerous suprabasal apoptosis with lymphocytic satellitosis, parakeratosis

ND: Hyperkeratotic erythema multiforme

Contributor's Comment:
Erythema multiforme (EM) denotes a disease histologically characterized by keratinocyte death (apoptosis) with lymphocytes satellitosis.[3] Historically, veterinary EM has been compared to human EM, thus been considered as one end of the spectrum of diseases including Stevens-Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN).[5,6] The

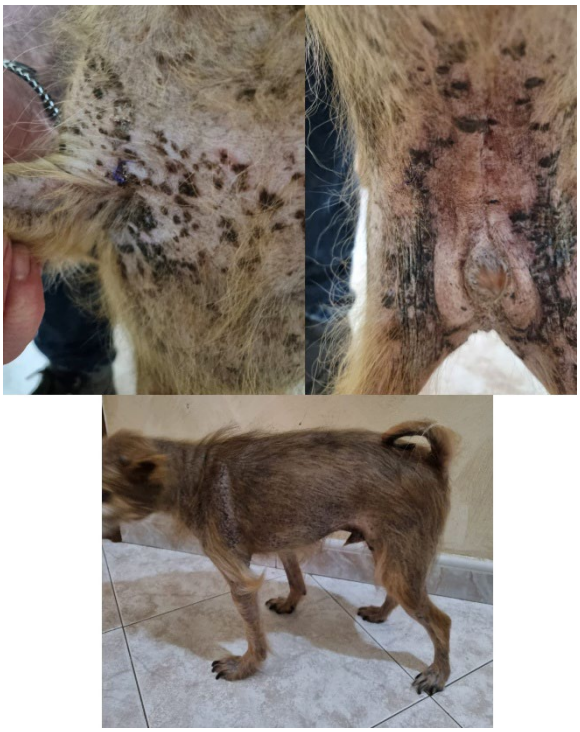

Figure 2-1. Haired skin, dog. Alopecic, ulcerated skin lesions are scattered throughout the body, particularly severe in the abdomen, thigh, neck, and chest. (Photograph courtesy of: San Marco Veterinary Clinic and Laboratory, https://www.clinicaveterinari

terms, 'erythema multiforme minor' (EM minor) and 'erythema multiforme major' (EM major) have been previously adopted to describe entities with significant differences in the severity of involvement, expressed as percentage of body surface.[3] Respectively, EM minor is characterized by target lesions, affecting maximum one mucosal surface, and less than 10% of body surface; EM major involves more than one mucosal surface affected, between 10% and 50% of body surface, with less than 10% epithelial detachment.[3] SJS involves more than 50% of body surface, with an epithelial detachment of 10%-30%; TEN is characterized by a generalized disease and more than 30% epithelial detachment.[3]

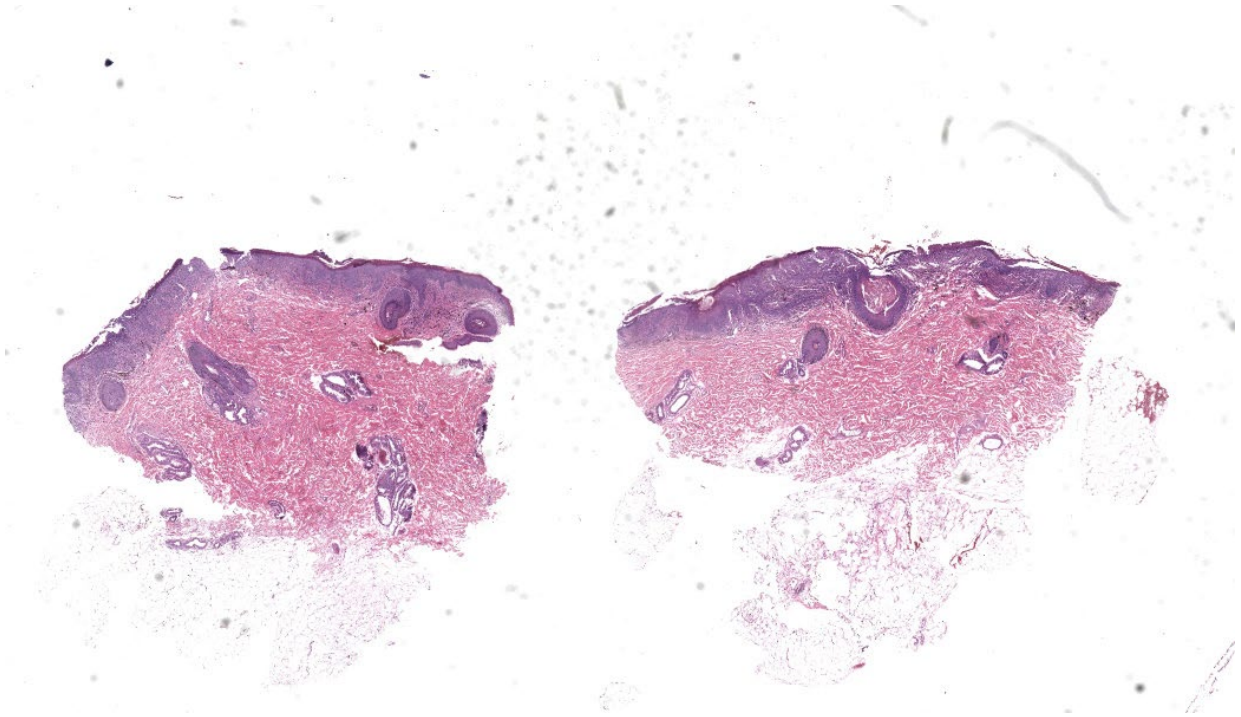

Figure 2-3. Haired skin, dog. The epidermis is hyperplastic, hyperkeratotic, and multifocally ulcerated with pustule formation. There is interface dermatitis with numerous lymphocytes, plasma cells, and macrophages, which often migrate into the epidermis and follicular epidermis. There is moderate pigmentary incontinence. (HE, 158X)

However, nowadays in human medicine, EM and SJS/TEN are considered different entities, and not a spectrum: EM is considered a separate disease, mostly associated with herpes simplex virus, while SJS and TEN are mostly drug-induced. [5,6] Unfortunately, there is no consensus about the criteria for the differentiation of these diseases in veterinary medicine.[5,6]

EM is a rare disease and has been reported in dogs, cats, horses, cattle, swine, and a ferret.[3,5] EM is a multi-factorial disease: adverse drug reaction is traditionally considered the most common cause, but also other triggers have been reported, including neoplasia, parvovirus infection and commercial dog food preservatives, and also idiopathic cases are reported.[2-6] EM is presumably a host-specific T cell-mediated hypersensitivity phenomenon directed towards different keratinocyte-associated antigens, thus eliciting the death of the keratinocytes through apoptosis.[3]

Grossly, EM is frequently characterized by erythematous macules, papules, and plaques with central clearing, usually with acute onset.[3.5.6] In later phases, there could be crusts, with a more targetoid appearance, arciform and serpiginous patterns.[3] Mucosal lesions include vesicles, bullae, and ulcers.[3] Fever and pain may be present. Lesions most commonly involve trunk, groin, and axillae, but may be present anywhere.[3]

Histologically, EM has the features of a cytotoxic (interface) dermatitis. Necrotic keratinocytes are present throughout the epidermis and the adnexal epithelia, often associated with lymphocytic satellitosis. The dermo-epidermal junction is obscured by lymphocytes and

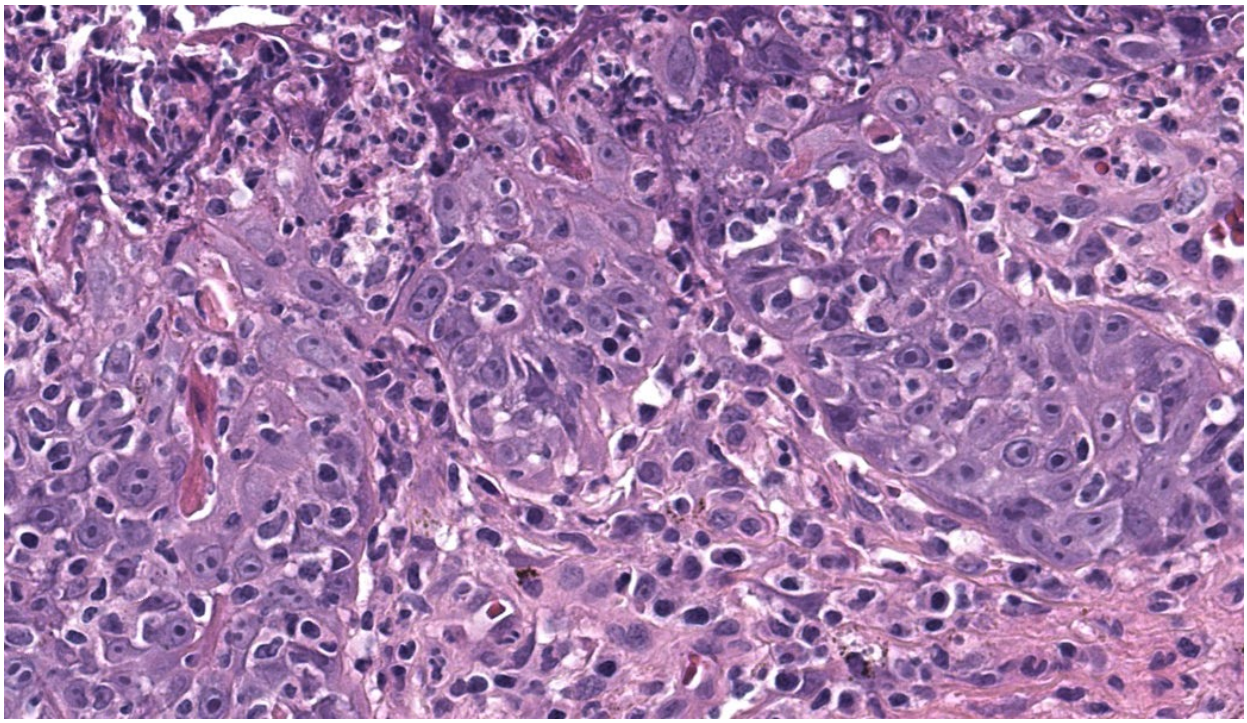

Figure 2-4. Haired skin, dog. There are numerous individualized and small aggregates of eosinophilic apoptotic keratinocytes at all levels of the epidermis. Numerous lymphocytes migrate into the inflamed epidermis. (HE, 960X)

macrophages. Basal keratinocytes could be degenerated.[3,5,6] Hyperkeratosis and parakeratosis are commonly seen in canine EM, as opposed to human EM, and may be severe in persistent forms of EM.[6] This latter form is called "hyperkeratotic EM".[1]

Based on the morphological features, the differential diagnoses include cutaneous lupus erythematosus, thermal or caustic burns, epitheliotropic lymphoma.[3,5]

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JPC Diagnoses:
Haired skin: Dermatitis, cytotoxic-interface, lymphocytic, chronic, marked, with transepidermal keratinocyte apoptosis and parakeratotic hyperkeratosis.

JPC Comment:
This classic case of erythema multiforme (EM) was much appreciated by participants as it stimulated great discussion on EM and other top differentials, cytotoxic dermatitis pathogenesis, and a handful of "boards-worthy" information. The contributor's well-written and thorough comment covers much of what was discussed in conference related to the differences between the human and canine manifestations of EM, so focus will be placed on other major discussion points.

The major histologic features to help differentiate EM from other conditions are the presence of suprabasilar and transepidermal apoptosis of keratinocytes and satellitosis of lymphocytes around affected keratinocytes.[5]

Note, however, that if lymphocytes are instead aggregating in and near the epidermis rather than just hovering around affected keratinocytes, epitheliotropic T-cell lymphoma should rise on the differential list. In EM, epithelial dysplasia may also be seen secondary to the concurrent inflammation and necrosis. The same features of transepidermal apoptosis and lymphocyte satellitosis can also be seen in the follicular epithelium, not just in the epidermis! Follicular epithelium may also exhibit hyperpigmentation and vacuolation secondary to inflammation. Parakeratotic hyperkeratosis is often seen in the hyperkeratotic form of EM but is not considered a key diagnostic feature of EM in general.[1,5]

Two other top differentials to consider when looking at a case of hyperkeratotic EM (HKEM) are exfoliative cutaneous lupus erythematosus (CLE) and generalized discoid lupus erythematosus (GDLE). CLE can look similar histologically, but will not have transepidermal keratinocyte apoptosis, will lack lymphocyte satellitosis, and won't have as much hyperkeratosis. GDLE is less proliferative than HKEM with scarring and skin atrophy, neither of which are seen in HKEM. GDLE will also lack the prominent suprabasilar and transepidermal apoptosis and lymphocytic satellitosis seen in HKEM.[1] Other diseases that can more closely mimic EM histologically (i.e. have transepidermal apoptosis, lymphocyte satellitosis, etc.) include SJS/TEN, which is typically acute, severe, and may present as diffuse necrosis, and cutaneous drug reactions, which can honestly look like anything.[6]

Clinical photographs and a thorough history are crucial to dermatopathology cases as a whole and, when it comes to hyperkeratotic EM, can significantly help with diagnosis. Grossly, canine EM typically appears as red papules to plaques that are centrally cyanotic and present on the trunk, groin, and axilla. Hyperkeratotic canine EM, however, can look like raised, hyperpigmented, lichenified plaques in similar locations, but predominantly affects the face and ears. The current school of thought is that hyperkeratotic EM is idiopathic and may target suprabasilar keratinocytes with subsequent proliferation of basilar cells that results in the parakeratotic hyperkeratosis seen histologically.[1,6]

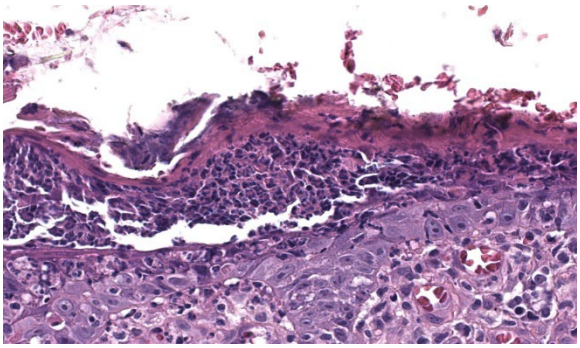

Figure 2-5. Haired skin, dog. Corneal pustules contain large numbers of necrotic neutrophils admixed with cellular debris and edema fluid. (HE, 960X)

In keeping with current dermatopathology terminology, EM is classified as a cytotoxic dermatitis. Other entities that fall under this designation include SJS/TEN, graft-vs-host disease, and cutaneous viral infections (i.e. poxvirus). Both EM and SJS/TEN are mediated by cytotoxic CD3+/CD8+ lymphocyte responses against keratinocytes that have been altered either due to infectious agents or drugs.[6] Apoptosis results from either direct cytotoxicity or through soluble mediators such as Fas ligand, granzymes, perforin, and granulysin.[1,6] For those taking the Phase I exam

soon, Fas ligand should ring a bell as the ligand that binds to the Fas death receptor in extrinsic apoptosis.

Although the pathogenesis of EM is not yet fully understood, CD3+/CD8+ lymphocytic cytotoxic responses against keratinocytes are seen in both human and canine EM diseases. In human EM, a recent study found that T-lymphocyte/NK cell cytotoxicity and Janus kinase (JAK)-signal transducer and activator of transcription (STAT) signaling were highly upregulated.[1] As such, JAK inhibitors have become a promising source of treatment modality for EM patients, both human and canine. If JAK is inhibited, STAT cannot be phosphorylated and cannot translocate to the nucleus to upregulate target gene transcription. Interferon genes can be targets of the JAK/STAT pathway, so the effectiveness of JAK inhibitors in EM cases may be related to the inhibition of interferon-y and type I interferon production.[1]

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CASE III:

Signalment:

1 year and 11 months old, Mare, Standardbred Horse (Equus cabal/us)

History:

The horse was referred to the large animal university hospital due to watery diarrhea, loss of weight and intermittent fever since 1 week. On presentation at the clinic, the horse had a decreased general condition. A sternal subcutaneous edema and swollen legs with crusting and small hemorrhages in the skin, especially on the distal extremities and around the coronary bands, were noted. There was multifocal alopecia on ventral neck, abdomen and distal extremities. In addition, the chestnuts on the legs were easily peeled off. Rectal examination was normal, but ascites (a clear transudate) was evident on abdominocentesis. Lactate level in the abdominal fluid was 5.1 mmol/L (normal ref:< 2 mmol/L). On blood gas analysis, acidosis was evident (pH 7.12).

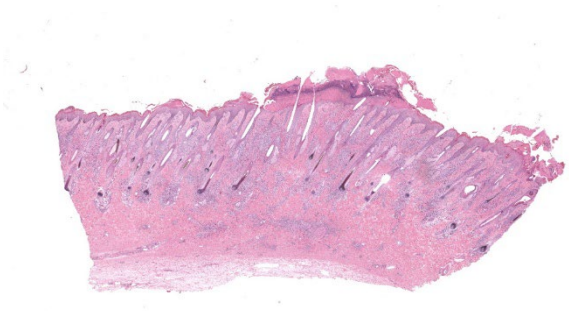

Figure 3-1. Haired skin, horse: At subgross magnification, there is a diffuse perivascular and periadnexal cellular infiltrated. The overlying epidermis is hyperplastic and there is an area of partial thickness epidermal necrosis which is covered by a serocellular crust. (HE, 7X)

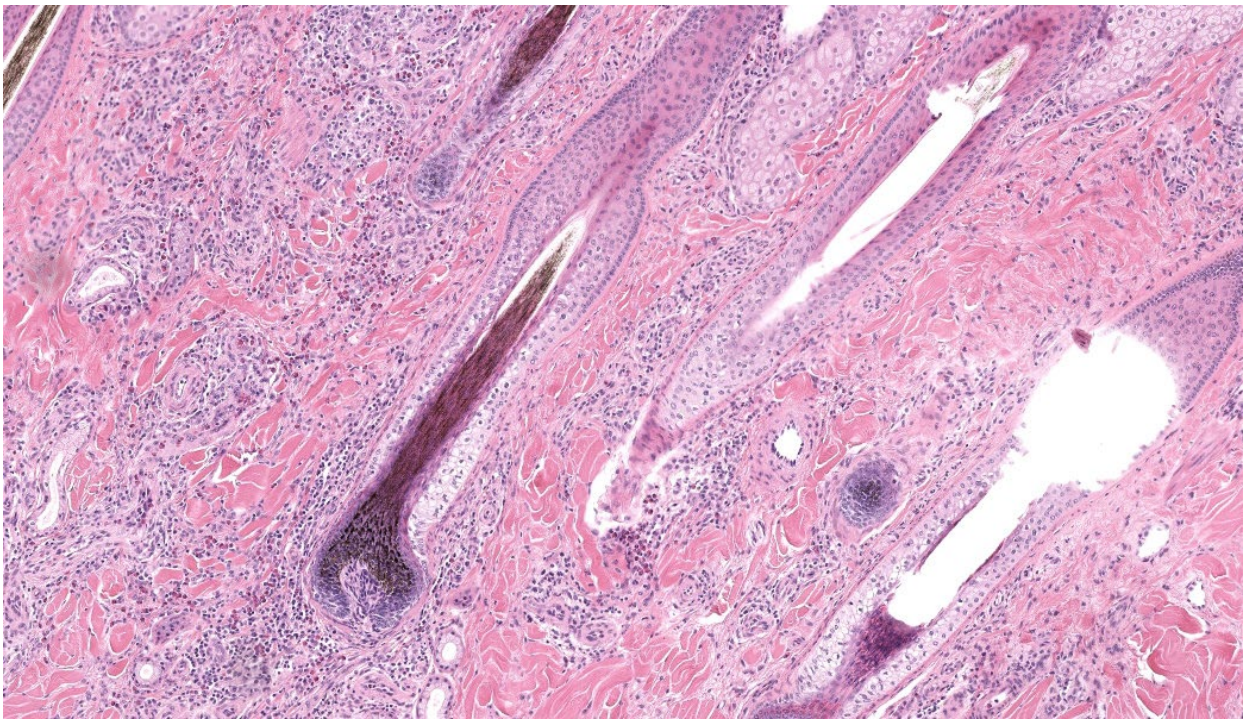

Figure 3-2. Haired skin, horse: Higher magnification of the perivascular chronic inflammation within the dermis. (HE, 154X)

Hematology and total protein values were within normal reference range. Further blood works and diagnostics were declined by the owner, and the horse was euthanized and subsequently submitted for necropsy.

Gross Pathology:
The horse was in slightly poor body condition, with a mild generalized muscle atrophy and dull hair coat with multifocal alopecia, most evident on the ventral neck, abdomen and distal extremities. On closer inspection of the alopecic areas, there were abundant crusting, erosions and ulcerations of the skin, especially around the coronary bands and pastern on all four limbs. A moderate subcutaneous edema was evident on ventral abdomen and distal extremities. Free within the abdominal and thoracic cavity respectively, there were 2 liters of a straw-colored transudate. In the mucosa of the small intestine, large intestine and cecum, there were multifocal to coalescing, variably brownish colored, round "button like" ulcers of approximately 0.5-4 cm in diameter, with elevated borders of firm consistency. The ulcers were often covered by light, dry, fibrinonecrotic material. There was also a diffuse, mild to moderate submucosal edema. In the non-glandular parts of stomach, there was severe hyperkeratosis. The liver was slightly decreased in size with a firm consistency, and on cut surface abundant fibrous streaks were evident, especially dissecting along bile ducts. The pancreas was moderately enlarged, firm in consistency and diffusely light in color. Visceral and peripheral and lymph nodes varied from mildly to moderately enlarged, were slightly edematous, and varied in appearance; some showed distinct follicle formation and some were more homogenously light on cut surface. The bone marrow was light to dark red in color.

Laboratory Results:
N/A

Microscopic Description:
Haired skin, coronary band. Expanding and

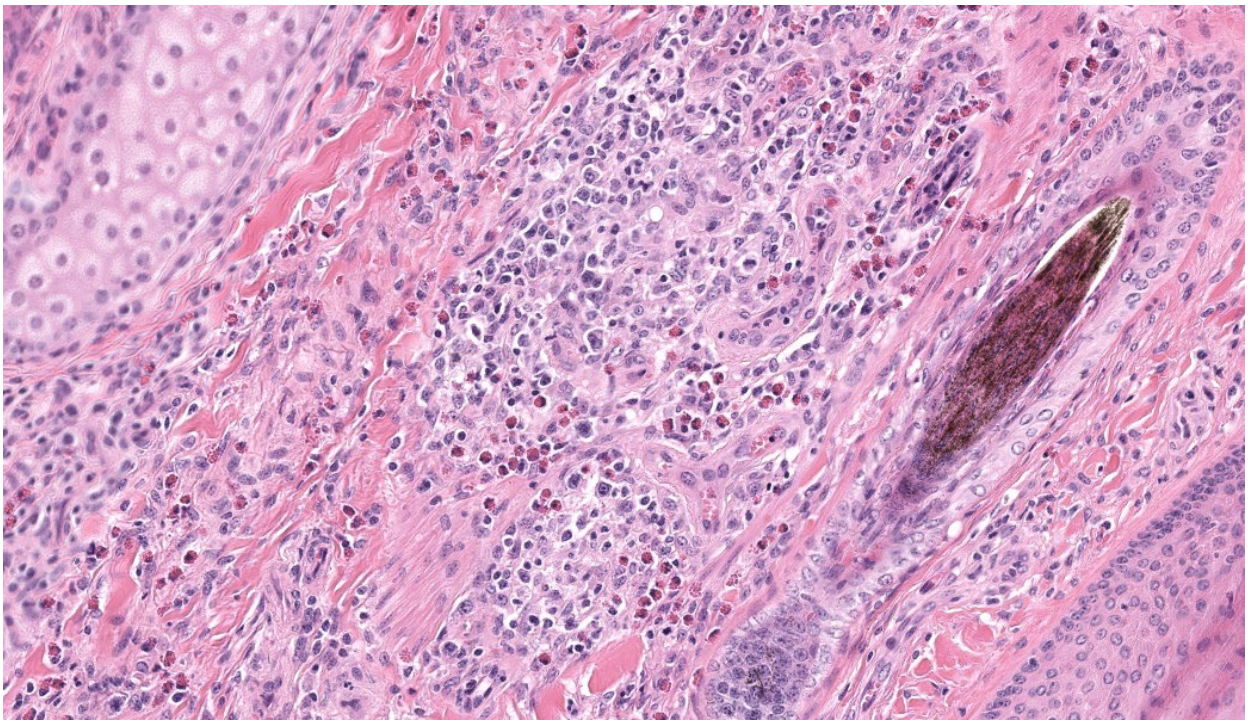

Figure 3-3. Haired skin, horse: Eosinophils are a prominent component of the inflammatory infiltrate (HE, 154X)

infiltrating the entire dermis are multifocal to coalescing perivascular, periadnexal and interstitial aggregates of moderate numbers of lymphocytes, eosinophils and histiocytes, fewer plasma cells and occasional neutrophils. Multifocally within dermis are few small areas of intensely eosinophilic, fragmented collagen fibers admixed with eosinophilic cellular- and basophilic nuclear debris, surrounded by epithelioid macrophages and multinucleated giant cells (eosinophilic granulomas). Intramurally and intraluminally within multiple hair follicles are moderate numbers of eosinophils, lymphocytes and histiocytes and few multinucleated giant cells (mural and luminal folliculitis), and adjacent follicular epithelium display moderate spongiosis. In the dermal-epidermal interface, there is a multifocal mild edema. The epidermis shows mild lymphocytic infiltration, mild spongiosis and occasional apoptotic keratinocyte, diffuse mild acanthosis and mild rete ridge formation (epidermal hyperplasia), moderate parakeratotic and orthokeratotic hyperkeratosis and multifocal erosions and ulcerations, the latter being covered by large serocellular crusts spanning over several adnexal units. Serocellular crusts show abundant viable and degenerated neutrophils, occasional eosinophil, cellular debris, fibrin, free keratin and hair fragments and occasional small basophilic bacterial colonies. There are also small epidermal intracorneal pustules multifocally. Several arteriolar walls in deep dermis show infiltration of few eosinophils and lymphocytes (vasculitis). The deep dermis displays mild diffuse edema.

Contributor's Morphologic Diagnoses:
Haired skin, coronary band: Dermatitis and folliculitis, lymphoplasmacytic, histiocytic and eosinophilic, multifocal to coalescing, moderate, with eosinophilic granulomas, epidermal intracorneal pustules, serocellular crusts and orthokeratotic and parakeratotic hyperkeratosis

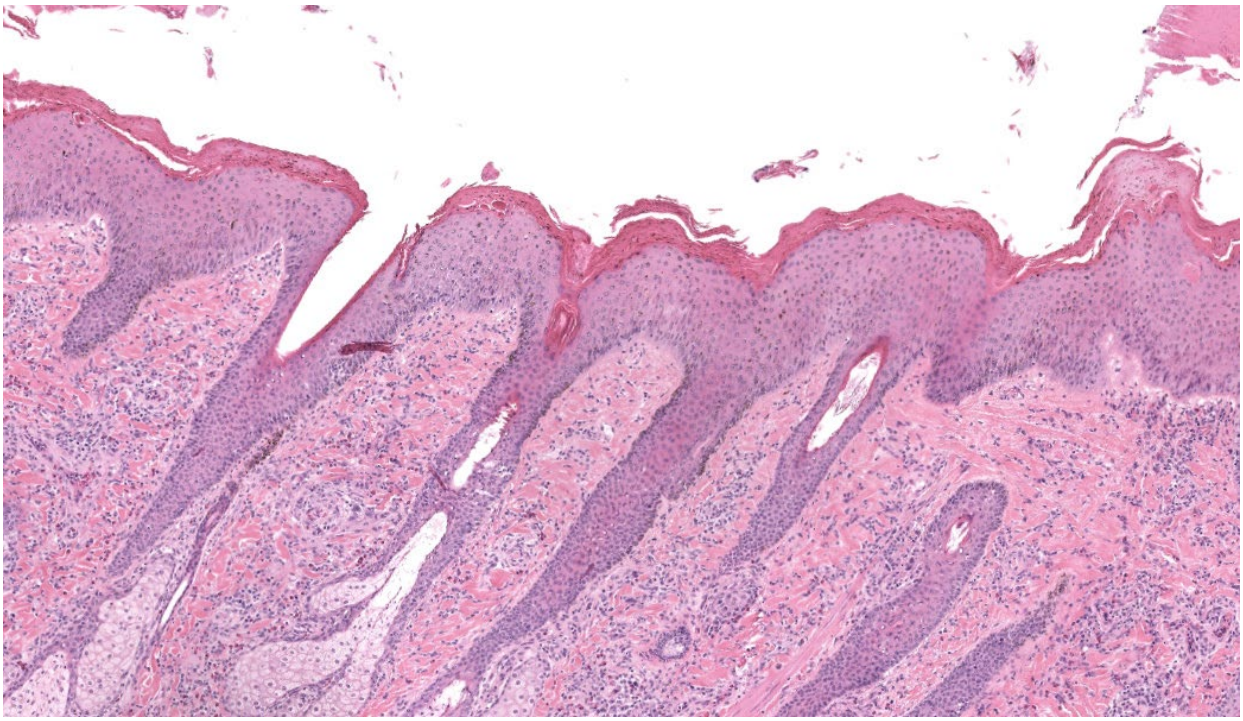

Figure 3-4. Haired skin, horse: There is moderate parakeratotic hyperkeratosis of the hyperplastic epidermis. (HE, 154X)

Equine multisystemic eosinophilic epitheliotropic disease (MEED)

Contributor's Comment:

Equine multisystemic eosinophilic epitheliotropic disease (MEED) is a rare chronic disease and constitutes part of inflammatory bowel disease (IBD) in horses.[13,15,17] MEED typically affects young Standardbred and Thoroughbred horses even though horses of older age and other breeds also may be affected.[3,8,9,10,11,13,14,18,19,24] Seasonality with cases occurring in spring or summer is reported in some studies.[11,14] Clinically, horses with MEED present with progressive weight loss, pitting edema, alopecia and exudative, exfoliative dermatitis characterized by scaling, crusting and skin ulcerations.[3,6,10,11,13,14] Lesions often originate around coronary bands, sometimes with associated loss of chestnuts, and progressively becomes more generalized to also include head and the rest of the body.[3,11,13,14] Most affected horses die or are euthanized within 8 months of diagnosis.[13] In clinical cases described in the literature, pruritus is variably evident, as well as fever, diarrhea and peripheral eosinophilia.[3,6,10,11,13,14,19] Peripheral eosinophilia is reported in approximately 14% of cases.[3,13] Serum biochemical evidence of liver disease and/or hypoproteinemia may also be seen, and in a few cases, respiratory symptoms have been noted.[3,6,8,9-11,18,19] In our case, there was no peripheral eosinophilia and no hypoproteinemia present at clinical work-up. Serum biochemistry was not investigated; hence, liver values were unknown.

On postmortem examination, several organs are commonly affected in cases of MEED, including skin, pancreas, liver, common bile duct, gastrointestinal tract and lungs.[13] Histologically, the disease is characterized by eosinophilic and lymphoplasmacytic infiltration, sometimes with eosinophilic granuloma formation.[13] In the skin, various inflammatory

patterns have been reported in MEED, including perivascular, lichenoid interface, interstitial, diffuse, and granulomatous.[13,14] Eosinophils, lymphocytes and plasma cells are the main cellular elements.[13,14] Other histological findings in the skin include epidermal hyperplasia, orthokeratotic and parakeratotic hyperkeratosis, epitheliotropic infiltration of eosinophils and lymphocytes, apoptotic keratinocytes, eosinophilic folliculitis, furunculosis, eosinophilic granulomas, and lymphoid nodules.[13] Coagulated protein and collagen degeneration may be seen within deep dermal vessel walls.[14] In our case, most of these lesions were present in examined sections of the skin. Within the gastrointestinal tract, lesions include ulcers on the tongue and/or within oral cavity, hyperkeratosis of the esophagus and non-glandular stomach, and mucosal ulcerations within the small and/or large intestine, as well as marked fibrosis in some organs, such as pancreas and liver; in the liver especially dissecting along bile ducts.[11,14] Fibrosis may be so severe that loss of exocrine tissue is evident within pancreas, and in the liver, there may also be biliary hyperplasia.[11,14] Lymph nodes may be enlarged due to eosinophilic infiltration, and increased numbers of eosinophils can be seen in bone marrow.[6,9,13,14,18,19] In our case, all of these findings were present except oral ulcerations.

Cases of equine MEED has been reported since 1960's in Sweden, and was in 1985 described under the name of eosinophilic granulomatosis (EG).[11] A case series was also reported from Canada the same year.[14] Since then, various case reports of MEED have been published from around the world, including the US, Germany, Ireland, Belgium, Brazil, Italy and Spain.[3,6,8,9,10,18,19,24] Systemic eosinophilic disorders, often referred to as hypereosinophilic syndrome (HES), have also been described in other species, such as dogs, cats, ferrets, donkeys, and humans.[4,5,7,16,20]

The underlying cause of MEED is yet unknown.[13] For equine IBD, a delayed hypersensitivity reaction has been proposed.[15] For MEED specifically, recurrent type I hypersensitivity reactions caused by dietary, inhaled, or parasitic antigens have been suggested.[11,13] In one recently published report, authors suggest that larval migrans seen in their case could have contributed to development of MEED.[24] In our case, there was no evidence of ecto- or endoparasitism on either gross or histological examination. A genetic cause of MEED has been discussed, since Standardbreds and Thoroughbreds are over-represented in MEED cases.[13] Another hypothesis is that clonal proliferation of T-lymphocytes trigger eosinophil proliferation through secretion of cytokines such as interleukin-5, which has been proposed as an underlying cause for HES in humans.[4] In the horse, MEED has been seen concurrently with intestinal T cell lymphoma, which may support this theory. Also in other species, such as the cat, dog and ferret, hypereosinophilic syndromes have been reported together with various T cell neoplasms. [1,2,9,12] In our case, there was no evidence of concurrent lymphoma.

Our case fits well with a diagnosis of MEED with regards to both clinical picture, gross findings, and histological findings. Differential diagnoses for lesions in the skin include autoimmune disorders, such as pemphigus foliaceus (PF), equine sarcoidosis, hairy vetch *(Vicia villosa*) intoxication, and insect bite hypersensitivity. PF presents with a similar clinical picture of crusting of the skin; however, on histopathological examination, consistent findings in PF patients are serocellular crusts or intraepidermal pustules and vesicles containing rafts of, or individualized, acantholytic

cells, which were not seen in our case.[13,22] In equine sarcoidosis, a nodular to diffuse lymphogranulomatous dermatitis with multinucleated giant cells and vasculitis is commonly seen.[13] Hairy vetch toxicosis is mainly seen in cattle, but may also occur in horses.[13] In horses, it is characterized by a nodular, granulomatous dermatitis. Eosinophilic infiltration may be seen in cattle with hairy vetch toxicosis but it is rarely seen in horses.[13] Insect bite hypersensitivity, commonly caused by *Culicoides* spp in horses, is usually severely pruritic and presents as a superficial or superficial to deep perivascular dermatitis, dominated by eosinophils and lymphocytes. Eosinophilic folliculitis, erosions and ulcerations may also be seen as a result of self-trauma.[13] Another differential diagnosis discussed for this case, mainly based on the ulcerative lesions within the intestine, was *Rhodococcus equi* infection. However, no pyogranulomatous lesions supporting *Rhodococcus equi* infection were present in the lymph nodes. Infection by *Salmonella enterica* ssp. *enterica* serovar t*yphimurium* may as well give rise to button like ulcers within the large intestine, but taken all together, the combined clinical, gross and histological picture in this case supported a diagnosis of MEED.[21]

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JPC Diagnoses:
Haired skin: Dermatitis, perivascular, lymphohistiocytic and eosinophilic, chronic, moderate, with epidermal hyperplasia and parakeratotic hyperkeratosis.

JPC Comment:
The contributor's comment in this case provides an exceptional overview of multisystemic epitheliotropic eosinophilic disease (MEED) in horses and its major differentials, all of which were discussed during conference. MEED is currently considered to be an abnormal manifestation of inflammatory bowel disease (IBD) in horses. The cutaneous manifestation of MEED classifies as a perivascular dermatitis pattern, and the depth of inflammation and affected vasculature can assist with the diagnosis of MEED compared to others that would be confined more to the superficial dermis (i.e. insect bite hypersensitivity). Conference participants ultimately all agreed with the contributor's diagnosis of MEED in this case.

If lesions are restricted to the GI tract, other causes of inflammatory bowel disease, intestinal parasitism, and idiopathic focal eosinophilic enteritis (IFEE) should rise higher on the differentials list. There was an excellent case of IFEE seen earlier this year in Conference 1, Case 3, the contributor of which provided a fantastic comparison between IFEE and MEED in their comment. Additionally, a thorough overview of eosinophils was covered in the JPC comment for Conference 2, Case 3 this year as well, and those two comments are great supplementals to this case.

As a quick refresher, the differentiation and maturation of eosinophils are dependent on expression and presence of certain transcription factors and cytokines, such as interleukin-5 (IL-5). IL-5 is the most important of these in eosinophil differentiation, maturation, and survival. As referenced by the contributor, there is a case report of MEED with concurrent GI lymphoma in a horse, contributing to

the hypothesis that clonal expansion of T-lymphocytes may contribute to eosinophil proliferation via secretion of eosinophil-promoting cytokines, such as IL-5, in cases of hypereosinophilia seen in some lymphomas.[4] Mature eosinophils contain granules that are full of cytotoxic compounds that are released in response to stimuli (i.e. certain infectious agents, allergens). Normally, T-helper type 2 (Th2) cells that are in proximity to the stressor produce high levels of IL-5, triggering eosinophil infiltration, activation, and subsequent release of additional cytokines, chemokines, and eosinophil granules. There is still substantial speculation on the cause(s) of MEED, but current literature suggests that it is likely a multifactorial, systemic presentation of a hypersensitivity reaction and that causes may vary between affected individuals, although parasites seem to be overrepresented in case reports.[23]

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CASE IV:

Signalment:
Six day-old piglet, male, cross-breed (*Sus scrofa domestica*)

History:
Sow farm where six weeks before the submission of this case, the herd experienced four litters with abortions and few newborn animals with cutaneous problems. All affected litters corresponded to multiparous sows. In each litter there was 3 or 4 affected piglets, except in the last one, which 7 out of 8 newborn piglets displayed cutaneous lesions. The affected newborn piglets usually died during the first week of life. This case corresponds to a lactating piglet of 6 days of age with generalized cutaneous lesions from last litter, which died naturally.

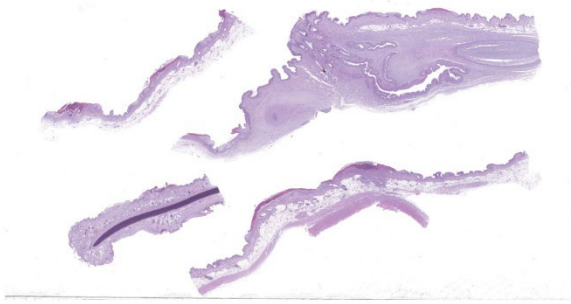

Figure 4-1. Haired skin, pig. Multiple sections of haired skin, to include the pinna, the prepuce and two unlabeled sections of skin are submitted for examination. (HE, 8X)

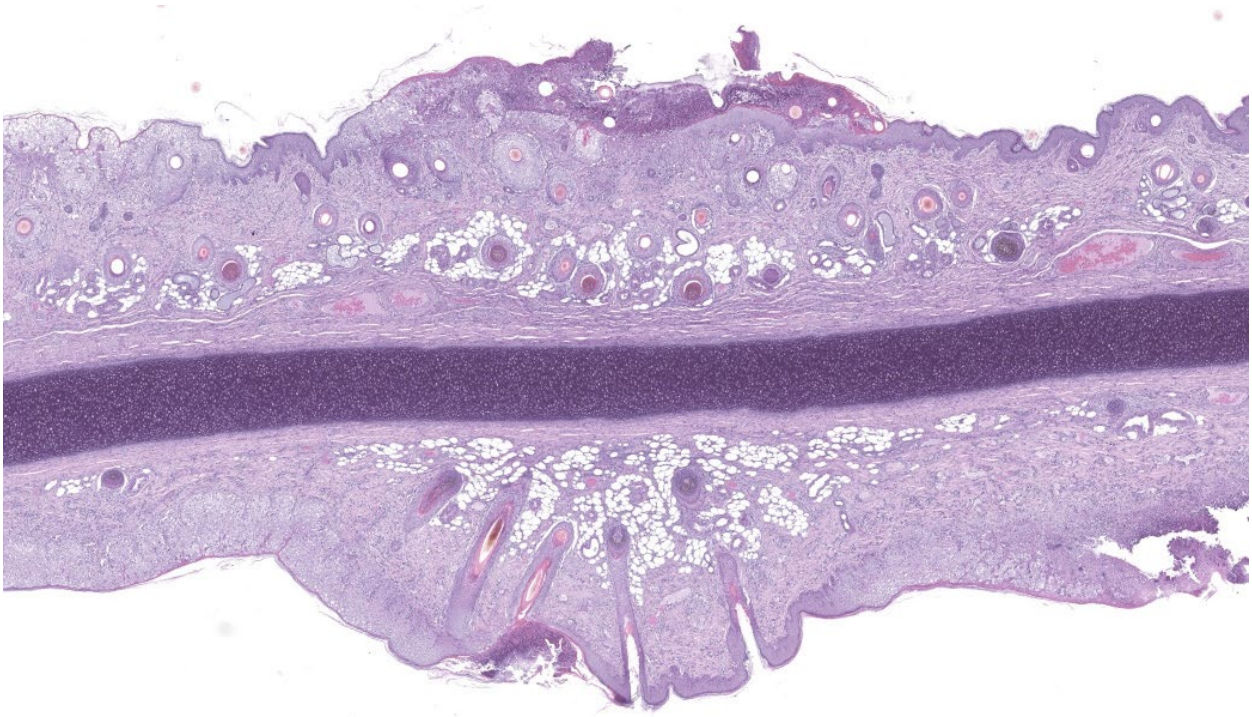

Figure 4-2. Pinna, pig. There is diffuse epidermal hyperplasia with ballooning edema, necrosis, and overlying serocellular crust. (HE, 125X)

Gross Pathology:
Six-day-old piglet of 1.16 kg weight with poor body condition and prominent bone protuberances. In a multifocal to generalized pattern throughout the skin and tongue, there were circular 0.1 to 0.5 cm in diameter lesions characterized by slightly prominent, firm, and well circumscribed aspect (papules and pustules); most of them were brownish in color with central umbilication and crusted. Significant lesions were not found in internal organs or in the subcutaneous tissue.

Laboratory Results:
N/A

Microscopic Description:
Haired skin (ear, prepuce, and inguinal area): affecting 20% of the evaluated section there is a proliferative and necrotizing process that mainly affects the epidermis. The epidermis and hair follicle epithelium show the following features: stratum corneum with diffuse mild compact hyperkeratotic orthokeratosis with multifocally serocellular crusts composed by cellular debris, degenerated keratin, degenerated neutrophils, and multiple superficial coccoid bacterial colonies (secondary contamination). Also, stratum spinosum shows multifocal marked thickening (acanthosis), and numerous keratinocytes display ballooning degeneration and intracytoplasmic perinuclear 2-5 µm eosinophilic inclusion bodies. Multifocally, in the most affected areas, there is marked neutrophilic exocytosis, and numerous keratinocytes lost intercellular connections and undergo lytic necrosis. Superficial and mid dermis show perivascular to diffuse, moderate to severe inflammatory infiltrates composed by viable and degenerated neutrophils, macrophages, and lesser numbers of lymphocytes and plasma cells. Significant lesions were not seen in the hypodermis.

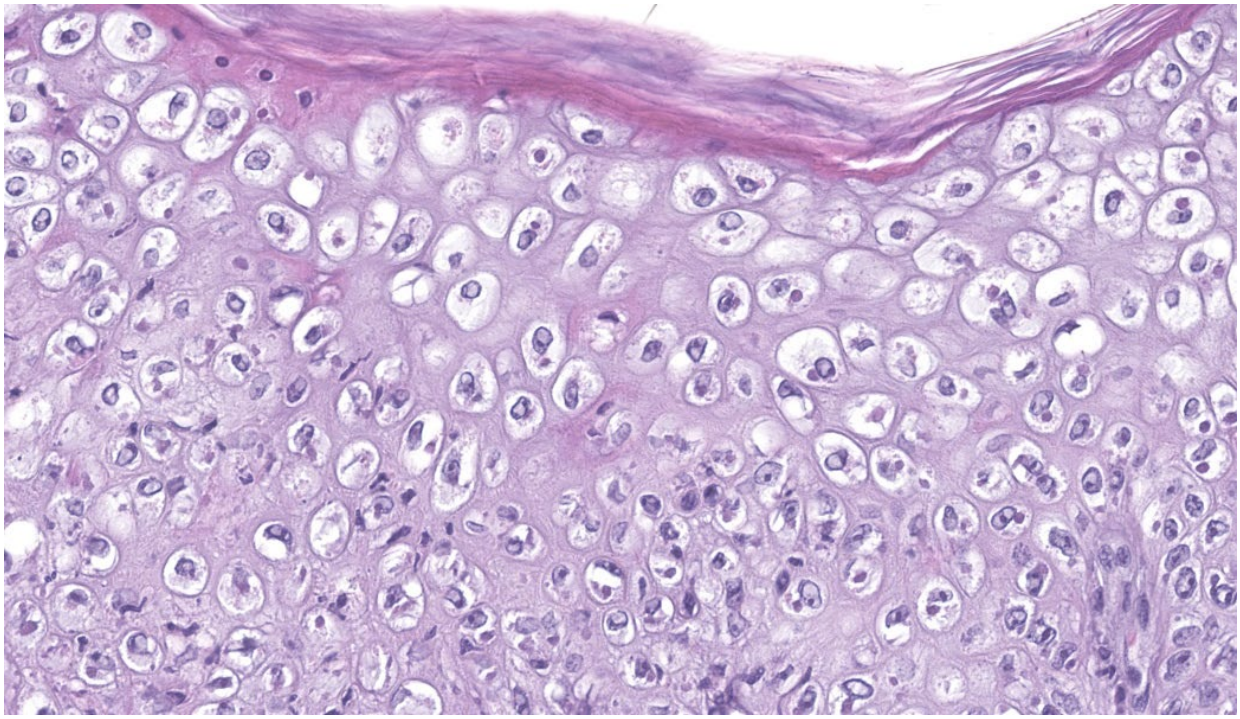

Figure 4-3. Pinna, pig. Within the proliferative epidermis, keratinocytes within the stratum spongiosum are expanded by abundant intracellular edema ("ballooning degeneration") and contain one or more irregularly round intracytoplasmic viral inclusions.

Contributor's Morphologic Diagnoses:
Morphologic diagnosis: Haired skin; severe, subacute, proliferative, necrotizing, and crusting dermatitis with intracytoplasmic eosinophilic inclusion bodies. Etiologic diagnosis: Poxviral dermatitis. Etiology: Swine poxvirus.

Contributor's Comment:
The clinical case reflects typical clinical signs and lesions of congenital swine poxvirus infection. Swine pox (SwP) is a sporadic disease of pigs caused by swine pox virus (SwPV) belonging to the *Poxviridae* family. SwP is a skin disease of worldwide distribution, generally associated with poor sanitary status of herds, and can be vectored by pig lice (*Haematopinus suis*) and domestic flies (*Musca domestica*).[4,8] The disease is pathologically characterized by the formation of pustular/papular skin lesions in different regions of the body, with more severe forms in young pigs (<3-4 months), including neonates with the condition (congenital SwP).[6,7]

SwPV is the only member of the genus *Suipoxvirus* in the subfamily *Chordopoxvirinae*. As all poxviruses, it has a DNA genome that replicates in the host cell cytoplasm. SwPV has a linear double-stranded DNA molecule with 150 genes, of which 146 conserved genes encode proteins essential for survival in the host cell.[1,7] SwPV replication in infected cells can generate two forms of virions: 1) mature virions (MV), which are the vast majority, and are released by budding or after cell lysis, and 2) extracellular enveloped virions (EEV), which leave the cell by exocytosis.[7] The difference between the two forms is the stability in the ambient, being MVs very stable and EEVs relatively fragile.[7]

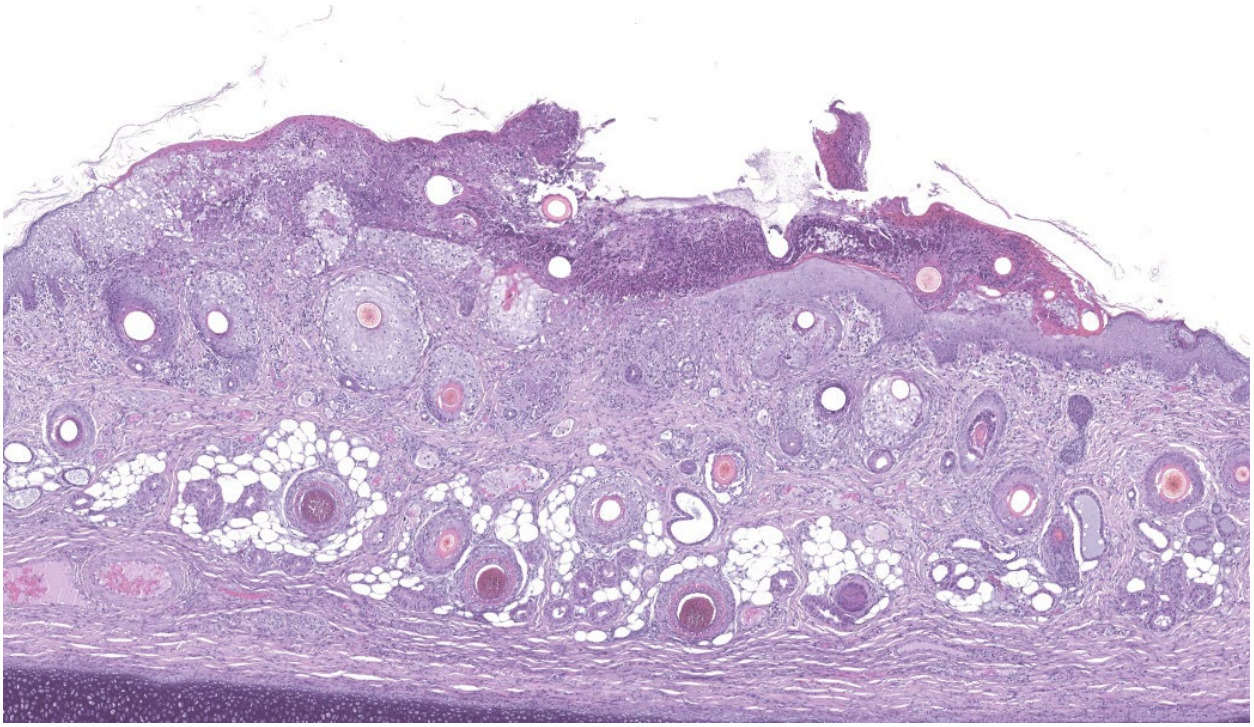

Figure 4-4 Pinna, pig. There is focal partial thickness necrosis of the virally infected hyperplastic epithelium. (HE, 125X)

The clinical signs associated with SwPV infection are directly related to age and viral load. The most affected animals are relatively young (<3-4 months of age), and the condition has high morbidity at the herd level, although mortality is usually very low.[4,7] In contrast, SwPV infection in adult animals is usually mild/subclinical and self-limiting. It has been suggested that congenital infections may result from infected and viremic sows during gestation, causing fetal membrane infection.[6] The pathogenesis of congenital SwPV infection in pigs has not been completely elucidated; however, compartmentalization of placental membranes in swine probably explains why some fetuses are affected and others are not.[4,6,7]

The topography of the skin lesions is commonly found throughout the body but more evident on the flanks, ventral abdomen, legs, inguinal areas, and ears. The incubation period of SwPV infection ranges from 4 to 14 days and the lesions evolve from macules, papules, and vesicles to umbilicated lesions with purulent contents, followed by crusting. Congenitally affected piglets usually have cutaneous lesions at birth, being stillborn or dying within a few days. Lesser affected animals can survive and heal the cutaneous lesions.

The typical histological features of SwPV infection comprises hydropic degeneration of keratinocytes of the epidermal stratum spinosum and follicular epithelium during the papular phase. As a result, thickening of the epidermis due to mild spongiosis can be observed; however, epidermal hyperplasia caused by SwPV is usually less prominent than that caused by the other poxviruses.[7] Other finding are eosinophilic inclusion bodies in the cytoplasm of infected cells.[7] Regarding inflammation, the damage caused by virus

replication on keratinocytes causes recruitment of neutrophils, eosinophils, lymphocytes and histiocytes, forming intraepithelial pustules, as well as in the superficial and mid-dermis.[4,6,7]

The presumptive diagnosis of SwP is based on the observation of typical macroscopic skin lesions and the presence of epidermal hyperplasia with ballooning degeneration of keratinocytes and inclusion bodies on histopathology. Differential diagnoses of SwPV infection are infectious diseases such as vesicular diseases (foot-and-mouth disease, vesicular exanthema of swine, vesicular stomatitis, swine vesicular disease and Seneca virus A infection), early stages of ringworm, localized streptococcal and staphylococcal epidermitis, and non-infectious diseases such as pityriasis rosea, allergic skin lesions, and sunburn.[6,7]

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JPC Diagnoses:
Haired skin: Dermatitis, necrotizing and proliferative, subacute, multifocal, severe, with ballooning degeneration and intracytoplasmic viral inclusions.

JPC Comment:
This was a truly phenomenal case of congenital swinepox, complete with clear viral inclusions and all the classic histologic features of the disease. The JPC extends sincere gratitude to the contributor of this case for providing such an exceptional example of this entity for the Wednesday Slide Conference!

One of the very first questions posed to conference participants was, “If poxvirus is a dsDNA virus, why are the inclusions cytoplasmic instead of intranuclear?” This is because poxviruses are unique among DNA viruses in that they possess all their own required machinery, including their own DNA-dependent RNA polymerase, to carry out replication and transcription independent of the host cell nucleus.[9] Poxviruses can even go so far as to form their own membrane-bound "mini-nuclei" within the cytoplasm, derived from rough endoplasmic reticulum.[9] These cytoplasmic sites contain all the components needed for viral DNA replication and protein synthesis. As such, poxviral inclusions will be seen in the cytoplasm of infected keratinocytes instead of in the nucleus.

The contributor lists some great differentials to consider for swinepox in pigs where the condition is not thought to be congenital. For congenital cutaneous conditions, however, only swinepox virus and parvovirus are reported to cause lesions in neonatal pigs.[6] In conference, it was also mentioned that vaccinia virus, another poxvirus that was previously used for smallpox vaccination in humans, was once considered a cause of poxviral dermatitis in pigs due to its broader species tropism, but this is no longer seen due to the cessation of the use of vaccinia virus for smallpox vaccines. Congenital swinepox is thought to occur via intrauterine infection resulting in a low-level viremia within the sow that allows the virus to spread to the fetal membranes.[6] Swine placental membranes are

compartmentalized, so while some fetuses are affected, others may not be. [6]

The pathogenesis of poxviruses involves the inhibition of a cytosolic pathogen recognition receptor (PRR) known as protein kinase R (PKR), which is a crucial part of the host immune system that limits viral replication in an infected cell via phosphorylation of eukaryotic initiation factor 2α (eIF2α).[3] PKR recognizes double-stranded RNA (dsRNA) produced during viral replication and helps control major signaling pathways involved in the immune response, such as the integrated stress response (ISR), mitogen-activated protein kinases (MAPKs), and the NF-κB pathway.[2] During the poxviral replication process, long dsRNAs are generated as intermediates for translation of the viral genome. When a dsRNA fragment is longer than 33 base pairs (bp), two PKR molecules bind to the RNA and become dimerized, followed by autophosphorylation to become an active kinase.[2] Once activated, PKR can then either undergo nuclear translocation to act on the above-listed transcription factors or it can phosphorylate cytoplasmic eIF2α, which is a competitive inhibitor of eIF2B, the factor that recycles eIF2 for subsequent rounds of translation.[2,5] This inhibition globally halts new protein synthesis for both host and viral mRNA.[5] Poxviruses produce a pair of proteins, known as E3 and K3, that antagonize PKR and enable viral activity within cells.[3] Protein E3 binds dsDNA and inhibits PKR activation, while protein K3 acts as an eIF2α analog for PKR, limiting activation of eIF2α by making less PKR available for eIF2α binding.[3]

Conference discussion concluded with a review of other significant poxviruses in veterinary species, of which the most notable were cowpox, due to its wider species tropism and penchant to use rodents as reservoir hosts, monkeypox, due to its current relevance in the U.S., and Ectromelia virus in mice, also known as mousepox. To wrap everything up with a bow, participants reviewed what poxviral virions look like on electron microscopy, which Dr. Bradley, promptly tossing the stereotypical dumbbell reference out the window, affectionally refers to as "tater tots" or "squished tater tots." Conference participants unanimously agreed that "tater tots" needs to catch on pronto.

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