



WEDNESDAY SLIDE CONFERENCE 2011-2012

Conference 13

18 January 2012

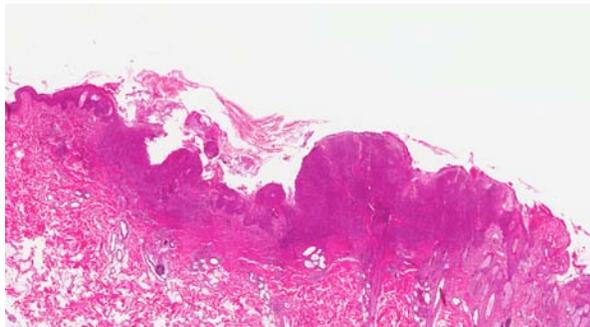
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**CASE I:** E1726/10 (JPC 3164890).

**Signalment:** 13-year-old male neutered domestic shorthair cat (*Felis catus*).

**History:** The animal was presented to the veterinarian with a mass of about 1.5 cm in diameter in the skin at the left lateral neck. The owner noticed the mass one month prior to presentation. Pruritus had not been noticed and the cat did not show additional tumors or other diseases. Metastases were not detected and following resection of the mass no relapse has occurred within two months.

**Gross Pathology:** The tissue sample submitted for histopathological examination had an extension of 2.5

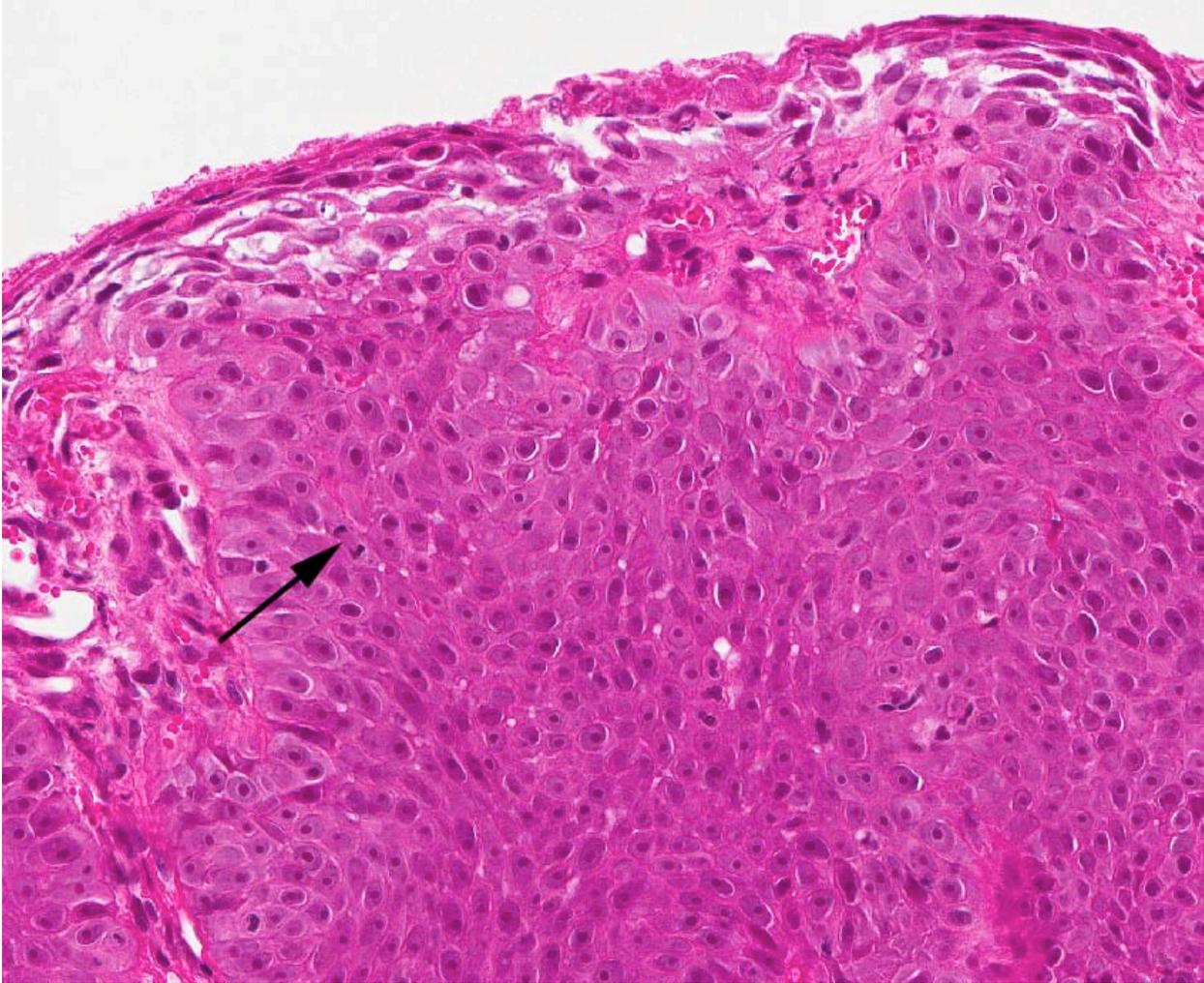


1-1. Haired skin, cat. The epidermis is focally and markedly thickened by a poorly demarcated, moderately cellular, unencapsulated, verrucous, infiltrative neoplasm. (HE 4X)

x 1.5 x 1.0 cm consisting of skin and subcutis. In the center there was a round, superficially rough area of approximately 1.0 cm in diameter with alopecia. The affected skin displayed a slightly thickened, irregular epidermis.

**Contributor's Histopathologic Description:** Haired skin: Multifocally, there are areas of mild to severe thickening of epidermis and follicular infundibular epithelium. In most areas, the basement membrane is intact with neoplastic cells confined to the epidermis. Multifocally overlying affected areas, there is a mild parakeratotic hyperkeratosis. In the unaffected areas there is a mild orthokeratotic hyperkeratosis.

In the thickened epithelial areas the normal germinal layer of the epidermis is replaced by multiple layers of neoplastic keratinocytes. The stratum granulosum and stratum corneum are mostly unaffected. Neoplastic cells have an increased size (about 30-50  $\mu\text{m}$  in diameter), a polygonal shape and a small to moderate amount of homogenous to finely granular eosinophilic cytoplasm. Distinct cell borders and prominent intercellular bridging are present. Nuclei are large, round to oval, centrally placed, and vesicular with finely stippled chromatin and one to two prominent round magenta nucleoli. There is a mild to moderate anisocytosis and anisokaryosis. The number of mitotic figures range from 0 to 4 per high power field. Multifocally, dark basophilic round structures are present distributed within the neoplastic cells, interpreted as apoptotic bodies. In some areas the



1-2. Haired skin, cat. Bowenoid disease characterized by markedly dysplastic keratinocytes without apparent maturation at all levels of the epidermis, as well as a mitotic figure (arrow). (HE 240X)

above described neoplastic cells penetrate the basement membrane and invade the underlying dermis, forming small nests or cords. There is multifocal erosion and focal ulceration of the epidermis, associated with hemorrhage and mild to moderate infiltration of neutrophils. In the dermis a mild, perivascular infiltration of neutrophils, lymphocytes and macrophages is present and few mast cells are observed. Multifocally there is moderate fibrosis of the dermis. No p53-positive tumor cells were detected by immunohistochemistry using a monoclonal anti-p53-antibody.

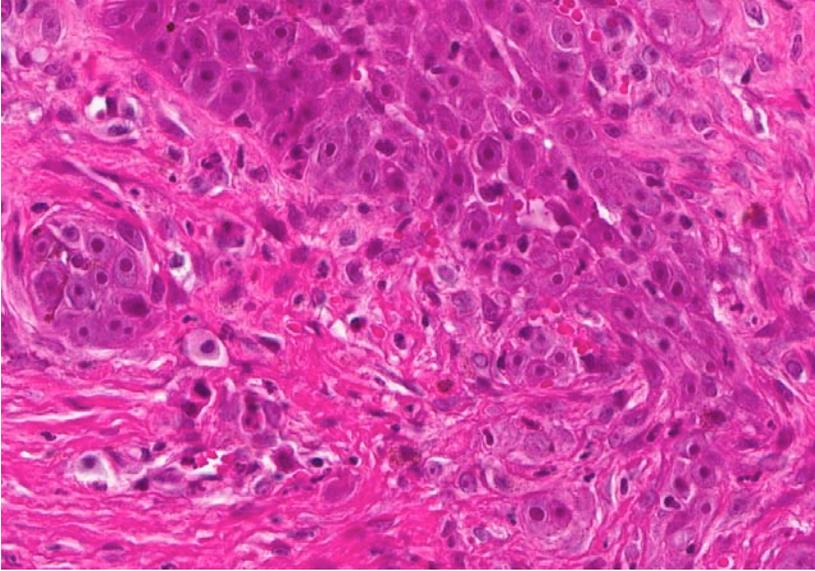
**Contributor's Morphologic Diagnosis:** Skin, squamous cell carcinoma in situ and focal transition to squamous cell carcinoma with dermatitis, suppurative and erosive to ulcerative, moderate, acute, diffuse.

**Contributor's Comment:** The morphologic findings are compatible with a multicentric squamous cell carcinoma (MSCCa) in situ, which shows transition to

squamous cell carcinoma. Multicentric squamous cell carcinoma in situ, also referred to as Bowenoid in situ carcinoma (BISC) or Bowen-like disease, is an uncommon premalignant lesion in middle-aged to old cats and rarely reported in dogs.<sup>6,8,17</sup>

Grossly, irregular, slightly elevated to heavily-crusting plaques and verrucous or papillary lesions up to 5.0 cm in diameter are found on haired, pigmented or non-pigmented skin at any site of the body. Usually, multiple lesions occur, but also solitary MSCCa in situ are seen infrequently.<sup>1,6,8</sup> Lesions are reported to be chronic, not painful, and only mild pruritus is noted.<sup>1</sup> There is neither a casual relationship to sunlight exposure nor a breed or sex predilection.<sup>6,7,8</sup>

Histologically, the neoplastic keratinocytes are confined to the epidermal and follicular infundibular epithelium with the basement membrane remaining intact.<sup>1,6</sup> Some authors differentiate between an irregular nonhyperkeratotic and a verrucous



1-3. Haired skin, cat. Multifocally, at the deep margin, neoplastic keratinocytes breach the basement membrane, infiltrating the subjacent dermis as individual and small groups of cells.

hyperkeratotic type depending on the character and degree of epidermal thickening and hyperkeratosis.<sup>1</sup> According to this classification, the present case would belong to the non-hyperkeratotic type due to severe acanthosis of the epidermis and follicular infundibular epithelium with a mildly undulating surface and mild orthokeratotic hyperkeratosis, not showing verrucous surface contours, epithelial spires and pit-like invaginations filled with keratin as it is described for the verrucous hyperkeratotic type.<sup>1</sup>

Several studies suspect that papillomavirus infection may be associated with feline MSCCa in situ. In two studies, papillomavirus-antigen was detected in 11% and 48% of MSCCa in situ, respectively, using immunohistochemistry (IHC).<sup>2,13</sup> Additionally, it has been hypothesized that feline viral plaque, in which a high proportion of papillomavirus-antigen was detected by immunostaining, could be a precursor lesion of MSCCa in situ.<sup>16</sup>

One study found 11 out of 18 cases positive for papillomavirus L1 gene in PCR-analysis, suggesting that this method may be more sensitive than IHC.<sup>11</sup> The authors admit that the failure to demonstrate papillomaviral DNA in every lesion may suggest that MSCCa in situ is not caused by papillomavirus infection. However, they also state that the 7 negative cases may have been previously but transiently infected with papillomavirus, which may have caused cellular transformation.<sup>11</sup> Furthermore, a close relationship to human papillomaviruses was discovered, which led to the hypothesis of interspecies virus transmission.<sup>11</sup> Subsequently, multiple papillomaviruses (namely *Felis domesticus*-papillomavirus type 1, type 2 and a novel

papillomavirus) from a swab of feline viral plaques and non-lesional skin were amplified, suggesting that papillomavirus can infect the epidermis without causing appreciable disease as well.<sup>12</sup>

In one report, infestation with *Demodex cati*, a normal resident of the skin in cats, was found in lesional sites of MSCCa in situ in 4 cats. Local cutaneous immunodeficiency due to epithelial dysplasia has been hypothesized as a predisposing factor for focal multiplication of mites.<sup>9</sup> In some cases, it is proposed that immunosuppression due to FIV or FELV infection may be a possible predisposition.<sup>9,12</sup>

For differential diagnosis, difficulty in distinguishing between the two basic types of squamous cell carcinoma in situ in cats have to be considered: MSCCa in situ and actinic keratosis (also named solar keratosis).<sup>2</sup> Actinic keratosis usually occurs as solitary lesion in white animals or in locations of unpigmented skin (like pinna, planum nasale, dorsal muzzle and eyelids).<sup>2</sup> Its histological appearance is less hyperplastic and hair follicles are less deeply affected than in MSCCa in situ.<sup>2</sup> Nevertheless, an accurate classification by clinical and histological findings is sometimes difficult.<sup>2,8</sup> Therefore, immunohistochemical detection of papillomavirus-antigen, which could be indicative of MSCCa in situ, and of p53-protein, which is frequently accumulated after UV-induced mutation of the p53 gene in actinic keratosis could be performed to arrive at the diagnosis.<sup>2</sup>

Similar to the present case, 17% to 25% of feline cases MSCCa in situ become locally invasive through the basement membrane and then have to be classified as squamous cell carcinomas, the most common malignant neoplasm of the feline skin.<sup>1,7,8</sup> These lesions, belonging to the well differentiated squamous cell carcinomas, occasionally still show “bowenoid” features like dorsoventrally elongated nuclei, that are tilted in one direction (“windblown” pattern) or bizarre multilobulated nuclei with smudgy chromatin.<sup>8</sup>

It has to be kept in mind that the described squamous cell carcinoma may also have developed due to UV-light induced mutations of tumor suppressor genes, unrelated to the diagnosed MSCCa in situ.<sup>8</sup>

Other skin tumors should be considered as additional differential diagnoses. Basal cell carcinomas and basosquamous carcinomas, which arise from basal

cells, are usually located in the dermis. However, they can be associated with the epidermis and are defined by other characteristics: in basal cell carcinomas, extensive proliferation of stromal fibroblasts and horizontal orientation of the tumor silhouette are frequently found. The appearance of bimorphic histologic features, showing basaloid cells peripherally and centrally abrupt keratinisation is indicative for basosquamous carcinomas.<sup>7,8</sup>

**JPC Diagnosis:** 1. Haired skin: Squamous cell carcinoma.  
2. Haired skin: Bowenoid in situ carcinoma.

**Conference Comment:** Bowenoid in situ carcinoma (BISC) differ from solar-induced squamous cell carcinoma (SCC) in that they can occur in darkly pigmented skin or non-sun-exposed haired skin, extend along the outer root sheath and follow the hair follicles, and lack evidence of solar elastosis, such as linear bands of degenerated basophilic elastin accumulation arranged parallel to the skin surface. BISC is frequently associated with papillomavirus. With time, these slow growing tumors may break through the basement membrane and are then classified as a traditional SCC, as is seen in the present case. Occasionally, koilocytes and other cytopathic effects of the papillomavirus can still be observed, but usually other evidence of papillomavirus infection, such as immunohistochemical positivity, is lacking.<sup>6,10</sup>

SCC is typically locally invasive and slow to metastasize; however, SCCs arising from internal sites such as the tonsil, stomach, and urinary bladder are more prone to metastasize, and metastasis is often to the lungs and regional lymph nodes. In cattle, SCC is common on eyelids, conjunctiva, and the vulva; in horses, it is common on the penis, prepuce, eyelid and conjunctiva, and is also found in the nonglandular stomach; in rodents and pigs, SCC is also common in the nonglandular stomach; in sheep and goats, the vulva in recently sheared sheep is a common site as well as the pinnae; in rabbits it is found in subungual tissues, the eyelid and extremities; and SCC can also occur at brand sites (especially freeze brands) in livestock.<sup>3,4,5,14,15</sup>

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**CASE II: B19851 (JPC 4002876).**

**Signalment:** A four-year-old male cat (*Felis vulgaris*).

**History:** A four-year-old male cat was presented with thickening and erythema of the inner surfaces of the left ear. The ear was painful and curled. The outer surfaces were unaffected. The left pinna was partially removed and submitted for histopathology.

**Gross Pathology:** Besides the thickened and curled left ear with erythema, there were no other grossly visible pathologic findings.

**Contributor's Histopathologic Description:** The lesion is centered around the pinnal cartilage. It consists of an inflammatory infiltration of mainly neutrophils and moderate numbers of macrophages, multinucleated giant cells (foreign body type), lymphocytes and plasma cells. Several neutrophils are invading the pinnal cartilage. The latter is irregularly lined, angularly deformed (wrinkled and curled over 180 degrees) and possesses a loss of basophilia (cartilage degeneration). Collagenous tissue surrounds the pinnal cartilage (perichondrial fibrosis). The dermis is edematous and diffusely infiltrated by neutrophils, lymphocytes and plasma cells. Perivascular accumulations of mononuclear and polymorphonuclear cells are present.

**Contributor's Morphologic Diagnosis:** Pinna: diffuse, chronic, suppurative to granulomatous chondritis with degeneration and deformation of the pinnal cartilage.

**Contributor's Comment:** Feline relapsing polycondritis is a very rare disease and only a few

reports of cats with the disease are found in the literature.<sup>2,3</sup> There is no sex predilection for the disease, but predominantly young to middle aged cats are affected.<sup>3</sup> In humans, the disease is believed to be an immune-mediated disease of type II collagen, which is restricted to cartilage.<sup>2,3</sup>

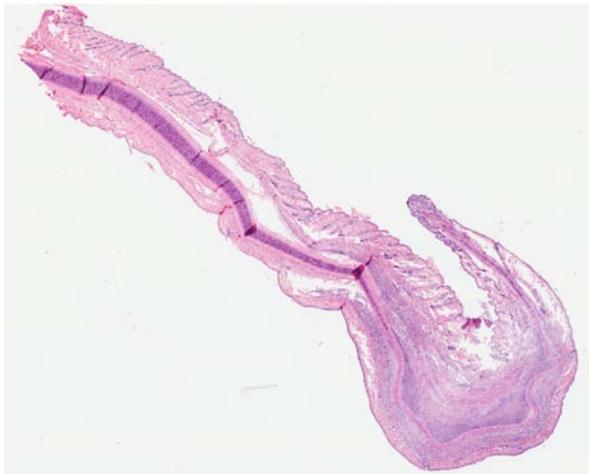
Sometimes the disease is also called auricular chondritis, because the main gross lesions are ear swelling and discoloration, erythema, pain and curling of one or both ears. However, two case reports describe involvement of additional cartilaginous tissues as reported in people.<sup>1,3</sup>

Histologically, there is degeneration, loss of basophilic staining and necrosis of the ear cartilage. There is also infiltration of mononuclear and polymorphonuclear cells, and perichondrial and perivascular fibrocyte and capillary endothelial cell proliferation. The histological lesions observed in this case are similar to those reported in the cases described in the literature.

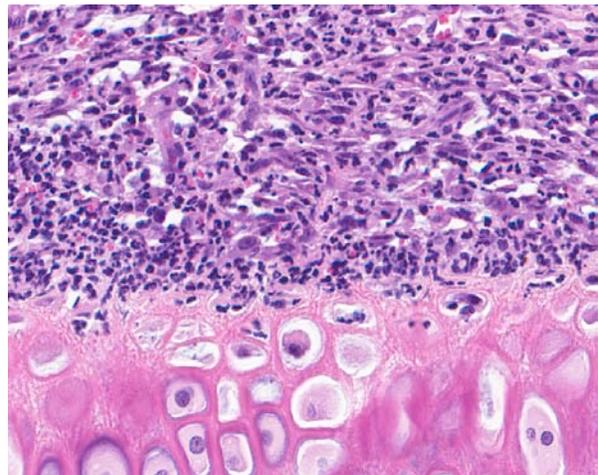
**JPC Diagnosis:** Ear, pinna: Cellulitis, chronic-active, diffuse, moderate with mild neutrophilic chondritis, cartilage degeneration, and granulation tissue.

**Conference Comment:** Conference participants discussed the comparative pathology of feline relapsing polycondritis and auricular chondritis of laboratory rodents, to which some strains of mice, and aged Sprague-Dawley, Wistar, and fawn-hooded rats are predisposed.<sup>4</sup>

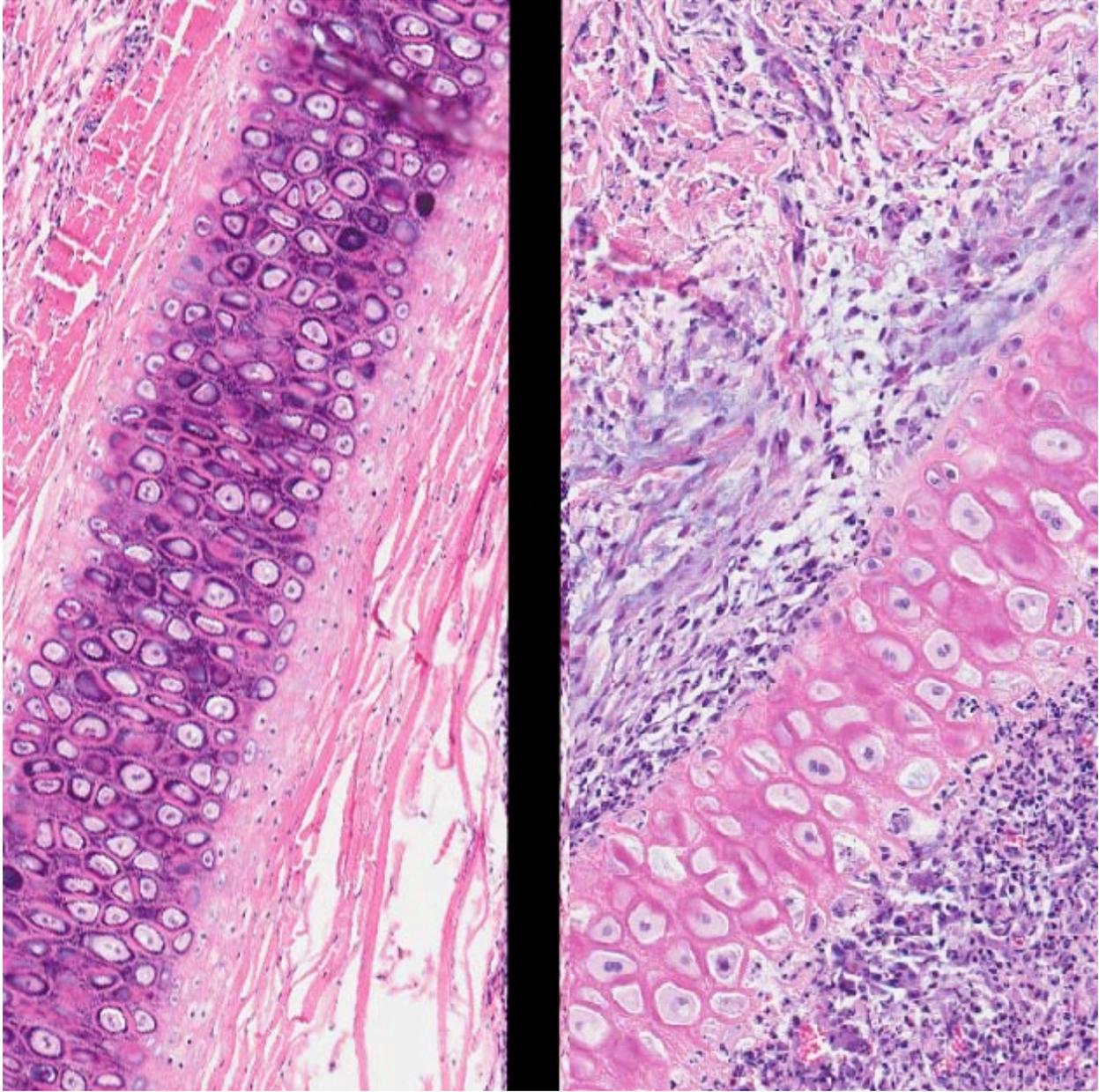
In rats, trauma from cagemates or metal ear tags is suspected as the inciting cause of auricular chondritis, but the disease frequently occurs without history or evidence of trauma. Unlike the feline disease,



2-1. Ear pinna, cat. There is focally extensive inflammation centered on the pinnal cartilage, resulting in focal thickening and folding at the ear tip. (HE 4X)



2-2. Ear pinna, cat. Area of granulation tissue with marked neutrophilic inflammation adjacent to the pinnal cartilage. Small numbers of neutrophils have breached the perichondrium and infiltrated the cartilage. (HE 200X)



2-3. Ear pinna, cat. Mild degeneration of cartilage (right) in the area of the inflammation as evidenced by a pink discoloration due to a decreased amount of glycosaminoglycans in the matrix. (HE 120X, 140X)

auricular chondritis in rats is always bilateral, even when the metal ear tag is present in only one ear, and increases in incidence with age.<sup>5</sup> The disease presents grossly as firm, multinodular to diffuse thickening of pinnae, and bilateral lesions extend peripherally from the base of the pinnae. Occasionally, pinnae are uniformly thickened rather than having nodular lesions. There is degeneration and lysis of the auricular cartilage plate with granulomatous inflammation and proliferative immature cartilaginous nodules and fibrosis, and osseous metaplasia is characteristic in advanced lesions.<sup>5</sup>

Auricular chondritis in rats has been proposed as a model for relapsing polychondritis in humans, which involves several cartilage-containing tissues, including the ear.<sup>5</sup> In humans, relapsing polychondritis is associated with auricular chondritis, inflamed cartilage in other sites, and antibodies to type II collagen, IgG and C3 complement. Antibodies to type II collagen have not been demonstrated in the spontaneous auricular chondropathy of rats, and unlike relapsing polychondritis in humans, only the auricular cartilage is involved.<sup>4,5</sup>

In mice, it is speculated that metal ions from ear tags, such as copper and iron, incite an autoimmune process via activation of matrix metalloproteinases. These metal ions supply reactive oxygen species that induce inflammation and fibrosis, and oxidation of cartilage collagen renders the collagen fibrils more brittle and prone to mechanical fatigue. Tagged ears have increased amounts of metallothionein (MT-I and MT-II) and increased expression of Th1 cytokines, including interferon- $\gamma$ , tumor necrosis factor- $\alpha$ , and interleukin-2; it is postulated that the lesion represents a delayed-type allergic contact dermatitis in response to the metal ions.<sup>4</sup> There are two proposed mechanisms for the fibrosis and osseous metaplasia seen in advanced lesions. In the first, cartilage degeneration, characterized by chondrolysis and splitting of the pinnal cartilage plate leads to perichondrial fibrous proliferation, which differentiates into fibroadipose tissue and progresses to fibrochondrous and/or osseochondrous tissue. In the second proposed mechanism, there is focal granulomatous inflammation without chondrolysis, and fibroblasts proliferate within the granulomatous inflammation and then differentiate into fibrochondrous tissue with subsequent chondrous and osseous differentiation.<sup>5</sup>

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**CASE III: S164/09 (JPC 3134629).**

**Signalment:** 14-day-old male kitten Siberian cat (*Felis catus*).

**History:** This cat is one of two littermates which were both born with fully developed hair coat. Beginning on day 11, both kittens lost most of their fur of the trunk with only a few hairs remaining on the head, the feet and tail. Both kittens died unexpectedly after unspecific clinical symptoms and one was submitted for pathological examination.

**Gross Pathology:** At necropsy the kitten had alopecia affecting mainly the trunk. The skin appeared normal in the alopecic and haired areas. The liver was slightly enlarged, friable and of smudgy yellowish color. All other organs had signs of congestion.

**Contributor's Histopathologic Description:** Histologically, the principal lesion is an abnormal structure of hair shafts. Hair bulbs including the dermal papillae are prominent and appear unchanged. Most parts of the inferior segments of the hairs are also regularly formed. Failure of proper keratinization is present in the upper third of the follicle resulting in a collapse of the medullary cavity with attenuated hair shafts becoming compact, hyaline masses. Large numbers of hair shafts fail to penetrate the epidermis. Instead, twisted, coiled, or sometimes "S"-shaped hair shafts are found within the isthmus or infundibular parts of follicles. Infundibular openings are dilated containing masses of lamellar keratin. Adnexal glands presented no obvious changes and were interpreted to be within normal limits. However, conclusive evaluation without an appropriate age-matched control tissue was considered difficult.

Few mild lymphoplasmacytic infiltrates are present in the superficial and perifollicular dermis. The mostly bilayered epidermis is unremarkable with multifocal to segmental mild orthokeratotic hyperkeratosis.

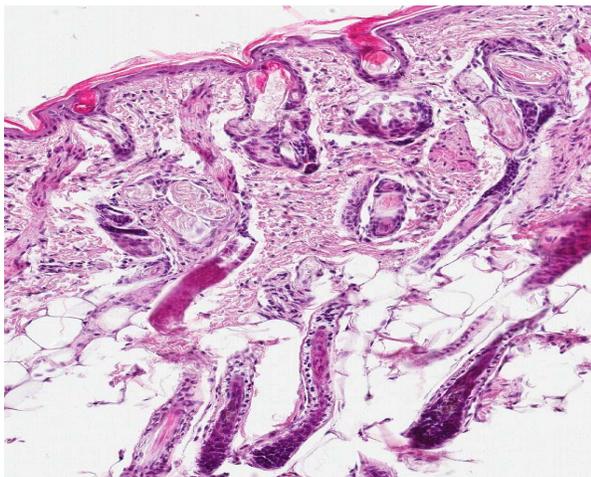
**Contributor's Morphologic Diagnosis:** Haired skin: Trichomalacia (hair follicle dysplasia with defective hair shaft formation).

**Contributor's Comment:** Lesions are consistent with dysplastic hair shaft formation. Several kinds of follicular dystrophies have been described in humans, domestic and laboratory animals.

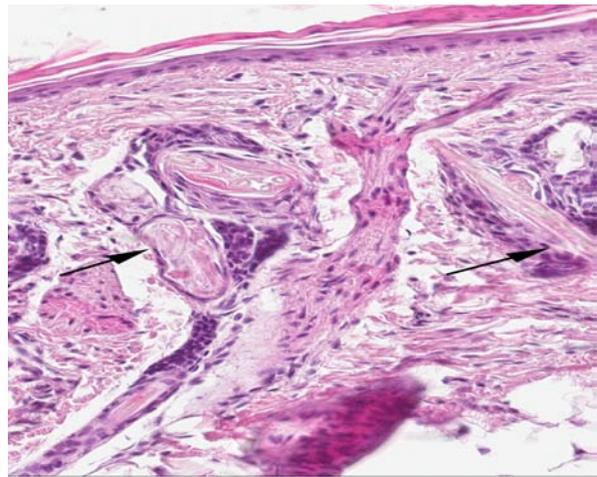
The main clinical feature, alopecia occurring at or shortly after birth, can be induced by changes in either quantity or quality of hair shafts. Congenital changes are based most frequently on inherited abnormal morphogenesis and therefore are termed hair follicle dysplasias. There are several kinds of dysplasias, depending to the differentiation level of affected cells (single differentiated cell or progenitor cell). Accordingly, changes in related tissues like cutaneous appendages, nails or claws and teeth may occur.

The hair follicle with its "product", the hair shaft, is a complex unit underlying tightly regulated cyclic changes.<sup>6</sup> Classification relies on differentiation between reduced hair follicle quantity and quality.<sup>7</sup>

Alterations in hair follicle quantity: Developmental reduction of hair placodes during organogenesis or defective morphogenesis with permanent loss of hair follicles can both lead to congenital alopecia. Delineation is often difficult because variable subsets of hair follicles are existent and are irregularly distributed over different body regions.



3-1. Haired skin, dog. Hair follicles exhibit dysplasti at the level of the ostium, with dilation and abundant keratin debris. The hair bulbs are normal, and their placement within the subcutis suggests that this is a puppy. (HE 100X)



3.2. Haired skin, dog. At higher magnification, dysplastic follicles flank arrector pili muscles. The dilated follicles contain poorly formed, broken hair shafts or keratin debris, and the inner root sheath is disorganized, with some cells exhibiting cloudy swelling. (HE 200X)

Aplasia of hair follicles with dental dysplasia affects more than one tissue derived from the ectoderm, mostly apocrine glands. Several forms have been reported in humans, various breeds of dogs,<sup>10</sup> mice,<sup>2</sup> and cattle,<sup>1</sup> with only few of the underlying signaling pathway defects characterized yet.<sup>2</sup> Aplasia of hair follicles without dental dysplasia with a dominant autosomal inheritance has been described in pigs.<sup>7</sup>

Alterations in hair follicle quality: Structural changes leading to reduced, defective or absent hair shaft production can be subdivided into those resulting from morphological changes of the hair follicle itself or those where morphologically unchanged hair bulbs form defective hair shafts.

Especially in the dog, several breeds are affected with hairlessness resulting from hair follicle dysplasia with defects in hair follicle development, for example Mexican<sup>5</sup> or Peruvian hairless dogs and Chinese crested dogs.<sup>11</sup> In contrast to horses with only rare reports, diverse forms have been described in various breeds of cattle. Some of these have already been characterized as autosomal recessive or dominant, partly lethal traits.<sup>7</sup>

Hair follicle dysplasia without defects in hair follicle development (trichomalacia) is classically represented by nude mice amongst few others.<sup>8</sup> Beside few breeds of cats, (e.g. Sphinx breed) and dogs, 7 mainly in man, numerous forms of trichomalacia have been observed.<sup>4</sup>

A special form of dysplasia affects the neuroectodermally derived follicular melanocytes which also contribute to regular hair follicle development.<sup>3</sup> Histopathological changes are specific and identical in both syndromes with formation of enlarged melanin granules in melanocytes and later aggregation of perifollicular melanophages.<sup>7</sup> Depending on the affected breed and coat colors, color dilution alopecia and black hair follicular dysplasia have been differentiated.<sup>13</sup>

The case submitted here fulfills the relevant criteria for *hair follicle dysplasia without defects in hair follicle development (trichomalacia)* because of the unchanged appearance of hair follicles. Further changes in ectoderm-derived tissues, like apocrine glands or teeth, were not observed. The occurrence in both animals of the litter is suggestive of an inherited genetic defect. The queen had been mated to the identical sire before, without any abnormality in the offspring. Unfortunately the littermate was not available for pathological examination and confirmation of similar changes in hair shaft formation.

Death of this kitten was attributed to acute hepatic failure with severe hepatocellular degeneration and

lipidosis (peripheral lipomobilization syndrome) based on the results of pathological examination of all other organ systems, including histology.

**JPC Diagnosis:** Haired skin: Trichomalacia, diffuse, moderate.

**Conference Comment:** The main abnormality in this case is the presence of abnormal hair shafts with no cuticle, cortex, or medulla along with malformed keratin fragments. Trichomalacia refers to degeneration of the hair shaft and is manifest grossly as alopecia with broken hair shafts in the presence of normal follicles.<sup>12</sup> In large animals, trichomalacia may be caused by certain nutritional deficiencies, such as copper, vitamin A, and folic acid; or by intoxication with hypervitaminosis A, D, or E, and with selenium and thalium toxicity.<sup>9</sup> Conference participants discussed psychogenic alopecia, but this is ruled out because the patient is a kitten and the lesion is diffuse instead of sparse.

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**CASE IV: T10-7475 (JPC 4002870).**

**Signalment:** Six-week-old male English setter dog (*Canis familiaris*).

**History:** Two of nine puppies in a litter of English setter dogs developed erythematous cutaneous lesions at the age of 2 weeks. Oral amoxicillin was given twice daily. After a week, the 2 puppies developed full body crusts, scabs, blistered footpads, and pustules on the lips and the eyelids. The puppies were still in a good body condition and nursing well. Other puppies in the litter were apparently healthy and doing well. Treatment was switched to cefadroxil antibiotic with low-dose prednisone added into the suspension. At 4 weeks of age, a total of 4 puppies were affected. Cefadroxil and prednisone were given to all 4 puppies with daily antimicrobial shampoos. The lesions worsened irrespective of treatment with anthelmintic, antibiotics, anti-fungal and anti-inflammatory drugs. There was some response to daily dosing of dexamethasone. Two severely affected puppies were hospitalized for more intensive care and diagnostic evaluation. Full thickness skin biopsy was taken from one of the puppies. Given the poor prognosis due to severity of the lesions and deteriorating health status, the 2 puppies were euthanized after 2 weeks of hospitalization (8 weeks of age) and necropsied.

**Gross Pathology:** Grossly, there were extensive skin erythema with alopecia on the face, body, and extremities. The tongues and oral mucosae were multifocally eroded and ulcerated.

**Laboratory Results:**

Skin scrapings were negative for mites. Heavy growths of *Staphylococcus intermedius* and beta *Streptococcus* sp. Group C and moderate *Rhizopus* sp. were obtained from culture on hair and scab. Tissues from the tongue, lymph node, spleen, skin, and small intestine from both euthanized puppies were positive for Canine parvovirus-2 (CPV-2) and negative for Canine distemper virus (CDV) and Canid herpesvirus 1 by **fluorescent antibody** test (FAT). Negative-staining electron microscopy detected parvovirus particles in the intestinal contents. The skin and small intestine were positive for CPV-2b and negative for CDV by polymerase chain reaction (PCR). The mucocutaneous junctions and small intestines stained positive for CPV by immunohistochemistry (IHC).

**Contributor's Histopathologic Description:** The epidermis of skin on the body, lips (mucocutaneous junction), ears, and footpads, from both puppies was mild to moderately hyperkeratotic (parakeratotic), irregularly acanthotic, multifocally necrotic, and occasionally covered with serocellular crusts. In all layers of the epidermis, there was scattered individual

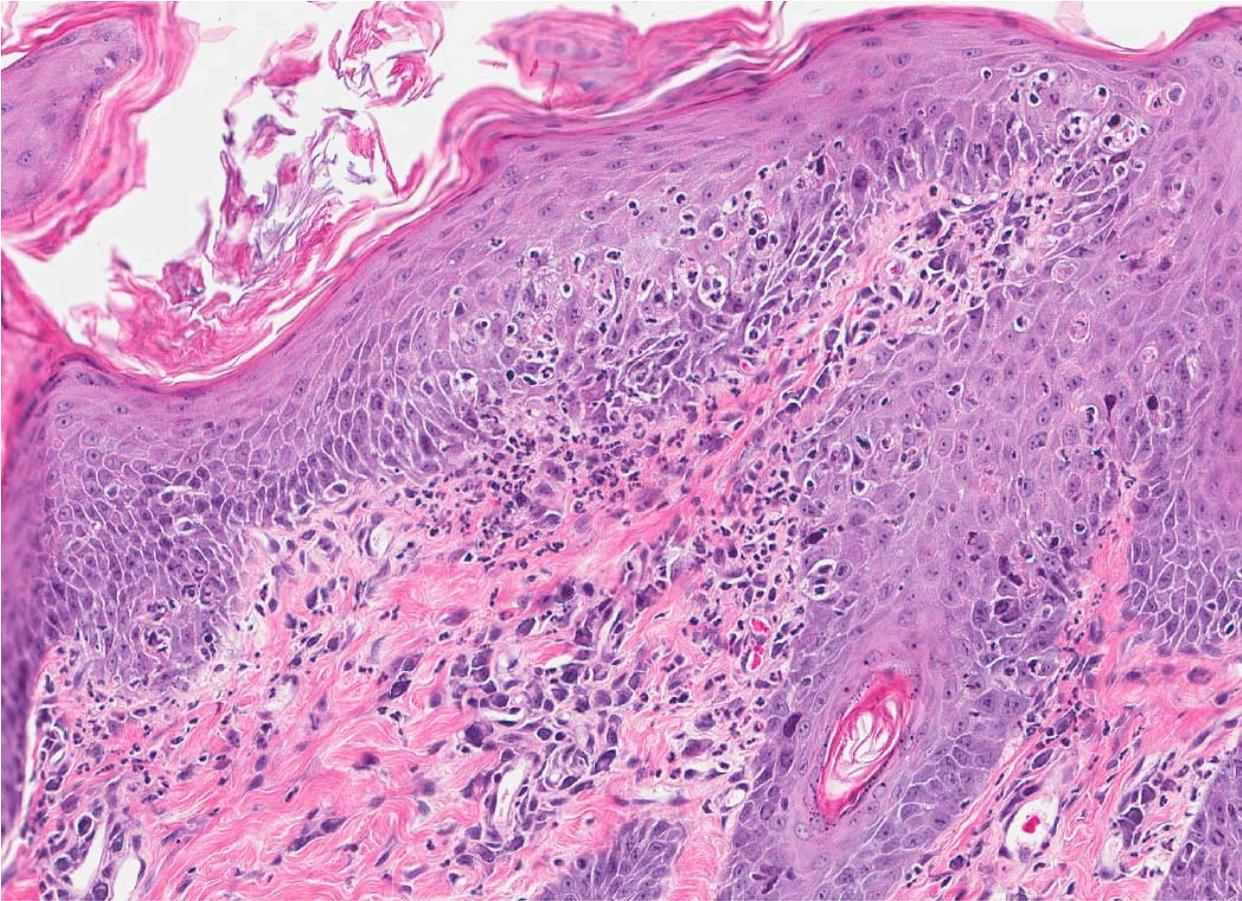


4-1. 6-week-old male English setter puppy with full body crusts, scabs, blistered footpads, and pustules on the lips and the eyelids. Photograph courtesy of The University of Georgia, College of Veterinary Medicine, Department of Pathology, Tifton Veterinary Diagnostic and Investigational Laboratory, Tifton, GA 31793 <http://www.vet.uga.edu/dlab/tifton/index.php>

keratinocyte apoptosis with lymphocyte satellitosis (varies from slide to slide). The individual cell apoptosis occasionally extended to the infundibular and upper sections of the hair follicles and associated sebaceous glands. Few basophilic to amphophilic intranuclear inclusions were present in the apoptotic basal cells and the overlying cells of stratum spinosum. Similar intranuclear inclusions were present in a few mast cells in the papillary dermis, the mucosal cells of the tongue, the small intestine crypt enterocytes, and the myocardiocytes of the heart in both puppies and in the mucosal cells of the oropharynx overlying the tonsil and in the epithelial cells of the esophageal glands in one of the puppies. The microscopic findings in the other tissues besides skin were typical of parvovirus infection. The findings in the other examined tissues were unremarkable.

**Contributor's Morphologic Diagnosis:** Epidermitis, and folliculitis, necrotizing, subacute with parakeratosis and intranuclear and intracytoplasmic inclusions.

**Contributor's Comment:** The gross and microscopic lesions are consistent with erythema multiforme (EM). Erythema multiforme is a cutaneous reaction of multifocal etiology seen uncommonly in dogs and rarely in cats.<sup>3</sup> In dogs, EM is most commonly idiopathic or reported in association with administration of antibiotics, anthelmintics and anti-inflammatory drugs, infections such as staphylococcal dermatitis, and folliculitis, and pseudomonas otitis externa, feed, and a commercial nutraceutical product.<sup>4,6-8</sup> It is also described in association with CPV-2 in a dog.<sup>1</sup> A group of chronic and persistent idiopathic EM is seen in older dogs ("old dog EM") without a history



4-2. Haired skin, dog. Necrotizing dermatitis with marked neutrophilic infiltration of the epidermis. (HE 180X)

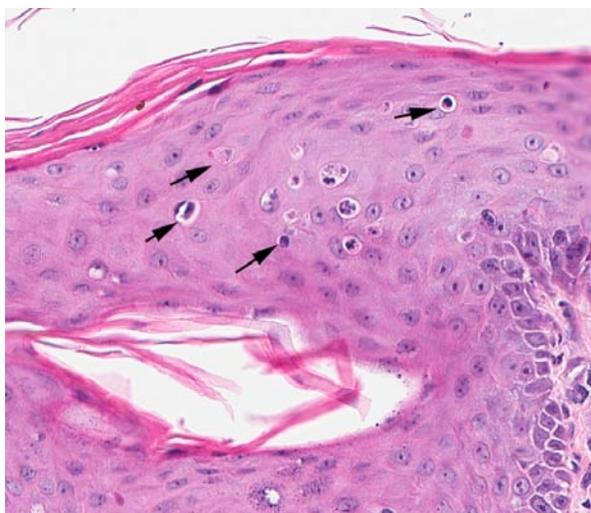
compatible with known triggers. Lesions are more exudative and proliferative, and predominantly involve the face and ears.<sup>3</sup> In humans, most cases were associated with drug administration and infections such as Herpes virus and *Mycoplasma pneumoniae*.<sup>5</sup>

Despite recognition of multiple etiologic and triggering causes, the pathogenesis of EM is not completely understood.<sup>6,7</sup> It is believed to be a host-specific T-cell mediated hypersensitivity reaction in which the immune response is directed against keratinocyte-associated antigens associated with the triggering causes.<sup>3</sup> In EM, cluster of differentiation (CD)44 was markedly up-regulated in keratinocytes and infiltrating cells and is involved in T-lymphocyte activation and site-specific extravasation of lymphocytes into tissues.<sup>7</sup> Keratinocyte apoptosis is probably produced by signals from intraepithelial CD8+ T lymphocytes.<sup>8</sup> Lymphocytes bind to the antigenically altered keratinocytes and trigger cell death via apoptosis. Keratinocyte apoptosis is principally seen in the basal cell layer in exfoliative cutaneous lupus erythematosus of the German shorthaired pointer dog, discoid lupus

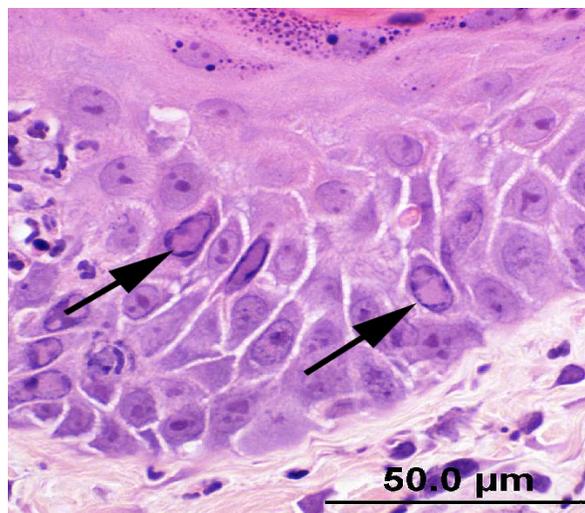
erythematosus, and systemic lupus erythematosus. Keratinocyte apoptosis in EM, however, is seen at all levels of the epidermis.<sup>3</sup>

Erythema multiforme occurs in 2 forms that may overlap one another and to toxic epidermal necrolysis. Erythema multiforme minor is characterized chiefly by an acute onset of cutaneous erythematous macules and papules. In EM major (Stevens-Johnson syndrome), widespread mucosal lesions, extensive necrotizing and vesicular skin lesions, and signs of systemic illness such as pain, lethargy, and pyrexia are present.<sup>2</sup> Based on this, the EM seen in the current cases was classified as EM major.

Because of the diversity of triggering factors associated with EM, recognition of the underlying cause for each individual case is important to propose the best treatment regimen. Age or sex predilection is not documented in dogs and cats. Extensive studies and documentation are needed to determine breed predilection to EM in dogs. Canine parvovirus infection was confirmed in several tissues and organs



4-3. Haired skin, dog. Degenerating and necrotic keratinocytes within all layers of the epidermis. Adjacent to them are infiltrating neutrophils. (HE 400X)



4-4. Haired skin, dog. Rhomboidal intranuclear viral inclusions within basal keratinocytes, characteristic of canine parvovirus-2 (arrows). Photograph courtesy of The University of Georgia, College of Veterinary Medicine, Department of Pathology, Tifton Veterinary Diagnostic and Investigational Laboratory, Tifton, GA 31793 <http://www.vet.uga.edu/dlab/tifton/index.phpv>(HE 600X)

from the puppies by FAT, PCR, IHC, and electron microscopy. The EM observed in this litter of English setters was associated with systemic CPV-2b infection involving various tissues and organs.

**JPC Diagnosis:** Haired skin: Keratinocyte necrosis, multifocal, moderate, with neutrophilic epidermitis and folliculitis, marked parakeratosis, pustule formation, and viral intranuclear inclusion bodies.

**Conference Comment:** Conference participants debated that the multifocal single-cell death in the epidermal keratinocytes may be the result of the cytopathic effect of canine parvovirus, and not an indication of erythema multiforme (EM). Consideration is also given to toxic shock syndrome (TSS), in which early lesions resemble EM, although apoptotic keratinocytes are typically surrounded by neutrophils possibly due to the presence of bacterial toxins. Although the cause of skin lesions associated with TSS has not been determined, superantigen exotoxins which stimulate lymphocytes to release cytokines, including tumor necrosis factor-alpha may play a role.<sup>2</sup>

The puppies in this case started showing clinical signs when only 2 weeks old. Participants did not expect such young puppies to have developed an immune response directed against their own keratinocytes at such an early age. Also, conference participants felt that the keratinocyte satellitosis was predominantly neutrophilic and not lymphocytic. Additional features of EM that were not evident in our slide include a lymphohistiocytic infiltrate obscuring the dermoepidermal junction and around superficial blood

vessels (interface dermatitis), subepidermal clefting and vesicle formation along the basement membrane, vacuolation of the basement membrane zone (hydropic degeneration), pigmentary incontinence, and, less commonly, severe dermal edema with vertical orientation of dermal collagen (gossamer collagen).<sup>2,3</sup>

The pathogenesis of EM is not fully understood, but is thought to be a host-specific T cell-mediated hypersensitivity reaction with a cellular immune response directed against various keratinocyte-associated antigens, including those associated with drugs, infections (viral, fungal, bacterial), neoplasia, various chemical contactants, foods and connective tissue disease. CD8+ T lymphocytes bind to antigenically altered keratinocytes (ICAM-1, MHC II, CD1a, and CD44 expression is upregulated) and trigger cell death via apoptosis. Apoptotic keratinocytes coalesce, leading to erosion, ulceration or hyperkeratosis. Studies support a combined type III and type IV immune reaction.<sup>2,3</sup>

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