D - Dermatology
ISCHEMIC SKIN DISEASE IN THE DOG

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A. Introduction, General Information, and Definitions

1. Vasculitis is defined as a process by which inflammation is directed against vessel walls. Microhemorrhage into surrounding tissue is a frequent sequela.
2. 'Cell poor' vasculitis or 'vasculopathy' is a subgroup of vasculitis characterized by vascular damage, vascular depletion, and only sparse inflammation. Loss of endothelial cells and thickening of the vessel wall are noted.
3. Ischemic dermatopathy is a term used to group multiple vasculopathic syndromes unified by similar clinical and histopathologic characteristics.
4. Diascopy is a useful and simple clinical tool used in the diagnosis of skin diseases with a vascular component. A clear microscope slide is pressed onto skin to determine if erythema is due to dilated blood vessels or hemorrhage into the skin. Blanching of the skin indicates that erythema is due to dilated blood vessels and inflammation. If erythematous skin does not blanch, diascopy confirms hemorrhage and suggests either vasculitis or vasculopathy.

B. Classification of Ischemic Dermatopathies

1. Canine familial dermatomyositis (DM) – A juvenile onset heritable inflammatory disease of uncertain etiology affecting skin and muscle, seen predominantly in the Collie, Shetland Sheepdog, and their related cross-breeds.
2. Dermatomyositis-like disease (DM-Like) – A juvenile-onset ischemic dermatopathy that is clinically and histopathologically identical to canine dermatomyositis, but in a breed without proven breed predilection, and therefore without known familial predisposition.
3. Localized post-rabies vaccination panniculitis (Post-Rabies) - A localized ischemic skin disease associated with a rabies vaccination site and temporal link with the vaccination.
4. Generalized vaccine-induced ischemic dermatopathy (GVIID) – A generalized ischemic skin disease with a temporal linkage with rabies vaccination, but with more severe generalized post-rabies vaccination-associated disease.
5. Generalized idiopathic ischemic dermatopathy (GIID) – An adult-onset generalized ischemic dermatopathy without a correlative history indicating the likelihood of induction by a rabies vaccine reaction.
6. These 5 syndromes are united by very similar clinical and histopathologic similarities. Groups 1 and 2 above develop as juvenile onset disease and are clinically indistinguishable from each other. Group 3 develops as focal skin disease at the site of vaccination. Group 4 and 5 develop as generalized, more severe, and usually adult-onset skin disease. Skin disease seen with group 4 and 5 may be generalized beyond the expected distribution pattern of most cases of DM (group 1) and DM-like disease (group 2).
7. The term, "canine familial dermatomyositis" currently should be reserved for dogs with clinical and histopathologic evidence of a juvenile onset heritable inflammatory disease affecting skin and muscle in a breed known to be at increased risk.

C. Etiology and Pathogenesis

1. The etiology of ischemic dermatopathies is not known. Multifocal immunologic damage to blood vessels probably results in ischemic damage to the skin and other susceptible organs. Cutaneous hypoxia probably leads to follicular atrophy and other associated chronic hypoxic skin changes.
2. Post-rabies vaccination associated disease is presumed to be due to an idiosyncratic immunologic reaction to rabies antigen that partially targets vessels. Rabies viral antigen can be documented in the walls of dermal blood vessels and in the epithelium of hair follicles via immunofluorescent testing. Since this syndrome is seen predominantly in very small dogs, it is

tempting to speculate that the disease may be partially linked to increased antigenic load in comparison to the body size of the dog, since the same volume of rabies vaccine is given to all dogs subcutaneously.

3. Hereditary or individual predispositions, coupled with a secondary environmental trigger have long been hypothesized for dermatomyositis in humans. Similar factors probably initiate and drive canine ischemic dermatopathy. Autoimmune and viral etiologies coupled with hereditary predilection have been postulated for dermatomyositis in humans.

4. All ischemic dermatopathies share both clinical and histopathologic features that could result from cell-poor vasculitis leading to a long-term lack of cutaneous vascular sustenance. Skin hypoxia could lead to follicular atrophy and associated chronic skin changes. Lesions that occur over bony prominences can be explained by enhanced susceptibility to trauma and lesions on distal extremities can be explained by poor collateral circulation that does not allow appropriate vascular sustenance.

5. Complement-mediated microangiopathy leading to ischemia is considered to be the pathophysiological basis of skin lesions in human dermatomyositis. Complement C5b-9 membrane attack complex has been demonstrated in small blood vessels within muscle from a dog with vaccine-induced ischemic dermatopathy and cell poor vasculitis.

D. Comparison of Clinical Features

1. Clinical features shared by all 5 subgroups of canine ischemic dermatopathy given above include alopecia with crusting and post-inflammatory, mottled pigmentary change. Hyperpigmentation is seen in breeds predisposed to enhanced pigmentation secondary to inflammation; in other breeds, hypopigmentation can occur. Erosion and ulceration occurs in more severe cases, especially if trauma, secondary infection, or coexistent pruritic disease are present.

2. Dogs with Canine familial dermatomyositis (DM) and Dermatomyositis-like disease (DM-Like) (Group 1 & 2) share identical clinical features and hence will be grouped in the discussion below.

3. Dogs with Generalized vaccine-induced ischemic dermatopathy (GVIID) & Generalized idiopathic ischemic dermatopathy (GIID) share similar clinical features and will be grouped in the discussion below. However, dogs with GVIID usually have a demonstrable focal lesion at the subcutaneous vaccine site compatible with the lesions seen with localized post rabies vaccination panniculitis. Even dogs without a correlative history of recent rabies vaccination should have likely vaccination sites checked for compatible lesions, as the focal lesions may be subtle and easily missed.

E. Histopathologic Features (adapted from T.L. Gross)

1. The histopathologic features of all ischemic dermatopathies are similar. Diagnosis of cell-poor vasculitis relies on recognition of subtle ischemic changes in the skin. Altered staining of collagen and 'fading' atrophy of hair follicles are the most characteristic features. The epidermal and dermal changes overlying post-rabies vaccination panniculitis are identical to those seen with other ischemic dermatopathies.

2. Scattered degeneration of individual basal cells and prominent degeneration of follicular basal cells are noted.

3. Secondary dermal-epidermal vesiculation occurs in more severely affected animals. Vesicles contain red blood cells and occur above the basement membrane. Artifactual dermal-epidermal separation "usable artifact of Stannard") may occur at biopsy specimen margins.

4. Dermal inflammation consists of diffuse, mild lymphocytic and histiocytic inflammation that encircles hair follicles.

5. Diffuse pallor of dermal connective tissue with pale-staining, smudged, collagen probably results from tissue ischemia.

6. Vascular lesions are subtle. Loss of endothelial cells, mummification of small vessels, or hyaline mural alteration may be seen. Leukocytoclasia may be present.

7. Severely atrophic or faded, atrophic hair follicles may be a direct consequences of ischemia and basal cell degeneration.

8. Myositis with mixed inflammation, regeneration, fibrosis, and atrophy may be present. Random biopsy may not show muscle lesions.

9. Localized post-rabies vaccination panniculitis also shows a nodular localization of lymphocytes and other mononuclear cells in the lower dermis and panniculus. Amorphous basophilic deposits resembling vaccine product may be present.

F. Canine Familial Dermatomyositis (DM) & Dermatomyositis-like disease (DM-Like) (Group 1 & 2)

1. Signalment predilections

a. Breeds - DM - Shetland Sheepdogs, Collies, and related crossbreeds.

b. Breeds - DM-like - Chow Chow, Beauceron Shepherds, Welsh Corgi, Lakeland Terrier, German Shepherd Dog, and Kuvasz (published). Additionally, Miniature Schnauzers, Miniature Dachshunds, Fox

Terriers, and other breeds have been confirmed by Ihrke or Gross.

c. Age - Both are juvenile-onset diseases; lesions usually occur by 6 months of age. d. Sex - Sex predilection has not been noted.

2. Initial lesions - Rare transient papules, pustules, and vesicles eventuating in crusted erosions, ulcers, and alopecia.
3. Chronic lesions - Scarring is seen with chronicity. Pigmentary aberrations give rise to poikilodermatous change with either hyper or hypopigmentation.
4. Sites - Initial lesions occur over bony prominences (sites of mild trauma), especially on the muzzle; in periorbital and perioral locations; and on the dorsal paws. Similar lesions occur on distal extremities with poor collateral circulation, and on pressure points susceptible to shearing injury and trauma. The pinnal tips, pinnal folds, nail folds, tip of the tail, other bony prominences can be affected. Nail dystrophy and sloughing may be seen.
5. Pain and pruritus occur if ulceration or secondary pyoderma are present.
6. Relapse - Photo-aggravation, trauma or estrus can trigger relapse.
7. Muscle involvement - Subtle, may be limited to the temporal and masseter muscles. Difficulties with mastication and swallowing can occur. Concurrent clinical, electromyographic, or histologic evidence of muscle disease aids in diagnosis.
8. Severely affected dogs - Growth retardation, megaesophagus, lameness, and widespread muscle atrophy. The tongue may fasciculate causing difficulty in prehension. Infertility can occur in severe dermatomyositis.
9. Diagnosis - Compatible skin lesions, confirmatory skin biopsy, muscle disease.
10. Prognosis - Mildly affected dogs may achieve clinical remission. Severely affected dogs with generalized disease exhibit cyclical lifelong disease.

G. Localized Post-Rabies Vaccination Panniculitis (Post-Rabies)

1. Signalment predilections

a. Breeds - Marked breed predilection for Toy & Miniature Poodles, and Bichon Frises. Shih Tzu, Lhasa Apso, Maltese, Silky Terrier, Yorkshire Terrier, Chihuahua, Toy Manchester Terrier, American Eskimo, Poodle crossbreeds, and Miniature Dachshunds also have been confirmed by Ihrke or Gross.

b. Age & sex predilections have not been noted.

2. Initial lesions - An alopecic macule or plaque develops at the site of prior subcutaneous rabies vaccine deposition. The time between vaccination and noting of the lesion usually is between one and three months. Average lesion size is 2 to 10 cm in diameter. Smaller satellite lesions may be present. A few hairs may remain within the boundaries of the lesion. Visible inflammation commonly is minimal.
3. Chronic lesions - Hyperpigmentation may be an occasional sequela, especially in black Miniature Poodles and other breeds that tend to respond to inflammation by hyperpigmentation.
4. Sites - Neck and shoulder region near the scapula where most subcutaneous rabies vaccinations are given. Gravitational drift may result in lesions ventral to vaccination site.
5. Systemic signs - A small subgroup of dogs display lethargy, depression, and fever. Elevated liver enzymes have been noted. Systemic signs may precede the skin lesion or occur concomitantly.
6. Diagnosis – History of vaccination, compatible skin lesions, confirmatory skin biopsy.
7. Prognosis – Most lesions remain small and are asymptomatic. Exacerbation has been observed after revaccination.

H. Generalized vaccine-induced ischemic dermatopathy (GVIID) & Generalized idiopathic ischemic dermatopathy (GIID)

1. Signalment predilections

a. Breeds – Miniature and Toy Poodle, Shih Tzu, Shetland Sheepdog, Lhasa Apso, Pomeranian, and Yorkshire Terrier may be at increased risk for both types of adult-onset generalized ischemic dermatopathy. Long-haired toy or miniature breeds seem to be at greater risk.

b. Age & sex predilections have not been noted.

2. Clinical skin lesions – Individual lesions are those of DM and DM-like disease but may be more severe and more generalized. More severe lesions are located over bony prominences and on distal extremities. Similar, but usually less severe lesions are seen over much of the skin surface.
3. Muscle atrophy – Variable, but may be marked.
4. Systemic signs – Some dogs with GVIID display lethargy, depression, and fever. Elevated liver enzymes have been noted. Systemic signs may precede the skin lesion or occur concomitantly.
5. Prognosis - Generalized vaccine-induced ischemic dermatopathy may gradually diminish in severity over time. Dogs with GIID usually exhibit lifelong disease with some cyclical

recrudescence. Revaccination can exacerbate disease.

I. Other reported Ischemic Dermatopathies

1. Other syndromes have been reported that share features with cell-poor vasculopathies and ischemic dermatopathies.
2. Reported diseases include familial cutaneous vasculopathy of German Shepherd Dogs, and cutaneous vasculitis in Jack Russell Terriers.

J. Familial Cutaneous Vasculopathy of German Shepherd Dogs

1. Familial cutaneous vasculopathy of German Shepherd Dogs is a rare vascular disease affecting predominantly the pawpads of German Shepherd Dog puppies. Pedigree analysis indicated probable autosomal recessive inheritance. Most published cases (26 dogs) were seen in Canada, with another from the United States, and another from Italy.
2. Immunologic attack on collagen has been hypothesized as a mechanism.
3. A temporal association with puppy vaccination and recrudescence with repeat vaccination was seen in some of the dogs, similar to some ischemic dermatopathies.
4. Clinical features - The prime clinical feature is depigmented, swollen pawpads. Erosions, ulceration, and hairloss with adherent crusting occur
5. Sites - Pawpads are affected preferentially. Similar lesions may be present on the pinnae, tail tip, and nasal planum.
6. Other clinical signs - Lymphadenopathy may occur. Systemic signs include pain, lethargy, pyrexia, and pain on ambulation.
7. Histopathologically identical lesions were seen in the pawpads of a Fox Terrier and Miniature Schnauzer with presumed ischemic lesions affecting the muzzle and ears (T.L. Gross). 'Pawpad vasculopathy' may be one manifestation of ischemic dermatopathy in some breeds. Coexistent mild skin lesions may be overlooked.

K. Cutaneous Vasculitis in Jack Russell Terriers

1. A syndrome characterized by cutaneous vasculitis has been reported in 5 Jack Russell Terriers. The most prominent histologic feature was a cell poor vasculitis.
2. The range of reported age of onset and clinical features both were wide.
3. Familial predisposition is suggested by all affected dogs being of the same breed.
4. Most likely, these cases also reflect canine ischemic dermatopathy.

L. Diagnosis & Differential Diagnosis – Overview

1. All of the ischemic dermatopathies are diagnosed by clinical features and skin biopsy. Electromyographic examination is recommended if DM or DM-like disease are suspected.
2. Clinical differential diagnoses for canine DM and DM-like disease include juvenile-onset demodicosis, dermatophytosis, facial pyoderma, and discoid lupus erythematosus.
3. The diagnosis of post-rabies vaccination panniculitis is simplified by localization to a site of prior vaccination, breed predilections, plus a temporal link to vaccination.
4. More severe cases of GVIID and GIID must be differentiated from other inflammatory diseases where extensive alopecia and pigmentary changes are seen. Differential diagnoses include other vasculitides, severe erythema multiforme and epitheliotropic lymphoma. Generalized demodicosis and generalized dermatophytosis also may resemble ischemic dermatopathy. Most cases of GVIID have a focal lesion at a prior vaccine site. Skin scrapings should be performed to rule out demodicosis and fungal culture should be performed to rule out dermatophytosis. Skin biopsy is required for definitive diagnosis.

M. Management of Ischemic Dermatopathies - Overview

1. Management of ischemic dermatopathies is challenging. Response to therapeutic manipulations can be slow and perception of response is highly subjective.
2. Minimally affected dogs require little management; the disease may be largely cosmetic.
3. Severely affected dogs are difficult to manage. Dogs with substantial concomitant muscle disease (DM & DM-like) may have difficulties in prehension and swallowing. Megaesophagus leading to aspiration pneumonia occurs in severely affected dogs.
4. Medications aimed at diminishing or preventing inflammation may be beneficial.
    a. Omega-3 and Omega-6 fatty acid supplementation may offer some benefit.
    b. Vitamin E (200 – 800 IU/day) may be beneficial.
5. Pentoxifylline (Trental®, Hoechst-Roussel), available as a 400mg coated tablet (200 – 400 mg/day / 10-30 mg/kg/day). The drug is a methylxanthine derivative with rheologic and immunomodulatory effects. Pentoxifylline increases red blood cell deformability, alters tissue response to multiple cytokines, and diminishes production of TNF-alpha.

6. The use of corticosteroids for the treatment of ischemic dermatopathies is controversial. Anti-inflammatory effects may be beneficial, but overuse is detrimental. Potent topical corticosteroids may diminish epidermal thickness leading to increased skin fragility. Systemic corticosteroid overuse can lead to iatrogenic hyperglucocorticoidism and highly deleterious side effects such as 'corticosteroid-induced-owner-loss-of-hope!

N. Factors Complicating Management – Adjunctive Recommendations

1. Restrict potential for cutaneous trauma - Rough play with other dogs, especially puppies can lead to profound exacerbation of skin lesions.
2. Prevent self-trauma in response to concomitant skin diseases – Any coexistent skin disease characterized by pruritus must be relentlessly managed long-term to prevent the cycle of self-trauma followed by further ischemic damage. The most commonly present troublesome coexistent pruritic skin diseases include flea allergy dermatitis, canine atopic dermatitis, and food allergy.
3. Secondary infection or bacterial or yeast overgrowth - Either *Staphylococcus* or *Malassezia* can markedly exacerbate inflammation and pruritus and contribute to additional pruritus and self-trauma complicating management.
4. Long-term surveillance to prevent recurrence of pruritic skin diseases or secondary pyoderma and *Malassezia* dermatitis - Surface cytologic examination looking for organism overgrowth should be performed whenever inflammation seems to be exacerbating in an ischemic dermatopathy.
5. Minimize solar exposure – Sun exposure can exacerbate ischemic dermatopathies.
6. Localized demodicosis restricted to the site of the skin lesions of dermatomyositis has been noted in multiple Shetland Sheepdogs. The significance of these findings is not known, but may indicate focal aberrations in immune surveillance.

O. Suggested Readings

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