Dermatomyositis in a family of Working Kelpies

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Keywords
Ischemic dermatopathy, canine, vasculitis

Summary
Eight members of a family of Working Kelpies were presented with signs compatible with dermatomyositis. Alopecia, crusts, ulcerations of the skin, depigmentation of nasal planum and lips, onychodystrophy and atrophy of the masticatory muscles were present with varying degree. Histopathology of the skin, but not from muscles was performed in three dogs and confirmed the clinical diagnosis. Different immunomodulating drugs (steroids, cyclosporine, mycophenolate mofetil, pentoxifylline, doxycyline/niacinamid, omega-3 fatty acids and vitamin E) were used with variable success. Dermatomyositis is an immune-mediated disease and a genetic predisposition is known in humans and certain canine breeds, mainly Shetland Sheepdogs and Collies, but also for the Beauceron. The responsible genes have not been identified so far. It is assumed that the Working Kelpie derives from the Collie which could explain a hereditary predisposition in the Kelpie.

Schlüsselwörter
Ischämische Dermatopathie, Hund, Vaskulitis

Zusammenfassung
Acht eng verwandte Mitglieder einer Linie von Working Kelpies zeigten Symptome einer Dermatomyositis in Form von Alopezie, Krusten, Ulzerationen der Haut, Depigmentation von Nasenspiegel und Lefzen, Onychodystrophie und Muskelatrophie, vor allem der Kaumuskeln. Die Symptome waren bei den betroffenen Tieren unterschiedlich stark oder nur teilweise ausgeprägt. Die klinische Diagnose wurde bei drei Hunden durch histologische Untersuchung von Hautbioptaten, nicht jedoch Muskelbioptaten bestätigt. Therapeutisch kamen verschiedene immunmodulatorische Medikamente (Steroide, Ciclosporin, Mycophenolat-Mofetil, Pentoxifyllin, Doxycylin/Niacinamid, Omega-3-Fettsäuren, Vitamin E) mit unterschiedlichem Erfolg zum Einsatz. Bei der Dermatomyositis handelt es sich um eine immunvermittelte Erkrankung mit genetischem Hintergrund bei Mensch und Hund. Die verantwortlichen Gene sind weitgehend unbekannt. Für die Hunderassen Collie und Shetland Sheepdog besteht eine Prädisposition. Zudem wird eine familiäre Häufung beim Beauceron beschrieben. Da die Rasse Working Kelpie im 19. Jahrhundert aus schottischen Hunden des Collie-Typs entstanden ist, wäre eine genetische Prädisposition für die Dermatomyositis erklärbar.

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Introduction

Dermatomyositis is a rare systemic immune-mediated disease, affecting humans and dogs (5, 19). A genetic background is proven in juvenile dermatomyositis in man (1, 14) and in canine familial dermatomyositis (9–12, 19). The hallmark of the pathogenesis is a chronic vasculopathy causing tissue ischemia. In dogs ischemic dermatopathies include five subtypes: canine familial dermatomyositis; juvenile-onset ischemic dermatopathy; focal post-rabies vaccination reaction; generalized vaccination-induced ischemic dermatopathy and adult-onset generalized ischemic dermatopathy (7). Common clinical symptoms are skin atrophy, scaly patches of alopecia or even scarring ulcers with a predominantly acral distribution (17). Progressive myopathy can lead to atrophy of masticatory muscles, megaesophagus and recurrent lameness or an abnormal "high-stepping" gait (15, 17).

Canine familial dermatomyositis has mainly been reported in the Shetland Sheepdog and the rough coated Collie (9, 11) but also in a family of Beaucerons and a litter of Portuguese Waterdogs (2, 3). The genetic basis remains elusive in humans and dogs (4, 14, 19). An autosomal dominant mode of inheritance with an incomplete penetrance is suspected in the Collie (12). In gene expression studies in Shetland Sheepdogs more than 200 altered genes, mostly encoding proteins related to the immune sys-

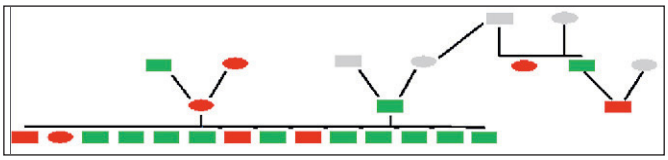


Fig. 1 Family tree showing the relationship between the affected animals. Circle: female, rectangle: male, red: affected, green: normal, grey: unknown status.

Abb. 1 Der Stammbaum zeigt die Verwandschaftsverhältnisse der betroffenen Tiere. Kreis: Hündin, Rechteck: Rüde, rot: betroffen, grün: gesund, grau: Status unbekannt.

tem, were found. Nonetheless no disease-specific autoantibodies were detected (19).

Case presentation

Patients and history

Eight members of a closely related cohort of Working Kelpies were presented with similar skin lesions and masticatory muscle atrophy of differing severity (▶Fig. 1). Based on severity and distribution of the lesions, dogs were divided into two groups: generalized/severe phenotype (group A; dogs 1–3) and mild phenotype (group B; dogs 4–8).

Dogs of **group A** showed early onset of cutaneous signs. Dog 1 (male) was 5 months old when owners noticed ulcerations and crusts on the distal tail and necrosis of the pinnae. Later on alopecia, erythema, erosions and superficial crusts appeared on the bridge of the nose, at the prepuce, distal limbs and paws. The nasal planum was depigmented (▶Fig. 2) and onychodystrophy and onychomadesis were present. Dog 2 and dog 3 were from the same litter and are full siblings of dog 1, who belonged to an earlier litter. First cutaneous signs occurred at the age of 4 months in dog 2 (male). At time of presentation, with 18 months of age, disease had progressed to severe atrophy of the masticatory muscles and multifocal alopecia at the bony prominences of the face. Nasal planum and ear margins were ulcerated with necrosis of the skin and cartilage of the pinnae (▶Fig. 3a, ▶Fig. 3b). Alopecia and smaller ulcerations were present on the tail and distal limbs, especially at the dorsal aspects of the digital joints. Generalized onychomadesis and onychodystrophy of the regrowing claws were noticed (▶Fig. 3c). Mild dry seborrhea and patchy alopecia were visible on the lateral trunk. Face and ears were pruritic and a "high-stepping gait" was shown. Owners of dog 3 (female) reported that onset of disease was at 4–5 months of age. This dog was presented at the age of 2.5 years. Masticatory atrophy was only mild and skin lesions were almost identical but not as severe as in dog 2 (▶Fig. 4). The dog also exhibited multifocal onychomadesis and onychodystrophy.

Dogs of **group B** (dogs 4–8) were less severely affected. Dog 4 (male), dog 5 (male) and dog 6 (female) showed alopecia and crusting on ear margins. In addition, dog 6 had facial hypotrichosis. Atrophy of the temporal muscles was noticed since puppyhood in dog 7 (female) (▶Fig. 5a). The disease progressed until the dog was one year of age: alopecia and scales on the tail and ear margins were observed (▶Fig. 5b). Thereafter no further progression was noticed until 7 years of age. Dog 8 exhibited mild ulcerations on the pinnal apex and atrophy of temporal muscles with 3 years of age.

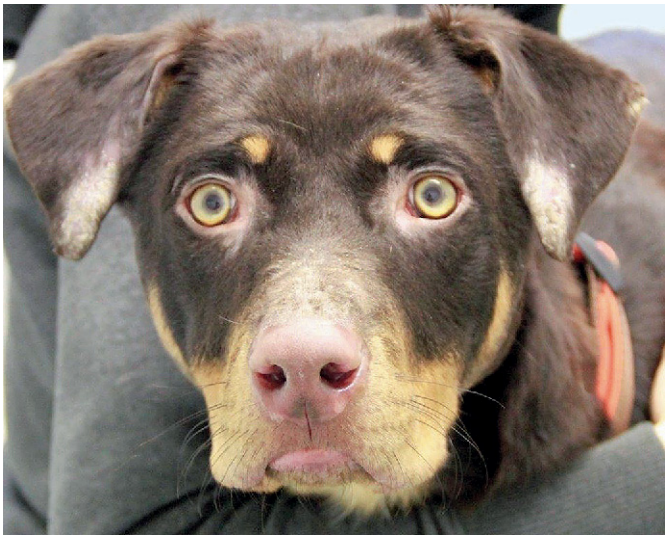


Fig. 2 Dog 1. Symmetric scales and crust on pinnae, hypopigmented nasal planum, eyelids and lips.

Abb. 2 Hund 1. Symmetrisches Auftreten von Schuppen und Krusten an den Pinnae, Depigmentation des Nasenspiegels, der Augenlider und der Lefzen.

Diagnostics

Differential diagnoses are shown in ▶Table 1. Diagnostic work up in group A included superficial and deep skin scrapings to rule out mite infestations. Skin scrapings and dermatophyte cultures were negative in all dogs. Leishmania antibody titer was negative in dog 1 and was not performed in dogs 2 and 3. They lived in a non-endemic area and neither they nor their mother had ever been abroad. Cytological examination showed a secondary bacterial infection of ulcerated lesions. Skin biopsies were taken from alopecic and crusted lesions of the flank, paws and face in all three dogs of group A. In all biopsies a marked follicular atrophy, especially of the secondary follicles was present. Dermal collagen fibers were smudged and their fibrillar character was lost (▶Fig. 6a). The walls of the capillaries and the small blood vessels were either hyalinised or mummified with loss of endothelial cells. Leukocytoclasia was rarely present. These findings are compatible with a cell-poor vasculitis (▶Fig. 6b).

Within the superficial, mid and deep dermis an interstitial scattered inflammatory infiltrate composed of mostly lymphocytes but also some neutrophils was seen. Multifocally, but mostly around the adnexa melanophages were present. The dermis was expanded

Fig. 3 Dog 2. a) Facial alopecia and crusts on the pinnae, hypopigmentation and ulcerations of the nasal planum. b) Alopecia, crusts, erythema and scales on the ear margins. c) Onychodystrophy, alopecia, erythema, scales and crusts on the distal extremities and the tip of the tail.

Abb. 3 Hund 2. a) Alopezie und Krusten im Gesicht und an den Pinnae, Depigmentierung und Ulzeration des Nasenspiegels. b) Alopezie, Krusten, Erythem und Schuppen an den Ohrrändern. c) Onychodystrophie, Alopezie, Erythem, Schuppen und Krusten an den distalen Gliedmaßen und an der Schwanzspitze.

by abundant edema. Some of the biopsies showed a cell-poor interface dermatitis and vacuolation of the follicular outer root sheath. According to the given history, histopathological diagnosis was ischemic dermatopathy compatible with canine familial dermatomyositis.

Treatment and outcome

Initial treatment consisted of prednisolone (2 mg/kg/24 h p. o.; CP-Pharma GmbH, Burgdorf, Germany), pentoxifylline (dog 1: 15 mg/kg/8 h p. o., dogs 2 and 3: 30 mg/kg/12 h p. o.; Trental®, Sanofi-Aventis GmbH, Frankfurt, Germany), vitamin E (600 mg/dog/24 h p. o., Doppelherz Vitamin E, Queisser Pharma GmbH, Flensburg, Germany) and omega-3 fatty acids (dog 1: 1 ml/10 kg/24 h p. o., Doils joint oil, Nutriceuticoils NV, Haaltert, Belgium, dogs 2 and 3: 500 mg/dog/12 h p. o., Super-Marine-Omega-3 Kapseln, Concept Vp, Schwerte, Germany) (▶Table 2).

Dog 1 additionally received doxycyline (5 mg/kg/12 h p. o., Ratiopharm GmbH, Ulm, Germany) and niacinamide (250 IU/dog/12 h p. o., Niacinamide 250 Jarrows Formulas®, Jarrow GmbH, Berlin, Germany) in the beginning. Initial response was satisfying and prednisolone was tapered to 1 mg/kg/48 h p. o. With lower doses the disease could not be controlled, so cyclosporine (5 mg/kg/24 h p. o., Atopica®, Novartis GmbH, München, Germany) was given for several months. After one year of therapy mycophenolate mofetil (15 mg/kg/24 h p. o., Cellcept®, Roche Pharma AG, Reinach BL, Switzerland) was used instead, due to inadequate response. Maintenance therapy consisted of mycophenolate mofetil (15 mg/kg/48 h p. o.), pentoxifylline (15 mg/kg/12 h p. o.) and essential fatty acids. In case of relapse prednisolone was added (1 mg/kg/24 h p. o.) and mycophenolate mofetil was given daily.

In dog 2 prednisolone was replaced by triamcinolone (0.2 mg/kg/24 h p. o., Volon®, Dermapharm AG, Grünwald, Germany) when polyuria and polydipsia occurred. Response to treatment was quick, ulcerations healed and hair partially grew back. Triamcinolone was tapered to a maintenance dose of 0.05 mg/kg/72 h p. o. and was raised in acute flares to 0.1 mg/kg/72 h p. o. In dog 3 the lowest dose of prednisolone to control the disease was 0.25 mg/kg/48 h p. o. In dogs 2 and 3 pentoxifylline and vitamin E were used as further long-term treatment.

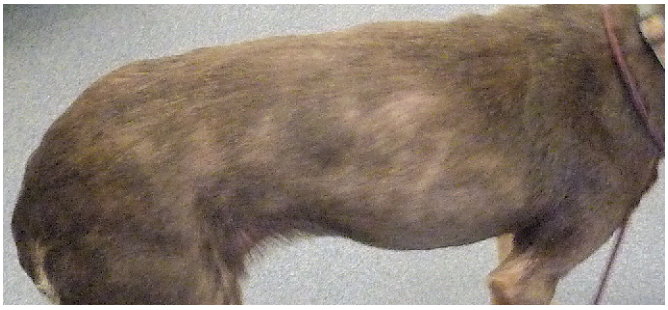


Fig. 4 Dog 3. Multifocal areas of alopecia and hypotrichosis on the trunk.
Abb. 4 Hund 3. Multifokale Alopezie und Hypotrichose am Rumpf.

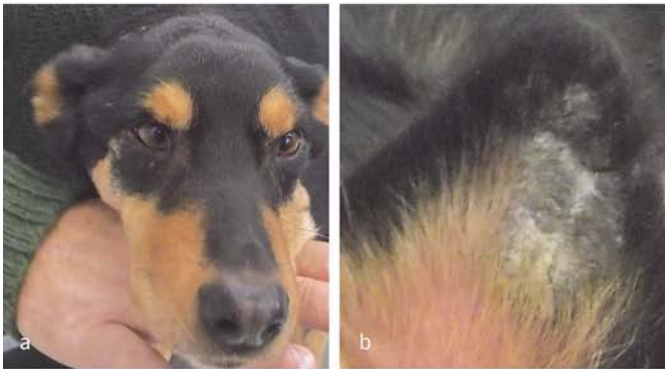


Fig. 5 Dog 7. a) Severe atrophy of temporal muscles. b) Mild crusts and scales on the ear margin.
Abb. 5 Hund 7. a) Hochgradige Atrophie der Temporalismuskulatur. b) Geringgradige Schuppen und Krusten an der Ohrspitze.

Table 1 Clinical differential diagnoses listed according to their probability.
Tab. 1 Klinische Differenzialdiagnosen geordnet nach ihrer Wahrscheinlichkeit

Immune-mediated diseases	Infectious diseases
Ischemic dermatopathy/dermatomyositis	Parasitic: leishmaniasis, sarcoptic mange, demodicosis
Vasculitis	Bacterial: pyoderma (secondary)
Cutaneous lupus erythematodes	Fungal: dermatophytosis, malassezia dermatitis (secondary)
Proliferative thrombovascular necrosis of the pinnae	
Symmetric lupoid onychodystrophy	
Uveodermatological syndrome	
Allergic dermatitis	

A supportive topical treatment was used in all three patients. Infected lesions were treated with chlorhexidine spray (Douxo® Chlorhexidin PS Mikroemulsion-Spray, Albrecht GmbH, Aulendorf, Germany) in dog 1 and with gentamicin/betamethasone creme (Diprogenta® Creme, Kohlpharma GmbH, Merzig, Germany) in dog 3. Hydrocortiosone-aceponate spray (Cortavance® 0.584 mg/ml Spray, Virbac GmbH, Bad Oldesloe, Germany) and mometasone creme (Ecural® Fettcreme, CC Pharma, Densborn, Germany) were used in non-infected lesions when needed in dog 1 and dogs 2 and 3, respectively.

None of the dogs went into complete remission and disease waxed and waned despite therapy. Maintenance treatment was adjusted according to the clinical signs during the follow-up period (36 months in dog 1, 14 months in dog 2, and 5 months in dog 3).

No diagnostic work-up and therapy was performed in dogs of group B at owners' request. Reexamination as adult dogs showed no progression of disease.

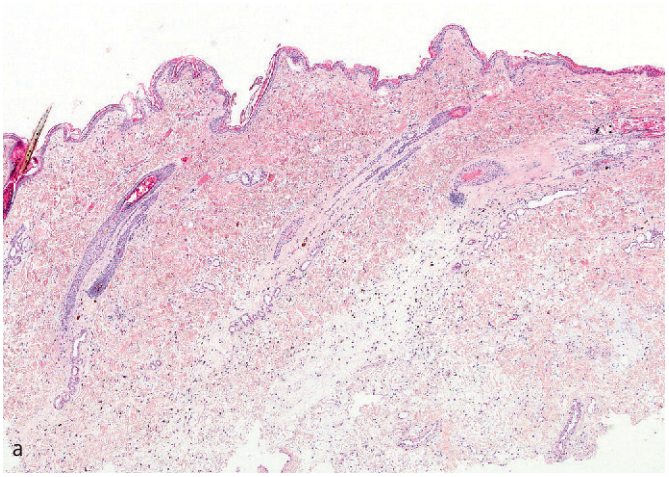
Discussion

To our knowledge this is the first case series of familial dermatomyositis in Working Kelpies. Dermatomyositis can occur in any dog breed, but a familial disposition is reported in rough coated Collies, Shetland Sheepdogs, Beaucerons and Portuguese Water Dogs (2, 3, 10, 11). Canine familial dermatomyositis is compared to juvenile onset dermatomyositis in humans (13, 17). Despite the hereditary component, environmental factors (UV-light, infectious agents, drugs, vaccines) may contribute to the disease in humans (1, 5). All here reported cases belong to the same family of Working Kelpies and multiple generations are affected. Therefore a genetic predisposition in this family is very likely. Presumably, the Kelpie derived from Scottish Collies in the 19th century (6). A close relationship between Collie and Kelpie could explain a genetic predisposition.

Differential diagnoses such as infectious diseases (demodicosis, leishmaniasis, scabies) and non-infectious diseases (cutaneous lupus erythematodes, uveodermatological syndrome, allergic dermatitis) were ruled out during the diagnostic work-up. Diagnosis of an ischemic dermatopathy, further classified as canine familial dermatomyositis, was based on the clinical and histopathological findings, which are compatible with literature (8, 9, 17). In chronic

Table 2 Overview of medical treatment in group A.
Tab. 2 Überblick über die medikamentöse Behandlung der Hunde aus Gruppe A

Therapy	Dog 1	Dog 2	Dog 3
Prednisolone	Initial: 2 mg/kg/24 h, tapered, discontinued, temporarily reintroduced in relapses	Initial: 2 mg/kg/24 h, tapered, discontinued due to side effects	Initial: 2 mg/kg/24 h; maintenance: 0.25 mg/kg/48 h
Triamcinolone		Initial: 0.2 mg/kg/24 h maintenance: 0.05 mg/kg/72 h	
Cyclosporine	5 mg/kg/24 h for several months		
Mycophenolate mofetil	15 mg/kg/24 h for 1 year, maintenance: 15 mg/kg/48 h		
Pentoxifylline	15 mg/kg/8 h, maintenance: 15 mg/kg/12 h p. o.	30 mg/kg/12 h	30 mg/kg/12 h
Doxycyline/ niacinamide	5 mg/kg/12 h 250 IU/dog/12 h for several months		
Vitamin E	600 mg/dog/24 h	600 mg/dog/24 h	600 mg/dog/24 h
Essential fatty acids	500 mg DHA/EPA/12 h	500 mgDHA/EPA/12 h	500 mg DHA/EPA/12 h
Various topicals	Chlorhexidine, hydrocortisone-aceponate spray	Mometasone creme	Initial: gentamicin/betamethasone creme (infected ulcerations), mometasone creme



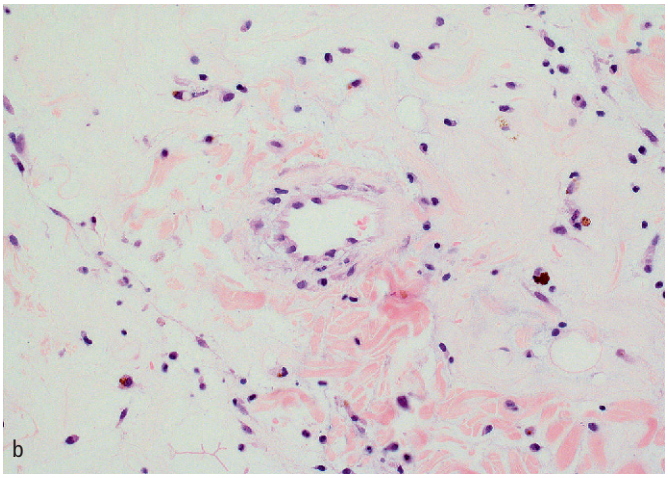


Fig. 6 Histological findings. a) Representative skin biopsy. Severe atrophy of the hair follicles and marked dermal edema, which is most severe around and underneath the adnexae. Scattered interstitial inflammatory infiltrate in the superficial, mid and deep dermis with melanophages. Hematoxilin and eosin (HE), 20x. b) Representative vascular lesion. Blood vessel showing activated endothelial cells. The vascular wall is partially hyalinized and disrupted and infiltrated by few lymphocytes and neutrophilic granulocytes. The blood vessel is surrounded by a severe edema. Interstitial infiltration of lymphocytes, plasma cells and scattered melanophages. HE, 400x.

Abb. 6 Histologische Befunde. a) Repräsentatives Hautbioptat. Hochgradige Atrophie der Haarfollikel, hochgradiges dermales Ödem, besonders ausgeprägt im Bereich der Adnexe. Es findet sich ein gemischtes, interstitielles Entzündungszellinfiltrat in der oberflächlichen, mittleren und tiefen Dermis mit Melanophagen. Hämatoxilin und Eosin (HE), 20x. b) Repräsentative Gefäßveränderungen. Das Blutgefäß zeigt aktivierte Endothelzellen. Infiltrate von wenigen Lymphozyten und neutrophilen Granulozyten in der teilweise hyalinisierten und unterbrochenen Gefäßwand. Das Blutgefäß ist umgeben von einem hochgradigem Ödem. Interstitielles Infiltrat von Lymphozyten und Plasmazellen, einzelne Melanophagen. HE, 400x.

cases classical histopathological features are follicular atrophy and smudging of dermal collagen as results of ischemia. Mild to moderate mucin deposition and edema may be found (7, 9). A cell-poor interface dermatitis is often present and a cell-poor vasculitis may be seen (7, 17). In dogs with clinical signs of myositis muscle biopsies can detect a mixed inflammatory infiltrate with lymphocytes and plasma cells and fibrosis of muscle fibres (17). A muscle biopsy could have confirmed the diagnosis, but this would have required general anesthesia. This invasive procedure was avoided, as the clinical and histopathological picture matched clearly with dermatomyositis. According to literature, muscle biopsies are not taken routinely in suspected cases and it is possible to establish the diagnosis without them (17).

Clinical onset in the predisposed breeds can be as early as 7 weeks of age (12). Patients can present with cutaneous lesions in combination with typical signs of myositis, but like in human medicine, disease can be limited to the skin and occasionally dogs are seen with only muscular disease (15). Cutaneous signs vary in severity and consist of scarring alopecia, erythema, depigmentation, cutaneous atrophy, ulcerations or erosions and onychodystrophy (7, 17).

Spontaneous remission has been described for milder cases and superficial lesions can heal without scaring (7, 15). In severe cases, early diagnosis with immediate treatment leads to a better prognosis (1, 14). Steroids are the initial treatment of choice, but their side effects can mimic signs of dermatomyositis. Therefore the use of corticoid-sparing drugs is recommended. Sometimes side effects are diminished by changing the corticosteroid (16). This was successful in dog 2, as severe polydipsia and polyuria occurred. Cyclosporine (calcineurin inhibitor), azathioprine (purine analogue) and mycophenolate mofetil (purine analogue), all affecting the T cell-mediated immunity, are often combined with glucocorticoids, especially in severe and refractory cases (1, 14, 16). In milder cases the combination of tetracycline/doxycyline and niacinamide is used because of its immune-modulating properties (16). The xanthine derivate pentoxifylline is an anti-inflammatory, hemorheologic agent and its positive effect on dermatomyositis is proven (18). Vitamin E, an antioxidative drug and essential fatty acids with anti-inflammatory properties may be beneficial (16).

Dogs in group A received various immune-modulating drugs with only partial response (Table 2). They require lifelong medication to alleviate clinical signs and to control recurrent flares. In dogs of group B, no further diagnostics were performed. Therefore dermatomyositis can only be suspected. Nevertheless, the described dogs were closely related family members, making dermatomyositis the most likely diagnosis.

Conclusion for practice

In dogs with primary non-pruritic skin disease with alopecia, acral ulcerations and crusts, atrophy of skin and masticatory muscles, ischemic dermatopathy should be considered. A thorough work-up to establish the diagnosis and to rule out differentials should be performed including cytology, skin scrapings, fungal culture, *Leishmania* antibody titer and skin biopsies.

Conflict of interest
The authors confirm that they do not have any conflict of interest.

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