Necrotizing eosinophilic dermatitis in three dogs

Necrotiserende eosinofiele dermatitis bij drie honden

[1]J. Declercq, [2]G. Vercauteren

[1]Small Animal Practice Jan Declercq, Poortersstraat 16-18, B-8510 Marke, Belgium
[2]Vet-Path bvba, Kruisken 9, B-9991 Adegem, Belgium

jan.declercq@dierenarts-jandeclercq.be

ABSTRACT

In this paper, necrotizing eosinophilic dermatitis with an acute onset and a rapidly progressive clinical course is reported in three dogs. Early skin lesions were characterized by intensely pruritic, erythematous and firm intact papules and plaques. The lesions enlarged and evolved quickly into coalescing nodular target shaped lesions with central exudation, ulceration and necrosis. The lesion distribution pattern was mainly the neck and the dorsolateral trunk. Oral involvement was observed in one dog. The histopathology was characterized by eosinophilic dermatitis and panniculitis targeting dermal and subcutaneous blood vessels with secondary involvement of hair follicles. While causation remained unproven in these cases, a hypersensitivity reaction to medications or other foreign antigens was suspected.

SAMENVATTING

In dit artikel wordt bij drie honden necrotiserende eosinofiele dermatitis beschreven met een acuut ontstaan en snel verloop. De eerste huidletsels werden gekenmerkt door intens jeukende erythemateuze en stevig aanvoelende intacte papels en plaques. De letsels werden snel groter en evolueerden tot samenvloeiende targetoïde nodulen met centrale exsudatie, ulceratie en necrose. De letsels kwamen hoofdzakelijk voor op de hals en op de dorsolaterale romp. Eén hond vertoonde ook orale letsels. Het histopathologisch beeld toonde in de drie gevallen eosinofiele dermatitis en panniculitis gericht op de dermale en subcutane bloedvaten met secundaire aantasting van de haarfollikels. Een overgevoeligheidsreactie op medicatie of op andere lichaamsvreemde antigenen kunnen mogelijk de oorzaak zijn geweest.

INTRODUCTION

Eosinophilic dermatitis in the dog is a reaction pattern of the skin and has been reported in a few clinical entities. The most common condition is eosinophilic furunculosis of the face (Gross, 1992; Curtis et al., 1995; White et al., 1995; Guaguère et al., 1996; Gross et al., 2005). It has a peracute onset with a rapidly fulminating course. Initial lesions are variably pruritic and later on painful. The lesions consist of hemorrhagic papules and pustules, as well as edematous nodules that ulcerate and crust. They develop predominantly on the face. The histopathology reveals a folliculocentric eosinophilic inflammation. Eosinophils infiltrate the hair follicle wall and accumulate both intramurally and intraluminally. Explosive follicular rupture is characteristic (furunculosis). Eosinophilic degranulation may focus around collagen fibers (flame figures). Severe dermal edema and dermal mucin deposition are frequently observed (Gross, 1992; Yager et al., 1994; Gross et al., 2005). Fibrinoid necrotizing vasculitis is rarely seen (Yager et al., 1994). The pathogenesis probably involves an acute hypersensitivity response to arthropod venom (particularly hymenoptera and spiders).

Canine cutaneous eosinophilic granulomas are relatively rare, present often solitary or in limited numbers and are characterized by nodules or plaques (Gross et al., 2005). The histopathology is identical to the feline eosinophilic granuloma, with eosinophils and granulomatous inflammation around eosinophilic-debris coated collagen. The proposed etiopathogenesis is a hypersensitivity reaction to insect bites, environmental or food allergens.

Canine eosinophilic dermatitis with edema, i.e. Wells'-like syndrome, is characterized by an acute onset of an intense erythematous maculopapular eruption, which is most pronounced on the ventral abdomen. Marked regional edema (facial, pinnae, hocks) also occurs in some cases. The histopathology is characterized by a marked eosinophilic inflammation, collagen flame figures and dermal edema. Hair follicles are not involved. More than 50% of the dogs reported developed the condition following treatment for severe gastrointestinal disease, and a causal drug association is proposed (Mauldin et al., 2006).

Dermatophytosis may occasionally have marked, eosinophil-predominated, folliculocentric inflammation associated with free hair and keratin in the dermis. Multifocal kerions may be considered in the differential diagnosis for nodular skin lesions with an eosinophilic infiltrate (Yager et al., 1994; Gross et al., 2005; Declercq et al., 2011), in addition to foreign body reactions and neoplasms.

The purpose of this paper is to report the occurrence of distinctive eosinophilic dermatitis in three dogs.

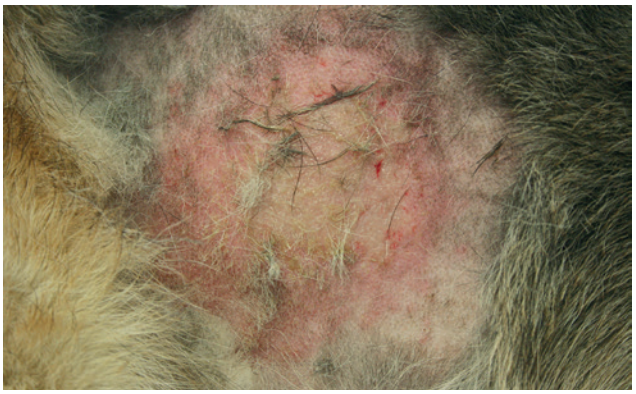

Figure 1. Right flank of the German shepherd dog in case one. The surrounding hair was clipped to enhance visibility. The picture illustrates an intermediate skin lesion that was characterized by a large, well-demarcated, erythematous plaque with central yellowish exudation and erosion.

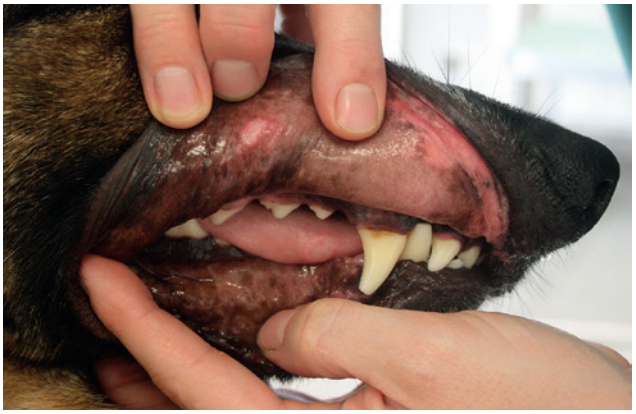

Figure 2. Oral cavity of the German shepherd dog in case one. Note the presence of an ulcerated plaque on the labial mucosa and a nodule with central ulceration on the right margin of the tongue.

CASE DESCRIPTIONS

Case 1

A three-and-a-half-year-old, intact, female German shepherd dog was presented with a weight bearing right forelimb lameness of a ten-days' duration. Physical examination revealed a moderately swollen and painful carpus. The radiograph of the joint did not reveal additional abnormalities. The dog was treated with a fourteen-day course of meloxicam oral suspension (Metacam, Boehringer Ingelheim, Ingelheim/Rhein, Germany) 0.1 mg/kg once daily with instructions for limited exercise on a leash. The dog was re-examined five days later, because it had suddenly developed severe pruritus that was associated with the presence of skin lesions. Before presentation, the patient had monthly preventive treatment against fleas. Physical examination revealed a pruritic dog with multifocal skin disease. Few but large lesions (7 cm in diameter) were present on the dorsolateral trunk, on the lumbosacral region, at the dorsal base of the tail and at the right lateral stifle. Two small lesions were seen in the oral cavity. Skin lesions were large, well-demarcated, erythematous and pruritic plaques with central yellowish exudation and erosion. The lesions could be easily mistaken for pyotraumatic dermatitis, i.e. 'hot spot' (Figure 1). The lesion on the tail had progressed to a more nodular shaped lesion with a central necrosis (eschar). Oral lesions consisted of an ulcerated plaque on the right labial mucosa and an ulcerated nodule on the right margin of the tongue (Figure 2). Coat brushings and skin scrapings were performed to rule out ectoparasitic diseases. By microscopic examination of collected skin debris, the presence of fleas or other ectoparasites could not be detected. Cytologic examination of a surface touch imprint revealed a purulent septic inflammation with phagocytized coc-shaped bacteria. Based upon the history of drug administration prior to the onset of the skin lesions, a cutaneous adverse drug reaction to meloxicam was now considered most likely. Skin biopsy specimens were taken from truncal lesions; the histopathological findings are described below. While awaiting the skin biopsy results, the owner was instructed to discontinue the meloxicam therapy. The dog received oral carprofen (Rimadyl, Zoetis, Louvain-la-Neuve, Belgium) 2 mg/kg twice daily and oral cephalexin (Keforal, Eurocept Pharmaceuticals, Ankeveen, the Netherlands) 20 mg/kg twice daily, based upon the presence of a bacterial infection. Dramatic resolution of the pruritus and the disappearance of the lesions occurred during the fourteen days following discontinuation of meloxicam. Oral carprofen and cephalexin treatment was continued for another week. The dog has remained clinically normal for many years following the cessation of the meloxicam administration.

Case 2

A fifteen-and-a-half-year-old, castrated, male Yorkshire terrier was admitted for large bowel diarrhea of

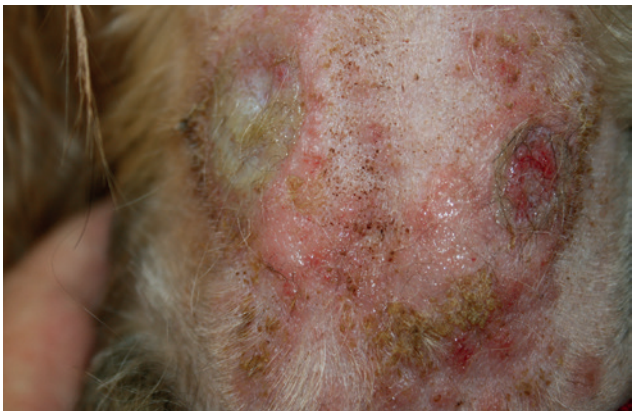

Figure 3. Ventrolateral position of the neck of the Yorkshire terrier in case two. The coat was clipped to enhance visibility. Note coalescing erythematous intact papular lesions (early lesions) and nodules with central exudation and ulceration (late lesions).

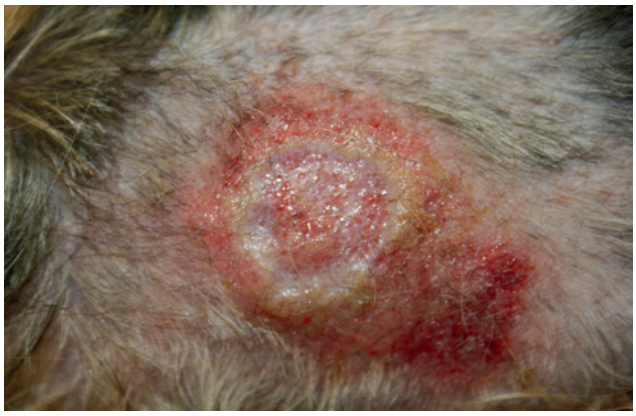

Figure 4. Ventrolateral position of the neck of the Yorkshire terrier in case two. The picture illustrates a typical late lesion, i.e. a nodule with cavitated ulceration in the center.

two-days' duration. On presentation, the patient was bright, alert and in fair body condition. General physical examination was unremarkable. The most likely differential diagnosis was felt to be dietary indiscretion. The dog was treated with a subcutaneous injection of dexamethasone (Rapidexon, Dechra, Lille, Belgium) at 0.1 mg/kg and with oral spiramycin-metronidazole (Stomorgyl, Merial, Diegem, Belgium) according to the instructions on the packing leaflet. The dog was re-examined eight days later because it had suddenly developed severe pruritus that was limited to the ventral neck. Dermatologic examination revealed severe dermatitis that involved the ventrolateral neck. The skin condition was characterized by coalescing erythematous and exudative papules and nodules (Figure 3). Two larger nodular lesions had a cavitated ulceration in the center (Figure 4). Cytologic examination of the lesions by fine-needle sampling showed numerous eosinophils and some neutrophils. Skin biopsies were obtained. The histopathological results are described below.

The proposed treatment included the discontinuation of the spiramycin-metronidazole treatment based on the possibility of a cutaneous adverse drug reaction, and an oral treatment with prednisolone. However, further treatment was declined and the owner requested euthanasia.

Case 3

A three-and-a-half-year-old, intact, female French bulldog with a history of atopic dermatitis was presented for recurrence of allergic dermatitis. The dog was treated with a subcutaneous injection of triamcinolone (Kenacort-A, Bristol-Myers Squibb, Brussels, Belgium) at 0.15 mg/kg and with a fifteen-day course of oral amoxicillin-clavulanate (Clavobay, Bayer, Diegem, Belgium) at 15 mg/kg twice daily. At the end of the oral treatment, the owner had noted a swelling of the left pinna. The dog was admitted for a second opinion. Physical examination revealed a large left-sided aural hematoma associated with otitis externa. Cytologic examination of stained samples taken from the ear canal showed *Malassezia* spp and coc-shaped bacteria. Topical ear treatment was initiated with an antimicrobial (marbofloxacin), antifungal (clotrimazole) and anti-inflammatory preparation (dexamethasone) (Aurizon, Vétoquinol, Aartselaar, Belgium). The aural hematoma was treated one week later by surgical drainage and tacking polypropylene sutures (Prolene, Johnson & Johnson, Dilbeek, Belgium). Seven days post-surgery, the dog was re-presented with an acute onset of intensely pruritic skin lesions. The owner had observed the first lesion on the left lateral thigh. On dermatological examination, lesions were mainly present on the entire neck and on the dorsolateral trunk. The face, pinnae, ventral abdomen and feet were not involved. The post-surgical healing of the left pinna was satisfactory. Early skin lesions consisted of erythematous firm papules and nodules. Intermediate skin lesions were coalescing nodules with central yellowish exudation, erosion and ulceration (Figure 5). Late skin lesions had a necrotic center with eschar formation (black adherent crust). In some areas, focal skin necrosis had resulted in dehiscence of unaffected skin (Figure 6). Fine-needle biopsy samples were taken from early and intermediate skin lesions. Cytological examination revealed a pyogranulomatous inflammation with numerous eosinophils but no bacteria. The clinical differential diagnoses included drug reaction and cutaneous vasculopathy/vasculitis. The rapidly progressive clinical course of the condition did not allow to await the results of the histopathological examination of the skin biopsies taken from early and intermediate lesions. These results are described below. The dog received oral prednisolone (Prednisolone, Kela Laboratories, Sint-Niklaas, Belgium) at 1.5 mg/kg once daily for two weeks. A rapid clinical response was observed and the stiches on the left pinna were removed. The treatment was then reduced to alternate days at the same dosage for another two weeks. At that time, the

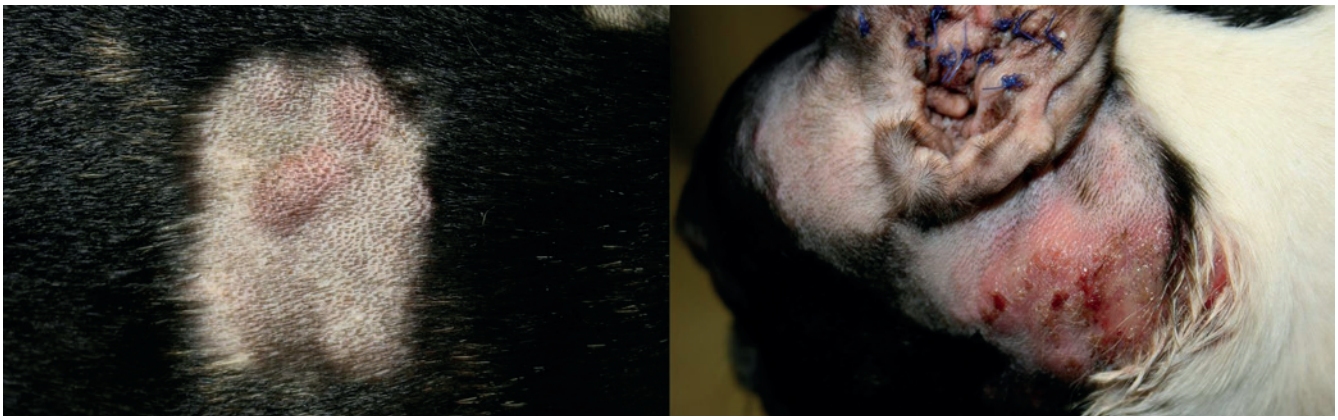

Figure 5. Early lesions (lateral trunk) and intermediate lesions (lateral neck) in the French bulldog in case three. The pictures illustrate lesion progression. Early lesions were erythematous and firm intact papules and nodules. Coalescing intermediate lesions were nodules with central exudation, erosion and ulceration.

Figure 6. Dorsal position of the neck and trunk of the French bulldog in case three. The picture was taken in a late stage of the condition. Late lesions were characterized by nodules with necrotic centers and eschar formation (black adherent crusting). Note the dehiscence of focal necrotic skin of unaffected skin.

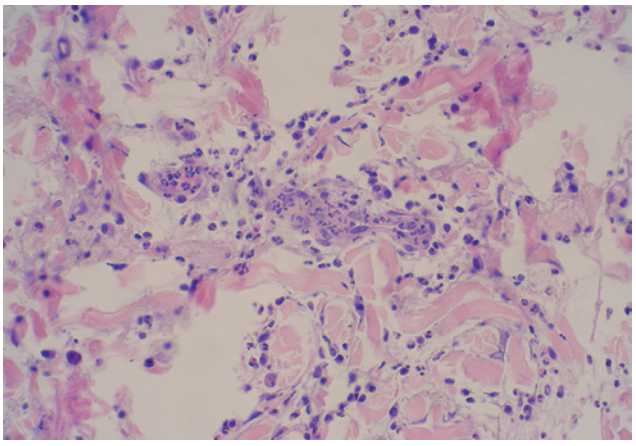

Figure 7. Vascular lesions of the German shepherd dog in case one. A smaller dermal blood vessel with thickening of the vessel wall due to infiltration of eosinophils and endothelial cell swelling. Within the vascular wall as well as in the perivascular tissue, there is mild fibrin deposition. The perivascular tissue is infiltrated with eosinophils, lymphocytes, plasma cells and histiocytes. Hematoxylin and eosin stain 400x.

lesions had completely resolved and the dosage was reduced to 1 mg/kg every other day for a final ten days. During the subsequent three years, there was no recurrence of the skin condition.

HISTOPATHOLOGICAL RESULTS

In all three cases, histopathology revealed an eosinophilic vasculitis with ischemic tissue damage and eosinophilic to mixed perivascular to interstitial dermatitis and panniculitis. Vascular lesions involved small, medium-sized and larger dermal and subcutaneous blood vessels (Figures 7, 8, 9). They consisted of swelling of the endothelial cells, mural infiltration of mainly eosinophils, fibrinoid change (fibrinoid deposits in or fibrinoid necrosis of the affected vessel walls) and intraluminal fibrin thrombi. Leucocytoclasia was, if present, minimal. In case two, several thrombi were infiltrated with young fibroblasts (early organization).

The surrounding, dermal and subcutaneous tissue was frequently edematous with multifocal fibrin exudation and sometimes microhemorrhage (Figure 7). Also, several areas of pallor of dermal collagen were found (Figure 8). In cases two and three, early fibroblast proliferation also occurred in the surrounding tissue. Vascular inflammation extended perivascularly where it admixed with lymphocytes, plasma cells, neutrophils and histiocytes (Figures 7, 8, 9). In case three, eosinophilic inflammation was associated with flame figure formation.

The overlying epidermis was multifocally, and in case two, almost diffusely necrotic with crusting and sometimes ulceration (Figure 10). In case one, there was focal superficial bacterial pustulation. Ischemic necrosis extended in the superficial dermis and also frequently involved hair follicle infundibula. In case two, ischemic necrosis extended in the mid-dermis to the level of the follicular isthmus. The wall and lumen of the follicles were sometimes infiltrated with eosinophils and neutrophils. In case three, there was associated follicular mucinosis. The deeper portions

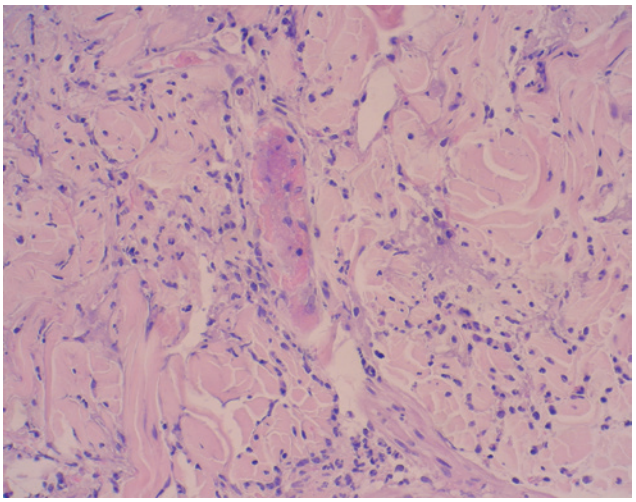

Figure 8. Vascular lesions of the German shepherd dog in case one. A smaller dermal blood vessel showing thrombosis. In the perivascular tissue, there is edema, multifocal pallor of the collagen and infiltration of eosinophils, lymphocytes, plasma cells and histiocytes. Hematoxylin and eosin stain 400x.

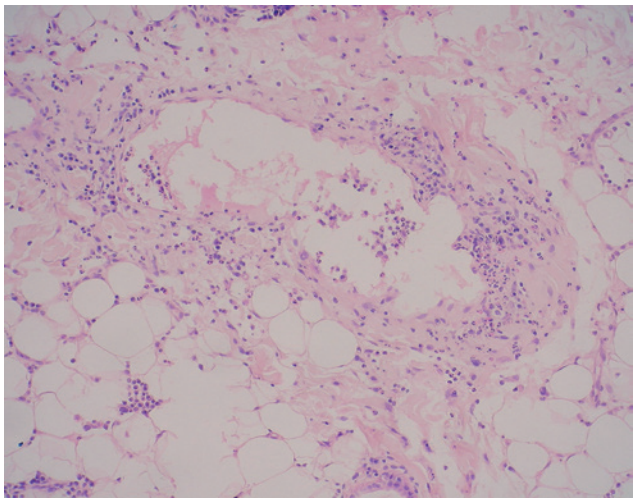

Figure 9. Vascular lesions of the Yorkshire terrier in case two. A larger subcutaneous blood vessel with mural infiltration of eosinophils and multifocal endothelial cell swelling. Very early fibrin clot in the vessel lumen. The perivascular tissue is infiltrated with eosinophils, lymphocytes, plasma cells and histiocytes. Hematoxylin and eosin stain 200x.

of the hair follicles as well as the remaining vital follicles showed frequent moderate to severe atrophy (Figure 10).

The necrotic tissue as well as the underlying intact tissue were variably infiltrated with neutrophils and eosinophils. In areas with necrosis of the overlying epidermis, the dermal infiltrate was more severe and diffuse and consisted of neutrophils variably admixed with plasma cells and fewer lymphocytes and histiocytes. In case two, the dermal inflammation underlying the necrotic tissue created a dense band-like infiltrate at the junction necrotic-vital tissue (Figure 10).

DISCUSSION

The three cases presented in this paper were selected on the base of similar clinical and histopathologic features. All dogs had an intensely pruritic eosinophilic skin condition characterized by an acute onset and rapidly progressive clinical course. Early lesions were characterized by erythematous and firm papules and plaques that progressed to nodular lesions with central yellowish exudation, ulceration and necrosis. These morphologic aspects indicated vascular involvement in the pathogenesis of this condition. The lesion distribution pattern was predominantly the neck and the dorsolateral trunk. Oral involvement was present in one dog. The face and the ventral surfaces of abdomen and thorax were not involved in any of the dogs. The condition in the three dogs had a varying disease severity and extensiveness. The dog in case one had a multifocal condition with a few lesions. The dog in case two had a regional condition with coalescing lesions that remained limited to the ventrolateral neck. The dog in case three had a more extensive and severe condition that involved larger parts of the body. None of the present cases satisfied the clinical criteria (pruritus severity score, morphologic aspects of the lesions, lesion distribution pattern) of the reported eosinophilic conditions in dogs (eosinophilic furunculosis of the face, cutaneous eosinophilic granuloma, canine Well's-like syndrome).

The histopathological features were similar in the three dogs and were characterized by eosinophilic

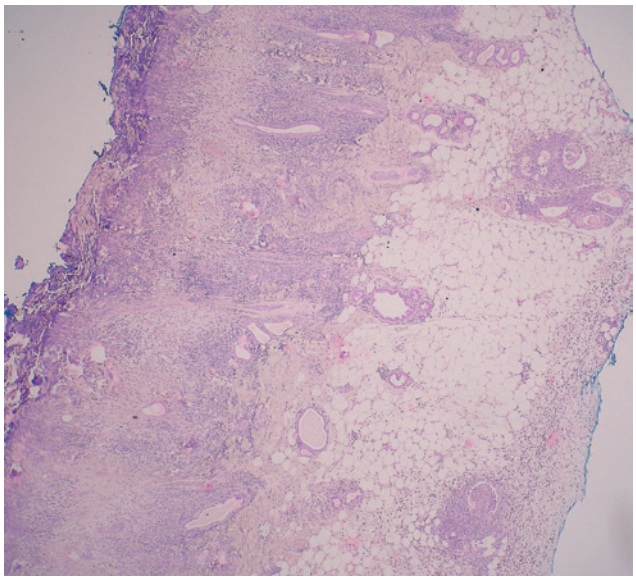

Figure 10. Affected skin of the Yorkshire terrier in case two. The epidermis, superficial dermis and superficial hair follicles are diffusely necrotic with crusting. Residual follicular structures are atrophic. The necrotic tissue is separated from the underlying vital tissue by a band-like inflammatory infiltrate. Even at low magnification, intravascular thrombi are apparent in the subcutaneous blood vessels. Hematoxylin and eosin stain 40x.

dermatitis and panniculitis targeting primarily dermal and subcutaneous blood vessels with secondary involvement of hair follicles. Prominent vascular lesions (eosinophilic vasculitis) and associated ischemic damage (epidermal, superficial dermal and follicular necrosis; pallor of the dermal collagen, follicular atrophy) have not been seen in other reported eosinophilic conditions in dogs.

Proving a cause-and-effect relationship in the present cases is difficult and speculative. The patient in case one had suddenly developed intensely pruritic skin lesions five days after receiving oral meloxicam. It was not known if the dog had previously received treatment with non-steroidal anti-inflammatory drugs of the oxicam-type. Withdrawal of the drug and treatment with cephalexin resulted in a dramatic resolution of pruritus with disappearance of the lesions within fourteen days. The close temporal relationship with the administration and discontinuation of the drug suggested a drug-induced causation. A cutaneous adverse drug reaction occurs seven to ten days after the first administration of the drug and most adverse drug reactions resolve within two weeks after removal of the suspected agent (Scott and Miller, 1999). The probability of a cutaneous adverse drug reaction by applying the Naranjo Probability Scale was estimated as probable.

The cause of the disease in the dog in case two, one week after being treated for diarrhea with oral spiramycin-metronidazole and with a subcutaneous injection of dexamethasone is not clear. Severe eosinophilic dermatitis, resembling Wells' syndrome mostly following treatment for gastrointestinal disease, which may have causal drug association (metronidazole), has been reported in dogs (Mauldin et al., 2006). Canine Wells'-like syndrome, i.e. eosinophilic dermatitis with edema, may be moderately pruritic. The lesions consisted of erythematous maculae and plaques located predominantly on the ventral surfaces of the abdomen and thorax. The histopathology was characterized by eosinophilic dermatitis and edema without follicular involvement. Mild vascular lesions have been reported but were never severe enough to suggest a primary vasculitis. The clinicopathological aspects of the condition in patient 2 were quite different. However, triggering of its condition by the administered spiramycin-metronidazole cannot be completely discarded.

The dog in case three had been exposed to various medications immediately prior to lesion development and had an ear surgery with non-absorbable suture material. Triggering by the administered drugs or by a tissue reaction involving non-absorbable suture material may be considered as possible inciting causes. The resolution of an atypical case of pemphigus foliaceus following removal of monofilament nylon suture material from the abdominal wall has been reported in a dog (Bell, 2001).

Response to treatment information was only available for cases one and three. Case one was treated by withdrawal of meloxicam and received instead carprofen for its initial forelimb lameness combined with cephalexin based upon the presence of a secondary bacterial infection. Case three had a rapid clinical response to oral prednisolone at 1.5 mg/kg.

In summary, in this paper, distinctive eosinophilic dermatitis is documented in three dogs with clinical and histopathological evidence of prominent vascular involvement in its pathogenesis. While causation remained unproven, a hypersensitivity reaction to drugs or other foreign antigens was suspected.

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