

Degenerative granulomatous mural folliculitis and cytotoxic dermatitis in a dog

Degeneratieve granulomateuze murale folliculitis en cytotoxische dermatitis bij een hond

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ABSTRACT

A variant of degenerative granulomatous mural folliculitis with cytotoxic dermatitis is reported in a dog that presented with multifocal, well-demarcated, annular alopecia with peripheral crusting. The skin condition might have been drug-induced and responded well to oral ciclosporin.

SAMENVATTING

In deze casus wordt een variant van degeneratieve granulomateuze murale folliculitis met cytotoxische dermatitis beschreven bij een hond aangeboden met multifocale, goed omschreven, annulaire alopecie met een korstige periferie. De mogelijk medicatie-geïnduceerde huidaandoening vertoonde een uitstekende respons op een orale behandeling met ciclosporine.

INTRODUCTION

Degenerative granulomatous mural folliculitis (DGMF) is a rare and presumed immunological alopecic syndrome in dogs. Only one case has been reported in the scientific literature (Scott, 1999), and a few additional cases have been mentioned in textbooks or abstracts (Gross et al., 1993; Gross et al., 2005; Welle et al., 2009; Miller et al., 2013). The wide range in severity and diversity of lesions noted, both clinically and histopathologically, suggests a multifactorial etiology. The most frequently documented cause of DGMF in dogs is drug reaction (Scott, 1999; Gross et al., 2005; Miller et al., 2013). The condition is clinically characterized by highly variable alopecia that may be multifocal or coalescing and generalized. Scaling and crusting may be present. In long-standing cases, alopecic skin often has a smooth, shiny appearance with variable degrees of hypopigmentation. Pruritus is usually not present (Scott, 1999; Gross et al., 2005; Welle et al. 2009). Histopathologic examination reveals granulomatous to pyogranulomatous mural folliculitis with destruction of follicles and sebaceous glands. There may be pronounced perifollicular granulomatous inflammation. Mural follicular inflammation includes histiocytes, lymphocytes and neu-

trophils. Multinucleated giant cells may be present. Interface dermatitis and apoptosis (increased eosinophilia of keratinocytes) are generally mild but uncommon (Gross et al., 2005; Welle et al., 2009). Endstage lesions may be severe follicular atrophy and dropout.

Cytotoxic dermatitis (interface) represents a number of reaction patterns that may occur in the skin consequent to the infiltration of reactive T lymphocytes (Yager, 2014; Affolter et al., 2015). This term focuses on cell death of keratinocytes and hence, includes single cell necrosis/apoptosis of basal cell as well as more superficial keratinocytes. This can occur with or without an inflammatory infiltrate that obscures the dermo-epidermal junction. The aim of this report is to describe a mixed pattern of degenerative granulomatous mural folliculitis and cytotoxic dermatitis in a dog.

CASE DESCRIPTION

A seven-year-old, intact, male Miniature poodle was presented to the referring veterinarian with alopecic and crusted lesions on the dorsal neck and thorax. Apart from the skin lesions, the dog appeared to be in good health. One month prior to the onset



Figure 1. Right dorsolateral thorax of the dog. A small area, on the left side of the picture was clipped for visualization. Coalescing and well-circumscribed annular hyperpigmented patches with alopecia in the center and scaling and crusting at the peripheral borders.

of the skin condition, the dog had been treated for coughing with amoxicillin clavulanate (Clavubactin, Le Vet Pharma, Oudewater, the Netherlands) at 12.5 mg/kg twice daily for ten days and tolfenamine-acid (Tolfedine, Vétoquinol, Aartselaar, Belgium) at 3 mg/kg once daily for three days. The skin lesions were treated with a topical phytopharmacum containing Melaleuca, Origanum, Cinnamomum and Cymbopogon (Curax gel, Phytovet, Putte, Belgium). In spite of this treatment, the dog had developed new lesions and became pruritic. Systemic treatment was initiated with cefalexin (Therios, Sogeval, Laval, France) at 20 mg/kg twice daily. Whilst on cefalexin therapy, the skin condition had worsened rapidly. Based upon the results of a bacterial culture and antibiotic sensitivity

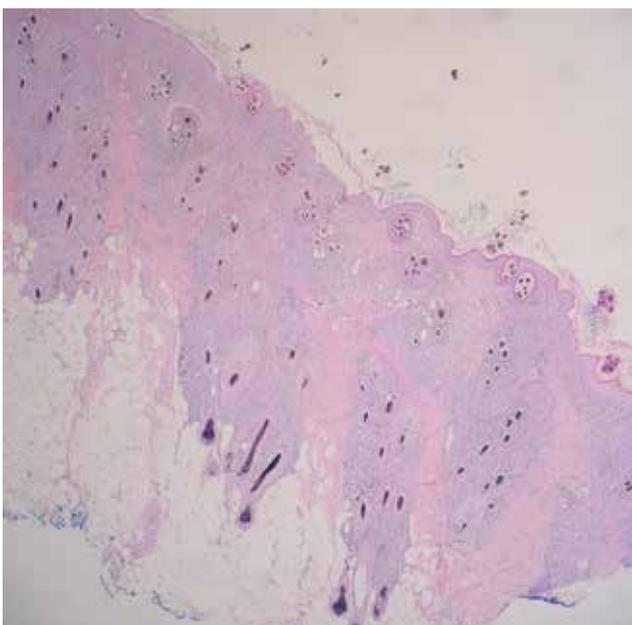


Figure 3. Overview of panfollicular inflammation with loss of sebaceous glands. Hematoxylin and eosin stain, 100x.



Figure 2. Dog in left lateral decubitus, anterior view of the right stifle. Alopecic hyperpigmented skin with patchy hypopigmentation and a shiny appearance.

testing, the treatment was changed to marbofloxacin (Marbocyl, Vétoquinol, Aartselaar, Belgium) at 2 mg/kg once daily. As the skin lesions also had failed to respond to the last treatment, the dog was referred with a three-month course of skin disease.

At referral, the history and physical examination revealed no abnormalities other than moderate pruritus associated with an alopecic cutaneous eruption. The condition was more or less symmetrical and limited to the top of the head, the entire neck, over the dorsolateral thorax, and on all aspects of the limbs. The skin lesions were coalescing, well-circumscribed, annular hyperpigmented patches with alopecia in the center and severe scaling and crusting at the peripheral borders. Removal of the crusts revealed ulcerations

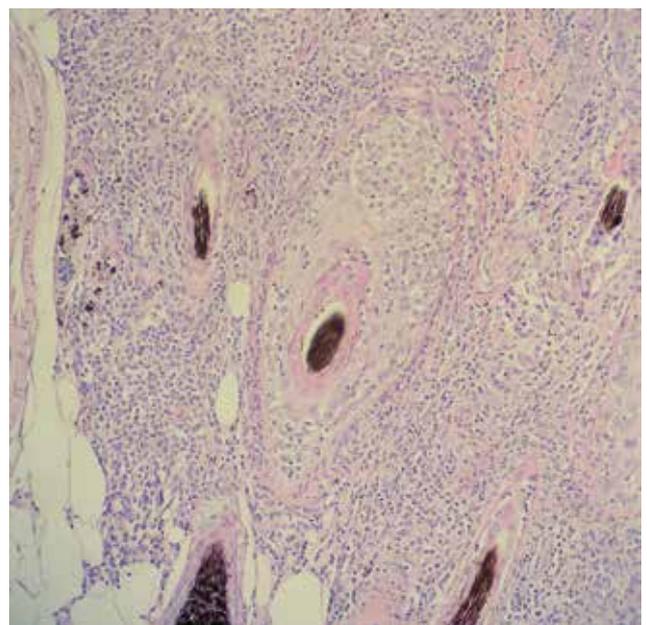


Figure 4. Closer view of an inflamed follicle. Histiocytes within the follicular wall and perifollicular infiltration of mainly lymphocytes and plasma cells. Hematoxylin and eosin stain, 200x.

(Figure 1). The exposed skin on the limbs was hyperpigmented with foci of hypopigmentation and had a smooth shiny appearance (Figure 2). The peripheral lymph nodes were normal. Clinical differential diagnoses included, but were not limited to, cutaneous adverse drug reaction (CADR), erythema multiforme (EM) and generalized discoid lupus erythematosus (GDLE). Two excisional biopsy specimens were taken from the lateral thorax. Histopathological examination showed two reaction patterns. The predominant pattern was a granulomatous to pyogranulomatous mural folliculitis tracking down the full length of the hair follicles (from the infundibulum to the hair bulb) with loss of sebaceous glands (Figure 3). Mural inflammation included mainly histiocytes, neutrophils, lymphocytes and a few multinucleated giant cells (Figure 4). Neutrophilic luminal folliculitis was seen in the superficial portions of the hair follicles. There was a multifocal mild to moderate perifollicular infiltration of lymphocytes, plasma cells and less histiocytes. Endstage lesions were complete drop out of hair follicles and loss of sebaceous glands, often with aggregates of melanophages (Figure 5). The second and minor pattern was a multifocal mild interface dermatitis with scattered transepidermal single cell necrosis, occasionally with lymphocytic satellitosis and a moderate pigmentary incontinence (Figures 6 and 7). These areas occasionally had severe overlying serocellular crusting. The hair follicles showed similar but minor changes. A diagnosis of mixed degenerative granulomatous mural folliculitis and cytotoxic dermatitis was made.

The history and histopathological findings were considered to be consistent with CADR. The dog was treated with ciclosporin oral solution (Neoral Sandimmun, Novartis, Vilvoorde, Belgium) at 6 mg/kg once daily. Six weeks later, a marked clinical improvement was noticed. The dog was no more pruritic and the lesions had progressively regressed. The treatment was continued at the same dosage for another two months. After that time, the lesions had resolved completely and there was residual cicatricial alopecia.

DISCUSSION

The main clinical feature of degenerative granulomatous mural folliculitis is alopecia that may be patchy and multifocal, or coalescing and generalized. Erythema, scaling and crusting may be present. Advanced cases reveal a shiny smooth alopecic skin with variable degrees of hypopigmentation (Scott, 1999; Gross et al., 2005; Welle et al., 2009). The prominent clinical features in the dog of this report were alopecia and crusting. The skin lesions on the dorso-lateral thorax were well-demarcated, hyperpigmented patches with alopecia in the center and severe scaling and crusting at the peripheral borders. Severe crusting is not a prominent feature of DGMF. The clinical lesions of the present dog resembled those that have

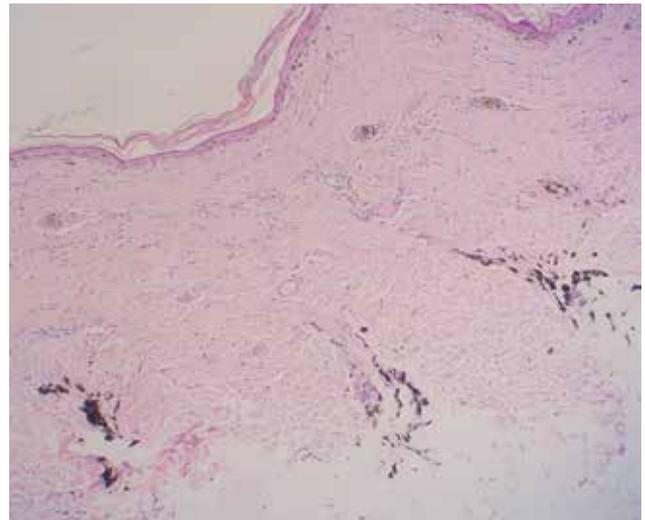


Figure 5. Endstage lesions. Hair follicles are completely eradicated. Melanomacrophages indicate previous follicular structures. Minimal superficial dermal inflammation. Hematoxylin and eosin stain, 100x.

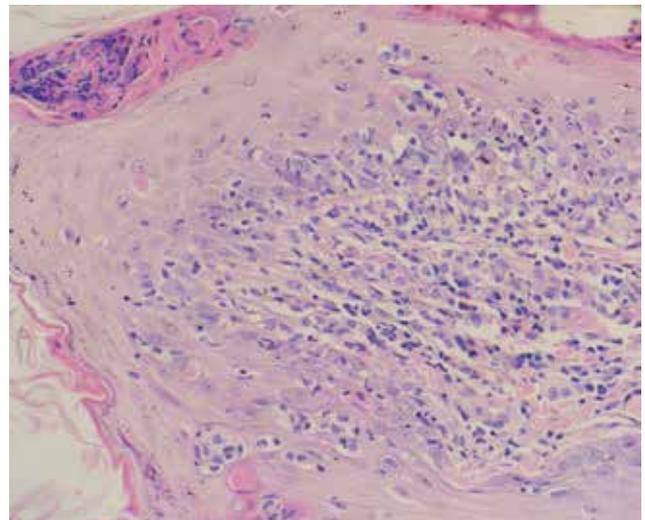


Figure 6. Mild lymphocytic-rich interface dermatitis with scattered keratinocyte apoptosis in multiple epidermal levels. Note suprabasilar keratinocyte apoptosis with lymphocytic satellitosis. Hematoxylin and eosin stain, 400x.

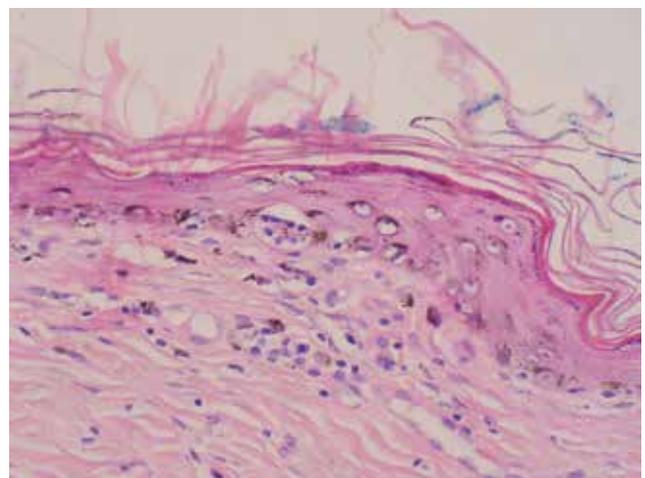


Figure 7. Cell-poor interface dermatitis with a basal keratinocyte apoptosis with lymphocytic satellitosis. Hematoxylin and eosin stain, 400x.

been reported in GDLE (Banovic et al., 2016) and in erythema multiforme (Yager, 2014). The alopecic lesions on the extremities revealed hyperpigmentation of the skin with foci of hypopigmentation and the exposed skin had a smooth shiny appearance. These features were consistent with those described in advanced cases of DGMF.

The predominant pattern on histopathology in the present case was degenerative granulomatous to pyogranulomatous mural folliculitis with loss of sebaceous glands and sequential diffuse effacement and drop out of hair follicles. The histopathology of DGMF may have marked perifollicular granulomatous inflammation tracking down along the hair follicles (Gross et al., 2005; Welle et al., 2009). Perifollicular inflammation in this case was mainly lymphoplasmacytic and mild to moderate. Severe granulomatous perifollicular inflammation was not observed. Histiocytes and giant cells can infiltrate the walls of follicles secondary to follicular necrosis with subsequent granulomatous inflammation towards hair shafts mimicking primary granulomatous mural folliculitis (Gross et al., 1993). A secondary inflammatory event was considered unlikely as granulomatous mural inflammation was present in intact hair follicles. GDLE may be considered as a differential diagnosis clinically and histopathologically. Lymphocytic mural folliculitis does occur in GDLE, although the predominant microscopic feature in this condition is a lymphocyte-rich interface dermatitis (Banovic et al., 2016). In the dog of this report, lymphocytes were mainly part of the perifollicular inflammation. In the present case, the interface dermatitis was only a minor pattern and was multifocal and mild. The cytotoxic component was characterized by a mild interface dermatitis with scattered keratinocyte apoptosis of multiple epidermal levels, very occasionally with a lymphocytic satellitosis. This last finding is also seen in GDLE (Banovic et al., 2016) and is a more florid finding in EM. The histological lesions differed from 'classic' EM in that there was less basilar apoptosis and hydropic degeneration and a lower degree of superficial keratinocyte apoptosis (Gross et al., 2005; Yager, 2014). The histopathologic patterns did not support the diagnosis of GDLE or EM. The skin condition was diagnosed as a variant of DGMF with a lymphocyte-mediated, cytotoxic component.

The history and mixed histopathologic reaction patterns were considered to be compatible with CADR. A drug reaction occurs at least 7-10 days after the first administration of the drug (Scott et Miller, 1999). The dog in the present report developed clinical signs after treatment with amoxicillin clavulanate for ten days and with tolfenamine-acid for three days; both are commonly incriminated drugs. The dog had not received tolfenamine-acid previously and therefore amoxicillin clavulanate was likely to be the causative drug. The owner had observed the initial skin

lesions twenty days after amoxicillin clavulanate had been discontinued. This timing of events was unusual as most cutaneous adverse reactions to drugs resolve within two weeks with removal of the suspected agent (Scott and Miller, 1999). The skin condition in the Miniature poodle had rapidly progressed when cefalexin treatment was initiated, which can be considered as a minor rechallenge. Amoxicillin clavulanate and cefalexin are related drugs of the same class, the beta-lactam family of antibiotics. The probability of CADR by applying the Naranjo system was estimated as probable. The drug-induced etiology for the dog reported here must still be regarded as putative as no rechallenge using the suspect medication was performed, a criterion not applicable for ethical considerations.

In conclusion, in this report, a dog is presented with DGMF and cytotoxic dermatitis. The condition might have been drug-induced and responded well to oral ciclosporin.

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