Putative paraneoplastic pemphigus in a dog: clinical and microscopic findings

Mogelijke paraneoplastische pemfigus bij een hond: klinische en microscopische bevindingen

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ABSTRACT

In this case report, a dog with clinical and histopathological features of paraneoplastic pemphigus is described. A Lhasa apso with severe ulcerative oral and predominant facial skin disease had a thoracic mass histopathologically diagnosed as a thymoma. A concurrent disease-association was suspected. Cytologic examination of the oral lesions provided early clues to the dog's ulcerative condition.

SAMENVATTING

In dit artikel wordt een hond beschreven met klinische en histopathologische symptomen van paraneoplastische pemfigus. Een lhasa apso met ulceratieve stomatitis en een voornamelijk faciale dermatitis vertoonde een thoracale massa, histopathologisch gediagnosticeerd als een thymoom. Een oorzakelijke associatie van de huidaandoening en het thymoom werd verondersteld. Het cytologisch onderzoek van de orale letsels was een vroege aanwijzing voor een mogelijke diagnose van paraneoplastische pemfigus.

INTRODUCTION

Paraneoplastic pemphigus (PNP) is a very rare, severe ulcerative autoimmune disease affecting the mucosa and mucocutaneous junctions. It is seen in conjunction with neoplasia and is considered a 'marker' of internal disease (Olivry, 2004; Gross et al., 2005; Elmore et al., 2005). The histopathology of the skin lesions reveals suprabasilar epithelial acantholysis typical of pemphigus vulgaris (PV), as well as keratinocyte apoptosis with satellitosis resembling lesions of erythema multiforme (EM). Mild lymphocytic interface dermatitis has been described in the literature (Olivry, 2004).

Three cases of PNP have been reported in dogs, one with a thymoma (Stannard et al., 1975), one with a thymic lymphoma with hepatic metastasis (Lemmens et al., 1998) and one with a splenic sarcoma (Elmore et al., 2005). In a meta-analysis of three dogs with PNP, all three exhibited skin lesions for two to four weeks prior to diagnosis (Olivry, 2004). In all dogs, there were extensive erosions and ulcers in the oral cavity, at mucocutaneous junctions as well as in haired skin. The lesions originated in the oral cavity, and oral involvement was always severe. The dogs exhibited halitosis, hypersalivation and anorexia. Systemic signs consisted of hyperthermia, lethargy and depression.

Two cases have been described in dogs with typical clinical and histological features of PNP (Olivry et al., 2000; Gross et al., 2005). The dogs showed no evidence of neoplasia upon systemic evaluation. A variant of spontaneous PV was the proposed diagnosis in one of the dogs (Olivry et al., 2000), and drug reaction was suspected in the other dog (Gross et al., 2005).

In the present paper, the clinical and microscopic findings in a dog with putative paraneoplastic pemphigus are described.

CASE DESCRIPTION

An eight-year-old, intact, male Lhasa apso was referred for diagnosis and treatment of a severe and painful ulcerative condition of a two-months duration, involving the oral cavity, and perioral and nasal mucocutaneous junctions. Up till then, treatment had consisted of a variety of antibiotics perorally and a dental care procedure with poor results.

On admission, the dog was lethargic, drooling, anorectic and had a rectal temperature of 39.3°C. Physical examination revealed an oral and predominantly facial skin disease. Severe ulceration was present on the tongue ('sloughing' glossitis and formation of pseudomembranes), hard and soft palate, buccal and labial mucosa, haired and non-haired lips and chin (Figure 1). Less severe ulceration was observed at the mucocutaneous junctions of the nose, around the eyes and on the forelimbs. Tentative clinical diagnoses were erythema multiforme, drug reaction, autoimmune skin disease and epitheliotrophic T-cell lymphoma.

Initial laboratory tests included a blood urea and creatinine evaluation. Both values were in the normal reference range and the dog was anesthetized for further examination. Cytologic examination was performed on scraping smears of labial mucosa obtained by means of a curette. In all samples, there was a predominance of epithelial cells, which were accompanied by a purulent inflammation, moderate numbers of small lymphocytes and eosinophils, and a small number of mast cells. Epithelial cells were observed in large sheets or clusters and as numerous individual cells. Small lymphocytes were frequently arranged around rounded single epithelial cells (satellitosis) (Figure 2). Neutrophils with intracytoplasmatic cocci were also present. Biopsy specimens of labial mucosa and lips were obtained. While awaiting the results of the histopathological examination, the dog was treated with oral prednisolone (Prednisolone, Kela Laboratories, Sint-Niklaas, Belgium) at 1.5 mg/kg once daily and with cefovecin (Convenia, Zoetis Belgium SA, Louvain-la-Neuve, Belgium) 8 mg/kg one-time only subcutaneously. Histopathology of mucosal and skin biopsies revealed mixed morphologic patterns of suprabasilar acantholysis consistent with pemphigus vulgaris (PV) and scattered individual keratinocyte apoptosis and satellitosis consistent with erythema multiforme (EM). Suprabasilar acantholysis with residual basal cells and irregular acantholysis affecting multifocally the lower spinosum, resulted in large clefts that often had numerous acantholytic cells within the lumen of the cleft (Figures 3 and 4). Keratinocyte apoptosis was not always associated with satellitosis and was not often concurrently observed with epidermal clefting (Figure 5). Some sections had numerous eosinophils within the lesional epidermis and adjacent superficial dermis (Figure 6). Lymphocytic interface dermatitis was not identified. The dermis or submucosa contained an infiltrate of lympho-

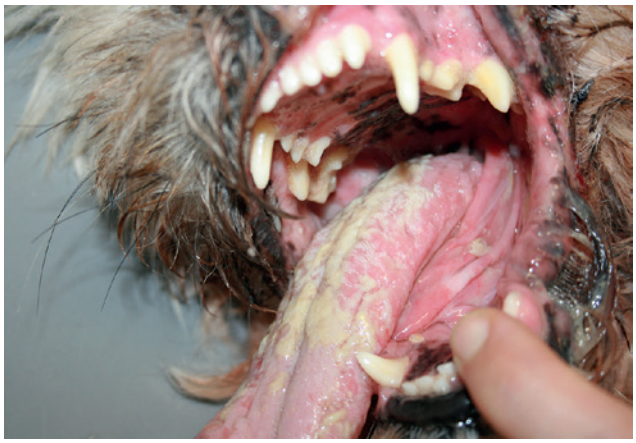

Figure 1. Tongue of the Lhasa apso at initial presentation. Severe ulcerative glossitis and ulceration of the oral mucosa are present. Note the yellowish sheets of sloughed lingual mucosa (pseudomembrane formation).

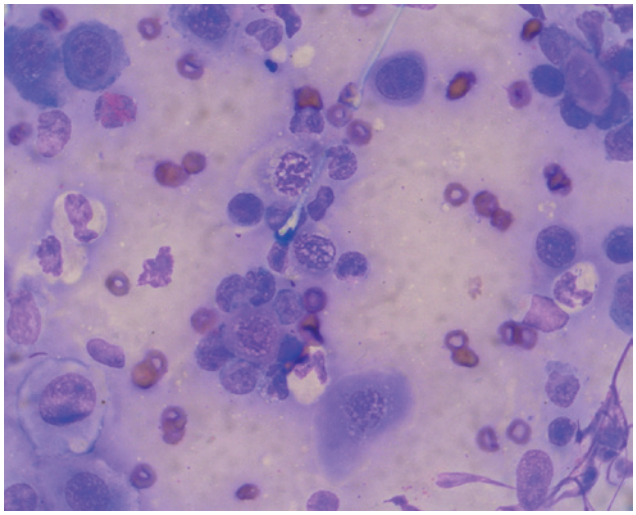

Figure 2. Cytologic view of a scraping smear of labial mucosa of the Lhasa apso. Note the presence of four rounded individual epithelial cells with lymphocytic satellitosis. Diff-Quik stain 400x.

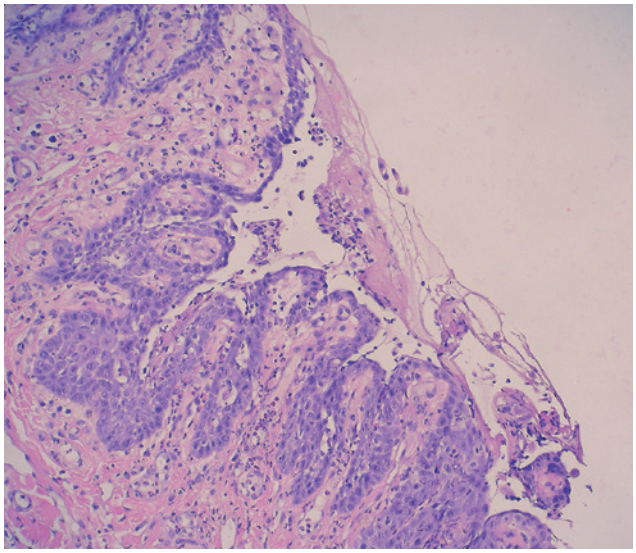

Figure 3. Photomicrograph of the lip of the Lhasa apso. Suprabasilar acantholysis and acantholysis affecting the lower spinosum.

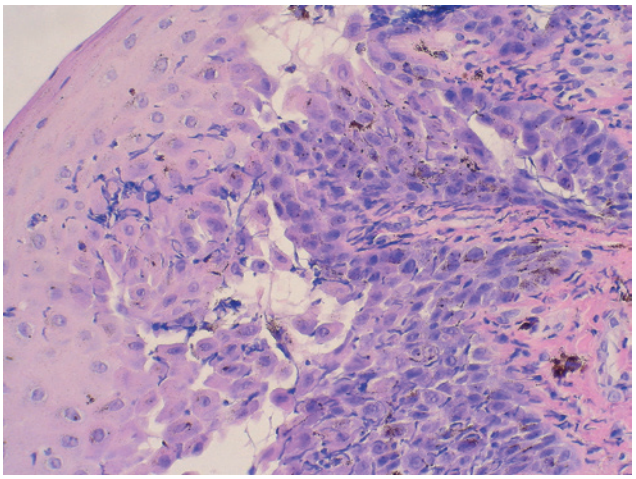

Figure 4. Photomicrograph of the oral mucosa of the Lhasa apso. Irregular acantholysis affects the lower spinosum, leaving multiple layers of keratinocytes on the floor of the cleft. Note the presence of numerous acantholytic cells within the lumen of the cleft. Hematoxylin and eosin stain 400x.

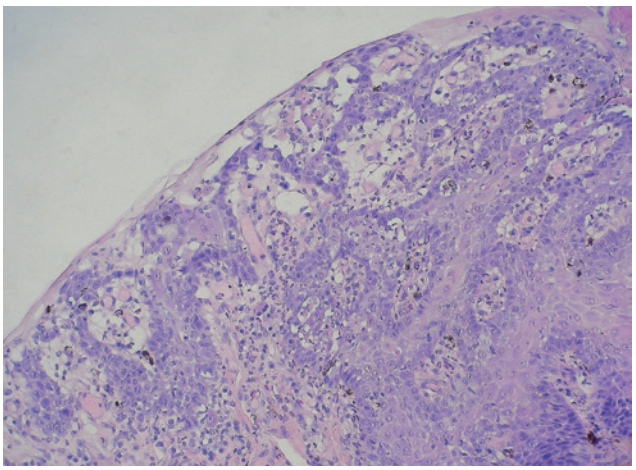

Figure 5. Photomicrograph of the lip of the Lhaso apso. Note suprabasilar acantholysis and scattered keratinocyte apoptosis with and without lymphocytic satellitosis. Note the presence of eosinophils within the dermal infiltrate. Hematoxylin and eosin stain 200x.

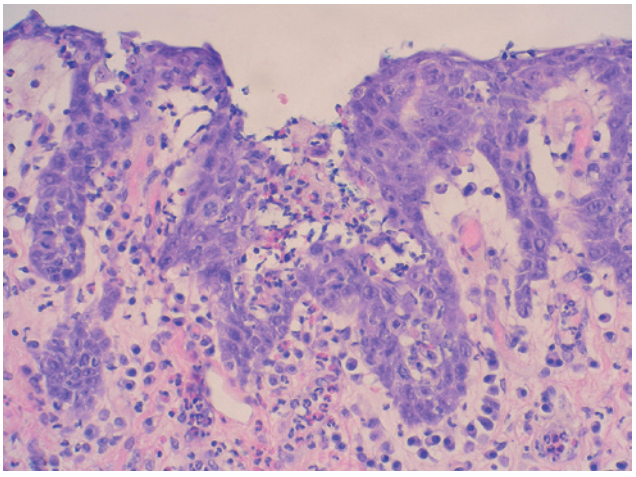

Figure 6. Photomicrograph of the lip of the Lhasa apso, illustrating the presence of numerous eosinophils in lesional epidermis and subjacent superficial dermis. Hematoxylin and eosin stain 400x.

cytes, macrophages and plasma cells. Occasionally, in some sections, eosinophils predominated the dermal infiltrate.

Clinical and microscopic findings were considered consistent with a diagnosis of PNP. The dog was screened for the presence of an internal neoplasia. Abdominal ultrasound did not reveal any abnormalities. Radiography of the thorax revealed a large mass in the cranial thorax (Figure 7). Ultrasound guided fine-needle aspiration of the mass was performed. Tissue samples were of low cellularity and revealed small, well-differentiated lymphocytes; no epithelial cells were found to support the presumptive diagnosis of thymoma.

At that time, the cutaneous signs of the skin condition had already been present for five months, and the dog did not show respiratory signs. The extent and severity of the lesions had continued to worsen despite treatment with glucocorticoids. The dog exhibited a severe ulcerative dermatitis affecting the oral mucosa, mucocutaneous junctions of the face, chin, ventral neck and forelimbs. The footpads were unaffected (Figures 8 and 9). The owner declined surgical removal of the thoracic mass and requested euthanasia. Post-mortem examination revealed a multilobulated and cystic mass in the cranial mediastinum. The histopathological diagnosis was thymoma.

DISCUSSION

In this paper, a dog presenting with clinical and histopathological features of PNP is described. The dog had a severe and painful ulcerative condition involving the oral cavity, mucocutaneous junctions as well as haired skin. Lesions included erythema and extensive ulceration. Severe oral ulceration is a hallmark of PNP in the dog. The histopathologic findings of suprabasilar acantholysis and keratinocyte apoptosis were consistent with the diagnosis of PNP, in which mixed morphologic patterns are typically found and mostly consist of concurrent microscopic features of both pemphigus vulgaris and erythema multiforme (Gross et al., 2005). Suprabasilar acantholysis was not often strictly above the basal cell layer in the dog of the present report, as is seen in classical pemphigus vulgaris, but also affected the lower spinosum, a microscopic feature of PNP, which has been recognized in the dog (Gross et al., 2005). In classical pemphigus vulgaris, suprabasilar clefts contain occasionally free-floating acantholytic keratinocytes (Gross et al., 2005). The histopathological findings in the dog of the present report were characterized by epithelial clefts with numerous free keratinocytes in the lumen. All these findings differed from ‘classic’ PV; hence, the term PV-like condition could be considered in this case. Lymphocyte-rich interface dermatitis with apoptosis of basal and suprabasilar keratinocytes is a hallmark of EM. In two cases of PNP, only mild lymphocytic interface dermatitis has been described (Lemmens et al., 1998; Elmore et al., 2005). Erythema multiforme

associated with thymoma and treated with thymectomy has also been reported in a dog with hyperemic stomatitis and skin lesions (Tepper et al., 2011). Histopathology of the erythema multiforme case revealed individual keratinocyte necrosis and hydropic degeneration of the basal layer of the epidermis and florid interface. These findings are consistent with 'classic' EM. As true lymphocytic interface dermatitis was not observed in the present case, lymphocytic cytotoxic dermatitis is a more appropriate term. A remarkable microscopic finding in cytologic and histologic samples of the dog of this report, was the presence of eosinophils. The dog had no history of allergic skin disease or parasitic dermatitis. The role of eosinophils in the pathogenesis of its skin condition is not clear.

Histopathology and immunologic studies, including the identification of targeting antigens, as well as the documentation of underlying neoplasia, are required for the diagnosis of PNP (Gross et al., 2005). Direct and indirect immunofluorescence studies were not performed in the present report as these techniques are not routinely available. To obtain a definitive diagnosis of PNP and to prove that the skin lesions and neoplasia are not two separate entities, the disappearance of the skin lesions with tumor removal and their recurrence with tumor regrowth should be demonstrated (Elmore et al., 2005; Hill et al. 2013). In the dog of this report, the requested euthanasia of the patient precluded this type of clinical assessment.

Cutaneous cytology is a valuable tool in veterinary dermatology and is performed routinely in acantholytic skin diseases, such as pemphigus foliaceus and pemphigus erythematosis. Cytologic examination of skin lesions in cases of pemphigus vulgaris is considered unrewarding due to the absence or low number of acantholytic epithelial cells. In the diagnostic approach of the dog in the present report however, cytologic examination of scraping smears of oral mucosa obtained by means of a curette, provided early clues to the dog's ulcerative condition. The presence of numerous non-neoplastic single and rounded epithelial cells in cytologic samples may suggest an acantholytic skin disease, and the presence of epithelial cells with lymphocytic satellitosis is supportive of concurrent cytotoxic dermatitis. Cytology of oral lesions has been performed in one case of PNP (Lemmens et al., 1998). Microscopic examination in this case did not reveal the presence of acantholytic keratinocytes. The collection technique is crucial in obtaining representative cells from the primary lesion. Scraping smears generally produce smears of greater diagnostic quality than impression smears (Cowell et al., 1989). Early recognition of PNP by cytologic examination of oral lesions can allow early tumor removal and immunosuppressive treatment.

In conclusion, dogs with PNP may present with PV-like and EM-like (cytotoxic) histopathological features. Routine performance of cytologic examination of oral lesions, using a proper technique of sampling, may provide early diagnostic clues to this very rare entity.

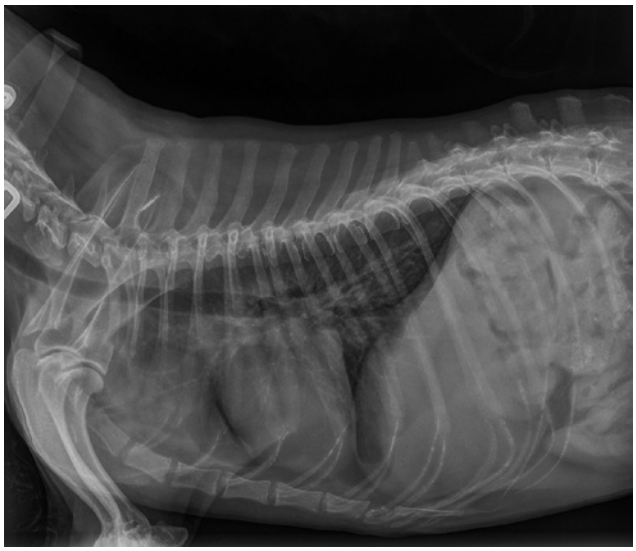

Figure 7. Left lateral radiographic view of the thorax of the Lasa apso, showing a large cranial mediastinal mass.

Figure 8. Lesion progression of the Lhasa apso. Note the mucocutaneous distribution of facial lesions and involvement of nasal mucosa.

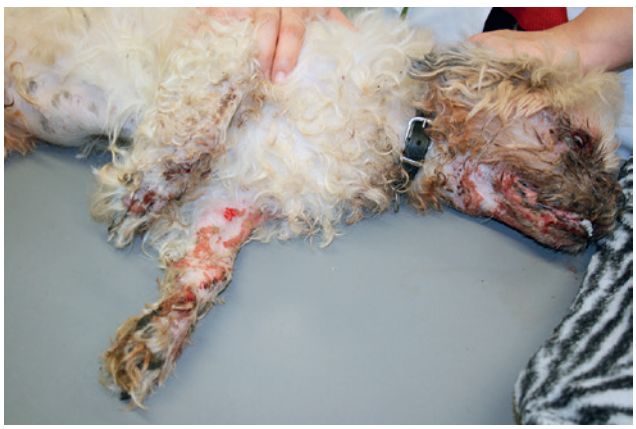

Figure 9. Lesion progression in the Lhasa apso. Widespread ulceration is present on the chin, ventral neck and forelimbs.

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