# Canine histiocytic syndrome manifested as ulcerative gastroenterocolitis, skin lesions and lymphadenopathy – a case report

V. Revajova, M. Levkut, M. Kozak, J. Bilek, D. Magic, Jr., R. Herich

University of Veterinary Medicine, Kosice, Slovak Republic

**ABSTRACT**: Histiocytic syndrome was diagnosed in a 7-year-old boxer bitch using histological and immunohistochemical methods. Necropsy confirmed the presence of enlarged superficial lymph nodes, two large ulcerated oval cutaneous masses one on the left lateral thoracic wall and one near to the vulva. In the gastrointestinal tract there were multiple ulcers apparently overlying nodules located in the submucosa of stomach, ulcers in the ileocaecal valve, and enlargement of lymphoid nodules in the small intestine manifested ulcerative gastroenteritis. Histologically, the thoracic wall mass showed infiltration of the tissue by macrophages with cytoplasmic vacuoles. The vacuoles contained PAS-positive polysaccharides. The macrophages were positive for alpha-1-antitrypsin and lysozyme by immunostaining. Lysozyme is a marker for phagocytic macrophages/histiocytes and may be used to confirm cells of this lineage in cases when there is any doubt.

**Keywords**: dog; histiocytic disorder; skin; intestine; lymph nodes

Canine histiocytic proliferative disorders include reactive diseases such as cutaneous and systemic histiocytosis and neoplastic diseases such as cutaneous histiocytoma and localized and disseminated histiocytic sarcoma (malignant histiocytosis). Their aetiology and pathogenesis is unknown. Canine histiocytic proliferative diseases may be limited to the skin and subcutaneous tissue or may be more generalized, affecting several organ systems (Affolter and Moore, 2000).

Histiocytic ulcerative colitis (HUC) is an uncommon idiopathic inflammatory disease of the large bowel characterised by aggregates of histiocytes in the lamina propria. The disease is well recognized in young Boxer dogs (Hall et al., 1994) and there is an apparent familial predisposition among affected dogs (Hall et al., 1992). Early lesions are characterized histopathologically by the presence of a mixed inflammatory infiltrate (neutrophils and macrophages) subjacent to degenerative epithelium (Russell et al., 1971). Where lesions are particularly extensive, severe mucosal ulceration occurs with prominent infiltration of *lamina propria* and by neutrophils, macrophages, lymphocytes, plasma cells and mast cells (van Kruiningen et al., 1965; Kennedy and Cello, 1966; Sander and Langham, 1968).

In the case presented, the combination of intestinal and skin lesions, and lymphadenopathy is unusual.

## MATERIAL AND METHODS

**Case history.** A 7-year-old boxer bitch was presented for clinical examination with signs of puerperal eclampsia and pneumonia developing 6 days after parturition. The bitch was lethargic, anorexic, pyrexic, and mildly dehydrated; there was catarrhal conjunctivitis and a haemorrhagic-purulent vulval discharge. Symptomatic treatment with antibiotics, vitamin C and calcium improved the animal's condition.

Four weeks later, a firm, oval cutaneous 5 × 7 × 1 cm diameter mass was observed on the left lateral thoracic wall; the mass was slightly painful but freely

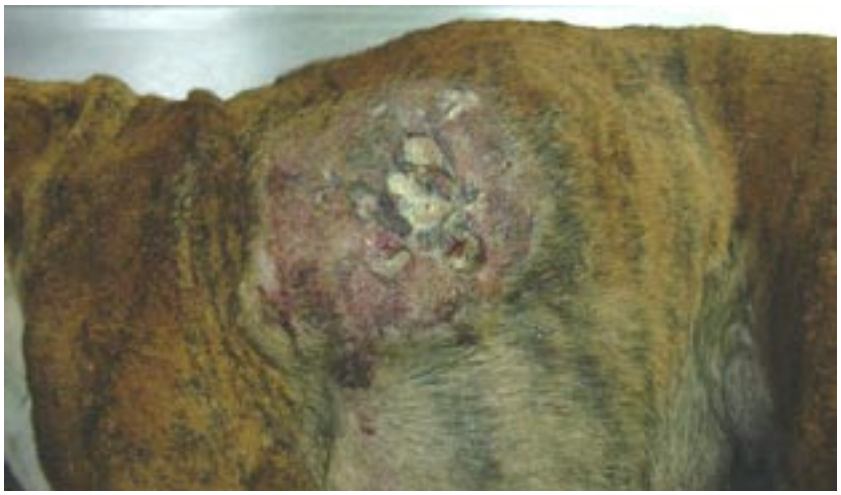

Figure 1. Cutaneous histiocytic mass with haemorrhages and necrosis

moveable. Faeces were dark with traces of blood and coated with mucus. During the next four weeks the mass on the thoracic wall increased in size to 20 × 10 × 3 cm in diameter and the surface became ulcerated (Figure 1). All palpable peripheral lymph nodes including retropharyngeal, submandibular, prescapular and popliteal became enlarged to about twice normal size.

Cytologic examination of fine needle aspirates from the skin mass revealed the presence of many macrophages with phagocytic debris and smaller numbers of neutrophils, lymphocytes, and plasma cells.

There was progressively increasing anorexia and weight loss of 8 kg over the following four weeks. There was no response to supportive therapy and the dog was euthanatized on humane grounds.

**Necropsy.** Detailed *post mortem* examination of 7-year-old boxer bitch showed pathomorphological changes in the skin, lymph nodes and gastrointestinal tract.

**Samples.** Samples of cutaneous mass, prescapular and visceral lymph nodes, lungs, stomach, ileocaecal valve, caecum, and large intestine were collected.

**Histopathology.** The tissue was fixed in 10 per cent formol saline and submitted for routine histopathological examination. After wax embedding, 5 μm sections were stained with haematoxylin and eosin (HE), periodic acid-Schiff (PAS) method, by Gram, and Grocott (Vacek, 1990).

**Immunohistochemistry.** Rabbit polyclonal antibodies to human lambda and kappa light chains (dilution 1 : 10) expressed in some lymphoid cells, and lysozyme, alpha-1-antitrypsin expressed (dilution 1 : 200) in histiocytes were used as primary antibodies. Biotin-Streptavidin amplified peroxidase detection system (Biogenex, USA) was used to detect a positive reaction.

Tissue sections were placed on poly-l-lysine coated slides, deparafinized in the sequence xylene (2 × 10 min), and 70% alcohol (5 min). After incubation to block of the endogenous peroxidase activity in 3% $H_2O_2$ (30 min), the sections were washed in distilled water, then digested in 0.4% pepsin in 0.01 N HCl at 37°C for 30 min, and washed again in distilled water. The sections were incubated with primary antibodies diluted in PBS for 14–16 hours at 4°C, followed by incubation with biothynilated anti-immunoglobulins and finally with peroxidase-labelled streptavidin in PBS. The immunological reaction was identified by diamino-benzidine. Sections were counter-stained with Mayer's haematoxylin.

## RESULTS

### Necropsy

Necropsy confirmed the presence of enlarged superficial lymph nodes in which normal lymph node architecture was not apparent. There was haemorrhage and necrosis within the cutaneous mass on the thoracic wall that was composed mostly of solid fawn tissue. The only other lesions affected the alimentary tract. The mucosa of the stomach (Figure 2), ileocaecal valve, caecum and large intestine was covered with multiple ulcers apparently overlying nodules located in submucosa.

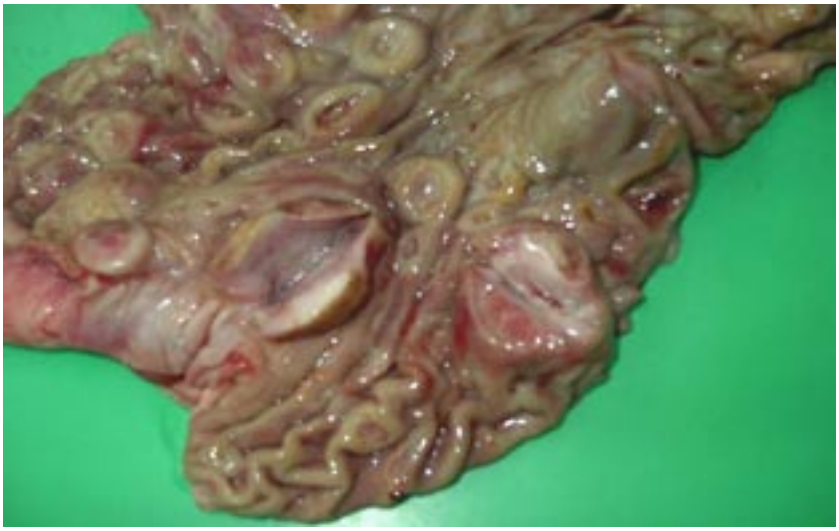

Figure 2. Histiocytic ulcerative gastritis

## Histopathology and immunochemistry

Histologically, the nonencapsulated thoracic wall mass was infiltrated by histiocytes. The diffuse cellular infiltrate was spread to the middermal vascular plexus and expanded into superficial dermis. Mild diffuse infiltrates were also seen in the epidermis. The histiocytes had large, round to oval, indented of folded and twisted nuclei and abundant pale eosinophilic cytoplasm with occasional small cytoplasmic vacuoles. The histiocytes with cytoplasmic vacuoles containing PAS-positive polysaccharides were similarly positive for alpha-1-antitrypsin and lysozyme by immunostaining (Figure 3). Similar cells were present in the deeper mucosa underlying ulcers through the alimentary tract. Special stains failed to identify infectious agents.

The enlarged lymph nodes were infiltrated by numerous histiocytes in the subcapsular and medullar sinuses, the paracortex, and along the trabeculae. Infiltration of the cortex and paracortex by lymphocytes, neutrophils, and giant cells were frequent. The lymphocytes were positive for kappa and lambda immunostaining.

## DISCUSSION

The intestinal lesions in the dog described here are typical of those seen in histiocytic colitis in dogs. It

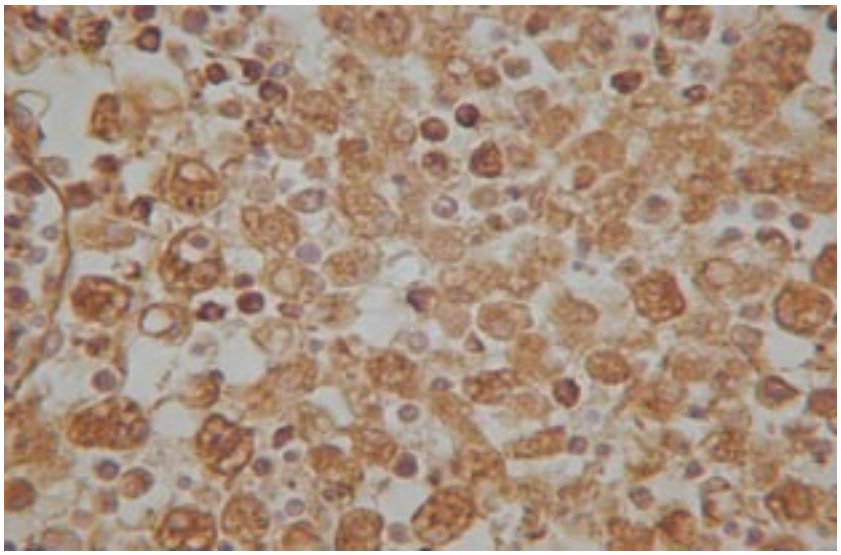

Figure 3. Tissue macrophages with cytoplasmic vacuoles positive for lysozyme. Biotin-streptavidin peroxidase complex, counterstained by Mayer's haematoxylin (bar 2 μm)

is suggested that the accumulation of histiocytes is caused by a defect in lysosomal function in some boxer dogs (Barker et al., 1993). The combination of intestinal and skin lesions, and lymphadenopathy, in the present case is unusual.

Several other histiocytic proliferative disorders have been described in dogs including cutaneous histiocytosis, malignant histiocytosis, and systemic histiocytosis. Cutaneous histiocytosis in dogs is not associated with lymph node or visceral involvement (Mays and Bergeron, 1996). Fever, depression, weight loss and irregular lymphadenopathy are features of malignant histiocytosis (Wellman et al., 1985), or disseminated histiocytic sarcoma, a rare, malignant neoplasm of Langerhans' cell origin in dogs (Scott et al., 2001). Malignant transformation of fixed tissue histiocytes and macrophages affects any organ in which the mononuclear phagocytes are normally found. Spleen, liver, bone marrow, skin, lungs and lymph nodes are most commonly involved. In malignant histiocytosis of lymph nodes there is initial involvement of the nodal sinuses, which are expanded by morphologically atypical malignant histiocytes, with high mitotic rate and abnormal configuration of chromatin. Striking phagocytosis of erythrocytes, leukocytes, platelets, and nuclear and cytoplasmic debris is seen, particularly in the more differentiated histiocytes (Bonner, 1988). Pancytopenia and hepatosplenomegaly are a consistent feature of malignant histiocytosis that were absent in the present case.

Systemic histiocytosis in Bernese Mountain dogs is another disease in which there may be skin and lymph node lesions but the alimentary tract is not involved. Affolter and Moore (2000) have recently reviewed canine cutaneous and systemic histiocytosis. Cutaneous and subcutaneous lesions in both conditions had identical histopathological features characterized by multinodular infiltrates predominantly observed in deep dermis and panniculus. The pleocellular infiltrates, consisting of mainly histiocytes, small lymphocytes, and neutrophils, accumulated around vessels and formed perivascular cuffs. Eosinophils were occasionally seen and plasma cells were rare. These authors suggested, that canine cutaneous and systemic histiocytosis are result from an accumulation of activated dermal dentritic antigen-presentating cells and therefore represent a reactive histiocytosis of dermal dentritic cells with similar histologic features but distinct clinical presentation.

Our findings of κ and λ positive plasma cells and PAS+ cells in the gastrointestinal lesions are consistent with the work of German et al. (2000) with respect to immunohistochemical findings in HUC Boxer dogs. HUC lesions in the colon were characterized by increases in IgG+ plasma cells, PAS+, CD3+, L1+ cells (L1+ cells are demonstrated in canine macrophages and neutrophils) and MHC class II positive cells in the *lamina propria*, in conjunction with MHC class II expression, and decreased goblet cell numbers in the epithelium. Their observations are similar to those documented in human inflammatory bowel disease, especially ulcerative colitis and suggest an important role for the mucosal immune system in the pathogenesis of canine HUC.

In conclusion, the histiocytic disorders are characterized by the proliferation of macrophage or Langerhans cell lineages (Cline, 1994). Pathologically, the lesions of histiocytosis appear as reactive infiltrates, possessing little of the cellular atypicality and homogeneity characteristic of malignancy. Although the aetiology of these phenomena is unknown, histiocytosis syndromes appear to represents a reactive autoimmune disorder triggered by unknown stimuli (Lipton, 1983). Gutiérez-Ravé Pecero et al. (1991) reported a case of phenytoin-induced hemocytophagic histiocytosis indistinguishable on clinical and histopathological grounds from malignant histiocytosis. They stated that reactive and malignant histiocytosis are not really two distinct entities with different aetiologies, but continuum of host responses to several insults with different degrees of aggressiveness depending on the host immune status.

We suppose that skin lesions associated with ulcerative gastroenterocolitis resulted from severe attack to phagocytic system, and following therapy. This is supported by arising of extensive ulcerative mass located in the skin close to the shoulder, in the area for application of drug. Finding of reactive plasma cells in affected tissue only confirms development of canine HUC. Mucous diarrhoea, later with blood following appearance of skin lesions gives suggestion digestive tract to be affected first.

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*Corresponding Author*

MVDr. Viera Revajova, PhD., University of Veterinary Medicine, Department of Pathological Anatomy, Komenskeho 73, 041 81 Kosice, Slovak Republic
Tel. and fax +421 55 633 81 91, e-mail: revajova@uvm.sk