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Original article

Haptoglobin as a treatment monitoring factor in feline plasmacytic gingivostomatitis

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Abstract

Introduction: feline plasmacytic gingivostomatitis is an important and fairly common chronic disease. Its complex aetiology – which involves infectious agents, immunological disorders, and even genetic factors adds to the considerable difficulty of its treatment.

Materials and Methods: the study was performed on 33 cats, 26 animals diagnosed with plasmacytic gingivostomatitis (study group) and 7 clinically healthy cats (control group). The study extended over four examination periods during which clinical and X-ray examinations, morphological and biochemical blood tests, as well as haptoglobin essays were performed.

Results: the biochemical and haematological parameters were within normal limits. Blood serum haptoglobin measured on the first day of the treatment was above physiological levels, however its serum concentration decreased as the treatment progressed.

Conclusions: in the present study, despite the bacterial inflammatory condition of periodontal pockets, after the treatment was concluded and symptoms alleviated, neither clinical examinations nor haptoglobin essays revealed deviations from values commonly accepted as normal. Fluctuations in blood serum haptoglobin levels proved to be a useful prognostic in determining the duration of necessary treatment.

Key words: cat, feline plasmacytic gingivostomatitis, haptoglobin

Introduction

Feline plasmacytic gingivostomatitis, often described as lymphocytic/plasmacytic gingivitis stomatitis (LPGS) or feline gingivitis stomatitis (FGS) typically affects between 2 and 4% of the cat population.

The multi-factor aetiology of the disease, which involves infectious agents, immunological disorders, as well as certain genetic predispositions, significantly hinders any efforts to control the inflammatory process. Lesions are typically located in the pharyngeal arch and soft palate regions. They take the form

of hyperaemic and hypertrophic deformities of the oral mucosa. The disease process often also extends to molar and pre-molar gingiva, as well as the mucosa of the root of the tongue and pharynx (Reubel et al. 1992, Johnson 2006).

The progression of plasmacytic gingivostomatitis is strongly affected by the general state of the dentition as well as factors promoting immunosuppression (Addie et al. 2003). The latter most significantly include malnutrition, avitaminosis, particularly vitamin A deficiency, local and general infections, bacterial toxins and mycotoxins present in the feed, parasitic invasions, administration of drugs with immunosuppressive side-effects, or vaccines with temporary, postvaccinal immunosuppressive effects (Gliński and Kostro 2005).

The acute phase response which involves haptoglobin (Hp) plays the decisive role in maintaining the organism's homeostasis which can be adversely affected by stress or infection (Eckersall and Bell 2010). In the case of feline plasmacytic gingivostomatitis, both these factors occur in the course of the disease process. Acute phase proteins are not only markers of the early immunological response but also take part in the inflammatory process and act as ligands of immune system cells. A key role in the non-specific opsonisation of micro-organisms is played, apart from the complement system, by acute phase proteins such as C-reactive protein (CRP), serum amyloid A (SAA), LPS binding protein and mannose, as well as fibronectin and leukotrienes. Meanwhile Hp, an h2-globulin synthesized in the liver, significantly impacts the organism's immune response by regulating B lymphocyte proliferation, thus modulating antibody synthesis. It also regulates functions of Langerhans cells and participates in the activation of T lymphocytes in the process of antigen presentation in the lymphatic system.

Determining the blood serum levels of acute phase proteins is recommended for the purposes of prognostics and treatment monitoring, as well as general health assessment (Rubel et al. 1992, Bistrián 1999).

The goal of the present research was to evaluate the severity of inflammation occurring in the course of feline plasmacytic gingivostomatitis, based on blood cell counts and biochemical blood tests as well as measurements of haptoglobin (Hp), an acute phase protein, concentration.

Materials and Methods

The study was conducted on patients treated dentally at the Department and Clinic of Animal Surgery of the Faculty of Veterinary Medicine of the Univer-

sity of Life Sciences in Lublin. Patients diagnosed with systemic diseases were qualified for the study based on medical history analyses and clinical examination. All study protocols were approved by the Local Ethics Committee of University of Life Sciences in Lublin. Prior to data collection, the owners of cats qualified for the research were informed of the purpose of the study and gave consent to their animals' participation. The study group was composed of 26 mixed-breed cats of both sexes aged between 3 and 10 years, diagnosed with plasmacytic gingivostomatitis. The control group included 7 clinically and radiologically healthy cats aged between 3 and 8 years. The study group and control group animals were subjected to observation which involved examinations, medical procedures, and evaluation of the effectiveness of the treatment administered.

The assessment of the severity of lesions in the oral cavity of cats was performed under general anaesthesia. Cats were premedicated with medetomidine (Domitor, Orion Pharma) at a dose of 50 µg/kg, intramuscularly, approximately 10 minutes before general anaesthesia. Propofol (Scanofol, ScanVet) at 5 mg/kg was administered intravenously for induction. General anaesthesia was maintained with isoflurane. Dental examinations were performed using a calibrated Williams probe.

Biopsy aspirate BAC was taken from the area of the healthy mucosa as well as from the inflammatory/proliferative tissue. The material was solidified in 10% buffered formalin (pH 7.2) for 24 (48h) and, as a routine precaution, submerged in paraffin blocks used to obtain 4 µm thick samples. Standard hematoxylin and eosin (H+E) stain was used. Histopathological examinations confirmed the LPGS diagnosis and excluded the possibility of oral cancer (including cornified squamous carcinoma).

Before administering basic dental treatment to experimental group animals, intraoral X-rays were taken to determine the severity of the resorptive lesions in alveolar processes. The examination was performed in the following positions: Antero-Posterior and Lateral using an RTG PICKER auto apparatus (with primary parameters: KV 40, mAs 100). The apparatus offers the functionality of adjusting the programmed parameters to generate a better quality image) with digital indirect radiography using a Konica Minolta Regius 110 scanner (Fig. 1). This was followed by the surgical procedure of removing tartar with an ultrasound scaler (Woodpecker, UDS-P). Once tartar was removed, crown surfaces were polished with paste (Stomazél, Eurowet, France). Teeth with exposed roots or showing symptoms of odontoclastic erosion were extracted. Prednisolone (Depo-Medrol, Pfizer, UK) dosed at 1 mg/kg b.m. and 5% gentamicin



Fig. 1. X-Ray of the alveolar bone of the left mandible in a cat with severe periodontitis. Dilatation of the alveolar bone with partial resorption of the root apex of P1 and P2 teeth. Lack of one root and crown of M1 tooth.

(Gentamycyna, Biovet, Puławy) dosed at 1 mg/kg b.m. were administered locally on the mucosa along the dental arch (Wiggs and Lobprise 1997). Recommendations included dental hygiene and antibiotic treatment with cefovecin (Convenia, Pfizer, UK) – 8 mg/kg b.m. in single s.c. administration (Six et al. 1997, Khazandi et al. 2014).

The research material in the form of blood samples drawn from cats diagnosed with LPGS was collected 4 times (on the day of diagnosis before using pharmacological treatment as well as 7, 14, and 28 days from the start of the treatment), which naturally divided the study into 4 distinct periods:

Sampling I – the first day of treatment before using pharmacological treatment

Sampling II – 7 days after start of treatment

Sampling III – 14 days after start of treatment

Sampling IV – 28 days after start of treatment

Haematological tests and biochemical tests

The tests included white blood cell (WBC), and red blood cell (RBC) counts, as well as haemoglobin (HGB) and haematocrit (Hct) level measurements in blood samples collected for the respective study periods. The examinations were performed with the use of an haematological analyser (MEDONIC HESKA CBC-DIFF Veterinary Haematology System).

The blood serum was tested for the levels of urea nitrogen, creatinine, as well as alanine aminotransferase (ALT) and aspartate aminotransferase (AST) activity using a SPOT CHEM EZ SP 4430 analyser, on PANEL V strips (for creatinine, GPT/ALT, total protein, ALP, glucose, and urea nitrogen).

Blood serum haptoglobin concentration

The haptoglobin level in feline blood serum was determined with the ELISA method using an ELISA Kit, reactivity Cat (Feline) ABIN 956173 in accordance with the method described by the manufacturer (Life Diagnostics).

Statistical analysis

A statistical analysis was performed to confirm normal distribution of the data obtained. The Shapiro-Wilk test was applied, and since the test demonstrated normality of the distribution in all the groups, the t-Student test was used for comparisons between independent groups to determine whether mean values differed significantly between particular groups ($p \leq 0.05$).

Results

Clinical examination

Dominant clinical symptoms observed in the sick animals included: varying appetite, pain while eating, unpleasant odour from the oral cavity, and excessive salivation, sometimes with traces of blood or pus in the saliva. During clinical examinations, tenderness of the oral cavity was observed, accompanied by oedema and hyperaemia of the patients' pharyngeal arches and soft palates on both sides. Furthermore, the hyperaemia, hypertrophy and oedema of the mucosa often extended to the molar and pre-molar gingiva as well as the mucosa of the root of the tongue, pharynx, cheeks and lips (Table 1, Fig. 2).

Table 1. Comparison of clinical symptoms in individual cats.

	Symptoms	Number of cats
Medical history	loss of appetite	26
	pain while eating	26
	odour from the oral	14
	excessive salivation	16
Clinical examination	oedema, hyperaemia, hypertrophy of the mucosa of premolar and molar gingiva	26
	oedema and hyperaemia of the mucosa pharyngeal arches and soft palates	16
	oedema, hyperaemia, hypertrophy of the mucosa of the root of tongue and cheeks	4



Fig. 2. Severe course of the feline plasmacytic gingivostomatitis. Bilateral severe redness and gingival swelling of the mandibular and maxillary teeth. Hyperaemic and hypertrophic deformities of the mucosa.

Histopathological examination

A 0 to 3 scale was used where degree 0 indicated the control animals without inflammatory lesions within the oral cavity. Degrees 1 through 3 were used to classify LPGS cats on the basis of histopathological examinations.

Degree 1 – unilateral, mild gingivitis in the premolar and molar regions of the maxilla or mandible, without proliferation to oral mucosa, including the palatoglossal arch (19 cats).

Degree 2 – (moderate inflammation) bilateral gingivitis and buccal mucosa inflammation with slight hyperplasia. Moreover, cats in this group were diagnosed with proliferation of the disease to the root of the tongue (6 cats).

Degree 3 – severe inflammation with ulcerations, gingival hyperplasia and bilateral proliferation of the palatoglossal arch mucosa. Lesions were in the form of hyperaemic and hypertrophic deformities of the mucosa (8 cats).

Table 2. Blood cell count results in the experimental cats.

Sampling	Evaluated parameters (x ± SD)			
	WBC (10 ³ /μl)	RBC (10 ⁶ /μl)	HGB (g/dl)	Hct (%)
I	9.4 ± 0.3	7.3 ± 0.9	10.8 ± 1.3	29.3 ± 2.1
II	14.5 ± 1.5	7.3 ± 0.3	10.6 ± 0.4	32.8 ± 2.2
III	6.9 ± 1.0	8.2 ± 0.7	11.4 ± 0.8	31.2 ± 1.1
IV	8.6 ± 1.5	9.3 ± 0.6	9.0 ± 0.4	36.4 ± 1.2
Control	11.5 ± 1.2	7.3 ± 1.1	11.2 ± 2.3	30.2 ± 1.1
Normal	5.5-19.5	5.0-11.0	8.0-15.0	25.0-45.0

White blood cell count (WBC), red blood cell count (RBC), haemoglobin concentration (HGB) and haematocrit level (Hct) in cats suffering from plasmacytic gingivostomatitis (four blood samplings) and healthy cats (control), as well as referential (normal) values.

Table 3. Results of biochemical blood tests in the experimental cats.

Sampling	Evaluated parameters (x ± SD)			
	BUN (mg/dl)	CR (mg/dl)	ALT (U/l)	AST (U/l)
I	22.5 ± 2.1	1.4 ± 1.1	91.2 ± 2.0	28.8 ± 2.0
II	23.0 ± 1.1	1.3 ± 0.2	32.1 ± 0.8	12.5 ± 0.5
III	18.9 ± 0.9	1.3 ± 0.1	89.3 ± 2.1	8.5 ± 0.9
IV	20.2 ± 0.7	1.0 ± 0.4	33.51 ± 1.4	16.3 ± 0.5
Control	18 ± 1.2	2.3 ± 0.3	22.0 ± 0.9	1.0 ± 0.01
Normal	19-34	1.0-1.8	30-100	12-56

Urea nitrogen (BUN) and creatinine (CR) levels as well as alanine aminotransferase (ALT) and aspartate aminotransferase (AST) activity in the blood serum of sick cats (four blood samplings) and healthy cats (control), as well as referential (normal) values.

Haematological tests and biochemical tests

The WBC count results in the sick animals were between $6.9 \pm 1.0 \times 10^3/\mu\text{l}$ (sampling III) and $14.5 \pm 1.5 \times 10^3/\mu\text{l}$ (sampling II). Only during sampling II did the WBC value exceed the mean control value ($11.5 \pm 1.2 \times 10^3/\mu\text{l}$) (Table 2).

The mean WBC count one week after the start of the treatment was significantly higher than that recorded on the first day of the treatment or during sampling II and IV. The result obtained from sampling II was also statistically significantly higher than that obtained in the control group.

The erythrocyte count in sick cats fluctuated within normal ranges, between $7.3 \pm 0.3 \times 10^6/\mu\text{l}$ (first day of treatment) and $9.3 \times 10^6/\mu\text{l}$ (sampling IV- 28th day of treatment) (Table 2).

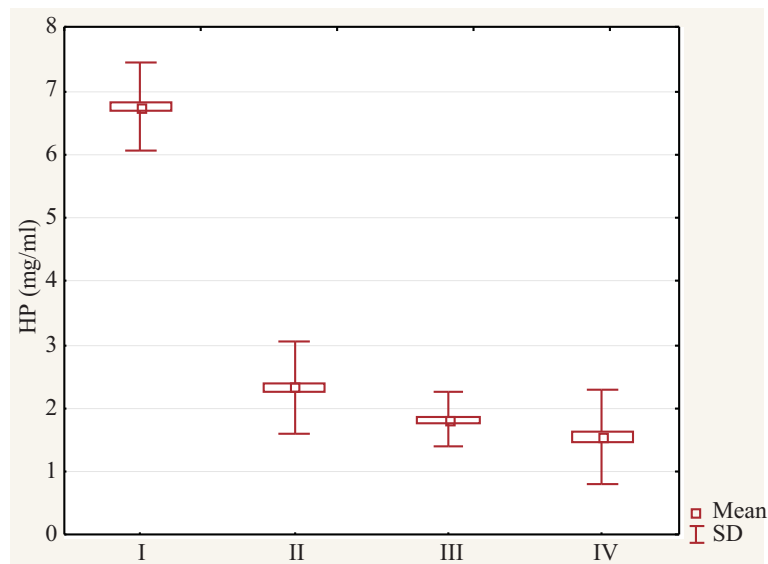
Furthermore, the mean haemoglobin concentration (HGB) in all cats suffering from plasmacytic gingivostomatitis remained within normal ranges (8.0 – 15.0 g/dl). The discrepancies in terms of HGB values observed between sampling I-IV were not statistically significant ($p > 0.05$).

The mean haematocrit level (Hct) observed in sick cats during the subsequent blood samplings (I, II, III, IV) were, respectively: $29.3 \pm 2.1\%$; $32.8 \pm 2.2\%$; $31.2 \pm 1.1\%$; 36.4 ± 1.2 . The results were not statistically significant.

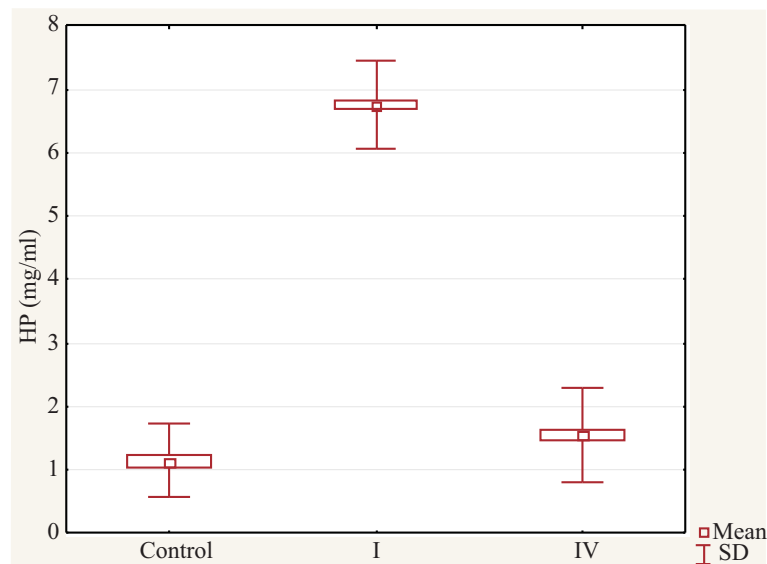
Urea nitrogen levels varied between the respective sampling periods from 18.9 ± 0.9 mg/dl (sampling III) to 23.0 ± 1.1 mg/dl (sampling II), the latter being the highest recorded value (Table 3). In all study periods, the blood urea nitrogen level differed from the values observed in the control group and was outside the accepted normal value range of 19-34 mg/dl. However, said discrepancies were not statistically significant ($p > 0.05$). The lowest blood serum creatinine level in sick cats was observed during sampling IV (1.0 mg/dl) while the highest at the start of the treatment – sampling I (1.4 ± 1.1 mg/dl).

In all study periods, it remained lower than the levels observed in the control group (2.3 ± 0.3 mg/dl) as well as the accepted normal value for cats (1.7 mg/dl). These discrepancies, however, were also statistically insignificant.

In all sick cats regardless of the sampling period,



Graph 1. Juxtaposition of the experimental cats (I, II, III, IV).



Graph 2. Juxtaposition of the control group with experimental cats I and IV.

the alanine aminotransferase (ALT) activity was statistically significantly higher than that observed in the control group (22.0 ± 0.9 U/l). The ALT activity varied between 33.51 U/l (sampling IV) and 91.2 ± 2.0 U/l (sampling I) (Table 3). In all the cats, the alanine aminotransferase (ALT) activity was statistically significantly higher than that found in the control group (1.0 ± 0.01 U/l). The highest activity of the enzyme was observed at the time of the diagnosis (28.8 ± 2.0 U/l) and the lowest 14 days after the start of the treatment – III (8.5 ± 0.9 U/l). The discrepancies were not statistically significant.

Haptoglobin level

The mean haptoglobin level in the control group was 1.14 ± 0.29 mg/ml. Significant discrepancies in haptoglobin levels were recorded between the respective blood Sampling periods (Graph 1). During the treatment, the highest mean Hp level was observed at the start of the treatment (Sampling I), and in the subsequent study periods the Hp values decreased in a highly significant manner ($p < 0.001$) eventually reaching, 28 days into the treatment, levels similar to those observed in the control group

(Graph 2). The mean haptoglobin levels recorded in the experimental groups were as follows:

- Sampling I: 6.74 ± 0.35 mg/ml
- Sampling II: 2.33 ± 0.36 mg/ml
- Sampling III: 1.82 ± 0.21 mg/ml
- Sampling IV: 1.55 ± 0.37 mg/ml
- Control group: 1.14 ± 0.29 mg/ml

Discussion

Feline plasmacytic gingivostomatitis is an important disease to consider, particularly due to the therapeutic problems it entails. Clinical examinations of the studied cats revealed the incidence of the typical symptoms of plasmacytic gingivostomatitis, namely the presence of an unpleasant odour in the oral cavity, inflammatory condition and bleeding during the probing of periodontal pockets, tooth mobility, and soft tissue oedema. Data obtained from interviews indicated the presence of pain during feeding (Williams and Aller 1991). In the conducted study, prognoses related to the patients' health were based on the observed behaviour (changes) of haptoglobin levels in the blood serum of sick cats undergoing treatment.

In our own research, the measured biochemical and haematological parameters were within the accepted normal ranges. The activity of both transaminases (ALT and AST) could not be correlated with infection-induced severe liver function disorder. In the case of viral infections affecting this organ, as well as systemic bacterial infections, the ALT and AST values would reach levels 10-50 times above the respective maximum normal values, which is accompanied by an increase in white blood cell counts. It seems that changes in AST and ALT activity noted in the studied cases of feline plasmacytic gingivostomatitis could not, as is the case in dogs suffering from severe oral infections, be related to a generalization of the disease process. Following recovery, cats did not display clinical symptoms of changes in the analysed parameters that would indicate damage to the heart, kidney or liver. Meanwhile, studies focusing the impact of pathogenic bacterial microflora related to periodontal diseases on the condition of internal organs in dogs in the clinically most advanced stages of the disease revealed, apart from elevated ALP and AST activity, significantly increased values of WBC count and urea levels (Polkowska 2011).

Acute phase proteins constitute very sensitive indicators of inflammation although they are also characterised by low specificity. Changes in their blood serum concentration and peritoneal exudate have been used as biomarkers in cases of feline infectious

petronitis, cancer, and lymphoma (Correa et al. 2001, Giordano et al. 2004). As observed by Eckersall et al. (2010), it is necessary to continue studying the potential for using Hp as a biomarker of inflammatory conditions in cats. This acute phase protein is believed to be a valuable prognostic with regard to the recovery process. Elevated levels of haptoglobin play an important role in wound healing processes and chronic inflammatory conditions (Eckersall and Bell 2010).

The reference Hp concentration in cats is, on average, within the range of 0.7-2.0 mg/ml. In the course of an inflammation, however, it can increase to even 10 mg/ml (Giordano et al. 2004, Tizard 2013). In our own research the Hp level at the start of the treatment significantly exceeded physiological values – it fluctuated between 6.2 and 7.3 mg/ml (with the mean value of 6.74 mg/ml). Meanwhile, the mean level observed in healthy cats was 1.14 mg/ml, with all values remaining within the range of 0.8 mg/ml to 1.5 mg/ml. The recorded changes in Hp concentration reflected the severity of the inflammatory process and could be used, together with the results of clinical and radiological examinations, as the prognostic basis for determining the course of the treatment. This is because Hp levels in cats suffering from various inflammatory conditions are generally high, sometimes reaching up to 10 mg/ml. They typically also remain at the level of roughly 4.9 ± 2.9 mg/ml during convalescence (Kostro and Gliński 2003). While the CRP and SAA levels tend to increase rapidly after the occurrence of an inflammatory stimulus, Hp levels become elevated several days later, which is why haptoglobin is considered to be a marker of chronic inflammation (Seida et al. 2012).

The behaviour of Hp confirms the opinion that the main problem in feline plasmacytic gingivostomatitis stem from inflammatory conditions related to the proliferation of plasmacytic cells and lymphocytes to the gingiva and other oral tissues in a process facilitated by infectious agents. Inflammatory lesions are the consequence of increased reactivity of the immune system (Lyon 2005). The significance of factors influencing said reactivity is further evidenced by the fact that once dental plaque is removed (especially after tooth extraction) and due to the resulting minimisation of immunological stimulation by bacterial agents forming plaque, the disease process regresses.

Antibiotic treatment itself leads to only temporary improvement. The use of chemotherapeutic agents results in limiting the number of bacteria forming dental plaque but does not completely eliminate the problem of microfloral presence which directly or indirectly contributes to triggering the immune-inflammatory response in the host (Bellel et al. 2008).

Conclusion

The development, progression and generalisation of an infection is primarily dependant, alongside the type of bacteria and intensity of the local disease process, on the local and systemic immunity of the organism. Its weakening, or in some cases complete suppression, leads to bacteraemia. In our own studies, once the treatment was completed and lesions in the cats' oral cavities healed, haptoglobin concentrations returned to levels commonly accepted as normal. The fact that the haptoglobin concentration was elevated at the start of the treatment and continued to decrease in the subsequent study periods to eventually return to levels similar to those observed in the control group confirms the effectiveness of surgical treatment of feline plasmacytic gingivostomatitis using cefovecin. Furthermore, changes in haptoglobin levels may prove useful in prognosing the expected duration of the treatment.

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