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Reduction of anti-*Leishmania* antibody levels and outcome in a domestic ferret (*Mustela putorius furo*) with renal disease treated with a miltefosine plus allopurinol combined therapeutic protocol

Jacobo Giner[1,2]*, Diego López-Sahuquillo[1], Álex Gómez[2], Diana Marteles[2], Maite Verde[2], Antonio Fernández[2], Sergio Villanueva-Saz[2]

1. Centro Veterinario Menescalia, Valencia, Spain. 2. Animal Pathology Department, Veterinary Faculty, University of Zaragoza, Spain.
*menescalia@menescalia.com

Background

Domestic ferrets in the Mediterranean basin are exposed to the endemic parasite *Leishmania infantum* as revealed by a recent seroprevalence survey [1]. Equally, the first clinical cases of leishmaniosis in ferrets have been published recently [2,3]. Two different therapeutic protocols have been described to treat two ferrets with leishmaniosis: meglumine antimoniate plus allopurinol [4] and miltefosine plus allopurinol (MPA) [3]. This case report describes the second clinical case of leishmaniosis in a ferret treated with a combination of MPA.

Case report

A 4-year-old intact female ferret with one-year chronic splenomegaly and hyperglobulinemia of unknown origin was clinically evaluated because of progressive weight loss, polyuria/polydipsia and hyporexia during the previous three weeks. On physical examination, this ferret was in good condition, active and alert, normothermic and properly hydrated. Abnormal clinicopathological findings included a marked increase in blood urea nitrogen (BUN), creatinine and globulins serum levels, low urinary density, and renal proteinuria (Table 1).

Renal ultrasound findings were non-specific, so a chronic kidney disease was diagnosed, discarding other diffuse or focal parenchymal renal disorders as well as disorders of the collecting system. Diffuse echogenic changes of the splenic parenchyma were associated with extramedullary hematopoiesis. Medium levels of antibodies against *Leishmania infantum* were detected by ELISA with an optical density result of 0.71 (cut-off: 0.20). A combined anti-*Leishmania* therapeutic protocol with miltefosine (Milteforan®) at 2 mg/kg/q24h during 28 days *per os* (PO) and allopurinol (Zyloric® 100 mg) at 10 mg/kg/q12h PO *sine die* was established. Equally, the ferret was treated with benazepril (Fortekor® 2,5 mg) at 0,25 mg/kg/q24h (PO) and telmisartan (Semintra® 4 mg/ml) at 1 mg/kg/c24h (PO) to decrease proteinuria. A follow-up visit one month after the treatment was initiated demonstrated a clinical response with an improvement in quality of life and body weight. At this time, serum biochemical profile revealed serum creatinine and BUN concentrations within the reference range, indicating an improvement in renal function. Moreover, a decrease in serum globulins and anti-*L. infantum* antibody levels were observed (Table 1). Unfortunately, the ferret was rechecked only after an additional four months when the progression of the renal disease was diagnosed. Antibody levels were close to cutoff, but globulin concentration had further increased (Table 1). The patient was humanely euthanised owing to end-stage renal disease. Kidney histopathology revealed membranoproliferative glomerulonephritis (Figure 1), as it occurs in dogs with renal disease associated with leishmaniosis.

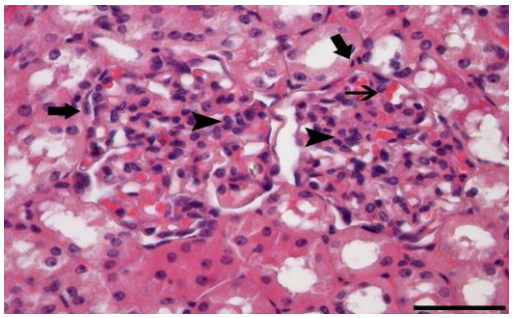

Figure 1: Histological section of affected renal tissue from this ferret. Glomerulonephritis (40x). Bowman's capsule is thickened by hypertrophied parietal epithelial cells (thick arrows). Glomerulus with severe hyperplasia of mesangial cells (arrowhead) and thickening glomerular capillary loops (thin arrow).

Table 1: Body weight and laboratory parameters followed up in blood serum and urine samples from one of the previous follow-ups three months before (T-3) the serological diagnosis of leishmaniosis (T0), and after one (T1) and five (T5) months of therapy.

Parameter	Diagnosis T-3	T0	T1	T5	Reference range
Body weight (g)	755	605	690	**455**	500-900
Serum biochemical markers					
ALT (U/L)	152	132	86	126	82-289
ALKP (U/L)	56	84	83	**89**	9-84
Glucose (mg/dL)	131	107	106	170	94-207
Creatinine (mg/dL)	0.6	**1.4**	0.4	**>16.0**	0.4-0.9
BUN (mg/dL)	24	**47**	42	**>130**	10-45
TP (g/dL)	**6.8**	**8.7**	7.1	**10.2**	5,2-7,3
Albumin (g/dL)	2.6	2.9	**2,5**	3.2	2,6-3,8
Globulins (g/dL)	**4.2**	**5.8**	**4.3**	**7.0**	1,8-3,1
Alb/Glob ratio	0.5	0.6	0.6	0.5	
Urinalysis					
Leucocytes	Nd	Negative	Nd	Negative	Negative
Nitrite	Nd	Negative	Nd	Negative	Negative
pH	Nd	6	Nd	Negative	6
Glucose	Nd	Negative	Nd	Negative	Negative
Ketones	Nd	Negative	Nd	Negative	Negative
Urobilinogen	Nd	Normal	Nd	Normal	Normal
Bilirubin	Nd	Negative	Nd	Negative	Negative
Blood/Hemoglobin	Nd	Negative	Nd	Negative	Negative
Sediment	Nd	Inactive		Inactive	Inactive
Creatinine (mg/dL)	Nd	47	Nd	17	
Proteins (mg/dL)	Nd	**42**	Nd	**>400**	
UPC	Nd	**0.9**	Nd	**>24.03**	<0.5
USG	Nd	**1.020**	Nd	**1.014**	1.026-1.060
Anti-*L. infantum* antibodies (ELISA OD)	0	**0.71**	**0.37**	**0.24**	>0.20

Abbreviations: ALT= alanine amino-transferase, ALKP= alkaline phosphatase, TP= total protein concentrations, Alb/Glob= albumin to globulin concentration ratio, BUN= blood urea nitrogen, UPC= urine protein to creatinine concentration ratio, USG= urine specific gravity, ELISA= enzyme-linked immunosorbent assay, OD= optical density, Nd= not determined. Out-of-range values are highlighted in bold.

Conclusion

This case report describes treatment with MPA combined therapy in a domestic ferret antibody-positive to *L. infantum* and with clinical signs compatible with leishmaniosis. Progression of renal disease was the cause of euthanasia. The MPA protocol initially improved the animal's clinical condition, however in case of renal disease a guarded prognosis should be issued and treated ferrets should be frequently monitored. This is also required because the safety of used drugs is unknown.

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