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CASE REPORT

Companion or pet animals

Selective IgA deficiency and presumptive polyclonal spike in the beta fraction in a dog with leishmaniosis

Sergio Villanueva-Saz[1] | **Luis Martinez-Lostao**[2] | **Andres Yzuel**[3] | **Antonio Fernández**[1] | **Maite Verde**[1]

[1]Animal Pathology Department - Clinical Immunology Laboratory, Veterinary Faculty, University of Zaragoza, Zaragoza, Spain

[2]Immunology Department, Lozano Blesa University Clinical Hospital, Zaragoza, Spain

[3]Clinical Immunology Laboratory, Veterinary Faculty, University of Zaragoza, Zaragoza, Spain

Correspondence
Sergio Villanueva-Saz, Animal Pathology Department - Clinical Immunology Laboratory, Veterinary Faculty, University of Zaragoza, Zaragoza, Spain.
Email: svs@unizar.es

Abstract

A 1-year-old, entire, crossbred, female dog examined for apathy, lethargy, unilateral nosebleed of 2-month duration and the presence of symmetrical ulcerative dermatitis (small ulcers covered by a haemorrhagic crust and surrounded by alopecia on the tip of the ear pinna). Laboratory alterations included anaemia and hyperglobulinemia with a presumptive polyclonal spike in the beta fraction. High antibody levels to *Leishmania infantum* were detected by enzyme-linked immunosorbent assay. An anti-*Leishmania* therapeutic protocol was established and a reduction of the anti-*Leishmania* antibodies was detected by an end point sera dilution enzyme-linked immunosorbent assay during the first weeks of therapeutic protocol, while C-reactive protein concentration was reduced during the period of time when meglumine antimoniate was administered. A good clinical response to the treatment was detected after initiating the anti-*Leishmania* treatment. Quantitative serology is useful in the short-term, because using a two-fold serial dilution technique correlates with the clinical response.

BACKGROUND

Canine leishmaniosis is a zoonotic disease caused by *Leishmania infantum*. The most typical clinical signs associated to the disease include lymphadenomegaly, cutaneous lesions, anorexia and ocular lesions.[1] The most typical laboratory alterations detected are an important elevation of total protein and total globulins with serum-protein electrophoresis alteration. Polyclonal gammopathy was the most common electrophoretic pattern observed.[2]

Acute phase proteins (APP) are proteins that change their concentration in serum in response to inflammatory stimuli. These proteins could be divided into positive APP (C-reactive protein, serum amyloid A, haptoglobulin, ceruloplasmin, α2-macrogloublin, α1-acid glycoprotein, fibrinogen and complement) based on an elevation serum concentration or by contrast, negative APP (albumin, transferrin, transthyretin, retinol-binding protein and adiponectin).[3] Some of these APPs are considered as biomarkers for monitoring the response to the treatment in different diseases, including canine leishmaniosis. Among APPs, C-reactive protein is the protein with a major increase in serum concentration when signs of inflammation are present in the dog.[4] In canine leishmaniosis, an elevation in C-reactive protein and haptoglobulin has been described in animals with an active infection.

On the other hand, after an anti-*Leishmania* treatment is administered, a decrease of C-reactive protein can be detected.[5]

Two different therapeutic protocols have been described to treat dog with clinical leishmaniosis, including meglumine antimoniate plus allopurinol or miltefosine plus allopurinol.[6] In both protocols, monitoring is recommended during and after *anti-Leishmania* treatment considering different laboratory parameters such as complete blood count, biochemical profile, serum protein electrophoresis and urinalysis after the first month of treatment and then every 3–4 months. Traditionally, serology is not recommended after 6 months of initial anti-*Leishmania* treatment,[6] due to the lack of correlation between antibody levels and clinical status improvement.[7]

This report describes a case of selective IgA deficiency and presumptive polyclonal spike in the beta fraction detected by serum protein electrophoresis associated with *L. infantum* infection with a good response to treatment with meglumine antimoniate and allopurinol as anti-*Leishmania* treatment.

CASE PRESENTATION

A 1-year-old, entire, female crossbred dog with a history of unilateral nosebleed that occurred 4 months before referral. On physical examination, the dog was in good conditions, active and alert, normothermic and properly hydrated. Cardiac auscultation was within normal limits. Respiratory sounds were also normal and there was evidence of lymph node enlargement with generalised exfoliative dermatitis.

The dog was from the city of Zaragoza (41° 39′ 24.6276″ N, 0° 52′ 45.912″ W).), a very highly endemic area for canine

leishmaniosis. The dog was not being treated with long-acting topical anti-parasitic repellent against sandflies and/or mosquitoes.

INVESTIGATIONS

A medical history of the patient was recorded. Anticoagulated blood sample was analysed by an automated haematology analyser (LaserCyte Idexx, Westbrook, USA) to perform a complete cells blood count. Clinical biochemistry was analysed with an automatic analyser (Catalyst One Idexx, Westbrook, USA), including the following parameters: alanine aminotransferase (ALT), alkaline phosphatase (ALKP), gamma glutamyl transferase (GGT), total bilirubin (TBil), total cholesterol (Cho), glucose (GLU), total protein concentrations (TP), creatinine (CRE), blood urea nitrogen (BUN), calcium (Ca), inorganic phosphorus (P) and C-reactive protein (CPR). Urine analysis was performed, including urine specific gravity (USG) and urine sediment analysis.

Serum protein electrophoresis was also performed by agarose gel electrophoresis (AGE) system with HYDRAGEL Kit (SEBIA, Evry, France). Serum was electrophoresed for 21 minutes at 92 V hours and stained with diluted Amidoschwarz dye at pH 2 (4 g/L Amidoschwarz dye and 6.7% ethylene glycol). The AGE procedure was conducted according to the manufacturer's instructions, and commercial human serum was used as the control (normal control serum, Sebia, Evry, France). The electrophoretic curve for each sample was displayed. Protein fractions were determined as the percentage optical absorbance, and the absolute concentration in grams per decilitre was automatically calculated from the total serum protein concentration. Serum protein electrophoresis was run manually with agarose gels (Sebia, Evry, France) and densitometer (Shimadzu CS-9000, Kyoto, Japan) was used for scanning the electrophoretograms.

As canine leishmaniosis was the most prevalent disease with the presence of skin lesions, epistaxis and elevation of total proteins, it was necessary to rule out *L. infantum* performing a quantitative serology based on in-house ELISA technique.[8] Briefly, each plate was coated lightly with 100 μl/well of the 20 μg/ml antigen solution (strain MHOM/FR/78/LEM 75 belonging to *L. infantum* zimodeme MON-1) in 0.1 M carbonate/bicarbonate buffer (pH 9.6) and incubated overnight at 4°C. Plates were then frozen and stored at −20°C. One hundred microlitres of dog serum, diluted 1:800 in phosphate buffered saline containing 0.05% Tween 20 (PBST) and 1% dry skimmed milk (PBST-M) were added to each well. The plates were incubated for 1 hour at 37°C in a moist chamber. After washing the plates three times with PBST for 3 minutes, followed by one wash with PBS for 1 minute, 100 μl of protein A conjugated to horseradish peroxidase (Thermo Fisher Scientific, Waltham, MA, USA) diluted 1:20,000 in PBST-M was added to each well. The plates were incubated for 1 hour at 37°C in a moist chamber, followed by washes with PBST and PBS as described above. The substrate solution (ortho-phenylene-diamine) and stable peroxide substrate buffer (Thermo Fisher Scientific, Waltham, MA, USA) were added (100 μl per well) and developed for 20 ± 5 minutes at room temperature in the dark. The reaction was terminated by adding 100 μl of 2.5 M H_2SO_4 to each well. Absorbance values were read at 492 nm (reference wavelength) in an automatic microELISA reader (ELISA Reader Labsystems Multiskan, Midland, Canada). Each plate included serum samples from a dog infected with *L. infantum* as confirmed by cytological examination as a positive control (calibrator) and serum samples from a healthy, non-infected dog from the blood donor programme as a negative control. The same calibrator serum sample was used for all assays, and the plates with an interassay variation greater than 10% were tested again. All samples and controls were analysed in duplicate. The results were quantified as ELISA UNIT (EU) compared to a positive control serum sample used as a calibrator that was arbitrarily set to 100 EU. The cutoff value was set to 30 EU (mean + 4 standard deviations of values from 70 apparently healthy dogs from a non-endemic area and that were not included in this study). Sera with an EU ≥200 were classified as high positive, with an EU ≥100 and <200 as moderate positive, and with an EU >30 and <100 as low positive. All samples with an optical density (OD) equal or higher than 3 were studied using a two-fold serial dilution.[9] The samples were started at 1:800 dilution and continued for 10 further dilutions in the same ELISA plate. The results were quantified as EU related to a calibrator arbitrarily set at 100 EU with an OD of 1.00 at the 1:800 dilution. The values of the dilutions at which the OD was close to 1.00 was chosen for the calculation of the EU using the following formula: (sample OD/calibrator OD) × 100 × dilution factor.

Laboratory findings revealed total protein increase, hyperglobulinemia, anaemia and CPR. The rest of the biochemical parameters were within the reference ranges. Urinalysis showed no abnormalities. Serum protein electrophoresis was also performed to investigate the nature of hyperglobulinemia. The electrophoresis revealed spike in the beta fraction (Figure 1).

Protein bands, forming the different electrophoretic regions, were identified using electrophoretic immunofixation (IFE) (Hydragel 4 IF Sebiat, Evry, France), a highly specific method was used to identify the exact location of proteins.[10] This method is based on the recognition of a single protein by addition of a specific antibody (antisera) to the agarose gel substrate after electrophoretic migration

LEARNING POINTS/TAKE HOME MESSAGES

- To the best of our knowledge, this is the first case report describing the presence of an important reduction of anti-*Leishmania* antibodies after starting anti-*Leishmania* treatment.
- Canine leishmaniosis should be included in the differential diagnostic list for patients presenting presumptive polyclonal spike in the beta fraction in endemic areas of *Leishmania infantum* infection.
- C-reactive protein could be used as a biomarker in association with serum protein electrophoresis to evaluate the treatment response against *Leishmania*.
- Low levels of immunoglobulin A deficiency could be detected in dogs with infectious conditions such *Leishmania infantum*.

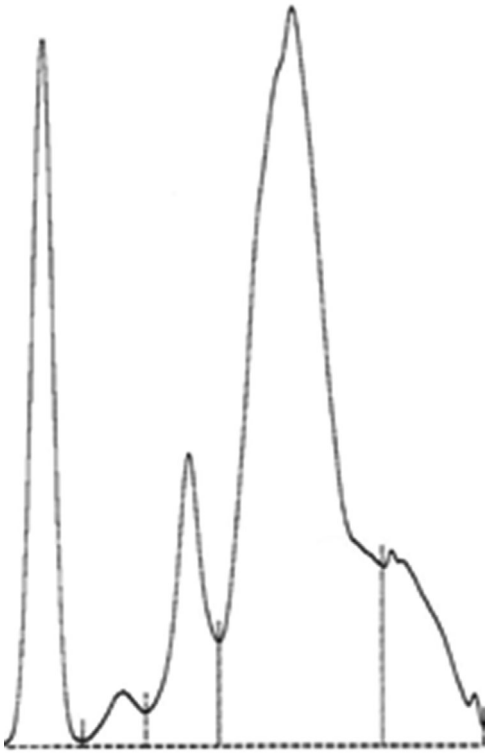

FIGURE 1 Electrophoretogram using agarose gel electrophoresis. A presumptive polyclonal spike in the beta fraction is detected

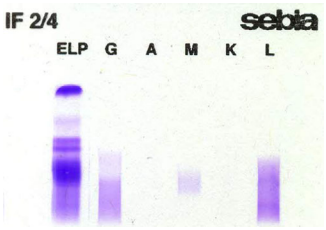

FIGURE 2 Protein characterisation using immunofixation before the treatment. A polyclonal pattern composed by IgM and IgG is detected

(Hydrasys 2 Scan Focusing, Sebia, Evry. France). In our case, the antisera used was the same that has been applied in human medicine based on company recommendations due the conserved structure among mammals and the possibility of cross-reaction phenomenon among human and dog antibodies. No monoclonal band was observed in any of the three major immunoglobulins analysed, classifying it as polyclonal pattern composed by IgM and IgG and the absence of IgA (Figure 2).

Protein levels (IgG, IgA and IgM) were analysed in the serum samples by nephelometry. IgG, IgA and IgM were analysed using IMMAGE 800 (Beckman-Coulter, USA) nephelometer. Additionally, a total of 10 dogs, including different breeds with similar age to the present case report and classified as healthy, were included to evaluate the limit of detection of this technique. All dogs had higher levels than detection limit.

DIFFERENTIAL DIAGNOSIS

There are different causes of hyperglobulinemia in dogs.[10] This alteration could be the result from increases in any or all the serum protein fractions, including α-globulins, β-globulins and γ-globulins. In the present case report, the shape of the electrophoretogram was very useful to characterise the hyperglobulinemia with the presence of a polyclonal betagammopathy that accompanies an elevation in γ-globulins as a consequence of *L. infantum* antigenic stimulation. This situation could be explained because immunoglobulins such as IgA, IgM and specific subclasses of IgG migrate in the β-globulin fraction. The most common causes of polyclonal gammopathy include inflammatory diseases (infectious, immune mediated), liver disease and suppurative dermatopathies.

The differential diagnosis list of ulcerative dermatitis[11–13] includes infectious diseases (leishmaniosis, mucocutaneous bacterial pyoderma), immune-mediated diseases (fly bite dermatitis, pemphigus and subepidermal bullous dermatoses, cutaneous and systemic lupus erythematosus, idiopathic vasculitis, cold agglutinin disease, proliferative thrombovascular necrosis of the ear pinnae, proliferative arteritis of the nasal philtrum, superficial necrolytic dermatitis, uveodermatological syndrome, dermatomyositis, actinic dermatosis,), drug (adverse drug reactions), environmental causes (frostbite), nutritional cause (zinc-responsive dermatosis) and skin tumour (epitheliotropic lymphoma).

TREATMENT

Treatment was focused on the parasite *L. infantum*. An anti-*Leishmania* therapeutic protocol was established with allopurinol at 10 mg/kg twice a day PO sine die and meglumine antimoniate at 40 mg/kg twice daily (BID) subcutaneously for 5 weeks. The patient did not require any other treatments.

An anti-*Leishmania* therapeutic protocol was established with allopurinol at 10 mg/kg BID PO sine die and meglumine antimoniate for 3 weeks at increasing doses every week to control possible drug adverse effects from 25 mg/kg BID the first week to 40 mg/kg BID the third week subcutaneously.[6,14]

OUTCOME AND FOLLOW-UP

The nosebleed was resolved in 15 days after starting anti-*Leishmania* treatment, while ulcerative dermatitis was resolved 2 months later (Day 125). Follow-up visits were carried out during the period of meglumine antimoniate treatment. Four months after completing the meglumine antimoniate treatment, a follow-up visit to the attending veterinarian was made. At this follow-up visit, a physical examination and laboratory test were performed including CBC, serum biochemistry and serum protein electrophoresis (Table 1). In addition, serum protein electrophoresis using AGE was performed detecting a normal pattern serum protein electrophoresis (Figure 3) with the presence of IgG pattern detected by IFE (Figure 4).

DISCUSSION

Selective immunoglobulin A deficiency (IgAD) is the most prevalent type of primary immunodeficiency in humans and dogs.[15] In humans, this selective immunodeficiency may be

TABLE 1 Haematological, biochemical parameters and serology determined in the leishmaniotic dog at the first veterinary examination before treatment and during the follow-up

		After treatment								
Parameter	**Before treatment**	**Day 7**	**Day 14**	**Day 21**	**Day 28**	**Day 35**	**Day 65**	**Day 125**	**Day 185**	**Reference range**
Haematology WBC (K/μl)	11.58	8.66	13.99	13.34	13.41	11.34	13.70	13.63	10.81	5.05–16.76
Neutrophils (K/μl)	8.78	4.32	9.14	7.93	7.78	5.59	6.93	7.42	5.55	2.95–11.64
Lymphocytes (K/μl)	1.85	2.97	3.37	3.88	4.40	4.42	5.00	4.93	4.25	1.05–5.10
Monocytes (K/μl)	0.91	0.96	1.01	1.07	1.01	0.87	0.81	0.59	0.54	0.16–1.12
Eosinophils (K/μl)	**0.01**	0.36	0.41	0.44	0.21	0.41	0.92	0.67	0.46	0.06–1.23
Basophils (K/μl)	0.03	0.05	0.06	0.02	0.01	0.05	0.04	0.02	0.01	0.00–0.10
RBC (M/μl)	**4.72**	**4.70**	**4.53**	**4.73**	**5.28**	5.94	7.58	6.34	7.85	5.65–8.87
Haematocrit (%)	**26.4**	**26.4**	**24.8**	**25.0**	**29.4**	**33.1**	43.0	39.4	51.2	37.3–61.7
Haemoglobin (g/dl)	**9.2**	**9.4**	**8.7**	**8.9**	**10.0**	**11.3**	14.7	13.2	18.2	13.1–20.5
MCV (fl)	**55.9**	**56.2**	**54.7**	**52.9**	**55.7**	**55.7**	**56.7**	62.1	65.2	61.6–73.5
MCH (pg)	**19.5**	**20.0**	**19.2**	**18.8**	**18.9**	**19.0**	**19.4**	**20.8**	23.2	21.2–25.9
MCHC (g/dl)	34.8	35.6	35.1	35.6	34.0	34.1	34.2	33.5	35.5	32.0–37.9
RDW (%)	20.5	19.4	19.3	19.5	20.1	21.6	**22.5**	**22.5**	16.1	13.6–21.7
Plateles (K/μl)	397	406	450	278	335	483	375	199	278	148–484
Reticulocytes (K/μl)	14.6	55. 5	88.8	**125.3**	**137.8**	**162.2**	32.6	105.2	62.8	10.0–110.0
% Reticulocytes	0.3	1.2	2.0	2.7	2.6	2.7	0.4	1.7	0.8	
Reticulocyte haemoglobin (pg)	25.3	24.5	**20.4**	**19.9**	**20.2**	**22.2**	24.2	25.1	25.7	22.3–29.6
Blood chemistry										
ALT (U/L)	64	38	27	33	16	16	13	43	30	10–125
ALKP (U/L)	30	30	29	24	35	38	37	40	31	23–212
TBil (mg/dl)	0.5	0.3	0.4	0.5	0.4	0.4	0.3	0.3	0.1	0.0–0.9
Cho (mg/dl)	138	120	140	115	123	140	166	155	149	110–320
Glu (mg/dl)	79	80	86	79	87	89	82	84	86	74–143
Crea (mg/dl)	0.8	0.9	1.0	1.0	1.0	1.2	1.2	1.3	1.3	0.5–1.8
BUN (mg/dl)	19	14	14	15	13	17	17	21	20	7–27
P (mg/dl)	4.8	4.2	4.9	5.6	5.9	5.4	4.5	3.6	3.3	2.5–6.8
Ca (mg/dl)	9.1	8.8	8.9	9.0	9.3	9.1	9.2	8.8	9.0	7.9–12.0
GGT (U/L)	0	0	0	2	0	0	0	3	4	0–11
Amylase (U/L)	845	1167	1229	1394	1331	906	1001	727	817	500–1500
Lipase (U/L)	389	399	465	582	859	806	879	715	1094	200–1800
Electrophoretograms of serum proteins (AGE)										
Total protein (g/dl)	**9.1**	**9.3**	**9.5**	**9.7**	**9.5**	**9.6**	**8.7**	6.6	6.5	5.4–7.1
Albumin (g/dl)	2.4	2.5	2.5	2.5	2.5	2.6	2.8	2.5	2.7	2.3–4.0
Globulins (g/dl)	**6.8**	**6.8**	**7.1**	**7.2**	**7.0**	**7.0**	**5.9**	4.0	3.7	2.5–4.5
Alpha 1 globulins (g/dl)	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.3	0.2–0.5
Alpha 2 globulins (g/dl)	0.9	0.7	0.7	0.7	0.7	0.8	0.6	0.7	1.0	0.3–1.1
Beta globulins (g/dl)	**4.6**	**4.7**	**5.1**	**5.2**	**4.9**	**4.7**	**4.0**	**2.3**	1.6	0.9–1.6
Gamma globulins (g/dl)	**1.1**	**1.2**	**1.1**	**1.1**	**1.2**	**1.3**	**1.1**	0.8	0.8	0.3–0.8
A/G	0.3	0.4	0.3	0.3	0.4	0.4	0.5	0.6	0.7	
Acute phase protein										
CPR (mg/dl)	**1.8**	**1.7**	**2.4**	**3.6**	**3.0**	0.9	0.4	0.3	0.3	0.0–1.0
Globulins level										
IgA (mg/dl)	<6.67	NA	NA	NA	NA	NA	NA	NA	<6.67	NA
IgG (mg/dl)	596	NA	NA	NA	NA	NA	NA	NA	487	NA
IgM (mg/dl)	180	NA	NA	NA	NA	NA	NA	NA	135	NA
Urine analysis										
USG	1035	1030	1032	1038	1034	1035	1036	1034	1032	1015–1040

(Continues)

TABLE 1 (Continued)

Parameter	Before treatment	After treatment								Reference range
		Day 7	Day 14	Day 21	Day 28	Day 35	Day 65	Day 125	Day 185	
Urinary sediment	–	–	–	–	–	–	–	–	–	
Serology										
One dilution (EU)	312(+++)	264(+++)	242(+++)	238(+++)	275(+++)	197(++)	173(++)	105(++)	102(++)	≥21
Two-fold serial dilution (EU)	527,519	410,015	322,226	280,120	205,414	172,902	160,526	83,767	81,278	

Note: Abnormalities are highlighted in bold.
Abbreviations: A/G, albumin:globulin ratio; Ig, immunoglobulin; MCH, mean corpuscular haemoglobin; MCHC, mean corpuscular haemoglobin concentration; MCV, mean corpuscular volume; NA, not available; RBC, red blood count; RDW, red blood cell distribution; WBC, white blood count.

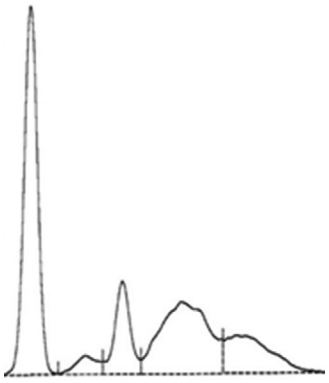

FIGURE 3 Electrophoretogram using agarose gel electrophoresis at Day 185. The electrophoresis revealed normal pattern serum protein

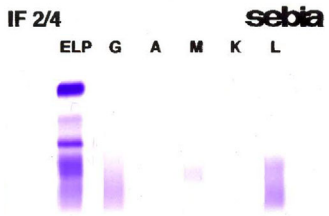

FIGURE 4 Protein characterisation using immunofixation after treatment at Day 185. An IgG pattern is detected

asymptomatic or on the contrary, the presence of insidious symptoms from mild to severe, including respiratory infections, gastrointestinal infections, autoimmunity diseases and/or allergic diseases. It was first reported in the early 1960s,[16] and 20 years later, the presence of this selective IgAD was described in dogs.[17] It is important to point out that IgA concentrations are found to vary widely between breeds, which explains the lack of a generally accepted diagnostic reference range for IgA deficiency in dogs.[18] However, in the present case report, IFE technique determined the absence of IgA pattern before the treatment and after the treatment at Day 185 (Figure 4). Moreover, IgA levels were lower than detection limit of the second technique performed before and after the treatment (Table 1).

Generally, canine immunodeficiency disorders are less characterised in comparison to human medicine. Two different types of canine immunodeficiencies are described: primary immunodeficiency associated to puppies and typically breed-related or secondary immunodeficiency in adults. This second condition in dogs is a consequence of a variety of causes, including drugs, neoplastic disorders, infectious diseases, inflammatory and allergic diseases among others. In humans and dogs, these disorders are associated with a mutation in the gene encoding the Ig alpha chain, with a relative low concentration in mucosal areas or in the serum. Selective IgAD has been described in several breeds, including German shepherd dog and English bull terrier.[19,20]

Canine leishmaniosis is a vector borne disease caused by *L. infantum*. The parasite is able to compromise the dog's immune response, making it susceptible to other co-infections and/or disorders.[21]

Coexistence of *Leishmania* and a selective IgAD is not described in the literature. It is difficult to establish the cause–effect relationship. If the IgAD is the consequence of the presence of the parasite or by contrast, the selective immunodeficiency may predispose an increase in the susceptibility to the infection. Some different factors, including breed, concomitant diseases (infectious diseases, neoplasia, endocrinopathies), immunosuppression status and nutritional factors, can directly influence the susceptibility to infection.[22] Although it is not possible to explain the relationship between the parasitic disease and selective immunoglobulin deficiency, the results of this case report document the ability of *Leishmania* to infect dogs with a type of immunodeficiency. In the present case report, selective IgAD is not secondary to the parasite infection because 6 months after clinical presentation, no clinical signs or clinicopathological abnormalities have been detected except for the fact that the dog presents this selective IgAD.

The relationship between the presence of anti-*Leishmania* IgA and dogs suffering clinical leishmaniosis has been evaluated in urine and serum samples.[23] The role of the IgA is associated to mucosal immunology as first level of protection in mucosal secretions. The absence of IgA in serum samples might favour the presence of the parasite in mucosal areas, including nasal cavity, with the appearance of lesions such as epistaxis.

Traditionally, quantitative serology is not recommended before 6 months after initial anti-*Leishmania* treatment. However, recent evidences confirm that an early reduction of anti-*Leishmania* antibodies is detected after 30 days after the first meglumine antimoniate injection. In our case report, a marked reduction of the anti-*Leishmania* antibodies was detected during the meglumine administration based on the serial dilution method ELISA in comparison to one dilution method.[8] The reason for this difference between one dilution and the ELISA serial dilution method is due to in the first case, a high anti-*Leishmania* antibodies concentration is present

in the serum sample analysed. This condition produces a saturated signal in the ELISA technique, whereas the use of sample dilutions by serial dilution ELISA method decreases the amount of anti-*Leishmania* antibodies avoiding ELISA limits. The reduction of the level of anti-*Leishmania* antibodies during the meglumine antimoniate administration correlates with the clinical course and laboratory findings such as CPR.

The use of CPR as biomarker in canine leishmaniosis has been evaluated in dogs undergoing leishmaniosis treatment.[24] The measurement of this APP could be of interest because it could help clinicians to make decisions during the follow-up. A decrease in serum protein electrophoresis during meglumine antimoniate treatment is detected even before the improvement. The reduction of CPR concentration is a laboratory parameter that can help clinicians to evaluate the response to anti-*Leishmania* therapy in short-term, together with the quantitative serology.

The clinician should be aware that early reduction of anti-*Leishmania* antibodies can be detected using serial dilution ELISA method after starting meglumine antimoniate treatment in dogs with leishmaniosis. Moreover, anti-*Leishmania* antibodies reduction correlates with CPR reduction during meglumine antimoniate administration.

CONFLICT OF INTEREST

The authors declare they have no conflicts of interest.

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ETHICS STATEMENT

No ethical committee approval was necessary.

AUTHOR CONTRIBUTIONS

All authors made substantial contributions. Sergio Villanueva-Saz and Maite Verde managed the case. Antonio Fernández and Luis Martínez performed the laboratory analyses. Sergio Villanueva-Saz and Andres Yzuel drafted the manuscript. All authors participated in critically appraising the manuscript and revising it for intellectual content. All authors gave final approval of the completed manuscript.

ORCID

Sergio Villanueva-Saz https://orcid.org/0000-0001-6209-4282

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