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What is your Diagnosis?

SYSTEMIC LUPUS ERYTHEMATOSUS – DIAGNOSTIC AND TREATMENT CHALLENGES

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STUDY TOPIC

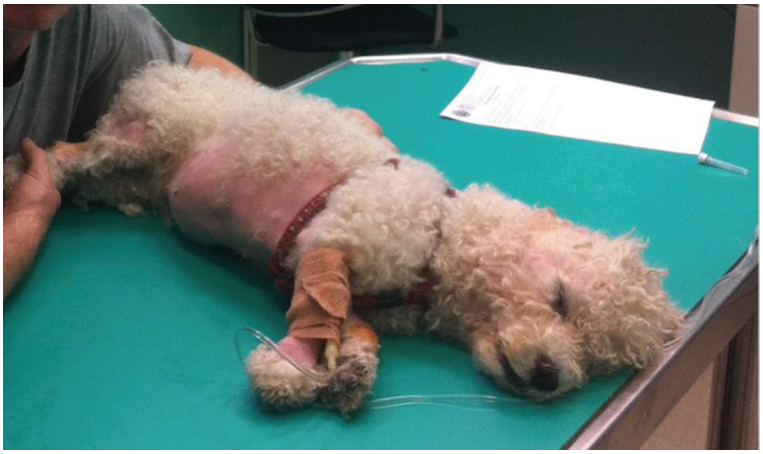

Figure 1. The patient at admission.

CASE PRESENTATION

History

A five and a half year old neutered female Bischon Frise was referred to the Clinic for Internal Medicine, Faculty of Veterinary Medicine, Zagreb, Croatia, for further

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diagnostic work-up of a 3-month history of orthopedic difficulties (shifting-leg lameness), fever (ranging from 39.2-39.8°C), weight loss, and frequent periods of lethargy and anorexia. Before admission, the dog was treated by several veterinarians, mainly with combinations of non-steroidal anti-inflammatory drugs and antibiotics. At the time of admission, the dog was taking thyroid hormone supplementation (levothyroxine) continuously for two months due to the low values of thyroid hormones measured, but without any improvement. During the previoius month, skin problems had also occurred. The dietary history consisted of cooked meat (chicken, veal, beef) as well as various treats.

Physical investigation

Physical examination revealed Body Condition Score (BCS) of 2/9, lethargy, reluctance to move, fever (39.6°C), mild enlargement of popliteal lymph nodes, moderately painful and swollen carpal joints, diffuse skin scaling with erythema as well as symmetrical alopecia on both elbows, knees and abdomen, and unilateral alopecia on the right cheek (Figure 1).

Routine haematology and serum biochemistry showed marked leukocytosis with a left shift, mild anemia, mild hypoalbuminemia (with normal total proteins), moderately increased activity of creatine kinase (CK) and severely increased C-reactive protein (CRP) concentration (Table 1).

Thoracic and abdominal radiography were unremarkable, while radiography of carpal and tarsal joints revealed only minor tissue swelling with no signs of bone or cartilage destruction.

Table 1. Haematology and biochemistry results at admission

Laboratory parameter	Patient	Reference value*
WBC [x10^9 /L]	28.6^{H}	6-17
RBC [x10^12 /L]	5.2^{L}	5.5-8.5
HCT[%]	35^{L}	37-55
PLT	241	200-700
NSG [%]	6^{H}	0-1
TP [g/L]	65	55-75
ALB [g/L]	21^{L}	26-33
CK [U/L]	690^{H}	-160
CRP [mg/L]	150^{H}	0-10

*Reference values from Laboratory of the Clinic for Internal Medicine, Faculty of Veterinary Medicine, Zagreb, Croatia. (WBC – white blood cell count, RBC – red blood cell count, HCT – haematocrit, PLT – platelet count, NSG – non-segmented neutrophils, TP – total protein concentration, ALB – albumin concentration, CK – creatine kinase, CRP – C-reactive protein, H – above the reference range, L – below the reference range).

What is your diagnosis?

- What are your differential diagnoses for fever/pyrexia, joint pain and skin lesions combined with increase in CRP?
- How would you evaluate this patient further?
- How would you treat and monitor this patient?

INTERPRETATION

1. Differential diagnoses

On the basis of history, clinical presentation and laboratory findings at admission, the following differentials were considered:

- systemic lupus erythematosus (SLE)
- non-erosive immune-mediated polyarthritis
- pemphigus erythematosus
- pemphigus foliaceus
- steroid responsive meningitis-arteritis (SRMA)
- neoplasia
- vector-borne diseases
- kidney disease
- bacterial/fungal/viral infections
- musculoskeletal disorders

2. Further evaluation

In order to confirm/exclude each differential, the following diagnostic plan was performed:

- Creatine kinase concentration (muscular involvement) with potential muscle biopsy if needed.
- Urine analysis, urine protein to creatinine ratio (UPCR) and systolic blood pressure (kidney diseases).
- Abdominal ultrasonography (systemic changes).
- Fine needle aspiration (FNA) of enlarged lymph nodes (infections, neoplasia, vector-borne diseases with leishmaniasis being the most consistent with clinical signs).
- Idexx SNAP 4DXplus test as well as PCR for vector-borne diseases (*Anaplasma*, *Borelia*, *Erlichia*, *Babesia* spp. and *Leishmania).*
- Synovial fuid analysis (SLE, non-erosive immune-mediated polyarthritis).
- Cerebrospinal fluid (CSF) analysis with cytology and culture (SRMA).
- The antinuclear antibody (ANA) test (SLE).
- Dermatology workup (pemphigus erythematosus, pemphigus foliaceus).

The results of procedures performed were:

- Systolic blood pressure was normal (150 mmHg).
- Urine analysis showed marked proteinuria with UPCR of 2.2 and with no sediment abnormalities noticed on light microscopy.
- Abdominal ultrasonography revealed nonspecific, mild changes, mainly in the spleen, liver, and kidneys.
- FNA of the popliteal lymph nodes showed reactive hyperplasia with predominance of small lymphocytes.
- Idexx SNAP 4DXplus test as well as PCR for *Anaplasma*, *Borelia*, *Erlichia*, *Babesia* spp. and *Leishmania* were negative.
- Cardiology workup performed as a part of preanesthesia work-up (due to CSF tap and arthrocentesis sampling) was unremarkable.
- Synovial fuid analysis revealed an increased nucleated cell count (90,000 cells/μl), consisting primarily of nondegenerate neutrophils (>80%).
- Cytology and culture of CSF analysis was unremarkable.
- Both urine and synovial fluid were negative for bacteria and *Mycoplasma*.
- The antinuclear antibody test (ANA) was positive with a titer of 1:800.

On the basis of four major and two minor signs present (Table 2) and a positive ANA titer, the diagnosis of SLE was confirmed.

3. Treatment and monitoring

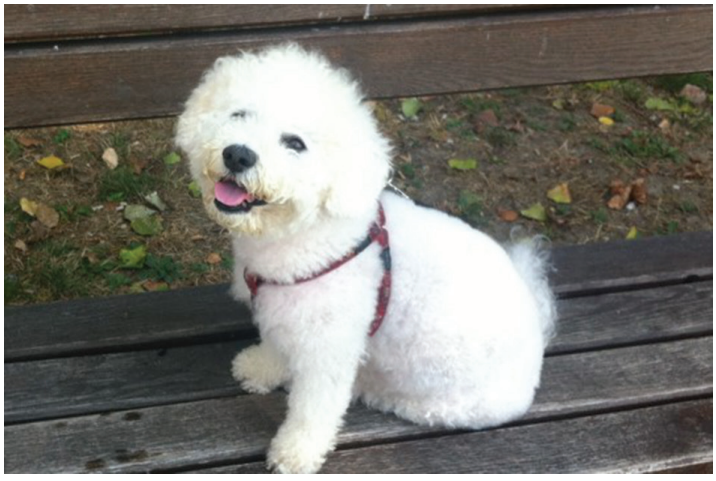

Figure 2. The patient after 18 months of prednisone monotherapy.

While awaiting the above-mentioned laboratory results, the dog was hospitalized for fluid, analgesia and antibiotics therapy for a ten-day period during which periocular hair loss developed. The thyroid supplementation therapy was discontinued at admission.

After confirmation of SLE as the diagnosis, corticosteroids were included in the therapy (prednisone 2 mg/kg every 12 hours) resulting in rapid improvement of clinical signs. This was followed by patient discharge with frequent controls. After 14 days of prednisone therapy, the patient was clinically much better (started eating, gaining weight), so the prednisone dose was reduced by 25% and this level of reduction was repeated approximately every 30 days. At the moment (18 months after establishing the diagnosis) the patient is still receiving prednisone (1.64 mg/kg every third day) and remains without any observable symptoms (Figure 2), with laboratory parameters (complete blood count, CRP concentration) within the reference ranges. During the treatment there were no severe side effects of prednisone monotherapy (neither considering clinical symptoms nor blood or urine analyses) compatible with corticosteroid treatment, as well as no relapse, so there was no requirement for the use of any other immunosuppressive drugs.

As the patient status improved and because of the history of low thyroid hormone levels, thyroid function testing was repeated (total T4, free T4, and canine TSH). The results were within the normal range.

DISCUSSION

Systemic lupus erythematosus is an autoimmune disease which results in immune complexes deposition in tissues, resulting in inflammation and damage to various organs. SLE is rare in dogs, but is believed to be underdiagnosed and with no clear etiology so far.

Because of its variable presentation, progressive and unpredictable nature, SLE is often difficult to diagnose. The occurrence of clinical signs depends on organ involvement and may be acute or chronic with relapsing and remitting courses (the symptoms can wax and wane), mystifying both owner and clinician. Furthermore, the symptoms of this disease is to mimic all kinds of other diseases, which makes the diagnostics both expensive and difficult.

The definitive diagnosis is confirmed when two major signs and positive serologic test results are present or one major and two minor signs and positive serologic test results are present (Table 2). Measurement of ANA antibodies is a sensitive indicator for diagnosing SLE in dogs although ANA-negative cases of SLE do occur.

The treatment requires immunosuppressive medications, usually combined and considered as a life-long therapy with potentially serious side effects, making both the disease and its treatments aggravating. The treatment requires great owner devotion and frequent monitoring of medication effectiveness as well as early recognition of severe side effects.

The prognosis of SLE is variable, and relatively guarded, with concurrent organ dysfunction being often responsible for death or euthanasia. Regardless of the drug protocol used, there is great expectance of subsequent relapses that could involve

different organ systems and clinical signs than at the initial presentation. The case described here is a rare example of such a long period of prednisone monotherapy (18 months so far) without any severe side effects as well as with excellent life quality of the patient. This should encourage clinicians to persevere with a comprehensive protocol for diagnosis establishment when faced with any severely ill patient.

Table 2. Criteria for diagnosis of SLE (Signs that were present in this patient are marked bold).

MAJOR SIGNS	MINOR SIGNS
Polyarthritis	**Fever of unknown origin**
Dermatologic lesions (consistent with SLE)	CNS signs
Glomerulonephritis	Oral ulceration
Polymyositis	**Lymphadenopathy**
Hemolytic anemia	Pericarditis
Immune-mediated thrombocytopenia	Pleuritis
Immune-mediated leukopenia	

Authors' contributions

MB, MT, FK, IJ, IK, IŠ, MC and VM have all included in clinical management of the patient as well as writing this paper.

Declaration of conflicting interests

The authors declare that they have no competing interests

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SISTEMSKI ERITEMATOZNI LUPUS – IZAZOVI U DIJAGNOSTICI I LEČENJU

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Kratak sadržaj

Slučaj psa rase Bischon Frise starog pet i po godina, sa simptomima kao što su: naizmenična hromost na različitim ekstremitetima, groznica, gubitak težine, letargija i anoreksija, vraćen je na drugo stručno mišljenje. Dijagnostički postupak je vodio do sumnje na SLE. Temeljan klinički pregled, hematološka i biohemijska ispitivanja, testiranje na vektorski prenosive bolesti, analiza urina, rentgenski snimak toraksa, abdomena, karpalnih i tarzalnih zglobova, ultrazvučni pregled abdomena, ispitivanje sinovijalne i cerebrospinalne tečnosti je obavljeno radi isključenja diferencijalnih dijagnoza. Pozitivan ANA test sa četiri glavna i dva sporedna klinička znaka, potvrdio je ovu dijagnozu. Monoterapija prednizonom se pokazala dovoljnom.