WHAT IS YOUR DIAGNOSIS?

A 2 year old, female neutered Shar Pei was presented to the R(D)SVS Emergency Critical Care Service for investigation of acute onset unilateral epistaxis. The dog was a rescue dog from Spain and had been in the owner’s possession for one year. The dog was up to date with vaccines, flea and worming treatment. The dog had no previous medical conditions apart from some mild hyperkeratosis on the pads and occasional sneezing over the last year. On physical examination, the dog was bright, alert and responsive. The heart rate was 126 beats per minute with no arrhythmia and good pulse quality. Systolic blood pressure was 138mmHg. There was no abnormal respiratory noises audible on thoracic auscultation although the dog was very tachypneic at 84 breaths per minute. The oral mucous membranes were pink and moist, capillary refill time was 2 seconds and skin turgor was normal. Abdominal palpation was unremarkable and all peripheral lymph nodes were within normal limits. The rectal temperature was 39.1°C. There was moderate bleeding from the left nostril, which was causing the dog anxiety and discomfort.

1. What are your differentials for epistaxis?

2. What initial investigations would you like to do?
1) Differential Diagnoses for Epistaxis

Coagulopathy

1. Thrombocytopenia - Platelet destruction - immune mediated (idiopathic, drug induced, *Ehrlichia*)
   - Lack of platelet production - bone marrow disease (neoplasia, aplastic anaemia, infection)
   - Consumption of platelets (e.g. DIC)
2. Thrombopathia - Platelet dysfunction
   - Congenital - von Willebrand’s disease
   - Acquired – NSAID use, hyperglobulinaemia, uraemia, DIC
3. Coagulation Factor Deficiency
   - Congenital (haemophilia A and B)
   - Acquired (rodenticide toxicity, hepatic disease, DIC)

Local disease

1. Foreign Body
2. Trauma
3. Infection (Aspergillosis)
4. Neoplasia (carcinoma, adenoma, lymphoma)
5. Vascular anomaly

Systemic vascular disease

1. Hypertension – Cushings disease, renal disease, idiopathic.
2. Hyperviscosity – hyperglobulinemia, polycythaemia

2) Initial Investigations

1. A blood sample was taken for the following tests:
   - Biochemistry - within normal limits apart from:
     | Albumin* | 23.1 | 26 - 35 | g/l |
     | Globulin* | 64.0 | 18 - 37 | g/l |
     | Protein (total)* | 87.1 | 58 - 73 | g/l |
- Haematology – mild non-regenerative anaemia (HCT 27%), normal platelet count
  - Anaplasma, Ehrlichia, Borrelia, heart worm serology – negative
  - PT and APTT within normal limits.
  - Urinalysis (within normal limits. Urea protein creatinine ratio 0.35).

2. Computer Tomography was performed which showed non-contrast enhancing material in the left ventral nasal cavity (blood) and thickened mucosa along the left nasal turbinates.

3. Rhinoscopy revealed no foreign bodies, masses or Aspergillosis plaques. Turbinates were erythematous and there were multiple blood clots.

4. Nasal biopsies revealed mild, diffuse, chronic rhinitis with no signs of neoplasia or pathogens.

5. Microbiology – no bacterial or fungal growth.

3) **How do you interpret the results of the diagnosis tests and what further testing would you like to undertake?**

From the above results, we can conclude that a space-occupying lesion or an infection with in the nasal cavity was unlikely as well as a coagulopathy due to clotting factor deficiencies or thrombocytopenia. The main abnormalities seen is the fact that there is a mild non-regenerative anaemia and a severe hyperglobulinaemia with a mild hypoalbuminemia. This could suggest that the epistaxis is due to systemic disease causing hyperviscosity and interfering with platelet function. Thrombocytopenia was confirmed with an increased buccal mucosal bleeding time. Von Willebrand testing was negative.

As there is a hyperglobulinemia and a hypoalbuminemia we know that here is an absolute hyperproteinenaemia and this is not caused by dehydration. Hyperglobulinaemia is usually associated with an infectious, inflammatory or neoplastic process. Protein electrophoresis can be used to help focus the cause of the hyperglobulinaemia. Infectious and inflammatory diseases such as chronic pyoderma, FIP, leishmaniosisis, immune mediated diseases tend to produce a polyclonal gammapathy, whereas some neoplastic processes such as lymphoma and multiple myeloma tend to produce a monoclonal gammapathy.

Protein electrophoresis on this dog showed a polyclonal gammapathy to be present making infectious/inflammatory cause more likely. Due to the travel history of the dog, leishmaniosis was suspected. A Leishmania PCR was positive, and Leishmania antibody titres results were very high giving us a confirmed diagnosis of Leishmaniosis.
Discussion

*Leishmania spp* is a parasitic organism that can cause cutaneous, mucocutaneous and visceral lesions in mammals. The primary reservoirs are canines and humans and the vectors are sand-flies. As a sand-fly bites a host, promastigotes are infected into the blood stream and are engulfed by macrophages. Here they multiply into amastigotes with phagolysosomes that separate and protect them from host cell defences. Eventually that macrophage will rupture disseminating the amastigotes, which generally congregate in the spleen, lymph nodes, bone marrow and the dermis. Leishmaniosus is a chronic disease and can incubate from 3 months to 7 years. T-lymphocyte regions in the lymphoid organs eventually become depleted, whilst at the same time there is proliferation of the antibody producing B-lymphocyte regions. This causes a large amount of unregulated B-cell activity causing excessive formation of circulating immune complexes (CIC). These CICs can stimulate the complement cascade causing vasculitis and pathology throughout the body leading to polyarthritis, ocular lesions, dermal and mucocutaneous lesions, glomerular nephritis, necrosis and occasionally nervous system involvement. Most mortality from the disease is due to eventual kidney failure.

Clinical signs can be varied, but include:

- Weight loss, Polyuria, Polydipsia, Muscle wastage, Gastrointestinal signs, Cough, Epistaxis, Sneezing, Splenomegaly, Lymphadenopathy, Facial alopecia, Dermatitis, Rhinitis, Hyperkeratosis, Conjunctivitis, Uveitis, Swollen painful joints.

To help guide prognosis and treatment a staging system has been created, summarized below:

**Stage 1** – very mild clinical signs eg. dermatitis, low positive to negative antibody titres with no other laboratory findings. – *Good prognosis*.

**Stage 2** – stage 1 clinical signs plus worsening skin lesions such as ulcerations of foot pads, fever, weight loss and epistaxis, low to high positive antibody titres, mild non-regenerative anaemia, hyperglobulinaemia, hypoalbuminemia with hyperviscosity syndrome.
- Sub stage a – no azotaemia and a normal UPC
- Sub stage b – no azotaemia and UPC 0.5-1.
  *Good – guarded prognosis*

**Stage 3** – medium to high antibody titres, all clinical signs and laboratory findings in stage 2 findings plus CKD (chronic kidney disease) IRIS stage 1, UPC >1 plus signs such as vasculitis and glomerular nephritis – *Guarded to poor prognosis*
Stage 4 – as for stage 3 plus CKD IRIS stage 3, UPC >2 and signs such as pulmonary thromboembolism and end stage renal disease – Poor prognosis

Treatment for leishmaniosis is often long, expensive and does not eliminate the parasite. Meglumine antimoniate is a pentavalent antimonial that inhibits protozoal enzymes required for glycolytic and fatty acid oxidation. This needs to be administered as a subcutaneous injection at 75-100mg/kg every 24 hours for 4 to 8 weeks. The injections have been known to cause cellulitis and the drug itself can be nephrotoxic. Careful consideration should be made whether the drug should be used in animals in Stage 3 and it should not be used in Stage 4.

An alternative to option is miltefosine. This is an alkylphospholipid with direct toxic effect to Leishmania spp and enhances T-cell and macrophage activation. This can be given orally at 2mg/kg/day for 4 weeks. This drug can cause gastrointestinal signs, and is not recommended for animals in Stage 4.

Both these drugs should be used with a combination of a 6-12 month course of allopurinol at 10mg/kg orally every 12 hours. Allopurinol is a hypoxanthine compound that gets metabolised by Leishmania spp to produce products that inhibit parasite replication. The use of allopurinol in combination with either miltefosine or meglumine antimoniate can cause reduction in clinical signs; however, if stopped there can be relapses. Some animals may need to stay on allopurinol for life and there can still be renal deterioration despite this. Side effects of allopurinol are minimal; however, the drug can predispose animals to forming xanthine uroliths.

Long term monitoring of albumin, globulin, urea, creatinine and UPC is recommended and Leishmania titres should be repeated 6 months’ post initiation of treatment. Relapses do occur and often animals will need repeated courses of miltefosine or meglumine antimoniate.

In this case, the dog was classified as having leishmaniosis Stage 2a, and the UPC and kidney parameters were normal. The dog was started on miltefosine and allopurinol and within two weeks the epistaxis and hyperkeratosis on the pads had resolved.

Summary

Leishmaniosis can be a frustrating, expensive and a lifelong condition to manage. Relapses are common and deterioration despite medications can occur. However, with early diagnosis and initiation of therapy infected animals can have a good quality of life. Prevention is key and all animals traveling to areas where Leishmania spp is
present should have protection against sand-flies with a delmethrin impregnated collar or permethrin spot on.

References:

3. Nelson, Couto, Small animal internal medicine, Third edition, Part 13, Chapter 104, p1303
4. Green, Infectious diseases of the cat and dog, Fourth edition, Section 4, Chapter 73, p 734-748
5. Tilley Smith, The 5 minute veterinary consult, canine and feline, Third edition, p420-421