AN ATYPICAL CASE OF CANINE MULTIPLE MYELOMA

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SIGNALEMENT:
A 13 year-old neutered male Shi-tzu.

CLINICAL HISTORY:
The dog was presented for a one-day history of respiratory distress.

CLINICAL FINDINGS:
On presentation, the dog had hyperthermia (40°9C) and respiratory discordance. The dog was hospitalized for oxygen supplementation and fluid therapy. Once stabilized, examination revealed pale mucous membranes, mixed dyspnea, abdominal pain and decreased vigilance. Analgesic therapy (morphine 0.2 mg/kg IV q4h) was performed. Ultrasound examination, high cPLi and a first CBC (day 3) with pancytopenia and a degenerative left shift suggested an acute suppurative pancreatitis. After treatment (ranitidine 2mg/kg IV q8h, sucralfate 1 single dose package PO q8h, lovenox 1000UI/kg SC q8h, myrtazapin ½ tablet PO q24h, doxycyclin 20 mg/kg PO q24h and buprenorphin 20 μg/kg IV q6h), the dog condition improved but pale mucous membranes persisted.
DIAGNOSTIC PROCEDURES:
Several clinical pathology investigations were performed during hospitalization (tables 1 to 3 - figures 1 to 3).

The complete blood count (CBC) (Sysmex XT-2000iV®, Sysmex Corporation, Kobe, Japon), revealed a pancytopenia with a severe normocytic, hypochromic and non-regenerative anemia (Hemoglobin (Hgb) 5 g/dL, Reference Interval (RI) : 12.4-19.2 g/dL); Red Blood Cell Count (RBC) 2.23 $10^{12}$/L (RI : 5.1-7.6 $10^{12}$/L); Hematocrit (Ht) 15.8 %, RI : 35-52 %; Mean Cell Volume (MCV) 70.9 fl, RI : 60-71 fl; Mean Cell Hemoglobin Concentration (MCHC) 31.6 g/dL, RI : 34.4-38.1 g/dL; reticulocyte count 36.8 $10^6$/L, RI : 19.4-150.1 $10^6$/L), with severe metarubricytosis (96 for 100 leukocytes) and dyserythropoiesis (sideroblasts, binucleation, foliated metarubricytes, nuclear abnormalities, gigantism, maturation asynchronism), severe panleucopenia 0.52 $10^9$/L (RI : 5.60-20.40 $10^9$/L), neutropenia 0.28 $10^9$/L (RI : 2.90-13.60 $10^9$/L), lymphopenia 0.13 $10^6$/L (RI : 1.10-5.30 $10^6$/L)), with left-shift (0.05 $10^6$/L) and toxic neutrophils, and severe thrombocytopenia 5 $10^9$/L (RI : 64-613 $10^9$/L) with signs of dysmegakaryopoiesis (Figures 3 and 4).

During the follow-up and after pancreatitis treatment, the dog condition improved but the pancytopenia persisted, with a worsening of dyserythropoiesis and metarubricytosis. A bone marrow biopsy aspiration was performed and revealed a medullary hypoplasia secondary to a severe erythroid and myeloid hypoplasia and an infiltration by plasma cells (63% of the total nucleated cells). Plasma cells were moderately modified (Figures 4 and 5).

A multiple myeloma (MM) was suspected and a serum protein electrophoresis (SPE)
(Figure 6) was performed. A mild narrow gamma-globulin peak was observed on the SPE which was highly suggestive of a monoclonal peak. Ehrlichiosis and parvovirosis were negative.

Additional tests (immunoelectrophoresis, bone radiographs) were denied by the owner of the dog.

TREATMENT AND FOLLOW-UP:
A specific myeloma treatment (melphalan 3.2 mg/kg PO q24h for 5 days each 3 weeks and prednisolone 0.5 mg/kg PO q24h for 10 days, then 0.5 mg/kg PO q48h) has been performed. The follow-up was done by the dog owner's veterinarian and one month after inducing the treatment, the dog was alert, eated normally and the CBC improved. On follow-up one year after diagnosis, a control SPE was normal and CBC was within the RI.

INTERPRETATION:
A multiple myeloma associated with a severe myelophhtysis and a secondary myelodysplastic syndrome was suspected.

DISCUSSION:
MM has been often described in dog, but is rare (2). Suspicion is usually based on clinical signs (lameness, pain, spontaneous fractures (7), hepato-splenomegaly (9)) or on clinical pathology results (hyperproteinemia with hyperglobulinemia (1,2,3), hypercalcemia (4), non regenerative anemia, thrombocytopenia and leukopenia (6)). The final diagnosis involves at least two of the following criteria: a- monoclonal gammopathy. b- lytic bone lesions. c- atypical plasma cell proliferation in bone marrow
and d- Bence-Jones proteinuria (5). In dogs, the most common monoclonal proteins (M-proteins) are IgG and IgA, which occur with nearly equal frequencies (5).

In our case, we described a very unusual MM without hyperprotidemia and/or hyperglobulinemia. The diagnosis, according to the defined criteria, has been done on bone marrow examination performed for dyserythropoiesis and pancytopenia and on SPE performed after the bone marrow examination.

In people, diagnosis is based on major and minor criteria (5) and three types of multiple myelomas are described : a- Monoclonal Gammopathy of Undetermined Significance (MGUS), characterized by bone marrow plasma cells under 10% and an Ig concentration under 30 g/L; b- Smoldering Multiple Myeloma (SMM), characterized by bone marrow plasma cells over 10% and an Ig concentration over 30 g/L; this form may progress in classical MM and c- MM characterized by bone marrow plasma cells over 30% and an Ig concentration over 30g/L. MGUS and SMM are asymptomatic forms, without hypercalcemia, renal insufficiency, anemia or bone lytic lesions (10). IL-8 is an essential cytokin in the evolution from SMM to MM (11). A study on fourteen human patients highlighted a co-occurrence of MGUS and myelodysplasia; SMM seems to be rarely associated with myelodysplasia (12). In veterinary medicine, such a classification has not been clearly defined until now. Rare cases of gammopathies in dogs without hyperproteinemia/hyperglobulinemia have been yet described and always associated with either hypercalcemia or bone lytic lesions or other classical signs (1) but never with dysmyelopoiesis. According to some results, our case could be suspected to be an atypic form of MM, with some characteristics of MGUS or SMM, even if this dog’s bone marrow was highly infiltrated by plasma cells.

Cases of MM in dogs with history of multiple chronic infectious/inflammatory diseases
Ehrlichiosis, Leishmaniosis...) have been described and suggest that chronic infection and uncontrolled long-term immune system stimulation could contribute to the MM pathogenesis (5). In our case, a context of chronic pancreatitis has been diagnosed and could result in a chronic inflammatory context which could have contributed to the MM.

To conclude, this case is an unusual MM with neither hyperprotidemia nor hyperclacemia, but a severe dyserythropoiesis and pancytopenia.

Table 1: Hematology results (Sysmex XT-2000i V)
T = blood transfusion on day 4

<table>
<thead>
<tr>
<th>Analytes</th>
<th>Day 3</th>
<th>T</th>
<th>Day 5</th>
<th>Day 7</th>
<th>Day 10</th>
<th>Day 18</th>
<th>Reference interval</th>
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<tbody>
<tr>
<td>RBC (10^{12}/L)</td>
<td>2.23</td>
<td></td>
<td>3.63</td>
<td>3.71</td>
<td>2.3</td>
<td>2.24</td>
<td>5.1-7.6</td>
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<td>HGB (g/dL)</td>
<td>5.0</td>
<td></td>
<td>8.6</td>
<td>8.6</td>
<td>5.3</td>
<td>5.4</td>
<td>12.4-19.2</td>
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<tr>
<td>HCT (%)</td>
<td>15.8</td>
<td></td>
<td>24.9</td>
<td>25.4</td>
<td>16.9</td>
<td>18.2</td>
<td>35-52</td>
</tr>
<tr>
<td>MCV (fL)</td>
<td>70.9</td>
<td></td>
<td>68.6</td>
<td>68.5</td>
<td>73.5</td>
<td>81.3</td>
<td>60-71</td>
</tr>
<tr>
<td>MCH (pg)</td>
<td>22.4</td>
<td></td>
<td>23.7</td>
<td>23.2</td>
<td>23</td>
<td>24.1</td>
<td>21.9-26.3</td>
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<tr>
<td>MCHC (g/dL)</td>
<td>31.6</td>
<td></td>
<td>34.5</td>
<td>33.9</td>
<td>31.4</td>
<td>29.7</td>
<td>34.4-38.1</td>
</tr>
<tr>
<td>RETIC (10^{6}/L)</td>
<td>36.8</td>
<td></td>
<td>81.3</td>
<td>79.0</td>
<td>55.2</td>
<td>123.4</td>
<td>19.4-150.1</td>
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<tr>
<td>Metarub (% for 100 leukocytes)</td>
<td>96</td>
<td></td>
<td>114</td>
<td>262</td>
<td>224</td>
<td>306</td>
<td></td>
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<tr>
<td>PLT (10^9/L)</td>
<td>5.0</td>
<td></td>
<td>15.0</td>
<td>10.0</td>
<td>11.0</td>
<td>15.0</td>
<td>64.0-613.0</td>
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<tr>
<td>WBC (10^9/L)</td>
<td>0.52</td>
<td></td>
<td>1.26</td>
<td>0.79</td>
<td>1.09</td>
<td>0.950</td>
<td>5.60-20.40</td>
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<td>Band Cell (10^9/L)</td>
<td>0.05</td>
<td></td>
<td>0.13</td>
<td>0.05</td>
<td>0.09</td>
<td>0.04</td>
<td>0-0.500</td>
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<td>NEUTROPHILS (10^9/L)</td>
<td>0.28</td>
<td></td>
<td>0.90</td>
<td>0.36</td>
<td>0.35</td>
<td>0.68</td>
<td>2.90-13.60</td>
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<tr>
<td>LYMPHOCYTES (10^9/L)</td>
<td>0.13</td>
<td></td>
<td>0.13</td>
<td>0.30</td>
<td>0.52</td>
<td>0.13</td>
<td>1.10-5.30</td>
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<td>MONOCYTES (10^9/L)</td>
<td>0.06</td>
<td></td>
<td>0.05</td>
<td>0.08</td>
<td>0.09</td>
<td>0.06</td>
<td>0.04-1.60</td>
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<tr>
<td>EOSINOPHILS (10^9/L)</td>
<td>0</td>
<td></td>
<td>0.05</td>
<td>0</td>
<td>0.09</td>
<td>0.04</td>
<td>0.010-1.50</td>
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<td>BASOPHILS (10^9/L)</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>Rares</td>
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Table 2: Hemostasis results (Idexx Laboratories).

<table>
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<tr>
<th>Analytes</th>
<th>Results (day 3)</th>
<th>Reference interval</th>
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<tbody>
<tr>
<td>TQ (sec)</td>
<td>8.5</td>
<td>&lt;8.8</td>
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<tr>
<td>TCA (sec)</td>
<td>9.8</td>
<td>&lt;13.5</td>
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<tr>
<td>Fibrinogen (g/L)</td>
<td>4.09</td>
<td>1.20-1.90</td>
</tr>
<tr>
<td>TT (sec)</td>
<td>11.4</td>
<td>&lt;18</td>
</tr>
<tr>
<td>D-Di (mg/L)</td>
<td>1.59</td>
<td>0.023-0.65</td>
</tr>
<tr>
<td>AT III (%)</td>
<td>108</td>
<td>107.9-128</td>
</tr>
</tbody>
</table>

Table 3: Biochemistry results (Selectra XL, VITALAB), urinalysis and ionogram (Nova8+, Nova Biomedical).
Ehrlichia serology, Parvovirosis PCR and c-PLI (Idexx Laboratories).
U: urinary

<table>
<thead>
<tr>
<th>Analytes</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
<th>Day 6</th>
<th>Day 7</th>
<th>Reference interval</th>
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</thead>
<tbody>
<tr>
<td>c-PLI(µg/L)</td>
<td></td>
<td>865</td>
<td></td>
<td></td>
<td></td>
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<td>serology</td>
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<tr>
<td>Parvovirosis</td>
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<td>negative</td>
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<td></td>
<td></td>
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<tr>
<td>PCR</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TP (g/L)</td>
<td>12</td>
<td>50</td>
<td>54</td>
<td>58</td>
<td>60</td>
<td></td>
<td>49.0-71.0</td>
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<tr>
<td>Alb (g/L)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>28.0-39.0</td>
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<td>Glob (g/L)</td>
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<td></td>
<td></td>
<td></td>
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<td>21.0-41.0</td>
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<tr>
<td>Glu (g/L)</td>
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<td>0.86</td>
<td></td>
<td></td>
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<tr>
<td>Lactates (µmol/L)</td>
<td>1.93</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Na+ (mmol/L)</td>
<td>155</td>
<td>145</td>
<td>150</td>
<td>153</td>
<td>140</td>
<td>153</td>
<td>140-153</td>
</tr>
<tr>
<td>K+ (mmol/L)</td>
<td>4.3</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4.1-5.3</td>
</tr>
<tr>
<td>Cl- (mmol/L)</td>
<td>115</td>
<td>117</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>107-115</td>
</tr>
<tr>
<td>Free Ca2+(mmol/L)</td>
<td>1.26</td>
<td>1.25</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.13-1.33</td>
</tr>
<tr>
<td>U Spec gravity</td>
<td>&gt;1.050</td>
<td>1.038</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>U pH</td>
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<td>7.5</td>
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<td></td>
<td></td>
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<td></td>
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<tr>
<td>U Prot</td>
<td>2+</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>U Bil</td>
<td>1+</td>
<td>2+</td>
<td></td>
<td></td>
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<td></td>
</tr>
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</table>
Figure 1: Blood smear (x100) stained with MGG (day 3): pancytopenia
Figures 2 and 3: Blood smear (x1000) stained with MGG (day 3); dyserythropoiesis
Figures 4 and 5: Bone marrow smear (x100 and x1000) stained with MGG (day 13); plasma cells infiltration
Figure 6: Serum protein electrophoresis (Hydrasis2scan SEBIA)

Total proteins = 70 g/L  
A/G = 0.62

<table>
<thead>
<tr>
<th>Protein fraction</th>
<th>g/L</th>
<th>Reference interval (g/L)</th>
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<tbody>
<tr>
<td>Albumine</td>
<td>26.8</td>
<td>26-33</td>
</tr>
<tr>
<td>Alpha 1</td>
<td>4.1</td>
<td>2-5</td>
</tr>
<tr>
<td>Alpha 2</td>
<td>8.0</td>
<td>3-11</td>
</tr>
<tr>
<td>Beta</td>
<td>8.8</td>
<td>7-13</td>
</tr>
<tr>
<td>Gamma</td>
<td>22.4</td>
<td>5-13</td>
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References:


