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MYELODYSPLASTIC SYNDROMES

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Myelodysplastic syndromes (MDS) are a heterogeneous group of hematologic diseases arising from stem cells. They are unified by their features which include: peripheral blood with cytopenia(s) and bone marrow cytologic features of dysplasia which can also occur in one or more cell lines. In addition to dysplasia, there are elevated levels of blast cells when a bone marrow differential count is obtained. Dysplasia is characterized by abnormalities in the nucleus and cytoplasm. Nuclear abnormalities include fragmentation, hypo- or hypersegmentation, and abnormalities of shape. Cytoplasmic abnormalities include: asynchrony of cytoplasm compared to nucleus, cellular giantism and abnormal granulation. Myelofibrosis is also common in cats and humans with all types of MDS. MDS is considered a “preleukemic or preneoplastic” state, as tranformation to acute myelogenous leukemia is common.

One popular classification and prognostication scheme used by human hematologists is the French-American-British (FAB) system. Patients with higher blast counts or Auer rods in the bone marrow cells have a poorer prognosis and their disease commonly transforms into leukemia. The FAB system does not take into account any karyotypic abnormalities or genetic mutations associated with MDS that are now known to influence prognosis.

Modifications of the FAB system have been made to account for the differences between MDS in animals and people. The systems are compared in tabular form below. Refractory anemia with excess blasts and excess blasts in transformation have been combined into one group, MDS – excess blasts. One study of 16 cats with MDS, the age ranged from 9 months – 14 years. Median was 2 years. This young age reflects the high percentage of cats that were FeLV positive (15/16) Clinical signs are vague and referable to cytopenias: petechiae, pallor, fever, and weakness. Organomegaly is found in chronic myelomonocytic leukemia, but not the other forms of MDS.

CAUSES OF MDS

MDS arise from a mutational event in pluripotential stem cells conferring a growth advantage and leading to clonal abnormalities in hematopoiesis. Cells have accelerated apoptosis and the resulting decrease hematopoiesis is the major cause of cytopenias found in peripheral blood. Predisposing factors to the mutations are radiation therapy, benzene, cigarette smoke, and prior treatment with alkylating agents. In cats, FeLV infection is a predisposition, and up to 80% of cats with MDS are FeLV positive.

Both karyotypic abnormalities and genetic mutations have been associated with human cases of MDS. One of the most common changes is the loss of a portion of the long arm of chromosome 5. The genes involved in hematopoiesis have been mapped to this region and include M-CSF, GM-CSF, IL-4, platelet derived growth factor receptor, and others. Mutations in ras genes have been found in 10-25% of patients.

CLINICAL FEATURES OF MDS

Humans with MDS have a median age of 70 years. Dogs with MDS range from 5-13 years of age, and no breed or sex predilection has been identified. One study of 16 cats with MDS, the age ranged from 9 months – 14 years. Median was 2 years. This young age reflects the high percentage of cats that were FeLV positive (15/16) Clinical signs are vague and referable to cytopenias: petechiae, pallor, fever, and weakness. Organomegaly is found in chronic myelomonocytic leukemia, but not the other forms of MDS.

DIAGNOSIS

Typically, a hypercellular BM, with peripheral cytopenias is found. Anemia is the most common cytopenia, occurring in almost all cases. Blast cell counts <30% have arbitrarily been defined as MDS and blast counts greater than 30% blasts are defined as leukemia. The presence of myeloid cells are indicated by the presence of cells staining positive for Sudan black or myeloperoxidase. Monocytic differentiation is characterized by nonspecific esterase positivity.

In evaluating a patient with potential MDS, the following differential diagnoses should be considered: acute leukemia, Poodle macrocytosis, congenital dyserythropoiesis, polymyopathy and cardiac disease in English Springer Spaniels, B12 malabsorption of Giant Schnauzer, B12 deficiency, folic acid deficiency, iron deficiency, lead toxicity and vincristine therapy.

FAB classification of MDS

<table>
<thead>
<tr>
<th>Cytologic feature</th>
<th>FAB Classification System</th>
<th>Veterinary Classification</th>
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<tbody>
<tr>
<td>Bone marrow blasts &lt;5%</td>
<td>Refractory anemia</td>
<td>MDS - erythroid predominant Bone marrow erythroid cells &gt;50%</td>
</tr>
<tr>
<td>Bone marrow blasts &lt;5% with sideroblasts.</td>
<td>Refractory anemia with ringed sideroblasts</td>
<td>MDS - refractory cytopenia Bone marrow erythroid cells &lt; 50%</td>
</tr>
<tr>
<td>Bone marrow blasts 5-20% blasts.</td>
<td>Refractory anemia with excess blasts</td>
<td>MDS - excess blasts Bone marrow erythroid cells &lt; 50%</td>
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<tr>
<td>Bone marrow blasts 20-30%. Peripheral blood blasts &gt;5%.</td>
<td>Refractory anemia with excess blasts in transformation</td>
<td>MDS - excess blasts Bone marrow erythroid cells &lt; 50%</td>
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<tr>
<td>Bone marrow blasts 5-30%. &gt;1000 monocytes/ul.</td>
<td>Chronic myelomonocytic leukemia</td>
<td>Chronic myelomonocytic leukemia</td>
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TREATMENT

Transfusion Support - Many patients with MDS will require red blood cell transfusion since anemia is one of the most common features of MDS. RBC transfusion should be reserved for those animals with asymptomatic anemia. Platelet and granulocyte transfusions are impractical in most situations.

Hematopoietic Growth Factors promote cell differentiation and production. They usually act on late progenitors and MDS is thought to be a primitive stem cell since all cell lines are involved; consequently, they have not been widely effective in MDS. Factors which are available include granulocyte colony stimulating factor (G-CSF), erythropoietin (EPO), and granulocyte monocyte colony stimulating factor (GM-CSF). Canine and feline EPO have been cloned but are not commercially available, as has canine G-CSF. Recombinant human EPO has successfully used in one dog with MDS-erythroid predominance.

Steroids - Both glucocorticoids and anabolic steroids have been described in the treatment of MDS. Glucocorticoids are not used in humans with MDS as the disease is not believed to be immune mediated. Danazol has been used in humans with MDS with an improvement in 50% of cases with anemia and thrombocytopenia. Those patients were believed to have immune mediated thrombocytopenia.

Immunosuppressive Agents - Various immuno-suppressive agents are often tried in veterinary patients with MDS. Azathioprine and cyclosporine have not been shown to have an effect in this group of diseases.

Chemotherapy Agents - Cytosine arabinoside administered in a continuous low dose regimen was initially believed to induce differentiation in dysplastic cells. This is no longer believed to be true. Combination chemotherapy regimens have been used to treat patients with MDS at high risk for developing acute myelogenous leukemia. Restoration of normal hematopoiesis in patients with MDS can be attained using protocols with or without anthracycline agents, but neither has conferred an improved survival time.

Bone Marrow Transplantation (BMT) - Successful BMT is the only potentially curative treatment for MDS, but because BMT is typically reserved for patients less than 55-65 years, its usefulness is limited. It is considered experimental in veterinary patients.

OUTCOME

Four potential outcomes can occur in patients with MDS: First, the disease may progress to leukemia, which occurs in 20% of all human patients with MDS. Second, the disorder may resolve, either spontaneously or with treatment. Third the animal may die from complications related to the cytopenias. Finally, the animal may live with a chronic, but compensated form of the disease. Death is typically due to marrow failure or tumor progression. Because MDS is an uncommon diagnosis, there are no follow up studies to determine the frequency of each outcome. In humans, MDS with higher levels of blasts are more likely to progress to acute myeloid leukemia and consequently, they have a shorter survival time (less than 1 year compared to > 4 years). In one study of 16 cats with MDS overall survival was 2+/- 18 months. Cats with lower blast cell counts had a longer survival, 5 months versus 2 months. In a study of 12 dogs with MDS, those with refractory anemia responded to human recombinant erythropoietin and had a longer survival time than dogs with other MDS; however mean survival time was 13.6 days.

REFERENCES