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Paraneoplastic syndromes are abnormalities mediated through a tumor product that affects a distant organ or tissue. Paraneoplastic syndromes are important because some (hypercalcemia, hypoglycemia) can be life-threatening and require treatment prior to identification of the underlying disease; failure to consider tumors could lead to therapy that delays diagnosis. Suspicion of a tumor may be aroused only by the paraneoplastic syndrome in the absence of other clinical signs. Some infectious diseases mimic paraneoplastic syndromes, so recognition is critical for accurate diagnosis and prognosis. Response to therapy, or tumor recurrence, may be reflected in resolution, or reappearance, of paraneoplastic syndromes.

### Table 1. Paraneoplastic syndromes observed in the CBC

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>Mechanisms</th>
<th>Associated tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythrocytosis</td>
<td>Erythropoietin production by tumor</td>
<td>Renal (adenocarcinoma, lymphoma, fibrosarcoma), hepatic tumors, nasal fibrosarcoma</td>
</tr>
<tr>
<td>Anemia</td>
<td>Immunologic destruction of rbca, bone marrow suppression/ hypoplasia (hyperestrogenemia); blood loss through GI ulcer caused by hyperhistaminemia</td>
<td>Lymphoma, multiple myeloma, Sertoli cell tumor, mast cell tumor (MCT)c</td>
</tr>
</tbody>
</table>
| Neutrophilia          | Production of colony-stimulating factors, tumor necrosis/ inflammation      | Fibrosarcoma, carcinoma (renal tubular, salivary, sweat gland), rectal adenomatous poly |}

### Paraneoplastic syndromes recognized on laboratory results

Some common laboratory abnormalities, their proposed mechanisms, and associated tumors are in Tables 1 and 2; there are many other causes for the abnormalities listed.

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>Mechanisms</th>
<th>Associated tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoglycemia</td>
<td>Production of insulin or insulin-like compound</td>
<td>Insulinoma, hepatic tumors (carcinoma, hepatoma), other carcinomas (mammary, pulmonary, salivary), GI leiomyomas and leiomyosarcomas</td>
</tr>
<tr>
<td>Hypercalcemia</td>
<td>Production of PTHrp or other humoral mediator; increased production of PTHa</td>
<td>Lymphoma, various carcinomas (anterior, posterior, salivary), nasal, mammary, thyroid, pulmonaryb, thymoma, multiple myeloma, parathyroid adenoma/adenoma-carcinoma</td>
</tr>
<tr>
<td>Hyperglobulinemia</td>
<td>Secretion of intact, or pieces of, immunoglobulins</td>
<td>Multiple myeloma, lymphoma, leukemia</td>
</tr>
<tr>
<td>Low urine specific gravity</td>
<td>Decreased responsiveness to ADH; manifestation of hyperviscosity syndromeb</td>
<td>All tumors causing hypercortisolemia or hypercalcemia; intra-abdominal sarcomas; tumors causing erythrocytosis or hyperglobulinemia</td>
</tr>
</tbody>
</table>

### Erythrocytosis can cause hyperviscosity syndrome

Erythrocytosis can cause hyperviscosity syndrome, signs of which are attributed to poor tissue perfusion/oxygenation from increased blood viscosity and include retinal hemorrhage, neurologic abnormalities (stupor, seizures), polyuria/polydipsia, weakness and lethargy. Thrombocytosis, often clinically silent, may increase the risk for thromboembolism as has been described in a cat with metastatic bronchogenic carcinoma. Clinical signs of thromboembolism are variable and reflect the organ/tissue affected. Profound thrombocytosis (> 700,000/µl) can cause an artifactual serum hyperkalemia.

A hypoglycemic animal should have neither increased nor normal insulin concentration; the presence of either with hypoglycemia is suggestive of an insulin-secreting tumor. Abdominal ultrasonography can help...
rule out other intra-abdominal tumors that can cause hypoglycemia, and evaluate the liver, a common site of insulinoma metastasis.

Hypercalcemia is often considered of malignant origin until proven otherwise. Hypercalcemia mediated by parathyroid hormone (PTH) or parathyroid hormone-related protein (PTHrp) is usually accompanied by low, or low normal, serum phosphorous in a non-azotemic patient. After a thorough physical examination and review of routine laboratory results, assessment of PTH and PTHrp can be useful if hypercalcemia is seen with hypophosphatemia. Normal or increased PTH with hypercalcemia would suggest primary hyperparathyroidism; low PTH would suggest humoral hypercalcemia of malignancy. A normal PTHrp does not exclude a neoplastic cause of hypercalcemia. Increased PTHrp should prompt an aggressive tumor search paying particular attention to the anal sac region, thoracic and abdominal cavities. Lymphadenomegaly may be detectable only on thoracic radiographs or abdominal ultrasonography, so imaging may be bedone with, or instead of, measurement of PTH and PTHrp.

Giving glucocorticoids to hypercalcemic patients can delay the diagnosis of lymphosarcoma if this disease is not readily apparent. Some infections that cause granulomatous inflammation can also cause hypercalcemia, lymphadenomegaly, and pulmonary nodules.

Multiple myeloma (MM) can cause monoclonal gammopathy and hyperviscosity syndrome. A careful physical examination to pinpoint sites of bone pain may focus radiographic studies, but absence of bone lesions does not exclude the diagnosis. Other tests that can support a diagnosis of MM are nuclear scintigraphic bone scans, bone marrow examinations, urine globulin measurements, and negative infectious disease serology. Ehrlichia canis infection can cause monoclonal gammopathy and bone marrow plasmacytosis, two features of MM. Other infections (leishmaniasis, FIP) associated with monoclonal gammopathy should be considered if the travel/environmental history is appropriate.

**Miscellaneous syndromes**

Fever can result from production of centrally-acting cytokines, or from inflammation/necrosis. Neoplasia is a clinically important cause of fevers of unknown origin.

Coagulation disorders are common in patients with tumors. Some tumors, such as hemangiosarcoma, can cause DIC. Platelet function abnormalities (thrombocytopenia) can arise in animals with immunoglobulin-secreting tumors such as MM and plasmacytomas. Thrombocytopenias should be suspected if a patient has a bleeding disorder despite normal coagulation times or platelet counts that exceed 50,000/µl. Buccal mucosal bleeding times are the most accessible means of documenting a thrombocytopenia.

Thromboembolic disease can be a complication of neoplasia. Tumors can contribute to a hypercoagulable state and thromboembolic disease through endothelial injury, blood stasis, and imbalance of pro- and anti-coagulant factors. The tumor can serve as an embolus if portions of the tumor protruding into the vessel lumen break free from the main tumor mass.

Polyuria/polydipsia (PU/PD) is a common paraneoplastic syndrome. Hypercortisolemia secondary to pituitary or adrenal gland tumors, hypercalcemia, and intra-abdominal sarcomas (defective ADH response from an unidentified circulating factor) all cause PU/PD. Peripheral neuropathies have been observed with carcinomas of the bronchus, thyroid and mammary glands, osteosarcomas, MCT, and malignant melanomas. Myasthenia gravis has been recognized with thymomas, cholangiocellular carcinoma and melanoma. Hypertrophic osteopathy (HO) can be seen in association with a variety of tumors in both the thoracic and abdominal cavities; masses of other origins (e.g. granulomas or other inflammatory nodules) can also be a cause of HO.