RABBIT THYMOMA VS LYMPHOMA: DIAGNOSTIC AND THERAPEUTIC OPTIONS

Jennifer Graham, DVM, DABVP (Avian / Exotic Companion Mammal), DACZM
Associate Professor of Zoological Companion Animal Medicine
Cummings School of Veterinary Medicine at Tufts University
200 Westboro Road
North Grafton, MA, 01536

RABBIT THYMOMA AND THYMIC LYMPHOMA

The thymus of the rabbit is persistent, large, and located cranial to the heart, extending into the thoracic inslet. Thymoma, thymic lymphoma, and thymic carcinoma have all been reported in rabbits. Thymomas are more commonly diagnosed in rabbits than thymic lymphoma and carcinoma. The overall incidence of thymoma in rabbits is low (around 7% of reported neoplasms in 55 colony rabbits with an age range of 1-4 years) with no apparent sex predilection. The mean age at presentation was 6.7 years based on one survey of 19 cases. A thymoma is a benign neoplasm of thymic epithelial cells and is usually composed of lymphoid and reticuloepithelial cells. Rabbit thymomas are generally slow growing, potentially locally invasive tumors that rarely metastasize. Thymomas in dogs are generally classified as differentiated epithelial, lymphocyte rich, or clear cell. The World Health Organization (WHO) classifies thymomas in humans into 6 categories: Types A, AB, B1, B2, B3, and C (thymic carcinoma) based on differentiation and outcome. Classification schemes for thymomas are controversial due to heterogeneity of the subtypes and proposals have been made to separate thymic epithelial neoplasms into three broad categories based on their degrees of organotypical differentiation.

Thymic lymphoma is a malignant neoplasia involving the lymphoid component of the thymus (T-lymphocytic origin). Thymic lymphoma can affect other organs and occur systemically. Lymphoid cells may be small mature cells or pleomorphic with prominent nucleoli. Differentiation of thymoma and thymic lymphoma is challenging with cytologic examination alone and biopsy may be required for definitive diagnosis. The presence of thymic hyperplasia in normal rabbits, variation of lymphocyte proliferation in thymomas, potential for non-diagnostic samples in cystic thymomas, and decreased exfoliation of neoplastic epithelial cells compared to lymphocytes are all factors contributing to the difficulty of differentiating thymoma from thymic lymphoma.

Clinical signs

Rabbits with a cranial mediastinal mass may present with difficulty breathing. Since rabbits are obligate nasal breathers, open-mouth breathing is generally not seen. Signs of a rabbit in respiratory distress can include nostril flaring, tachypnea, and increased abdominal excursions. A heart murmur may be present due to compression of the heart by the mass. Bilateral exophthalmos with third eyelid prolapse may be seen due to pooling of blood in the retrobulbar venous plexus secondary to cranial vena cava compression. Vascular compression can also lead to edema of the head, neck, and forelimbs. In early cases, minimal clinical signs are noted and mediastinal masses may be reported as incidental findings.

Suspected paraneoplastic syndromes in rabbits include hemolytic anemia and exfoliative dermatitis. Paraneoplastic hypercalcemia has been reported as questionable in rabbits with thymoma; although hypercalcemia was described in five of nineteen cases of thymoma in a
recent retrospective study. Rabbits with thymoma may present with generalized scaling and sebaceous adenitis. Myasthenia gravis has not been reported in association with thymoma in rabbits.

**Diagnosis**

Rabbits with thymic masses may have a normal complete blood count, elevated white blood cell count, or anemia. Lymphocytosis is often noted but heterophilia with monocytosis, basophilia, eosinophilia, and thrombocytopenia has been reported. Various biochemistry abnormalities, including hypercalcemia, have been described in rabbits with mediastinal masses but not identified as significantly associated with overall survival. Thoracic radiographs are important to diagnose a mediastinal mass. Abdominal radiographs and ultrasound are helpful to rule out abdominal masses or lymphadenopathy. If a thoracic mass is seen ultrasound-guided fine-needle aspirate of the mass is recommended for cytologic evaluation. Cytologic evaluation of cases with thymoma generally yields predominantly mature lymphocytes as opposed to lymphoblasts, which would support a diagnosis of lymphoma. A cutting needle biopsy can yield a sample for histopathology and immunohistochemistry staining. Monoclonal antibodies including CD3, CD79a, and cytokeratin allow distinguishing of T cells, B cells, and epithelial cells of rabbits, respectively. Computed tomography with contrast or MRI is recommended to determine the location and extent of the thoracic mass, especially if surgery or radiation therapy are treatment options. Additional diagnostics that may be warranted include aspirates or biopsy of enlarged peripheral lymph nodes or subcutaneous masses, bone marrow aspiration, and skin biopsy. Flow cytometry and PARR have not been validated for the diagnosis of rabbit mediastinal masses to date. Although more invasive, thoracoscopy or thoracotomy with biopsy can be considered to obtain a definitive diagnosis.

**TREATMENT**

Treatment options for mediastinal masses in rabbits can include chemotherapy, surgery, or radiation therapy. Consultation with an oncologist is recommended when clients are interested in pursuing chemotherapy or radiation and clients should be informed of risks, benefits, and potential side effects. Remember that rabbits are prey species with specialized gastrointestinal physiology and do not tolerate the stress of treatment in the same manner as a dog or cat.

**Chemotherapy**

Anecdotal information is available on the use of various chemotherapeutic agents in rabbits. If rabbits have underlying disease conditions such as pasteurellosis or encephalitozoonosis, chemotherapy may be contraindicated. Additionally, side effects from chemotherapy can include severe anemia, enteritis, typhlitis, and nephrotoxicity. Rabbits with thymomas have been treated with immunosuppressive therapy including prednisone. Steroids should be used with caution in rabbits and risks of immunosuppression should be discussed with owners prior to use. A multiagent CHOP-based protocol is commonly used in cases of canine lymphoma. Chemotherapy protocols described in humans include various combination treatments of cisplatin, doxorubicin, cyclophosphamide, prednisone, vincristine, etoposide, and epirubicin. Single-agent ifosfamide has also been described. In humans, the best response to therapy is determined by histologic tumor type, with lymphocyte-rich thymoma responding best to chemotherapy.
**Surgical excision**

In cases of a solitary mass that is surgically resectable, surgery is the treatment of choice for thymoma in all species. Median sternotomy may be required for adequate access to remove large mediastinal masses. Surgical excision of thymoma has been reported in rabbits but the risk of surgical or anesthetic-related complications is high. Postoperative survival ranged from 8 months to 3 years in three rabbits treated with surgery alone. In a series of rabbits treated by median sternotomy for mediastinal masses, 7 of 14 rabbits survived 6 months or longer. One rabbit died during surgery, 6 died within 10 days after surgery, 1 survived 6 to 12 months, 4 survived 12 to 14 months, and 2 survived more than 24 months. Factors negatively impacting surgical outcome of mediastinal masses in rabbits can include cardiac dysfunction, perfusion abnormalities, stress, and pain. Combination therapy of surgery and radiation treatment offers an excellent prognosis for thymomas in canine and feline patients.

**Radiation therapy**

Radiation therapy (RT) is the author’s preferred treatment option for palliative treatment of rabbits with mediastinal masses likely to be radiation responsive. In a recent study of 19 rabbits with thymoma that were treated with radiation, median overall survival was 313 days; when 3 rabbits that died acutely during the first 14 days of treatment were excluded, median survival was 727 days. Median survival for rabbits with thymoma treated with RT is shorter than that reported in dogs and cats treated with surgery. Uncommon complications associated with radiation included radiation-induced myocardial failure, radiation pneumonitis, and alopecia. Tumors generally respond rapidly and decrease in size after only a few treatments. The number of anesthetic episodes and radiation-associated side effects, including late-term side effects such as pulmonary or myocardial fibrosis, should be considered prior to treatment. Cost must also be taken into consideration. A possible significant prognostic variable when considering radiation therapy for treatment of thymoma in rabbits is body weight. Rabbits below a mean weight of 1.57 kg (but not below a median of 1.45 kg) were reported to have shorter survival time of 19 rabbits with thymoma treated with RT. This study included rabbits treated with definitive and coarsely fractionated protocols (24 to 48 Gy). Further study is warranted to determine ideal RT prescription, prognostic indicators, and potential side effects in rabbits.

**Palliative aspiration**

Some thymomas have a large cystic component. Aspiration of cystic fluid may help improve quality of life by relieving dyspnea. Ultrasound-guided cyst aspiration is recommended to avoid damage to vital structures.

**Monitoring and supportive therapy**

Frequent physical examinations and thoracic radiographs can help monitor response to therapy. Frequent monitoring of respiratory function and oxygen supplementation may be beneficial to dyspneic patients. Appetite stimulants and anti-nausea medications are reported to be beneficial to canine and feline patients undergoing treatment for mediastinal masses. Nutritional support to anorectic rabbit patients can be beneficial but care must be taken to avoid causing stress and worsening of respiratory signs. Analgesia is vital if more invasive diagnostic or surgical options are pursued.
References


