Removal of a thymoma via median sternotomy in a rabbit with recurrent appendicular neurofibrosarcoma

Tracy L. Clippinger, DVM; R. Avery Bennett, DVM, MS; A. Rick Alleman, DVM, PhD; Pamela E. Ginn, DVM; Jamie R. Bellah, DVM

- A thymoma may not be clinically evident unless it is large enough to cause abnormal respiratory tract signs or a paraneoplastic syndrome develops.
- Ultrasound guided fine needle aspiration is a safe, minimally invasive method for diagnosis of masses in the cranial portion of the mediastinum. Needle or excisional biopsy may be required to definitively distinguish or confirm a diagnosis of thymoma or lymphoma.
- A minimally invasive thymoma may be surgically excised via median sternotomy in rabbits.
- Neurofibrosarcoma is a locally invasive tumor with a tendency to recur unless excision has been wide and complete, and adjunctive radiotherapy or chemotherapy is administered.

A 9-year-old 3.1-kg (6.8-lb) spayed female domestic rabbit (Oryctolagus cuniculus) was evaluated for a mass on the right elbow. Physical examination revealed an asymmetric 3 × 2 × 2-cm mass at the caudal lateral aspect of the elbow. The mass was movable with few attachments to underlying structures. The rabbit was euthyric with no history of exercise intolerance.

Serum biochemistry profile results revealed a calcium concentration of 14.3 mg/dl (reference range, 5.6 to 12.5 mg/dl). A sample of the mass on the elbow obtained by fine needle aspiration for cytologic examination was nondiagnostic and contained primarily necrotic cellular debris, severely degenerated neutrophils, and low numbers of scattered immature mesenchymal cells. Aerobic bacterial culture of the aspirate yielded no growth.

Diagnostic imaging of the right elbow and thorax was performed with the rabbit under isoflurane in oxygen anesthesia delivered via mask. Radiographs of the right elbow revealed a soft-tissue mass caudal to the right humerus, but there was no evidence of bony invasion. Thoracic radiographs revealed a mass of soft tissue density in the cranial portion of the mediastinum that was causing caudodorsal displacement of the cardiac silhouette and compression of the caudal lung lobes (Fig 1). Ultrasound examination confirmed both masses to be cavity soft tissue dense lesions of mixed echogenicity that contained fluid. An ultrasound guided fine needle aspiration of the thoracic mass was performed. Cytologic preparations from the thoracic mass were highly cellular and contained primarily well-differentiated small to intermediate-size lymphocytes (Fig 2).

From the Departments of Small Animal Clinical Sciences (Clippinger, Bennett, Bellah) Physiological Sciences (Alleman), and Pathobiology (Ginn) College of Veterinary Medicine, University of Florida, Gainesville, FL, 32610-0126.

Figure 1—Lateral radiographic view of the thorax of a rabbit. Notice the mass (M) of soft tissue density in the cranial portion of the thorax that is displacing the cardiac silhouette (H) caudodorsally and compressing the caudal lung lobes.

Figure 2—Photomicrograph of a tissue aspirate obtained from a thymoma in the rabbit in Figure 1. Small, well differentiated lymphocytes (open arrows) predominate. Low numbers of lymphoblasts (small closed arrow) and clumps of anaplastic epithelial cells (large closed arrows) are also present. Wright-Giemsa stain, bar = 10 μm.

Low numbers of lymphoblasts and clumps of anaplastic epithelial cells were also seen. These epithelial cells displayed a variable nucleus-to-cytoplasm ratio, marked anisokaryosis, prominent pleomorphic nuclei, and clumped chromatin. The location and cytologic appearance were consistent with a diagnosis of thymoma. Because of the potential life-threatening com-
lications of surgical removal of the thoracic mass, sequential surgeries were planned.

Two weeks after initial examination, the rabbit was anesthetized for thoracic surgery. Oxybuprocine hydrochloride (0.1 mg/kg [0.05 mg/lb] of body weight, IM) and midazolam hydrochloride (0.1 mg/kg [0.05 mg/lb], IM) were administered as preanesthetic medications. After induction of anesthesia with isoflurane in oxygen, the rabbit was intubated, and anesthesia was maintained with low concentrations of inhalant and an adjunctive agent, fentanyl citrate (4 μg/kg [1.8 μg/lb], IV, q 15 min administered 3 times during manipulations of the sternebrae and ribs). Intermittent positive pressure ventilation was used to assist respirations during the surgical procedure. Dopamine hydrochloride (5 to 10 μg/kg/min [2.3 to 4.5 μg/lb/min], IV infusion), ephedrine sulfate (50 μg/kg [22.7 μg/lb], IV once), and dobutamine (5 to 7.5 μg/kg/min [2.3 to 3.4 μg/lb/min], IV infusion) were administered to treat hypotension. Cefazolin sodium (25 mg/kg [11.3 mg/lb], IV once) was also administered during surgery.

The ventral aspect of the chest was prepared for aseptic surgery. The 8-cm (3.1-in) skin incision was made along the ventral midline that extended from 1 cm (0.4 in) cranial to the manubrium to the xiphoid process. The muscle insertions on sternebrae were elevated to expose sternebrae. A scalpel blade was used to score the sternum from the manubrium to the fourth sternebrae, which was then split by use of a bone cutter. Mini-Gelpi retractors were used to expose the mass in the cranial portion of the mediastinum. Blunt and sharp dissection were used to isolate the mass from the heart, great vessels, lungs, and surrounding structures. Hemostatic ligation clips were used to control hemorrhage. After removal of the mass, the thoracic cavity was irrigated with sterile saline (0.9% NaCl) solution. Sternebrae were apposed, using a figure-of-eight pattern of 2-0 polydioxanone suture. Muscle fascia and subcutaneous tissues were apposed in 2 layers with a simple continuous pattern of 4-0 polydioxanone suture. Surgical staples were used to appose the skin. An 8-F red rubber chest tube was placed to allow postoperative evacuation of the pleural space. The mass on the elbow was sampled again for cytologic evaluation. Anesthetic recovery was unremarkable. Buprenorphine hydrochloride (10 μg/kg [4.5 μg/lb], IM, q 8 h) was administered for 36 hours to provide analgesia. The chest tube was removed 24 hours after surgery when notable quantities of air or fluid could not be aspirated.

The rabbit was released from the hospital 3 days after surgery. Histologic examination of the thoracic mass confirmed the diagnosis of lymphocytic thymoma. Sections of tumor were stained, using immunoperoxidase methods, for expression of B (CD79a and BLA36) and T (CD3) cell markers. Most lymphocytes labeled with CD3 markers. Rare, widely scattered lymphocytes and plasma cells labeled with both CD79a and BLA36. Neoplastic cells extended to the margins of sections that contained adipose tissue. Cytologic evaluation of the mass on the right elbow revealed moderate numbers of anaplastic mesenchymal cells and a presumptive diagnosis of sarcoma was made.

The rabbit was readmitted 18 days later for excisional biopsy of the mass on the right elbow while under isoflurane in oxygen anesthesia. The calcium concentration was 12.6 mg/dl. Histologic examination of the mass on the elbow revealed highly cellular interwoven bundles and whorls of neoplastic spindle-shaped cells in a sparse collagenous extracellular matrix with a small amount of mucinous material. Small bundles of nerve fibers were embedded within the mass. Sections of tumor, stained for S-100 protein, were negative. Extensive necrosis was evident and tumor cells were found in subcutaneous tissues at the surgical margins. The histologic diagnosis was neurofibrosarcoma. Chemotherapy or radiotherapy, directed at remnants of thymoma tissue in the cranial portion of the mediastinum, and brachytherapy or limb amputation, as adjunctive therapy for neurofibrosarcoma, were recommended, but the owner declined.

Three months after initial examination, the rabbit was admitted with a rapidly growing, 2-cm diameter spherical mass on the plantar surface of the right rear foot between the proximal phalanges of digits 2 and 3. Tumor regrowth was not evident on the right elbow. Cytologic examination of this mass revealed a predominant cell population of large, uniform, individual mesenchymal cells, suggestive of a mesenchymal tumor. Thoracic radiographs confirmed that the sternotomy site had healed, the cardiac silhouette was appropriately located, and there was no evidence of a mass in the cranial portion of the mediastinum. A mild anemia (Hct, 32%; reference range, 33 to 50%) was evident, but the calcium concentration was within reference range. An excisional biopsy was performed on the plantar mass, which was confirmed to be a second neurofibrosarcoma. After surgery, self-mutilation of the third and fourth digits of the right rear limb resulted in exposed, devitalized, avascular bone. Amputation of the distal phalanges of those digits was performed, but the owner declined histologic evaluation of the removed tissue.

Nine months after initial evaluation, the rabbit was euthanized at the owner's request. Three distinct masses 5 × 3 × 2 cm to 8 × 6 × 5 cm were found in the right axilla and overlapping the humerus. A 5 × 3 × 3-cm ulcerated mass surrounded the bones of all remaining phalanges on the right rear foot. Postmortem examination confirmed recurrence of the peripheral soft tissue sarcomas at previous surgical sites. Histologic examination of sections of these 3 appendicular masses revealed highly cellular masses of neoplastic spindle-shaped cells with arrangement and morphology similar to that of the previously excised elbow mass. A large peripheral nerve fiber was found in the mass from the right axilla. Sections of tumor did not stain for S100 protein. Gross or histologic evidence of regrowth of the thymoma was not found.

To the best of our knowledge, this is the first report of a successful surgical removal of a thymoma in a rabbit. A mediastinal mass was excised from a geriatric rabbit via a right fourth intercostal thoracotomy, but persistent pneumothorax hindered ventilation after surgery, and the rabbit did not recover. For the rabbit of our report, a median sternotomy approach
was selected, because it allowed greater exposure of the cranial portion of the thorax for meticulous dissection of the large mass from surrounding vital structures.

The incidence of thymoma in rabbits is low and the diagnosis is typically made at postmortem examination. In a review of naturally developing tumors of the domestic rabbit, it was noted that many rabbits die before reaching the cancer-prone age group. Thymomas are rare tumors that typically develop in middle-aged to older animals. Thymomas develop from thymic epithelium in the cranioventral portion of the mediastinum and displace thoracic structures caudodorsally. The space-occupying effect may account for signs such as coughing, tachypnea, dyspnea, and exercise intolerance, and for cranial vena cava syndrome, wherein compression or invasion by the tumor impairs venous return to the heart and results in edema of the head, neck, or forelimbs. Respiratory distress and bilateral exophthalmos were found in 2 rabbits with thymoma. Animals with clinically silent thymomas commonly have signs related to a paraneoplastic syndrome (e.g., myasthenia gravis, autoimmune diseases, polymyositis, hematologic abnormalities, hypercalcemia of malignancy, and second concurrent neoplastic disease) or an unrelated disorder.

Radiology and ultrasonography of the thorax and collection of fluid from the cystic mass were used to make an ante mortem diagnosis of thymoma on the basis of mass location and cytologic findings. Histologic evaluation of the excised mass revealed a consistent association of epithelial cells with a mature lymphocytic population, which was necessary to classify the mass as thymoma. The results of immunohistochemical labeling for T cell markers were consistent with the diagnosis of a thymoma. It is not surprising that small numbers of cells within the mass were labeled with B cell markers, because neoplastic transformation of the thymus may be preceded by some degree of immune dysregulation. Lymphoma was the primary differential diagnosis because of an overwhelming population of lymphocytes on cytologic and histologic examinations. Differentiation of lymphoma from thymoma is important to guide treatment and to render a prognosis. Noninvasive thymoma may be treated definitively with surgical excision, whereas lymphoma may be medically treated with chemotherapy.

Prognosis for animals with thymomas is typically judged by gross resectability of the tumor and the presence and extent of associated syndromes. Complete surgical resection of noninvasive encapsulated thymomas provides good long term survival rates. Animals with thymomas that invade adjacent organs or metastasize to extrathoracic locations have a grave prognosis because remission has been difficult to achieve with radiotherapy or chemotherapy. Although neoplastic cells were found on histologic examination to extend into adjacent periglandular adipose tissue in the rabbit of our report, recurrence of thymoma was not macro- or microscopically evident at necropsy 9 months later.

The rabbit in our report developed 2 neoplastic masses at separate appendicular locations that were classified as mesenchymal cell tumors. The specific tissue of origin may be difficult to identify in mesenchymal soft tissue sarcomas; a single neoplastic mass may be given various names depending on the site of biopsy or stage of growth. Neurofibromas and neurofibrosarcomas are tumors that originate from endoneurial or epineurially located fibroblasts within the nerve sheath. Demonstration of close association with the nerve may be necessary to differentiate a neurofibrosarcoma from a fibrosarcoma or hemangiopericytoma. Self-mutilation of the rear foot may have been related to abnormal sensation, which supports involvement of a peripheral nerve. Immunohistochemistry may aid in the differentiation, but not all tumors can be identified with specific tumor tissue markers. The neurofibrosarcomas in this case report did not label with S100 protein, a calcium binding protein in many mesenchymal tumors. Lack of S100 labeling in the tumors from the rabbit of our report does not exclude the diagnosis of neurofibrosarcoma. These tumors were considered primary, because there was no direct anatomic path by which tumor cells could have metastasized from the front to the hind limb. The known behavior of these types of tumors and the lack of visceral metastasis also mitigates against metastasis. Neurofibroma or neurofibrosarcoma has not been reported in rabbits, and an association between these tumors and thymoma has not been reported in rabbits or other species.

Proximal demarcation of tumors of the nerve sheath may be inconspicuous during gross inspection at surgery, because tumor cells may extend within the nerve trunk. Radical excision of the tumor and amputation of the limb if there is appendicular involvement must be considered to offer the best prognosis. Radiotherapy may be used as an adjunct to incompletely excised and recurrent soft tissue sarcomas. For the rabbit of this report, the owner’s concerns about palliation of disease, duration of anesthesia and surgery, cost, and the pet’s quality of life did not allow more definitive treatment of the appendicular neurofibrosarcomas such as radical excision, amputation, or adjunctive radiotherapy.

The rabbit in our report had a high serum calcium concentration before surgery that decreased after excision of the thymoma, which is typical for animals with paraneoplastic hypercalcemia. However, classification of this initial calcium concentration as evidence of a paraneoplastic syndrome is controversial. Serum calcium concentrations of 16.8 mg/dl and 14.7 mg/dl in a rabbit with thymoma were attributed to a paraneoplastic syndrome; however, this rabbit also had a serum calcium concentration < 12.0 mg/dl when reexamined before tumor removal. Other factors must be considered for their role in calcium homeostasis in rabbits. Dietary calcium proportions and digestibility directly affect serum calcium concentration, which may typically range up to 16 mg/dl. Excess calcium is excreted in urine as calcium carbonate. Calcium concentrations would need to be measured serially before and after excision of a thymoma to rule out the influence of diet or other metabolic abnormalities in rabbits and to support a diagnosis of paraneoplastic hypercalcemia.
References


