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CHAPTER 21

Cardiovascular and Lymphoproliferative Diseases

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PART I **CARDIOVASCULAR DISEASES**

Sharon M. Huston, DVM, Diplomate ACVIM (Cardiology)

CARDIAC DISEASE

Cardiac disease has become increasingly recognized in domestic rabbits. Despite their frequent use as laboratory models for cardiac disease in humans, little is known about the pathogenesis and treatment of naturally occurring heart disease in rabbits. Reports of spontaneous heart disease are sporadic and case numbers are often low. Despite this, a complete cardiac evaluation and systematic approach can lead to a correct diagnosis and successful treatment of rabbits with cardiovascular disease.

Normal Cardiovascular Structure

The rabbit heart differs from that of other small animal species in several ways. The tricuspid valve is composed of two rather than three cusps; the aortic nerve is not associated with chemoreceptors but only with baroreceptors; and the rabbit pulmonary artery and its branches are heavily muscular.[6] Additionally, the myocardium has limited collateral circulation and is therefore predisposed to ischemia mediated by coronary vasoconstriction.[26]

Examination of the Rabbit with Cardiovascular Disease

Information gathered from a thoughtful history and complete physical examination comprise the most important part of the cardiac evaluation.

History A thorough general history, including husbandry, diet, and past or present illnesses, should be obtained for rabbits suspected of having cardiac disease. Tachypnea, dyspnea,

syncope, anorexia, weight loss, and malaise may be signs of heart disease in rabbits.

Physical examination Take care to minimize the handling of a rabbit in cardiac distress; a complete physical examination and further diagnostic testing sometimes must be delayed until the rabbit is clinically stable. In rabbits suspected of having cardiac disease or respiratory distress, focus the initial examination on observing the respiratory rate and pattern, obtaining the heart rate and rhythm, auscultating the thorax, examining the mucous membranes, and palpating the pulses. Normal heart rate is 180 to 250 beats/min and normal respiratory rate is 30 to 60 breaths/min.

Rabbits with heart disease may have cyanotic or pale mucous membranes, arrhythmia, or heart murmurs. Rabbits with congestive heart failure often have tachycardia, tachypnea, and labored breathing. Pulses may be irregular or weak. Auscultating the thorax systematically is the most important part of the cardiac examination. It is important to listen over the entire thorax to localize heart murmurs and detect arrhythmias and lung sound abnormalities. A pediatric stethoscope allows better localization of heart sounds in rabbits and is preferred for cardiac auscultation; a larger-diaphragm stethoscope enhances auscultation of the lungs. Auscultatory findings vary among rabbits with congestive heart failure, and these findings are not pathognomonic. The examiner may hear muffled heart and lung sounds with pleural effusion and increased bronchial sounds or crackles with pulmonary edema.

DIAGNOSTIC METHODS

Diagnosis of cardiovascular disease is based on complete history and physical examination findings complemented by appropriate diagnostic tests. Thoracic radiographs, electrocardiography, echocardiography, and routine blood tests are useful in reaching a definitive diagnosis and treatment plan.

Radiography

Thoracic radiography provides critical information in the patient with cardiopulmonary disease, namely cardiac shape and size, pulmonary pattern, vascular pattern, and other thoracic lesions. Congestive heart failure and respiratory disease can be differentiated by evaluating thoracic radiographs. Radiographic findings supporting a diagnosis of cardiac disease are similar to those in other species and include cardiac enlargement, pulmonary vascular enlargement, pulmonary interstitial and alveolar pulmonary pattern of pulmonary edema, and pleural effusion. Figures 21-1 and 21-2 show thoracic radiographs of a normal adult rabbit and a rabbit with heart disease, respectively.

Electrocardiography

Electrocardiography (ECG) is a simple and practical diagnostic test in rabbits with suspected or confirmed cardiac disease. An ECG is critical to diagnose and manage arrhythmias or syncope. The ECG may also be a helpful addition to the cardiac database. To minimize skin trauma, file the alligator-style ECG clips. Normal rabbit rhythm is sinus and does not include respiratory sinus arrhythmia.[33] Recently, normal rabbit ECG values were determined in a novel study of 46 clinically normal domestic rabbits (B. Reusch, personal communication, 2003). ECG reference ranges are summarized in Table 21-1.

Echocardiography

Echocardiography provides a sensitive, accurate, and noninvasive means of assessing the heart. Most rabbits easily tolerate echocardiography, making it a practical diagnostic tool. Because of the rabbit's rapid heart rate and small size, optimal evalua-

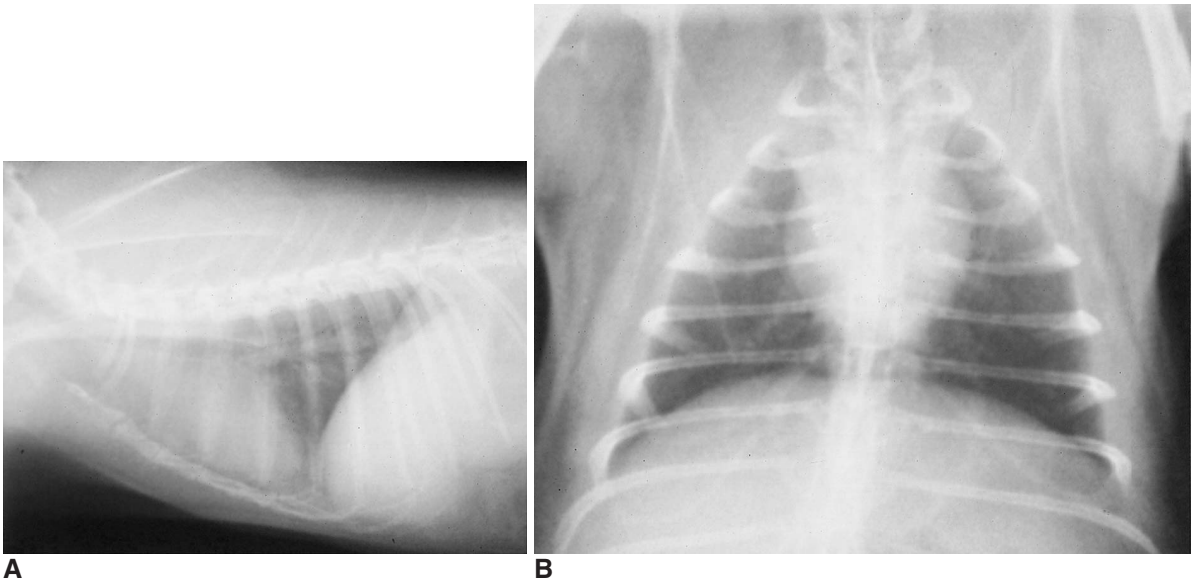

Figure 21-1 Normal thoracic radiographs of a rabbit. **A,** Right lateral projection. **B,** Ventrodorsal projection.

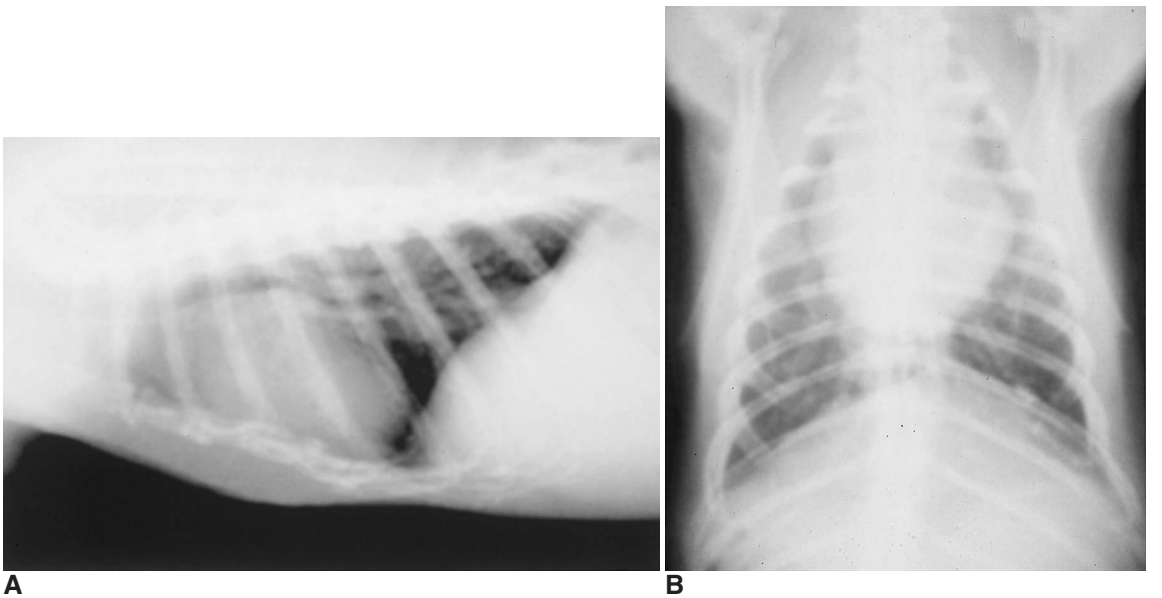

Figure 21-2 Severe, generalized cardiac enlargement in a 9-year-old French lop rabbit. **A,** In the right lateral view, the cardiac silhouette is generally enlarged and can be seen throughout four intercostal spaces. The intrathoracic trachea and carina are dorsally elevated, and the main stem bronchi are compressed and deviated by an enlarged left atrium. The caudal border of the heart is rounded by left atrial and left ventricular enlargement. The cranial border of the heart is rounded, and the trachea is elevated cranial to the carina because of right atrial and ventricular enlargement. **B,** In the ventrodorsal view, an enlarged left auricle is evident as a bulge between the 2- and 3-o'clock positions. The left ventricular apex is rounded by an enlarged left ventricle. An enlarged right atrium is evident as a bulge between the 9- and 11-o'clock positions.

TABLE 21-1
Electrocardiographic Values in Clinically Normal Pet Rabbits

ECG Parameter	Values
Heart rate	198-330 beats/min*
Measurements (lead II)	
P wave	
Duration (width)	0.01-0.05 sec
Amplitude (height)	0.04-0.12 mv
P-R interval	
Duration	0.04-0.08 sec
QRS complex	
Duration	0.02-0.06 sec
R-wave amplitude	0.03-0.039 mv
Q-T interval	
Duration	0.08-0.16 sec
T wave	
Amplitude	0.05-0.17 mv
Electrical axis (frontal plane)	–43 to +80 degrees

From B. Reusch, A. Boswood, A. Petrie, unpublished data.
*This range should be used as a guide; lower values are expected in acclimated rabbits.

tion requires a high-frequency transducer and high frame rate ultrasound machine. Two-dimensional and M-mode echocardiography assess cardiac structure, chamber size, wall thickness, and motion, as well as extracardiac structures, masses, and pleural effusion. Color-flow and spectral Doppler echocardiography assess direction and velocity of blood flow, further defining cardiac conditions. Normal echocardiographic values have been published for several breeds of rabbits reported as study controls (Table 21-2). Sedative drugs used for restraint may affect cardiac measurements.

DISEASES AND MANAGEMENT

Congestive Heart Failure

In rabbits, congestive heart failure is the clinical condition in which pulmonary edema, pleural effusion, or hepatomegaly develops as a result of structural or functional cardiac disease. The goal of therapy is to relieve congestion, control future retention of sodium and fluids, and improve cardiac performance. To this end, numerous management strategies are used during the acute stage. Place the patient in a quiet cage with supplemental oxygen. Administer parenteral furosemide (1-4 mg/kg IV or IM q4-12h) and nitroglycerin 2% ointment ($^1/_8$ inch applied transdermally q6-12h). In a rabbit with pleural effusion, perform therapeutic pleurocentesis if the rabbit is dyspneic.

Long-term therapy of congestive heart failure should include a diuretic (furosemide 1-2 mg/kg PO q8-24h) combined with treatment directed at the underlying precipitating cause. Knowledge of the cardiac disease process is the basis of specific

TABLE 21-2
Echocardiographic Values in Clinically Normal Rabbits

Parameter	Dutch Belted Rabbits* (n = 6)	Japanese White Rabbits† (n = 4)	New Zealand White Rabbits‡ (n = 8)
Body weight (kg)	2.32 ± 0.36	3.0 (mean)	1.5-2.0 (range)
Age (mo)	7 mo (mean)	>13 mo	—
LVEDD (cm)	1.17 ± 0.19	1.69 ± 0.05	1.4 ± 0.2
LVESD (cm)	0.70 ± 0.09	1.15 ± 0.05	—
%FS	39.50 ± 5.39	—	—
IVSD (cm)	0.25 ± 0.05	0.33 ± 0.03	0.3 ± 0.0
LVPWD (cm)	0.31 ± 0.08	0.33 ± 0.03	0.2 ± 0.0
LA (cm)	—	1.05 ± 0.25	—
Ao (cm)	0.67 ± 0.10	1.07 ± 0.12	—
LA/Ao	1.38 ± 0.32	—	—
RADs (cm)	0.61 ± 0.08	—	—
RA/Ao	0.88 ± 0.17	—	—
EPSS (cm)	0.05 ± 0.05	—	—
MVEFS (mm/sec)	70.17 ± 31.82	—	—
RVOT velocity (m/sec)	0.83 ± 0.10	—	—
LVOT velocity (m/sec)	0.65 ± 0.14	—	—
LVET (sec)	0.08 ± 0.01	—	—
VCF (circumference/sec)	4.74 ± 0.45	—	—
MV E (m/sec)	—	0.44 ± 0.12	—
MV A (m/sec)	—	0.46 ± 0.17	—
MV E/A	—	1.0 ± 0.2	—
MV DT (msec)	—	41.3 ± 2.5	—

Values are mean ± SD.
LVEDD, Left ventricular *(LV)* end-diastolic dimension; *LVESD*, LV end-systolic dimension; *%FS*, % LV fractional shortening; *IVSD*, intraventricular septal thickness at end-diastole; *IVSS*, intraventricular septal thickness at end-systole; *LVPWD*, LV posterior wall thickness at end-diastole; *LA*, left atrium; *Ao*, aorta; *LA/Ao*, left atrium to aortic ratio; *RADs*, right atrial dimension in systole; *RA/Ao*, right atria to aorta ratio; *EPSS*, E point to septal separation; *MVEFS*, mitral valve E-F slope; *RVOT*, right ventricular outflow tract; *LVOT*, left ventricular outflow tract; *LVET*, left ventricular ejection time; *VCF*, velocity of circumferential fiber shortening; *MV E*, mitral valve E wave; *MV A*, mitral valve A wave; *MV E/A*, mitral valve E to A ratio; *MV DT*, mitral valve deceleration time.
*Data adapted from Marini RP, Li X, Harpster NK, et al: Cardiovascular pathology possibly associated with ketamine/xylazine anesthesia in Dutch belted rabbits. Lab Anim Sci 1999; 49:153-160. (Rabbits sedated with diazepam.)
†Data adapted from Saku K, Fujino M, Yamamoto K, et al: Cardiac function of WHHL rabbit, an animal model of familial hypercholesterolemia. Artery 1990; 17:271-280. (Rabbits sedated with xylazine and ketamine.)
‡Data adapted from Plehn JF, Foster E, Grice WN, et al: Echocardiographic assessment of LV mass in rabbits: models of pressure and volume overload hypertrophy. Am J Physiol 1993; 265:H2066-H2072. (Rabbits sedated with pentobarbital sodium.)

treatment of the underlying condition. Drug dosages for rabbits are not available for all cardiac medications, but drugs and dosages published for cats or ferrets may be successfully used on a milligram per kilogram basis. Angiotensin-converting enzyme inhibitors such as enalapril maleate (0.25-0.5 mg/kg PO q24-48h, begin q24h) may be beneficial in treating rabbits with congestive heart failure. Digoxin (0.005-0.01 mg/kg PO q24-48h) may benefit rabbits with mitral and bicuspid regurgitation, dilated cardiomyopathy, or supraventricular arrhythmia. If digoxin is used, monitor serum digoxin levels. During acute and chronic management, it is critical that clinical and radiographic signs, hydration status, appetite, and body weight as well as serum blood urea nitrogen, creatinine, and electrolyte concentrations are monitored.

Congenital Heart Disease

Congenital heart disease in rabbits is rarely reported. Ventricular septal defect, diagnosed with echocardiography, has been described.[35] A ventricular septal defect, pulmonary hypertension, and valvular cyst identified at necropsy have been described in a New Zealand white rabbit.[23]

Arrhythmia

Arrhythmias in domestic rabbits have not been reported. However, we have diagnosed arrhythmias in several rabbits that exhibited syncope and an irregular heart beat (Fig. 21-3). In a rabbit with an arrhythmia, base the treatment protocol on ECG

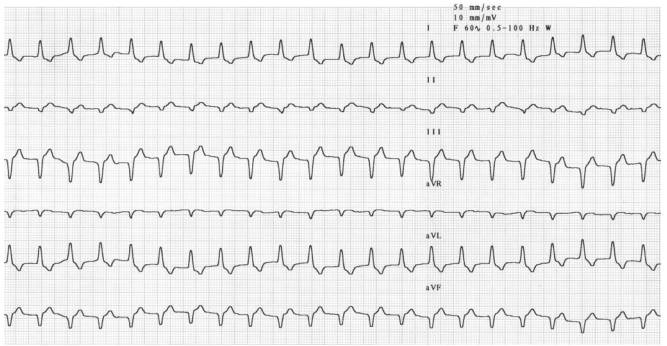

Figure 21-3 Six-lead, simultaneous electrocardiogram in a rabbit with ventricular tachycardia.

findings and clinical signs. Dosages are published for lidocaine, verapamil, atropine, and glycopyrrolate. Other antiarrhythmic drugs may be used at dosages published for cats or ferrets. In a controlled study, glycopyrrolate was more effective than atropine sulfate in increasing heart rate.[32]

Myocardial Disease

Numerous myocardial diseases have been reported in rabbits, and cardiomyopathy is a common postmortem finding in older rabbits.[35] Idiopathic hypertrophic cardiomyopathy and dilated cardiomyopathy have been diagnosed by echocardiography (Fig. 21-4).[33] Vitamin E deficiency produces a muscular dystrophy in which the myocardium may be affected.[3] In experimental studies, myocardial disease has been created through inoculation of *Trypanosoma cruzi*[36] and administration of doxorubicin.[44] Infectious myocardial diseases are rare in pet rabbits. Known infectious organisms include *Pasteurella multocida*, *Salmonella* species, *Encephalitozoon cuniculi*,[26] and coronavirus.[8] The alpha-agonist drug detomidine has been associated with myocardial necrosis and fibrosis in New Zealand white rabbits.[19] A similar ischemia-mediated process is suggested in association with ketamine/xylazine administration.[26]

Valvular Disease

Mitral and tricuspid insufficiencies are not uncommon and have been identified in pet rabbits.[33] A focal murmur is the most common clinical finding. Valvular disease is diagnosed with

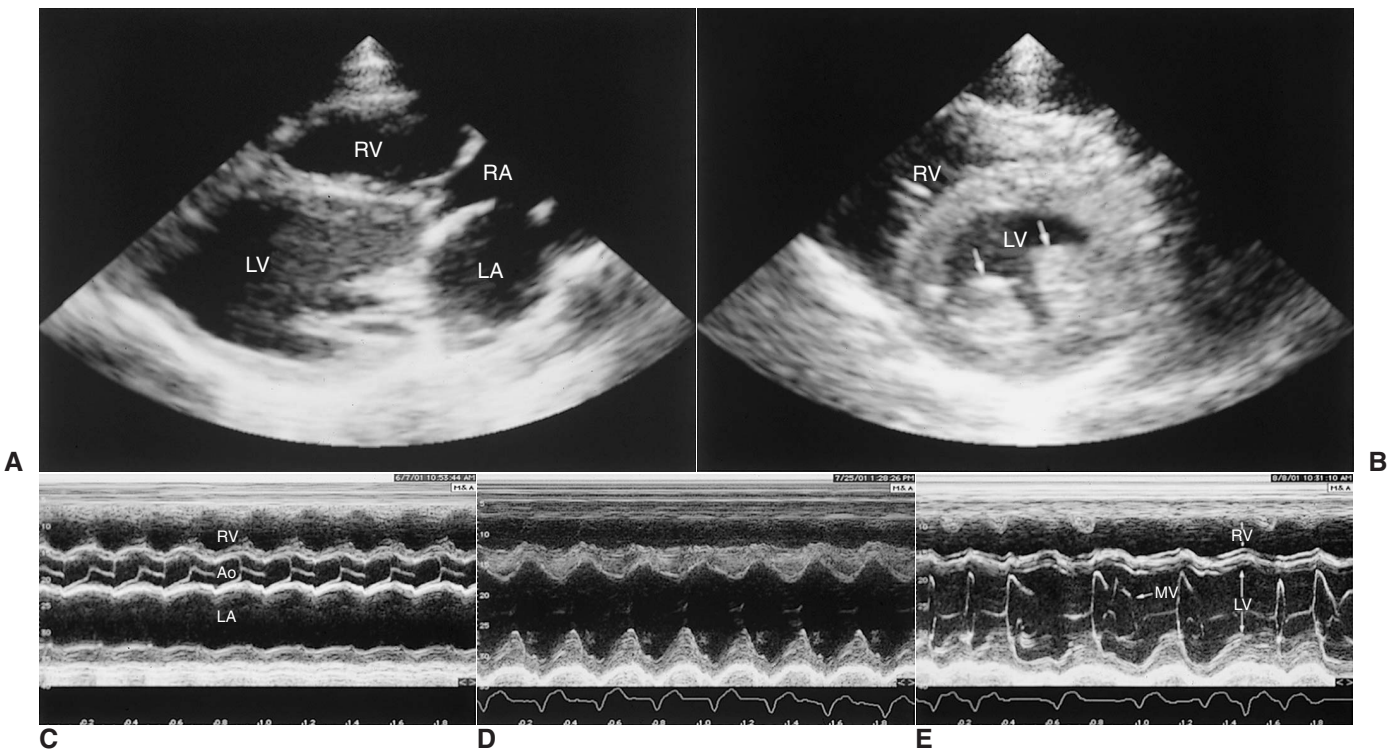

Figure 21-4 Standard echocardiographic views in rabbits with cardiac disease. **A,** Right parasternal, long-axis, four-chamber view. Notice the left and right ventricular dilation in this rabbit with mitral and tricuspid insufficiency. **B,** Right parasternal, short-axis, left ventricle papillary muscles view. Notice the prominence of the left ventricular papillary muscles (*arrows*) in this rabbit with left ventricular hypertrophy. **C,** Parasternal, short-axis M-mode echocardiogram in which the M-mode beam is directed across the right ventricle, aortic valve, and left atrium. Note the dilation of the left atrium. **D,** Parasternal, short-axis, M-mode view of the left ventricle in which the M-mode beam is directed across the right ventricle (*top*) and left ventricle (*bottom*). Notice the dilated left ventricle and the decreased excursion of the septum compared with the posterior wall in this rabbit with cardiomyopathy and ventricular tachycardia. **E,** Parasternal, short-axis M-mode echocardiogram of the left ventricle and mitral valve. Note the irregular rhythm. *LV,* Left ventricle; *LA,* left atrium; *RV,* right ventricle; *RA,* right atrium; *Ao,* aorta; *MV,* mitral valve.

two-dimensional and Doppler echocardiography (see Fig. 21-4). Echocardiographic findings most often include thickening of one or both atrioventricular valves, dilation of cardiac chambers, and turbulent regurgitation of blood detected by Doppler.

Valvular endocarditis, caused by *Staphylococcus aureus,* has been reported in rabbits.[40]

Vascular Disease

Spontaneous arteriosclerosis of the aorta and other arteries has been observed in nearly all rabbit breeds. Clinical signs, if present, may include lethargy, anorexia, and weight loss. The cause is unknown. In rabbits with spontaneous arteriosclerosis, arterial walls and other soft tissues mineralize; the aortic arch and descending thoracic aorta are most commonly affected. Radiopaque vessels, caused by calcification, may be visible on radiographs.[24,38]

Pulmonary hypertension associated with high altitude has been reported in a rabbit.[17] Lesions included right ventricular hypertrophy and pulmonary artery proliferation from hypoxia.

PART II LYMPHOPROLIFERATIVE DISORDERS

Katherine E. Quesenberry, DVM, Diplomate ABVP

Lymphoproliferative disorders are seen occasionally in pet rabbits. Before the 1960s, rare cases of lymphoproliferative disease in domestic rabbits had been reported in the European literature. In 1968, lymphoma was first reported in a domestic rabbit in the United States. In that report, generalized lymphoid neoplasia involving the lymph nodes, liver, spleen, lungs, and gastrointestinal tract was described in a New Zealand white rabbit from a research colony.[43] Since then, lymphoproliferative diseases have been reported in both laboratory and pet rabbits. Most of these cases have involved generalized lymphoma; however, cutaneous lymphoma, leukemia, and thymomas have also been described.

Rabbits are used extensively to study disease pathogenesis in experimental studies of induced lymphoid neoplasia. However, few studies have investigated the cause of naturally occurring lymphoid disorders in rabbits. In one of the first reports, lymphoma was described in a series of rabbits from a breeding farm,[25] leading to speculation that a breed or strain susceptibility exists or an infectious agent is associated with disease.[12,25,43] A strain susceptibility was demonstrated in Wirehair (WH) rabbits[12]; this susceptibility is associated with a single autosomal recessive gene, *Is.* In the WH strain, affected rabbits die at 5 to 13 months of age, usually with generalized lymphoma involving visceral organs and lymph nodes similar to the distribution of organ involvement seen in other domestic animals.[12] This pattern of susceptibility was also thought compatible with vertical transmission of a virus, as occurs with feline leukemia virus. Some have speculated that lymphoma in rabbits is caused by an oncogenic C-type tumor virus, similar to viruses associated with lymphoma in rodents. In an early study, tissues samples from an adult New Zealand white rabbit with generalized lymphoma were examined in an attempt to document the presence of virus.[42] Results of electron microscopic examination, tissue culture, immunodiffusion studies with FeLV antiserum, and immunofluorescent tests were negative for the virus. However, in another study, viruslike particles were demonstrated by electron microscopy in the kidneys of a 7-month-old New Zealand white rabbit with generalized lymphoma.[15]

TYPES OF LYMPHOPROLIFERATIVE DISORDERS

Multicentric Lymphoma

Multicentric lymphoma is the most common type of lymphoproliferative disease in rabbits. It has been reported in several rabbit breeds, including New Zealand white, Japanese white, Dutch, and Netherland dwarf rabbits.[5,16,39,41,42] A hereditary predisposition to lymphoma involving the *Is* recessive gene has been demonstrated in the WH strain of rabbits.[12] Clinically, lymphoma has been observed in a variety of rabbit breeds, including satin, mini lop, and tan breeds. Lymphoma can occur in rabbits of all ages, from animals less than 1 year of age to geriatric animals.* In pet rabbits with lymphoma seen at the Animal Medical Center in New York City, ages have ranged from 2 to 9 years, with most averaging 4 to 5 years.

Both T-cell– and B-cell–origin lymphoma have been documented in rabbits. In a domestic rabbit with lymphoma and lymphocytic leukemia, the neoplasia was of T-cell origin.[41] In a pet Dutch dwarf rabbit, T- and B-cell infiltrates were observed in the skin, lung, kidneys, liver, intestine, and lymph nodes. In this rabbit, the diagnosis was multicentric, T-cell–rich, B-cell lymphoma with cutaneous involvement.[14]

Rabbits with multicentric lymphoma often exhibit nonspecific general signs, such as anorexia, lethargy, emaciation, pallor, diarrhea, and rhinitis. In a 2-year-old rabbit seen at the Animal Medical Center, the presenting clinical sign was severe upper respiratory stridor. At necropsy, lymphoma was present in the nasal turbinates and sinus, stomach, liver, spleen, kidneys, lymph nodes, and bone marrow. Another rabbit with multicentric lymphoma presented with acute onset of hind limb paresis and gastrointestinal stasis. At necropsy, neoplastic cells compatible with large cell lymphoma (immunoblastic) were found in the spleen, kidneys, lungs, cecum, intestines, lymph nodes, and adrenal glands; no lesions were found in the spinal cord.

Laboratory findings depend on the organs involved. Results of plasma biochemical analysis may be unremarkable or reveal increases in concentrations of aspartate aminotransferase, creatine phosphokinase, blood urea nitrogen, and creatinine. Rabbits may be moderately to severely anemic[12,46]; in young rabbits, fluctuating and depressed hematocrit values were considered the best diagnostic tool for early identification of lymphoma.[12] In rabbits with multicentric lymphoma seen at the Animal Medical Center, most had hematocrit levels in the low normal range (30%-33%; reference range, 30%-50%[2]). The white blood cell (WBC) count is often within reference ranges; however, some rabbits with lymphoma have leukemia (see below). In young rabbits with multicentric lymphoma, high WBC counts were less frequent than a relative predominance of lymphoid cells, including immature and atypical cells, representing 80% to 90% of total WBCs. In an 18-month-old rabbit

*References 5, 12-16, 27, 39, 41-43, 46.

seen at the Animal Medical Center, the WBC count was 10,000 cells/μL, with 63% lymphocytes. Lymphoma was present in the bone marrow of this rabbit.

At necropsy, neoplastic lesions are commonly found in the gastrointestinal tract, kidneys, liver, spleen, lymph nodes, adrenal glands, gonads, and bone marrow.* Less common sites of neoplastic infiltrates are the auditory meatus, eye, and heart.[5]

Cutaneous Lymphoma

Cutaneous lymphoma can be either epitheliotrophic lymphoma of T-cell origin (*mycosis fungoides*) with a potential to metastasize to visceral organs, or visceral lymphoma with cutaneous involvement. Several cases of cutaneous lymphoma have been reported in rabbits.[18,46] In a 18-month-old Netherland dwarf rabbit with multiple subcutaneous swellings over the shoulders, cutaneous lymphoma was diagnosed by histologic examination of biopsy samples.[18] At necropsy, no gross or histologic evidence of lymphoma was found in any other organ system, and no viral particles were seen on electron microscopic examination of neoplastic tissue. In another report, three domestic rabbits were diagnosed with cutaneous lymphoma.[46] Two rabbits were young (7 months and 1 year) and the third was 9 years. One young rabbit had erythematous alopecia and hemorrhagic crusts of the chin and ventral neck. At necropsy, neoplastic lymphocytes were found in the skin, lymph nodes, and lungs. In skin sections, the lymphocytes infiltrated the entire dermis and into the epidermis. The second rabbit had bilateral blepharitis that was unresponsive to treatment. At necropsy, superficial and deep lymph nodes were markedly enlarged, and lungs had reddened areas. Lymphocytic infiltrates were found in the skin, lungs, liver, kidneys, and heart. In the skin sections, lymphoid infiltrates were primarily in the subcutis and deep dermis. The third rabbit had nonpruritic alopecia of the left lateral thorax. Cutaneous lymphoma was diagnosed by biopsy of a skin sample; in this rabbit, lymphocytes infiltrated the superficial dermis and epidermis. The rabbit lived for an additional year after diagnosis, with no response to treatment with interferon alpha-2b (see Treatment below). A necropsy was not performed. In all three rabbits, immunologic staining of tissue sections confirmed the lymphoma to be of T-cell origin.

In two cases of cutaneous lymphoma seen at the Animal Medical Center, both rabbits presented because of a subcutaneous mass. In one 7-year-old rabbit, cutaneous lymphoblastic lymphoma was diagnosed by excisional biopsy of a subcutaneous nodule on its dorsal neck. Three more masses developed within 1 month and were excised. The rabbit died 2 months after the first biopsy, and at necropsy, lymphoma was found in the cervical, mesenteric, and thoracic nodes. In a second rabbit, a large, hemorrhagic mass was present on the ventral thorax. This rabbit was euthanized. On histologic examination, lymphoma involving the skin mass and spleen was diagnosed.

Leukemia

Three cases of lymphoblastic leukemia and one case of myeloid leukemia have been documented in rabbits.[5,10,28,41] In rabbits with lymphoid leukemia, WBCs have ranged from 30,000 to more than 100,000 cells/μL. In all rabbits with lymphoblastic leukemia, neoplastic cells were present in bone marrow, lymph nodes, and other organs typical of stage V lymphoma.

Thymoma/Thymic Lymphoma

Thymomas have been reported in three rabbits,[4,21,45] and we have seen three cases of rabbits with mediastinal masses confirmed as either thymoma or thymic lymphoma. Thymomas are composed of variable mixtures of lymphoid and reticular-epithelial cells. In some cases, the lymphoid cells are small, mature cells; in others, lymphocytes are pleomorphic with prominent nucleoli. Thymic lymphoma denotes lymphoma involving the thymus, with other organ involvement. However, distinguishing thymoma from thymic lymphoma clinically can be difficult.

In all reported and clinical cases, rabbits had a mediastinal mass identified radiographically (Fig. 21-5). In two reported cases and in two of the clinical cases, rabbits had exophthalmos. In these rabbits, eyes could be retropulsed with no evidence of pain, suggesting the exophthalmos was not caused by the presence of a space-occupying mass. Prolapse of the third eyelid was described in one reported case[45] and seen in one clinical case. These signs are consistent with a diagnosis of cranial vena caval syndrome caused by the space-occupying mass compressing the vessels of the anterior thorax and impeding vascular return to the heart.[4] Increased respiratory rate was reported in one rabbit[21] and seen in one clinical case. In one rabbit, hypercalcemia (14.7 mg/dL) was described as a paraneoplastic syndrome, similar to dogs with thymoma.[45] However, because the influence of diet and calcium metabolism on the serum calcium concentration in rabbits was not considered in this case, this conclusion is possibly erroneous.

In two of the clinical cases, rabbits with mediastinal masses also had high WBC counts. In these rabbits, WBCs were 42,000 and 18,000 cells/μL, with more than 70% lymphocytes. On microscopic interpretation of a blood smear of the first rabbit, the cells were characterized as small lymphocytes with cleaved nuclei and scant cytoplasm. A bone marrow aspirate showed no marrow infiltration, confirming the diagnosis of lymphoma. In this rabbit, cytologic examination of an aspirate of the thoracic mass was diagnostic of lymphoma. This rabbit was treated with radiation therapy. In the second rabbit, no further diagnostic tests were performed. Both rabbits were eventually euthanatized. No bone marrow involvement was found at necropsy in either rabbit. On histopathologic examination, the mass in the first rabbit was identified as a thymoma, not thymic lymphoma; therefore the final diagnosis remains in question. The second rabbit was diagnosed as thymic lymphoma.

In all reported and clinical cases except one, rabbits died or were euthanatized within 6 months of diagnosis. In one reported case, the thymoma was successfully excised; this rabbit was euthanatized 9 months after diagnosis because of recurrent appendicular neurofibrosarcoma.[4] In the third clinical case of thymoma, the rabbit was treated with a low dose of prednisone (0.5 mg/kg q24h), with no other therapy. After 1 month, the tumor had not changed in size. The rabbit was euthanatized 5 months later because of labored breathing and poor clinical condition. In the rabbit treated with radiation therapy, the tumor regressed; however, the rabbit was euthanatized 3 months after diagnosis because of lethargy and severe pleural edema. On histologic examination, the mediastinum was markedly fibrotic with

*References 5, 12, 16, 42, 43, 46.

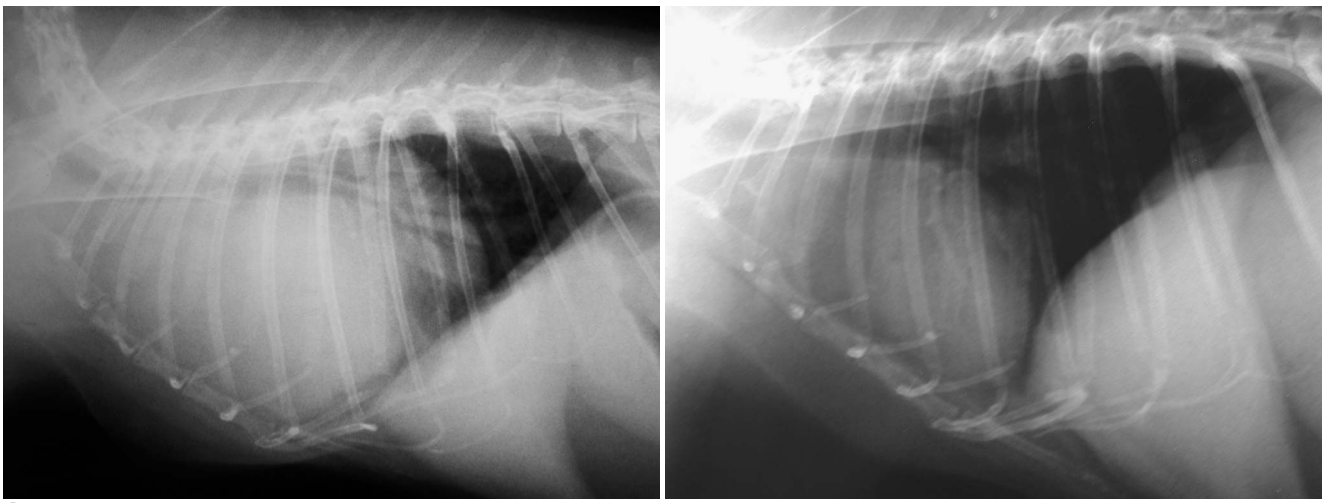

Figure 21-5 Right lateral thoracic radiographs of a mini-lop rabbit with a thymic mass, leukocytosis, and lymphocytosis. At necropsy, the mass was identified histologically as a thymoma. **A,** At presentation, the mass displaced the heart caudally. The normal cardiac silhouette is not visible. **B,** One week after the first dose of radiation therapy. The mass has regressed considerably in size, and the heart is in a more normal position.

sterile granulomatous inflammation and thrombi in mediastinal vessels. Chronic active pyelonephritis was found with numerous *E. cuniculi* organisms in renal tubular cells and lumen.

DIAGNOSIS

The diagnostic workup of a rabbit with a lymphoproliferative disease is similar to that of other small animals. If complete blood count (CBC) results reflect either a high WBC count with lymphocytosis or a normal WBC count with an inverse lymphocyte/neutrophil ratio, repeat the test to confirm the findings. If anemia is found on a routine CBC, consider ruling out possible lymphoma and perform additional tests. Submit a blood sample for a plasma biochemical analysis to look for evidence of multiorgan involvement. Take both thoracic and abdominal radiographs, and perform an abdominal ultrasound examination to visualize architecture of abdominal organs and to identify abdominal masses or enlarged lymph nodes. Submit a bone marrow sample for evaluation, and take a biopsy of any enlarged peripheral lymph nodes or subcutaneous masses. If a thoracic mass is present, perform an ultrasound-guided fine-needle aspiration if possible, and submit the sample for cytologic examination.

TREATMENT

Little information is available on treating rabbits with lymphoproliferative diseases. Much of this information is anecdotal, with protocols based on those used in other small animals. At best, the prognosis with treatment is guarded to poor.

Chemotherapy

Although much information has been published about chemotherapeutic agents in experimental studies in rabbits, only one report describes the use of chemotherapy in a clinical case. As mentioned, a 9-year-old rabbit with cutaneous lymphoma was treated with recombinant human interferon α_{2b} at 1.5 million units per square meter administered subcutaneously three times weekly.[46] After 1 month, no response was seen, and isotretinoin (4 mg/kg q24h on food) was added to the treatment for 2.5 weeks. After 2 months, no change was seen in the lesions, and all treatments were discontinued.

Anecdotal information is available on the use of doxorubicin in pet rabbits. One recommended dose is 1 mg/kg given intravenously over at least a 20-minute period, repeated every 3 weeks. The CVP/COP (cyclophosphamide, vincristine, prednisolone) protocol, with or without doxorubicin and L-asparaginase, has also been recommended.[31] We have used prednisone (0.5 mg/kg q12h for 28 days) in one rabbit that underwent concurrent radiation therapy (see below). This rabbit died with pleural effusion and severe *E. cuniculi* infection.

Because of the lack of information available on the benefits of chemotherapy in rabbits, the potential risks must be considered before treatment. In one study, rabbits that were experimentally infected with spores of *E. cuniculi* were treated with cyclophosphamide (50 mg/kg first dose, then 15 mg/kg weekly for a 12-week period). In these rabbits, clinical signs of encephalitozoonosis developed between weeks 4 and 6, and all rabbits died during week 6. No signs of infection were seen in control rabbits. These results indicate that immunosuppression induced by cyclophosphamide gave rise to lethal encephalitozoonosis. Most likely, the rabbit we treated with prednisone and radiation therapy also developed encephalitozoonosis because of immunosuppression. Other side effects can include severe anemia, enteritis, typhlitis, and nephrotoxicity. In an experimental study of rabbits given daunorubicin or doxorubicin at 3 mg/kg weekly for 10 weeks, cardiotoxicity was documented with daunorubicin but not with doxorubicin.[20] Both drugs produced hemotoxicosis manifested by aplastic anemia. Rabbits treated with doxorubicin exhibited more weight loss and had higher mortality rates than those treated with daunorubicin. A single dose of L-asparaginase

at 10,000 IU/kg when given intravenously can induce a hyperinsulinemic, insulin-resistant, diabetic syndrome in rabbits.[22] However, in small animals L-asparaginase is currently given intramuscularly or subcutaneously; therefore route of administration may factor in toxicity. The neurotoxic effects of vincristine have been well studied in rabbits.[11,29,30]

Radiation

No reports describe the use of radiation in treating rabbits with lymphoid disorders. However, rabbits have been used in research studies regarding effects of irradiation on soft tissues.[7,9] We have used radiation therapy to treat one rabbit with a thymoma. The rabbit was given a short course of radiation treatment with 800 rad (8 Gy) per treatment on days 0, 7, and 21. The tumor was considerably smaller after the first treatment (see Fig. 21-5, *B*). However, 1 month after the final treatment the rabbit was euthanized because of pleural effusion and poor clinical condition. As described previously, fibrotic tissue was found at the tumor site at necropsy, with thrombosis of mediastinal vessels.

Surgical Excision of Cutaneous Tumors and Thymomas

Surgical excision of thymomas has been described in two rabbits. In one rabbit, a right fourth intercostal thoracotomy was performed and the mass was excised. A chest drain was placed, but pneumothorax persisted after surgery and the rabbit was euthanized.[45] In another rabbit the mass was removed by median sternotomy.[4] A chest drain was kept in place 24 hours, after which it was removed and the rabbit recovered uneventfully. When the rabbit was euthanized 9 months later, no evidence of tumor recurrence was present.

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