

## Lymphangiosarcoma Associated with Primary Lymphedema in a Bouvier des Flandres

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**A** 4-year-old, spayed female fawn Bouvier des Flandres presented to the Ontario Veterinary College Veterinary Teaching Hospital with a history of bilateral hind limb edema and an inguinal mass. The hind limb edema had been present since the dog was acquired at 8 weeks of age and was unchanged with time. Forty-five days before referral, a firm mass was noted in the left inguinal region.

On presentation, the dog had bilateral, pitting, nonpainful edema of the hind limbs (Fig 1). The edema was marked below the tarsi but could be palpated into the inguinal region. Both sides appeared to be equally affected. The popliteal lymph nodes were not palpable, and the left hind limb was moist from the tarsus distally. Clear fluid was noted to be weeping from an area distal to the tarsus, and this finding was assumed to be lymphorrhea (leakage of lymph through the skin). On the basis of historic and physical examination findings, a tentative diagnosis of primary lymphedema was made. In addition, a firm, irregularly shaped approximately 4 × 4-cm mass could be palpated in the left inguinal region. The mass extended dorsally toward the pelvis, and a dorsal margin could not be palpated.

Initial diagnostic tests, including CBC, serum biochemistry, prothrombin and partial thromboplastin times, urinalysis, and 3-view thoracic radiography, were within normal limits. Cytologic evaluation of the lymphorrhagic fluid indicated high cellularity composed of >95% small lymphocytes. An ultrasound examination of the abdomen and inguinal mass was performed. Abdominal ultrasonography showed no clinically relevant findings. Ultrasonography of the inguinal mass showed it to be a 3 × 3-cm well-encapsulated lobulated mass that appeared to be extra-abdominal. An ultrasound examination was performed over both of the popliteal fossae, and popliteal lymph nodes could not be identified. Needle biopsies of the inguinal mass were obtained, and immunohistochemistry (including analysis for cytokeratin, vimentin, factor VIII-related antigen, and actin) was consistent with a diagnosis of hemangiosarcoma or lymphangiosarcoma.

Lymphoscintigraphy of the hind limbs was performed and indicated a marked delay in lymphatic filling and an absence of popliteal lymph nodes. Results of lymphoscintigraphy confirmed the diagnosis of primary lymphedema.

The dog was treated with rutin, a benzopyrone (67 mg/kg PO q24h).

Additional imaging of the mass by magnetic resonance imaging was recommended before surgical resection but was declined by the owner. Surgical resection of the inguinal mass was performed preserving a 3-cm margin circumferentially and 1 fascial plane deep. Edema was noted in the subcutaneous tissue surrounding the inguinal mass at the time of resection, and lymph continually accumulated in the surgical field. Reconstruction of the inguinal area was achieved with bilateral flank fold flaps by means of a previously described technique (Fig 2).<sup>1</sup> An active drain was placed, and a large amount of lymph fluid drained continuously from all incision sites. Histopathologic evaluation of the mass was diagnostic of lymphangiosarcoma (Fig 3). Because of the presence of neoplastic cells adjacent to an abnormal vessel resected at surgery near the surgical margin, it was considered unlikely that complete excision was achieved.

Postoperatively, analgesia was provided with a transdermal fentanyl patch<sup>a</sup> (4.4 µg/kg/h for 72 h), meloxicam<sup>b</sup> (0.1 mg/kg PO q24h for 7 days), and oxymorphone<sup>c</sup> supplemented as needed (0.05 mg/kg IV). The hind limbs were hobbled above the tarsi to prevent splaying and to protect the surgical repair. Postoperative complications included wound dehiscence that required intensive management. The reason for the dehiscence likely was multifactorial, including the copious production of lymph that drained from the incisions, decreased healing in patients with lymphedema, and self-trauma of the surgical site. Lymphedema in the hind limbs was markedly improved in the immediate postoperative period, and improvement was attributed to lymph leakage at the surgical site. The dog was treated with cephalixin<sup>d</sup> (22 mg/kg PO q8h for 35 days) and enrofloxacin<sup>e</sup> (6.7 mg/kg PO q24h for 25 days) on the basis of repeated culture and sensitivity testing and was managed by the referring veterinarian after initial wound care was completed. Communication with the referring veterinarian and owner indicated that the wounds were healing well.

Postoperative radiation therapy was not considered an option in this dog because of the proximity of the radiation site to the colon. The treatment plan was to reevaluate the dog after the wounds had healed and to assess for local recurrence and distant metastasis at that time. If no evidence of gross metastasis or recurrence was found, chemotherapy would be initiated as adjunctive therapy. Eight weeks postoperatively, the dog presented to the referring veterinarian with acute onset of a head tilt. Two days later, the dog developed partial and generalized seizures and was euthanized at the owner's request. A postmortem examination was declined.

Lymphedema is characterized by the accumulation of

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**Fig 1.** Left hind limb of dog on presentation, indicating marked edema. The limb is shaved from the tarsus distally to the paw.

highly proteinaceous edema fluid in the interstitium due to the failure of sufficient lymphatic drainage and is attributed either to congenital lymphatic abnormalities or acquired lymphatic obstruction.<sup>2-6</sup> Lymphedema can be further divided into primary and secondary categories. Causes of secondary lymphedema include infection, trauma, foreign body, neoplasia, surgery, parasitism, arteriovenous fistulas, radiation therapy, venous obstruction, or dermatophytosis.<sup>2-4</sup> Although the cause of primary lymphedema is unknown, it is postulated to be precipitated by dysplasia of the lymphatic system, which results in dilated, minimally functional lymphatic vessels.<sup>2,3</sup> Many humans and animals with primary lymphedema have absent or hypoplastic popliteal lymph nodes.<sup>2-4</sup>

Primary lymphedema can be hereditary or nonhereditary, and although it is congenital, signs may not appear until the animal is several years old.<sup>3</sup> It can involve one or more extremities and is seen more commonly in the hind limbs.<sup>2</sup> Rarely, primary lymphedema can be generalized, a form that usually is fatal early in the neonatal period.<sup>3</sup> Initially, the edema is pitting and painless and, if bilateral, may affect one limb more severely than the other. As time progresses, fibrosis can occur in the edematous limb, resulting in a nonpitting edema.<sup>2,5</sup> Pain and lameness usually are not associated with primary lymphedema unless complications such as infection or cellulitis occur.<sup>2,5</sup> Lymphorrhea can occur in animals with severe lymphedema.

Primary lymphedema has been reported in a German Shorthaired Pointer, a Rough Collie, a Rottweiler, a Borzoi, a Belgian Tervuren, a Great Dane, an Old English Sheepdog, English Bulldogs, Poodles, Labrador Retrievers, German Shepherds, and mixed breeds related to Old English

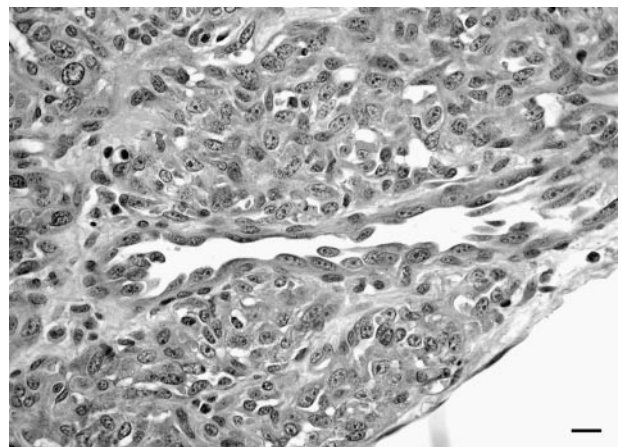


**Fig 2.** Ventral aspect of the inguinal region postoperatively, showing reconstruction with bilateral flank fold flaps and placement of an active drain.

Sheepdogs, Labrador Retrievers, German Shorthaired Pointers, and Poodles.<sup>3</sup> In total, 52 cases of primary lymphedema have been reported in the dog.<sup>3</sup> Primary lymphedema has not been reported previously in a Bouvier des Flandres.

The diagnosis of lymphedema initially is based on physical examination findings and historic information. The differentiation between primary and secondary lymphedema sometimes is difficult, because clinical signs of primary lymphedema may not develop until later in life.<sup>7</sup> To rule out causes of secondary lymphedema, initial diagnostic testing should include CBC, serum biochemistry, urinalysis, fecal analysis, microfilaria testing, thoracic radiography, and abdominal ultrasonography.<sup>3,7</sup> Skin biopsies usually show varying degrees of edema and abnormal lymphatics.

Further investigation into the competence of the lymphatic system may include lymphangiography or lymphoscintigraphy.<sup>3,5,7</sup> Direct lymphangiography in the dog is well described.<sup>5,7</sup> Lymphoscintigraphy does not provide as much specific anatomic information as lymphangiography,<sup>5</sup> but it



**Fig 3.** Photomicrograph of the inguinal mass, diagnosed on histopathology with special stains as lymphangiosarcoma. The neoplastic cells are forming channels of varying sizes throughout this image. Hematoxylin-eosin stain; bar = 10  $\mu$ m.

has the advantage of being less invasive than direct lymphangiography. Lymphoscintigraphy has become the standard for the diagnosis of lymphedema in human patients<sup>8</sup> and is being used more frequently in veterinary medicine.<sup>5-7</sup> In normal dogs, the regional lymph nodes are identified along with evidence of normal lymph movement as time progresses. In dogs with lymphedema, fluid movement through the lymphatics will be delayed, and lymph nodes may be absent.<sup>7</sup>

Normally, the lymphatic system should remove large molecules and excessive fluid from the interstitium. If macromolecules are not properly cleared from the interstitium, oncotic pressure increases and draws more fluid into the region. Infection can be a recurrent problem in approximately 20% of humans with lymphedema.<sup>2</sup> Although the mechanism for recurrent infection is unknown, it is thought to be due to decreased immune surveillance in conjunction with a protein-rich fluid medium for bacterial growth.<sup>2,3,6-10</sup> One of the most important aspects of managing lymphedema is appropriate skin care to avoid pyoderma and cellulitis and prompt treatment of infection with antibiotics.<sup>3,5</sup> Several surgical methods have been used in attempts to increase lymph flow. In the past, surgical intervention has been advocated, but this approach has been relatively unsuccessful and generally is reserved for severe cases.<sup>2,5,7,8</sup> Conservative treatment of lymphedema involves the use of gentle massage and elastic bandages.<sup>3,5,7</sup>

Proposed pharmacologic treatment of lymphedema has included diuretics, corticosteroids, anticoagulants, and fibrinolytic inhibitors, but none of these treatments has proven effective.<sup>3,5,7,11</sup> More promising treatment of lymphedema in humans and dogs has involved the use of benzopyrones such as coumarin, rutosides, and rutin.<sup>3,5-7,9,11</sup> The proposed action of these compounds is proteolysis by stimulation of macrophages, providing a route for the reduction of tissue protein concentrations.<sup>6,9</sup> Some studies in humans have identified a reduction in lymphedema after use of benzopyrones,<sup>9</sup> whereas another study identified no improvement and possible hepatotoxicity.<sup>10</sup> Selenium recently has been shown to be beneficial in secondary lymphedema.<sup>11</sup>

Although rare, one of the most important complications of chronic lymphedema is the development of neoplasia.<sup>8,12</sup> Neoplasia is more commonly associated with secondary lymphedema than with primary lymphedema, with only 12 cases of lymphangiosarcoma associated with congenital primary lymphedema having been reported in human patients.<sup>12</sup> To our knowledge, no such cases have been reported previously in animals.

Regardless of the initial cause of the lymphedema, vascular neoplasia associated with lymphedematous extremities carries a very poor prognosis because metastases and local recurrence occur early in the course of the disease.<sup>12</sup> Early and radical resection still is considered the best chance for long-term survival, but radiation therapy also

has been recommended as the primary treatment.<sup>12</sup> Chemotherapy has not provided adequate tumor control.<sup>12</sup>

Primary lymphedema is a rare disorder in animals. Because of the potential hereditary nature of this disorder, breeding an affected animal should be discouraged. No specific treatment regimen has been widely accepted, but measures should be taken to reduce edema because neoplasia has been associated with chronic lymphedema in humans. To our knowledge, the dog of this report represents the 1st documented case of a dog with lymphedema developing an associated malignancy. Early radical resection followed by radiation therapy may offer the best chance for prolonging survival, but a poor prognosis seems justified.<sup>12</sup>

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### Footnotes

- <sup>a</sup> Fentanyl (Duragesic), Janssen-Ortho, Markham, Ontario, Canada
  - <sup>b</sup> Meloxicam (Metacam), Boehringer Ingelheim, Burlington, Ontario, Canada
  - <sup>c</sup> Oxymorphone (Numorphan), Dupont Pharma, Mississauga, Ontario, Canada
  - <sup>d</sup> Cephalixin (Novo-lexin), Novopharm, Toronto, Ontario, Canada
  - <sup>e</sup> Enrofloxacin (Baytril), Bayer Corp, Toronto, Ontario, Canada
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