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CASE REPORT

Primary multifocal muscular T-cell lymphoma with cutaneous involvement in a dog: A case report and review of the literature

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Abstract

Canine lymphoma represents a heterogeneous group of lymphoid neoplasms, with multicentric nodal lymphoma being the most common presentation. Musculoskeletal involvement is uncommon, and primary muscular lymphoma is a very rare presentation. Only a few cases have been described in dogs, which were of variable classification and immunophenotype. Here, we report the case of a 5-year-old female neutered Beagle that presented with an intramuscular mass on the right shoulder and associated lameness and lethargy. One month after initial presentation, multiple cutaneous nodules appeared on the head, and staging with advanced imaging revealed additional masses affecting other muscles. Cytology, histopathology, immunohistochemistry, and PCR for antigen receptor rearrangements of one of the muscle masses and skin lesions supported a diagnosis of peripheral T-cell lymphoma with large granular lymphocytes at both sites. The dog was euthanized after diagnosis due to the poor prognosis. This is the first report of primary muscular peripheral T-cell lymphoma with large granular lymphocytes and cutaneous involvement in the dog. Despite being a rare presentation, lymphoma must be considered a differential in dogs presenting with a discrete, intramuscular, soft tissue mass.

KEYWORDS

canine, histopathology, lymphoid, musculoskeletal, neoplasia, skin

1 | CASE PRESENTATION

A 5-year-old female neutered Beagle was presented to the referring veterinary surgeon with a rapidly growing mass on the right shoulder associated with lethargy and right forelimb lameness. Three days before the onset of clinical signs, the dog had a dental procedure at the referring veterinary surgeon due to severe periodontal disease, and no masses were detected on examination. An intravenous catheter was placed in the right cephalic vein for the procedure. The following investigations were performed by the referring veterinary surgeon before presentation to our institution. Samples of the mass were submitted for bacterial culture with no organisms isolated; cytology and histopathology of the mass were consistent with large cell lymphoma; and fine-needle aspirates of the spleen and one normal-sized prescapular lymph node were consistent with extramedullary hematopoiesis and reactive lymph node, respectively. The dog was treated with antibiotics, anti-inflammatory doses of prednisolone, gabapentin, and paracetamol with no improvement. One month after the initial presentation, the dog was referred for further investigations and treatment.

On examination, the dog was quiet, alert, and responsive. There was no palpable peripheral lymphadenopathy. The main finding on

examination was a large, firm, mass lesion caudal to the right shoulder, measuring 8 cm × 6 cm × 6 cm, which appeared to involve most of the triceps muscle. The mass was warm and painful to touch, and the dog was nonweight bearing lame and very painful on manipulation of the mass. The dog also had several cutaneous nodules on the head (cheek, chin, top of the head, and muzzle), which had appeared 3 days previously. The nodules were pink, raised, erythematous, and well-defined, measuring between 5 and 15 mm in diameter. There was no periodontal disease. There was mild pyrexia at 39.1°C.

Further staging investigations were performed at our institution, including hematology and biochemistry, which were unremarkable. Abdominal ultrasound was largely unremarkable apart from gallbladder sludge, irregular gallbladder wall thickening, and nonspecific hyperechoic liver parenchyma. Thoracic computerized tomography (CT) revealed a large muscular mass at the caudal aspect of the right humerus extending from the caudal aspect of the shoulder to the caudal aspect of the elbow, following the path of the triceps muscle. Additional smaller masses affecting different muscles along the dorsal aspect of the neck, left thoracic limb, thoracic wall, and head were also detected on CT (Figure 1). Fine-needle aspirates of the muscular mass on the left thoracic limb revealed a monomorphic population of large lymphoid cells with moderate amounts of moderately basophilic cytoplasm, and several lymphoid cells exhibited small clusters of cytoplasmic magenta granules (Figure 2). The nuclei were round to indented with stippled chromatin and variably distinct single large nucleoli or multiple smaller nucleoli, and many mitotic figures were also present (Figure 3). Cytology was consistent with lymphoid neoplasia. A similar cytologic picture was also noted on impression smears of one of the cutaneous nodules on the cheek. Excisional biopsies of the skin lesions of the cheek and muzzle and Tru-Cut biopsies (Carefusion) of the muscle mass on the left thoracic limb detected on CT were collected and submitted for histopathology.

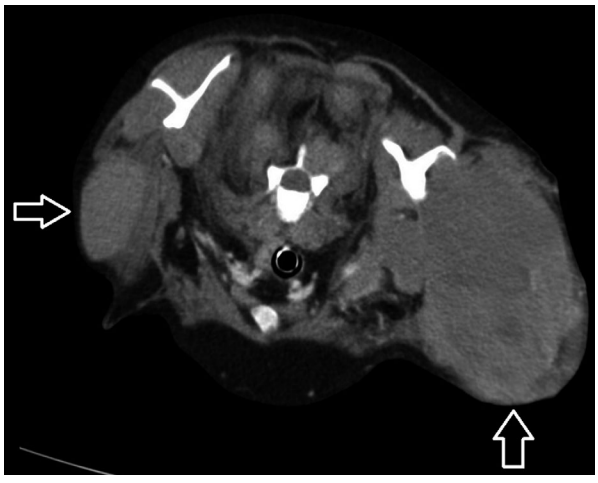

FIGURE 1 Computerized tomography (CT) scan images of the mass lesion on the caudal aspect of the right humerus of a dog (vertical arrow). A smaller, additional mass on the left thoracic limb can also be appreciated (horizontal arrow)

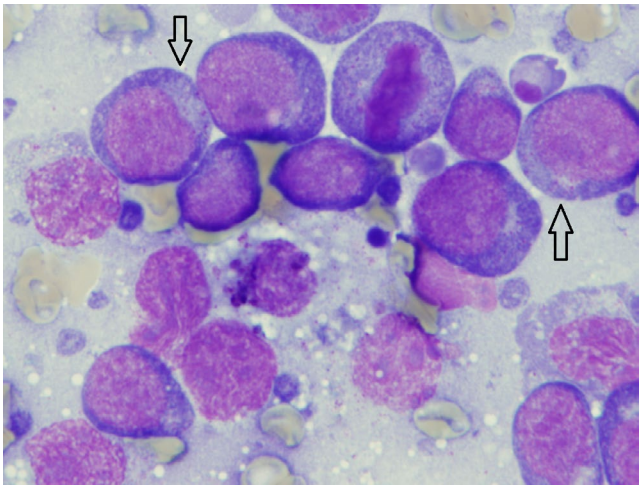

FIGURE 2 Photomicrograph showing cytology from the muscular mass on the left thoracic limb of a dog, May-Grünwald Giemsa (×1000). There is a monomorphic population of large lymphoblasts with moderate amounts of moderately basophilic cytoplasm, and several lymphoblasts exhibit magenta granules (arrows)

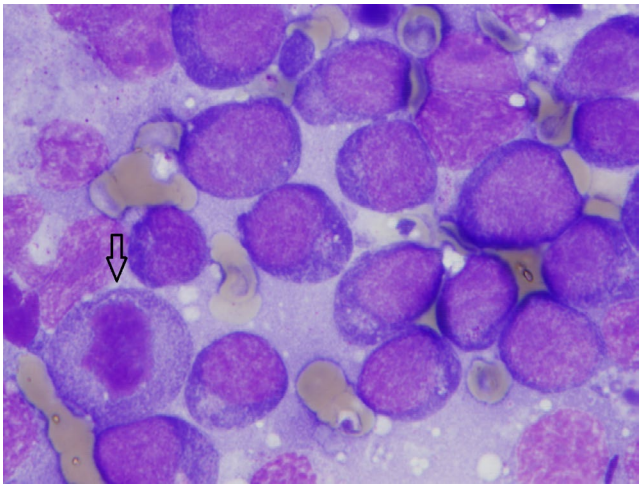

FIGURE 3 Photomicrograph showing cytology from the muscular mass on the left thoracic limb of a dog, May-Grünwald Giemsa stain (×1000). The nuclei of the lymphoblasts are round to indented with variably distinct single large nucleoli or multiple smaller nucleoli. Many mitotic figures are also present (arrow)

In the samples from the cheek and muzzle, there was extensive infiltration of the dermis and subcutis by sheets of medium-sized to large round cells with a scant/moderate amount of cytoplasm, occasional nuclear folding, and indentation or mildly irregular nuclear outlines. Mitotic figures were up to 18 per high power field ×400 magnification. Dense neoplastic infiltrates in the dermis caused compression of adnexal structures. Most hair follicles surrounded by the neoplastic infiltrates were in the telogen phase. Sebaceous glands and apocrine epitrichial sweat glands were still present, although in some areas were markedly compressed and

occasionally undetectable. Immunohistochemistry confirmed the absence of neoplastic epidermotropic infiltration associated with hair follicles; however, mild intraepithelial infiltration of CD3 positive neoplastic lymphoid cells was noted in rare apocrine gland profiles. Neoplastic infiltrates showed patchy areas of necrosis, particularly in the sample from the muzzle. In the sample from the cheek, there was focally extensive epidermal ulceration. Neoplastic infiltrates also extended into the panniculus carnosus muscle with a perineural distribution associated with small nerves. Histopathology of the muscle biopsy showed extensive and coalescing endomysial infiltrates. There were sheets of medium-sized to large neoplastic round cells identical to those observed in the skin biopsy. The infiltrates caused separation and compression or complete obliteration of myofiber fascicles (Figure 4). Immunohistochemistry revealed that the neoplastic cells were diffusely positive for cluster of differentiation 3 (CD3) and negative for cluster of differentiation 20 (CD20), paired box 5 (Pax5), and multiple myeloma oncogene 1 (MUM-1) (Figures 5 and 6). Morphologic features and immunophenotyping were consistent with a diagnosis of peripheral T-cell lymphoma (PTCL). There were rare, small lymphocytes with membranous immunoreactivity for CD20 scattered within the neoplastic population, interpreted as reactive B lymphocytes. Rare, medium-sized to large cells with weak to moderate membranous staining for CD20 were also noted. While this finding could suggest CD20 expression in rare neoplastic cells, confocal immunofluorescence was not available to investigate co-expression of B- and T-cell markers in this small fraction of neoplastic cells. Immunohistochemistry for granzyme B or perforin was not available to characterize the intracytoplasmic granules of the neoplastic lymphoid cells noted on cytology. Phosphotungstic acid hematoxylin (PTAH) staining was performed on the biopsies of the cheek and muscle lesions, and neoplastic lymphoid cells did not reveal the presence of intracytoplasmic purple granules, although adequate PTAH staining was confirmed by detection of sarcoplasmic cross striations in the skeletal myocytes present in the sections. PCR for antigen receptor rearrangements (PARR) was run on DNA extracted from scrolls taken from the paraffin blocks of the biopsy specimens from the muscle mass on the left thoracic limb and skin lesion on the cheek. PARR results confirmed a clonal T-cell receptor (TCR) rearrangement in both samples.

Due to a poor quality of life, disseminated disease, and perceived poor prognosis, the owners elected euthanasia and did not provide consent to a full postmortem examination.

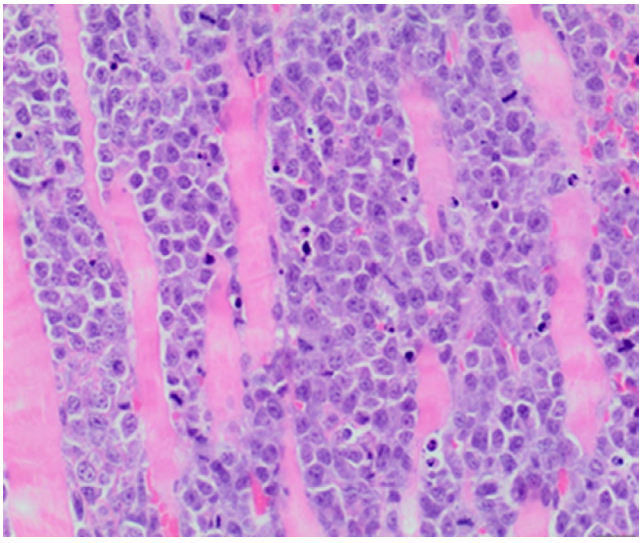

FIGURE 4 Photomicrograph of a biopsy specimen from the left thoracic limb muscle mass of a dog. Diffuse endomysial infiltration of medium-sized to large neoplastic round cells causing separation and compression of myofibers. H&E stain, ×20 objective

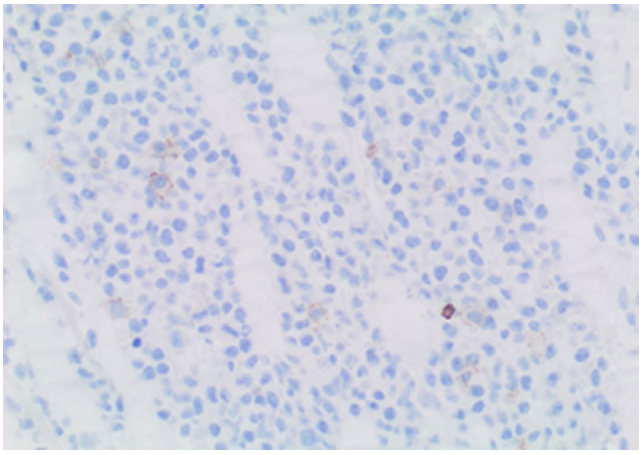

FIGURE 5 Photomicrograph showing cluster of differentiation 20 (CD20) immunostaining. Only rare small lymphocytes feature membranous staining for CD20 and are interpreted as reactive B lymphocytes. Counterstain Gill's Hematoxylin, ×20 objective

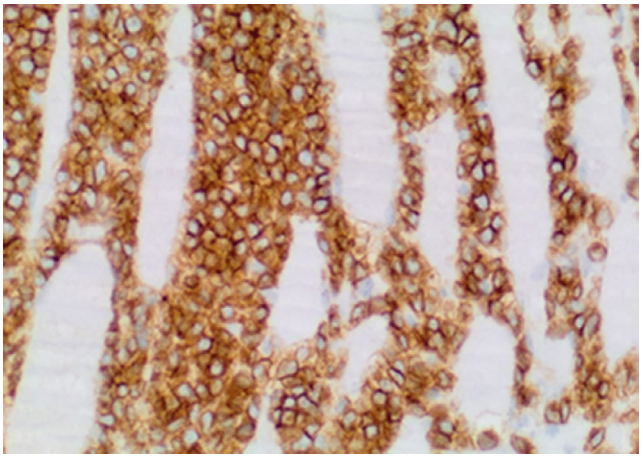

FIGURE 6 Photomicrograph showing cluster of differentiation 3 (CD3) immunostaining. Neoplastic round cells show diffuse strong membranous stain for CD3, consistent with T-cell lymphoma. Counterstain Gill's Hematoxylin, ×20 objective

2 | DISCUSSION

Canine lymphoma encompasses a heterogeneous spectrum of neoplasms that arise from lymphocytes, mostly from lymphoid tissues such as lymph nodes, spleen, thymus, and bone marrow, but can potentially occur at any location. Multicentric lymphoma is the most common presentation of canine lymphoma, accounting for 75%-80% of all lymphoma cases. Musculoskeletal involvement is uncommon and usually part of disseminated disease.[1] Primary muscular lymphoma is a very rare presentation, with only a few canine cases reported, with variable classifications and immunophenotypes.[2-4] In cats, muscular lesions have been reported as part of disseminated epitheliotropic T-cell gastrointestinal lymphoma and as part of a nonspecified lymphoid neoplasia.[5,6] To our knowledge, this is the first report of primary muscular PTCL with cutaneous involvement in the dog. The presence of large granular lymphocytes identified on cytology of the muscular mass could suggest a diagnosis of large granular lymphocyte (LGL) lymphoma; however, unfortunately, immunohistochemistry for granzyme B or perforin was not available to support this diagnosis. While expression of granzyme B and perforin is a reported feature of LGL lymphomas in dogs,[7] cases lacking expression of granzyme B and perforin have also been reported,[8] so a diagnosis of LGL lymphoma could also not be ruled out. The clinicopathologic features of this case, however, did not fit the previously reported presentations of LGL lymphoma in dogs,[8] and PTAH staining, which is usually positive in LGL tumors, was negative in our case, making this diagnosis less likely.[7]

Diffuse skeletal muscle lymphoma with cutaneous lesions developing later in the disease course has been previously reported in a dog,[9] but in that report, the cutaneous lesions were diagnosed as epitheliotropic T-cell lymphoma, and the muscle biopsies were consistent with B-cell lymphoma and concurrent polymyositis, suggestive of the coexistence of these two lymphoma types in the same patient. This contrasts with the current case where both the muscular and cutaneous lesions were consistent with PTCL with large granular lymphocytes. The muscular lesions in the current case were also discrete masses rather than diffuse neoplastic infiltration within the muscle, and this is consistent with the findings of previous case reports of canine primary muscular lymphoma and human muscular lymphoma.[10-12] Primary skeletal muscle lymphoma is also a very rare neoplasia of people, accounting for only 0.5% of all extranodal lymphomas, with most cases usually being B-cell or non-Hodgkin's lymphoma.[13,14] This contrasts with the current case and three previously reported canine cases, two of which were T cell (one anaplastic large T-cell lymphoma and one low-grade T-cell lymphoma).[3,4] The most commonly affected muscles are the muscles of the extremities,[14-16] which has also been noted in the canine cases. Recurrence of multicentric nodal lymphoma within the muscle has also been reported in people,[17,18] as has been muscular and cutaneous lymphoma as a part of disseminated disease.[19] A case of primary skeletal muscle non-Hodgkin's B-cell lymphoma with cutaneous involvement and without evidence of other systemic dissemination has been reported in a male patient, although no immunophenotyping of the cutaneous lesions was undertaken.[20]

Imaging muscular lymphoma in people usually reveals discrete muscular masses and, less commonly, diffuse muscular enlargement.[21] Magnetic resonance imaging (MRI) features of human primary musculoskeletal lymphoma include poorly defined mass lesions with intermediate signal intensity on T1W and T2W images involving more than one anatomic compartment, subcutaneous tissues, and extension along neurovascular bundles.[22] These features are uncommonly noted in other malignant tumors of the muscle and can, therefore, aid in differentiating lymphoma from other differential diagnoses.[21] MRI is the imaging method of choice for the characterization of soft tissue masses in people; however, in veterinary medicine, most patients undergo CT for cost reasons. In the current case, the masses were relatively homogeneous and isoattenuating to the neighboring muscles on plain CT and slightly hyperattenuating on postcontrast images compared with the surrounding muscles. This appearance has also been described in people, as muscular lymphoma can appear as a homogeneous isoattenuating mass to the surrounding skeletal muscle on plain and postcontrast CT images,[23] with postcontrast enhancement also reported.[24]

The prognosis of primary muscular lymphoma in human patients treated with multimodal surgery, radiotherapy, and chemotherapy, or alternatively with chemotherapy alone, is good[20]; however, due to the sparse literature, in veterinary medicine the prognosis for canine patients with muscular lymphoma is still to be established. Reported outcomes to date have been poor, with a survival time of 6 weeks reported in a patient with anaplastic large T-cell lymphoma treated with a high-dose COP protocol,[4] and a 5-day survival time reported in a patient with a presumed muscular B-cell (CD3 negative) lymphoma treated with corticosteroids alone.[2] In contrast, a dog with a low-grade, T-cell muscular lymphoma treated with various chemotherapy protocols experienced a prolonged survival of 713 days,[3] highlighting how the biological behavior of muscular lymphoma might mimic the behavior of similar grade lymphomas at other body sites. In the current case, the patient had been receiving prednisolone before referral with no improvement, which could have been reflective of an insufficient dose (anti-inflammatory dose of 0.5 mg/kg SID) or an inherently worse response of this high-grade T-cell lymphoma to treatment. A similar poor response to therapy has also been shown in cats.[25]

Different mechanisms of lymphomatous involvement of the muscle have been described, and the most common is the direct invasion from adjacent affected lymph nodes or bone,[22] with other mechanisms, including metastatic spread with disseminated disease and, least commonly, primary extranodal muscular lymphoma.[10] The pathogenesis of primary muscular lymphoma is unknown. Human skeletal muscle lymphoma tends to occur in the lower extremities, and one proposed explanation for this could be that the extremities are more prone to injuries, with human primary muscular lymphoma reported after soft tissue injury,[18] at drug injection sites,[13] and associated with the chronic inflammation of infections or immune-mediated diseases.[12] In the current case, there was no history of trauma; however, an intravenous cannula had been placed in the right thoracic limb 3 days before the onset of lameness and swelling of the same shoulder, and the patient had undergone a dental

procedure for severe periodontal disease, with multiple areas of abscessation and 21 dental extractions. It is unclear if there is any correlation or causality between cannula placement and the dental procedure with the development of muscular lymphoma.

It would have been invaluable to perform a full necropsy on the dog in this study to address or rule out infiltration of other organs. Although the hepatic appearance on abdominal ultrasound was felt to be typical of steroid hepatopathy, fine-needle aspirates of the liver would have been useful to rule out lymphoma infiltration.

In summary, we describe a rare case of primary muscular PTCL with large granular lymphocytes and cutaneous involvement in a dog. The etiology of canine muscular lymphoma is still unknown, but chronic inflammation or trauma could play a role. Although people with primary muscular lymphoma might experience a good prognosis with multimodal treatment, the prognosis of canine muscular lymphoma is still to be determined. Despite being a rare presentation, lymphoma must be considered as a differential in dogs presenting with a discrete, intramuscular, soft tissue mass.

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