Tarsal villonodular tenosynovitis (giant cell tumor of tendon sheath) in a dog

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ABSTRACT: A 12-year-old female mixed-breed dog presented with lameness, pain, and an enlarged, non-ulcerated, nodular mass in the region proximal to the tarsal joint of the right pelvic limb. Surgical excision was performed, revealing a 6.5 cm mass adherent to the deep flexor tendon and adjacent tissues. The cut section had cysts filled with blackened clotted material, which exuded reddish serous fluid. Microscopically, the cysts were filled with red blood cells and were either demuded or covered by synoviocytes. In addition, the mass was characterized by marked fibrovascular connective tissue associated with siderophages and multinucleated giant cells. These findings were consistent with those of pigmented villonodular tenosynovitis, a rare condition affecting several animal species and humans.

Key words: giant cell tumor of tendon sheath, joint, lameness, tendon, dog.

PATHOLOGY

Tenossinovite vilonodular pigmentada (tumor de células gigantes da bainha tendínnea) tarsal em um cão

RESUMO: Uma cadela de 12 anos, sem raça definida, apresentou claudicação, algia e aumento de volume não ulcerado, de aspecto nodular, na região proximal à articulação do tarso do membro pélvico direito. A excisão cirúrgica foi optada e revelou uma massa de 6,5 cm de diâmetro, aderida ao tendão flexor profundo e aos tecidos adjacentes. Ao corte, exsudava líquido seroso avermelhado e cistos preenchidos por material coagulado enegrecido foram observados. Microscopicamente, a massa apresentava formações císticas frequentemente preenchidas por hemácias, que encontravam-se ora revestidas por sinoviócitos, ora desnudas. Havia ainda acentuada quantidade de tecido fibrovascular associado a siderófagos e células gigantes multinucleadas. Esses achados foram consistentes com tenossinovite vilonodular pigmentada, uma rara condição que afeta diversas espécies de animais e humanos.

Palavras-chave: tumor de células gigantes da bainha tendínnea, articulação, claudicação, tendão, cão.
trauma to the site, but with insidious, progressive growth. The animal presented with lameness and pain in the affected area. On physical examination, a nodular mass measuring approximately 5×6 cm was seen on the medial side of the RPL, extending from the cranial to the caudal surface in the topographic region of the tarsus. On palpation, the lesion was predominantly soft and interspersed with few firm areas. Complementary tests such as blood count, biochemistry, cytology of the lesion, ultrasound, and chest radiography in three projections for metastasis delete were requested; additionally, the mediolateral and craniocaudal views of the tibio-tarsal joint of the affected limb were obtained. The results of the blood tests, abdominal ultrasound, and chest radiographs were normal. Radiographically, the RPL showed an increase in soft tissue mass in the medio-distal third of the tibia with defined limits and contours and interspersed with some areas of mineral radiopacity, but with no evidence of bone involvement (Figure 1).

Fine-needle aspiration puncture of the lesion drained 10 mL of serosanguineous fluid with low viscosity and cellularity, composed mainly of erythrocytes and macrophages, indicating the presence of erythrophagocytic activity, occasional lymphocytes and neutrophils, and rare spindle cells without obvious malignancy criteria. The lameness and pain persisted, necessitating the need for high limb amputation surgery. The animal received pre-anesthetic medication with 0.2 mg/kg methadone intramuscularly, induced with 2 mg/kg etomidate because of a history of cardiovascular disease, and 0.25mg/kg midazolam intravenously. For anesthetic maintenance, isoflurane and fentanyl 7.5μg/kg were

Figure 1 - Tarsal pigmented villonodular tenosynovitis in a dog Radiographic examination of the lateral aspect of the right pelvic limb shows a nodule with increased radiopacity originating from the tarsal joint and extending to the adjacent tissues of the tibial and fibular bones. The center of the nodule shows small radiopaque and irregular areas that represent the bone tissue interspersed with the soft tissue of the mass.

Inset: Macroscopic image of the nodule in the cross-section shows a cystic aspect composed of thin whitish trabeculae. Additionally, discrete areas at the periphery of the mass of compact white tissue are seen with blackened multifocal clots.
administered. During the procedure, cephalothin (30 mg/kg) was administered and repeated two hours after the surgical procedure, along with bupivacaine as a “splash” for local anesthesia during nerve sectioning. Sectioning of the musculature in the region, ligation of the femoral vein and artery, sectioning of the sciatica, and coxofemoral disarticulation were performed. In the immediate post-operative period, the patient received dipyrone 25 mg/kg, methadone 0.2mg/kg, and meloxicam 0.1mg/kg. The animal was discharged from the hospital on the same day as the surgery, with dipyrone 25mg/kg TID for 7 days, tramadol 4mg/kg TID for 5 days, omeprazole 1mg/kg SID for 10 days, and amoxicillin with potassium clavulanate 20mg/kg BID for 10 days, along with post-operative recommendations.

Gross examination of the amputated limb revealed a mass measuring 6.5cm in diameter, located in the tarsal joint and adherent to the peripheral tissues. The mass was soft with multifocal to coalescent cystic structures at the cut surface with a thin whitish wall, and black clotted material was observed in the lumen (Figure 1). During dissection, the mass was adherent to the deep flexor tendon, but bone lysis was not observed. For histopathological analysis, the samples were processed routinely after fixation in 10% buffered formalin solution and then stained with hematoxylin and eosin (H&E).

On histological examination, the dermis and the synovium were expanded by multiple cysts frequently filled with red blood cells, proteinaceous eosinophilic material, fibrin, and cellular debris (Figures 2A and 2B). The cysts were lined by a monolayer of synoviocytes, in addition to denuded areas (Figure 2C); some cells lining the cysts were ciliated. The cystic areas were surrounded by fibrovascular connective tissue containing moderate to marked multifocal inflammatory infiltrates of macrophages with brownish (hemosiderin) or yellowish (hematoxidin) cytoplasmic pigments and a moderate number of multinucleated giant cells (Figure 2D). Furthermore, a moderate inflammatory infiltrate of lymphocytes and plasma cells predominantly adjacent to the synoviocytes and eventual multifocal areas of bone metaplasia with formation of bone trabeculae and osteoclasts were noticed (Figure 2E). There were extensive areas of stromal cells organized in sheets. In the midst of individual cells with strongly eosinophilic cytoplasm, several nuclei with dispersed chromatin and similar to synoviocytes were observed with moderate anisocytosis and anisokaryosis.

The sample was submitted for immunohistochemical analysis with a detection system using the peroxidase-labeled universal polymer method (MACH4 Universal HRP-Polymer kit) (Biocare Medical®) with antibodies to vimentin (dilution1/200) (V9, Zymed®), a “ready-to-use” pan-cytokeratin (panCK) (AE1/AE3, Dako®), and ionized calcium binding adaptor molecule 1 (Iba-1) (dilution 1/1.000) (FUJIFILM Wako Chemicals®), which was revealed using the Romulin AEC chromogen kit (Biocare Medical®) and counterstained with Harris’ hematoxylin. Stromal cells and synoviocytes had diffuse and strong cytoplasmic immunolabeling for vimentin, while the giant cells displayed mild and multifocal cytoplasmic immunolabeling with this marker. Multifocal macrophages showed strong cytoplasmic immunolabeling for Iba-1 (Figure 2F). No panCK labeling was observed in the sample.

Post operatively, the dog presented a favorable outcome without recurrence of the aforementioned clinical signs. No nodules in the other joints or other diseases related to PVNTS have been observed till date (approximately 10 months follow-up).

PVNTS is rare in animals, with only a few similar cases reported in dogs. However, when reported, it is more frequently observed in large breed adult dogs and often shows a unilateral presentation similar to that observed in this study; although, a few cases of bilateral presentations have also been reported (MARTI, 1997; CAMPBELL et al., 2014; DEMPSEY et al., 2018). PVNTS affecting the radio-carpal-metacarpal, scapular-humeral, and tibio-fibulo-patellar joints, and the sheath of the metatarsal tendon has been reported in dogs; however, involvement of the tarso-tibio-fibular joint has not been previously reported (YOUNG & HUDACEK, 1954; MARTI, 1997; HANSON, 1998; CAMPBELL et al., 2014; DEMPSEY et al., 2018). In this case, the lesion was localized, involving the deep digital flexor tendon in intra-articular presentation and extending to the extra articular region surrounding the tendon. In humans and horses, the injured and hypertrophied synovial membrane may appear macroscopically as a single nodular structure, commonly appearing localized than diffuse, or it may exhibit several diffuse nodules around the tendon located intra- or extra-articularly (MARTI, 1997; GREENSPAN et al., 2007; CAMPBELL et al., 2014; DEMPSEY et al., 2018).

The nature of PVNTS is controversial, given its morphological characteristics and clinical behavior, indicative of both inflammatory and neoplastic lesions. The debate regarding its etiology is still ongoing (IHMS et al., 2017). However, based on recent canine studies, the term PVNTS was
chosen by the authors in this research (AKERBLOM & SJÖSTRÖM, 2006; DEMPSEY et al., 2018). A recent study in humans to determine the etiology of the lesion considered the “landscape” theory, which describes the lesion as a neoplastic entity in which a large part of the cellularity is inflammatory. Thus, it is classified as a tenosynovial giant cell tumor (TGCT), in which a minority of intratumoral cells express genes encoding cytokines for macrophages (macrophage colony-stimulating factor [CSF1]). Most cells found

Figure 2 - Histopathological and immunohistochemical aspects of tarsal pigmented villonodular tenosynovitis in a dog.

A: Cystic areas filled with amorphous and eosinophilic material or red blood cells, in addition to multifocal areas of mineralization (H&E, 40x); B: Multiple cystic areas composed of thin, bare walls, containing collagenous connective tissue (H&E, 40x); C: Cystic areas are sometimes covered by layers of synoviocytes, with mononuclear inflammatory cells adjacent to them (H&E, 200x); D: Increased deposition of collagenous tissue with extensive hemorrhage and infiltration of siderophages (H&E, 100x); E: Well-differentiated bone trabeculae associated with osteoblasts, osteocytes, and multinucleated giant cells (H&E, 400x); F: Discrete immunostaining for Iba-1 in the cytoplasm of monocytic cells and multinuclear giant cells that are adjacent to bone trabeculae (chromogen 3-amino-9-ethylcarbazole, 400x). (H&E, hematoxylin and eosin stain; IHC, Iba-1, ionized calcium binding adaptor molecule 1).
The histological evaluation of this case showed that the main feature was the inflammatory nature of the lesion; although, we also observed cells similar to synoviocytes with moderate anisocytosis and anisokaryosis among the stromal cells, which could be bi- or multinucleated. With respect to the immunohistochemical aspect of PVNTS, the panCK antibody was used to discard epithelial cells on the surface of the cysts and confirmed the synovial origin with the morphological aspects, in addition to excluding epitheloid components characteristic of the subtypes of synovial cell sarcoma (CRAIG et al., 2002; POOL & THOMPSON, 2002). The immunoreactivity patterns observed in this study were similar to those described by other authors (MALATESTA et al., 2005; IHMS et al., 2017) in a lynx and giraffe, with strong and diffuse immunolabeling for vimentin, suggestive of the collagenous origin of the stroma and negative results for panCK. The multifocal and discrete cytoplasmic labeling for the Iba-1 antibody suggests that mononuclear and multinucleated cells represent activated monocytic cells (WEST et al., 2006; IHMS et al., 2017). Based on these findings and West et al (2006) studies wherein the reactive cells express antibodies to both synoviocytes and macrophages, it can be suggested that their origin, albeit not definitive, can be derived from synoviocytes type A.

Although, PVNTS shows benign biological behavior with a favorable prognosis, it can interfere with an individual’s quality of life causing morbidity, pain, and discomfort, (HANSON, 1998). Therefore, surgical resection is the recommended treatment for PVNTS, with very low recurrence rates (BARCLAY et al., 1980; SANCHIS-ALFONSO et al., 2000; LACERDANETO et al., 2011; PATEL et al., 2017). PVNTS is a proliferative entity that uncommonly affects the joints of different domestic and wild animals and should be considered as a differential diagnosis in animals presenting lameness and swelling in joints. An accurate histopathological diagnosis is necessary for appropriate treatment. Further studies should be conducted to determine an accurate etiology.

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**DECLARATION OF CONFLICT OF INTEREST**

The authors declare no conflicts of interest. The founding sponsors had no role in the design of the study, in the collection, analyses, or interpretation of data, in the writing of the manuscript or in the decision to publish the results.
AUTHORS’ CONTRIBUTIONS

The authors contributed equally to the manuscript.

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