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DEVELOPMENT AND OUTCOME OF FELINE INJECTION – SITE SARCOMA IN AN ADULT CAT – CASE REPORT

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ABSTRACT

Feline injection – site sarcomas (FISS) are aggressively behaving fibrosarcomas with a rate of metastasis ranging from 10 to 25%. The main treatment of soft tissue sarcomas is surgical excision with clean margins and subsequent radiotherapy and systemic chemotherapy.

We present a case of an adult male cat with recurrent fibrosarcoma, which anamnesis and aggressive tumor development pointed to FISS. A fine needle biopsy first suggested and then histopathology confirmed that diagnose. Two months after the surgery a new tumor mass appeared on the site of the excision. The rapidly growing tumor penetrated the abdomen wall, occupying almost entire abdomen, affecting the internal organs and the right lumbar region muscles, observed by a conventional X-ray examination. A developing central necrosis provoked fistulation and formation of a large wet ulcerative wound in the state of a constant inflammation and tissue disintegration.

The local treatment failure and the progressing poor general condition leaded to carry out a humane euthanasia of the animal.

Key words: FISS, recurrent fibrosarcoma, metastasis, histopathology.

Introduction

Background: Since the early 1990s the malignant mesenchymal tumors known as feline injection – site sarcomas (FISS) or feline vaccine-associated sarcomas have been observed in practice (Hendrick & Goldschmidt 1991; Hendrick et al., 1992). As an etiopathological factor for their development was supposed inflammation after vaccination or other drug injections prompting iatrogenic ultimate malignant transformation of surrounding fibroblasts and myofibroblasts (Hendrick & Brooks1994; Hendrick et al., 1994; Hendrick, 1999) and deposition of applied antigens. Because these formations contain inflammatory infiltrates, primarily macrophages, that are frequently reported to phagocytize bluish "foreign material" (Esplin et al., 1993, Hendrick & Brooks1994) and may include giant cells, they are linked to injection related events. Also a connection with an overexpression of certain mitogens stimulating or suppressing proliferation (platelet-derived growth factor (PDGF), epidermal growth factor (EGF), and transforming growth factor-beta (TGF-beta)) was established in the development of FISS, which is not common in the other soft tissue sarcomas. There is a considerable number of researches determining and evaluating the exact role and involvement of vaccination process or injections in sarcoma occurrence and their relation or lack of such. Besides that, recent genetic studies in the United States demonstrated mutations in tumor suppressive gene in cats, participating in sarcoma development. According to VCA Animal Hospitals (VCA) experts (Gollakner & Ward) the association between vaccines and sarcomas is still very controversial and recent researches questionize the exact mechanism for feline sarcoma phenomenon. On the other hand several studies through the years of the epidemiology and pathogenesis estimated an incidence of one in 1,000 to 0.63 in 10,000 in vaccinated cats (Kass et al., 1993; Gobar & Kass 2002) and other injections or applications of long-acting steroids and antibiotics (Giudice et

al., 2010). Moreover, Phelps et al. (2011) reported a 14% local recurrence rate in cats treated with radical excision (5 cm margins and two fascial planes deep) but this must be interpreted carefully, because for over one-third of the cats the information is lost, so the real percentage is supposed to be bigger. These data suggest a complex network of triggers and consequences and the topic is still in the process of research. Morphologically, these types of sarcomas are mainly locally invasive but tumor recurrence and metastases located in lungs and regional lymph nodes could be found. Those possibilities were reported to be significant prognostic factor associated with survival time in cats – based on multivariate analysis and on the histologic grade of tumors connected with chance for development of distant metastasis (Romanelli et al., 2008). Metastatic rate according to literature data has been calculated between 10 and 25% (Hershey et al., 2000) or more. Moreover it was reported that no decrease in disease prevalence or age increase was related to the changes done in feline vaccine formulations and vaccination protocols from 1992 to 2010 (Wilcock et al., 2012), supporting the hypothesis of gene – related mechanisms. Soft tissue sarcomas, reported as FISS, occur in the subcutis and their histological types were diagnosed as: malignant fibrous histiocytoma, rhabdomyosarcoma, myxosarcoma, liposarcoma, nerve sheath tumor, poorly differentiated sarcomas, extraskeletal osteosarcoma and chondrosarcoma, but fibrosarcoma is the most commonly diagnosed (Esplin et al., 1993; Hendrick & Brooks 1994; Hershey et al., 2000; Dillon et al., 2005; Saba, 2017), other reported vaccine-associated fibrosarcomas in cats as separated nosological unit (Dernell et al., 1998). According to the Veterinary Society of Surgical Oncology soft tissue sarcomas in cats are divided into VAS (vaccine associated sarcomas) and non-VAS, which are very uncommon in cats. VAS are located mainly in the interscapular, dorsolateral thoracic flank, paralumbar and femoral regions. Non-VAS occupy mainly the head (including oral cavity), limbs, bones, tail and other.

***Principle treatment and prognostic factors*:** The main treatment of soft tissue sarcomas (also in dogs and humans) is surgical excision with more than 2 cm margins in healthy tissues around (Davidson et al., 1997), because of the extensive infiltration and invasion of surroundings. In cats this is a serious challenge and wide surgical margins may include bone, muscle, and other structures even limb amputation or removal of tissue "en bloc" without incising tumor itself (Ogilvie, 2004). Appropriate preoperative planning and identification of resection margins guarantee appropriate case management. The addition of radiotherapy, systemic chemotherapy and immunotherapy could be included, especially for high-grade tumors with unclear margins and metastatic potential (Dernell et al., 1998). Once FISS has been confirmed, regional and thoracic radiographs are recommended for verification of local invasion and metastatic disease (pulmonary metastases mainly). Computed tomography scan, magnetic resonance imaging or at least ultrasound are useful for radiation or surgical margins planning. Complete blood count, serum biochemistry profile and hormones, feline immunodeficiency virus/feline leukemia virus (FIV/FeLV) detection (FIV Ab/FeLV Ag Test Kit) and urinalysis tests could be included as part of the patient's database. Histological type and grade, resection margins, size, location and appropriate postoperative treatment are the most important factors for recurrence expectancy.

Clinical case report: This case concerns a 12 years old male unneutered mixed breed cat. The animal developed fast growing tumor formation, palpated initialy as a firm under skin lump with the size of a bean, observed in the right paralumbar region. Over the next 3 months, the formation grew rapidly, reaching more then 10 centimeters in length and 3 – 4 centimeters in width, and the tumor margins became clearly defined. This oval nodal structure had two cord-like outgrowths and was fixed at a wide base to the underlying muscles (Fig. 1).

Figure 1: Macroscopic view of fibrosarcoma formation, domestic cat.

Due to the discomfort, the animal licked the formation and caused a superficial wound. Vaccines against rabies, leukemia, feline immunodeficiency virus, panleukopenia, herpes, and calicivirus infection, chlamydia have never been given. In connection with diagnosed microsporia the animal was given a series of three vaccines five years ago. The anamnesis also revealed that several months earlier the cat passed through medical treatment of urinary retention and urolithiasis, associated with a long – lasting therapy and multiple injectable applications, including antibiotic suspensions. The patient's history and the location of the mass pointed to possibility of FISS development. When it was noticed by the owners, the size changes were measured occasionally and a decision for biopsy was done. Fine needle aspiration with cytology was done as the least invasive. May Grunwald Giemsa – rapid method (DiaPath, Italy) stained smears revealed sarcoma tumor cells, red blood cells, macrophages and Malassezia yeast (Fig. 2).

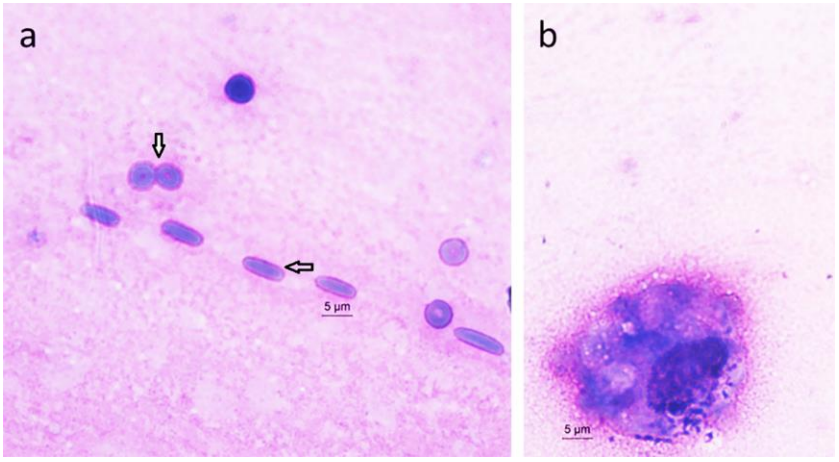

Figure 2: Tumor biopsy: (a) Yeasts (left arrow, transparent) and red blood cells (down arrow, white filled); (b) Sarcoma cell. May Grunwald Giemsa – rapid kit.

Radical surgical excision was done and materials for histological evaluation were preceded. Tumor specimens were fixed in 10% buffered formalin (pH 7) (Alkaloid AD, Skopie) and embedded in paraffin (Emmonya, Biotech Ltd, Bulgaria), sliced into 5 – 10 μm, dewaxed in xylene (Alkaloid AD, Skopie) and H&E stained with Mayer's Hematoxylin (Emmonya, Biotech Ltd, Bulgaria) and Eosin (Bio optica, Milano, Italy) according to routine histological techniques for the production of microscopic observation preparations. Investigations were performed on a Leica DM 5000B microscope, Germany and microphotographs were taken. Histopathological findings confirmed fibroblastic sarcoma of greater degree of pleomorphism, undifferentiated anaplastic spindle shaped cells arranged in a storiform pattern in some regions, situated within collagenous stroma and changed blood vessels (Fig. 3a,b,c). Most cells had elongated nuclei and thin cytoplasmic processes, and some had giant nuclei with prominent nucleoli, increased number of mitotic figures was found (Fig.3b). Central parts were lymphoplasmacytic infiltrated with focal necrotic regions, easily crumbling during histological processing (Fig. 3a).

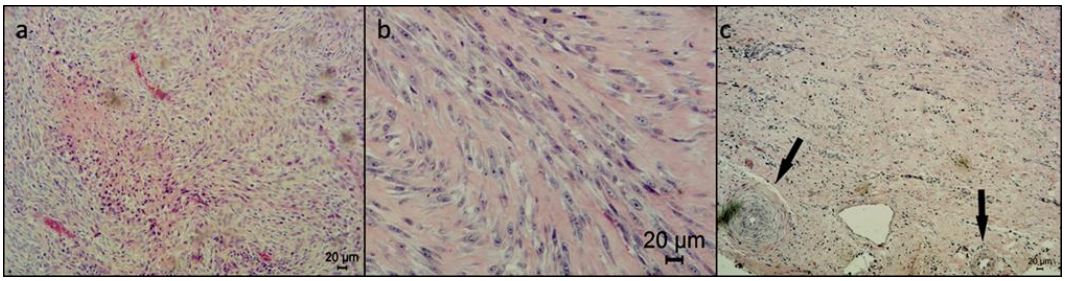

Figure 3: Fibrosarcoma: (a) Lymphoplasmacytic inflammation of necrosis within the sarcoma center; (b) FISS neoplastic tissue organized of pleomorphic neoplastic spindle cells revealing anisokaryosis and collagen fibers in the peripheral tumor regions, higher magnification; (c) Arterial dysmorphia (arrows)– neoplastically changed internal and external elastic laminar and intimal hyperplasia (left corner). Haematoxylin and eosin staining.

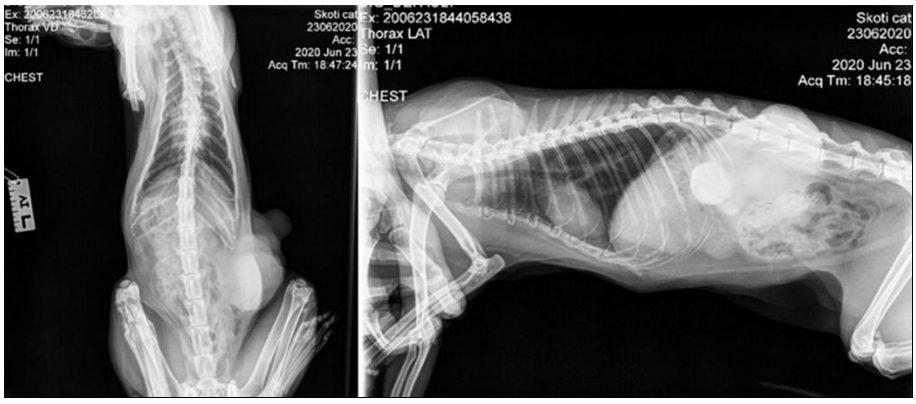

Figure 4: Rö – imaging revealing the tumor size and location.

Standard conservative treatment was administered on the patient for the following ten days. Local treatment with iodine medicines was applies and the sutures were removed 8 days later. For all that time evidence of inflammation, impaired wound healing or suture rupture was not visible.

The wound healing developed normally, the wound shrunk and formed scab. Unfortunately, gradually a growing number of granulation tissue islets were noticed. About two month later the mass grow again and later was defined as 5–7 cm mass of tumor tissue in stage of inflammation, ulceration, and central necrosis with fistulation. The general condition became poor but with possessed appetite at the beginning. Rö – imaging was done (Fig. 4).

Lung metastases were not confirmed, but profuse neoplastic permeation of the abdominal wall and in depth in the abdomen was observed by x-ray. We observed multifocal tumor regrowth following the surgical excision. The process stared as multi sites recurrences around the scar, so the process of regrowth started before even the fur to cover the defect, until the tumor tissue developed in one single tumor mass.

Discussion

Based on the histopathological findings and according to the anamnesis data, the site of occurrence and behavior of the tumor after surgical removal, and the cell profile – fibrosarcoma was diagnosed as FISS. In our case, tumor initiation may be associated with multiple injections in this part of the body, most of them antibiotic suspensions from the group of penicillins and corticosteroids with long action, supposed as risk factors (Kass et al., 2003, Srivastav et al., 2012). Similar cases have been described by other researchers (Zabielska-Koczywąs et al., 2017), but are much rarer than post-vaccine VAS sarcomas. The behavior of the tumor after incision, namely the recurrence rate at the site of the incision is from 35 – 40.8% and lung metastases occurred in 10 – 12% of the cats (Martano et al., 2005) or more according to other data. Characteristic is a rapid infiltrative involvement of the surrounding tissues, which is found to be the main postoperative complication, but the penetration of the neoplasia into the abdominal cavity, observed here was the real problem. More distant metastases (in lungs) were not detected in our case. Analysis of the cell profile observed by us was compared with the literature data. The reported findings include profound anisokaryosis and hyperchromasia, cellular gigantism, numerous mitotic figures, liquefactive necrosis, and numerous lymphoid aggregates around the periphery of the tumor (Hendrick & Brooks1994), some of which observed also in our case. A number of clinical studies in cats have shown that as the primary tumor gets larger it exerts pressure and invade the overlying tissues, lead to skin ulceration, necrosis, persistent bleeding and inflammation, external infections, and most of all – pain. But particularly, the major reason for unfavorable outcome becomes the secondary multifocal tumor regrowth with ulceration following surgery. As it is announced most of such tumors will recur locally, especially when were only surgically treated, with reported median times to recurrence ranging from 2 months to >16 months (Davidson et al., 1997; Hershey et al., 2000). Excision with clean margins was announced as practically almost impossible. In our case the same was observed. In progress, the rapid spread of adjacent tissues and in depth of the abdominal cavity, the cat's age and anesthesia problems, as a background, owners decided to euthanize it. In medical practices the local treatment failure very often leads to humane euthanasia. In fact, that is reported as the most common cause of death in cats with FISS (Saba, 2017). The constant pain and the inability to provide very long-term analgesia along with rapid tissue breakdown and local infection, makes it impossible to maintain patients with this type of tumor, even in the absence of metastases. All these along with poor general state and loss of appetite, extreme physical and mental fatigue, apathy, immobility and constant need for local treatment of the ulcerated wound and supply of systemic antibiotics provoked the owners to quit.

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