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CASE REPORT

Mammary Adenocarcinoma after Ten-Year Medroxyprogesterone Acetate Supplementation in an Ovariectomized Cat

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ABSTRACT

Mammary tumors are common in feline medicine. They are often malignant with a high risk of metastasis and guarded prognosis. Intact females are at greater risk of its development than spayed ones. The underlying cause is unknown, however there are a few predisposing factors. A strong relationship was established between progestagens and mammary tumors' occurrence. It was also proven that gonadectomy prior to first estrus significantly lowers their incidence. Since, intact females are those to receive exogenous progestagens, it is difficult to confirm the difference between drug derived and internally synthesized progestagens and the subsequent pathological changes. In the reported case, queen received medroxy-progesterone acetate for 10 years, despite it was ovariectomized when one year old. The role of endogenous reproductive hormones in the etiology of the mammary neoplasia and CEH is excluded, the mastopathic and metropathic changes, can only be attributed to the effect of exogenous progestagene administration.

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INTRODUCTION

Mammary gland neoplasia is one of the most frequent tumors being seen in every day practice. In queens large amount (about 80%) of the masses are malignant and diagnosed afterwards as adenocarcinomas, with a high risk of metastases, most commonly to lungs, lymphoid tissue, or liver (Hughes and Dobson, 2012). Intact queens, same as bitches, are at much greater risk of developing mammary gland neoplasia, than spayed females. No genetic predisposition has been found until now, however, higher incidence of mammary gland tumors is noted in some breeds (Siamese). Usual time for presentation is 10-12 years of age, but sometimes younger queens may also be affected. Diagnosis is, in most of the cases, obvious, based on clinical signs and examination. The differential diagnosis should include mammary gland hyperplasia, cysts, galactostasis, mastitis or extra-mammary pathologies. Prognosis in most of the cases, especially with suspected malignancy, is poor with survival rate around from six month to three years, depending on tumor size and treatment (Jonhston and Kustritz, 2001). Treatment of choice generally is the surgical removal within safe margins. If the female is not spayed, that needs to be performed simultaneously with the mastectomy, as it should prevent future problems and reduce progesterone levels. A case of mammary adenocarcinoma after 10 years medroxyprogesterone acetate (MPA) supplementation in an ovariectomized cat is reported here.

History: The 11-year-old, domestic shorthair female cat, considered intact, has been administered 5 mg of MPA (medroxyprogesterone) once a week, for 10 years, to prevent potential estrus cycles. The cat was presented to our Clinic due to anorexia, depression and the presence of painful mammary mass, 3- 4 cm in size, with ill defined borders and ulcerated, necrotic centre with small amount of bloody exudate.

Clinical examination: The physical examination revealed a moderate depression, dehydration and presence of mass lesion affecting 4 and 5 left mammary gland, 3- 4 cm in size, with ill defined borders and ulcerated, necrotic centre with small amount of bloody exudate. The local temperature of the mass and the surrounding skin was raised. The body temperature was also raised (39.7°C) and the cat was clearly uncomfortable.

Treatment: Since the blood tests returned normal, and no other symptoms were seen on clinical examination, the symptomatic treatment with antibiotics (amoxycylin with clavulanic acid 8.75 mg/kg, BID) and NSAID's (meloxicam 0.3 mg/kg starting dose SID, maintained with 0.05 mg/kg SID) was prescribed. The MPA administration was ceased and a progesterone antagonist (aglepriston, 15 mg/kg) was applied. Within the first 3 d of treatment the general condition of the queen improved substantially, the mass reduced in size and became less painful (Fig. 1). The chest x-rays were clear and three weeks after the first visit a routine spay was performed that revealed absence of both ovaries. The lack of ovarian tissue was confirmed on histopathological examination and in cat's records found by the owner. The mammary mass was also removed and diagnosed as adenocarcinoma. In the uterus cystic degeneration was found. The wounds healed without complications and skin sutures were removed 10 d post operation. The general health of the cat was good for the next 5 months. Around the sixth month after surgery the cat was presented with anorexia, ascites and major depression. The ultrasound scan revealed extensive liver mass and the cat was euthanized.

Postmortem findings: On post mortem examination there were two big liver tumors affecting right, left and middle lobes with plenty of small masses on liver (Fig. 2), spleen and mesenterium. The chest cavity was clear. On the histopathological examination the liver masses were diagnosed as adenocarcinoma (Fig. 3).

Histopathological diagnosis: For histological and immunohistochemical studies sections of mammary and liver tumors were used. The following antibodies were used (RT): monoclonal mouse anti-human Ki-67 Antigen -clone MIB-1 (1:100); monoclonal mouse anti-human PgR – clone PgR636 (1:50). Incubations (15 min, RT) were performed with secondary biotinylated antibodies and with streptavidin-biotinylated peroxidase complex (LSAB2, HRP) and the substrate: 3,3'-diamino- benzidine (7 min, room temperature). All the above were bought from DakoCytomation, Denmark. Meyer's hematoxylin as counter stain and Primary Negative Control in controls was used. Microphotographs were processed by Olympus BX53 optical microscope and computer-assisted CellA software (Olympus Soft Imaging Solution GmbH, Germany). Expression of PgR and Ki-67 antigen was evaluated quantitatively as the percentage of positive cells (0-5% = no reaction (-), 6-25% = weak reaction (+), 26-50% = moderate reaction (++), above 50% = intense reaction (+++). Both Ki-67 (Fig. 4) and PgR (Fig. 5) antigens' expression were high suggesting significant metastatic potential and progesterone depended development and growth of the mammary and liver neoplasia.

DISCUSSION

Mammary gland tumors are the third most common neoplasia in cats, after lymphosarcoma and skin tumors (England and Von Heimendahl, 2010). The main underlying cause is still unknown, however there have been identified a few factors predisposing to that type of neoplasia. Reproductive hormones are suspected to have a significant role in the etiology of these tumors. Both estrogen and progesterone receptors have been identified in mammary gland masses. Estrogens are responsible for simple ductular development and progesterone for complex ductular side-branching and lobuloalveolar growth. There has been also demonstrated the higher concentration of aromatase in neoplastic cases than in normal mammary tissue. As proven in humans and other species, mammary carcinomas showing aggressive features like high proliferation rate, hormonal related metaplasia, or evidence of metastasis, are usually associated with progressive clinical behavior, poor prognosis and decreased survival times (McAloose *et al*., 2007).

In many investigations there has been established a strong relationship between previous progestagens use and subsequent mammary gland tumors' occurrence. It has also been suggested that entire felids receiving contraception might be at higher risk of mammary neoplastic changes (Keskin *et al*., 2009) comparing to the untreated ones. Moreover, it has been proven that early gonadectomy (prior to first estrus) significantly lowers the incidence of mammary gland neoplasia to about 0.05% (Johnston and Kustritz, 2001). Despite that, in many countries injectable or oral progesterone derivates are still commonly used for estrus control.

Mammary gland during normal reproductive cycle is regularly subjected to the endogenous estrogens and progesterone. The suspected side effects of progesterone and its derivates might be endocrine, uterine or mammary disorders. Clinical trials in rodents proved the increased tumorigenicity of synthetic progestins over endogenous progesterone (Nagasava *et al.*, 1998; Helguero *et al.*, 2003). Since, in domestic animals, usually intact females are those to receive the treatment with exogenous progestagens, it is very difficult to establish the difference between both, drug derived and internally synthesized progestagens, on the subsequent pathological changes. In the reported case, the only source of progestagens, which could be related to the tumor development, was the continuous exogenous medroxyprogesterone supplementation. Hence, it might be concluded that progestins might play an important role in mammary tumor development in cats. There are several reports presenting cases of mammary fibroepithelial hyperplasia or mammary carcinoma in intact female and male cats associated with exogenous progesterone administration (Misdorp, 1991; Jurka and Max, 2009; Jacobs *et al.*, 2010). However, in those cases, the use of the exogenous progestagens was limited to estrus suppression, or justified by other underlying health issues, which might have had affected the overall health of the investigated animals. In none of the mentioned cases the megestrol acetate supplementation lasted for a very long time in otherwise healthy, and especially, already spayed female. In the presented case, due to owner's true belief of having non-spayed queen, the megestrol acetate had been regularly administered for about 10 years to a gonadectomized female. During that time the cat did not show any other problems apart from minor upper respiratory tract and alimentary issues.

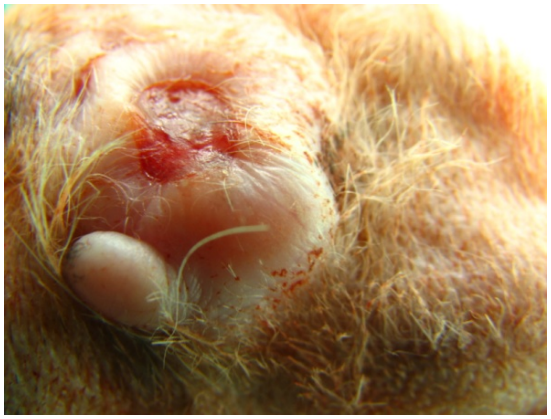

Fig. 1: Healing of the ulcerated mammary mass in the female cat after 3 days of treatment.

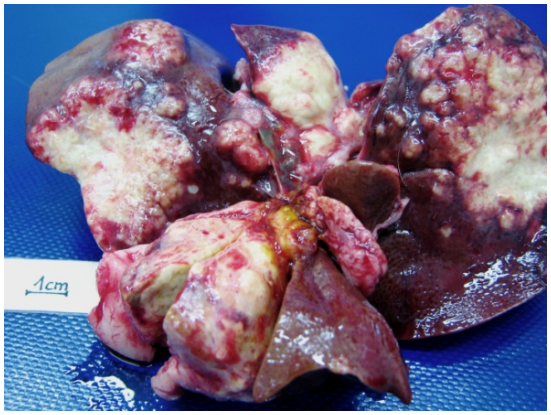

Fig. 2: Spread adenocarcinoma tumor in liver of the female cat - post mortem examination.

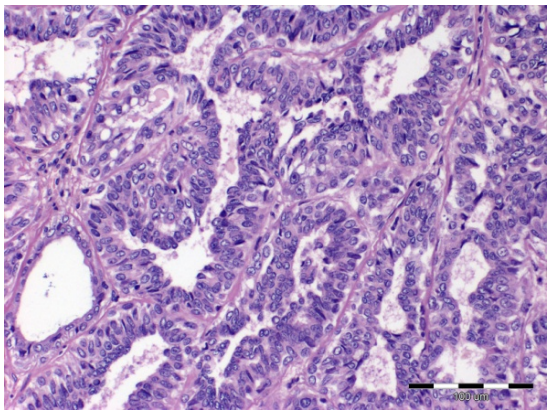

Fig. 3: Histopathological manifestation of mammary gland adenocarcinoma in the female cat.

Consequently, it seems to be justified to conclude that development of the aggressive mammary neoplasia with high mitotic rate and high PgR antigens expression might have been associated solely to exogenous MPA supplementation, obviously with the assumption of mammary tissue estrogen and progesterone sensitization around puberty. As it has also been previously suggested that entire felids receiving contraception might be at higher risk of mammary neoplastic changes comparing to the untreated ones (McAloose *et al.*, 2007), the above reported case

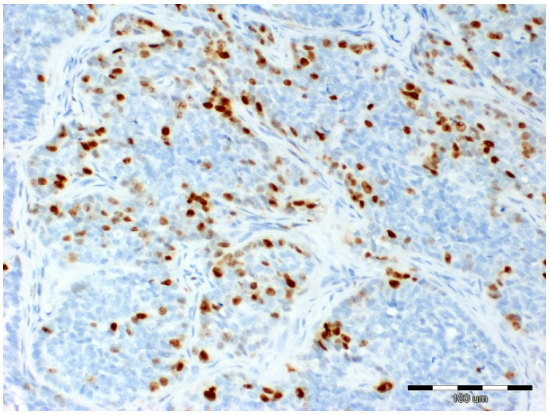

Fig. 4: Mammary gland adenocarcinoma in the female cat, immunohistochemical staining shows high expression of Ki-67 antigen in cells.

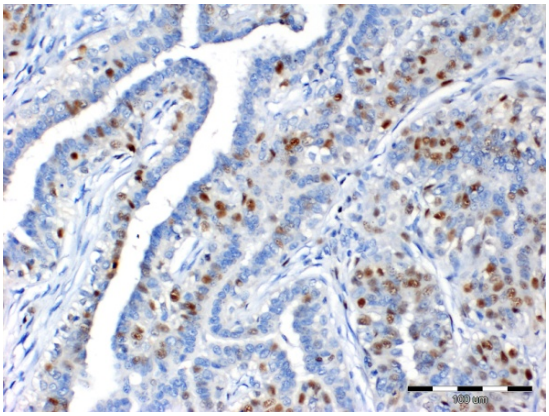

Fig. 5: Mammary gland adenocarcinoma in the female cat, immunohistochemical staining shows high expression of PgR in cells.

undoubtedly confirms the detrimental association between exogenous MPA and mammary neoplasia.

In conclusion, to the authors best knowledge, this is the first recorded case of the long term MPA supplementation, in an gonadectomized female. In this particular case, not only the extraordinary long and continuous contraceptive treatment with MPA in a spayed female cat, but also the subsequent, typical for hormonal related, changes of the uterine wall and neoplasia of mammary gland were worth noticing. Moreover, it could be stated that the pathological changes in uterine body and mammary adenocarcinoma, were caused only by the exogenous MPA administration, proving that this still commonly used drug, can alone be responsible for aggressive neoplastic modification in mammary tissue.

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