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Feline fibroepithelial hyperplasia and current treatment protocols

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ABSTRACT

Due to prolonged exposure to daylight, the seasonal oestrus cycle in cats has reached the point where it can spread almost throughout the year. This situation has brought many problems with it. Mammary tumors and mammary gland hyperplasia are the most common conditions in mammary tissue as a result of exogenous progesterone applications for reproductive control. In this review, information about the etiology, pathogenesis, clinical detection and especially current and successful treatment options for mammary gland hyperplasia in cats is given.

Keywords: aglepristone,mammary, ovariectomy, ovariohysterectectomy, progesterone

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Introduction

In cats, there are 4 to 5 pairs of mammary complexes, arranged in a symmetrical fashion, starting from the thorax and extending to the inguinal region. These structures are called axillary, thoracic, abdominal and inguinal mammary complexes according to their location (Gultiken, 2016). Approximately 80% of the masses in feline mammary glands are neoplastic (Görlinger et al., 2002). This makes the regular examination of the mammary tissue very important.

Mammary gland formations in cats are classified as hyperplasias and dysplasias, benign epithelial neoplasms, malignant epithelial neoplasms, special types of malignant epithelial tumors, malignant mesenchymal tumors, carcinosarcoma, hyperplasia/ dysplasia of the teat, neoplasms of the teat, non-neplastic lesions of the mammary gland (Zappulli et al., 2019). Approximately 20% of non-tumoral masses in cats are often present as mammary gland hyperplasia (Görlinger et al., 2002). In addition, atypical FEH of the teats in a Syphnx cat was reported by the reseachers (Ozenc & Bozkurt, 2014). Therefore, it is very important to make the differential diagnosis by using suitable diagnostic techniques.

Mammary hyperplasia in cats is one of the side effects of progestins (Enginler and Senünver, 2011). It was first identified in 1973 and was called feline mammary hypertrophy (Allen, 1973) but they are commonly known as fibroepithelial hyperplasia (FEH) or feline mammary hyperplasia (Görlinger et al., 2002). It is formed as a result of benign, progesterone-induced fibroglanduler proliferation of the mammary gland (Gultiken, 2016). In other words, it is also considered a form of mammary dysplasia characterized by rapid, abnormal growth of one or more mammary glands without milk production (Solano-Gallego & Masserdotti, 2016).

Fibroepithelial hyperplasia occurs mostly in young female cats (Uçmak et al., 2011) whereas FEH was reported also in male cats (Küçükbekir et al., 2020) although it can be observed in adult and geriatric cats.

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Fibroepithelial hyperplasia most often occurs between 13 weeks and 2 years of age, during the first oestrus, pregnancy or pseudo-pregnancy (Uçmak et al., 2011). However, the frequently reported age range for FEH is 6 months to 10 years (Concannon & Myers-Wallen, 1991). In chronic cases, ulcerations may occur due to the enlargement of the mammary lobe and exposure to trauma. Although it is considered a benign formation, ulcerative lesions resemble mammary tumors, especially in cases of advanced FEH (Payan-Carreira, 2013). Since mammary tumors in cats are approximately 85% malignant, differential diagnosis is very important at this point (Loretti et al., 2005). Fibroepithelial hyperplasia is a luteal stage disease and it is reversible (Payan-Carreira, 2013). The mammary lobes tend to shrink when the progestative effect disappears (Giménez et al., 2010; Leidinger et al., 2011). Spontaneous regression of the mammary lobes is usually observed as a result of luteolysis, ovariectomy/ovariohysterectomy, parturition, or natural abortion (Johnston et al., 2001; Keskin et al., 2008).

Epidemiyology and Pathogenesis: No racial predisposition has been detected in cats in mammary gland hyperplasia, and it is observed that the incidence is higher in domestic and crossbred cats in uncontrolled breeding areas when environmental and climatic conditions are taken into account (Allen, 1973)

It can occur in all female and male cats treated with progesterone, regardless of age (Hayden et al., 1981; Görlinger et al., 2002). The risk of mammary gland hyperplasia in complex with mammary tumors become higher with increasing age. In such cases, biopsy can be applied as a differential diagnosis (Murphy, 2009).

Progesterone and its synthetic analogues play an active role in many cases (Hinton & Gaskell, 1977; Bethlehem & Van der Luer, 1993; Souza et al., 2002; MacDougall, 2003; Loretti et al., 2005). Various progestins are used to prevent or suppress sexual activity in female cats (Romagnoli & Concannon, 2003). Cases of FEH have also been reported in male cats treated with medroxyprogesterone acetate (MPA) and megestrol acetate (MA) applications (MacDougall, 2003; Burstyn, 2010).

The growth and development of the mammary gland is under the control of progesterone. Progesterone exerts this effect mostly on progesterone receptors on epithelial and stromal cells. Local activation of progesterone receptors triggers structures that are specific for each mammary gland and stimulate mammary gland cellular proliferation (Payan-Carreira, 2013). Cyclic changes between estrogen and progesterone in physiological conditions stimulate or suppress the cyclic activation of progesterone receptor-mediated mechanisms (Conneely et al., 2003). The decrease in progesterone receptors is directly related to the decrease in progesterone activity. In a recent study, two isoforms of progesterone receptors (A and B) were detected at high rates in the epithelium of the mammary ducts in tissue samples taken from FEH lesions. However, when the progesterone receptor amounts in samples from mammary carcinomas and FEH lesions were compared, the rate in FEH samples was quite high (Mol et al., 2012). Progesterone dominance causes down-regulation of estrogen receptors (De Las Mulas et al., 2000). Therefore, it is possible that the duration and amount of circulating progesterone may affect the presence of estrogen receptors in the mammary tissue. Enginler and Senünver (2011) proved that significantly higher estrogen receptor labelling in mammary tissues of healthy cats were observed than MPA induced group.

The mammary gland is known as a non-pituitary source of growth hormone (GH) (Mol et al., 1996; de Melo et al.,2021). Progesterone releases insulin-like growth factors, which are active mitogens, usually released from mammary gland fibroblasts, and induces the release of GH. Therefore, FEH can also occur in the mammary glands with a synergism between progesterone, GH, and insulin-like growth factor (Ordás et al., 2004; de Melo et al.,2021).

Clinical presentation: Initial lesions are usually soft, fluctuant, jelly-like and sharply circumscribed structures (Uçmak et al., 2011). Indicated swollen mammary gland volumes are between 1.5 and 18 cm (Seixas Travassos, 2006). Generally, non-pregnant cats have asymmetrical swellings, while pregnant cats have more homogeneous swollen lesions (Payan-Carreira, 2013). In advanced cases, the lesions are edematous, inflamed, and gradually darkening in color due to the gradual swelling of the breast lobes and their anatomical location in an area open to trauma. It can also be seen that alopecia is formed in these areas. Severe inflammation, bleeding areas and necrosis can be observed with increasing trauma. Necrotic areas are most often observed in the axillary and inguinal lobes. While initial lesions do not cause pain, advanced swelling may cause severe pain and related conditions such as loss of appetite and reluctance to walk. Regardless of size, when FEH develops in pregnant cats, there is no milk production in the mammary glands (Görlinger et al., 2002). After birth, kittens are lost due to not being fed. Again, ulceration in advanced lesions make the mammary gland prone to mastitis and abscess, resulting in systemic diseases (Burstyn, 2010).

No FEH-specific conditions are observed in most laboratory tests (Leidinger et al., 2011). If mastitis and ulceration are present, increased leukocyte count and anemia may be observed. While urea, creatinine and liver enzymes in blood biochemistry are within normal limits at the initial level, they may increase due to systemic infection in advanced cases (Payan-Carreira, 2013).

Diagnosis: Diagnosis should always be based on clinical findings and anamnesis (Gaviria et al., 2010). Mammary tumors (benign or malign) should definitely be taken into consideration in the differential diagnosis. While evaluating in terms of the tumoral structures, injuries in the mammary tissue, ulceration and general condition evaluation should be taken into consideration seriously (Mayayo et al., 2018). Generally, it is not difficult to diagnose in cases where more than one mammary gland is swollen. Contrary to tumoral formations, the affected glands in FEH cases show swelling of almost similar sizes (Lana et al., 2007). The age of the animal can often be considered as a clue, but it should not be forgotten that FEH can be observed in advanced ages. Progestin applications to prevent urine spray in tomcats that have reached sexual maturity and are kept indoors are valuable in the diagnosis of FEH (Küçükbekir et al., 2020). In pregnancy, there is no enlargement of the mammary glands until the last period under normal conditions. The presence of swollen mammary glands in the early or mid-term pregnancy may be deceptive, and this situation may be considered physiological, and it may be quite late in diagnosing FEH. It should be noted that there will be rapid loss of offsprings due to inability of feding. If there is no advanced pregnancy, the swellings in the mammary glands should be carefully examined. In case of swelling developed in a single mammary gland, the distinction between FEH and mammary tumor should be made very carefully in middle and/or advanced-aged cats. Although not a judgement, FEH lesions are more voluminous and softer than mammary gland tumors (Sorenmo, 2011). In addition, measurement of blood progesterone level can also help in diagnosis, as FEH formation shows that the ovulation has taken place or that it has been treated with progestin (Payan-Carreira, 2013). However, although FEH formation is associated with progesterone, serum progesterone measurement is not a diagnostic method with sufficient sensitivity (de Melo et al., 2021).

Cytology or biopsy is preferred in histopathological examinations. In cytological diagnosis, FEH lesions should exhibit the following two criteria: One of the single type epithelial cells and one of the spindle-shaped mesenchymal cells should be found, as well as moderate anisocytosis and anisokaryosis should be observed. Abundant eosinophilic extracellular matrix can be expected to be observed in close proximity to cells. It is difficult to distinguish between benign and malignant structures. Therefore, cytological analyzes should be evaluated together with the patient's anamnesis and clinical findings (Leidinger et al., 2011). In addition, FEH lesions are highly proliferative (Pereira, et al., 2004) and it should not be forgotten that they may display a malignant appearance in a misleading way (Allen, 1973). For all these reasons, fine needle aspiration biopsy should be preferred, although it is more costly, when a definitive diagnosis is requested (Wehrend et al., 2001; Vitasek &Dendisova, 2006).

Besides mammary ultrasonography is also helpful in the diagnosis of FEH, as well as a fast and reliable method in the evaluation of the structure of the mammary gland. In cases of FEH the mammary gland has a higher echogenity than the normal and lactating ones (Payan-Carreira, 2013).

Radiological examination is usually performed in the laterolateral position. Radiologic examination in FEH lesions is not a diagnostic method of much interest, as this imaging only shows enlargement of the mammary glands, intact abdominal wall, and homogeneity within the diseased mammary glands (Burstyn, 2010).

The response to aglepristone application is also evaluated for the diagnosis of FEH. From the third day of the application, reduction of the swellings in the mammary glands and clinical improvement are also considered in the diagnosis (Payan-Carreira, 2013).

Treatment:Primarily, in most animals diagnosed with FEH, swelling of the mammary glands, the possibility of infection and necrosis may require treatment, but is generally considered a benign disease state (Görlinger et al., 2002). However, spontaneous recovery is rarely observed and this process can take weeks or even months (Loretti et al., 2004).

Since it is a progesterone-related disorder, the first step in the treatment approach of FEH should be to eliminate the progesterone effect on the tissue. Therefore, if there is any ongoing hormone therapy, it should be discontinued (Payan-Carreira, 2013).

The determined treatment approach, treatment costs, recovery time and the possibility of recurrence should be discussed with the cat owners, and in cases of mastitis, ulcer, abscess or systemic infection in addition to FEH, treatment should be started after the owner is adequately informed. In addition to the chosen treatment protocol, broad-spectrum antimicrobial therapy (such as amoxicillinclavulanic acid / cephalosporin) and fluid replacement may be required. In painful cases, short-term treatment with

non-steroidal anti-inflammatory drugs (such as meloxicam, ketoprofen or carprofen) can be used to relieve symptoms (Payan-Carreira, 2013).

In the treatment, only antiprogestin will be used, or ovariectomy or ovariohysterectomy can be applied (Johnston et al., 2001; Keskin et al., 2008). Until the late 90's, ovariectomy or ovariohysterectomy was used mostly as a treatment option (Wehrend et al., 2001). Especially in the operation, with the lateral (left flank) approach, further damage to the already traumatic mammary tissue is prevented. In most of the patients treated in this way, shrinkage and healing were observed in the mammary tissues after 3 to 4 weeks post-operatively, but some cases that did not show any regression from time to time reported (Görlinger et al., 2002).

Although mastectomy has been tried as the first approach in cases in ancient times, it is not recommended today due to the delay in healing, the size of the operation wound and surgical complications. It is only applied as a last option in cats who do not respond to ovariohysterectomy and medical treatment (Payan-Carreira,2013; Küçükbekir et al., 2020).

Today, medical treatment approaches are available in most countries. Economic constraints may affect the drug chosen and this may change the recovery time. It also takes longer for progestin to regress if exogenous antiprogesterone drugs are not chosen. Many studies have proven that a progesterone receptor blocker, Aglepristone (Alizine®, Virbac, France), can successfully reverse FEH with a variety of treatment protocols (Görlinger et al., 2002; Nak et al., 2004; Sontas et al., 2008; Jurka & Max, 2009; Enginler and Senünver, 2011; Uçmak et al., 2011). Aglepristone binds to progesterone receptors in target tissues with 9 times more affinity than natural progesterone without activating the hormone response, and its residence time in the organism is 6 days, according to the manufacturer's information (Payan-Carreira, 2013) . Although not licensed for use in cats, aglepristone is widely used in abort induction and pyometra treatment.

In FEH cases, Aglepristone is administered subcutaneously at a dose of 15 mg/kg, divided into two equal parts and administered subcutaneously from the inside of the hind legs. There are basically two reasons for this application. Firstly, aglepristone is stored in the fat tissue, the inner part of the hind legs is poor in fat, and secondly, the hair loss can occur in the area where aglepristone is applied, the inner part of the hind legs is a sparse and anatomically inconspicuous region (Görlinger et al., 2002).

Aglepristone is often used alone (Little, 2011). In FEH cases with also lactation, aglepristone can be combined with a dopamine agonists such as cabergoline (Uçmak et al., 2011). Cabergoline is a prolactin inhibitory dopamine agonist that is used to stop milk production in lactating animals. It is given orally once a day at a dose of 5µg/kg in cats and dogs, and it is usually sufficient for 5 to 7 days (Uçmak et al., 2011). Cabergoline is also used in the treatment of mastitis. It should not be forgotten that it can lead to severe nausea, vomiting and hypotension during its use.

Bromocriptine is a similarly effective dopamine agonist as cabergoline, but its behavioral side effects are more severe than cabergoline. It is used in cats at a dose of 0.25 mg / cat / day (Payan-Carreira, 2013).

Aglepristone has been used in many studies on FEH, and as a result, the most frequently used and recommended forms of use are as Table 1.

Some authors have reported that ovariohysterectomy is the primary treatment for FEH (Medeiros et al., 2007; Motta & Silveira, 2009). Although mammary gland regression may occur up to 5 to 6 months after ovariectomy, the lesion tends to subside 3 to 4 weeks after ovaries are removed (Amorim, 2007; Gimenéz et al., 2010). However, it was also noted that 53 days after surgical sterilization, the lesions in the mammary tissue still persisted and the mastectomy had been performed due to the recurrence of FEH on 7 months after the surgical sterilization (Motta & Silveira, 2009).

Considering all these reasons, it seems that the first treatment option for FEH is the use of antiprogestin, but in the absence of an adequate response, the next most prudent alternative treatment is ovariectomy/ovariohysterectomy. This is a less invasive, well tolerated and effective method with lower mortality compared to surgical techniques such as mastectomy. If the cat is pregnant, the abortion can form as a result of treatment with antiprogestin. To avoid the pregnancy loss, conservative treatment should be managed until the pregnancy is over. Although mastectomy, reported as the surgical treatment of FEH, is still used indiscriminately, it currently does not provide effective protection for FEH (Silva, 2008). However, this technique is only indicated when there is no response to clinical therapy, extensive ulceration and/or necrosis, or associated with carcinoma of the mammary gland (Vasconcellos, 2003; Medeiros et al., 2007). Such a procedure is generally not recommended for young cats, as mastectomy is a complicated surgical procedure and possible post-operative complications are more likely to occur (Gimenéz et al., 2010).

Table 1. Drugs and treatment protocols for FEH and brief information about the studies.

Authors	Drugs and protocols	Brief information about the study
Uçmak et al., 2011	15 mg/kg aglepristone twice a week for 3 weeks and cabergoline 5µg/kg once a day for 1 week every day	In the examination at the end of three weeks, significant shrinkage of the mammary glands and cessation of milk secretion were observed. After 6 weeks from the beginning of the treatment, it was observed that the mammary glands completely shrunk, and at the end of the study, it was determined that aglepristone and cabergoline could be used successfully in cats with FEH.
Jurka & Max, 2009	10 mg/kg/day aglepristone was administered as 2 doses 24 hours apart and the treatment was continued until the mammary tissue was completely healed	In the study, aglepristone treatment was started with 14 cats at the specified dose, and complete regression of the mammary tissue was achieved in an average of 3.9 weeks in the treatment. As a result of the study, a 5 week treatment with aglepristone was recommended for cats with FEH.
Sontas et al., 2008	10 mg/kg/day aglepristone was applied for 4 or 5 conecutive days, and then the last dose was administered on the 7th day	There was a decrease in the size of the mammary tissue 2 days after the begining of the treatment, and significant regression was observed from the 6th day. It took 4 weeks for the mammary tissue to return to normal. No side effects were observed during the treatment and it was concluded successfully.
Görlinger et al., 2002	20 mg/kg/day aglepristone was administered once a week as a single dose and the treatment continued for 4 weeks	Aglepristone was administered subcutaneously at a dose of 20 m g/kg/day once a week to 7 cats with common symptoms of tachycardia, weakness, skin ulcers and anorexia, and all cats except 1 cat showed complete and permanent improvement in symptoms after 1-4 weeks of treatment. Skin irritation at the injection site was observed in 2 cats in the study, and abortion and subsequent endometritis was observed in 2 pregnant cats. In conclusion, this study shows that cats were successfully treated with aglepristone.
Wehrend et al., 2001	10 mg/kg/day aglepristone administered for 4 or 5 consecutive days	About 5 days after the first injection, significant reductions were observed in the size and tissue stiffness of the mammary gland, and it took 3-4 weeks for the tissue to fully return to normal. Similar results were obtained when compared to ovariectomized animals, and no side effects were observed in the treatment.
Nak et al., 2004	10 mg/kg/day aglepristone administered on days 1, 2 and 7	In the study, aglepristone was applied at the indicated days and doses, and it was observed that the mammary tissues were completely healed on the 21st day without any side effects. Ovariohysterectomy was performed due to the risk of recurrence.
Vitasek & Dendisova, 2006	10 mg/kg/day aglepristone administered on days 1, 2, 7, 14 and 21	A seven month old female cat was treated with 10 mg/ kg of aglepristone subcutaneously on days 1, 2, 7, 14, and 21, with complete regression of the mammary glands observed within 6 weeks. No adverse events were observed.

Conclusions

In this review, etiology, pathogenesis, clinical detection of mammary gland hyperplasia in cats and current treatment options are reported. As a result, FEH is common in intact, exogenous progesterone administered, pregnant or non-pregnant cats, usually young cats. It has also been reported to occur in female and male cats. These cases can be successfully treated with various aglepristone protocols. Cabergoline can be added to the treatment protocol if there is milk secretion. Another treatment options are ovariectomy, ovariohysterectomy and mastectomy which is now abandoned except for mandatory conditions. Preventing the use of progestin, which is one of the effective factors in the formation of FEH, is also important for both female and male cats.

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