
Feline Mammary Fibroepithelial Hyperplasia: A Clinical Approach

Rita Payan-Carreira

Additional information is available at the end of the chapter

<http://dx.doi.org/10.5772/55550>

1. Introduction

Feline mammary masses are frequently suspected of being mammary tumours. Immediate attention is required as over 80% of mammary tumours in cats are malignant [1,2], albeit mammary masses in cats are less common than in dogs. However, prevalence of mammary tumours is highly variable with the geographic region, as it tends to be lower in areas where most cats are neutered at a young age. Due to the negative prognosis generally attributed to feline mammary tumours, little attention has been paid to benign mammary growths and mastectomy is still often performed to deal with feline mammary fibroepithelial hyperplasia.

Feline mammary fibroepithelial hyperplasia represents a benign, progesterone-associated fibroglandular proliferation of one or more mammary glands that may occur in both the female and male cat [3,4]. It is also named feline hypertrophy, fibroadenomatous changes, mammary hyperplasia or fibroadenoma complex [3-5].

Feline mammary fibroepithelial hyperplasia (FEH) is characterized by the sudden onset of mammary swollen within a short period of 2 to 5 weeks, frequently concerning several mammary glands. When exuberant it is often at the origin of the consultation [6-9]. Ulceration and abscessation of the mammary gland may occur due to gland enlargement and trauma, in chronic situations [9,10].

Feline mammary fibroepithelial hyperplasia is considered to be a benign condition, yet its behaviour and gross appearance is similar to mammary neoplastic lesions, in particular when solitary ulcerated or violaceous lesions are present. Although it rapid growth may cause concern, fibroepithelial mammary lesions are reversible, and the volume of the mammary masses tend to decrease after luteolysis or at the end of exogenous progesterogen activity [4,5,11].

Tentative diagnosis of mammary fibroepithelial hyperplasia should be based on the gross appearance of the lesions and on the history despite that most frequently, historic information is limited or incomplete, as a previous occurring estrus is seldom detected. Thus, diagnosis of feline mammary fibroepithelial hyperplasia is a clinical issue, and is not difficult to be established when all the mammary glands show a rapid enlargement, independently of the size of the swollen mammary gland [4,9]. This diagnosis may be further supported by the raised blood progesterone levels or by reported recent progestin treatment. However, when fibroepithelial lesions develop in only one mammary gland, distinguish between hyperplasia and mammary tumour may become more challenging. Biopsies or excision of the mammary lesions are frequently performed. Nevertheless, differential diagnosis with mammary carcinomas has to be carefully established, as around 85% of all mammary neoplasias are malignant [9].

As FEH is a non-neoplastic progesterone-associated disorder, it is possible for most situations to apply medical treatment. Administration of antiprogestins remains the elective medical treatment, and its schedule and duration is usually related to the severity of the problem at presentation. Complete excision of the mammary chain, under the supposition of a mammary tumour, may become a really aggressive surgery. Nowadays, with the available medical options mastectomy should be avoided in case of FEH.

Recurrence of the situation, although possible, remains controversial [6,11-13]. Nevertheless it is an important issue when discussing the therapeutic approach with owners. Ovariohysterectomy remains an option in animals not intent to reproduction and in animals submitted to progesterone-based contraception, even if postponed until mammary glands regress into the normal size.

The objective of this work was to present and discuss the clinical approaches available to establish the diagnosis and the therapeutic options for feline mammary fibroepithelial hyperplasia. The final purpose in the diagnosis and treatment of such disease is not only to confirm that the clinical situation was correctly identified, but also to select the most suitable therapeutic approach to each patient, and also avoiding precipitate mastectomy and other complications of the surgical act, with the minimum repercussions on patients' welfare.

2. Epidemiology of the feline mammary fibroepithelial hyperplasia

Feline mammary fibroepithelial hyperplasia occurs in intact queens of any age, in pregnant females and in female or male cats under progestin treatment [6-8,14]. It predominantly affects younger intact female cats, a segment of the population that also presents an increased ratio of spontaneous ovulation [15,16]. The reported age range for FEH is 6 months to 13 years [17-20]. Not so frequently, the condition may also be seen in aged females, associated or not with a contraceptive treatment, and sporadically in hormonally treated male tomcats. In a local study, the age range for FEH was 10 months to 10 years (the median for the age was 3 years), and the condition was exclusively diagnosed in queens [21]. This contrast with the usual age

at presentation in case of mammary neoplasia, which is middle-aged queens, since the risk for mammary tumour increase with the cat age, particularly at 10-12 years [1,22].

Moreover, few reports exist on the occurrence of FEH in males under treatment with antiandrogenic drugs, such as delmadinon acetate (Meisl et al., cited in [8]) and cyproterone acetate [12], frequently used by cat fanciers for eliminating the urine spraying in intact adult tomcats. Infrequently, descriptions of FEH in spayed queens or male cats supposedly not submitted to steroid treatment have been published [11,23], but the doubt remained on the absence of an involuntary hormonal treatment.

It is generally accepted that the incidence of this disturbance may reach up to 20% of the mammary masses detected in cats, its prevalence varying with the country or the region, which reflect cultural differences in the reproductive management of domestic and free-roaming felids. In a study developed in the north of Portugal, based on the excisional material sent for histopathology analysis, the mammary fibroepithelial hyperplasia reach 13% of the feline mammary masses [21]. Nevertheless, according to our experience, incidence of FEH seems to be in regression among the group of animals submitted to progesterone-based contraception, may be due to the fact that most contraceptive treatments are now based in oral, veterinary drugs (such as Megescat®) instead of human design depot products (like Depo-Provera®). Nevertheless, the medroxyprogesterone acetate and the megestrol acetate are the most frequently reported progestin associated to FEH, in particular when the drug is injected [13,14,18,24].

Mammary enlargement is usually observed within 1-2 weeks after estrus or within 2-6 weeks after hormone treatment.

Apparently, no breed predisposition has been suggested for FEH. Even so, the majority of the cases were described in domestic shorthaired cats, which could simply be due to the fact that it may constitute the majority of the population worldwide.

3. Pathogenesis of the feline mammary fibroepithelial hyperplasia

The exact pathogenesis of FEH remains unclear, although sex steroid involvement has been acknowledged for long. Progesterone or its synthetic analogues have being recognized as being at the origin of most of the FEH situations described.

The interaction between the activity of the mammary gland and the sex steroids is recognised for long. In brief, development and growth of the mammary gland is under the control of progesterone, which effects are mainly mediated through the progesterone receptor (PR) on stromal and epithelial cells [25]. Local activation of PR triggers a cascade of specific and sequential series of molecules, specific for each glandular element, which stimulates mammary gland proliferation. In physiological conditions, the cyclic changes between estrogens and progesterone stimulate or repress the cyclic activation of such PR-mediated pathways [25]. A decrease in PR levels is associated to a reduction of progesterone activity. Progesterone has

been reported as having a major role in mammary ductal branching [26,27], while estrogens acting via the ER have been associated to ductal elongation and bifurcation [27].

An aberrant regulation of those pathways may be at the origin of the disturbed response to the progesterone stimulation and contribute to the development of mammary gland hyperplastic or neoplastic growth. It is possible that such response may be associated to two factors: the extreme sensitivity of the feline mammary gland to sex steroids action, as referred in older studies (Bässler, cited in [17]); and the fact that the mammary gland is usually very thin when non-pregnant or non-lactating [28].

In a recent study, the two progesterone receptors (PR) isoforms (A and B) have been evidenced in tissue samples from fibroepithelial hyperplasia lesions, with predominant expression in the ductal epithelium. It was also reported a higher expression of PR in the stroma of FEH lesions in comparison to those found in stroma from mammary carcinomas [29]. The presence of estrogen receptors (ER) in FEH lesions remains a subject of controversy, as the number of cases where ER has been detected varies along the reports [20,30,31]. Nevertheless, a slight reduction in ER expression seems to accompany the process. Expression of PR in a progesterone-target tissue is dependant of the previous stimulation by estrogens via ER, while progesterone effects also include the down-regulation of estrogen receptors. So it is also possible that the length of progesterone dominance or the circulating levels of progesterone may influence the amount of ER found in mammary tissue in the available studies.

The potential role of estrogens in the development of fibroepithelial hyperplasia needs clarification, as it may influence the relationship between the progesterone and estrogen receptors in mammary gland tissue. Further, in one recent study the concentrations of estradiol in animals suffering from FEH were higher than values typical for the luteal phase, both in case of the first appearance of fibroepithelial hyperplasia and in recurrences [13].

Progestagens (progesterone and synthetic progestins) influences on feline mammary glands result in the stimulation of the cellular proliferation through PR stimulation. It was proposed that binding of progestagens to PR would enhancement the local GH expression [29,32]. The GH presents a mitogenic action, which is mediated by insulin-like growth factor-1 (IGF-1) [32,33], a molecule shown to possess a strong mitogenic and anti-apoptotic effect on the mammary epithelial cells. The increased expression of GH, GH receptor and IGF-I was demonstrated in FEH lesions [29].

For fibroadenomatous hyperplasia associated to the cyproterone acetate administration it was found that this drug may present a "gestagenic" effect, which it was suggested to contribute to the development of fibroepithelial hyperplasia of mammary glands [12].

Comparative studies of the proliferative index (measured by Ki67/MIB1 expression) in feline fibroepithelial hyperplasia and other mammary tumours showed that, in spite of being a benign disturbance, it shows a very high proliferative index similar to the one observed in invasive mammary carcinomas [34,35]. Fibroepithelial hyperplasia, which exhibits unique morphological and biological features, is characterised by rapid proliferation of epithelium and stroma [35]. Regardless its classification as a hyperplastic lesion, with a favourable biological behaviour, all cases of fibroepithelial hyperplasia exhibited high rates of cell

proliferation, with mean values similar to those of carcinomas in accordance with the results of a previous investigation [35].

Despite that increase expression of PR has been found in the FEH lesions in comparison to normal diestrous mammary tissue samples, the blood levels for progesterone are usually within the normal levels for the species [6], although cats may present considerable variation in their progesterone blood levels [36]. This is suggestive that the disease would correspond to a disturbed, exaggerated response of the tissue to the circulating hormones.

4. Morphological and pathological features of mammary fibroepithelial hyperplasia lesions

Macroscopically, FEH lesions appear as firm, well-circumscribed but unencapsulated masses, that may present two types of macroscopic patterns: the solid type, of smooth-surfaced tissue with scant fluid; and the parenchymal, intraductal pattern, with fluid-filled spaces [18]. The two patterns can be combined in the same lesion, or one of them can predominate over the other. The cut surface is solid, diffusely white or grey-white and homogeneous [9,37,38]. Areas containing gelatinous material may be found, disposed as cleft-like spaces created by the enlarged ducts [21,37] (Figure 1). Although necrosis or ulceration are rare [17], they can be found in long lasting situations or whenever the reduction of the mammary gland swelling was attempted by progestin administration.

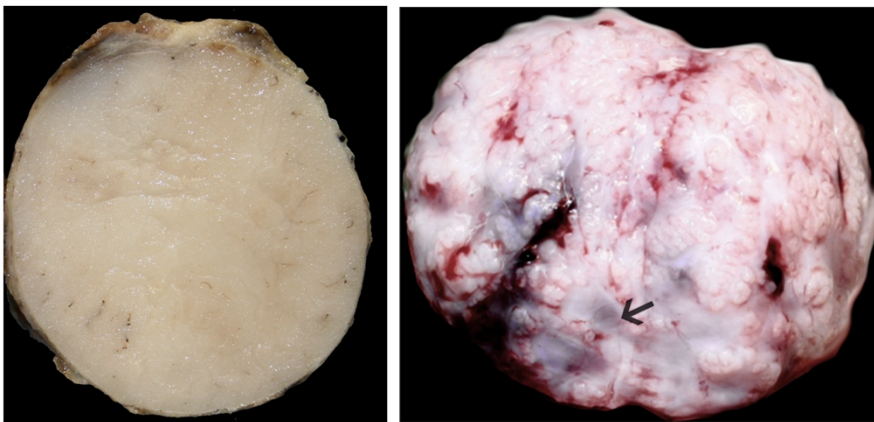


Figure 1. Gross appearance of feline mammary fibroepithelial hyperplasia lesions. On the left, the cut surface of a formalin-fixed lesion showing a solid pattern. On the right, the cut surface of a fresh lesion showing several cleft-like areas (arrow), typical of the intraductal pattern.

Microscopically, the two patterns are similar [18]: the diseased mammary gland is characterized by the proliferation of glandular fibroepithelial elements. The lesions correspond to well-

demarcated, non-encapsulated growths within the mammary gland [17,31], with the ducts forming pseudo-acinar or cystic structures, encircled by a loose, myxoid stroma [21]. Although the proportions of epithelial and connective tissue are variable with the lesion and distinct from the one found in the normal gland, the branched ducts and stroma retains its organization in lobular-like units. The branching ductal structures are lined by several layers of epithelial cells and surrounded by markedly proliferating and oedematous connective tissue. Loose periductal connective tissue, that gives higher prominence to the mammary stroma, is loose-textured and merged in the periphery to the more dense collagenous tissue that separates the mammary lobules [9,17,31,37,38]. Mitotic figures are commonly found both in the epithelium and the stroma [17,31], and apocrine differentiation is frequently found within the epithelial component. Further, it is often observed that the cells in the intralobular stroma lack polarity and show indistinct borders [17], and also some degree of cytological atypia, which is reactive [21]. Thereby, a falsely malignant appearance is created, which could be patent in the results for a fine needle aspiration biopsy. An inflammatory infiltrate is seldom found, and when present it is mostly of the lymphoplasmocitary type [21].

5. Clinical presentation

Usually, the main complaint for FEH is the existence of excessive mammary enlargement that evolved rapidly. This in fact characterises the disease.

Feline mammary glands thickness is minimal in cycling females, and also it does not change much until close to parturition [28]. Consequently, for most cases an increase of the volume of the mammary glands, either isolated or multiple, in otherwise clinically healthy animals, draws the attention of the cat owner. Time since the beginning of the mammary enlargement till the animal presentation seems to vary with the form of the FEH. It tends to be shorter in cases of more notorious swelling of multiple glands and may be longer in cases of solitary and smaller lesions.

The major clinical sign is the swollen, firm mammary gland tissue, that can be detected in as multiple, bilateral enlargement of the mammary chains, or develop as a solitary, unique lesion that may develop from any of the mammary glands (Figure 2). The size of the enlarged glands is quite variable, ranging from 1.5 to 18 cm [21]. In our experience, when multiple lesions develop, asymmetrical lesions are more frequently found in non-pregnant females, while females being pregnant tend to develop more homogeneous swellings of the mammary glands (Figure 2).

At the visual inspection, the skin covering the diseased mammary glands may be tense and erythematous, in particular in larger lesions. The nipples can be difficult to find due to the size of the gland. At palpation, the lesions are presented as diffuse, firm and consistent masses, or in some cases they present a soft and more gelatinous, floating consistency. If notorious swelling develops, the diseased mammary glands may become pendulous. In uncomplicated situations and unless the masses are too swollen, the lesions are not painful, although some distress may be elicited during mammary manipulation during the clinical examination. Further, when severe swelling of the mammary glands developed, locomotory problems may arise that

may induce some distress with movement or reluctance to walk and a reduction of appetite. Less severe lesions usually evolve in the absence of an inflammatory reaction.

Whatever the dimensions of the mammary glands, when FEH develops in pregnant females, no milk is produced in the diseased glands [23]. Consequently, after parturition, kittens are unable to nurse satisfactorily and usually the owners refer to litter vocalisation, restless and fading, with offspring death over a short-time period in postpartum.

In some severe or prolonged situations, the primary FEH may co-exist with mastitis or ulceration (Figure 2). In our clinic, mastitis is more frequently found in lactating females suffering from FEH. However, ulceration may develop secondary to perfusion problems derived from skin overstretching, with local ischemia, leading to abscessation, or also due to excessive grooming. Ulceration predisposes the diseased gland to mastitis or abscessation and subsequently to systemic illness [10-12]. In such situations, depending on the severity of the process, the skin may be wet, exudative, haemorrhagic and abnormal glandular discharge, with necrotic debris or purulent. Involvement of the regional lymph nodes is possible [10]. Then, the animal may be presented to consultation with fever, lethargy, anorexia, pale mucous membranes and dehydration.

Little information is available on the haematological and blood biochemistry changes in animals suffering from FEH. Nevertheless, in animals suffering from non-complicated mammary fibroepithelial hyperplasia, most parameters analysed (blood haematology and biochemistry) were within the normal range values for the species [11,14]. In animals with FEH co-existing with mastitis and ulceration, it can be found anaemia [10,39], normal to increase packed-cell volume [12,13,39] and the leukocyte count near the maximum normal limit or increased [10,12,39]. All these changes have been associated to inflammation and/or sequestration of fluid within the distended mammary tissue or to patient dehydration.

On what concerns the blood biochemistry, for most cases the values for blood urea and creatinine, or for the hepatic enzymes (such as the alkaline phosphatase, the alanine aminotransferase and the aspartate aminotransferase) were within the normal limits for cats [11-13], or slightly decreased [10].

6. Diagnostic evaluation

6.1. Reaching a tentative diagnosis

Diagnosis of feline mammary fibroepithelial hyperplasia is always a clinical issue, and should be based on the symptoms, the patient signalment and on history [39,40]. Differential diagnoses should include the mammary tumours (adenocarcinoma or carcinoma, mammary adenoma, or mammary sarcoma) and the mammary fibroepithelial hyperplasia.

Usually it is not difficult to establish a diagnosis when multiple glands are enlarged. An important criterion is the rapid onset of the mammary swelling, independently of the size of the swollen mammary gland. Also the age of the female may be suggestive of FEH, as it is

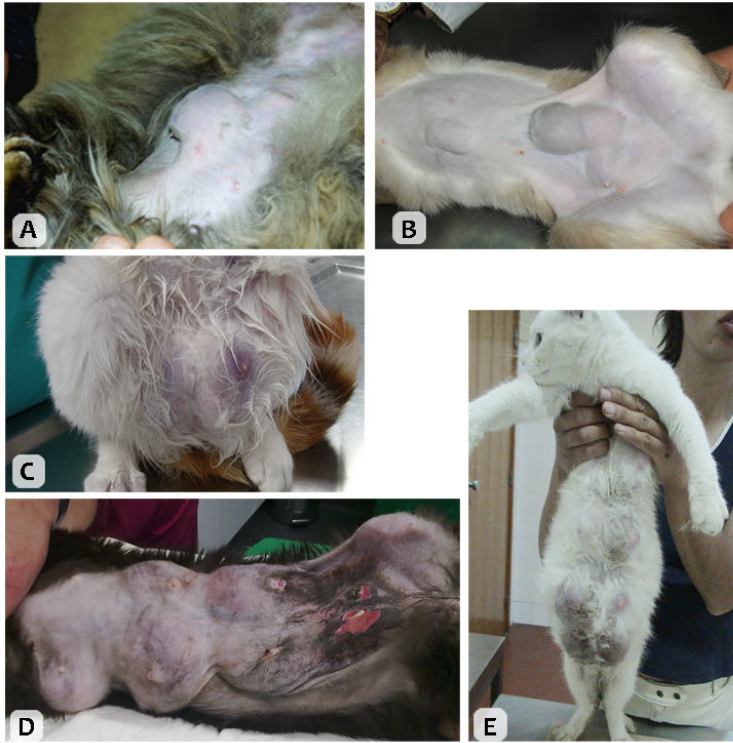


Figure 2. Diverse aspects of feline mammary fibroepithelial hyperplasia. A – A solitary lesion in a female cat submitted to megestrol acetate treatment. B - Multiple lesions showing asymmetric distribution of the diseased mammary glands, which also presented different dimensions, in a young spontaneous-ovulatory queen. C – In larger lesions, the skin around the nipple may be stretched, moist and violet, due to excessive grooming. D – FEH complicated with mastitis and ulceration in a female at post-partum day 6. E – FEH in a peri-partum young female that also showed skin erosion around the nipples of the caudal mammae.

more frequently found in young females. The sex of the animal should not be an exclusion criterion, as FEH also develop in males submitted to hormonal treatment for urine spraying or skin conditions. Neither it should be the reproductive status of the cat, as FEH can develop in neutered cats with pyoderma or miliary dermatitis following hormonal treatment with progestins. Moreover, a rapid enlargement of the mammary chains in a early or mid-pregnant females should lead to the suspicion of FEH, as the mammary glands shows little development until near parturition in cats. Unless an excessive swelling of the mammary exits, FEH is painless.

Yet, when fibroepithelial lesions develop in a single mammary gland, distinguishing between hyperplasia and mammary tumour may become more challenging, particularly in mature or older animals. As in other FEH conditions, the lesion develops at a very rapid rate, is frequently painless and although firm it is also turgid with a regular oedematous texture at palpation.

Although it should not be considered as a rule, frequently FEH solitary lesions reach larger volumes than those referred to feline mammary tumours [22], and are softer.

Discoloration of the skin underlying FEH lesions was once reported [41], but I was not able to confirm that association in my practice.

Occurrence of FEH indicates that the animal ovulated and endogenous progesterone is raised or that it was treated with progestins. Hence, the mammary fibroepithelial hyperplasia diagnosis may be further supported by determination of blood progesterone levels. However, one should be aware that progesterone levels may be low when the underlying cause are exogenous progestins, because nowadays progesterone analysis are quite specific and may not cross-label with the used progestin molecule. Thus, it is also of utmost importance to determine the existence of a recent progestin treatment.

6.2. Diagnostic endorsements

Biopsies are often referred as being the most acceptable form to confirm the diagnosis of mammary fibroepithelial hyperplasia. However, cytological differentiation between benign and malignant mammary lesions is difficult. The accuracy of cytological differentiation is low, and its specificity has not yet been attributable. Further, the cytological analysis should be interpreted together with the symptoms and the sudden onset of the clinical signs [11].

It should be remembered that mammary fibroepithelial hyperplasia lesions are highly proliferative [34,35] and that some degree of cytological atypia [21] are often described, which along with the described loss of cell polarity [17] and the occurrence of mitosis [17,31], can create a falsely malignant appearance that could biased the diagnosis. Consequently, if a histopathological diagnosis is wanted, an excisional biopsy is preferable to a fine needle aspiration, despite being more expensive.

Diagnosis of FEH in cytological specimens should meet the following criteria: Two different cells (one of uniform epithelial cells and one of spindle-shaped mesenchymal cells) should co-exist, and may display a moderate anisocytosis and anisokaryosis, with only minimal nuclear criteria of malignancy. A large amount of eosinophilic extracellular matrix is expectably found in close proximity to the cells (Meshner, cited in [11]).

Mammary ultrasonography may also be helpful on the diagnosis of feline mammary fibroepithelial hyperplasia. Furthermore it is a rapid and easily performed method for assessment of the mammary gland structure. Generally, the ultrasonographic mammary echogenicity is higher in FEH lesions when compared to normal and lactational feline mammary glands (Figure 3). On ultrasound images, FEH lesions present mainly as a well-circumscribed solid mass of granular, slightly hyperechoic texture, with regularly delimited margins. It is also common to found small cleft-like structures, appearing as irregular anechoic areas, without acoustic enhancement, and small hyperechoic foci scattered within the glands image, which are independent of the form of FEH (multiple or solitary form). The presence of clefts in mammary fibroepithelial lesions provided a more heterogeneous appearance to the ultrasound images. In our practice clefts are more frequently found in animals under progestin treatment. The ultrasound pattern is more homogeneous in solid lesions, whilst when the intraductal pattern dominates, anechoic areas corresponding to clefts of different shapes are found within the mammary gland parenchyma (Figure 4).

Radiology is of little interest in cases of FEH, as for most situations lateral abdominal surveys only shows the enlargement of the mammary glands, an intact body wall and sporadically homogeneous fluid opacity in the diseased mammary glands [10]. In comparison, ultrasonography can bring you more information through the assessment of the lesion echogenicity and pattern. However, when attempting to establish a differential diagnosis with mammary carcinoma, thoracic and abdominal radiographs are advised to screen for possible metastases and calcification.

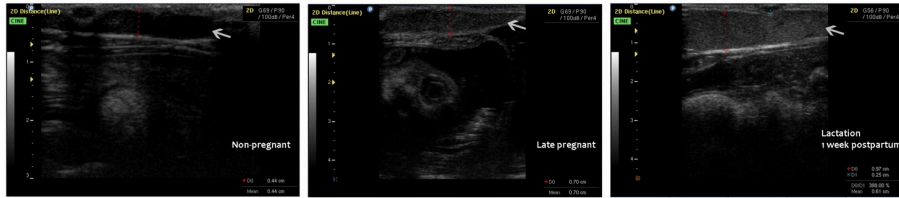


Figure 3. Ultrasound images of normal feline mammary gland in non-pregnant, late pregnant and lactating females (from left to right).

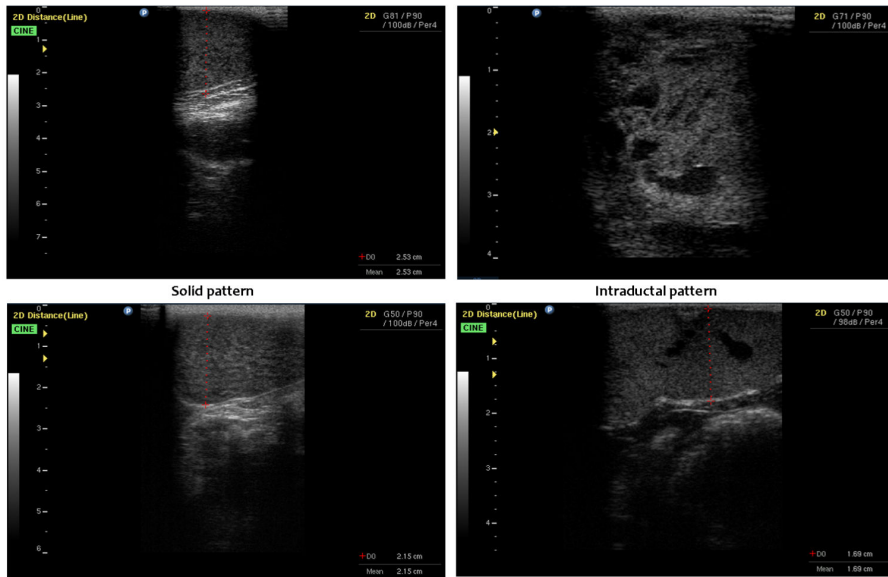


Figure 4. Ultrasound images of feline mammary fibroepithelial hyperplasia lesions. On the left, images from a solid pattern lesion. On the right, images from lesions presenting cleft-like anechoic areas, characteristics of the intraductal pattern.

Finally, confirmation of the tentative diagnosis can also be achieved through the response to Aglepristone treatment. Aglepristone as an antiprogestosterone drug can elicit a positive

response with a reduction of the mammary swelling and improvement of the clinical condition, which can be obtained around day 3 post-administration (for the doses and schedule, please see next section).

7. Therapeutic approaches

In most animals diagnosed with FEH, the extent of the swelling of the mammary glands and the possibility of necrosis and infection warrant treatment, though this is generally considered as a benign disturbance [23]. Even so, seldom sporadic recovery is observed [6], and when described it usually takes several weeks to months.

The feline mammary fibroepithelial hyperplasia being a progesterone-associated disturbance, the therapeutic approach should focus on the removal of the progesterone influences in order to revert the symptoms. Thus, discontinuing of any ongoing hormone therapy is mandatory.

Available approaches should be discussed with the cat owner, including a prevision of the costs for the treatment, the time to full recovery and the possibility for the occurrence of a relapse. For most FEH situations 21-24 days may be needed to fully revert the mammary gland enlargement, but it may vary with the selected therapeutic approach.

In addition to the treatment directed to feline mammary fibroepithelial hyperplasia, situations complicated with mastitis and skin ulceration or abscessation or systemic illness, additional treatment targeting the recovery of the inflammatory condition and the stabilization of the patient may be needed. Adequate broad-spectrum antimicrobial treatment (with Amoxicillin-Clavulanic acid or Cephadrine for example), or fluid replacement may be needed. Also, when pain or discomfort exists, short-time treatment with nonsteroidal anti-inflammatory drugs (such as Meloxicam, Ketoprofen or Carprofen) may be used to alleviate the symptoms.

7.1. Surgical approaches

Until the late 90's decade, ovariectomy or ovariectomy were considered the most suitable treatments [19]. The lateral surgical approach was preferable to the ventral to avoid the trauma of the mammary tissue. Excision of the ovaries usually leads to regression of the mammary tissue within three to four weeks, but in some situations regression was not achieved [11,23].

Mastectomy is discouraged as a first approach to the feline mammary fibroepithelial hyperplasia. Only in animals not responding to spaying or to the medical treatment, partial or total mastectomy may be considered, but the surgery is difficult to perform because of the extensiveness of the mammary glands. A radical mastectomy often leads to complications and is only to be recommended when other options have failed.

7.2. Medical approaches

Nowadays, medical therapeutic approaches are available in most countries. Economic constraints may influence the drug of choice, and this may influence the recovery time. Also,

when predicting the recovery time, one should be aware that FEH secondary to exogenous progestin would take longer to regress if antiprogesterone drugs are not selected.

Several studies demonstrated that the progesterone receptor blocker Aglepristone (Alizine®, Virbac, France) can successfully revert FEH [8,11,13,19,23]. Aglepristone is a molecule that competitively binds to the progesterone receptor without activating the hormone response cascade in target tissues. This drug binds to with a 9-fold affinity to progesterone receptor, and according to the manufacturer its residence time in the organism is of 6 days, if administered once in the dose of 20mg/kg or twice at 10mg/kg [23]. Although not licenced to be used in cats, this drug is commonly used to induce abortion or to treat pyometra in this species. By consequence, its application in cats is under the veterinarian responsibility.

Before starting the treatment with Aglepristone it is important to exclude pregnancy, as this drug may elicit abortion of a premature birth. When FEH develops in pregnant females it is mandatory that the therapeutic approaches are discussed with the cat owner in detail, and is important to mention that despite the mammary enlargement, the diseased glands will not produce milk and also that the kittens attempts to nurse may predispose to complications such as mastitis and ulceration, which will worsen the evolution of the primary condition.

Several therapeutic schedules have been described in the literature for Aglepristone in FEH (Table 1). Personally, I prefer to inject 10mg/kg of Aglepristone (Alizine®) on days 1 and 3, subcutaneously (SC), and to re-evaluate the situation a week later. If necessary, a second administration is performed following the same schedule. Rarely (only one situation in 25 cases treated with Alizine®) I needed to perform a third administration (again two doses 48h apart), in a female that was submitted to oral progestin treatment that started during estrus. Reduction of the mammary volume, in particular the mammary thickness, is the major parameter for assessment of the response to treatment. Mammary thickness can be assessed by ultrasonography. By using this schedule, it can be observed a slight reduction in the thickness of the disease mammary glands between days 1 and 3, which is predictive of the expected length of the treatment. For most cases, FEH recovery was obtained in 3 to 4 weeks, with only one situation (the one above mentioned) taking 6 weeks to obtain full regression of the mammary condition.

Varying with the reports, the a mean of 4 to 5 treatments (Table 1) are needed to recover from FEH [23,42], and full recovery was obtained in varying periods that last for 3 to 11 weeks [23].

Occasionally, short-term skin irritation at the site of injection has been reported [23], but it seldom originates a problem.

In some case descriptions, dopamine agonists such as Cabergoline and Bromocriptine were also used for FEH treatment [40]. Though these products were not licenced for cats in some countries, they are commonly used in the feline practice. Vomiting or anorexia are described as side effects in a small proportion of cases, as well as a slight depression of the blood pressure, although these symptoms tend to disappear with continued treatment. Nonetheless, its usefulness in the treatment of feline mammary fibroepithelial hyperplasia remain uncertain, as prolactin has not been described as one of the players in FEH pathogenesis and FEH lesions

Alizine® doses	Treatment schedule	References
0,33ml/kg/d corresponding to 10mg/kg/d	2 doses, 24h apart; Repeat at week intervals to full recovery	[13]
	4 to 5 consecutive days	[19]
	4 to 5 consecutive days and again on day 7	[8]
	On days 1, 2, 7, 14 and 21	[42]
	2 doses, 24h apart, for 4 consecutive weeks	
0,66ml/kg/d corresponding to 20mg/kg/d	Once a week, for 4 consecutive weeks	[23]
0,33ml/kg/d corresponding to 10mg/kg/d	On days 1, 2 and 7	[40]
0,5ml/kg/d corresponding to 15mg/kg/day		

Table 1. Administration regimens proposed for Aglepristone (Alizine®, Virbac, France) treatments in feline mammary fibroepithelial hyperplasia.

are negative to prolactin [43]. Nevertheless, such drugs may be helpful when it is need to discontinue the queen lactation, in cases where FEH develops in lactating females.

Cabergoline (Galastop®, Ceva Santé Animale, France) is a dopaminergic agonist that produces a selective and long-lasting inhibitory effect on prolactin secretion, which in turn may be helpful to supress lactation. In dogs and cats it also induces luteolysis, and consequently it may induces abortion. Cabergoline is used for interrupt lactation at a dose of 5µg/kg body weight, *per os* (PO), once daily for 5-7 consecutive days depending on the severity of the situation. It is also used for mastitis treatment. Its use was described in association with castration in a tomcat [11], or in association with aglepristone in an assumed pregnant young queen [44].

Bromocriptine (Parlodel® is the most frequently used pharmacological presentation) is used in the veterinary practice less often than Cabergoline, as it was found to induce abnormal behavioural effects, such as limb flicks, head/body shakes, and hallucinatory-like behaviour as well as excessive grooming [45]. This drug can be used at the dose of 0.25mg/cat/day, PO, for 5 to 7 days. Its use on FEH situations enrols the same concerns as for Cabergoline.

8. Prognosis

Generally, the prognosis for uncomplicated feline mammary fibroepithelial hyperplasia is good. The co-existence of mastitis or ulceration may induce some concern, particularly when the situation was left untreated for a long period. In rare situations, abscess formation and systemic illness worsen the prognosis.

Spontaneous regression of the enlarged mammary glands after removal of the progesterone influences may occur, but it may take up to 11 months. Nevertheless, ovariectomy or

withdrawal of the progestin treatment does not always result in regression of the masses. With the available progesterone antagonist, medical treatment of the condition has improved, and regression of the mammary swelling is usually obtained within a 4-8 weeks interval. It is possible that the co-existing mammary abscesses may require the surgical drainage of the abscess content, in a way to hasten the FEH regression [10].

Recurrence of the disease is controversial. Some studies refer that it is rarely observed [11]. However, in the absence of neutering, several reports of FEH in females describe the recurrence of the condition at a variable timing after the initial treatment [6,23,31]. Consequently, recurrence of the mammary lesions is important concern particularly in females that can maintain their full reproductive activity.

Thus, when debating the prognosis with the cat owner, it is important to discuss also the measures need for avoiding the recurrence of FEH. If a progestin administration for contraception was the causative agent it should be advised the cat spaying. This should also be advised whenever the female is not intended for breeding. In cases where the surgery for neutering is decided it can be performed later, when mammary enlargement regressed, making the procedure easier for the surgeon and less traumatic for the cat, avoiding undesirable trauma of the enlarged mammary glands during surgery. If progestin was used as treatment for skin disorders, alternative therapeutics should be found.

9. Concluding remarks

FEH is a progesterone-associated disease that is characterized by a very rapid swelling of mammary gland, which onset is usually within 2 to 4 weeks from the occurrence of an estrus or the administration of a progestin treatment. Occasionally, this primary lesion can be complicated with mastitis, ulceration or abscessation of the diseased mammary glands. Diagnosis of feline mammary fibroepithelial hyperplasia is exclusively a clinical issue, though some complementary methods of diagnosis may be helpful aids to confirm the diagnosis.

Treatment of feline mammary fibroepithelial hyperplasia has undergone major changes in the past three decades, and considerable improvement of cat welfare was achieved with the introduction of successful medical treatment. Nowadays, antiprogesterone drugs are available that ease the therapeutics and hastens a favourable outcome. With these drugs, the treatment targets the major causal mechanism, interrupting the progesterone-mediated pathways of mammary development and growth. Antiprogesterone molecules are now in the first line treatments for FEH, allowing to avoid massive mastectomy, a very aggressive approach to the cat. However, relapses are possible, and most frequently ovariectomy or ovari hysterectomy are advised to avoid recurrence of the problem.

Nevertheless, new studies on molecular pathways involved in the disease might strengthen additional interplaying factors of interest to design additional therapeutic approaches, as well as to highlight the factors underlying the relapses described in the literature in order to improve the medical treatment and the animal welfare.

Acknowledgements

This work was supported by the project from CECAV/UTAD with the reference PEst-OE/AGR/UI0772/2011, by the Portuguese Science and Technology Foundation.

Author details

Rita Payan-Carreira

Address all correspondence to: rtpayan@gmail.com

CECAV [Veterinary and Animal Research Centre] – University of Trás-os-Montes and Alto Douro, Dept. Zootechnics, Vila Real, Portugal

References

- [1] Murphy S. 2009. Mammary tumours in cats – causes and practical management. Conference proceedings of the European Society of Feline Medicine - ESFM Feline Symposium, 1st April 2009, Birmingham, UK: 11-15.
- [2] Giménez F, Hecht S, Craig LE, Legendre AM. 2010. Early detection, aggressive therapy: optimizing the management of feline mammary masses. *J Feline Med Surg.* 12(3): 214-24.
- [3] Johnson C. 1994. Diseases of the mammary glands. In: Sherding R. (Ed). *The Cat: Diseases and Clinical Management.* 2nd Ed. Churchill Livingstone, New York: 1874-5.
- [4] Johnston S, Root Kustritz M, Olson P. 2001. Disorders of the mammary gland of the Queen. In: *Canine and Feline Theriogenology.* W.B. Saunders Comp, Philadelphia: 474-85.
- [5] Hayden D, Johnston S, Kiang D, Johnson K, Barnes D. 1981. Feline mammary hypertrophy/fibroadenoma complex: clinical and hormonal aspects. *Am J Vet Res.* 42(10): 1699-703.
- [6] Loretta A, Ilha M, Breitsameter I, Faraco C. 2004. Clinical and pathological study of feline mammary fibroadenomatous changes associated with depot medroxyprogesterone acetate therapy. *Arq Bras Med Vet Zootec.* 56(2): 270-4.
- [7] Loretta A, Ilha M, Ordás J, de las Mulas JM. 2005. Clinical, pathological and immunohistochemical study of feline mammary fibroepithelial hyperplasia following a single injection of depot medroxyprogesterone acetate. *J Feline Med Surg.* 7(1): 43-52.

- [8] Sontas B, Turna O, Ucmak M, Ekici H. 2008. What is your diagnosis? Feline mammary fibroepithelial hyperplasia. *J Small Anim Pract.* 49(10): 545-7.
- [9] Rutteman G, Withrow S, EG M. 2001. Tumours of the mammary gland. In: Withrow S. and MacEwen E. (Ed). *Small Animal Clinical Oncology.* W.B. Saunders Comp, Philadelphia: 455-77.
- [10] Burstyn U. 2010. Management of mastitis and abscessation of mammary glands secondary to fibroadenomatous hyperplasia in a primiparturient cat. *J Am Vet Med Assoc.* 236(3): 326-9.
- [11] Leidinger E, Hooijberg E, Sick K, Reinelt B, Kirtz G. 2011. Fibroepithelial hyperplasia in an entire male cat: cytologic and histopathological features. *Tierarztl Prax Ausg K Kleintiere Heimtiere* 39(3): 198-202.
- [12] Jelinek F, Barton R, Posekana J, Hasonova L. 2007. Gynaecomastia in a tom-cat caused by cyproterone acetate: a case report. *Veterinari Medicina.* 52: 521–525.
- [13] Jurka P., Max A. 2009. Treatment of fibroadenomatosis in 14 cats with aglepristone – changes in blood parameters and follow-up. *Vet Rec* 165: 657-660
- [14] MacDougall L. 2003. Mammary fibroadenomatous hyperplasia in a young cat attributed to treatment with megestrol acetate. *Can Vet J.* 44(3): 227-9.
- [15] Gudermuth DF, Newton L, Daels P, Concannon P. 1997. Incidence of spontaneous ovulation in young, group-housed cats based on serum and fecal concentrations of progesterone. *J Reprod Fertil Suppl* 51:177–184.
- [16] Griffin B. 2001. Prolific cats: the estrous cycle. *Compend. contin. educ. pract. vet.* 23 (12): 1049-1057.
- [17] Allen HL. 1973. Feline Mammary Hypertrophy. *Vet Pathol.* 10: 501-508.
- [18] Hayden DW, Barnes DM, Johnson KH. 1989. Morphologic changes in the mammary gland of megestrol acetate-treated and untreated cats: a retrospective study. *Vet Pathol.* 26(2): 104-13.
- [19] Wehrend A, Hospes R, Gruber AD. 2001. Treatment of feline mammary fibroadenomatous hyperplasia with a progesterone-antagonist. *Vet Rec.* 148(11): 346-7.
- [20] Enginler SÖ, Şenünver A. 2011. The Effects of Progesterone Hormone Applications Used for Suppression of Estrus on Mammary Glands in Queens. *Kafkas Üniversitesi Veteriner Fakültesi Dergisi* 17 (2): 277-284.
- [21] Seixas Travassos MA. 2006. [Feline mammary lesions: a contribute to its biopathological characterization] In portuguese. PhD thesis, Univ. de Trás-os-Montes e Alto Douro. Pp 194.
- [22] Sorenmo KU. 2011. Mammary gland tumors in cats: Risk factors, clinical presentation, treatments and outcome. *Proceedings of the 36th World Small Animal Veterina-*

- ry Congress, Jeju (Korea), 14 to 17 October. OC-I10: 764–767 (www.ivis.org/proceedings/wsava/2011/189.pdf). Accessed on the 17th September 2012.
- [23] Görlinger S, Kooistra HS, van den Broek A, Okkens AC. 2002 Treatment of fibro -adenomatous hyperplasia in cats with aglépristone. *J Vet Intern Med.* 16: 710–713
- [24] Pukay BP, Stevenson DA. 1983. Mammary hypertrophy in an ovariohysterectomized cat. *Can Vet J.* 24(5): 143-4.
- [25] Conneely OM, Mulac-Jericevic B, Lydon JP. 2003. Progesterone-dependent regulation of female reproductive activity by two distinct progesterone receptor isoforms. *Steroids.* 68(10-13): 771-8.
- [26] Robinson GW, Hennighausen L, Johnson PF. 2000. Side-branching in the mammary gland: the progesterone-Wnt connection. *Genes Dev.* 14(8): 889-94.
- [27] Briskin C, O'Malley B. 2010. Hormone action in the mammary gland. *Cold Spring Harb Perspect Biol.* 2(12): a003178. Pp.15
- [28] Payan-Carreira R, Martins-Bessa A. 2008. Ultrasonographic assessment of the feline mammary gland. *J Feline Med Surg.* 10(5): 466-71.
- [29] Mol JA, Gracanin A, de Gier J, Rao N, Schaeffers-Okkens A, Rutteman G, Kooistra H. 2012. Molecular genetics and biology of progesterone signaling in mammary neoplasia. Proceedings of the joint meeting of the 7th International Symposium on Canine and Feline Reproduction and the 15th Congress of the European Veterinary Society for Small Animal Reproduction: 107-108 (www.ivis.org/proceedings/isufr/2012/107.pdf?LA=1). Accessed on the 22th September 2012.
- [30] Millanta F, Calandrella M, Bari G, Niccolini M, Vannozzi I, Poli A. 2005. Comparison of steroid receptor expression in normal, dysplastic, and neoplastic canine and feline mammary tissues. *Res Vet Sci.* 79(3): 225-32.
- [31] Martín de las Mulas J, Millán Y, Bautista MJ, Pérez J, Carrasco L. 2000. Oestrogen and progesterone receptors in feline fibroadenomatous change: an immunohistochemical study. *Res Vet Sci.* 68(1): 15-21.
- [32] Mol JA, van Garderen E, Rutteman GR, Rijnberk A. 1996. New insights in the molecular mechanism of progestin-induced proliferation of mammary epithelium: induction of the local biosynthesis of growth hormone (GH) in the mammary glands of dogs, cats and humans. *J Steroid Biochem Mol Biol.* 57(1-2): 67-71.
- [33] Ordás J, Millán Y, de los Monteros AE, Reymundo C, de las Mulas JM. 2004. Immunohistochemical expression of progesterone receptors, growth hormone and insulin growth factor-I in feline fibroadenomatous change. *Res Vet Sci.* 76(3): 227-33.
- [34] Millanta F, Lazzeri G, Mazzei M, Vannozzi I, Poli A. 2002. MIB-1 labeling index in feline dysplastic and neoplastic mammary lesions and its relationship with postsurgical prognosis. *Vet Pathol.* 39(1): 120-6.

- [35] Dias Pereira P, Carvalheira J, Gärtner F. 2004. Cell proliferation in feline normal, hyperplastic and neoplastic mammary tissue--an immunohistochemical study. *Vet J.* 168(2): 180-5.
- [36] Schmidt PM, Chakraborty PK, Wildt DE. 1983. Ovarian activity, circulating hormones and sexual behavior in the cat. II. Relationships during pregnancy, parturition, lactation and the postpartum estrus. *Biol Reprod.* 28(3): 657-71.
- [37] Moulton J. 1990. Mammary tumors of the cat. In: Moulton J. (Ed.) *Tumours in Domestic Animals*. 3rd Ed. University of California Press, Berkeley. p. 547-8.
- [38] Ginn P, Mansell J, Rakich P. 2007. Tumours of the mammary gland. In: Maxie M. (Ed.) *Jubb, Kennedy, and Palmer's Pathology of Domestic Animals*. Saunders, Elsevier, New York. p. 777-80.
- [39] Buritica EF, Echeverry DF, Lozada AF. 2010. Hiperplasia fibroepitelial mamaria felina: reporte de un caso. *Rev Ces Med Vet Zootec.* 5 (1):70-76.
- [40] Little S. 2011. Feline reproduction: common problems you will see in practice. Proceedings of the 63rd Canadian Veterinary Medical Association Convention. Halifax, Nova Scotia, Canada, the 6 to 9 July 2011. Pp. 4. (http://canadianveterinarians.net/SpeakerNotes2011/HTML/companion/companion_little_06-Feline_Reproduction.html). Accessed on the 18th September 2012.
- [41] Chisholm H. 1993. Massive mammary enlargement in a cat. *Can Vet J.* 34(5): 315.
- [42] Vitásek R, Dendisová H. 2006. Treatment of Feline Mammary Fibroepithelial Hyperplasia Following a Single Injection of Proligestone. *Acta Vet. Brno* 75: 295-297.
- [43] Trummel DK. 2007. Expression of Prolactin in Feline Mammary Adenomas and Adenocarcinomas. BSc Thesis in Animal Sciences. Oregon State Univ.
- [44] Uçmak M, Enginler SÖ, Gündüz MG, Kirşan I, Sönmez K. 2011. Treatment of Feline Mammary Fibroepithelial Hyperplasia with the Combination of Aglepristone and Cabergoline. *İstanbul Üniversitesi Veteriner Fakültesi Dergisi* 37 (1): 69-73.
- [45] Gonzalez-Lima F, Velez D, Blanco R. 1988. Antagonism of behavioral effects of bromocriptine by prolactin in female cats. *Behav Neural Biol.* 49(1): 74-82.