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How I treat Benign Mammary Hypertrophy in the Queen

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**Introduction** - Mammary hypertrophy (also known as mammary hyperplasia, mammary dysplasia, fibroadenoma complex, mammary fibroadenomatosis, fibroepithelial hyperplasia, fibroglandular mammary hypertrophy) is a benign disease consisting of a proliferation of one or more mammary glands of young or adult queen which was first reported in 1973. A common risk factor is administration of progestogens, especially in high doses (1-4). The proper dosage for progestogens in cats have been recently reviewed (5). It appears mistakes have been made in compiling information on leaflets of such drugs in some countries of the world, with queens being treated just once with high doses capable to cause the disease (6). However, exogenous progesterone is not always the cause, as demonstrated by a report in which 21 intact queens were presented with mammary hypertrophy with no history of exogenous progesterone therapy: 4/21 were pregnant, and 1 had been in oestrus 2-3 weeks before onset of mammary enlargement (3). The highest prevalence of the naturally occurring disease (i.e. not caused by progestogen administration) is in the young-adult female population.

**Clinical signs** - Administration of exogenous progestogens such as medroxyprogesterone acetate or megestrol acetate have been associated with full display of mammary hypertrophy signs both in female as well as in male cats: in these cases nodules ranging in size from 1 to >50 cm$^3$ are commonly observed (3, 4). Hayden et al. (3) described mammary hypertrophy in 11 queens (4 intact and 7 spayed) following therapy with megestrol acetate: the observed nodules were single (6 queens), in 2 glands (2 queens) and in 3 or more glands (3 queens). Histologically, nodules were characterized by fibroepithelial hyperplasia (7 queens), lobular hyperplasia (2 queens) and ductal ectasia (2 queens). Affected mammary glands are generally uniformly enlarged, while in rare cases they may contain one or more localized masses which are hard to distinguish clinically from neoplastic tissue. Pregnancy can be associated with the condition, and its presence should always be ruled out before any treatment is performed. In one case mammary hypertrophy was reported in a 5-month old queen, never observed to be in estrus, that aborted 2 foetuses shortly after being examined (3). In most cases mammary glands are observed to swell rapidly over a 2-3 day period: swelling typically starts from the inguinal glands on day 1, and by the end of day 2 or 3 all 4 pairs are uniformly swollen, with a very tense skin especially over the inguinal glands. Skin atrophy and necrosis is often the most serious complication, as the condition in itself may resolve within a few weeks without any treatment. However, complications may arise due to infection on the mammary skin, or the queen may show a short period of anorexia due to pain caused by the enlarged glands. In the author’s experience most queens do not seem to be excessively altered by the disease, they just keep moving around without problems and show no altered feeding or social behavior. The demonstration of the key role of progesterone (whether exogenous or endogenous) is the fact that luteolysis, ovariectomy, spontaneous abortion or...
parturition generally are associated with spontaneous remission of the disease and complete regression of the mammary enlargement.

**Pathogenesis** - Biochemical and immunohistochemical studies have revealed the presence of progesterone and estrogen receptors in hyperplastic mammary glands of cats (3, 7). High endogenous or exogenous progesterone concentration may induce local synthesis of GH and insulin-like growth factors (IGFs) in mammary epithelial cells as well as estrogen priming of the mammary tissue by progesterone inqueens, which has been suggested as a pathogenetic mechanisms for feline mammary hyperplasia (7, 8, 9).

In estrogen-primed mammary tissues it has been hypothesized that fibroepithelial proliferation is under the influence of progesterone (7). The progestational effect of inducing hyperplastic changes in the mammary gland of cats may depend on such estrogen priming suggesting that a hormone dependent-pathway is also responsible for the occurrence of mammary hyperplasia. In the queen estrogens probably act (like in other females of domestic species) by binding to estrogen receptors present in ductal epithelial cells and stromal cells of the mammary gland inducing these cells to synthesize intracellular receptors for progesterone. The increased expression of progesterone receptors in the mammary tissues may intensify the physiological response of the mammary gland to this hormone leading to hyperplastic changes. Therefore, it is feasible that the mitotic and proliferative influences of progesterone on the mammary gland also depend somehow on estrogen priming, just like what happens within other tissues of the reproductive tract e.g. uterus. A similar pathogenesis has been suggested for cystic endometrial hyperplasia and pyometra in the bitch. Immunohistochemistry shows a low prevalence of estrogen receptors in affected queens (33%, 7). However, these findings come from histopathological exams carried out in queens with obvious clinical signs: the situation at time of first visit may have changed remarkably from the onset of the disease. It is likely that estrogens and their receptors play an important role in the early stages of the development of feline mammary hyperplasia.

GH and IGF-I have been detected immunohistochemically in the cytoplasm of mammary ductal cells representing local synthesis of both hormones (6). This findings suggest that (i) local production of GH and IGF-I enhances the proliferation of the mammary tissue in an autocrine and/or paracrine manner, contributing to mammary gland enlargement (8,9) and (ii) mammary epithelial cells are capable of producing GH locally under adequate progesterone stimulus (9). In dogs and cats, endogenous or exogenous progesterone can induce GH overproduction. The origin of the increase in GH was demonstrated to be the mammary gland in which progestins have the ability to induce the expression of the GH gene stimulating the ectopic production of GH in the ductular epithelium. Synthetic progestins induce local expression of the gene encoding GH (GH mRNA) in the mammary tissue resulting in enhanced biosynthesis of GH. Local expression of GH-encoding gene, together with the expression of genes encoding for insulin-like growth factors such as IGF-I and IGF-II and their binding proteins (IGFBPs), creates a peculiar environment for proliferation and differentiation of the mammary epithelium primed by progesterone (8). Progesterone receptors may exert a stimulatory effect on mammary GH expression either by making the GH promoter available for binding of other transcription factors (chromatin remodelling), by direct activation of the GH gene promoter or both. GH is the major regulator of circulating concentrations of IGF-1, and IGF-I has a potential mitogenic effect on some tissues such as the uterus and is capable of regulating proliferation and differentiation events in the endometrium. Therefore, IGF-I might play an important role in the pathogenesis of feline mammary hyperplasia just like it is claimed to do for the pathogenesis of cystic endometrial hyperplasia in dogs (10).
**Diagnosis** - Although theoretically diagnosis can only be confirmed by histology, performing biopsies on hyperplastic mammary nodules is often not advisable, especially when swelling involves all glands and onset is very rapid. Neoplastic nodules generally take a relatively long time to develop, and when a queen with a hyperplastic mammary condition is presented, glands are typically so swollen and overlying skin so tense (and sometimes atrophic) that the biopsy wound rarely heals by itself, thus becoming a complication. The value of fine needle aspiration biopsies in diagnosing feline mammary hyperplasia is still a matter of speculation because this technique may be misleading and inconclusive when distinguishing hyperplasia from inflammatory, dysplastic and neoplastic lesions of the mammary gland. Differential diagnosis of feline mammary hyperplasia includes other conditions of cats which present with a similar clinical pictures characterized by enlarged mammary glands or swollen and lumpy ventral skin, such as: (i) mastitis (Mandel 1975); (ii) cysts of non-neoplastic mammary tissue (duct ectasia, mastosis), (iii) gynecomastia (11), (iv) lobular hyperplasia (4) and (v) granulomatous steatitis (nutritional panniculitis or "yellow fat disease") caused by hypovitaminosis E (12).

**Treatment** - Feline mammary hypertrophy can be treated by surgery (ovariectomy or ovariohysterectomy), mastectomy or both, and by immediate withdrawal of synthetic progestin therapy. However, performing surgery when the condition is full-blown may lead to potentially fatal complications (11). In general, mammary swelling regresses completely within 3-4 weeks following spaying (13). However, while full mammary growth usually happens quickly, regression can be slow, requiring up to five months after neutering for total disappearance of the lesions (11). When mammary hypertrophy occurs following progestogen administration, signs typically do not subside immediately following neutering or withdrawal of progestin therapy (14). In such cases, surgical removal of persisting nodules should be considered in order to perform histology and rule out presence of neoplasia. Recently, it was shown that the condition is responsive to targeted endocrine therapy with progesterone antagonists i.e. progesterone receptor blockers such as aglepristone (13, 15), which may be an option also for cats treated with long-acting progestogens. Although dose regimens for aglepristone in cats have not been reported, anecdotal treatments with 15 mg/kg are known to be effective as abortifacients or in case of a pyometra. Dosages for mammary hypertrophy may need to be higher or prolonged in time depending on whether it is a spontaneous disease or if it is due to progestogen administration.

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