Opis przypadku *Case report*

Diagnosis and management of mammary fibroadenomatous hyperplasia in cats: A case-based approach

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Summary

Fibroadenomatous Hyperplasia (Mammary fibroadenomatosis hyperplasia, MFH) is one of the most common mammary gland conditions diagnosed in young female cats undergoing hormonal contraception. This disease is classified as a benign, hormone-dependent proliferation of the glandular tissue of the mammary gland and its stroma. Clinically, it presents as a pronounced swelling of both mammary chains. Two cases of mammary fibroepithelial hyperplasia (MFH) were reported, one occurring spontaneously and the other following treatment with medroxyprogesterone. Both animals exhibited clinical signs of localized inflammation. Notably, serum amyloid A (SAA) concentrations and white blood cell (WBC) counts were markedly elevated, indicating a systemic inflammatory response. Treatment with the progesterone receptor antagonist aglepristone resulted in complete clinical recovery in both cases. Full remission of clinical signs was achieved approximately four weeks after treatment initiation. Moreover, both SAA levels and WBC counts were normalized by day 14. These findings confirm the efficacy of aglepristone in managing MFH and underscore the utility of monitoring SAA and WBC as markers of inflammation during therapy.

Keywords: Mammary fibroadenomatous hyperplasia (MFH), queen, aglepristone, antygestagen, serum amyloid A (SAA)

Mammary gland disorders in cats, characterized by abnormal tissue proliferation, represent a significant proportion of clinical cases encountered in routine veterinary practice. The vast majority of these lesions are malignant, whereas benign and non-neoplastic hyperplastic changes are diagnosed relatively infrequently. According to both literature data and clinical observations, mammary fibroadenomatous hyperplasia (MFH) is among the most commonly reported proliferative mammary conditions in cats (19, 20, 24). MFH is a non-neoplastic, hormone-dependent proliferation of mammary glandular epithelium and stromal tissue. Two forms of MFH can be distinguished: a diffuse form, characterized by lobular epithelial hyperplasia typically associated with endogenous progesterone activity, and a papillary ductal form, frequently observed in response to exogenous progestagen therapy (9). The pathogenesis of MFH involves progesterone-mediated upregulation of local growth hormone (GH) and insulin-like growth factor 1 (IGF-1) production within the mammary tissue, leading to marked glandular hyperplasia (8, 15). Clinically, this results in a bilateral, symmetric enlargement of the mammary chains, although in some cases the hyperplasia may be limited to one or several pairs of mammary glands. MFH is most commonly diagnosed in young, intact female cats, typically during their first or second estrus. However, reports in the literature indicate that MFH may also occur during pregnancy, pseudopregnancy, or the periparturient period, likely due to elevated serum progesterone concentrations during these physiological states. In most cases, however, MFH is associated with the administration of synthetic progestogens such as megestrol acetate or medroxyprogesterone

acetate often given at the owner's request to suppress estrus behavior during or between heat cycles (14). Additionally, cases of endogenous progesterone production secondary to functional ovarian or adrenal neoplasms have been described (11, 20) and there are rare reports of MFH in male cats as well (11, 13).

Diagnosis. The diagnosis of mammary fibroadenomatosis hyperplasia (MFH) is based on a thorough medical history and clinical examination. The anamnesis should determine whether the patient has previously received hormonal therapy, with particular emphasis on the administration of contraceptive agents. Clinical examination reveals characteristic changes in the mammary tissue. Initially, an acute enlargement of the mammary gland develops, which is non-painful and presents a consistency ranging from firm to doughy. This excessive hyperplasia of mammary epithelial cells is frequently accompanied by an inflammatory process, clinically manifested by the classical signs of inflammation: erythema, pain on palpation, increased local temperature, and visibly abnormal mammary gland discharge (5). These clinical signs are often accompanied by reduced appetite and, occasionally, lethargy. Fine-needle aspiration (FNA) of the affected mammary tissue typically reveals extensive fibroadenomatous proliferation with ductal epithelial hyperplasia (20). However, the cytological features observed microscopically are difficult to interpret and therefore provide limited diagnostic value; FNA can only suggest the presence of MFH. A much more reliable diagnostic method is histopathological examination of the mammary gland, which allows for a definitive diagnosis, but this can only be performed following surgical excision of the affected tissue. Ultrasonographic examination of the mammary glands and abdominal cavity, with particular attention to the ovaries and uterus, may also aid in the diagnosis of MFH. Affected mammary glands typically show a heterogeneous echotexture and increased echogenicity compared to unaffected areas. Reproductive tract ultrasonography is useful for confirming or ruling out concurrent pathological changes in the uterus or ovaries (17). Given the high incidence of malignant mammary tumors in cats and the frequent occurrence of metastases, including to regional lymph nodes and lungs it is critical to differentiate non-neoplastic proliferative lesions such as MFH from mammary neoplasms (16). Differential diagnoses should also include mastitis and mammary neoplasms, among which adenocarcinoma, adenoma, carcinoma, and various sarcomas are most commonly reported (5, 11). It is essential to consider that in every diagnosed case of non-neoplastic mammary gland proliferation in queens, such as MFH, pharmacological treatment may lead to complete regression of the lesion, avoiding the need for surgical intervention. From the perspective of a practicing veterinarian, this is a crucial point, as it enables a non-invasive therapeutic approach with the potential for full recovery.

Treatment. The therapeutic approach to mammary fibroadenomatous hyperplasia primarily involves reducing circulating progesterone levels. This is the most commonly achieved through the administration of antiprogestins, which have proven to be an effective and clinically successful method. Aglepristone (Alizin, Virbac S.A.) is the progesterone receptor antagonist most commonly employed, is not registered for use in cats. Even though it is not standard practice to treat cats with Alizin, literature data indicate the usefulness of that aglepristone in some clinical cases in queens (3, 4).

Alternatively treatment of mammary fibroadenomatous hyperplasia is a surgery – ovariohysterectomy, which may be considered as a curative procedure.

It is important to highlight that without appropriate pharmacological intervention, MFH lesions may progress to ulceration, secondary bacterial infection, and tissue necrosis. In refractory cases where conservative therapy fails, mastectomy should be considered as a last resort option.

Given the relatively high prevalence of MFH in feline patients and the occasionally dramatic therapeutic response to treatment, we undertook a retrospective review and documentation of clinical cases of MFH diagnosed at the Department and Clinic of Animal Reproduction, Faculty of Veterinary Medicine, University of Life Sciences in Lublin, over the past six months.

Cases description

Case Report 1. A 6-month-old European Shorthair female cat, weighing 3.5 kg with a body condition score (BCS) of 3/5, was presented to the Department and Clinic of Animal Reproduction, Faculty of Veterinary Medicine, University of Life Sciences in Lublin, due to the presence of mammary gland enlargement. According to the owner's report, the changes were first noticed approximately one month prior to the visit. The queen was intact and had never received hormonal contraception. About two weeks before the consultation, empirical treatment had been initiated, consisting of systemic antibiotic therapy and corticosteroids; however, no clinical improvement was observed. The owner additionally noted a decrease in appetite and lethargy.

Upon clinical examination, the cat was in good general condition. Rectal temperature was 38.5°C, heart rate 180 bpm, and respiratory rate 15 breaths per minute. Mucous membranes of natural orifices were pale pink, moist, and without pathological lesions. Physical examination of the mammary chain revealed bilateral enlargement, firm swelling, and induration of all mammary glands. The overlying skin was erythematous and exhibited increased local temperature (Fig. 1). An ultrasonographic examination of the mammary glands and abdominal organs was performed using an Esaote MyLab Twice ultrasound system with a linear probe (3-22 MHz). Ultrasound revealed significant enlargement and heterogeneous echotexture of the mammary tissue. Colour Doppler imaging demonstrated extensive vascularisation within the affected gland (Fig. 4). No pathological changes were observed in the abdominal

organs. The mesenteric lymph nodes and retroperitoneal space appeared normal. Fine-needle aspiration (FNA) cytology of the proliferative lesion was performed, revealing scattered epithelial cells with no cytological evidence of malignancy, occasional stromal cells, and numerous erythrocytes, foamy macrophages, and neutrophils in the background. The cytological findings were suggestive of fibroadenomatous hyperplasia with concurrent mastitis. To assess for systemic inflammation, haematological and biochemical blood analyses were carried out. All values were within normal feline reference ranges (Day 0) except for the white blood cell count (WBC), which was elevated at $22.4 \times 10^3/\mu L$ (Scil Vet abc Plus+ Horiba ABX analyzer), indicating an active inflammatory process (Fig. 5). Additionally, serum amyloid A (SAA) levels were markedly elevated, exceeding 34 µg/mL, which is more than six times upper the reference limit for cats (≤ 5 µg/mL). The SAA measurement was conducted using the Vcheck V200 analyzer (Bionote Inc.).

Fig. 1. Mammary glands of a 6-month-old intact female cat with no prior exposure to exogenous hormonal contraception. Author: Marco Wochnik, Department and Clinic of Animal Reproduction, Faculty of Veterinary Medicine, University of Life Sciences in Lublin, Poland

Fig. 2. Therapeutic effects on the mammary glands observed after the third dose of the drug. Author: Marco Wochnik, Department of Clinic of Animal Reproduction, Faculty of Veterinary Medicine, University of Life Sciences in Lublin, Poland

Case Report 2. A 12-month-old European Shorthair female cat, weighing 3 kg, was presented with symptoms similar to those described in Case 1, including mammary gland swelling, erythema, and pain on palpation (Fig. 3). The internal body temperature was recorded at 38.8°C, heart rate at 190 bpm, and respiratory rate at 18 breaths per minute. Based on the anamnesis, it was established that two months prior to presentation, the cat had received

Fig. 3. Mammary glands of a 12-month-old female cat receiving exogenous hormonal contraception. Author: Kamila Maj, Department of Clinic of Animal Reproduction, Faculty of Veterinary Medicine, University of Life Sciences in Lublin, Poland

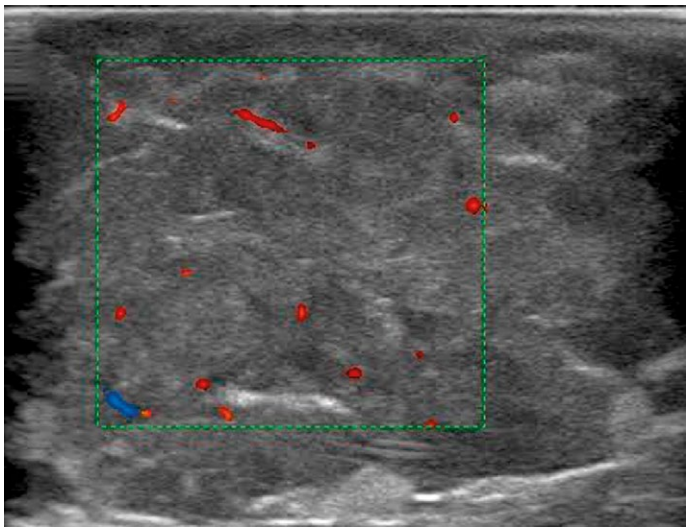

Fig. 4. Ultrasonographic (US) examination of the mammary gland revealed marked glandular enlargement with a heterogeneous echotexture and prominent vascularization on Doppler imaging. Author: Anna Jagiela-Wochnik, Laboratory for Radiology and Ultrasonography, Department and Clinic of Animal Surgery, Faculty of Veterinary Medicine, University of Life Sciences in Lublin, Poland

a hormonal injection to suppress estrusmedroxyprogesterone acetate (Depogeston 50 mg/mL, Biowet Puławy Sp. z o. o.). The patient was referred to the clinic by the owner after several visits to another veterinary practice, where she had been diagnosed and treated for pseudopregnancy. The therapy consisted of administration of cabergoline (Galastop, 50 µg/mL, CEVA SALUTE ANIMALE S.p.A.) at the dose of 0.1 mL/kg for 10 days, a broad-spectrum antibiotic at the dose of 1 mL/10 kg (Amoxicillin, 20% L.A., "Inex") and dexamethasone (Dexafort, Intervet International B.V.) at the dose of 0.05 mL/kg. However, this treatment failed to produce improvement, and as the disease progressed, the clinical signs related to the mammary glands significantly worsened.

As in the previous case, haematological and biochemical blood analyses were performed, along with serum amyloid A (SAA) measurement. The results revealed marked leukocytosis (27.3 × 10^3/µL, Scil Vet abc Plus+ Horiba ABX analyzer) and increase in SAA concentration, reaching 46 µg/mL, indicating a severe systemic inflammatory response (Fig. 5). The SAA analysis was also conducted using the Vcheck V200 analyzer (Bionote Inc.).

In both of the aforementioned cases, based on the collected anamnesis, clinical examination, and additional diagnostics, the queens were diagnosed with mammary fibroadenomatosis hyperplasia (MFH).

Results and discussion

Mammary fibroadenomatous hyperplasia is a commonly diagnosed condition in queens that have received hormonal contraception (11). In most cases, pharmacological treatment involving the administration of aglepristone, a progesterone receptor antagonist, results in favorable therapeutic outcomes and often leads to complete remission. The authors' clinical cases confirmed this. Both cats described were treated with Alizin (Virbac S.A.) at a dosage of 10 mg/kg body weight, administered subcutaneously, following a protocol consisting of three doses given on day 1, day 2, and day 5 after diagnosis. Notably, after the second dose, a significant improvement was observed, with marked reduction in mammary swelling and pain. After the third dose, a dramatic improvement in the general condition of the patients was noted (Fig. 2). In parallel with aglepristone administration, broad-spectrum antimicrobial therapy was initiated using amoxicillin (Clamoxyl L.A., Zoetis) at a dose of 15 mg/kg. Given the ongoing local inflammatory process within the mammary tissue, non-steroidal anti-inflammatory therapy was also implemented using tolfenamic acid (Tolfedine 4%, Vetoquinol S.A.) at a dose of 4 mg/kg. During the follow-up visit on day 14 after initiation of therapy, both patients showed a marked reduction in mammary gland swelling. Complete remission of clinical signs was achieved approximately four weeks after treatment onset, attributed to the progesterone-lowering effect of aglepristone.

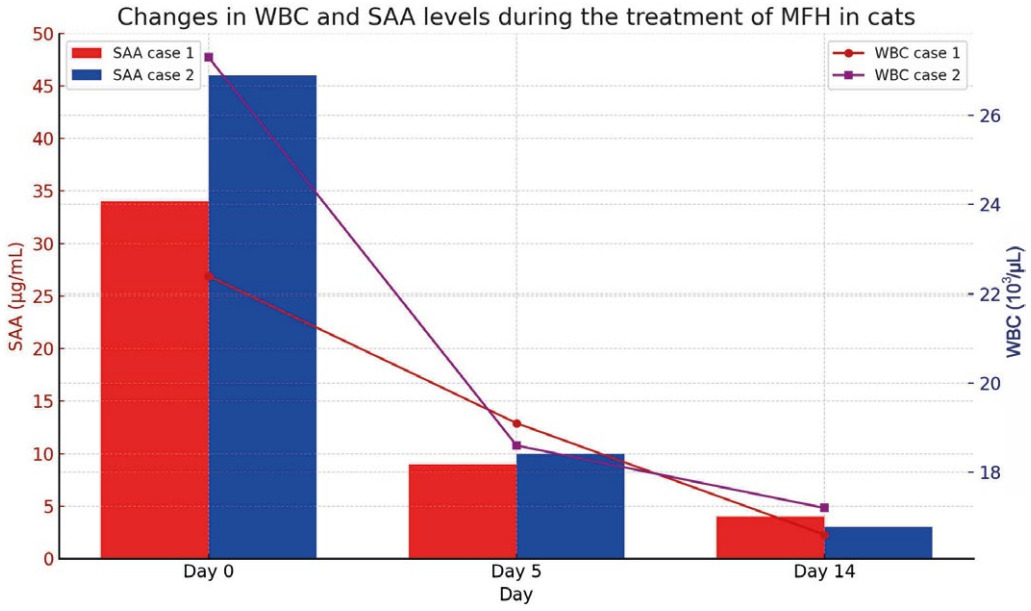

Fig. 5. Changes of WBC and SAA levels during the treatment of MFH in cats
Explanations: The level of WBC – according to Winnicka A. (SGGW, 2021, Warsaw). The level of SAA – according to the Vcheck manufacturer's instructions. Abbrevations: WBC – white blood cell; SAA – serum amyloid A; MFH – mammary fibroadenomatous hyperplasia; Day 0: 1st term of inflammatory marker's determinations; Day 5: 2nd term of inflammatory marker's determinations; Day 14: 3rd term of inflammatory marker's determinations

The presented own observations are consistent with the literature data indicating the efficacy of treatment of mammary fibroadenomatous hyperplasia (MFH) using Alizin (aglepristone) (5). However, there is a risk of disease recurrence during subsequent oestrous cycles. In such cases, surgical sterilisation is recommended as an adjunct to pharmacological treatment (7, 12, 14). Prolonged administration of aglepristone beyond the standard protocol has also been described, especially in queens previously exposed to long-term gestagen contraception. This phenomenon may be related to the influence of synthetic progesterone derivatives on the female organism (23). In our cases, a dosage of 10 mg/kg body weight of Alizin was sufficient to induce rapid remission. Nonetheless, individual variability in response to treatment must always be considered. In some instances, dosage and duration of therapy may require adjustment depending on clinical severity, promptness of treatment initiation, and therapeutic response (10). Improper management of MFH can lead to complications such as ulceration, infection, necrosis, and abscess formation within the mammary tissue (1). Conversely, spontaneous regression of mammary hyperplastic lesions has also been reported (1, 7). In cases of therapeutic failure or recurrence, ovariohysterectomy combined with mastectomy should be considered (6, 7, 11, 18). The importance of additional laboratory tests, particularly the measurement of the major acute-phase protein (APPs) in cats like serum amyloid A (SAA), should be emphasized. According to the literature, SAA is useful in diagnosis and prognosis of reproductive and mammary gland diseases in cats and dogs (2, 21, 22). Our observations corroborate with these findings, showing that effective pharmacological treatment of feline MFH correlates with a decrease in leukocyte count and normalization of serum SAA levels. Notably, on day five of treatment (2nd term of marker's determinations), leukocyte counts returned to within physiological reference ranges of cats, while SAA concentrations remained elevated, indicating a residual low-grade inflammatory process (Fig. 5). By the day 14 (3rd term of marker's determinations), both serum indicators of inflammation normalized, confirming resolution of the inflammatory process in queens (Fig. 5). These laboratory findings support the utility of APPs measurements in monitoring inflammatory status during therapy in cats. We consider acute-phase protein analysis indispensable in treating hormone-induced diseases accompanied by inflammation, such as feline MFH. Our experience suggests that pharmacological management using exogenous hormonal preparations may not always achieve desired effects due to individual patient variability in response to the active substance. Therefore, monitoring serum inflammatory markers, particularly acute-phase proteins (SAA), provides valuable guidance for therapy adjustments and effective patient management. This approach enables early detection of ongoing inflammatory process or treatment failure, allowing timely modification of therapy and optimization of convalescence, which is crucial for recovery and minimizing complications.

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