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Clinical, pathological and immunohistochemical study of feline mammary fibroepithelial hyperplasia following a single injection of depot medroxyprogesterone acetate

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Feline mammary fibroepithelial hyperplasia (FMFH) following a single injection of depot medroxyprogesterone acetate (MPA) was observed in eight intact young queens. The repository compound is marketed as a veterinary product by a local pharmaceutical company with an indication for contraception in cats. The drug was administered according to the recommended doses and injection frequencies. Serum hormone assays performed immediately before neutering and 3 weeks after neutering detected persistently high levels of progesterone suggesting that depot MPA was still exerting its influence. No corpora lutea were found in those cases ruling out ovaries as the main site of progesterone. Immunohistochemistry performed on the hyperplastic mammary glands detected progesterone receptors in the nuclei of ductal cells, and growth hormone (GH) and insulin-like growth factor-I (IGF-I) in the cytoplasm of ductal epithelium. Overdosing should be considered here as the animals received at least 10 mg/kg of depot MPA in a single injection. Progestin-induced local synthesis of GH and IGF-I in mammary epithelial cells is suggested as one of the pathogenic mechanisms involved in the development of FMFH.

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Feline mammary fibroepithelial hyperplasia (FMFH) is a growth disturbance of cats characterised by rapid, non-neoplastic proliferation of ductal epithelium and stroma of the mammary gland resulting in enlargement of one, several or all the mammary glands (Allen 1973). It is seen mainly in young, sexually intact queens at the time of puberty, during the first oestral cycle, pregnancy or pseudopregnancy. Current evidence indicates that FMFH represents a hormone-dependent lesion as high levels of endogenous progesterone induce an exaggerated proliferative response of the mammary glandular tissue (Hayden and Johnson 1986). A number of hormones have been implicated in the pathogenesis of this condition (Hayden and Johnson 1986, Mol et al 1996, Martin de las Mulas et al 2000, Ordás et al 2004) including synthetic progestins such as megestrol acetate and acetate medroxyprogesterone (MPA) (Hayden et al 1989).

MPA is commercially available as a repositol injectable product used as a contraceptive drug for dogs and cats. Currently, there are no products licensed to be used in the prevention or suppression of oestrus in queens in the USA and UK (Noakes et al 2001). Nevertheless, in other countries, parenterally administered progesterone-containing compounds are still available in the market for this purpose (Romagnoli and Concannon 2003). In Brazil, contraceptive

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therapy with depot injectable MPA has been used over the years in feline veterinary clinical practice. Recently, clusters of cases of FMFH have been described in this country. There is an increasing number of anecdotal reports from many local university veterinary hospitals and private practitioners of young cats treated with a single dose of MPA that developed mammary fibroepithelial hyperplasia.

The purpose of the present study is to report the signalment, history, clinical, pathological and immunohistochemical findings, management and outcome of eight cats that developed mammary fibroepithelial hyperplasia after the improper use of a single injection of MPA.

Materials and methods

Animals

From 1999 to 2003, eight cats with mammary fibroepithelial hyperplasia were admitted in three Brazilian university veterinary hospitals. Each of these animals received a single subcutaneous injection of depot MPA. One of these establishments has an annual caseload of approximately 900 cats. Similar statistical data were not available for the other two institutions.

Vaginal exfoliative cytology

Vaginal exfoliative cytology samples were obtained with a cotton swab from two animals (cases 7 and 8) when presented for the first time to the referring veterinarian. Smears were stained with Wright's Giemsa stain. The phase of the ovarian cycle for these animals was determined according to the microscopic findings in those smears.

Serum hormone assays

In two animals (cases 7 and 8), blood samples were taken for serum steroid hormone assays (progesterone and oestrogen) on two different occasions. The first set of samples for those assays was collected 19 days (case 8) and 30 days (case 7) after mammary gland enlargement was first noticed by the owners. Only progesterone levels were measured in the second set of hormonal analyses, ie, 19 days after neutering (cases 7 and 8), with an interval of 26 days (case 8) and 28 days (case 7) between the first and the second set of assays. Measurements of hormonal concentrations were undertaken through an immunoassay immunofluorimetric method for progesterone and radioimmunoassay for oestrogen. Each of those samples was analysed in the automated machine AutoDelfia™ (Perkin Elmer Brazil, Wallac, Turku, Finland).

Pathology

Surgical biopsy, necropsy, light microscopy

Samples of the affected mammary glands were obtained through surgical biopsy (cases 7 and 8), mastectomy (cases 2 and 5) or necropsy (cases 3, 4 and 8) and submitted for histopathology. One of the necropsied animals died spontaneously (case 4) and the other two (cases 3 and 8) were humanely euthanased at the owners' request. In two animals (cases 1 and 6), the condition was diagnosed during the first evaluation of the patients at the hospitals based only on the history and clinical picture. Mammary tissues of six animals (cases 2, 3, 4, 5, 7 and 8) and fragments of different organs including the ovaries and uteri from two queens (cases 7 and 8) were fixed in 10% buffered formalin and routinely processed for light microscopy.

Immunohistochemistry

Formalin-fixed, paraffin embedded tissue sections of the mammary glands of five animals (cases 2, 4, 5, 7 and 8) were analysed for the presence of oestrogen receptors, progesterone receptors, growth hormone (GH) and insulin-like growth factor-I (IGF-I) using an avidin–biotin-peroxidase complex (ABC) technique for monoclonal antibodies as previously described (Martin de las Mulas et al 2000, Ordás et al 2004).

Surgical procedures for the treatment of FMFH included neutering (ovariectomy as in case 3 or ovariohysterectomy as in cases 1, 2, 4, 6, 7 and 8), mastectomy (cases 2, 3 and 5) or both (cases 2 and 3). Ultrasonographic examination of the affected mammary glands was undertaken in one of the affected queens (case 7). Quantification of the levels of MPA in the pharmaceutical product used in those cats was not undertaken as a standard sample was not available and also because multiple lots of that medication were used on different occasions.

Results

A summary of the clinical and pathological findings, therapy and clinical outcome in eight cats with feline mammary fibroadenomatous change is given in Table 1.