Incidence of, risk factors for, and histological features of injection site sarcomas in cats

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Background and Introduction

Recent studies have suggested a causal association between injections and the development of fibrosarcomas at the injection sites in cats. There is a critical need for a rigorous study of factors associated with the development of feline injection site fibrosarcomas (FISS) in the UK, as detailed by the Veterinary Products Committee Working Group on Feline and Canine Vaccination.

Previously performed case-control studies use control groups that were not necessarily representative of the general cat population. Vaccinations have been widely implicated as a risk factor but other types of injection e.g. lufeneron have also been implicated.

FISS represent a group of clinically aggressive neoplasms that have been recognised for some years at distinct anatomical locations used for the administration of injections. These tumours have a heterogeneous histological appearance and this group of tumours has been poorly defined in the veterinary literature.

The true incidence of (FISS) is unknown, and estimates from studies performed in the United States vary from 1 case in 20,000 cats to as high as 1 case in 1,000 cats per year. The incidence of FISS in cats in the UK is unknown but is thought to be a rare disease.

A case-control study will be used to test the hypothesis that vaccination or drug administration via injection is associated with the occurrence of FISS.

This study will address the concerns of practitioners, industry representatives, government agencies, and owners by providing high quality data on the frequency of occurrence of injection site sarcomas in cats. The findings of this study will also have an impact on cat welfare as estimates of the incidence of and identification of risk factors for FISS may help to allay owner fears about the magnitude of the risk of vaccination. The findings of this study will generate refined hypotheses that can be tested in future targeted studies investigating the pathogenesis of FISS.

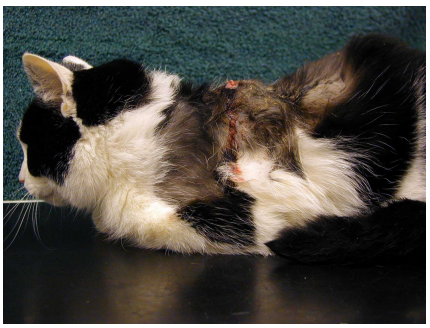

Fig1: The dorsal thoracic region is a common location for FISS in the cat. These tumours have a very aggressive clinical presentation.

Histopathology study

Objective: To form a consensus of expert opinion on the histological features of FISS and determine the histological criteria required for case definition in the epidemiological component of the study.

Methods:

Five diagnostic laboratories are involved in the study - IDEXX veterinary laboratories, Abbey Veterinary Services, Animal Health Trust, Cambridge University Veterinary School and Glasgow University Veterinary School. Each pathologist will independently examine 50 randomly selected slides of FISS, soft tissues sarcomas from non-injection sites and fibrosing panniculitis. A diagnosis will be made for each slide, and each tumour scored according to the degree of differentiation, mitotic figures and necrosis.

A consensus statement will be developed detailing the most consistent histopathological features of FISS and will be used to determine the case definition for the epidemiological study.

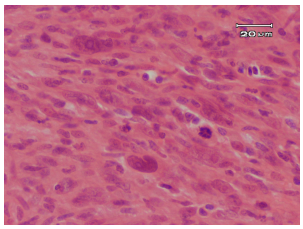

Fig 2: FISS consist of poorly differentiated cells with a high mitotic rate. (HE)

Incidence Estimation

Objective: To estimate the incidence of injection site sarcomas in the UK using a source population of cats who are registered with a sample of veterinary practices during the study period as the denominator.

Methods:

It is unknown how many cats there are in the UK or how many cat vaccines/injections are administered each year. Therefore multiple different denominators will be used to estimate incidence measures, for example:

- the number of cat visits to the submitting veterinary practices within the study period
- the number of cats registered at the submitting veterinary practices within the study period
- the number of cat visits for vaccination/lufenuron injections/microchips to the submitting veterinary practices within the study period
- the number of cat vaccines/lufenuron injections/microchips sold to the submitting veterinary practices within the study period

Case–control study

Objective: To examine the relationship between putative risk factors and the likelihood of developing injection site sarcomas. Risk factors that will be examined include;

- multiple injections at the same anatomical location
- adjuvanted vaccines vs. non-adjuvanted vaccines
- class of drug used
- microchip implantation
- topical insecticide application
- local trauma

Methods:

Selection of cases

Newly diagnosed (incident) cases of FISS will be identified through participating pathology laboratories (AHT, AVS, GUVS, CUVS and IDEXX).

Selection of controls

Different methods could be used for the selection of controls.

- Select control cats randomly from practices registered in the RCVS directory
- Select control cats from practices who regularly submit samples to the diagnostic laboratories
- Select control cats from the practice who submitted the case

Exposure and covariate assessment (for cases and controls)

A questionnaire will be used to collect data on demographic information, vaccination history, use of other injectable agents, microchips, feline leukaemia virus and feline immunodeficiency virus status, use of topical insecticides, and occurrence of abscesses/bite wounds. Exposure information will be collected from the veterinary practices and from owners for the previous 5 years or the lifetime of the cat if less than 5 years of age.

Sample size calculations

Using a 1:4 ratio of cases to controls will maximize the efficiency of the study to detect a significant risk factor. Multivariable sample size calculations to allow for control of a confounding variable such as age were undertaken performed using EGRET-SIZ to estimate the necessary study size and to perform sensitivity analyses around these estimates. A sample size of 960 (192 cases and 768 controls in a 1:4 design) would be sufficient to be 80% confident of detecting a significant ($P < 0.05$) two-fold increase in risk, assuming 10% primary exposure (e.g. FeLV vaccination) in the control group.

To allow for non-response, loss to follow-up and exclusion of cases and controls after data collection, we will aim to increase the sample size by 30% to 250 cases and 1000 controls for a total sample size of 1250 cats.

Logistic regression with calculation of odds ratios and 95% confidence intervals will be used to examine relationships between the exposures of interest and the outcome. Multiple logistic regression will be used to adjust all risk estimates for potential confounders and to assess the effects of veterinary practice and diagnostic laboratories, building up models using standard approaches. All biologically meaningful interactions will be examined and the final model will be assessed for goodness of fit.

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