CORRELATION BETWEEN COX2 EXPRESSION WITH CLINICAL AND DEMOGRAPHIC ASPECTS RELATED TO FELINE INJECTION SITE SARCOMAS

CORRELACIÓN ENTRE LA EXPRESIÓN DE COX2 Y LOS ASPECTOS CLÍNICOS Y DEMOGRÁFICOS RELACIONADOS CON SARCOMAS FELINOS ASOCIADOS A SITIOS DE INOCULACIÓN

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ABSTRACT

Feline injection site sarcomas (FISS; also known as vaccine associated sarcomas) are neoplasms of mesenchymal origin believed to arise from the neoplastic transformation of reactive fibroblasts at vaccine or other substance inoculation sites. In a recent study the authors have shown that cyclooxygenase 2 (COX2) expression in FISS is associated with the degree of inflammation and anaplasia of the tumor. The aim of the present work was to study the relationship between COX2 expression with demographic and clinical parameters of FISS. Demographic and clinical data were obtained from remission protocols of sarcomas diagnosed as FISS and from surveys answered by veterinarians. The expression of COX2 was determined by immunohistochemistry. An inverse correlation was observed between COX2 and the average time between recurrences and the age at clinical diagnosis of FISS. No correlation was observed between COX2 and the other studied variables (sex, breed, existence of recurrence, number of recurrences or survival time).

Keywords: COX2, clinical follow-up, sarcoma, inoculation, feline

RESUMEN

Los sarcomas felinos asociados a sitios de inoculación (SSI, también conocidos como sarcomas asociados a la vacunación) son neoplasias de origen mesenquimático relacionadas con la transformación neoplásica de fibroblastos reactivos en sitios de vacunación o de aplicación de otras sustancias. Recientemente, hemos demostrado que la expresión de ciclooxigenasa 2 (COX2) en SSI está asociada con el grado de inflamación y anaplasia del tumor. El objetivo del presente trabajo fue estudiar la relación entre la expresión de COX2 en SSI, con parámetros demográficos y clínicos. Los parámetros demográficos y clínicos fueron obtenidos a partir de protocolos de remisión de sarcomas que fueron diagnosticados como SSI, así como de encuestas realizadas por los veterinarios. La expresión de COX2 fue determinada por estudios inmunohistoquímicos. Se halló una correlación inversa entre COX2 y el tiempo medio entre recidivas y la edad al momento del diagnóstico clínico de SSI. No se halló ninguna correlación entre COX2 y las demás variables estudiadas (sexo, edad, existencia de recidivas, número de recidivas o tiempo de sobrevida).

Palabras clave: COX2, seguimiento clínico, sarcoma, inoculación, felino.

INTRODUCTION

Feline injection inoculation site sarcomas (FISS) are neoplasms of mesenchymal origin that appear in the body regions routinely used for the injection of vaccines or other *inocula* (1) (Fig. 1).

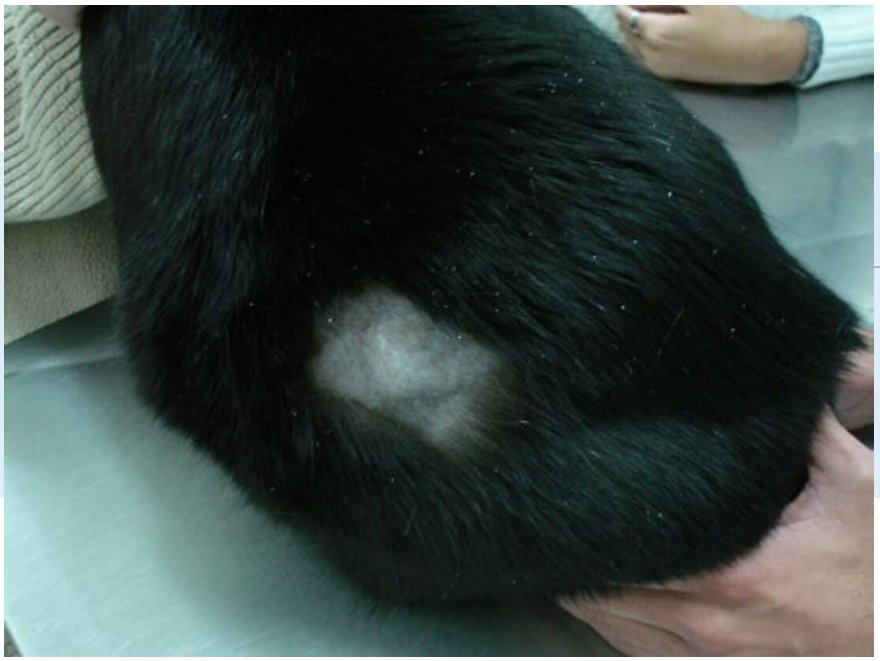

Fig 1. Cat with subcutaneous mass with irregular surface in the flank region diagnosed as FISS.

The most accepted hypothesis regarding FISS origin focuses on the role of the inflammatory process and the malignant transformation of reactive fibroblasts at the periphery of the generated necrotizing granulomatous panniculitis at the vaccine inoculation sites (2).

Several authors have shown that FISS express the proinflammatory enzyme cyclooxygenase 2 (COX2) (3,4,5). Likewise, COX2 expression is higher in neoplasms with high inflammation degree (ID) and minor in highly undifferentiated tumors with high anaplastic degree (AD III) (4).

The aim of the present work was to investigate the relationship between the expression of COX2 in FISS and the demographic parameters and clinical follow-up of the affected patients.

MATERIALS AND METHODS

A number of 117 cases diagnosed as FISS by two expert pathologists were studied. In all of them, AD, ID and COX2 expression were previously determined (4). Demographic and clinical data were obtained from the remission protocols of the samples (117 cases) as well as from surveys carried out by veterinarians (24 effective responses) (5). Breed, age, and sex were considered as demographic parameters while age at diagnosis, existence of recurrences, average time between recurrences, number of recurrences and survival time were considered as clinical parameters. The expression of COX2 was determined in paraffin-embedded tissue sections by immunohistochemistry using the immunop-

eroxidase technique using secondary antibodies bound to a polymer (EnVision HRP ®). 3,3 Diaminobenzidine tetrahydrochloride (DAB) (DakoCytomation, Glostrup, Denmark) was used as a chromogen. Hematoxylin was selected for counterstaining (4,5). The statistical correlation between the different variables was determined. For this purpose, a Bayesian correlation test was performed to assess the correlation between COX2 and demographic and clinical parameters. This methodology was applied using JASP software (https://jasp-stats.org/). Determinations with values of $p<0.05$ were considered as significant. In all cases, the discrete numerical data was analyzed using a square root transformation model; data expressed as proportions were analyzed using an arcsine transformation model (6).

RESULTS

The mean time between recurrences and COX2 expression ($p = 0.008$) and the age at clinical diagnosis and COX2 expression ($p = 0.003$) (Table 1) were inversely correlated. Therefore, the higher the expression of COX2, the shorter the mean time between recurrences, and the lower the age at diagnosis, the higher the expression of COX2. No correlation was found between COX2 expression and sex, breed, occurrence of recurrences, number of recurrences or survival time (Table 1).

Table 1: Bayesian correlation matrix.

Variables		Pearson cc	p value[1]
COX2	Sex	-0.02	0.4900
COX2	Age	-0.017	0.4310
COX2	Breed	NaN a[2]	----------
COX2	ACD	-0.571	0.0030*
COX2	TR	-0.607	0.0080*
COX2	Ryn	0.082	0.6370
COX2	NR	-0.172	0.2280
COX2	STd	-0.264	0.1610

Significant correlation was considered for values of $p<0.05$.. (2) NaN = Variance = 0, analysis was not performed. * = significant correlation. Pearson cc = correlation coefficient. COX2 = COX2 expression percentage. Age = age expressed in years reported at the time of sample submission. ACD = age expressed in years at clinical diagnosis. TR = average time expressed in days between recurrences. Rw/wo = with or without recurrence. NR = number of recurrences. STd = survival time in days.

DISCUSSION AND CONCLUSION

It is well known that COX2 is a proinflammatory molecule (7,8). In a recent work the authors have shown a close relationship between COX2 expression and inflammation in FISS (4), where COX2 expression is directly proportional to ID, being higher in the samples showing the highest ID (ID 3).

According to the findings reported by different authors, COX2 overexpression is associated with tumor cell proliferation and invasion, inhibition of apoptosis, suppression of immune surveillance and angiogenesis(7,9,10,11). This enzyme participates in the synthesis of multiple arachidonic acid derivatives, including PGE_2, which is closely related to carcinogenic processes (12).

In veterinary medicine, antineoplastic effects of COX2 inhibitors have been reported in canine tumors, such as transitional cell carcinomas and oral squamous cell carcinomas. Furthermore, favourable results were observed for the treatment of rectal polyps and inflammatory breast carcinomas in dogs (13).

Several authors have also shown that the inhibition of COX2 reduces the neoplastic cell proliferation of breast and colorectal cancer in humans (14,15,16). Here, the correlation between COX2 expression, age at diagnosis and the average time between recurrences in FISS was corroborated. Age at diagnosis and average time between recurrences were inversely correlated to COX2 expression. No prior information linking these variables was found in the consulted literature.

The use of COX2 inhibitors in FISS could inhibit the proliferation of neoplastic cells and promote an increase in the average time between recurrences. Furthermore, young animals with high COX2 expression could benefit the most from therapeutic protocols that include these drugs. In contrast to Carvalho et al. (17) who associate the highest COX2 expression with a shorter survival, we did not find a statistical correlation between the enzyme expression and the survival of felines with FISS. Although a wide surgical excision is the treatment of choice (18,19) protocols that include COX2 inhibitors may help to extend the period between recurrences when radical surgery is not feasible. Although not all FISS express COX2 (4,21), a large percentage of felines affected by these neoplasms could benefit from therapies with inhibitors of this enzyme.

Further studies are necessary to determine the therapeutic value of the use of COX2 inhibitors in FISS due to their potential inhibitory effect on cell proliferation. In the same way, COX2 expression and age at diagnosis should be studied in greater depth due to their potential prognostic value.

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DECLARATION OF COMPETING INTERESTS

There is no conflict of interest, including financial, personal or other relationships with other people or organizations that could inappropriately influence work.

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