UNIVERSITI PUTRA MALAYSIA

EXPRESSION OF PROLIFERATING CELL NUCLEAR ANTIGEN, VIMENTIN AND FIBROBLAST GROWTH FACTOR RECEPTORS IN CANINE MAMMARY GLAND TUMOURS AS POTENTIAL MARKERS FOR TUMOUR GROWTH AGRESSIVENESS AND HIGH GRADE

KABIRU SAHABI

FPV 2014 9

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By

KABIRU SAHABI

Thesis submitted to the Senate of Universiti Putra Malaysia in fulfilment of the requirement for the degree of Master of Science

July 2014

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DEDICATION

This thesis is dedicated to my parents and family in recognition of their outstanding contributions to my academic endeavours

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EXPRESSION OF PROLIFERATING CELL NUCLEAR ANTIGEN, VIMENTIN AND FIBROBLAST GROWTH FACTOR RECEPTORS IN CANINE MAMMARY GLAND TUMOURS AS POTENTIAL MARKERS FOR TUMOUR GROWTH AGRESSIVENESS AND HIGH GRADE

By

KABIRU SAHABI

July, 2014

Chairperson: Gayathri Thevi Selvarajah, PhD
Faculty: Veterinary Medicine

Canine mammary gland tumour (CMT) is the most common neoplasm that develops spontaneously in female dogs. In Malaysia, the prevalence, risk factors and the expression of potential prognostic markers in CMT have not been investigated. Thus, the objectives of this study were to determine the prevalence and risk factors of dogs in Malaysia diagnosed with mammary tumours and to determine the prognostic value and association of proliferating cell nuclear antigen (PCNA), Vimentin and fibroblast growth factor receptor (FGFR) with common clinicopathological parameters in CMT. The hypothesis of the study are; CMT is among the common neoplasia in intact female dogs diagnosed at the laboratory; malignant CMT is positive for Vimentin expression and have higher number of cells expressing PCNA; Vimentin and PCNA expressions are related to aggressiveness, proliferation, invasiveness and metastasis of CMT; FGFRs are expressed in CMT tissues. A retrospective study was conducted on CMT diagnosed at the Veterinary Histopathology Laboratory (VHL) of the Faculty of Veterinary Medicine (FVM), Universiti Putra Malaysia (UPM) in the period of 2006 to 2012. The study involving 48 CMT cases showed that the prevalence of CMT among all tumours diagnosed in this laboratory was 39%. Neuter status and breed were associated with CMT, as dogs with CMT were found to be intact and of pure breed. Immunohistochemical staining was performed to determine the expression of PCNA, Vimentin, FGFR2, FGFR3 and FGFR4 in 46 CMT tissues and to evaluate the relationship of their expression level with breed size, age, neuter status, involvement of inguinal mammary gland, number of glands involved, mitotic index, tumour size and grade and postsurgical survival in dogs with CMT. Vimentin expression has no association with any of these clinicopathological parameters and failed to predict the postmastectomy survival in CMT. The PCNA expression was significantly higher ($p=0.037$) in high grade tumours. Although both Vimentin and PCNA failed to predict postmastectomy

survival, a positive significant correlation (p=0.029) was observed between Vimentin and PCNA expression in CMT. High grade tumour was noted in intact dogs (p=0.034) that is significantly associated with poor postmastectomy survival (p=0.028). Forty-five tumours (97.8%) expressed FGFR2 and FGFR3. Forty-two (91.3%) tumours expressed FGFR4. Histopathology grade 3 tumours showed significantly higher (p=0.027) FGFR2 expression. The FGFR3 expression has no association with any clinical or histopathology parameters. Large breed size of dogs (p=0.044) and large tumours (p=0.045) were significantly associated with FGFR4 expression. All of these receptors were not able to predict postsurgical survival in CMT. This study concludes the following; (i) CMT is a common type of tumour diagnosed at the VHL, FPV, UPM with a prevalence of 39%; (ii) age, breed and intact neuter status of a dog contribute significantly to risk of CMT development; (iii) PCNA is a good marker for aggressiveness of tumour growth; (iv) histopathology grading can be used to determine prognosis in CMT; (v) expression of FGFR2 and FGFR4 are potential markers for aggressiveness of tumour growth and tumour stage, respectively. Overall the fibroblast growth factor signalling is a pathway important for the pathogenesis of CMT and may be the potential target for new therapeutics in the disease.

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ABSTRAK

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Master Sains

PENYATAAN ANTIGEN NUKLEUS SEL PEMPROLIFERATAN, VIMENTIN DAN RESEPTOR FACTOR PERTUMBUHAN FIBROBLAS PADA TUMOR KELENJAR MAMA KANIN SEBAGAI PENANDA BERPOTENSI UNTUK KEAGRASIFAN PERTUMBUHAN DAN GRED TINGGI TUMOR

Oleh

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Tumor kelenjar mama kanin (CMT) merupakan neoplasma paling biasa berlaku yang mengembang secara spontan pada anjing betina. Di Malaysia, prevalens, faktor risiko dan penyataan penanda prognosis potensi dalam CMT belum pernah diselidik. Justeru, objektif kajian ini ialah untuk menentukan prevalens dan faktor risiko pada anjing di Malaysia yang didiagnosis mengidap tumor mama dan untuk menentukan nilai prognosis dan perkaitan antigen nukleus sel pemproliferatan (PCNA), Vimentin dan reseptor faktor pertumbuhan fibroblas (FGFR) dengan parameter klinikopatologi dalam CMT. Hipotesis kajian ini ialah; CMT adalah diantara neoplasma yang paling kerap didiagnosis pada anjing utuh dalam makmal; CMT malignan adalah positif untuk penyataan Vimentin dan mengandungi bilang sel penyata PCNA paling tinggi; penyataan Vimentin dan PCNA berkaitan dengan keagresifan, pemproliferatan, kemangsangan dan metastasis CMT; penyataan FGFR berlaku pada tisu CMT. Satu kajian retrospektif telah dijalankan terhadap CMT yang didiagnosis dalam Makmal Histopatologi Veterinar (MHV), Fakulti Perubatan Veterinar (FPV), Universiti Putra Malaysia (UPM) untuk tempoh 2006 – 2012. Kajian yang melibatkan 48 kes CMT ini menunjukkan prevalens CMT di kalangan semua tumor yang diagnosiskan dalam makmal ini ialah 39%. Status neuter dan baka didapati terkait dengan CMT sebab anjing mengidap CMT adalah utuh dan daripada baka tulen. Pewarnaan imunokimia telah dilakukan untuk menentukan penyataan PCNA, Vimentin, FGFR2, FGFR3 and FGFR4 dalam 46 tisu CMT dan untuk menilai perkaitan penyataannya dengan saiz baka, umur, status neuter, penglibatan kelenjar mama inguinal, bilangan kelenjar terlibat, indeks mitosis, saiz dan gred tumor dan kemandirian pascasurgeri anjing mengidap CMT. Penyataan Vimentin tiada perkaitan dengan mana-mana parameter klinikopatologi tersebut dan tidak berjaya untuk meramalkan kemandirian pascamastektomi dalam CMT. Penyataan PCNA adalah tinggi tererti (p=0.037) dalam tumor gred tinggi. Walaupun penyataan Vimentin dan PCNA tidak

berupaya untuk meramalkan kemandirian pascamastektomi, suatu korelasi positif (p=0.029) wujud di antara penyataan Vimentin dan PCNA dalam CMT. Tumor gred tinggi berlaku pada anjing utuh (p=0.034) yang terkait secara tererti dengan kemandirian pascamastektomi (p=0.028). Empat-puluh lima (91.8%) tumor menyatakan FGFR2 dan FGFR3. Empat-puluh dua (91.3%) tumor menyatakan FGRF4. Tumor gred histopatologi 3 menunjukkan penyataan FGFR2 lebih tinggi tererti (p=0.027) daripada kumpulan kawalan. Penyataan FGFR3 tiada perkaitan dengan mana-mana parameter klinikal atau histopatologi. Anjing saiz baka besar (p=0.044) dan tumor besar (p=0.045) terkait tererti dengan penyataan FGFR4. Semua parameter ini tidak dapat meramalkan kemandirian pascasurgeri dalam CMT. Kesimpulan daripada kajian adalah seperti berikut; (i) CMT adalah jenis tumor yang biasa didiagnosis dalam MHV, FPV, UPM dengan prevalens 39%; (ii) umur, baka dan status neuter utuh anjing menyumbang secara tererti kepada risiko perkembangan CMT; (iii) PCNA adalah penanda baik untuk keagresifan pertumbuhan tumor; (iv) gred histopatologi boleh diguna untuk menuntukan prognosis dalam CMT; (v) penyataan FGFR2 dan FGFR4 masing-masing adalah penanda berpotensi untuk keagresifan pertumbuhan tumor dan peringkat tumor. Secara keseluruhan pengisyaratan faktor pertumbuhan fibroblast adalah arah laluan penting dalam patogenesis CMT dan mungkin merupakan sasar berpotensi untuk terapeutik baharu penyakit ini.

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ACKNOWLEDGEMENTS

I would like to sincerely acknowledge the support and guidance I received from my supervisors especially the chairperson; Dr. Gayathri Thevi Selvarajah, first for giving me the opportunity to work on an exciting project and for showing all her kindness, patience, guidance and support throughout the period of my study. To other members of my supervisory committee; Prof. Noordin Mohamed Mustapha, Associate Prof. Gurmeet Kaur Dhaliwal and Dr. Reuben Sunil Kumar Sharma, I humbly appreciate your diligent efforts, positive suggestions and valuable observations which have guided me on my academic endeavours.

I am grateful to Kebbi State Government, Nigeria, for granting me the financial assistance and study leave to pursue this programme. I remain thankful to my senior colleagues in the Ministry of agriculture and natural resources, Kebbi state, for their useful advice.

The assistance and advice from other colleagues and staff of the veterinary as well as Establishment departments are hereby acknowledged. I would like to acknowledge the contributions of the staff of parasitology laboratory, Mr. Saiful of serology laboratory, Mr. Kamarudin Awang Isa of virology laboratory, the staff of histopathology laboratory, staff of postmortem theatre and staff of UVH, all in the faculty of veterinary medicine.

Other people worthy of commendation include: Dr. AbdulRasheed Bello Aliyu, a brother who was most instrumental in my coming to Malaysia for Graduate studies and continued to assist me (academically and morally) all the way, Dr. Zeina Jasim, a sister who introduced me to the microtome and H & E., Dr. Faruk Bande, who introduced me to Bioinformatics softwares, Dr. M.S Anka and others too many to mention, I will forever remain indebted.

I am indebted to my beloved wife Safiyya and two children Halima (Baby) and Ammar who endeavoured to accompany me during the course of my study. They made my stay in Malaysia a joyous period. I thank them for their unique patience, motivation and understanding even as they found themselves in an entirely different environment. I sincerely appreciate the efforts of all my relatives and friends especially my younger brother Abdulkarim whom I regularly contacted regarding my personal activities at home. Special regards to all individuals who have assisted me in one way or the other and whose names could not appear here for reason of space.

Kabiru Sahabi

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LIST OF ABBREVIATIONS

BCA	Bicinchoninc acid assay
BRCA	Breast cancer susceptibility gene
BSA	Bovine serum albumin
CD	Cluster of differenciation
CG	Control group
CMT	Canine mammary gland tumour
CT	Computed tomography
Cox-2	Cyclooxygenase-2
DAB	Diaminobenzidine
DNA	Deoxyribonucleic acid
DYAR	Dog year at risk
ER	Oestrogen receptor
EMT	Epitheliomesenchymal transition
FGF	Fibroblast growth factor
FGFR	Fibroblast growth factor receptor
FNA	Fine needle aspiration
FVM	Faculty of veterinary medicine
GWAS	Genome wide association studies
H&E	Hematoxylin and eosin
HER-2	Human epidermal growth factor receptor-2
kDa	Killo dalton
MET	Mesenchymoepithelial transition
NCBI	National centre for biotechnology information
PAGE	Polyacrylamide gel electrophoresis
PBS	Phosphate buffered saline

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PBST	Phosphate buffered saline with tween 20
PCNA	Proliferating cell nuclear antigen
PR	Progesterone receptor
PVDF	Polyvinilidin difluoride
shRNA	Small hairpin RNA
siRNA	Short interfearing ribonucleic acid
SNP	Single nucleotide polymorphism
SDS	Sodium dodecyl sulphate
TBS	Tris buffered saline
TBST	Tris buffered saline with tween 20
TNM	Tumour lymphnode metastasis
UPM	Universiti Putra Malaysia
UVH	University Veterinary Hospital
VEGFR	Vascular endothelial growth factor receptor
VHL	Veterinary Histopathology Laboratory
VLSU	Veterinary laboratory services unit
WHO	World health organization

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CHAPTER 1

INTRODUCTION

Canine mammary gland tumours (CMT) are the most common neoplasia affecting female dogs with a prevalence of 50% of spontaneous tumour development reported in the United States (Kelsey *et al*., 1998; Zuccari *et al*., 2011) and up to 70% prevalence in dogs experimentally exposed to radiation (Benjamin *et al*., 1999). Similarly, a high prevalence with 111 dogs per 10,000 dog-years at risk was recorded in Sweden and 205 cases in 100,000 dogs per year in the United Kingdom have been recorded (Egenvall *et al*., 2005; Dobson *et al*., 2002). In India, a 39.87% prevalence has been reported (Dhami *et al*., 2010), while in South Africa, tumours of the female reproductive system represent 10.2% of total tumours affecting female dogs and mammary gland tumours make up to 80% of the tumours affecting the reproductive system (Bastianello, 1983).

The risk of CMT development is greatly influenced by exposure to ovarian hormones such as oestrogen and progesterone (Queiroga *et al*., 2011). Many studies suggest that the only form of prevention strategy for CMT development is by early spaying of female dogs (Sorenmo *et al*., 2000). Older female dogs (8-11years) have the highest occurrence of CMT, and the condition is rare in dogs that are less than 2 years of age (Sorenmo *et al*., 2011). Pure breed dogs are at a higher risk of developing CMT compared to mixed breeds (Philibert *et al*., 2003) and certain breeds in particular, such as Poodle and German shepherd dogs have been described with a higher risk (Itoh et al., 2005; Sorenmo *et al*., 2011).

Obesity is associated with increased risk of CMT development in dogs; those that are obese at one year of age or a year before CMT development (Philibert *et al*., 2003). The diet fed to dogs may pose a risk, where it has been reported that high intake of beef, pork and a low intake of chicken confers a higher risk of mammary gland tumour development in dogs (Alenza *et al*., 2000).

Typically, the dog with CMT is presented with one or more lumps affecting a single or multiple mammary glands (Mitchell *et al*., 1974). Depending on the stage of the disease, other symptoms such as anorexia, emaciation, pyrexia and symptoms of systemic disease may be evident at presentation (Sorenmo *et al*., 2011)

The diagnosis of CMT starts with history taking, which should include information on signalment, breed, age, neuter status, exposure to exogenous hormones and breeding information (Alenza *et al*., 2000; Sorenmo *et al*., 2011). A complete physical examination is important in determining the tumour size, adhesion to neighbouring tissues, ulceration and presence of other concurrent conditions. Other diagnostic aids include fine needle aspiration (FNA),

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radiographs, computer tomography, histopathology and immunohistochemistry (Cassali *et al*., 2011).

The therapeutic approach to CMT depends on the clinical presentation of the dog and the nature and spread of the tumour. The most common approach involves a lumpectomy or mastectomy followed by a course of chemotherapy with drugs such as doxorubicin, cyclophosphamide and gemcitabine (Cassali *et al*., 2011). Recurrence of tumour is dependent on the extent of advancement of the tumour; recurrence does occur in many of the cases of advanced tumours even after mastectomy and chemotherapy (Rasotto *et al*., 2012). The chances of local recurrence are increased in cases where wide surgical margins were not achieved during mastectomy, which most of the time can be confirmed on histopathology evaluation of ressected tissue margins. Metastasis to the regional lymph nodes or distant tissues, especially to the lungs, contributes to a decrease postsurgical survival in the dogs (Klopfleisch *et al*., 2011).

Histopathologically, several types of CMT have been diagnosed; ranging from benign adenomas to malignant tumours mainly adenocarcinomas, with several other histological subtypes described (Goldschmidt *et al*., 2011). A Tumour histology grading system (Goldschmidt *et al*., 2011) and staging system (Hampe and Misdorp, 1974) can be incorporated in the management of dogs with mammary tumours, where these evaluations can guide veterinarians to choose appropriate treatment strategies based on the known prognosis.

Several molecular markers have also been described for CMT, among which are tumour proliferation markers that can indicate the percentage of tumour cells that are in the proliferative state at a given time. The Ki-67 and proliferating cell nuclear antigen (PCNA) have demonstrated significant value as proliferation markers in CMT and their expression levels in tumour tissues have predicted postsurgical survival in the dogs (Pena *et al*., 1998).

Some molecular markers are expressed specifically at certain parts of the cell and appear to be useful at identifying the various phases of the tumour development and progression. Among others, Vimentin is an intermediate filament that is expressed in neoplastic cells undergoing epitheliomesenchymal transition (EMT) which enables the neoplastic cells of epithelial origin to acquire mesenchymal properties. This property is important for motility and tissue invasion, especially invasion of lymphatic system, endothelial cells of blood vessels and to establish secondary tumours in distant tissues (Wu *et al*., 2006).

Members of receptor tyrosine kinases which have been implicated in tumourigenesis and disease progression of several types of neoplasms especially in human are the fibroblast growth factor receptors (FGFR 1-4). These receptors are crucially involved in embryogenesis and wound healing due to their ability to promote cellular processes such as cell differentiation, proliferation, and survival (Kook *et al*., 2013). Derailed activities of these receptors, mostly as a result of mutations and single nucleotide polymorphisms

(SNP) have been proven to be involved in human neoplasia including breast cancer. Currently there are a few small molecule inhibitors developed as chemotherapeutics at various steps of clinical trials, specifically targeting these receptors in human neoplasms, such as acute myeloid leukaemia and breast cancer (Koziczak *et al*., 2004; Dutt *et al*., 2008; Lamont *et al*., 2011).

Although investigations are still ongoing, so far very little work has been done on canine mammary gland tumours in Malaysia, in terms of knowing the prevalence and risk factors involved in the development of CMT in dogs. It is also very important to examine the expression of some of the molecular markers previously described as prognostic predictors in CMT (PCNA and Vimentin), in the CMT cases diagnosed in Malaysia, and to relate these expressions to the clinicopathological parameters of the dogs. Although the members of the receptor tyrosine kinase mentioned earlier (FGFRs) have been well-investigated and even exploited therapeutically with success in human medicine, no work has been done on CMT to look at their basal expression in tumours and the clinicopathological relevance of the expression, let alone to exploit them as potential therapeutic targets.

The research objectives of the chapters described in this thesis are as follows:
1. To retrospectively determine the prevalence and risk factors of canine mammary gland tumours in dogs diagnosed at a veterinary histopathology laboratory in Malaysia
2. To determine the expression of PCNA and Vimentin in CMT tissues and to determine the clinicopathological relevance of histopathological malignant grade of tumours, PCNA and Vimentin expression in CMT tissues
3. To determine the expression of FGFR2, FGFR3 and FGFR4 in CMT and association of expression with selected histopathological characteristics and clinical factors of the affected dogs

The hypothesis which could be derived from the above mentioned gaps include: CMT is among the common neoplasia diagnosed at the laboratory as compared to other types of neoplasia in the dog where intact female dogs predominates; malignant CMT will be positive for Vimentin expression and have higher number of cells expressing PCNA that could be closely related to their aggressive nature with increased cell proliferation and invasive properties that enable them to metastasize; FGFR2 is highly expressed in various CMT tissues while FGFR3 and FGFR4 may be expressed in a smaller proportion of CMT.

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