



UNIVERSITI PUTRA MALAYSIA

**CLINICOPATHOLOGICAL CHANGES IN ADJUVANT INDUCED
ARTHRITIS IN CANINE STIFLE JOINT**

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**MASTER OF VETERINARY SCIENCE
UNIVERSITI PUTRA MALAYSIA**

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BY

SITI NORHAYATI BT. ISMAIL

**Thesis Submitted in Fulfilment of the Requirement for the Degree of
Master of Veterinary Science in the Faculty of Veterinary Medicine
Universiti Putra Malaysia**

August 2001



Dedicated to,

Mummy and Abah,

For your loves, support and trust,

Along, Cik Yong, Isma and Cici

Thanks for everything...

Abstract of thesis presented to the Senate of Universiti Putra Malaysia in
fulfilment of the requirement for the degree of Master of Veterinary Science

CLINICOPATHOLOGICAL CHANGES IN ADJUVANT INDUCED ARTHRITIS IN CANINE STIFLE JOINT

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August 2001

Chairman : Rashid Ibrahim, Ph.D.

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Osteoarthritis is the most common joint disease and cause of physical disability in man and animals. It is a complex disease with unknown etiology. Intra-articular injection of 1 ml. Freund's adjuvant was inoculated into twenty-five adult Mongrel dogs weighing between 10-15kg. Osteoarthritis was induced in the left stifle joint, while the right joint act as a control. The dogs were evaluated for clinical evidence of joint heat, effusion and pain, and gait abnormalities. Radiographs were obtained for soft tissue swelling, osteophytosis and degenerative changes. At the end of each trial period (week 1, 2, 3, 4, 5) the dogs were euthanised. The left stifle joint were opened, examined grossly and the articular cartilage and synovial membrane were harvested and fixed for histopathologic and electron microscopic studies.



Clinical signs of joint swelling and pain upon palpation, weight bearing lameness and reduced range of motion were observed within week 1 post-inoculation. These signs were positively correlated with the acute pathological lesions in the synovial membrane and articular cartilage; and in radiograph evaluation. Radiograph study revealed evidences of soft tissue swelling, increased intra-articular space, osteophytes formation; the clinical signs that were suggestive of degenerative changes in osteoarthritis. However, plain radiograph was found to be not informative enough in the early stage of osteoarthritis. Gross changes during post mortem revealed, swelling of the adjacent soft tissue, hypertrophy of the joint capsule and synovial membrane, and joint effusion. These were signs of inflammation of the joint tissues and it was believed that the inflammatory process was one of the major factors in the development of degenerative joint disease. Lameness evaluation was positively correlated with gross examination but negatively correlated with radiograph examination.

In histopathology study, there were signs of inflammation in the synovial membrane and formation of synovial pannus, which was thought to be related with the development of degenerative changes on the articular cartilage. Hyperplasia of intima and subintima layer, edema and congestion; flaking and erosion in articular cartilage, were observed as early as week 1 p.i. Under scanning electron microscopy, cartilage fibrillation and erosion, were observed as early as week 1 p.i. Significant positive correlation between the histological changes in articular cartilage with changes in the synovial membrane suggested that changes in the synovium preceded changes in the articular

cartilage. The synovial membrane was highly vascularised, causes respond to injury more promptly. In articular cartilage, it took time to heal since healing depending on the depth of lesion.

In this study, the pathogenesis of osteoarthritis was divided into three stages: the onset phase, which was observed within one week post-induction; the second phase or the intermediate stage and the end phase. Each structure, cells and tissues was found to have their own role in the production of osteoarthritis. Study on the pathogenesis must emphasize on these structures and cascade of events that occur during the production of osteoarthritis, which will aid in the treatment of osteoarthritis. The clinical, morphological and microstructure changes that occurred in osteoarthritis had been characterised, but the role of each in the aetio-pathogenesis of osteoarthritis is still not rigidly defined.

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

**PERUBAHAN PATOLOGI KLINIKAL DI DALAM INDUKSI ARTRITIS
ADJUVAN PADA LUTUT ANJING**

Oleh

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Osteoarthritis adalah penyakit yang selalu menyerang sendi dan menyebabkan ketidakstabilan fizikal dalam manusia dan haiwan. Ia adalah penyakit yang kompleks dan puncanya tidak diketahui. Suntikan intra-rawan sebanyak 1 ml. adjuvan Freund's telah diberikan kepada dua puluh lima ekor anjing Mongrel dewasa yang mempunyai berat 10-15 kg. Osteoarthritis telah dihasilkan di dalam lutut kiri anjing sementara lutut kanan bertindak sebagai kawalan. Anjing tersebut telah dimantau secara klinikal untuk mengesan kehangatan sendi, efusi dan kesakitan, dan ketidaknormalan pergerakan. Radiograf telah diambil untuk mengesan bengkakan tisu, osteopitosis dan perubahan degenerasi. Pada akhir setiap eksperimen (minggu 1, 2, 3, 4 dan 5), anjing-anjing tersebut dimatikan. Lutut kiri anjing-anjing tersebut telah diperiksa secara mata kasar, sampel sendi tulang rawan dan membran sinovial



telah diambil dan diawetkan untuk pemeriksaan histopatologi dan mikroskop elektron.

Tanda-tanda klinikal seperti pembengkakan lutut, kesakitan, ketempangan dan kesukaran pergerakan telah diperhatikan dalam minggu pertama selepas induksi. Tanda-tanda tersebut berhubung kait secara positif dengan lesi patologi akut di dalam membran sinovial dan tulang rawan; dan ujian radiograf. Pemeriksaan radiograf pula menunjukkan tanda-tanda kebengkakan tisu, tekanan tinggi antara rawan sendi, pembentukkan osteopit; adalah tanda-tanda klinikal yang menyokong penghasilan degenerasi dalam osteoarthritis. Namun begitu, gambar radiograf didapati tidak begitu meyakinkan dalam pembentukan awal osteoarthritis. Pemerhatian mata kasar semasa bedah siasat menunjukkan pembengkakan tisu keliling sendi, ketebalan kapsul sendi dan membran sinovial. Tanda-tanda tersebut adalah tanda-tanda inflamasi pada tisu sendi lutut dan dipercayai bahawa proses inflamasi adalah salah satu proses penting dalam pembentukan penyakit degenerasi sendi. Ujian ketempangan berhubung kait secara positif dengan ujian mata kasar, tetapi berhubungkait secara negatif dengan ujian radiograf.

Pemeriksaan histopatologi menunjukkan tanda-tanda inflamasi di dalam membran sinovial dan pembentukkan sinovial panus yang dipercayai mempunyai kaitan dalam pembentukan degenerasi di dalam sendi rawan. Hiperplasia di dalam lapisan sinovial intima dan subintima, edema dan kongesi; kelupasan dan hakisan rawan, kelihatan seawal minggu pertama selepas induksi. Di dalam imbasan mikroskop electron, pada permukaan rawan,

fibrilasi dan kehausan rawan dapat diperhatikan seawal minggu pertama selepas induksi. Hubungkait positif di antara perubahan lesi histologi dan rawan sendi yang didapati di dalam membran sinovial, meyakinkan bahawa pembentukan lesi membran synovial akan menyebabkan pembentukan lesi pada rawan sendi. Membran synovial dipenuhi pembuluh, dan tindakbalas terhadap kecederaan adalah lebih cepat. Bagi rawan sendi pula, ia mengambil masa untuk sembuh dan bergantung kepada kedalaman lesi.

Dalam kajian ini, patogenesis osteoarthritis dapat dibahagikan kepada tiga peringkat; peringkat permulaan, di mana perubahan diperhatikan dalam masa seminggu selepas induksi, peringkat kedua ataupun pertengahan dan peringkat akhir. Setiap struktur, sel dan tisu didapati mempunyai fungsi masing-masing dalam pembentukan osteoarthritis. Kajian mengenai patogenesis mestilah mengambil kira pada setiap struktur dan aliran proses yang berlaku semasa pembentukan osteoarthritis, yang dapat menolong dalam mengubati penyakit osteoarthritis. Perubahan klinikal, morfologi dan mikrostruktur yang berlaku semasa osteoarthritis telah dikaji, namun fungsi setiap satu dalam etio-patogenesis osteoarthritis masih belum dapat diterangkan dengan pasti.

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LIST OF ABBREVIATIONS

%	percent
μm	micrometer
<	Less than
DBKL	Dewan Bandaraya Kuala Lumpur
<i>et al.</i>	And others (Latin: et alii)
H&E	haematoxylin-eosin
HA	Hyaluronic acid
IL-1	interleukin 1
ILT-6	interleukin-6
kg	kilogram
mg/kg	milligram perkilogram
MIA	Sodium monoiodoacetate
ml	mililitre
mm	milimeter
NSAIDs	non-steroidal anti-inflammatory drugs
OA	osteoarthritis
OCD	osteocondritis dissecans
OsO ₄	osmium tetroxide
P	probability
p.i.	Post induction / post inoculation
PG	proteoglycan
PGE ₂	prostaglandin
PSGAG	Polysulphated Glycoaminoglycans
SEM	Scanning electron microscopy
TNF-α	Tumor necrosis factor

CHAPTER 1

INTRODUCTION

1.1 General Introduction

Arthritis in a simple definition is inflammation of the joint. Osteoarthritis, also known as degenerative joint disease is not a single disease or process, but rather the clinical and pathological outcome of a range of disorders (Nuki, 1999) characterized by progressive deterioration of the articular cartilage, synovitis and joint effusion (McIlwraith, 1996).

The purpose of joint is to support the greatest stability to the body during weight bearing and motion. Painless and full range of joint motion are needed for normal ambulation and performance of daily living chores (Leach and Jacobs, 1990). Interruption of normal joint mechanics leads to painful osteoarthritis and physical incapacity thereby reducing an individual's quality of life and increasing the burden on others (Bennet, 1990). Thus, diseases of joint are said to constitute the greatest single cause of disability encountered by the medical profession (McIlwraith, 1996).

Osteoarthritis is one of the most frequently encountered joint diseases in dogs (Bennet, 1984). Developmental diseases such as patella luxation and osteochondrosis of the femoral condyles, and traumatic and degenerative diseases such as rupture of the cranial cruciate ligament or primary degenerative joint disease are seen frequently in small animal practices (Payne and

Constantinescu, 1993). Although the cause of osteoarthritis varies, initial changes in many animals include inflammation of the synovial membranes and joint capsule without cartilage damage (Sherman *et al.*, 1999).

In dogs and cats, osteoarthritis is not idiopathic or primary. It is usually secondary to trauma, unstable joints, mal-alignment or conformation defects, or congenital conditions such as osteochondritis dissecans (OCD) and hip dysplasia (Payne and Constantinescu, 1993). Thus, proper diagnostic and management of joint disease depend on the understanding of basic anatomy and physiology of the musculoskeletal system (McIlwraith, 1996).

1.2 Osteoarthritis Study

Osteoarthritis (OA) or degenerative joint disease is a chronic disease involving cartilage degeneration and pain (Simmons *et al.*, 1999). It is an important orthopedic condition that affects diarthrodial joints and results in high morbidity (Anderson *et al.*, 1993). The most common joint that is affected with osteoarthritis is the stifle joint. In dogs, it has been identified as a common joint disease (Sherman *et al.*, 1999), accounting for approximately 37% of all lameness in this species of animal (Bennet, 1980). In dogs of more than 1-year old, osteoarthritis may affect as many as 20% of the dog (Anderson *et al.*, 1993).

Arthritis in humans and animals is characterised by joint degeneration, which is usually accompanied by intra-articular inflammation. Until recently, most emphasis in arthritis research has been focussed on intra-articular events