UNIVERSITI PUTRA MALAYSIA

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By

ABDINASIR YUSUF OSMAN

Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfillment of the Requirements for the Degree of Master of Veterinary Science

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Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfillment of the required for the Degree of Master of Veterinary Science

PREVALENCE OF CASEOUS LYMPHADENITIS IN SHEEP AND GOATS IN EAST COAST OF PENINSULAR MALAYSIA AND ITS PATHOGENESIS IN A MOUSE MODEL

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Chairman: Prof. Dr. Hj. Abdul Aziz B Saharee, PhD

Faculty: Faculty of Veterinary Medicine

A cross-sectional study was conducted in Peninsular Malaysia with the objectives of determining the serological evidence and the management practices that could be associated with CLA distribution among sheep and goats in different geographical regions. The etiopathogenesis of CLA was also studied with the objectives of describing the clinical, pathological,hematological and biochemical alterations following intraperitoneal exposure of mice to whole bacterium and exotoxin extracted from *C.pseudotuberculosis*.

In the coss-sectional study,all farmers had semi-extensive rearing system;27.6% (13/47) of farmers had periodical veterinary services; 10.6% (5/47) took note of animals with clinical signs of CLA; 14.8% (7/47) were aware of the zoonotic

potential of this disease. It was apparent that lack of sanitary measures and epidemiological studies led to the dissemination of this disease in Malaysia.

A total of 422 animals from 15 small ruminant farms (sheep and goats) in four states of East Coast of Peninsular Malaysia were screened during the period from January to April 2011.Agar gel precipitation test (AGPT) was conducted on serum samples collected from the animals. Forty seven samples out of 422 were positivefor CLA using AGPT test. The frequency of CLA infections was estimated at 11.1%. Management practices were analyzed through questionnaire. 224 mice, 2-3 weeks of old, were selected and divided into three groups, namely control, whole bacterium and exotoxin groups. Mice of the whole bacteriumgroup were exposed intraperitoneally to 1 ml of the inoculums containing 10^9colony-forming unit (CFU)/ml of live *C. pseudotuberculosis.* The exotoxingroup wasinjected intraperitoneally with a single dose of exotoxin extracted from *C.pseudotuberculosis*. The control group wasexposed intraperitoneally to 1 ml of phosphate buffered saline (PBS). The groups of exotoxin treated and whole bacterium challenged (*C. pseudotuberculosis*) showed prominent clinical signs that were characteristic of CLA, which included depression, anorexia, submandibular oedema, yellowish and bloody diarrhea, ruffledcoat, eye discharges, poorer general condition, and occasionally partial tremor of hindquarters. In necropsy, visceral abscess was the condition recorded

in whole bacterium and exotoxin groups. There were also congestion and hemorrhages in the lungs, liver, spleen, kidney and intestine.

Microscopically, there were lesions in the form of tuberculous granuloma (caseating tubercule), giant cells, infiltration of neutrophils and macrophages, degeneration, vacuolation (necrosis), haemorrhage, and microabscesses.Hematologically, there were significant decrease in Hb, thrombocytes count, and significant increase in WBC, neutrophils, monocytes counts in the infected group. There were also highly significant increases in the mean levels of CK,AST,ALP,and ALT. Phosphorus concentrations in the infected group were significant ($p<0.05$)compared to the control group.In the exotoxin and whole bacterium challenged groups, the concentrations of Serum Amyloid A (SAA), Haptogolbin (Hp), and α-1 Acid glycoprotein were significantly higher than in the healthy mice (control group).

This study shows thatlittle attention has been given to this devastating disease (CLA) and its economic importance allowing existence of endemic nature of the disease in this country. In addition, the present study also indicates that *C.pseudotuberculosis* causes disturbances which leadto severe damages in visceral organs.

Further epidemiological studies using reliable diagnostic tools, application of appropriate management practices, and extensive studies on blood picture and plasma proteins need to be carried out to eradicate this disease.

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

PREVALENS PENYAKIT BISUL NODUS LIMFA PADA BIRI-BIRI DAN KAMBING DI PANTAI TIMUR SEMENANJUNG MALAYSIA DAN PATOGENESISNYA DALAM TIKUS SEBAGAI MODEL

Oleh

ABDINASIR YUSUF OSMAN

Ogos 2012

Pengerusi : Prof. Dr. Hj. Abdul Aziz B Saharee, PhD

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Satu kajian keratan rentas telah dijalankan di Semenanjung Malaysia dengan objektifuntuk mengenalpasti pembuktian serologi dan amalan pengurusan yang boleh dikaitkan dengan kejadian panyakit bisul nodus limfa (CLA) dikawasan geografi yang berbeza.Etiopatogenesis CLA juga telah dikaji dengan objektif untuk menerangkan perubahan kepada tanda klinikal, patologi, hematologi dan biokimia berikutan suntikan melalui intraperitoneum pada tikus menggunakan seluruh bakteria dan eksotoksin yang diekstrak daripada*C.pseudotuberculosis.*

Dalam kajian rentas , semua penternak mempunyai sistem penternakan secara separa ekstensif; 27.6% (13/47) petani mendapat perkhidmatan veterinar secara

berkala; 10.6% (5/47) telah mengambil perhatian terhadap haiwan yang menunjukkan tanda-tanda klinikal CLA; 14.8% (7/47) menyedari potensi CLA sebagai penyakit zoonotik. Kekurangan langkah-langkah sanitari dan kajian epidemiologi telah membawa kepada penyebaran penyakit ini di Malaysia.

Sebanyak 422 ternakan (n = 422) daripada 15 ladang ruminan kecil (kambing biri-biri dan kambing) di empat negeri di Pantai Timur Semenanjung Malaysia telah disaring dalam tempoh daripada Januari 2011 hingga April 2011.Ujian agar gel pemendakan (AGPT) telah dijalankan ke atas sampel darah yang diambil daripada ternakan tersebut. Sebanyak empat puluh tujuh sampel daripada 422 adalah positif CLAdengan kaedah AGPT. Kekerapan jangkitan CLA dianggarkan pada 11.1%.Amalan pengurusan dianalisis dengan menggunakan kaedah soal selidik.Sebanyak 224 tikus, berumur 2-3 minggu, telah dipilih dan dibahagikan kepada tiga kumpulan, iaitu kumpulankawalan, kumpulan keseluruhan sel dan kumpulan eksotoksin.Tikus kumpulan keseluruhan sel telah disuntik secaraintraperitoneum dengan 1 ml inokulum yang mengandungi 10^9 unit pembentuk koloni (CFU) / ml *C. pseudotuberculosis*.Kumpulan eksotoksin telah disuntiksecara intraperitoneum dengan satu dos eksotoksin yang diekstrak daripada *C. pseudotuberculosis*.Kumpulan kawalan telah disuntik secara intraperitoneum dengan 1 ml PBS. Kumpulan eksotoksin dankeseluruhan sel *C. pesudotuberculosis* menunjukkan tanda-tanda klinikal yang jelas terhadap CLA,

iaitu kemurungan, anoreksia,edemasubmandibular, cirit-birit berdarah dan kekuningan, bulu kusam, lelehan pada mata, keadaan badan yang kurus, dan tikus menggigil. Pada kajian nekropsi, organ dalamdidapati bernanah pada kumpulankeseluruhan sel dan eksotoksin.Terdapat juga kongesti dan pendarahan di peparu, hati, limpa, buah pinggang dan usus.

Pemeriksaanmikroskospi, menunjukkan, lesi dalam bentukgranuloma tuberkulos (caseating tubercule), sel-sel gergasi, penyusupan neutrofil dan makrofaj, degenerasi, vaculasi (nekrosis), pendarahan, dan bintik nanah.Kajian hematologi pula menunjukkan terdapat penurunan yang signifikan dalam Hb dan kiraan trombosit yang signifikan dan peningkatan yang ketara bagi sel darah putih, neutrofil, kiraan monositdalam kumpulan yang dijangkiti.Terdapat juga peningkatan yang amat ketara ke atas nilai purata CK, AST, ALP, dan ALT. Kepekatan fosforus dalam kumpulan yang dijangkiti adalah signifikan berbanding dengan kumpulan kawalan ($p< 0.05$).

Dalam kumpulan eksotoksin dan keseluruhan sel,terdapat kepekatan Serum amailoid A (SAA), Haptogolbin (Hp), dan α-1 asid Glikoprotein yang jauh lebih tinggi daripada tikus yang sihat.

Kajian ini telah menunjukkan bahawa perhatian tidak diberi kepada penyakit yang serius ini (CLA) yang mempunyai kepentingan ekonomi sehingga

menyebabkanpenyakit ini wujud secara endemik di negara ini. Di samping itu, kajian ini juga menunjukkan bahawa *C. pseudotuberculosis* menyebabkan gangguan dan kerosakan teruk pada organ dalaman.

Kajian epidemiologi yang menyeluruh dengan menggunakan alat diagnostik yang sesuai,penerapanamalan pengurusan yang sesuai, dan kajian yang menyeluruh pada sel darah dan protein plasma perlu dijalankan bagi membasmi penyakit ini.

DEDICATION

To my late father ''May Allah blesshim with his supreme benevolence''.

To my caring, lovely mother and father who have shown me the way to the right path.

To my sister, brothers and all those who passed away in struggle for sovereignty of my fatherland.

To my patient and bleeding country, may Allah grant you peace.

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Life is changing to most people and success is measured in many ways. I have always believed that you should challenge yourself everyday and strive to achieve success, or at least satisfaction, through undergoing each challenge with a balance of knowledge and ability while maintaining sanity. The tools needed to face challenges have been gained through the help, advice and leadership of many people. This belief was imposed upon me, not in words but actions, first by my parents and secondly by counselors and instructors.

First I would like to thank Almighty Allah by the number of my heart beats, this dissertation would not have been completed without the support and his spiritual guidance and for blessing me with all those wonderful people whom I have met.

I would like to express my gratitude to my supervisor Prof. Dr.Hj. Abdul Aziz Saharee, who has been very helpful in my research. I thank him for his kindness and willingness to help. The opportunities that Prof. Dr.Hj.Abdul Aziz Saharee, Prof. Dr. Jasni Sabri,Dr.Faez Firdaus Jesse, gave me in joining the Laboratory of clinical studies at Universiti Putra Malaysia allow me to pursue my interest in CLA research. While conducting the studies, I really appreciated the great comments and suggestions fromProf. Dr. Jasni bin Sabri, Assoc.Prof. Dr. Siti Khairani binti Bejo and Dr. Faez Firdaus Jesse bin Abdullah who always provided support and guidance. I would also like to express my gratitude to

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Finally, my deep thanks go to my family whom without them this thesis migh not have been written,and to whom I am greatly indebted.

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Thanks to my dear Uncle, Adam Osman Ali, brothers; Elmi Yusuf Osman, and Aamir Elmi Ali and my lovely sister, Haweya Yusuf Osman. Thank you for your endless love and support,this dissertation is dedicated to them.

I certify that a thesis examination committee has met on 7 August 2012 to conduct the final examination of Abdinasir Yusuf Osman on his thesis entitled "Prevalence of Caseous Lymphadenitis in sheep and goats in East Coast of Peninsular Malaysia and its pathogenesis in a mouse model''. In accordance with the Universities and University College Act 1971 and the Constitution of the Universiti Putra Malaysia [P.U. (A) 106] 15 March 1998. The committee recommends that the student be awarded the degree of Master of Veterinary Science.

Members of the Examination Committee were as follows:

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This thesis was submitted to the Senate of Universiti Putra Malaysia and has been accepted as fulfillment of the requirement for the degree of Master of Veterinary Science.The members of the Supervisory Committee were as follows:

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DECLARATION

I hereby declare that the thesis is my original work except for quotation and citations which have been duly acknowledged. I also declare that it has not been previously, and is not concurrently, submitted for any other degree at Universiti Putra Malaysia or at any other institution.

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DR. ABDINASIR YUSUF OSMAN ALI

Date:

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

%	Percentage
µg	Microgram
µl	Microlitre
A:G	Ratio of albumin and globulin
AGP	Agar gel precipitation test
AHI	Anti-haemolysin- inhibition
Alb	Albumin
ALP	Alkaline phosphatase
ALT	Alanine transaminase
APD	Average pore diameter
APP	Acute phase proteins
APTT	Activated partial thromboplastin time
AST	Aspartate transaminase
$CaCL_2$ $2H_2O$	Dihydarte Calcium Chloride
CAMP	Christie Atkins Munch-Petersen
$CHOH.COONH_4$	Syrupy Ammonium lactate
CK	Creatine kinase
Cl	Chloride
CLA	Caseous lymphadenitis
Cm	Centimeter
Cp	Caeruloplasmin
CRP	C-reactive protein
D.Bill	Direct bilirubin
ddH_20	Distilled water
Dl	Deciliter
DVS	Department of Veterinary Services
ECER	East Coast Economic Regions
ELISA	Enzyme-linked immunosorbent assay
Fb	Fibrinogen
Fig	Figure
GFR	Glomerular filtration rate
GGT	Gamma-glutamyl transpeptidase
Glob	Globulin
H	Hour
Hb	Haemoglobin
Hp	Haptoglobin
I/P	Intraperitoneal
IFN	Interferon
J	Johor

K	Kelantan
K	Potassium
K_2HPO_4	Anhydrous Dipotassium hydrogen Orthophosphate
KH_2PO_4	Anhydrous Potassium dihydrogen Orthophosphate
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
Mg	Milligram
$MgSo_4*7H_2O$	Hepatahydate magnesium sulphate
Min	Minutes
Ml	Millilitre
N	Number of animals
Na	Sodium
NaCl	Sodium chloride
^oC	Degree Celsius
OD	Optical density
P	Pahang
PBS	Phosphate buffered saline
PCR	Polymerase chain reaction
PCV	Packed cell volume
pH	Hydrogen ion exponent
Phos	Phosphate
Pi	Post infection
PLD	Phospholipase D
PT	Prothrombin time
RBC	Total erythrocyte count
RES	Reticulo endothelial system
Rpm	Revolution per minute
SAA	Serum amyloid A
SD	Standard deviation
SDS	Sodium dodecyl sulphate
SDS-PAGE	Sodium dodcyl sulphate-polyacrilamide gel electrophoresis
SPF	Specific pathogen free
SPSS	Statistical program for social science
T	Terengganu
T.Bill	Total bilirubin
TEMED	Tetramethylethylenediamine
Tf	Transferrin
Thr	Thrombocytes
TPU	Taman Pertaninan University
U	Unit
UK	United Kingdom

UMK	Universiti Malaysia Kelantan
UPM	Universiti Putra Malaysia
USA	United States of America
V	Volt
v/v	Volume per volume
VRI	Veterinary Research Institute
WBC	White blood cells
α 1AGP	Alpha1 Acid Glycoprotein

CHAPTER 1

INTRODUCTION

Corynebacterium pseudotuberculosis is a causative agent of chronic infections in a number of different mammalian species, the most significant of which is caseous lymphadenitis (CLA) or cheesy gland, a chronic granulomatous infectious disease of sheep and goats that is characterized by abscessation of one or more lymph nodes.The organism was first isolated from a case of lymphangitis in a cow in 1888 by French bacteriologist Edward Nocard (Nocard,1896). Years later, another bacteriologist, Hugo von Preïsz, isolated analogous organism from a different case (Preïsz and Guinard, 1891).

In Malaysia, the first condition of CLA was detected in imported sheep during meat inspection at the Johor Bahru abattoir in 1960 (http://agrolink.moa.my/jph). A decade later, another case of CLA infected was reported when the organismisolated from a goat at theVeterinary Research Institute, Ipoh (VRI). One year later, however, the microorganism was isolated from an ovine case.

CLA is distributed globally and causes important economic losses for ovine and caprine breeders due to loss of body condition (wasting), subsequently reduced meat, wool, milk yields, segregation of affected animals and condemnation of

downgraded of affected carcasses and skins in abattoirs(Stoops *et al.,* 1984; Pacheco *et al*., 2007). It most commonly causes CLA in sheep and goats and, less commonly, pneumonia, hepatitis,mastitis, arthritis, orchitis, subcutaneous abscess, abortion, still birth and prenatal mortalities and mastitis in cattle and buffaloes (Kathleen*et al.*, 2007).

In Malaysian small ruminants,the average prevalence of CLA, was found to be 30% using two (AGPT and ElISA) combined diagnostics tests (Komala *et al.,*2008).In Australia, the average prevalence of CLA in adult sheep was reported to be 58%in 1973 and 53% in1984 (Batey, 1986a). In USA, particularly Western parts suggested that the average disease prevalence amongst adult ewes was around 42.5% (Stoops*et al.,*1984).Numbers of serological tests have been suggested to detect the evidence of CLA infection in animals; these include synergistic haemolysis-inhibition test (Brown *et al.,* 1987), a complement fixation test (Shigidi, 1979),*C.pseudotuberculosis* phospholipase D (PLD) antigen based ELISA (Dercksen *et al.,* 2000) and micro agglutination assay (Menzies and Muckle, 1989).Even though these tests might be considered as a fundamental point for revealing of subclinically infected animals, most of them have disadvantages, such as low sensitivity, poor specificity and lack of ability to differentiate between previously exposed animals and those still harboring the pathogen. The debate, therefore, remains whether such procedures should be engaged to current culling programs (Pacheco *et al.,* 2007).

The mode of transmission of *C.pseudotuberculosis* is not known for certain; however, the pathogen will definitely be released due to rupture of external or internal abscesses; the subsequent contamination of skin scratches, such as those caused by shearing, and fighting injuries with purulent material has been suggested as the core reason of transmission. Nevertheless, an erogenous spread has also been considered (Kaba *et al*., 2001).

CLA eradication is challenging due to the inefficacy of antimicrobial treatment (Piontkowski and Shivvers, 1998; Stanford *et al*., 1998; Williamson, 2001). The most important and consistent way of controlling this disease encompasses vaccination of animals, and detection and removing of infected animals (Pacheco *et al.,* 2007). However, this approach is hindered by limitations in recent diagnostic techniques (Pacheco *et al*., 2007).

Due to that reason, this study was conducted to look for better ways of detecting subclinical cases. Therefore, application of acute phase proteins (APP) as veterinary diagnostic method can be considered as one of the screening method for CLA disease infection. The proper identification of the disease is based principally upon clinical signs, and isolation of the agent from discharging abscesses. Identification of the cultured organisms as *C.pseudotuberculosis* is often accomplished by biochemical tests but is usually problematic due to extensive variability in biochemical characteristics of the pathogen (Cetinkaya *et al*., 2002).Little is known about CLA pathogenesis in experimental animals

particularly mouse model. Therefore, study of pathogenesis was carried out to obtain more information about the disease in these models. Furthermore, there are also very few reports of serological studies in small ruminants. Sero-epidimiological studies, therefore, have been conducted to assess the seroprevalence of infection with *C. pseudotuberculosis* in small ruminant flocks in four Malaysian states; namely Kelantan, Terengganu, Pahang, and Johor. This also assessed the producer's knowledge of CLA, the source of application of this knowledge and sought information about management factors on the farms associated with prevalence of CLA.

The objectives of this study were to:

1. To determine the seroprevalence of caseous lymphadenitis in the East Coast of Peninsular Malaysia.
2. To compare the clinical signs shown in mice following inoculation of live and exotoxin of *C.pseudotuberculosis.*
3. To determine and compare the changes in blood parameters of mice following infection by whole bacterium or by exotoxin of *C.pseudotuberculosis.*
4. To compare the cellular changes associated with infection by exotoxin and whole bacterium of *C.pseudotuberculosis.*

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