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Malignant Ovine Theileriosis (*Theileria lestoquardi*): A Review

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Abstract

Malignant Ovine Theileriosis (MOT) is a tick borne disease of sheep and goats, caused by *Theileria lestoquardi* and is considered a major constraint for sheep production in many areas of the world. It has been reported to infect lymphocytes *in vivo* and *in vitro* and the schizonts differentiate into macro-schizonts and micro-schizonts. To date, little is known about the mechanisms involved in the disease pathogenesis, but its high mortality is likely to be linked to the ability of *T. lestoquardi* to stimulate uncontrolled proliferation of the infected leukocyte. Consequently, severe tissue destruction and pulmonary oedema leading to respiratory failure are thought to be the cause of death. Despite an immense amount of small ruminant research, MOT remains an important disease of sheep and goats. Therefore, the present review outlines the current knowledge covering *T. lestoquardi* transmission, distribution, pathogenesis, diagnosis and control. The information may assist in filling the gaps in our knowledge about the economic impact of the disease and new research initiatives. We conclude that the development of a simple, affordable and applicable diagnostic test for an early detection at the field level, and the production of an effective vaccine could have a significant impact on the control of the disease.

Keywords: Malignant Ovine Theileriosis, *Theileria lestoquardi*, Distribution, Pathogenesis, Diagnosis, Control, Economic impact.

1. General Introduction

Malignant Ovine Theileriosis (MOT) or Malignant Small Ruminant Theileriosis (Smith and Sherman, 2011) is a parasitic disease of sheep, caused by *Theileria lestoquardi* and mainly transmitted by *Hyalomma anatolicum*. Sheep are considered a very receptive host for *T. lestoquardi*, as infection usually evolves into sub-acute and acute theileriosis even in indigenous sheep (Tageldin *et al*., 1992; El Hussein *et al*., 1998; Tageldin *et al*, 2005; El Imam *et al*., 2015). Globally, high morbidity and mortality rates have been reported in Iran (Hooshmand-Rad, 1977), Sudan (Salih *et al*., 2003; El Imam *et al*., 2015), and in Sultanate of Oman (Tageldin *et al*., 2005). Sheep from disease-free zones suffer high morbidity when introduced to endemic areas and significant mortality rates are expected (El Imam *et al*., 2015). Consequently, the improvement of livestock production in these zones is severely hampered. Accordingly, the disease is of high economic importance, especially in Sudan where export of sheep and sheep products are a major component of their national economy (El Imam *et al*., 2015). Despite the importance of the disease, there is a considerable lack of knowledge about many aspect of host-parasite relationship and breed susceptibility (Leemans *et al*., 1999 a,b).

2. Taxonomy

Species identification using DNA sequences is the basis for DNA taxonomy. Recently, molecular markers, such as the Major Piroplasma Surface Protein (MPSP), small subunit ribosomal RNA gene (18S), and rRNA internal transcribed spacer region (ITS), have been used in the phylogenetic analysis of *Theileria* spp. (Chae, *et al*., 1999; Gubbels *et al*., 2000; Gou *et al*., 2013). Nonetheless, the exact taxonomic *Theileria* spp. have been difficult to establish and are the subject of a considerable debate (Gubbels *et al*., 2002).

3. Life Cycle

In general, the majority of protozoan parasite life cycles are of a complex and dynamic nature (Mans *et al*., 2015). The parasites have a typical apicomplexan lifecycle involving several differentiation steps, interspersed with phases of proliferation in the mammalian hosts and the vector tick. The detailed *Theileria* life cycle has been reviewed (Shaw, 2003; Uilenberg, 2006; McKeever, 2009; Mans *et al*., 2015). Specific *Theileria* spp. are transmitted by specific tick species; however, the distribution of a particular *Theileria* spp. is directly related to the distribution range of its vector tick(s).

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4. Transmission

T. lestoquardi is transmitted from tick's stage to stage through *Hyalomma anatolicum* (Taha and El Hussein, 2010; Abdigoudarzi, 2013), *H. impeltatum* (El-Azazy *et al.*, 2001), *H. excavatum* (Hashemi-Fesharki, 1997), *H. detritum* (Abdigoudarzi, 2013), *Rhipicephalus sanguineus* (Razmi *et al.*, 2003) *R. turanicus* (Abdigoudarzi, 2013) and through vertical transmission (Zakian *et al.*, 2014).

5. Distribution

Historically, the disease was first described in 1914 by an Egyptian veterinary inspector from two Sudanese sheep exported to Egypt. Later, it was reported in Iraq (Latif *et al.*, 1977), India (Sisodia, 1981), Sudan (El Ghali *et al*., 1995), Turkey (Sayin *et al.*, 1997), Iran (Spitalska *et al.*, 2005), Saudi Arabia (El-Azazy *et al.*, 2001) and in Sultanate of Oman (Shayan *et al.*, 2011; Tageldin *et al.*, 2005). Surprisingly, it has not been reported in Jordan (Sherkov *et al*., 1977) or Israel (Pipano, 1991). Thus, more accurate and precise data are needed on the geographic distribution of the disease.

6. Pathogenesis

The disease is highly pathogenic to sheep (Leemans *et al.*, 1999 a,b; Tageldin *et al.*, 2005) and goats (Taha *et al.*, 2011). Even in indigenous sheep breeds, high morbidity and mortality rates were reported (El Hussein *et al.*, 1998; El Imam *et al.*, 2015). So far, little has been known about the mechanisms involved in the pathogenesis of *T. lestoquardi* infection (Leemans *et al.*, 2001). The pronounced pathology and high mortality are likely to be linked to the ability of *T. lestoquardi* schizonts to stimulate uncontrolled proliferation of the infected leukocyte inducing a phenotype typical of tumor cells (von Schubert *et al.*, 2010). Although these cellular transformation is known to be reversible and dependent on a viable parasite (Dobbelaere and Heussler, 1999) the parasitized cells acquire the capacity to metastasize and multiply in non-lymphoid as well as lymphoid tissues (Dobbelaere and Kuenzi, 2004; Shiels *et al*., 2006; Luder *et al.*, 2009). *T. lestoquardi* appears to transform mainly major histocompatibility complex class II-positive cells (Ahmed *et al.*, 1999; Preston *et al*., 1999) and production of a number of cytokine which may induce fever and play a role in anaemia, muscle wasting and necrosis (Dobbelaere and Heussler, 1999, Ahmed *et al.*, 1999, 2002). The mechanism employed by the *Theileria* parasite to regulate the bovine host cell is studied (Dobbelaere and Kuenzi 2004; Dessauge *et al.*, 2005; Shiels *et al.*, 2006; Dobbelaere and Baumgartner, 2009) but there is still a considerable lack of detailed knowledge regarding the ovine cells.

The hepatization and rubbery texture of the lungs and accumulation of excessive fluids and exudates in the chest cavity were reported (Tageldin *et al.*, 2005); these fluids may impair the host respiration (El Imam, 2010). Serious tissue destruction and pulmonary oedema indicate that emphysema, congestion and collapse (Plate 1) lead to a respiratory failure and provide clinical signs for sheep suffering from acute *T. lestoquardi* infection (Tageldin *et al.*, 2005). The slight distention of the gall bladder together with green bile (Plate 2) may also indicate acute *T. lestoquardi* infection (El imam 2010).

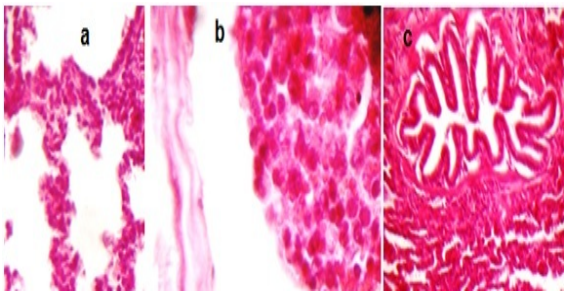

Plate 1. Photomicrograph of lung section showing (a) congestion, (b) emphysema and (d) collapse (H & E stain X100).

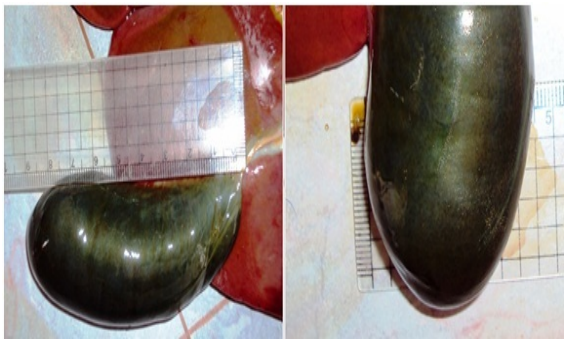

Plate 2. Photograph of distended gall bladder in *T. lestoquardi* infected sheep (a) length, (b) width.

7. Clinical Signs

The most prominent clinical signs of *T. lestoquardi* infections include generalized enlargement of the superficial lymph nodes (Plate 3.), high fever, listlessness, anorexia, emaciation, intermittent diarrhoea or constipation and loss of condition (Leemans *et al.*, 1999a; Tageldin *et al.*, 2005). Initially, infected animals have an apparently normal appetite, but in a few days after the onset of fever they cease eating and later on they become progressively emaciated (El Imam *et al.*, 2015). In fact, elevation of body temperature or fever is associated with many disease states since the hypothalamus is the control center for thermal regulation. Chemical (pyrogens) are released from body tissues and fluids when either or both are injured may influence and alter the hypothalamus function. Fever is the result of either cytokine receptor or Toll-Like Receptor (TLR) triggering; in autoimmune diseases, fever is mostly cytokine mediated whereas both cytokine and TLR account for fever during infection (Dinarello, 2004).

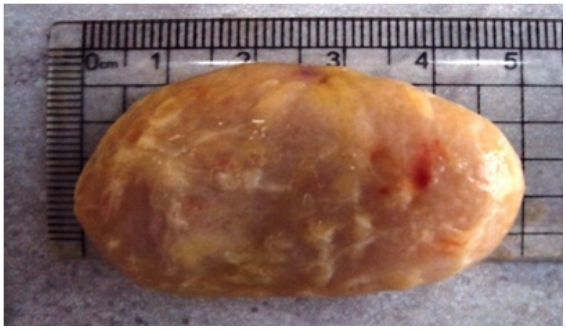

Plate 3. Photograph of enlarged superficial lymph node in *T. lestoquardi* infected sheep. However, the detailed explanation of mechanisms that cause fever in *T. lestoquardi* infections awaits full elucidation.

Sheep infected with *T. lestoquardi* also display anaemia due to erythrocyte destruction (Nazifi *et al*., 2011, 2012; El Imam *et al.,* 2015), but the precise cause of the anaemia is still unknown. Many studies have tried to clarify the mechanisms involved in the development of anaemia (Shiono, *et al.,* 2004; Nazifi *et al.,* 2011). Morphological changes to the surface of the RBC, an increase in osmotic fragility (Yagi *et al.,* 1989), abnormal RBC clearance (Yagi *et al.,* 1991), changes in membrane glycolipid components (Watarai *et al.,* 1995) and oxidative injuries (Shiono *et al*., 2001, 2003; Yagi *et al.,* 2002; Nazifi *et al.,* 2011) take place. In addition, an accelerated destruction of RBC in anaemic sheep could be attributed to the binding of autoantibody (IgG) to parasitized RBC that results in phagocytosis (Shiono *et al*., 2004). A marked fall in WBCs resulting in leukopenia that lasts for several days, and a fall in blood PCV and Hb are often reported (Nazifi *et al.,* 2012, Elsadig *et al.,* 2013, El Imam *et al.,* 2015).

8. Immune Responses

Little is known about the mechanisms involved in the protective immune response against *T. lestoquardi* (Leemans *et al.,* 2001) or the susceptibility of the various ovine breeds (Uilenberg, 1997). *T. lestoquardi* infects the monocytes/macrophages and B cells (Leemans, *et al.,* 2001). It is known that animals that survive infection are resistant to further challenge and indigenous sheep and goats usually acquire immunity at an early age (Hooshmand-Rad, 1985). Comparatively, goats show a greater resistance to the infection than sheep (Brown *et al.,* 1998) despite the fact that indigenous sheep in *T. lestoquardi* endemic areas have a strong natural resistance or tolerance to the disease. The mechanisms of this apparent breed resistance are unknown (El Imam *et al.,* 2015). Experience gained from defining the response to bovine *Theileria* should be useful for addressing this knowledge gap in small ruminants. However, specific studies mapping the small ruminant response against *Theileria* are required and may help to understand the immune responses to other tick borne disease.

9. Diagnosis

Routine field diagnosis of *T. lestoquardi* infection is usually based on a combination of host specificity, transmission mode, adult tick species, epidemiololgical data, clinical signs and pathological findings together with morphological demonstration of the parasite, ideally the macroschizont infected leukocyte. In the last decade, a considerable progress has been achieved in the development of diagnostic tests for tick and tick borne-diseases in general, but the high cost and technological requirements limit the routine field application (Minjauw and McLeod, 2003).

9.1. Microscopic Examinations

The direct method involves identifying the parasite in Giemsa's-stained blood smears (Plate 4) or lymph-node biopsy samples (Plate 5). The method is reliable for diagnosing clinical acute cases, but it is very subjective in pre-immunity and/or long-lasting carrier hosts, where low parasitaemia occur and schizont infected leukocytes cannot be detected. Thus, a level of expertise is required for differentiating mixed *Theileria* spp. infection on the basis of morphology (d'Oliveira *et al.,* 1995; Garcia-Sanmartin *et al.,* 2006). To overcome this problem, a number of serological tests for species-specific detection allowing have been developed.

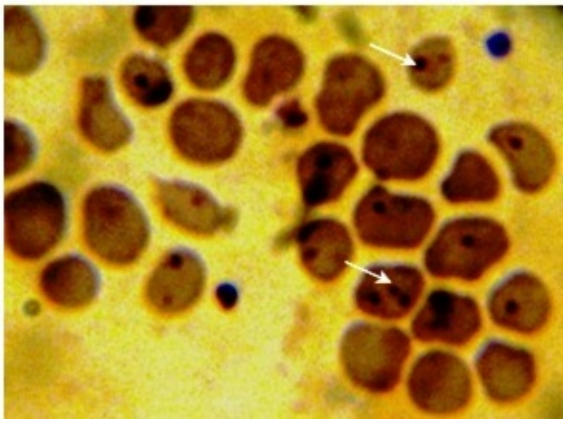

Plate 4. Photomicrograph of peripheral blood smear showing *T. lestoquardi* piroplasms infecting red blood cells (Giemsa's stain X100).

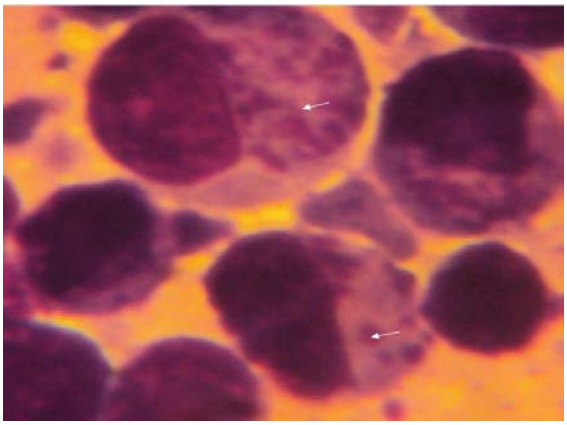

Plate 5. Photomicrograph of lymph node smear showing *T. lestoquardi* schizonts (arrow) infecting lymphocytes (Giemsa's stain X100).

9.2. Serology

Serological diagnostic tools for the major tick-borne protozoan diseases of livestock were reviewed (Bakheit *et al.,* 2007). Antibody detection tests, commonly used in

identification of *T. lestoquardi*, are the Indirect Fluorescent Antibody (IFA) test and the enzyme-linked immunosorbent assay (ELISA). Tests based on antibody detection can be of a little value for the diagnosis of an acute disease since the clinical signs of *T. lestoquardi*, as with other pathogenic *Theileria*, appear before antibodies can be detected. In addition, maternal immunity can produce false positive results. Furthermore, a lack of antibodies in carrier sera may result in long-term infection (Leemans *et al*., 1999a). *T. lestoquardi* and *T. annulata* exhibit astonishing similarities with regard to serology, thus the differential diagnosis between these species is subjective without the use of species specific reagents.

9.2.1. Indirect Fluorescent Antibody Test

The Indirect Fluorescent Antibody Test (IFAT) based on schizont or piroplasms antigen to detect the circulating antibodies against *T. lestoquardi* has been developed (Leemands *et al.,* 1997; Salih *et al.,* 2003; Taha *et al.,* 2003). In Sudan, we subjected lung impression smears during different courses of the disease to IFAT for further demonstration of *T. lestoquardi* schizont infected cell sequestrations in the pulmonary bed. The result of this was that crude antigens derived from in vivo gave clear and bright fluorescence emitted from intracellular schizonts (Plate 6). Our findings could have application significance in diagnosis and developing strategies for therapeutic attack on the parasite (A.H. El Imam and K.M. Taha: unpublished data). However, limitations of IFAT hinder the routine use at large scale epidemiological investigations where a high number of samples required to be screened. These limitations are mainly due to time constrains, the absence of a means of standardization and cross-reactivity with antibodies against other *Theileria* spp. that simultaneously infect sheep (Leemans *et al*., 1997).

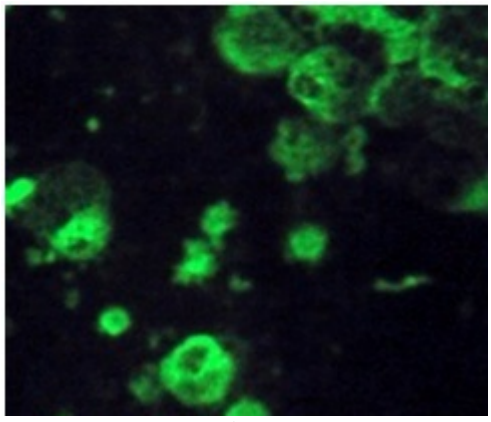

Plate 6. Photomicrograph of a lung impression smear showing massive T. *lestoquardi* schizonts sequestrations in the pulmonary bed (IFA test stain X100).

9.2.2. Enzyme-Linked Immunosorbent Assay

The Enzyme-Linked Immunosorbent Assay (ELISA) for serological detection of antibodies against *Theileria* spp. infecting sheep have been documented (Gao *et al*., 2002; Miranda *et al*. 2006; Abdo, 2010). Recently, a newly developed and characterized recombinant protein-based ELISA has been validated to resolve the problems associated with ELISA diagnosis of *T. lestoquardi* (Bakheit *et al*., 2006 a- c). Thus, it may be very useful and applicable for future epidemiological investigation of ovine theileriosis.

9.3. Molecular Based Tests

Advances in molecular biology have enabled identification and classification of several pathogens including *Theileria/Babesia* (Caccio *et al.,* 2000), *Ehrlichia/Anaplasma* (Arens *et al.,* 2003) and Rickettsia group (Christova *et al.,* 2003) at the genotypic level.

9.3.1. Polymerase Chain Reaction

The conventional Polymerase Chain Reaction (PCR) is more sensitive and specific (Figure 1) (A.H. El Imam and K.M. Taha: unpublished data) than other conventional methods (Almeria *et al.,* 2001) and is commonly used to detect ovine theileriosis (Aktas *et al.,* 2005; Altay *et al*., 2008) but it is subjective in mixed infections (Pin *et al*., 2005).

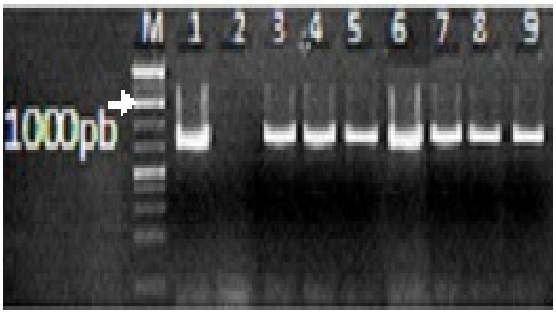

Figure 1. *T. lestoquardi* detected by PCR using *T. lestoquardi* specific primers. Captions: Lane $_{M,}$ standard size marker, L_1 positive control, L_2 negative control, L_{3-9} test samples.

9.3.2. Reverse Line Blot

Reverse Line Blot (RLB) assay was developed for simultaneous specific detection of different piroplasm species (Gubbels *et al.,* 1999). The assay is based on amplification of a fragment of the 18S, 16S ribosomal DNA from virtually all species of *Theileria/Babesia* and of *Ehrlichia* respectively (Schnittger *et al.,* 2004). The advantages of this diagnostic method are its reliability, sensitivity and specificity for the identification of different sheep tick-borne diseases. The RLB assay is a powerful tool and a practical assay since it is able to detect extremely low levels of parasitemia (Gubbels *et al.,* 1999). A possible disadvantage is that it relies on its ability to combine a pair of catch all primers with a region that allows species specific detection via hybridization, and this may not always be achievable for closely related species/gene combinations. It also requires sophisticated laboratory equipment and, due to a complex protocol with a need for controlled hybridization conditions, it may be subject to reproducibility problems in different laboratories. However, the small subunit ribosomal RNA gene (18S RNA gene) sequence data have been successfully used to improve the classification of previously known data and identify several novel *Theileria* and *Babesia* species (Altay *et al.,* 2007; Niu *et al.,* 2009; Oosthuizen *et al*., 2008, 2009; Niu *et al*., 2012; Ranjbar *et al.,* 2012).

9.3.3. Loop-Mediated Isothermal Amplification

Loop-mediated isothermal amplification (LAMP) is a novel molecular detection technique that allows target DNA to be amplified with high detection performance under isothermal conditions. The assay is a rapid method with high specificity and efficiency based on a set of four specifically designed primers that can recognize six or eight distinct sequences of the target gene (Notomi *et al.,* 2000; Nagamine *et al.,* 2002). LAMP can be applied using non-denatured template, and DNA extraction may also be neglected, since a drop of blood spotted on to filter paper meets the requirements for the initiation of the reaction (Nagamine *et al.,* 2001a). The test relies on a visual inspection of the reaction product turbidity (Mori *et al.,* 2001; Nagamine *et al.,* 2001b) or a detection of the amplified products through the addition of fluorescent dyes (SYPR Green) and results can be validated using agarose gel electrophoresis (Notomi *et al.,* 2000).

Furthermore, optimal conditions for detection of *T. lestoquardi,* under which the assay exhibited no cross-reaction with other closely related tick-borne diseases, have been established (Liu *et al.,* 2013). The suitability of LAMP for diagnosis of *T. lestoquardi* infection in the field was tested in Sudan, and so was its potential for application in epidemiological surveys (Salih *et al.,* 2012).

9.3.4. Restriction Fragment Length Polymorphism

Restriction Fragment Length Polymorphism (RFLP) of the PCR products allows differentiation between *T. lestoquardi* and *T. annulata* (Spitalska *et al.,* 2004) and between *T. annulata, T. lestoquardi* and *T. ovis* (Zaeemi, *et al.*,2011). It also seems to be useful for the differentiation between *T. separata* and *Theileria* spp. China (Bami *et al.,* 2009). High sensitivity and specificity of PCR–RFLP method have been recently proven and they appeared to be a very powerful tool to detect extremely low parasitemia rates, with discrimination between ovine *Theileria* species in mixed infections (Bami *et al.,* 2009; Zaeemi, *et al.,* 2011).

The development of a simple and applicable diagnostic test suitable for routine diagnosis and useful for detecting mixed infections could have a significant impact on the control of malignant theileriosis of sheep and goats. Thus, there is a pressing need to develop an affordable diagnostic test to detect an early infection at the field level.

10. The relationship between T. lestoquardi and T. annulata

T. lestoquardi and *T. annulata* exhibit a strong serological cross-reactivity (Leemans, *et al.,* 1997), similarities with regard to morphology (Brown, *et al.,* 1998), share the same vector and two immunogenic macroschizont proteins (Namavari *et al.,* 2008) and their geographic distribution tends to overlap (Taha *et al.,* 2013). Both species parasitize the similar host cell phenotypes (Leemans *et al.,* 2001) and are capable of infecting and transforming sheep peripheral blood mononuclear cells *in vitro* and *in vivo* (Brown *et al.,* 1998; Leemands *et al.,* 1999 a,b). Phylogentically, *T. lestoquardi* is more closely related to *T. annulata* than any other sheep or cattle *Theileria* and *Babesia* spp. (Schnittger *et al.,* 2000, 2003; Sparagano *et al*., 2006). In this concept, we amplified the V4 hyper variable region of *Theileria* 18S rRNA gene using the PCR protocol (DNA extracted from sheep blood, UDG-mix, RLB F2 and biotin labelled RLB R2). Amplification was performed according to the *Babesia/Theileria* touchdown PCR programme (Oosthuizen *et al.,* 2009). An in-house membrane was prepared containing the relevant *Theileria* and *Babesia* genus- and species-specific probes. The PCR products were then analysed using the RLB hybridization technique (Nagore *et al.,* 2004). Our result indicate that all probes bound only to their respective target species, except probes positive to *T. lestoquardi* that 100% contemporaneously reacted with *T. annulata* and *T. lestoquardi* (Figure 2). Our findings, confirmed the existence of cross-reaction and closer antigenic relationship between *T. lestoquardi* and *T. annulata* (A.H. El Imam and K.M. Taha: unpublished data). Thus, we concluded that *T. annulata* relatively evolved a common ancestor with *T. lestoquardi*.

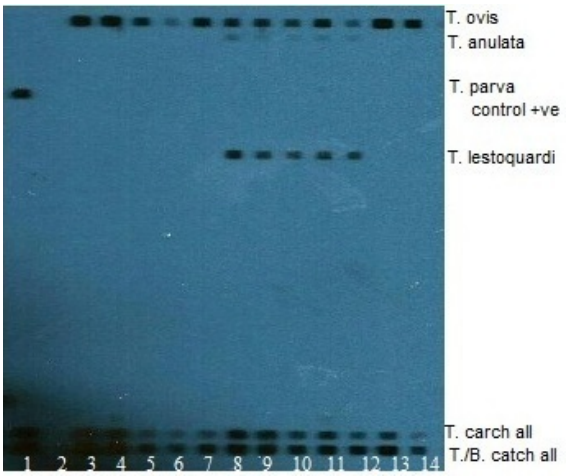

Figure 2. X-ray film of plotting RLB membrane, showing *T. lestoquardi* and *T. annulata* cross reaction.Captions: Lane $_1$, *T. parva* positive control, L_2 *Theileria/Babesia* negative control, L_{3-14} test samples.

11. Treatment

Little is known about the efficacy of the theilericidal drugs used for treatment of bovine theileriosis against *T. lestoquardi.* The chemotherapeutic efficacy of a number of compounds including parvaquone (Clexon) and buparvaquone (Butalex) have been tested for the treatment of the disease (Hooshmand-Rad, 1989). Although some of these drugs are likely to be effective (El Hussein *et al.,* 1993; Hashemi-Fesharki, 1997) they are not easily and quickly eliminated from the animal body and constitute a public health/hazard (McHardy, *et al.,* 1985). Recently, the therapeutic effect of the alkaloids extracted from a medical plant (*Peganum harmala*) has been investigated (Mirzaiedehaghi, 2006; Derakhshanfar and Mirzaei, 2008).

12. Control

The successful cultivation of *T. annulata* prompted the interest of researchers to attempt in vitro culture of *T. lestoquardi* schizont infected ovine cells and explore the possibility to generate an attenuated live vaccine. In addition, immunoprophylaxis trials of cell line vaccines have been successfully carried out in Iraq, Iran and in Sudan (Hooshmand-Rad, 1985; Hashemi-Fesharki, 1997; Ahmed *et al.,* 2013). In the last decade, the molecular characterization of sporozoite *T. lestoquardi* antigen-1 (SLAG-1) protein for inclusion in a sub-unit vaccine (Skilton *et al.,* 2000), parasite vacuolar H+ATpase as a potential molecular marker of attenuated *T. lestoquardi*-infected cell lines (Ali *et al.,* 2008) and 73-kDa protein (Namavari *et al.,* 2008) could be used in vaccine trials. It would be of interest to test whether the synergistic effect of combining recombinant SPAG1 and an attenuated cell line for vaccination against *T. annulata* (Darghouth *et al.*, 2006), also operates for *T. lestoquardi* immunization. The control of MOT has been achieved mainly by prevention of tick infestation using acaricides, although drug treatment of individual cases of valuable stock is now an important control method. In endemic areas, tick control is either not practiced, or used only occasionally to reduce excessive tick burdens as indigenous sheep rarely show disease.

In view of the relatively limited knowledge of sheep theileriosis and the importance of the disease it causes, an effective system of information exchange and some co-operation and co-ordination in research towards its control have been instituted. Globally, the collaborative effort among a number of international established research groups (Piro Vac, http://www.theileria.org/pirovac/ index. htm) to control and to combat MOT is promising.

13. Economic Impact

Due to the economic losses they cause, the most important representatives of the *Theileria* genus are the cattle-infecting species *T. parva* and *T. annulata*. In the case of *T. lestoquardi*, indigenous sheep are at risk in a situation where they are subjected to intensive tick control or when they are moved from disease free to endemic areas (Friedhoff, 1997; Tageldin *et al.,* 2005; El Imam *et al*., 2015). Globally, high morbidity and mortality rates in sheep and goats were reported (El Hussein *et al*., 1998; Taha *et al.,* 2011; Tageldin *et al.,* 2005; El Imam *et al*., 2015). The disease economic importance can therefore be predicted, especially in countries where export of sheep and sheep products are a major component of their foreign income. Animals that recover from *T. lestoquardi* may suffer from weight loss, reduced milk production and delayed maturity (Aisha *et al*., 2014). These animals also remain a carrier and may contribute to disseminating infection. Consequently, these losses have a major impact on animal welfare and stock-holder prosperity worldwide. A study performed in Tunisia indicated that the cost of the carrier state in cattle was greater than the losses caused by overt tropical theileriosis (Gharbi *et al.,* 2011). However, extensive studies on the economic impact of MOT and the impact of the carrier state over the clinical disease are needed.

14. Conclusion

In endemically unstable environments or when susceptible sheep are introduced to these infected environments, tick control or some other disease control measure is essential. Eradication is not a practical proposition due to environmental, managerial and resource constrains and to the lack of a strategy to generate infection-free animals, vector or environment (remove the ticks). Chemotherapeutic agents, such as parvaquone, buparvaquone and halofuginone, are available to treat *T. lestoquardi* infections but not curative and leading to the development of carrier states. In addition, the commercial production and dissemination of a live vaccine is not implemented, and there are difficulties in ensuring batch control. Perhaps delivery would not imperatively require a cold chain, *T. annulata* live vaccine can be also used at room temperature, and it needs to be investigated. It is envisioned that improved production and distribution of an effective live attenuated vaccine will contribute to controlling this important disease. The search for effective control measures towards an endemically stable situation with reduced reliance on chemotherapy and promotion of flock immunity or infected free ticks is difficult and long-term but a worthwhile goal. Precise information on the economic impact of MOT throughout the world is not available and is required.

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