

Tuberculosis in camelids: a review

U. Wernery & J. Kinne

Central Veterinary Research Laboratory, P.O. Box 597, Dubai, United Arab Emirates
E-mail: cvrl@cvrl.ae

Summary

Tuberculosis is a chronic, contagious, granulomatous disease caused by mycobacterial species belonging to the *Mycobacterium tuberculosis* complex. Camelids were not considered highly susceptible to tuberculosis, but in recent years increased numbers of cases have been experienced in some countries. In most of the cases, transmission probably occurs through contact with infected cattle or wildlife. None of the ante-mortem tests currently available can consistently provide accurate diagnosis of the infection in live camelids. Recently developed serological assays have the potential for rapid and accurate diagnosis of tuberculosis but still need to be validated.

Keywords

Camelids – Camelid tuberculosis – Clinical signs – Control – Diagnosis – Epidemiology – *Mycobacterium tuberculosis* complex – Pathology.

Introduction

Tuberculosis (Tb) is a chronic, contagious, granulomatous disease caused by mycobacterial species belonging to the *Mycobacterium tuberculosis* complex (MTC) (37). The disease affects many vertebrate animals and manifests particularly in lungs and lymph nodes but also in other organs. Camelids were not considered highly susceptible to Tb (11), but in recent years serious concern has arisen about Tb in New World camelids (NWCs), particularly llamas and alpacas, in some countries where they are reared (and not just countries in their native South America). For example, Tb is a serious emerging disease in the steadily increasing NWC population of the United Kingdom (UK) (42). Tuberculosis also affects Old World camelids (OWCs), including dromedaries and Bactrian camels (26).

Aetiology

The genus *Mycobacterium* of the family *Mycobacteriaceae* includes non-motile and non-spore-forming acid-fast rods of various lengths (29). Mycobacteria possess a waxy coat that makes it difficult for the host's defence mechanisms to destroy them and results in a slow chronic disease (34, 38). The following species are grouped in the MTC: *M. tuberculosis*, *M. canettii*, *M. africanum*, *M. bovis*, *M. pinnipedii*, *M. caprae* and *M. microti* (36). Of these, *M. tuberculosis*, *M. bovis*, *M. pinnipedii*, *M. caprae* and

M. microti have been isolated from camelids (2, 3, 8, 10, 12, 19, 20, 23, 27, 28, 31, 40, 43, 45). Atypical (non-MTC) mycobacteria have also been isolated from camelids; for example, *M. kansasii* has been associated with clinical signs and pathological lesions similar to those of classic Tb (14).

Zoonotic importance

Tuberculosis is one of the major global reportable zoonotic diseases, killing approximately 1.5 to 2 million people every year (36, 37). Although *M. tuberculosis* is responsible for most human cases, bovine Tb, caused by *M. bovis*, is an important zoonosis that can spread to people through ingestion of raw milk and sometimes by inhalation of infectious droplets (37). Outbreaks of bovine Tb are therefore of considerable concern to public health officials and personnel responsible for the health of animals in zoos, animal parks and private herds (3, 7, 8, 25, 42).

The number of *M. bovis*-associated human Tb cases has significantly declined in developed countries as a result of eradication programmes and pasteurisation of milk (37). Nevertheless, *M. bovis* still represents a zoonotic risk for people who are in close contact with infected animals; for example, a case of cutaneous Tb in a veterinary surgeon was associated with contact with an infected alpaca (42). Camel milk is also a potential source of infection, particularly as it is commonly consumed without boiling, and *M. bovis* was isolated from pooled milk samples from camels in Russia (1, 9).

Epidemiology

There is little published information on the epidemiology of Tb specifically relating to camelids. After the first description of Tb in OWCs by Littlewood (18) in the Egyptian Official Gazette in 1888, only sporadic reports were documented until Mason, in 1912, published his pathological observations on a series of 20 cases detected during a year's surveillance at Cairo abattoir (22). In 1987 Mustafa (26) mentioned in a brief review that disease was more commonly observed in farmed camels and those in close proximity to cattle but appeared to be rare among nomadic camels, suggesting that close contact facilitates transmission between domesticated animals. In 1991, Abdurahman and Bornstein (1) reported the disease to be relatively rare in Somalia, a country which at that time had one of the largest populations of OWCs in the world (35). A recent study in Ethiopian abattoirs has suggested a prevalence of 10%, based on the identification of gross lesions in 906 apparently healthy camels (21). Among animals with suspicious lesions, mycobacteria were cultured from 31 of 91 animals but only two of these isolates were MTC bacteria, both *M. bovis*. The prevalence of Tb in dromedaries is also rare in Dubai, where only four cases have been seen in a 25-year observation period (44). Although NWCs were once considered not very susceptible to Tb (11), many cases have been reported in recent years, some associated with high morbidity (8, 31, 39). One reason for this increase is that NWCs are increasingly being kept in areas where Tb is endemic (2, 4, 39).

Mycobacteria are generally not species-specific pathogens (37). Inter-species transmission may therefore occur and there are many potential sources of infection for camelids. *M. bovis* strains isolated from NWCs are often the same molecular types that are isolated from tuberculous cattle and badgers in the same geographical area, suggesting spillover of infection from non-camelid reservoirs (3, 4, 40). This presents a challenge for control if contact with the reservoir cannot be avoided. Badgers, for example, are an important wildlife reservoir for bovine Tb and are known to visit farm buildings and food stores, which they contaminate with faeces and urine, potentially transmitting *M. bovis* to other animals (30). In a rare case of *M. pinnipedii* infection affecting an OWC, the most probable source was a sea lion kept in the same zoo (25). Once infected, a camelid can introduce the disease into a non-infected herd, with subsequent spread to other camelids (41). The mode of transmission between camelids is unknown, but is presumed to be mainly horizontal, probably through infected aerosols (39, 41). Other potential routes of transmission, based on pathological and/or microbiological findings, include discharging skin lesions, faeces from enteric lesions, urine and congenital transfer (5, 24, 39, 41). In addition, the tick *Hyalomma asiaticum* has been suspected of transmitting *M. tuberculosis* to Bactrian camels (16).

Clinical signs

Tuberculosis is a chronic debilitating disease. The clinical signs in camelids include wasting, anorexia, respiratory distress, enlargement of superficial lymph nodes, recumbency and eventually death (1, 19, 39). Clinical signs are often associated with extensive respiratory pathology, and it is surprising that overt respiratory distress is sometimes not observed in animals with severe lung lesions (8, 39). Animals are occasionally found dead with no previous clinical observations (2, 39).

Pathology

The pathology of Tb in OWCs was described nearly 100 years ago in cases detected in an Egyptian abattoir (22, 23). Pathological reports on NWCs have also emerged in recent years (8, 32, 39). The organs most frequently affected in both groups of camelids are the lungs and associated thoracic lymph nodes, where typical caseonecrotic lesions can be particularly extensive. Mason (22) mentioned that all cases in OWCs had lesions at these sites, 60% of cases exclusively involving these sites; other affected tissues included the liver, spleen, kidney, trachea and pericardium. A similar distribution of lesions has been reported in NWCs (8, 32, 40, 41). Intestinal and cutaneous lesions have also been observed in llamas (42). The severity of pathological descriptions varies depending on how animals were selected for necropsy. Thus, animals selected following clinical disease often have severe pathology (Figs 1 & 2), whereas infected animals identified in ante-mortem immunological tests, and culled prior to development of clinical signs, are likely to have less severe gross lesions (Fig. 3) (44).



Fig. 1
Pulmonary tuberculosis in a dromedary bull with granulomatous pleuritis, consolidation and greyish discoloration of the lung



Fig. 2
Cut surface of the same dromedary lung with grey appearance due to caseous granulomas of different shapes and sizes



Fig. 3
Cut surface of a lung of a seropositive camel with central grey area due to tuberculous granulomas

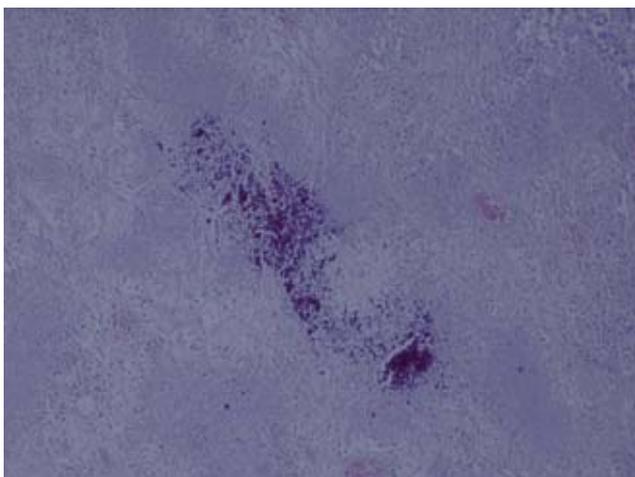


Fig. 4
Histopathology of the camel lung shown in Fig. 3 with large, partly calcified central necrotic granulomas (haematoxylin and eosin staining)

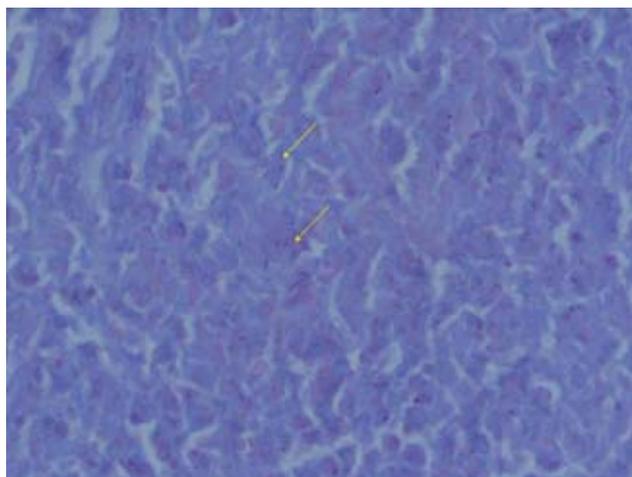


Fig. 5
Histopathology of the same camel lung with granulomas and single acid-fast rods (arrows) in epithelioid cells (Ziehl-Neelsen staining)

In most cases of Tb in camelids, tubercles are characterised histologically by granuloma formation, with infiltration by epithelioid macrophages, lymphocytes, plasma cells and neutrophils, central caseous necrosis and variable calcification and fibroblastic reaction (Fig. 4) (3, 10, 12, 17, 22, 23, 27, 31, 32, 39, 40, 46). Giant cells have rarely been described, except by Zanolari *et al.* (46), who found them in eight of 11 *M. microti*-infected NWCs. Results of Ziehl–Neelsen staining of sections have been variable, with most sections revealing few acid-fast bacilli (Fig. 5), although abundant numbers have been noted in some reports on NWCs (12, 27, 46).

Diagnosis

A definitive diagnosis can be made only at post-mortem examination by demonstration of typical gross lesions, followed by histopathology and confirmatory bacterial culture. Mycobacteria are slow-growing organisms that may require incubation on selective media, such as Lowenstein-Jensen (Fig. 6) or Ogawa, for up to eight weeks (29, 33). More rapid diagnosis can be made using polymerase chain reaction (PCR) assays (34, 38). Initial identification of MTC bacteria can be made by targeting

insertion sequences such as IS1081 or IS6110 (34, 38). Confirmation of mycobacterial species can then be made using primers for specific targets; for example, region of difference 4 (RD4) in *M. bovis* (34). In addition to providing a faster diagnosis than with traditional culture, PCR methods can also be used on formalin-fixed tissues when fresh samples are not available for culture; this approach was used to confirm Tb in an alpaca during investigation of a zoonotic incident (42). Nevertheless, there are currently some disadvantages associated with PCR. Firstly, it does not allow further discrimination of the isolate by molecular typing, which can be done using cultured isolates and is important for epidemiological studies. Secondly, poor sensitivity of PCR has been reported, possibly associated with low numbers and uneven distribution of the bacteria in tissues. Resilience of the mycobacterial cell wall inhibiting extraction of DNA may also affect the sensitivity of the assay, and, for fixed tissues, degradation of DNA associated with prolonged formalin fixation and the processing technique may be a factor (34, 38).

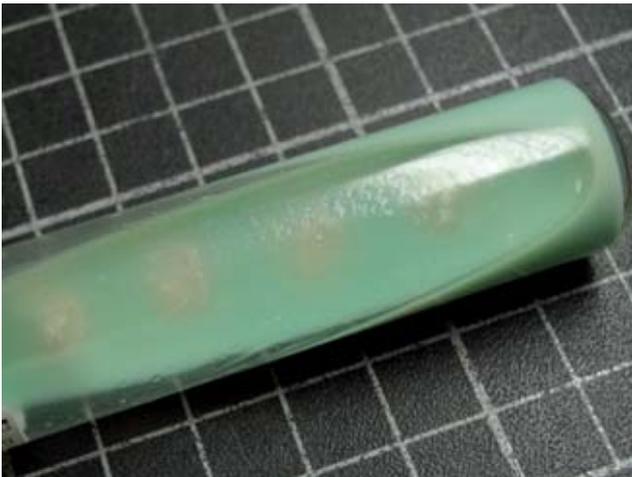


Fig. 6
Mycobacterial culture after six weeks on Lowenstein–Jensen medium

In live animals, clinical diagnosis is often difficult because of the lack of specific signs. Ancillary ante-mortem tests would therefore be useful to confirm the diagnosis. None of the tests currently available, including the classic tuberculin skin test (TST) and various blood assays, can diagnose Tb in camelids with certainty, and none has been properly validated in these animal species. Although estimates of sensitivity and specificity are provided in some reports, these calculations are usually of limited value because of the small number of animals studied.

Bovine tuberculosis is a World Organisation for Animal Health (OIE) listed disease and testing of camelids should follow the OIE guidelines (44). The official Tb screening



Fig. 7
Intradermal tuberculin test at the axilla of a dromedary

method for camelids traded internationally is the TST: the single intradermal comparative tuberculin test is used and the site of inoculation is the axilla (5). The axillary site was found to be superior to cervical and tail-fold sites in studies using small numbers of llamas and dromedaries (15, 44). For statutory testing, purified protein derivatives of bovine and avian tuberculin (each 0.1 ml) are injected into a shaved area of the axilla, and the thickness of the skin is measured immediately before and 72 h after the injections (Fig. 7). A positive result is indicated by an increase in skin thickness at the bovine site that is greater than the increase at the avian site.

Some reports indicate that the TST has reasonable sensitivity and specificity, whereas others indicate a low predictive value (3, 6). The reason for this variation between reports is not clear, but many causes of false-negative and false-positive reactions have been proposed in cattle, and it is possible that these could also apply to camelids (5). The statutory 72 h interval between injection of tuberculin and measuring the response to injection is based on the protocol for cattle, which have a swelling of greatest intensity 48 h to 72 h post injection (5). In dromedaries, however, the most potent response to tuberculin was detected when skin thickness was recorded five days after tuberculin injection (44). It might therefore be the case in camelids that the optimal testing regime has yet to be identified. A negative impact of this lack of reliability in the interpretation of the TST results is that testing for Tb in camelids has been discontinued in some zoological collections (3), resulting in reduced disease surveillance.

From these observations it became obvious that any programme to control camelid Tb based only on the TST faces severe limitations. These findings have stimulated research into blood-based assays. Serological tests for the

diagnosis of Tb have been developed since the 1980s and potentially offer a convenient and cost-effective means of Tb surveillance. Early attempts at developing enzyme-linked immunosorbent assays (ELISAs) did not convincingly discriminate between naturally infected and vaccinated animals and issues of cross-reactivity with other mycobacteria were not addressed (6). More recent serological tests include the multi-antigen print immunoassay (MAPIA) and the Vet TB Stat-Pak or 'rapid test' (20, 43). The MAPIA utilises a range of antigens printed onto nitrocellulose strips that are incubated with serum samples; the rapid test is a portable lateral-flow chromatographic assay that uses three MTC-specific antigens. These antigens have shown some promise for detecting MTC-infected camelids, but further validation is still required before they can be used reliably for field diagnosis (6, 19, 39, 44). Lyashchenko *et al.* (19) first used these tests in NWCs infected with *M. microti* and found that four of five culture-confirmed cases were seropositive in the MAPIA; two were positive in the rapid test. Dean *et al.* (6) showed that both these tests were more sensitive than the TST in a herd of llamas infected with *M. bovis*. The herd included 14 tuberculous llamas; 12 of these cases were confirmed by culture. Only two of the 14 were detected in the TST, but 11 were positive in the rapid test and all 14 in the MAPIA. Nevertheless, the specificity of the rapid test was low in this herd (MAPIA specificity not determined) (39): 44 of 54 (81%) animals that were positive in the rapid test had no detectable evidence of infection at necropsy. Wernery *et al.* (44) reported positive results in both the MAPIA and rapid test in three dromedaries infected with bovine Tb, confirmed at necropsy and by culture, indicating a possible diagnostic benefit in OWCs. The discovery of immunodominant proteins will help to refine and improve the diagnostic accuracy of these assays in camelids: to date, MPB83 has been the most dominant antigen in sera from camelids infected with *M. bovis* and *M. microti* (6, 19, 44).

The gamma interferon test (IFN- γ) and lymphocyte transformation assay are *in vitro* methods for measuring immune responses of circulating lymphocytes. The IFN- γ test is acknowledged by the OIE as an alternative to the TST for internationally traded cattle (44) but the currently used bovine IFN- γ assay (Bovigam, Prionics, Switzerland) is unsuitable for camelids. The lymphocyte transformation assay is not used for routine diagnosis because it is time

consuming and complicated to perform. Scientists in New Zealand have developed a blood test for the diagnosis of Tb in deer, which combines the lymphocyte transformation assay with ELISA and haptoglobin tests. This method has also been used in alpacas but its diagnostic benefit has not yet been demonstrated (13).

Treatment and control

Tuberculosis is a reportable disease in many countries and, where this is the case, control is the subject of statutory regulation, with culling of infected animals. Treatment of infected animals is therefore not usually attempted, although there are some reports of anti-Tb drugs being used in captive wild animals (36). After the diagnosis of Tb in two Bactrian camels kept in a zoo, prophylactic treatment of the remaining 17 camels was attempted using isoniazid incorporated into pelleted feed at a dose of 2.4 mg/kg, fed *ad libitum* (3). However, possibly due to isoniazid toxicity, several camels died, exhibiting signs of bone marrow suppression.

National control programmes are often based on intradermal tuberculin testing, but because of the limitations of this test in camelids, these programmes are unlikely to be successful; however, a combination of ante-mortem assays could improve the sensitivity of herd testing. Control depends on the removal of infected animals and prevention of further introduction of infection into the herd, but the disease will not be eradicated until infection is controlled in reservoir hosts, such as in wildlife (37). Vaccines are not yet available for camelids.



Le point sur la tuberculose chez les camélidés

U. Wernery & J. Kinne

Résumé

La tuberculose est une infection granulomateuse chronique et contagieuse causée par des espèces de mycobactéries appartenant au complexe *Mycobacterium tuberculosis*. Bien que les camélidés soient considérés peu sensibles à la tuberculose, on assiste depuis quelques années à une recrudescence de nouveaux cas dans certains pays. Il s'agit pour l'essentiel de camélidés ayant contracté l'infection après avoir été exposés à des bovins ou à des animaux sauvages infectés. Les analyses ante-mortem actuellement disponibles ne parviennent pas à établir un diagnostic fiable chez les camélidés vivants. Quant aux épreuves sérologiques récemment mises au point, elles semblent pouvoir assurer un diagnostic rapide et fiable de la tuberculose, mais leur utilisation chez les camélidés reste à valider.

Mots-clés

Anatomopathologie – Camélidés – Complexe *Mycobacterium tuberculosis* – Diagnostic – Épidémiologie – Lutte contre les maladies animales – Tuberculose cameline – Signes cliniques.



Estudio de la tuberculosis en los camélidos

U. Wernery & J. Kinne

Resumen

La tuberculosis es una enfermedad granulomatosa crónica y contagiosa causada por especies de micobacterias pertenecientes al complejo de *Mycobacterium tuberculosis*. Aunque no se pensaba que los camélidos fueran muy susceptibles a la tuberculosis, de unos años a esta parte se vienen registrando un número creciente de casos en ciertos países. Lo más probable es que la transmisión se haya producido casi siempre por contacto con ganado o animales salvajes infectados. Ninguna de las pruebas ante-mortem actualmente existentes sirve para garantizar un diagnóstico exacto de la infección en camélidos vivos. En fechas recientes se han elaborado ensayos serológicos que quizá puedan ofrecer un diagnóstico rápido y exacto de la tuberculosis, pero todavía deben ser validados.

Palabras clave

Camélidos – Complejo de *Mycobacterium tuberculosis* – Control – Diagnóstico – Epidemiología – Patología – Signos clínicos – Tuberculosis de los camélidos.



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