



Pathological Impact of Johne's disease in Cattle: A Review Article

S.A. Radam^{1*}; I.B. Falih¹; S.L. Hassan¹; H.B. AL-Sabaawy²

¹Department of pathology and poultry disease, Collage of Veterinary Medicine, University of Baghdad, Iraq.

²Department of pathology and poultry disease, Collage of Veterinary Medicine, University of Mousl, Iraq.

*Corresponding Author, S.A. Radam; E-Mail: suraradam@covm.uobaghdad.edu.iq

ABSTRACT

Johne's disease is an international healthiness problem affecting ruminants. It is caused by *Mycobacterium avium* spp. *paratuberculosis* (MAP). It has serious production-limiting important and also caused significant cost-effective loss in flocks due to direct impact on delayed/reduced breeding, infertility, culling, mortality, and milk reduction. This disease is problematic to diagnose because of elongated incubation times. Proof of identity this disease subclinical can shed the organism as a source of infection for other herds; so, it is critical for control. The present study deals with the morphological (grossly, histopathologically and histochemically) characterization of the disease in cattle. The corpse appears hidebound with sunken eyes and with persistent and non-responsive diarrhea. The necropsy of visceral showed gelatinization and outlying fat. Grossly chiefly pathological alterations in digestive tract such as severe congested of small intestine with marked thickening of its wall a combined with enlargement of mesenteric lymph nodes and gallbladder appear distension with severe thickening walls and blood mixed with bile. Histopathological examinations revealed severe infiltrations of inflammatory cells such as macrophages, lymphocytes, and epithelioid cells with multiple Langhans giant cells in bowel layers and mesenteric lymph nodes with diffuse lepromatous reaction were observed in these lymph nodes and other organs like liver, tonsils and kidney.

Keywords: Cattle, Giant cells, Granuloma, Johne's disease, *Paratuberculosis*.

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INTRODUCTION

Paratuberculosis is long-lasting emaciating disease characterized by granuloma in gut, lymphangitis, and lymphadenitis of regional L.N. It is an important infectious disease of domestic and wild ruminants worldwide caused severe commercial losses of ruminants characterized by alternating diarrhea at first and come to be more persistent and severe above (7) days or months lacking blood, mucus, epithelial debris, and wasting, limited weightiness loss (Roy *et al.*, 2017), reduced milk secretion, increased counter of somatic cell, mastitis, reduced fertility (Elzo *et al.*, 2009), roughening of hair coat, anemia with usual body temperature and food desire and when advanced affected animals become gaunt then die with terminal cachexia and dehydration (McAloon, *et al.*, 2016). This disease have length incubation period ranged from 2-5 years, communal in cattle and not often exposed theoretical symbols before 2 years old infrequently cases (Windsor *et al.*, 2010).

Etiology:

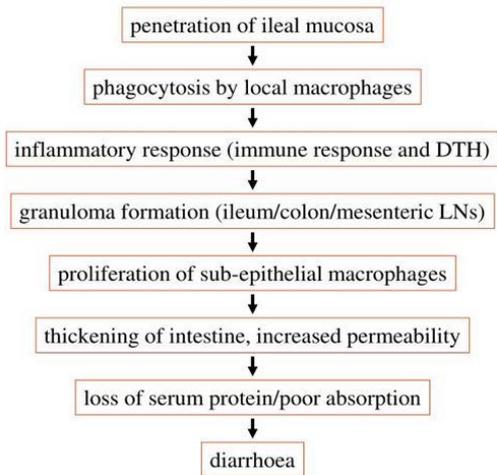
Mycobacterium paratuberculosis (Map) an importance pathogen caused a chronic, progressing granulomatous enteritis. It's an aerobic, non-spore formation, Gram+, non-motile, acid-fast bacilli with slowing growth intracellular parasite (Karen Stevenson *et al.*, 2015). It is correlated with *M avium* and wood pigeon bacillus *M silvaticum*, firstly sequestered of MAP by German Johne and Frothingham in 1895, Its infested ruminants & non-ruminants (cattle, sheep, goats, deer, etc.) (Grewal *et al.*, 2016).

MAP strains have been shared into at least two groups, Type II strains (type C) initially identification in cattle, but also wide host range including sheep, goats, camelids (Stevenson *et al.*, 2002), Type I (type S) strains mostly establish in small ruminants and other species such as cervids, camelids, camels, several cattle nearby connection with sheep (Whittington *et al.*, 2001).

Clinical Signs:

Johne's disease Clinically characterized by pattern of chronic and enlightened emaciation with diarrhea, green feces, bubbly and without blood or mucus and its consistency .It expands for tiny times then diarrhea coming back with greater than before severity. The affected animals are sunny, alert and consume good during the course of disease progress while progressive state saw edematous fluid in submandibular, rectal thickened or corrugated mucosa may feel. Clinical signs of JD do not seem up to animals aged extra than 3 – 4 years and some herds onset disease in 2-year-old (Ashwani Tiwari *et al.*, 2006).

Pathogenesis of paratuberculosis (Johne's disease)



Johne's disease causes a long-lasting diarrhea characterized by absorption deficiency which leads to starvation and damage of muscle. Infant animals are infested primarily via the fecal–oral when ingesting MAP attached to intestinal mucosa facilitated by M-cells and enterocytes (Bermudez *et al.*, 2010) forming close-fitting junctions in intestinal mucosa to amplify permeably (Bannantine *et al.*, 2013). MAP oxidoreductase (Alonso-Hearn *et al.*, 2008), fibronectin-binding protein (Secott *et al.*, 2002) and the histone HupB (Lefrancois *et al.*, 2011) have chief role MAP adhesion epithelial cell and/or invasive. largely bovine blood-monocyte-derived macrophages (BMDM) due to capacity of organism to avert macrophage stimulation, blocking acidification and maturation of phagosome, attenuate appearance of Ags to the immune system with excessive IL-10 expression from epithelial cells as one of the mechanisms by which MAP organisms suppress inflammatory, immune, and antimicrobial responses and promote their survival within host mononuclear phagocytesin macrophage recruitment and transepithelial migration (Lamont *et al.*, 2012).

Bacillus are phagocytosed by sub- and intra-epithelial macrophages (Lugton *et al.*, 1999). MAP ability to survival and replication within phagocytic cells acting as strategic in pathogenesis (Zhao *et al.*, 1997). Usage of a cultured route ideal show MAP lipid conformation transformed development of macrophages and phenotype of pro-inflammatory (Everman, 2015), typical granulomatous enteritis as host cellular immune response (Govardhan Rathnaiah *et al.*, 2008), described by thicken and grooved in intestine barrier (Figure 1B) and lymph nodes (Figure 2C). Tissue macrophages and dendritic cells have starring role in PAMP reorganization via toll-like receptors (El Chamy *et al.*, 2008).

Organizer of MAP infections be influenced by Th1 response and macrophages activated by (INF- γ) secreted by Th1 T lymphocytes (Stabel J.R., 2000), phagocytic cells make active &killing by nitric oxide(NO) which induced synthase established in cattle (Li *et al.*, 2011). MAP affects macrophages function by exclusive mRNA expression profiles (Tooker *et al.*, 2002), declined of apoptosis and antigen presentation (Coussens *et al.*, 2012), and cytokine that indicative significantly(Weiss *et al.*, 2001). MAP drives T helper cells and attractive IL-4, IL-5, IL-10, and inhibition of tissue conversion elements (Coussens *et al.*, 2005).

Gross And Histopathological Finding:

The infected animals appear thin or emaciated with advanced disease, independent edema and/or fluid in holes, grossly intestinal changed characterized by severe congested and marked thickening of its wall mostly appearance in distal small intestine while advanced cases extended from jejunum to colon with separate plaques presented in the disease at early also mesenteric lymph nodes enlargement (Figures 1 & 2) and gallbladder appear distension with severe thickened walls and blood mixed with bile (Gulliver *et al.*, 2015).

Histopathological lesion in cattle characterized by acid-fast bacilli readily detectible in both intracellularly and extracellularly with diffuse cellular infiltration of the lamina propria (Gonzalez *et al.*, 2005), combined with lymphocytes, plasma cells, eosinophils with occasional epithelioid cells and langhans' giant cells in tips or bases of the villi with disappearance of necrosis, hyperaemia or fibrosis these changes manifest in the submucosa friendship with lymphoid tissue, rise numeral of epithelioid cells and cell accumulated compress and obliterated the crypts contributed to thickened of digestive system as shown in Fig.3 (Gonzalez J *et al.*, 2005).

Pathological Impact of Johne's disease in Cattle

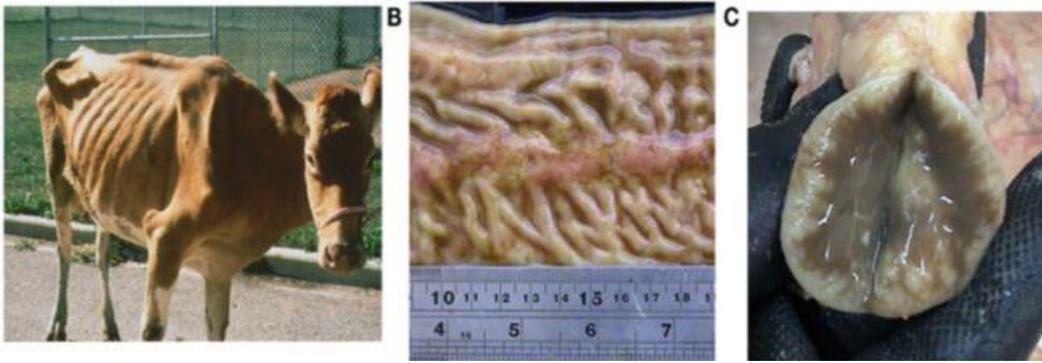


Fig. 1: (A) Severe weakened cow a combined with chronic diarrhea, malabsorption, muscular wasting, and malnutrition. (B) thickening of intestinal mucosa with projecting Peyer's patches (C) lymph node showed as white spots. Of hyperactive lymphoid tissue.

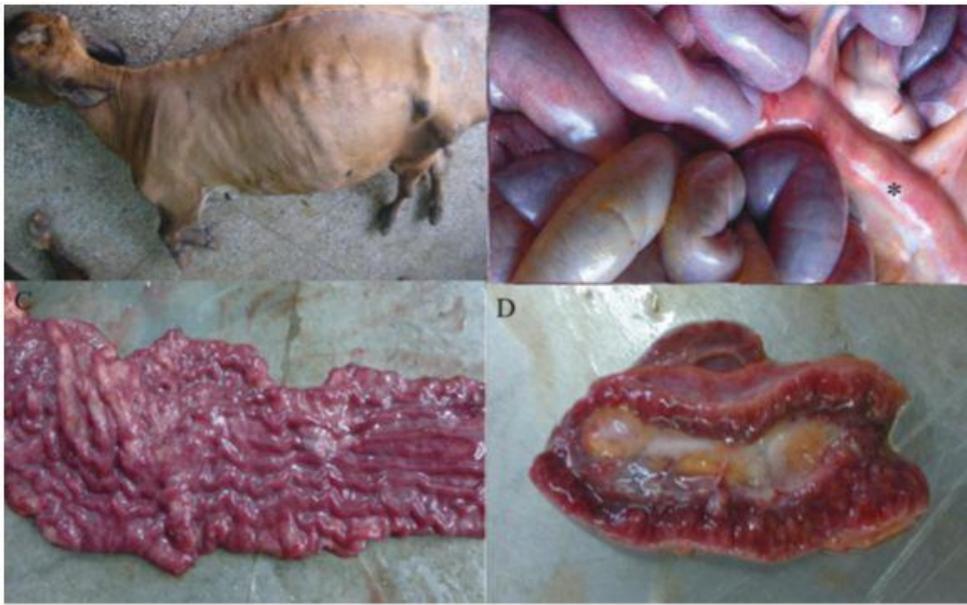


Fig. 2: Macroscopical changes in cattle affected by JD show hidebound condition (A); severe congestion in serosal capillaries of small intestine along with cording of mesenteric lymph nodes (B) marked thickening of the intestinal wall with typical longitudinal corrugations (C); multinodular appearance in mesenteric lymph node (D).

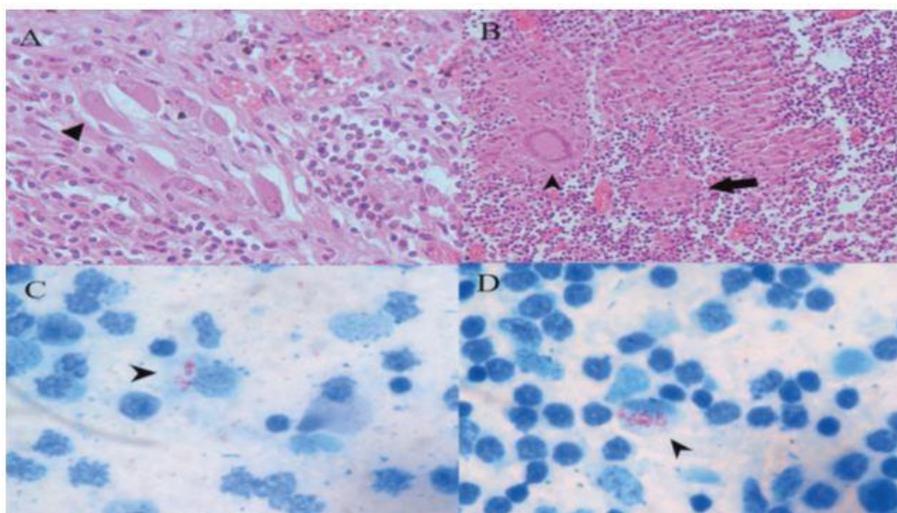


Fig. 3: Histopathological changes in the intestine and mesenteric lymph node of cattle infected by JD. Show (A) accumulation of epithelioid cells in lamina propria of small intestine (B) microgranuloma formation with langhans giant cells infiltrated in mesenteric LN.parenchyma (C) multiple AFB in the cytoplasm of macrophages in impression smear prepared from the small intestine (D) mesenteric lymph nodes.

Histopathological results of mesenteric and other regional LNs such as ileocecal enlargement and edematous with revealed multifocal lepromatous granuloma (epithelioid and giant cells in the paracortical areas with necrosis) that exchanged the cortex and medullary sinuses. he infected lymphatic vessels are bounded by lymphocytes and plasma cells and clusters of epithelioid cells in the lumen resulting in epithelioid granulomas which formed in wall then projected to lumen with improved records of real body macrophages full with cellular and karyorrhectic debris of apoptotic lymphocytes because the macrophages infested with mycobacteria have affinity to actuate apoptotic pathways, resultant in cell death (Koul *et al.*, 2004). Pathological straining induce lesser levels of apoptosis comparative to minus pathogenical strains (Weiss *et al.*, 2008). Also, it can labeled focal granulomas in liver, tonsil, other lymph nodes and frequently in kidney and lungs. liver histopathological examination showed overfilled of capillaries, portal vein, and hepatic vein in center of lobules, granulomatous & mononuclear cells infiltrate in portal tracts and trabeculae as shown in Figures 4, 5, and 6 (Del-Pozo. *et al.*, 2013).

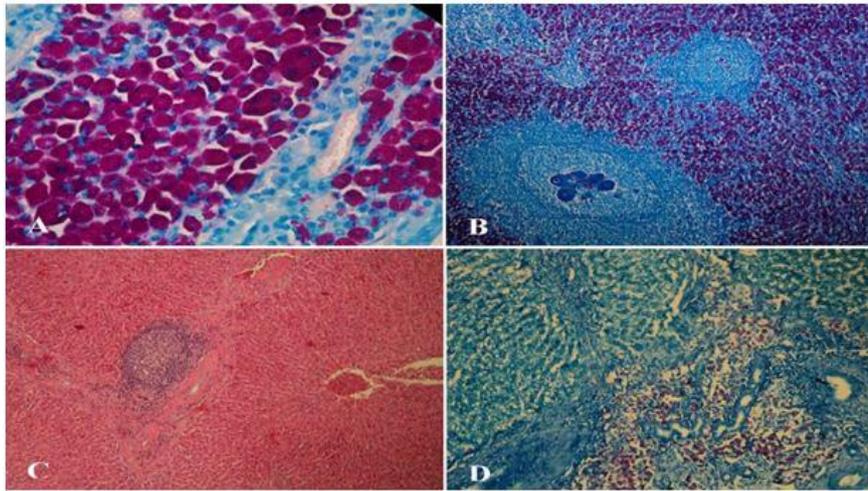


Fig. 4: (A) Ileum, acid-fast bacilli (AFB) engulfed by macrophages of lamina propria . (B) Mesenteric lymph node, necrotic granuloma & calcification with AFB in the cortex and lamina (C) Liver, granulomatous in portal area (D) Liver, present red color of AFB engulfed by macrophages in a portal area.

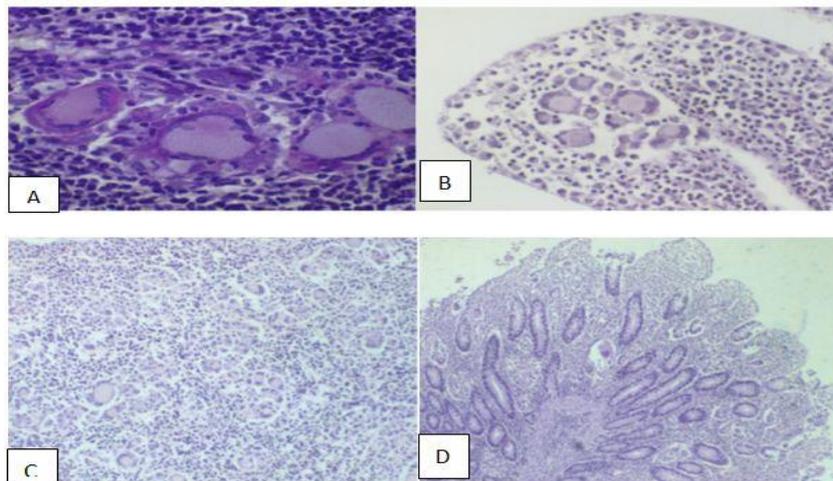


Fig.5 (A) Focal granulomatous lesion formed by aggregation of macrophages and Langhans giant cells in distal jejunal lymph node interfollicular area (B) Multifocal granuloma in intestinal villus apex caused focal thickening of mucosa C) Severe and diffuse multibacillary lesion in distal jejunal lymph node a combined with diffuse granulomatous lymphadenitis with macrophages and Langhans giant cells infiltration, (D) Diffuse multibacillary in distal jejunum infiltrated by macrophages correlated to fused of villi and thickening of mucosa.

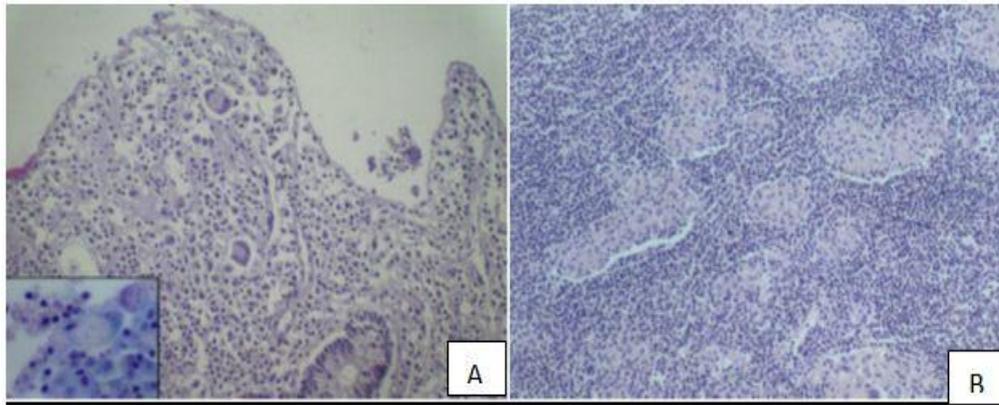


Fig. 6: (A) Diffuse intermediate lesion in ileocaecal valve with infiltration of macrophages, lymphocytes and Langhans giant cells which contain small amounts of mycobacteria causing short and thickened villi. (B) Severe diffused granulomatous lymphadenitis in distal jejunal LN.

Diagnosis:

Several methods used for diagnosis of subclinical/clinical cases of Paratuberculosis to categorize infected animals can vary based on the disease stage such as:

1) Histopathological section can be helpful in diagnosis the clinical cases diagnostic by histopathological and histochemical characteristic lesions from infected animals may serve as a cost-effective and specific technique for JD's diagnosis while subclinical cases other tests may be employed to complement histological diagnosis because it exhibit low-grade lesions with lower numbers of bacteria and may be difficult to diagnose with histopathology, a positive diagnosis of lesions indicated by present one or more giant cells and/or aggregation of three epithelioid macrophages which spot in the intestinal lamina propria and/or lymph node cortex with company of acid-fast bacillus of *M Paratuberculosis* (Whitlock *et al.*, 1996).

2) Ziehl–Neelsen Stain used to detected clinical cases of JD when the MAP appear as clumps of small, strongly acid-fast bacilli in feces, intestinal mucosa or cutting of lymph node surface (Coelho *et al.*, 2010).

3) Immunostaining methods can identify bacteria in tissue samples but ABs may cross-react with other mycobacteria these methods used by taken biopsies of ileum and regional lymph nodes, *M. avium* ssp. *paratuberculosis* may cultivate on sum of specific culture media (Berghaus *et al.*, 2006).

4) PCR assays are quite molecular techniques sensitive and rapid for diagnosis of JD *M paratuberculosis* recognized from colonies or liquid cultured medium target insert sequence IS900 and ISMAP02 of *M paratuberculosis* follow by limitation enzyme which analyzed PCR production (Donat *et al.*, 2016 and Nadine A. El-Sebay *et al.*, 2021).

5. Serology used for documentation of infection like ELISAs Which is more sensitive and detected subclinically in infected cattle also antibodies in milk, complement fixation and agar gel immunodiffusion tests, CFT and AGID also used in clinical cases (Weber *et al.*, 2009); the insensitive and nonspecific intradermal testing are common and purified protein derived tuberculin can detected DTH to MAP. The gamma interferon assay *in vitro* can recognize some subclinically septic case, Cross-reactivity with others lead to false positive reactions in both tests (Kalis *et al.*, 2003).

Different Diagnosis:

Johne's disease possible differential diagnostic in cattle from chronic fascioliasis, gastro-intestinal parasitism, enzootic bovine leucosis, mucosal disease, copper deficiency, left displacement of the abomasum, lipomatosis (fat necrosis), tumours of the gastro-intestinal tract, salmonellosis, coccidiosis, carbohydrate engorgement, yersiniosis.

Difference between Tuberculosis, Paratuberculosis and Pseudotuberculosis:

The TB is chronic disease causative by *Mycopacterium bovis* and formed granuloma typical characteristic by necrotic center which is amorphous caseated granular fragments with loss of cellular feature also acid-fast bacilli are present, these necrotic area circled by epithelioid cells, lymphocytes, histiocytes, fibroblasts and Langhans' giant cells (Domingo *et al.*, 2014) while paratuberculosis diffused lepramatous and *Corynebacterium pseudotuberculosis* is a Gram+ and small bacillus, It is the causative agent of Caseous Lymphadenitis (CLA) in goats and sheep, while in cattle caused a disease identified as Oedematose Skin Disease (OSD) (Tejedor *et al.*, 2008 and Nasr *et al.*, 2019), pseudotuberculosis characterized by ulcerative granulomatous seemed in three clinical forms: cutaneous, mastitic and visceral and can observed mixed forms as shown in Fig.7 (Almeida *et al.*, 2017).

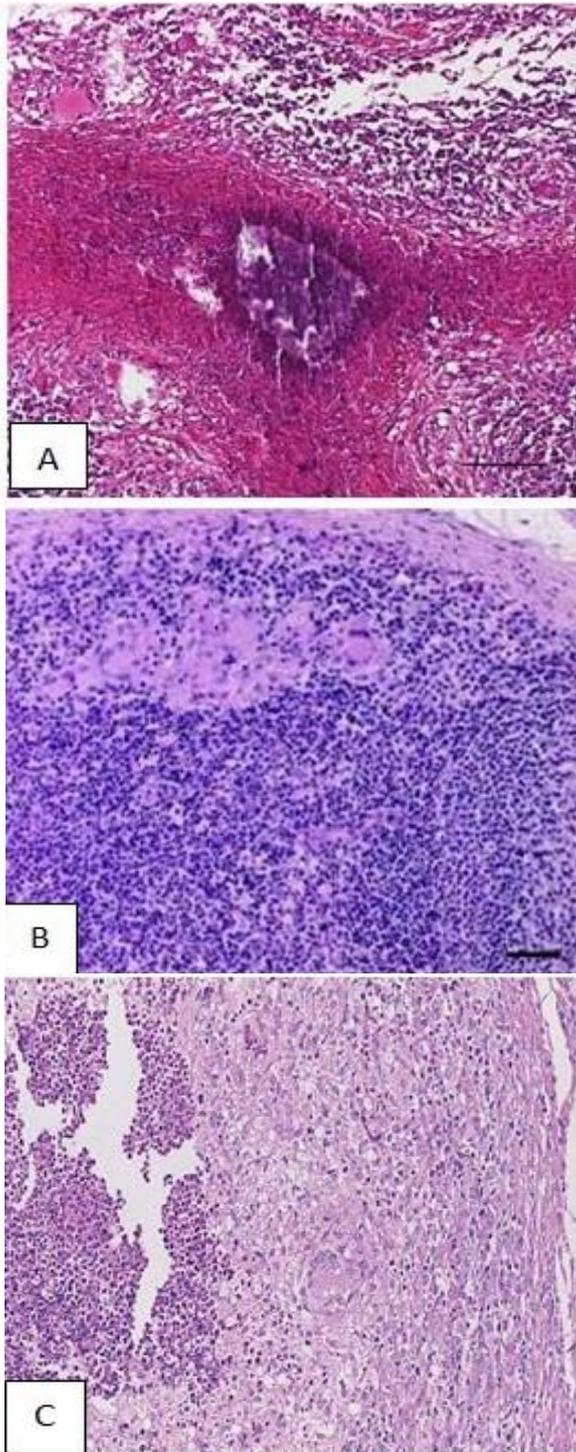


Fig.7: (A) Histological section of a bronchial lymph node characterized by caseous necrosis and mineralization, surrounded by multinucleated giant cells and lymphocyte, (B) Diffused lepromatous granuloma reaction (C)Ulcerative-granulomatous with pyaemic foci bounded by epithelioid and giant cells.

Epidemiology and Transmission:

JD is prevalent in New Zealand and south-eastern states of Australia dairy cattle and recently impression on the Australian cattle industries recognized generally though ordinary cattle and sheep infected attendant cross-

infections have been testified in strains of *M paratuberculosis* (Perez et al., 1996).

The transmission of Map depended on bacterial ability to survive within the environment, (Eppleston et al., 2014) recounted existence Type C Map strain wasn't impacted by position but Type S strain hazard death was 2.3 times greater at dry neighborhood situations comparative with Australia heating place. The capacity to spore-like kinds formation mark it warmth resilient and facilitated escape within environs (Lamont et al., 2012).

Evidence existence of diverse strain of Map in top soil, water, grass and manure of substantial significance for decline diffusion and exploration, as well as animal activities, farming carry out and of virulence influencing of strain on geographical distribution of these strains. Currently, whole genome sequencing show slight evidence for geographically distinct strains (Ahlstrom et al., 2014).

MAP is predominantly spread by the fecal-oral way when shed in huge quantities of organisms in the feces and intermittent in early stage of disease because it and upsurges in case of progresses disease and when infected animals are subjected to stress (Sweeney, 2011); virtual easiness of orally experimented transmission in young cattle and sheep.

The offspring of cattle can be born infected if dam in advanced phase of disease because it can shed MAP to variable grades in milk colostrum fecal contaminated of udder housed in polluted pens, and bacterial sums high during the first 2 months of the lactation for that the colostrum from infected cows is abundant risk for spreading of JD to Calves (Nielsen et al., 2008). The repetition of feeding collective colostrum or wasted milk spreading the infection to many calves during susceptible period of life, MAP may noticed in semen, saliva and milk (Slana et al., 2008). Calves greatest risk when exposure to the feces of adults infected with disease and transmitted the organism on fomites, other animals via aerosol unclean dust, the pathogen does not multiply outside a living host (Sweeney et al., 1992b).

Cross-species have role in transmission, outbreaks and maintaining infection cycles of JD, even before molecular strain typing which have great improved knowledge about cross-species transmission of Map was accessible, epidemiologic indication suggest that natural communication between cattle and sheep was rare because cattle and sheep harbor diverse strains were host modified, the simplicity of separating Map from cattle & uneasy from sheep additional to existence of different strains evidence that milder sickness marked when sheep strains are pass on to cattle (Fridriksdottir et al., 2000).

Control:

Because the economic losses in both dairy and beef cattle caused by paratuberculosis disease (Windso, 2014). It must control its depended on population-level measures, applying hygienic measurement and vaccination (Konboon *et al.*, 2018). Another risk factor outline of livestock in farm (Kirkeby *et al.*, 2017). Losses of dairy farmer consist of before, during or after culling (McAloon *et al.*, 2016), In beef cattle the losses be determined by farmer market (Webb Ware *et al.*, 2012), also killing rate of infection summarized (Kudahl *et al.*, 2009).

The control programs have variable aims from lessening of clinical cases and/or MAP incidence (Weber *et al.*, 2018), to remove MAP from herd also limited transmitted of MAP by inducing farm biosecurity through rearing of young stock (Donat *et al.*, 2017). The main strategy in dairy cattle is prevent calves interaction the feces of adult cows to improve calving area hygiene drawn-out to all managing regions to upturn successful (Ferrouillet *et al.*, 2009) and management of colostrum/milk feeding (Dore *et al.*, 2012). The most effective control strategy involves 'test-and-cull' which increased biosecurity of farm (Smith *et al.*, 2017).

Both healthy and 'test-and-cull' were essential to become stable the herd station, reduction of calf experience are most effective measure, followed by test occurrence (Camanes *et al.*, 2018). Culling the progeny which infested cows considered as portion of the control strategy rate of in utero infection (Whittington *et al.*, 2009). Pasture and grazing manage utilizing to lessor exposure of extensive grazed livestock (Eppleston *et al.*, 2014).

Even nonappearance linked between MAP and human disease (Groenendaal *et al.*, 2008). The zoonotic potential of *M. paratuberculosis* cannot be ignored, due to vital knowledge gaps in considerate its starring role of human disease (Waddell *et al.*, 2016), its influence on communal healthiness do not measured or described (Waddell *et al.*, 2016).

Immunization of ruminants revealed limited of disease by decreased of clinical frequency and decreasing faecal shed of MAP (*et al.*, 201470) but it isn't commonly used in cattle because threat interfering with ID testing for bovine tuberculosis (Bastida *et al.*, 2011). In contrast of Australian, Icelandic and Spanish sheep industries, inoculation widely used (Serrano *et al.*, 2017).

Declaration of competing interest

On behalf of all authors, I hereby declare that no conflict of interest may interfere with the publication of the manuscript.

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