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Clinicopathological studies on ulcerative lymphangitis in cattle: Alterations in serum inflammatory cytokines, anti-microbial, organs functions, and oxidative stress-related biomarkers

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Abstract

Background: Affection with *Corynebacterium pseudotuberculosis* (C. pseudotuberculosis) and development of cellulitis and/or abscess formation with cutaneous lymphangitis in cattle is rare to some extent, so literature about the biochemical changes that would accompany this infection is rare.
Aim: In this context, the present study was designed to screen the effect of the infection with C. *pseudotuberculosis* cutaneous lymphangitis on the release of some immune molecules, organ functions, and redox state in Baladi cows.
Methods: Fourteen Baladi cows from a small dairy farm in El-Behira, Egypt, were selected to complete this study. After bacteriological culture confirmation, seven of them were found suffering from cutaneous lesions due to infection with C. *pseudotuberculosis* (Diseased group), while the others were healthy (Healthy group). Serum samples were obtained to evaluate the presumptive changes in some clinicopathological parameters.
Results: Serum analysis revealed a significant decrease in the levels of interferon-gamma and interleukin-17 as well as a significant decrement in the concentration of beta-defensin (β-defensin) and lipocalin-2. While serum level of interleukin-10 recorded a significant increase in these animals when compared to healthy control animals. Concurrently, the affected animals recorded a significant elevation in serum levels of hepato-cardiac enzymes, urea, and creatinine in addition to disturbance in the serum redox state.
Conclusion: In conclusion, infection with C. *pseudotuberculosis* cattle may disturb the defensive immune state, body organ function, and redox state of the animals.
Keywords: *Corynebacterium pseudotuberculosis*, Lymphangitis, Cows, Cytokines, Redox state.

Introduction

Ulcerative lymphangitis (edematous skin disease) is a bacterial disease caused by *Corynebacterium pseudotuberculosis* (*C. pseudotuberculosis*) which affects many animal species including, horses, cattle, and sheep (Zavoshti *et al.*, 2009; Cahn and Line, 2010) and even camels (Tejedor-Junco *et al.*, 2008), but it rarely affects human beings (Peel *et al.*, 1997). In cattle, the disease usually appears in the form of cutaneous abscesses and/or cellulitis especially in limbs (Jaiswal *et al.*, 2017; Steerforth and Marutsov, 2017). *Corynebacterium pseudotuberculosis* is a gram-positive, nonmotile, pleomorphic, facultative anaerobic bacteria that grows sufficiently on blood-agar media and forms opaque whitish colonies (Coyle and Lipsky, 1990). *Corynebacterium pseudotuberculosis* virulence depends on the excretion of an exo-toxin (phospholipase D toxin) and its ability to survive within macrophages (Yozwiak and Songer, 1993) due to the presence of mycolic acids (MAs) containing outer membrane which serves as permeability barrier (Odhah *et al.*, 2022). Edematous skin disease was reported in cattle and buffaloes from many countries and the infection was confirmed through isolation and biochemical tests (Mohamed and Reda, 2015; Jaiswal *et al.*, 2017). In cattle, infection mainly occurs through skin abrasions or injuries and transmits to lymph vessels causing multiple abscesses along their courses, but involvement of lymph nodes is rare (Radostits *et al.*, 2004); in addition, metastasis to visceral organs may occur (Yeruham *et al.*, 1997; Steinman *et al.*, 1999). Also, toxemia could occur due to circulation of exo-toxin (Selim, 2001). Infection and outbreaks usually occur in summer as insects may share in disease dissemination (Mohamed and Reda, 2015). Mortality

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due to affection with edematous skin disease in cattle and buffaloes is low, but disease morbidity is high (Khalil *et al.*, 1995). For any disease, detecting serum biochemical changes may offer sufficient information for disease diagnosis, progression, and establishment of internal organs (liver, kidney, heart, and muscles) affections, in addition to monitoring disease prognosis and treatment efficiency (Agina, 2017). However, there is a paucity of research that discussed serum biochemical changes that accompany affection with edematous skin disease in cattle, so this study aimed to investigate some serum biochemical alterations in Baladi cattle affected with edematous skin disease.

Materials and Methods

Animals and clinical examination

During April 2023, this study was conducted on 14 Baladi cows; 2–4 years old and 300–350 kg body weight, belonging to small dairy farms in El-Behira governorate, Egypt. Seven were suffering from cutaneous abscess formation and cellulitis with lymphangitis (diseased group). From the animals' history, the appearance of lesions was determined about 3 weeks ago, the lesions were present in both forms, either open (ulcerative) or closed along different parts of the body especially hind limbs below the hock. Some animals had ulcerative lesions on the ventral abdomen, pre-scapular region, and neck (Figs. 1–3). Also, the pre-scapular and pre-femoral lymph nodes were enlarged in affected cows. The other seven cows were healthy and enrolled as a healthy control group. Healthy animals were monitored for 2 weeks after sampling to exclude affection of ulcerative lymphangitis. In addition, the animals that received any systemic treatment within the last 7 days before sampling were excluded. Body temperature, pulse rate, and respiratory rate were detected and recorded.

Bacteriological sampling and culturing

Double samples were obtained under aseptic conditions for bacteriological examination either directly from ulcerative lesions using swabs or through aspiration from closed lesions. The samples were transported in an ice box for bacteriological analysis. Samples were inoculated into nutrient broth at 37°C for 24 hours under anaerobic conditions. Then, they were streaked on sheep blood agar media and incubated for 48 hours at 37°C under aerobic conditions and in a CO_2 incubator (Bailey and Scott, 1990). The characteristic colonies of *C. pseudotuberculosis* bacteria were detected (granular appearance dull colonies) and bacteria were examined with the aid of Gram stain for morphological characterization (Gram-positive, pleomorphic rods arranged in a typical "Chinese letter" arrangement). For confirmation, several biochemical tests were applied including an indole test, gelatin hydrolysis test, urea production, and fermentation of glucose, galactose, lactose, and ribose sugars (Quinn *et al.*, 1994).

Blood sampling

Blood aliquots were obtained directly from the jugular vein of all the animals in plain vaccutainers, left to clot for 30 minutes at room temperature, and then the samples were centrifuged for 10 minutes at 3,000 r.p.m to separate serum samples which were stored at −20°C for further biochemical evaluation.

Evaluation of serum inflammatory cytokines and anti-microbial parameters

ELISA-based serum levels of interferon-γ (IFN-γ) (Cusabio, China), interleukin-17 (IL-17) (Mybiosource,

Fig. 1. Presence of abscess on the hind limb of an affected cow.

Fig. 2. Presence of abscess on the neck of affected cow.

Fig. 3. Ulcerative lesion with the presence of yellowish exudate on the neck of the affected cow.

USA), interleukin-10 (IL-10) (Cusabio, China), beta-defensin, and lipocalin-2 (LCN-2) (Mybiosource, USA) were determined.

Evaluation of hepatic and cardiac functions related to enzymes

Serum activity of alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyltransferase (GGT), creatine kinase MB (CK-MB), and lactate dehydrogenase (LDH) enzymes were evaluated using commercially available kits (Diamond Diagnostic, USA).

Evaluation of renal-function-associated parameters

Concentrations of urea and creatinine were detected in serum samples using commercial kits (Diamond Diagnostic, USA).

Evaluation of oxidant/antioxidant biomarkers

Serum concentrations of malondialdehyde (MDA) and reduced glutathione (GSH) with serum catalase (CAT) and superoxide dismutase (SOD) activities were determined in serum samples using commercially available kits (Bio-diagnostic, Egypt).

Statistical analysis

The comparison between the means of the determined parameters was done using an independent *t-test* with the aid of the SPSS 16.0 software package for Windows. The values are present as mean ± standard error.

Ethical approval

This study was approved ethically by the institutional animal care and usage committee, at Alexandria University.

Results

Changes in some clinical parameters (body temperature, respiratory rate and pulse rate)

Clinical examination of the animals revealed no statistically significant difference in body temperature, pulse rate, and respiratory rate between affected cows and the control group (Table 1).

Serum inflammatory cytokines and anti-microbial parameters

As shown in Table 2, serum levels of IFN-γ and IL-17 recorded a significant decrease in animals suffering from edematous skin disease; this decrement was associated with a significant reduction in serum levels of beta-defensin and LCN-2 when compared to mean values of control animals, while the serum level of IL-10 was increased in affected cows as compared to healthy cows.

Serum activity of hepatic and cardiac enzymes

Serum activity of AST, ALT, GGT, CK-MB, and LDH enzymes recorded a significant increase in animals affected with an edematous skin disease as compared to healthy cows (Table 3).

Serum level of urea and creatinine

In comparison with control healthy cows, serum concentration of urea and creatinine recorded a significant increment in animals affected with edematous skin disease (Table 3).

Serum oxidant/antioxidant biomarkers

The present data in Table 4 showed that serum level the of MDA was increased significantly in cows with edematous skin disease, while serum activity of antioxidant enzymes (CAT and SOD) and serum GSH levels were decreased in the same group when compared to control healthy animals.

Discussion

Corynebacterium pseudotuberculosis is a substantial member of the *Corynebacterium, Mycobacterium*, and *Nocardia* group, and this group possesses several bacterial species of medical, biotechnological, and veterinary interest. *Corynebacterium*

Table 1. Mean values of some clinical parameters in healthy and diseased cows.

	Healthy group	Diseased group
Body temperature (°C)	38.7 ± 0.19	38.4 ± 0.22 NS
Pulse rate (wave/minute)	70.9 ± 2.28	71.6 ± 2.32 NS
Respiratory rate (Breath/minute)	22.12 ± 1.12	21.03 ± 1.26 NS

Values are presented as means ± standard errors. (NS): Nonsignificant.

Table 2. Serum concentration of IFN-γ, IL-17, IL-10, β-defensin, and LCN-2 in healthy and diseased animals.

	Healthy group	Diseased group
IFN-γ (pg/ml)	54.17 ± 6.91	34.53 ± 3.78*
IL-17 (pg/ml)	415.14 ± 44.85	287.86 ± 40.46*
IL-10 (pg/ml)	43.49 ± 4.42	57.33 ± 4.04*
β-defensin (pg/ml)	616.29 ± 37.06	360.57 ± 38.30***
LCN-2 (ng/ml)	559.00 ± 63.85	358.43 ± 25.23**

Values are presented as means ± standard errors. (*): Significant at ($p < 0.05$); (**): Significant at ($p < 0.01$); (***): Significant at ($p < 0.001$).

Table 3. Serum concentration of hepato-cardiac enzymes, urea, and creatinine in healthy and diseased animals.

	Healthy group	Diseased group
AST (U/l)	72.00 ± 5.76	118.43 ± 6.24***
ALT (U/l)	34.43 ± 3.98	53.57 ± 4.81**
GGT (U/l)	27.29 ± 3.73	48.00 ± 4.49**
CK-MB (U/l)	65.14 ± 7.82	84.43 ± 10.29**
LDH (U/l)	336.71 ± 23.24	449.43 ± 36.00*
Urea (mg/dl)	22.57 ± 2.15	35.29 ± 2.31**
Creatinine (mg/dl)	1.57 ± 0.04	1.66 ± 0.03*

Values are presented as means ± standard errors. (*): Significant at ($p < 0.05$); (**): Significant at ($p < 0.01$); (***): Significant at ($p < 0.001$).

Table 4. Serum concentration of different oxidant/antioxidant parameters in healthy and diseased animals.

	Healthy group	Diseased group
MDA (µmol/l)	5.18 ± 0.50	9.49 ± 0.63***
CAT (U/ml)	3.84 ± 0.48	2.23 ± 0.23**
SOD (U/ml)	61.03 ± 6.22	38.30 ± 3.28**
GSH (µmol/l)	5.23 ± 0.49	3.05 ± 0.51**

Values are presented as means ± standard errors. (**): Significant at ($p < 0.01$); (***): Significant at ($p < 0.001$).

pseudotuberculosis mainly affects ovine causing caseous lymphadenitis, but it can also affect equines, bovines, camels, and humans (Bastos *et al.*, 2012). The ulcerative form of *C. pseudotuberculosis* is more common in cattle (Al-Gaabary *et al.*, 2005), and usually appears as a pyogenic cutaneous ulceration that is characterized by a sudden onset and lasting for several days (Oreiby *et al.*, 2014) and this would indicate the role of dermo-necrotic exotoxin that is produced from *C. pseudotuberculosis* (Quinn *et al.*, 1994). Regional lymph nodes were swollen to several times of their normal dimensions indicating that lymphatic tissues are a target for *C. pseudotuberculosis* as a facultative intracellular micro-organism (Conner *et al.*, 2000). The absence of alteration in temperature (no fever) and other clinical parameters is familiar upon affection of cattle with ulcerative lymphangitis (Steinman *et al.*, 1999). Biochemical changes are a very valuable tool for understanding the pathogenesis of any disease, as they offer the fundamental base for diagnosis and treatment of the disease process (Kaneko *et al.*, 2008). Based on this concept and concerning this study's findings, the decrease in serum level of IFN-γ, could be explained based on the findings of Rebouças *et al.* (2011), as their study declared that secretion of IFN-γ is considered a short-lived primary response of the body against infection with *C. pseudotuberculosis*, so its level was fluctuating and recorded its peak after 5 days from infection induction then declined till day 42 after infection. In addition, the decrease in serum level of IFN-γ could be owed to the ability of MAs immunogen which is present in the outer membrane of *C. pseudotuberculosis* bacteria (Odhah *et al.*, 2022) to induce depletion of T-lymphocytes (Kim *et al.*, 2014) which produce IFN-γ.IL-17 is a pro-inflammatory cytokine that is produced exclusively by T-cells (Moseley *et al.*, 2003). It is chiefly responsible for the production of anti-microbial peptides (such as defensin and mucin), remodeling proteins, induction of immune defense, and tissue repair (Fossiez *et al.*, 1996). On the other hand, an increased level of IL-17 was proved to be incorporated widely in the occurrence of sepsis (Rendon and Choudhry, 2012), as it may inhibit neutrophils' microbicidal function and migration (Ye *et al.*, 2001). Therefore, the decrease of IL-17 levels in diseased animals would be a defensive mechanism of the body against the sepsis process. In addition, the decrease in IL-17 production would induce synthesis of IL-10 (anti-inflammatory cytokine) to inhibit excessive inflammatory reaction in case of sepsis (Wu *et al.*, 2015) and this would explain the significant increase in serum level of IL-10 in animals suffering from infection in this study. Unfortunately, the enhanced production of IL-10 would inhibit the production of IFN-γ (Schroder *et al.*, 2003), and decrease antigen presentation (Sabat *et al.*, 2010) which may decrease pathogen clearance. Also, the detected decrement in peripheral blood IL-17 level would be a consequence of the previously mentioned inhibitory effect of *C. pseudotuberculosis* on T-cells (Kim *et al.*, 2014). β-defensin is one of the most abundant antimicrobial peptides which is produced by epithelial tissues (de Oca, 2010) including skin keratinocytes (Yang *et al.*, 2007). Also, β-defensin comprises an immune-modulatory effect besides its role as a link between adaptive and innate immunity (Yang *et al.*, 1999). Moreover, the decrease in IL-17 production would be reflected in the production of surface anti-microbial proteins (defensins and mucins) (Onishi and Gaffen, 2010), so serum level of β-defensin was decreased in animals affected with edematous skin disease. In the same manner, LCN-2 is considered an acute-phase protein that is secreted mainly from neutrophils besides the majority of body tissue cells during bacterial infection, so it is also called neutrophil gelatinase-associated lipocalin (Goetz *et al.*, 2002). LCN-2 exerts its anti-bacterial action and sharing in innate immunity through binding to iron-laden siderophores which scavenge iron from the host to deliver it to the bacteria for replication (Flo *et al.*, 2004). LCN-2 also contributes to immune-modulating, tissue repair, and epithelial cell regeneration (Santiago-Sánchez *et al.*, 2020). Unfortunately, secretion of LCN-2 is stimulated by IL-17 (Karlsen *et al.*, 2010), so its level would be decreased as a consequence of decrement in IL-17 production as recorded in animals suffering from *C. pseudotuberculosis* infection. Referring to serum biochemical changes, phospholipase D exo-toxin has the power to degrade mammalian sphingomyelin, especially at the endothelial cells level which increases vascular permeability and allows passage of bacteria into tissue space, then from these sites into the lymphatic system which distributes bacteria from the infection site to other body organs (Guimarães *et al.*, 2011). In this consistency, the elevated level of hepatic enzymes (AST, ALT, ALP, and GGT), renal function-associated biomarkers (urea and creatinine), in addition to cardiac muscle dysfunction-related biomarkers (CK-MB and LDH) could be explained relying on the findings of Al-Gaabary *et al.* (2010) who reported that infection of sheep with *C. pseudotuberculosis* was proved to induce hepatic distortion and necrosis with congestion and vacuolar degeneration of hepatocytes.

This infection also was implicated in the degeneration of renal tubular epithelial cells and myocardial fibers (Ibtisam, 2008). Our findings are to the results obtained by Mahmood *et al.* (2015), as their study illuminated that this alteration was recorded in response to the injection of phosplolipase D exotoxin or induced infection with *C. pseudotuberculosis* itself in goats. The elevated serum level of MDA and depletion of enzymatic and nonenzymatic antioxidants in animals suffering from edematous skin disease would illuminate the evoked oxidative stress due to infection with *C. pseudotuberculosis*. This redox imbalance was previously investigated upon inoculation of mice with *C. pseudotuberculosis* as the infection significantly induced a state of oxidative stress which was indicated by the increased production of peroxinitrite and malndialdehyde (lipid peroxides) (Awni *et al.*, 2020). Also, infection in sheep induced a significant elevation in serum level of MDA with a significant decrement in the concentration of GSH and activity of SOD and CAT enzymes (Polat *et al.*, 2023).

Conclusion

This study could conclude that infection with *C. pseudotuberculosis* in cattle did not affect the general clinical parameters of the affected animals, but it could impair hepato-renal and cardiac functions. It also would disturb redox balance and generate a state of oxidative stress. In addition, infection with this bacterium can disturb IFN-γ, inflammatory/ anti-inflammatory cytokines, and tissue anti-microbial molecules production, which would delay recovery and share in the persistence of the infection.

Acknowledgment

None.

Conflict of interest

The authors declare that there is no conflict of interest.

Data availability

All data are provided in the manuscript. Any extra data needed can be provided by the corresponding author upon reasonable request.

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