Dermatological signs in bovine tropical theileriosis (*Theileria annulata* infection), a review

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Summary

Bovine tropical theileriosis (*Theileria annulata* infection) is an important tick-borne disease in several regions of the world. This paper describes two clinical cases of tropical theileriosis in northern Tunisia with the uncommon sign of skin nodules. The density of nodules was estimated at 15–20 per 10 cm^2; they were distributed over the animal's body and were 0.5–2 cm in diameter.

Microscopic examination of the skin nodules 18 days after treatment onset showed a perivascular infiltrate of lymphocytes, macrophages and eosinophils. Nevertheless, no schizonts were observed. Appropriate treatment led to the recovery of one of the two animals with total disappearance of the skin lesions; the other animal died. A review of clinical cases of tropical theileriosis (*T. annulata* infection) with cutaneous lesions is presented. Various dermatological signs are described in the literature: skin nodules, haemorrhagic lesions, cutaneous gangrene, etc. Most authors reported the presence of schizonts in the nodular lesions. Dermatological involvement in bovine tropical theileriosis should be considered by field veterinarians and should be differentiated from other diseases with dermatological signs.

Keywords

Cattle – Nodule – *Theileria annulata* – Tunisia.

Introduction

Bovine tropical theileriosis (*Theileria annulata* infection) is a protozoan disease transmitted by several tick species, all belonging to the genus *Hyalomma* (1). It is an important tick-borne disease in several countries. The protozoan has a wide geographical distribution, including North Africa, southern Europe and a large part of Asia. Because the disease is associated with high economic losses and some mortality, the identification of clinical cases of tropical theileriosis by field veterinarians represents a cornerstone in controlling this disease and reducing its economic impact. This requires an excellent and exhaustive knowledge of all the clinical signs that may occur (2). The signs of tropical theileriosis are polymorphic and expressed with different frequencies, which may lead to misdiagnosis and an increase of the impact of the disease. Among these signs, several authors have reported cutaneous lesions due to *T. annulata* infection, including nodular, haemorrhagic and/or necrotic lesions. Skin lesions have been reported in different regions of the world in cattle and buffaloes (3).

Two clinical cases of tropical theileriosis in cattle that expressed skin lesions in northern Tunisia are reported here. In the second part of this paper, most of the published cases of dermatological lesions due to tropical theileriosis are reviewed.

Case report

Signs

Two Holstein–Friesian cattle from a farm consisting of seven animals in the north of Tunisia (Governorate of Ariana) presented signs of tropical theileriosis (fever,

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lymph node enlargement and hyporexia) with skin lesions in August 2015. The barn contained cracks and crevices favourable for the development of the tick vector *Hyalomma scupense* (1). The animals were examined and blood samples were collected in ethylenediamine tetra-acetic acid (EDTA). Giemsa-stained blood smears showed the presence of *T. annulata* piroplasms, with a parasitaemia percentage of 70% and 20% in the affected cow and the heifer, respectively. The five-year-old cow presented with fever, an increase in heart and respiratory rates, salivation, and was in poor physical condition, with oedema of the jaw and unilateral oedema of an eyelid (Table I). The vulva, udder and medial thighs showed haemorrhagic suffusion. The cow aborted at seven months of pregnancy (Figs 1, 2 and 3) and died despite treatment.

The heifer was two years old and 2.5 months pregnant; she presented the same signs but they were much milder (Table I), except for the ocular signs. The oedema of the jaw was also less severe. There was severe anaemia, but of different intensity, in both animals (Table II).

The anaemia of the cow was severe, with low levels of erythrocytes (3.6 × 1012/l [reference range: 5–10.10 × 1012/l]) and haemoglobinaemia (7 g/dl [reference range: 9–13.9 g/dl]); there was also a slight increase in granulocytes (70.8% [reference range: 30–65%]). Blood samples were collected from the animals into EDTA tubes; the blood smears were stained with Giemsa and examined under a microscope at ×1,000 magnification. The blood samples showed the presence of *T. annulata* piroplasms.

Table I
Comparison of the bovine tropical theileriosis signs before and after treatment
Abnormal findings are indicated in bold characters

Clinical indicator [reference values]	Cow (animal 1) [a]	Heifer (animal 2)	
	Before treatment	Before treatment	Four days after treatment
Age (years)	**5**	2	
Eyelids	**Unilateral oedema**	Normal	Normal
Lymph nodes	**Enlarged**	Normal	Normal
Temperature (°C) [38 to 39]	**40.5**	39	38.8
Heart rate (bpm) [65 to 80]	**122**	71	65
Respiratory rate (cpm) [15 to 35]	**75**	**36**	32
Mucosae	**Pale**	**Slightly pale**	Normal
Parasitaemia (%)	**70**	**20**	ND

a) The cow died after treatment
ND: not done
bpm: beats per minute
cpm: cycles per minute

Table II
Haematological results of the diseased cattle
Abnormal findings are indicated in bold characters
Reference values were adapted from Blood & Radostits (4)

Indicator	Diseased cow	Diseased heifer	Reference values
Leucocytes (10^9/l)	7.2	**12.8 (H)**	4–12
Lymphocytes (10^9/l)	**1.4 (L)**	6	2.0–7.0
Monocytes (10^9/l)	0.7	**1 (H)**	0–0.8
Granulocytes (10^9/l)	5.1	5.8	2.3–9.1
Lymphocytes (%)	**19.4 (L)**	46.9	20–60.3
Monocytes (%)	9.8	8.1	4–12.1
Granulocytes (%)	**70.8 (H)**	45	30–65
Erythrocytes (10^{12}/l)	**3.60 (L)**	5.16	5.0–10.0
Haemoglobin (g/dl)	**7 (L)**	8.4	8.0–15.0

L: low
H: high

Fig. 1
Oedema of the jaw in a cow with bovine tropical theileriosis

Fig. 2
Ocular oedema in a cow with bovine tropical theileriosis

Fig. 3
Haemorrhagic and ulcerative lesions in a cow with bovine tropical theileriosis

Polymerase chain reaction

The DNA was extracted from blood using a Genomic DNA Prep Kit (Biobasic Inc. Ontario, Canada) according to the manufacturer's instructions. Polymerase chain reaction (PCR) was performed with a set of primers (N517: 5′-GTTACGAACATGGGTTT-3′ and N516: 3′-GTAACCTTTAAAAACGT-5′) (Biobasic, Canada) that amplify a 721 base pair (bp) region of the *T. annulata* merozoite gene sequence (Tams-1) (5, 6).

The PCR mix consisted of 2 mM of each dinucleotide triphosphate (dNTP), 0.5 mM of each primer, 0.05 U/ml Taq polymerase (Vivantis, United States of America), 1 × Taq buffer (10×), 3 mM of $MgCl_2$ (25 mM), 3 ml of DNA template and distilled water to a total volume of 25 ml. The cycling conditions consisted of an initial denaturation step for 5 min at 94°C, followed by 30 cycles of denaturation at 94°C for 1 min, annealing at 55°C for 1 min, and elongation at 72°C for 1 min, followed by a final elongation at 72°C for 10 min. The amplified PCR products were electrophoresed in 1.5% agarose gels and visualised by staining with ethidium bromide under an ultraviolet (UV) transilluminator, using a Biospectrum® AC Imaging System. The electrophoresis showed specific positive blood samples.

Histopathology of nodules

The two cattle presented several skin nodules (Table III, Fig. 4). Samples from the nodules were examined directly and after Giemsa staining. Schizonts of *T. annulata* were not observed, nor were *Demodex* mites as reported by Uilenberg and Zwart (3) in cases of East Coast fever. Tissue samples from nodules were surgically excised, fixed in 10% formalin, embedded in paraffin, sectioned at 3 µm, stained with haematoxylin and eosin and examined by light microscopy. There was a perivascular infiltrate of lymphocytes, macrophages and eosinophils. Nevertheless, no schizonts were observed (Fig. 5). This could be explained by the fact that, owing to practical constraints, the biopsy was taken 18 days after buparvaquone treatment.

Table III
Characteristics of the skin nodules associated with *Theileria annulata* infection in the two reported clinical cases

Location	Diameter (cm)	Approximate density/10 cm²
Neck	0.5–1.5	18–22
Abdomen, chest and thoracolumbar region	1–2	15–20

Treatment and outcome

Treatment of both animals involved intramuscular injection of buparvaquone (Teldex, Médivet) at the conventional dose of 2.5 mg/kg, oxytetracycline (Engemycine 10%, MSD Santé Animale) at 10 mg/kg, flunixin meglumine (Fluxydin, Médivet) at 2.2 mg/kg, a cocktail containing vitamin B12 (Hémathopan B12, Mérial) (20 ml/animal) and a stimulant of rumen function (Rumactyl, Médivet). The animals were treated against ticks with deltamethrin (Vectocid 50 ND, Céva) at a concentration of 50 ppm twice a month. After two days, the cow died and the heifer recovered totally. At day 18, all the nodules except one had disappeared from the skin of the recovered animal (Figs 6 and 7).

Review of skin lesions due to *Theileria annulata* infection

Theileria annulata-induced skin lesions

Bovine dermatology is a neglected speciality in bovine pathology; this could be due to:
– the low level of care given by farmers to the aesthetic aspects of cattle compared with pet animals
– the possibility of culling diseased animals
– the fact that dermatology is a difficult field and needs specific skills.

Some dermatological signs are the expression of severe systemic diseases, which should be diagnosed and rapidly treated. In this paper, tropical theileriosis (*T. annulata* infection) is discussed; in this disease, cutaneous signs appear occasionally, subsequent to the acute phase (7). Indeed, several scattered publications have reported cutaneous signs due to tropical theileriosis. As reported above, two cases of cutaneous expression of bovine tropical theileriosis were found in Tunisia, and it is believed that an overview of the majority of clinical cases reported in the world literature will be very useful. These skin lesions have been reported for both *T. annulata* and *T. parva* infections (3). Most authors describe the signs of tropical theileriosis without reporting any skin lesions; hence, a synoptic review of all reported dermatological lesions in cattle with tropical theileriosis signs is presented in Table IV. The country of origin is included in the table, because there are genetic differences among *T. annulata* populations (8).

Differential diagnosis of skin lesions of bovine tropical theileriosis

Table V contains a list of diseases giving similar cutaneous lesions. Although the cutaneous form of tropical theileriosis

Fig. 4
Numerous skin nodules on the neck and shoulders of a cow with bovine tropical theileriosis

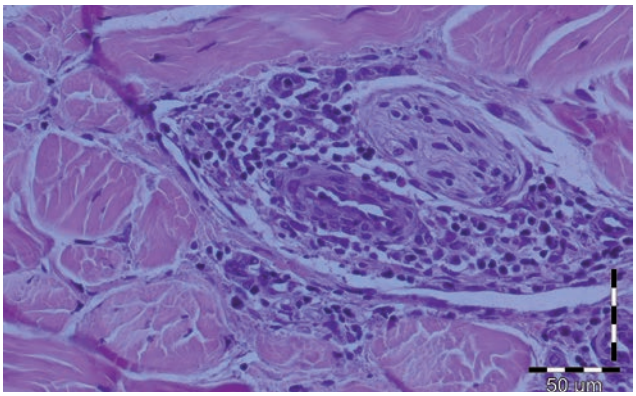

Fig. 5
Perivascular inflammatory infiltrate (lymphocytes, macrophages and eosinophils) (haematoxylin and eosin stain, ×400)

Fig. 6
Skin of a heifer with bovine tropical theileriosis four days after treatment
Note that a small nodule is still present on the left shoulder of the animal

Fig. 7
Nodules on medial thighs of a heifer with bovine tropical theileriosis four days after treatment

is easily differentiated from dermal diseases associated with pruritus (lice, flea infestations, etc.), the association of tropical theileriosis and any ectoparasite is of course possible. For example, Uilenberg and Zwart (3) reported one case of cutaneous nodules in which both *T. parva* schizonts and *Demodex bovis* were found. The multiplication of *Demodex* parasites was attributed to the immunosuppression caused by East Coast fever.

Conclusions

Dermatological signs in bovine tropical theileriosis are considered rare. Scattered clinical cases have been reported in several enzootic regions of the world. The presence of skin nodules may indicate a bad prognosis (14); in Tunisia, the majority of these animals die as a consequence of late diagnosis. Veterinarians in enzootic regions should be aware of this type of sign, which is expressed by an unknown number of cattle. Adequate preventive measures should be implemented to avoid complications (bacterial infections and myiases) of these skin lesions.

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Table IV
A review of reported dermatological lesions in clinical cases of bovine tropical theileriosis (*Theileria annulata* infection) throughout the world
To give an exact clinical and microscopic description, in some parts of the table, the text was transcribed as reported by the authors and should not be considered as plagiarism

Country (host species)	Number of skin cases/number of diseased animals	Description of clinical signs	Microscopic description	References
Algeria ***(Bos taurus)***	4	Only calves presented these signs, they appeared during the acute phase then disappeared when the animals recovered Two types of skin lesion were reported: – Localised dry gangrene on the internal face of the thighs and hock. When the skin is eliminated, bedsores and ulcerations are slow to resolve – Lenticular haemorrhagic eruptions, sometimes with nodules or vesicles affecting mucosae (scleral, pituitary, internal face of the lips and dental pad)	Periarterial lesions with schizonts more numerous than in spleen	(9)
Country not mentioned ***(B. taurus)***	NR	Observed in cattle with brown colour, exclusively observed in piebald animals Extensive severe skin inflammation. Dry loss of large parts of skin then replaced by new skin Constant association with digestive signs	ND	(10)
Israel ***(B. taurus)***	2	*Case 1 (bull):* erythematous eruption on the skin with numerous papules and pustules, particularly in the non-pigmented areas The bull recovered *Case 2 (cow):* erythematous skin with haemorrhages and papular eruptions	Infiltration with lymphatic cells Numerous intra- and extracellular schizonts	(7)
India ***(B. taurus)***		*Cross-bred calves* Haemorrhagic spots or patches in the skin of the ear, medial thighs, axilla, perineal region, around the anus and caudal fold Extensive haemorrhage in the subcutis in the axial and perineal region	Focal haemorrhages with parasitised lymphocytes packed in these areas	(11)
India ***(B. taurus)***	2	36 days, and a 1.5-month-old cross-bred calf Papules (2–4 mm in diameter) over the dorsal surface up to thoracic region and on the sides of neck and shoulder. When pressed: small amount of reddish exudate	Infiltration of lymphoid cells, mononuclear cells and macrophages in the dermis and in such places the epidermis had thinned out. Several macroschizonts (3–4 to 16 chromatin granules) and few microschizonts	(12)
Pakistan ***(B. taurus)***	3/4	Haemorrhages (extensive in two calves) in the subcutaneous tissues in calves aged 4, 12 and 16 days	NR	(13)
India ***(B. taurus × B. indicus)***	3/3	3-month-old calves Nodules 0.1–0.5 cm in diameter, haemorrhagic in the centre, on the face, neck and shoulder, extending to other parts of the body Severe itching; died after 2–3 days	Denuded epidermis, presence of schizonts Infiltrated by inflammatory cells and neutrophils Macrophages and rare lymphocytes Necrosis in the centre of the nodule	(14)
Iran ***(B. taurus)***	NR	On the whole body surface: numerous subcutaneous or intradermal nodules (0.3–1 cm in diameter), some of them quite prominent	Focal haemorrhages and aggregates of parasitised lymphocytes	(15)
Iran ***(B. taurus)***	NR	Nodules only in calves less than 2 months old	>15–20 schizonts per microscopic field	(16)
China ***(B. taurus)***	NR	Papular urticaria of skin lesions	Presence of schizonts	(17)

Table IV (cont.)

Country (host species)	Number of skin cases/number of diseased animals	Description of clinical signs	Microscopic description	References
India *(B. taurus)*	NR	Red papular cutaneous lesions 0.5–1 cm in diameter mainly in the skin of neck and perineal region Intense itching and scratching of the body	Large number of the theilerial schizonts in lymphoid cells	(18)
Pakistan *(B. taurus)*	11/112	Innumerable small (0.5–1 cm in diameter) swellings under the skin and muscles	NR	(19)
Egypt *(Bubalus bubalis)*	2/68	Not described by the authors	NR	(20)
Portugal *(B. taurus)*	15	*Signs:* Multifocal to coalescent white nodular skin lesions (0.2–3 cm diameter), similar to multicentric malignant lymphoma (sometimes haemorrhagic or with a haemorrhagic halo) *Necropsy:* haemorrhagic nodules and nodules with a haemorrhagic halo, particularly in the skin, subcutaneous tissue, skeletal and cardiac muscles, pharynx, trachea and intestinal serosa	Microscopy: large, round, lymphoblastoid neoplastic-like cells Immunohistochemistry: mostly CD3-positive T lymphocytes and MAC387-positive macrophages Presence of *T. annulata* schizonts	(21)
Iran *(B. taurus)*	11	Severe petechial and ecchymotic haemorrhages throughout the skin, particularly in hairless regions	Multifocal necrotic areas in the epidermis Dermatitis in the dermis beneath the necrotic foci Presence of *T. annulata* schizonts in the cytoplasm of the lymphocytes and macrophages	(22)
Tunisia *(B. taurus)*	2/2	15–22 cutaneous nodules/10 cm^2	Perivascular infiltrate of lymphocytes, macrophages and eosinophils. No schizonts were observed	Present study

NR: not reported

Table V
Skin diseases to be differentiated from skin forms of bovine tropical theileriosis (*Theileria annulata* infection)

Disease	Chronic evolution	Presence of other signs	Contagiousness	Impact on the general condition	Severity
Demodicosis (*Demodex bovis* infection)	+++	0	0	+	–
Warbles (*Hypoderma* spp. infestation)	+++	Possible	0	Possible	Generally 0
Besnoitiosis (*Besnoitia besnoiti* infection)	+++	0	0	++	++
Lumpy skin disease	++	Possible	+	Variable	Variable
Abscess	+++ or 0	Possible	–	Variable	Variable
Bovine leucosis	++	Possible	+	Variable	Variable
Allergy	0	0	0	Possible	Variable
Cutaneous tuberculosis (*Mycobacterium bovis* infection)	+++	Possible	+	Variable	Variable
Leptospirosis (*Leptospira* spp.)	+	+++	+	Variable	Variable

0: absent
+ rare
++ moderately frequent
+++ very frequent

'Molecular epidemiology network for promotion and support of delivery of live vaccines against *Theileria parva* and *Theileria annulata* infection in eastern and northern Africa' (SE 862/2-1).

Signes dermatologiques de la theiléríose tropicale bovine (infection à *Theileria annulata*) : une synthèse

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Résumé
La theiléríose tropicale bovine (infection à *Theileria annulata*) est une maladie majeure à transmission vectorielle présente dans plusieurs régions du globe. Les auteurs décrivent deux cas cliniques de theiléríose tropicale survenus dans le nord de la Tunisie, qui présentaient un tableau peu courant de lésions nodulaires. La densité estimée des nodules était de l'ordre de 15 à 20 nodules pour 10 cm² ; ils mesuraient de 0,5 à 2 cm de diamètre et étaient présents sur toutes les parties du corps de l'animal.
L'examen au microscope des nodules cutanés 18 jours après le début du traitement a révélé une infiltration périvasculaire de lymphocytes, macrophages et éosinophiles. En revanche, aucun schizonte n'a été observé. L'administration d'un traitement approprié a éliminé l'infection chez l'un des deux animaux, avec une disparition totale de ses lésions cutanées ; l'autre animal est mort. Les auteurs présentent une synthèse des cas cliniques de theiléríose tropicale (infection à *T. annulata*) s'accompagnant de lésions cutanées. Plusieurs manifestations dermatologiques sont décrites dans la littérature : nodules cutanés, lésions hémorragiques, gangrène cutanée, etc. La plupart des auteurs signalent la présence de schizontes dans les lésions nodulaires. Les manifestations dermatologiques associées à la theiléríose tropicale bovine doivent être prises en compte par les vétérinaires de terrain et faire l'objet d'un diagnostic différentiel par rapport à d'autres maladies présentant un tableau dermatologique comparable.

Mots-clés
Bovin – Nodule – *Theileria annulata* – Tunisie.

Estudio de los síntomas dermatológicos de la teileriosis tropical bovina (infección por *Theileria annulata*): una síntesis

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Resumen
La teileriosis tropical bovina (infección por *Theileria annulata*) es una importante enfermedad transmitida por garrapatas que afecta a varias regiones del mundo. Los autores describen dos casos clínicos de teileriosis tropical diagnosticados en el norte de Túnez que presentaban un síntoma inhabitual: nódulos cutáneos, con una densidad estimada de 15 a 20 nódulos por cada 10 cm². Los nódulos, distribuidos por todo el cuerpo del animal, tenían un diámetro de entre 0,5 y 2 cm. El examen microscópico de los nódulos a los 18 días de tratamiento reveló una infiltración perivascular de linfocitos, macrófagos y eosinófilos, pero no se observaron esquizontes. La administración del tratamiento apropiado llevó a la recuperación de uno de los dos ejemplares, con desaparición completa de las lesiones cutáneas, mientras que el otro murió. Los autores pasan revista a una

serie de casos clínicos de teileriosis tropical (infección por *T. annulata*) con presencia de lesiones cutáneas. En la bibliografía están descritos varios casos con síntomas dermatológicos: nódulos cutáneos, lesiones hemorrágicas, gangrena cutánea, etc. La mayoría de los autores señalan la presencia de esquizontes en las lesiones nodulares. Los veterinarios que trabajan sobre el terreno deben tener en cuenta que la teileriosis tropical bovina puede acompañarse de afectación cutánea y distinguir esta enfermedad de otras patologías que provocan síntomas dermatológicos.

Palabras clave
Ganado vacuno – Nódulo – *Theileria annulata* – Túnez.

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