Toxic epidermal necrolysis associated with *Mycoplasma bovis* in calves

S. Senturk, Z. Mecitoglu, E. Buyukcagaz, O. Ozuyigit

TOXIC epidermal necrolysis (TEN) is a rare dermatological disorder characterised by widespread erythema, necrosis and bullous detachment of the epidermis and mucous membranes, resulting in exfoliation of the skin and possibly leading to sepsis and/or death (Lyell 1956, Lebargy and others 1997). The epithelium of the gut and airways can also be affected, causing clinical signs such as profuse diarrhoea and respiratory distress. Studies conducted in human beings have revealed that detachment of the epidermis is a result of disseminated apoptosis of keratinocytes and that the death of these cells is most likely caused by cytotoxic lymphocytes, monocytes and macrophages (Paul and others 1996). TEN in human beings is most commonly a drug-induced disease caused by antibiotics (such as sulphonamides, macrolides, penicillins, ampicillin and some quinolones (eg, ciprofloxacin), antiepileptic drugs and NSAIDs. However, the disorder has other potential aetiologies in human beings, including *Mycoplasma pneumonia* infection, malignancy and vaccinations (Fournier and others 1995, Tay and others 1996). *M pneumonia*-related TEN cases in human beings are usually milder than drug-induced ones, and generally only 10 per cent of the skin is involved (Tay and others 1996). The pathophysiology of TEN has not been fully elucidated, but it has been suggested that this disease is an immune-related cytotoxic reaction that destroys keratinocytes expressing a foreign antigen (Paul and others 1996). TEN is a clinical diagnosis confirmed by histopathological analysis of skin lesions.

There are only two reports regarding TEN in cattle (Yeruham and others 1999a, b). These studies reported cases of TEN in calves; however, because no underlying cause for disease was detected, the cases were classified as idiopathic (Yeruham and others 1999b). This short communication describes an association between *Mycoplasma bovis* infection and TEN in three calves.

In a dairy herd, 25 calves between one and two months of age showed various signs of arthritis, pneumonia and dermatitis. Of these 25 calves, nine had pneumonia and arthritis, while six suffered only from arthritis and seven had only pneumonia of varying degrees of severity. The three remaining calves were suffering from pneumonia, arthritis and severe cutaneous lesions characterised by thickening of the epidermis, detachment of the epidermis from the dermis and blisters in the detachment site (Figs 1, 2 and 3); these calves are the subjects of this study. For diagnostic purposes, swab samples were collected from blisters and arthritic joints of the affected calves, and samples of tracheobronchial aspiration fluid were also collected. In addition, skin samples were obtained from all affected calves for histopathological examination.

Routine haematological values including total white blood cell count and differential cell count, haematoctrit, haemoglobin concentration, erythrocyte and platelet counts were evaluated using a haemocell counter (Cell-Dyn 3500; Abbott).

All freshly collected samples, including swab samples taken from blisters and arthritic joints as well as tracheobronchial aspiration fluid samples, were inoculated on to Columbia agar (COS 43041; bioMérieux) with 7 per cent defibrinated sheep blood, MacConkey’s agar (CM115; Oxoïd) and Levine eosin methylene blue agar (CM0069B; Oxoïd) for routine diagnosis. The plates were incubated for 24 hours at 37°C. Subsequently, all samples were inoculated directly on to Sabouraud dextrose agar for fungi (CM0041B; Oxoïd), incubated at 25°C and 37°C in the dark for a minimum of three weeks, and examined weekly for evidence of fungal growth. The samples collected from the blisters on skin, arthritic joints and tracheobronchial aspiration fluid were also streaked onto *Mycoplasma* agar base (CM0401B; Oxoïd) plates containing *Mycoplasma* supplement G (SR0059C; Oxoïd) for the isolation of *Mycoplasma* species and incubated for seven days at 37°C in a humidified atmosphere with 5 per cent CO₂. The plates were examined after the seventh day of incubation under 35X magnification for the typical ‘fried egg’ appearance. For histopathological examination, the skin specimens were fixed in 10 per cent neutral formalin, embedded in paraffin and 5 µm sections were cut. The sections were stained with haematoxylin and eosin (HE).

The skin lesions of all three calves were similar, and were characterised by the detachment of large epidermal sheets and the separation of the epidermis from the basal lamina. The lesions were localised around the ventral trunk, head and hind limbs, and approximately 10 per cent of the skin was involved in all three calves. TEN was suspected based on clinical findings, and this diagnosis was confirmed by histopathological analysis of the skin lesions. The calves had not been treated before the onset of the lesions; therefore, TEN was not related to any adverse drug reaction. The calves were treated with 2.5 mg/kg danofloxacin (Advocin; Pfizer) intramuscularly for seven days, a single dose 0.02 mg/kg dexamethasone (Devamed; Topkim) intramuscularly, and 600 mg pentoxyffylne (Trental CR 600;

**FIG 1:** Generalised epidermal exfoliation of the skin of a calf associated with *Mycoplasma bovis* infection.
The haematological results were within the normal limits except for the total and differential white cell counts. All three calves had leucocytosis (11.23 to 21.78 x 10⁹ cells/l, reference range 4 to 12 x 10⁹ cells/l) along with neutrophilia (7.87 to 21.78 x 10⁹ cells/l, reference range 0.7 to 6 x 10⁹ cells/l), indicating the presence of an infection. *M. bovis* was isolated from the bacteriological cultures of the joint, tracheobronchial aspiration fluid and skin samples.

Mycoplasma is known to cause TEN in human beings (Tay and others 1996), but this is the first report demonstrating a relationship between *M. bovis* infections and TEN in calves. In the histopathological examinations, coagulation necrosis was apparent throughout the epidermis. Vesiculation was rare in the dermoepidermal junction, and dermal inflammation, chiefly lymphocytic, was also weak.

In human beings, the estimated mortality associated with TEN varies widely in different reports from 10 to 70 per cent. Sepsis and multiple organ dysfunction syndrome (MODS) are the primary causes of death. Koh and others (2009) reported that the mortality rates in children are much lower than in adults. Similarly, in the present study, toxic epidermal necrolysis affected calves younger than two months of age. These calves did not show the clinical signs of MODS, such as lactic acidosis and azotaemia. According to the mentioned findings, the treatment administered was appropriate for calves suffering from TEN. The treatment of TEN includes monitoring the electrolyte balance, fluid replacement and nutritional support as well as preventing and treating the possible infection. The use of corticosteroids in TEN is much debated. Some reports have described a dramatic improvement in patients with TEN treated with corticosteroids (Becker 1998). The main mechanism of intended action is the reduction of the inflammatory and immune responses. However, some reports suggest that the administration of corticosteroids in TEN can be contraindicated due to a possible increase in the risk of sepsis, especially with prolonged use (Kelemen and others 1995). Becker (1998) suggested that administration of systemic glucocorticoids for more than 48 hours was associated with a higher rate of infection, a longer hospitalisation period and increased mortality. A single dose of the corticosteroid dexamethasone did not trigger any undesired effects in the three calves in the present study. Pentoxifylline improves blood flow through peripheral blood vessels and therefore helps with blood circulation in the dermis and epidermis. Redondo and others (1994) reported the use of pentoxifylline for its antiapoptotic properties in the treatment of TEN in human patients. It modulates TNF production, possibly by the inhibition of the mRNA transcript (Strieter and others 1988, Han and others 1990). Pentoxifylline has also been shown to inhibit T-cell activation and proliferation, as well as natural killer cell activity (Reed and Degowin 1992). Because of these positive effects, pentoxifylline was added to the treatment protocol for the calves.

Other possible medical treatments reported in the literature for the treatment of TEN in human patients include the use of plasmapheresis, intravenous immunoglobulins and ciclosporin (Brambilla and others 2002).

This report represents the first case of TEN thought to be associated with *M. bovis* in cattle. TEN should now be considered in the differential diagnosis of calves presenting with dermatological disorders, especially in the presence of pneumonia and arthritis.

### References


Aventis) twice a day orally for seven days. Improvement of the clinical signs was apparent at day 7 following the start of treatment, and all three calves had recovered by the fourth week of treatment.

FIG 2: Detachment of the epidermis on the hindlimbs and erythema on the ventral abdomen of a calf with arthritis associated with *Mycoplasma bovis* infection

FIG 3: Epidermal detachment and necrosis associated with *Mycoplasma bovis* infection

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