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CASE REPORT

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Malignant catarrhal fever in cattle in Spain

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Abstract

We report a case of malignant catarrhal fever in cattle in a mixed herd (ovine/bovine). The case occurred in the Basque Country (north of Spain) in April 2021. The infection was confirmed by polymerase chain reaction in a calf that had developed signs consistent with the 'head and eye' form of the disease. Just before its appearance, a group of five calves born at the farm (including the affected one), aged between 8 and 12 months, were temporarily housed in a pen adjacent to the sheep shed, and separated by a metallic fence that allowed direct contact. In Spain, there are no data on the incidence of malignant catarrhal fever, as there is no active surveillance programme in place. Furthermore, the disease is uncommonly considered in differential diagnoses.

BACKGROUND

Malignant catarrhal fever (MCF) is a sporadic, highly fatal lymphoproliferative disease of cattle and other ungulates (including deer, bison and pigs).[1–3] MCF is caused by the ruminant γ-herpesviruses alcelaphine herpesvirus 1 (AlHV-1) and the ovine herpesvirus 2 (OvHV-2), with this latter herpesvirus being the main responsible for the disease in cattle.[4]

MCF has a worldwide distribution and is economically significant, but it has greater impact on livestock in those regions where cows and sheep tend to coexist more closely.[5]

Ovine infections are almost always asymptomatic, but they are sources of virus for cattle, which are dead-end hosts. Other ruminants, including goats, may also harbour the virus.[6] The virus is shed intermittently with nasal and ocular secretions, and transmitted mainly by the respiratory route. Close contact with sheep by susceptible individuals is usually required, but transmission over notable distances has also been described.[7]

MCF outbreaks in cattle herds usually show low morbidity and high mortality rates, affecting mainly younger animals.[8] In cattle, the incubation period ranges from 2 to 10 weeks, but can extend up to 9 months.[9]

Various clinical forms of the disease have been characterised. The most common is the 'head and eye' form, in which the initial clinical signs are lethargy, anorexia and fever (41°C–41.5°C). Further clinical signs are profuse mucopurulent nasal discharge and ocular discharge with eyelid oedema. Due to obstruction of the nasal cavities with exudate, severe dyspnoea with stertor can be observed. The sclera becomes reddened due to congestion of vessels, and the cornea becomes progressively opaque. Necrosis can occur in the nasal and oral mucosa, with ulcers that cause severe pain; they are mainly located on the hard palate, back of the tongue, gums, gingiva and inside of the lips. Papillae of the cheeks may appear haemorrhagic and eroded. Sometimes hypersalivation with viscous saliva is observed. The skin on the muzzle may be extensively ulcerated and covered with scabs. The presence of ulcers in other areas of the skin, such as the skin–hoof junction, vulva, teats and scrotum is less common. In some cases, there may be a neurological condition that alters the animal's motor capacity or causes tremors. Superficial lymph nodes are often visible and enlarged. The duration of the disease is highly variable, and the mortality rate is close to 100%.[10–13]

In the peracute form, the course is especially rapid, with fever, dysentery and death in 12–24 hours.[14,15]

The digestive form is also characterised by a picture similar to that of the 'head and eye' form, but animals often show intense diarrhoea, and the ocular lesions are less evident. A mild form that occurs with transient fever and small mucosal erosions has also been described. This mild form can progress to a complete cure, convalescence with relapse or chronic MCF, in which persistent bilateral leukoma is the most characteristic sign.[14,15]

The most common findings at postmortem examination include ulcerative lesions in the oral and upper respiratory tract mucosa. These lesions usually extend along the digestive tract in the form of longitudinal erosions in oesophagus, erythema and haemorrhage in abomasum, catarrhal enteritis and swelling and ulceration of Peyer's patches. There may be

similar changes in the trachea and bronchi. The liver is oedematous, and there may be bleeding from the urinary bladder. The lymph nodes are swollen and, in some cases, haemorrhagic. At the ocular level, different degrees of corneal opacity can be observed and sometimes hypopyon. Finally, petechiae and congestion may be present in the central nervous system and meninges. The main histological lesions consisted of lymphocyte accumulation in a range of tissues, which can be associated with extensive vasculitis and necrotic lesions.[16]

Moderate to severe leukopenia is the most frequent alteration in the haematological analysis, with lymphopenia and neutrophilia often recorded.[17,18] Nevertheless, neutropenia has also been described.[19] Regarding serological analyses, several tests for the detection of antibodies are available. Competitive ELISA is a preferred test for the screening of infection in susceptible animals,[20] but the fact that seroconversion is not always present in acutely affected animals should be considered. Nucleic acid-based detection of MCF is the currently accepted method for diagnosis confirmation worldwide. The hemi-nested PCR is a World Organisation for Animal Health (OIE)-approved diagnostic test for the detection of OvHV-2 infection.[21]

Treatment is symptomatic, based on non-steroidal anti-inflammatory drugs that reduce suffering. However, euthanasia may be the most suitable treatment for severely affected animals for animal welfare reasons. There are no effective vaccines against MCF.

LEARNING POINTS/TAKE-HOME MESSAGES

- A case of malignant catarrhal fever is described in a calf from a mixed farm (ovine/bovine). It was associated with the fact that a group of five calves were temporarily housed in the sheep shed.
- This case draws attention to the importance of biosecurity in mixed farms (ovine/bovine). Co-housing sheep and cattle should be avoided, and adequate hygienic measures should be maintained when both species are handled by the same farmer.
- In Spain, as in other European countries, there is little data regarding the epidemiology and the incidence of the malignant catarrhal fever disease (lack of active surveillance plans). This case repot supports the inclusion of this disease among the differential diagnosis in cases clinically and epidemiologically consistent with malignant catarrhal fever.

CASE PRESENTATION

The case occurred in a farm, consisting of 35 Limousin suckler cows, and 160 Latxa breed ewes. It is located in the province of Álava (Basque Country, north Spain). The Limousin cattle herd is maintained in a semi-extensive system, in which the cows graze on meadows adjacent to the farm. The Latxa breed is a dairy, autochthonous breed from the Basque Country; in this farm, they are permanently housed indoors.

In addition to the national compulsory tuberculosis and brucellosis programme, the cattle herd is under a voluntary bovine viral diarrhoea virus (BVDV) and bovine herpesvirus 1 control programme. The last sampling involving these two viruses had been carried out in October 2019, with negative results.

In February 2021, a group of five calves (two males and three females) born on the farm, aged between 8 and 12 months, were temporarily housed in a pen adjacent to the sheep shed, and separated by a metallic fence that allowed direct contact (Figure 1). This period coincided with the lambing season

FIGURE 1 Sheep shed temporarily shared with calves

FIGURE 2 Gingiva with hyperaemia and ulcers in one calf suffering from catarrhal malignant fever

of the ewes. Sheep and cattle were attended by the same stockmen.

On 2 April, the routine vaccination against clostridial diseases (Toxipra-Plus, Laboratorios Hipra, Spain) was administered to cattle, including the aforementioned group of five calves (4 ml/animal, intramuscular injection). The same vaccine was applied to the ewes (2 ml/animal, subcutaneous injection).

About 12 hours after vaccination, the owner noticed that the five calves housed in contact with the sheep showed lethargy and anorexia. Ewes, that had also been vaccinated, did not show any signs of disease. After worsening of the symptoms, on 5 April, the veterinarian responsible carried out a physical exam, describing a nonspecific clinical picture affecting these calves, with fever (40.5°C–41.2°C) as the most consistent sign. The first presumptive diagnosis, based on the anamnesis, was a vaccine reaction. The veterinarian communicated the suspicion to the manufacturer of the vaccine, which initiated the corresponding pharmacovigilance protocol. On 9 April, one of the calves developed dysentery, dying hours later. The remaining four still showed unspecific signs, including fever.

On 21 April, another of the calves showed dysentery. In this case, a detailed physical exam was carried out. The main findings were profuse nasal/ocular mucopurulent secretion, blepharitis, congestion of the scleral vessels, ulcers and scabs on the muzzle, hyperemia in the oral mucosa, with ulcers on the gums (Figure 2) and inside of the lips and cheeks, lymph node enlargement, exudative papules and alopecic areas in the head, neck and shoulders. The rectal temperature was 41°C. The animal died 5 days later, while the remaining three recovered.

INVESTIGATIONS

On 21 April, blood samples were taken from the sick calf and its three remaining pen mates (that did not show symptoms anymore at that time). A complete haematological analysis was also performed (only from the sick calf) (Table 1).

TABLE 1 Results for haematologic parameters in a sick calf from the studied farm, and reference intervals

	Results	Reference intervals
White blood cell count	$0.57 \times 10^6/mm^3$	$4–12 \times 10^6/mm^3$
Red blood cell count	5.97*1012/L	5–10*1012/L
Haemoglobin concentration	9.1 g/dl	8–15 g/dl
Haematocrit	22.7%	24%–26%
Mean corpuscular volume	38 fl	40–60 fl
Mean corpuscular haemoglobin	15.2 pg	11–17 pg
Red cell distribution width	22%	0%–19%
Platelets	$11 \times 10^6/mm^3$	$100–800 \times 10^6/mm^3$
Neutrophils	$0.04 \times 10^6/mm^3$	$0.6–4.3 \times 10^6/mm^3$
Lymphocytes	$0.40 \times 10^6/mm^3$	$2.5–7.5 \times 10^6/mm^3$
Monocytes	$0.10 \times 10^6/mm^3$	$0.02–0.85 \times 10^6/mm^3$
Eosinophils	$0.01 \times 10^6/mm^3$	$0–2.4 \times 10^6/mm^3$
Basophils	$0.01 \times 10^6/mm^3$	$0–0.03 \times 10^6/mm^3$
Neutrophils (%)	7.8%	15%–47%
Lymphocytes (%)	71%	45%–75%
Monocytes (%)	17.6%	2%–7%
Eosinophils (%)	2%	2%–20%
Basophils (%)	1.6%	0.01%–2%

The most significant finding was severe leukopenia with neutropenia and lymphopenia. Thrombocytopenia was also found.

Regarding the aetiological diagnosis, a BVDV E^{rns} antigen ELISA was performed on the four samples collected (BVDV Ag Serum plus, Idexx Laboratories, Amsterdam, The Netherlands), with negative result in all cases. Likewise, a PCR was performed for the detection of bluetongue virus (BTV),

which identifies all currently known BTV serotypes (qRT-PCR BTV - S10),[22] also with negative results. In Spain, BTV is a disease of obligatory declaration, and the analysis was performed in the official animal health laboratory of the Basque Institute for Agricultural Research and Development.

Samples were also analysed for OvHV-2 by PCR[4,21] in the National Reference Laboratory (Central Veterinary Laboratory, Algete). The sick calf tested positive. However, it was not possible to perform a postmortem examination or pathological study in this animal to describe the typical lesions of MCF. The diagnosis was based on the combination of anamnesis, epidemiology and clinical signs, together with detection of OvHV-2 by PCR.

DIFFERENTIAL DIAGNOSIS

The clinical signs of the 'head and eye' form of MCF resemble those of other diseases that cause oral lesions.[23] Thus, BVD/mucosal disease (MD), foot and mouth disease (FMD), bluetongue and vesicular stomatitis may be considered as potential differential diagnoses when MCF is suspected.

Spain is an FMD-free country since 1986. Although FMD affected several European Union countries from 2001 to 2011, initially we decided to rule out other more common diseases in the studied area.

Thereby, considering that BVDV is endemic in Spain (and the last BVDV test on the farm had been carried out in 2019), and that BTV serotypes 1 and 8 had circulated in recent years in the north of the country, these were the initial diseases to rule out, together with MCF, which was the main presumptive diagnostic. BVDV persistently infected (PI) cattle may develop MD, with symptoms consistent with those observed in the farm.

The signs observed in the calf that died on 9 April (with dysentery) could also be consistent with salmonellosis or other digestive disorders. Unfortunately, no samples from this calf were available.

TREATMENT

On 5 April, the farm veterinarian gave an anti-inflammatory treatment (Meganyl, flunixin meglumine, 2 ml/45 kg vaginally [p.v.], intravenous [i.v.]). Symptomatic treatment was maintained until clinical signs disappeared. A broad-spectrum antibiotic was also incorporated to prevent secondary bacterial infections (Doxidol, doxycycline monohydrate, 1 ml/10 kg p.v., i.v.).

OUTCOME AND FOLLOW-UP

MCF could be confirmed by PCR in the calf showing symptoms on 21 April. The remaining calves could have suffered the mild form of the disease, while the calf showing dysentery (that died on 9 April) could have developed the hyperacute form. However, these facts could not be confirmed, and MCF was only verified in one animal.

It should be taken into account that relapse episodes of MCF have been described several months after the initial infection, sometimes with a fatal course.

The circumstances of the case and the possibility that it originated from the close contact to sheep were explained to the farmer, designing appropriate biosecurity measures and emphasising that any direct or indirect contact between both species should be avoided. Since then, the farmer has not kept the sheep and cattle together and has implemented biosecurity measures (in relation to machinery, equipment and protective clothing) when visiting both herds, in order to prevent indirect contagions.

DISCUSSION

The epidemiology of OvHV-2 infection in cattle and the reasons some cattle develop clinical signs of MCF remain unclear.[24]

Contact with sheep appears to be a consistent finding in affected cattle. OvHV-2 is carried by sheep as a lifetime subclinical infection. The virus is shed into the environment through nasal and ocular secretions, and clinically susceptible species (such as cattle) get infected mainly through inhalation, but also ingestion of virus secretions or contaminated food and water.[25] Cows generally are thought to be dead-end hosts and do not spread virus; this has the effect of limiting the spread of disease during outbreaks. Thereby, a feature of MCF, with respect to cattle, is that outbreaks are usually sporadic, with one or only a few individuals being affected. The explanation for absence of spread from MCF-susceptible animals is likely to be that the virus remains in a cell-associated manner in these species and cell-free virus is not produced.[26] OvHV-2 shedding from sheep may be higher during the periparturient period, which leads to a higher risk in case of living with cattle.[27]

In the present case, the time elapsed between the arrival of the calves into the ewes shed and the onset of the symptoms was adjusted to the incubation period for MCF.[9]

In Spain, only one MCF outbreak in cattle has been published to date, although the real incidence of the disease is unknown. This outbreak involved nine animals and occurred in Galicia (northwest Spain) in a mixed herd of dairy cattle and sheep in 1992.[10] There are no recent studies on the prevalence of MCF in Europe. Nevertheless, Scotland has reported, some years ago, an increase in the number of confirmed cases in certain areas.[28]

In the present case, the haematological analysis showed a more severe leukopenia than that described in other cases.[14,29] As previously described, lymphopenia was found[17,29] along with neutropenia (which has also been previously associated to MCF).[19] Thrombocytopenia was also found that could be subsequent to MCF-related vasculitis and haemorrhagic lesions.

BVDV/MD were considered in the differential diagnosis, since the farm had carried out the last control longer than a year and a half ago. This time would be sufficient for a hypothetical new infection with the birth and presence of PI animals, a necessary condition for MD. In addition, severe leukopenia is a very characteristic sign in BVDV infections.

The inclusion of BTV in the differential diagnosis was considered appropriate due to the geographical location of the farm. The farm is close to a large area in northern Spain where recent cases have been reported. Actually, the last outbreak of serotype 1 BTV in the Basque Country was described

in 2020.[30] Serotype 8 had also circulated in the region previously.

The development of clinical signs just after vaccination against *Clostridium* spp. could have been a mere temporal coincidence, but a causal relationship cannot be ruled out. Herd treatments, such as vaccination, trigger severe stress. For the particular case of MCF, it has been suggested that stress may facilitate the disease development.[31] Thus, the appearance of clinical disease in this animal, in which the virus would have previously completed the incubation period, may have been favoured by the immunodepression due to vaccination stress.

As no effective treatment and vaccine are available, biosecurity plays a fundamental role in MCF control. Avoiding co-farming of cattle with sheep would be the key measure. In the event that it is necessary to share personnel or machinery/equipment between both herds, emphasis should be placed on maintaining adequate protection measures to avoid indirect contagions (i.e., adequate protective clothing and fomites sterilisation).[5,15,26]

AUTHOR CONTRIBUTIONS

IM conceived and designed the project. MP and IM acquired the data. GA, PO and FJD analysed and interpreted the data. IM and FJD wrote the paper.

CONFLICT OF INTEREST

The authors declare they have no conflicts of interest.

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ETHICS STATEMENT

This article does not contain any studies involving experimentation with animals performed by any of the authors.

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