



## RESEARCH ARTICLE

### Malignant Catarrhal Fever Associated with Ovine Gammaherpesvirus-2 in Domestic Ruminants in Queretaro, Mexico

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#### ABSTRACT

Malignant catarrhal fever (MCF) is a fatal disease caused by a *Macavirus* of the *Herpesviridae* family that affects even-toed ungulates worldwide. The two most important subgroups are *Alcelaphine gammaherpesvirus-1* (AIVH-1) and *Ovine gammaherpesvirus-2* (OvHV-2). MCF, in Mexico, is considered an exotic disease according to the "Agreement classifying mandatory notifiable exotic and endemic diseases and plagues in terrestrial and aquatic animals in the United Mexican States". This study was undertaken in 2018 on a teaching farm in the Mexican Highlands with affected sheep, goats, cows, and deer, all with ulcerative lesions varying from minor to severe. Some animals were officially diagnosed as positive for OvHV-2 using semi-nested PCR by the organization responsible for such diagnoses in Mexico. The principal lesions observed include ulcerative and erosive lesions in the oral cavity and digestive tract; corneal opacity; interdigital fold lesions; and lymphadenomegaly. This represents an outbreak of OvHV-2-associated MCF in Mexico confirmed by WOAHA-approved diagnostic tests.

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#### INTRODUCTION

Malignant catarrhal fever (MCF) is a fatal disease caused by a *Macavirus* of the *Herpesviridae* family and *Gammaherpesviridae* subfamily that affects even-toed ungulates worldwide (Spickler, 2019; WOAHA, 2020). MCF has 10 members, 6 of which are known to naturally cause disease in susceptible species; due to their behavior and economic impact, the two most important subgroups are *Alcelaphine gammaherpesvirus-1* (AIVH-1) and *Ovine gammaherpesvirus-2* (OvHV-2) (Abd El Rahman *et al.*, 2020). AIVH-1, which is endemic in wildebeests and other wild ruminants, can cause lesions in cattle and is the principal cause of MCF in Africa. OvHV-2, which is transmitted by domestic and wild sheep, affects cattle, multiple species of deer, elk, bison, pigs, buffalo and domestic goats; OvHV-2 represents the most important cause of MCF outside of Africa, zoos and wild animal parks (Foyle *et al.*, 2013; Headley *et al.*, 2012).

MCF is a disease that affects lymphoid organs. Although the pathogenesis is not completely understood, it is associated with cytotoxic T lymphocyte (CTL) dysfunction, leading to lymphoproliferative lesions and

vascular damage caused by CTL in respiratory and gastrointestinal epithelium, as well as in medium caliber arteries distributed throughout the body. (Uzal *et al.*, 2016). Typical lesions in susceptible species include: ocular discharge; panophthalmitis; generalized lymphadenopathy; inflammation and necrosis of the digestive, respiratory, and urinary tracts; dermatitis; arthritis; and neurologic signs secondary to encephalitis (O'Toole and Li, 2014).

Despite being a worldwide disease, no confirmed cases had been reported in Mexico before 2018. MCF [*Ovine gammaherpesvirus-2* and *Caprine / Alcelaphine* (AIVH-2)] was classified as an exotic disease in Mexico in an agreement published on November 29<sup>th</sup>, 2018 in the Official Journal of the Federation (Mexican Secretary of Agriculture, Livestock, Rural Development, Fisheries and Food, 2018). Exotic animal diseases, such as MCF, can have important repercussions on the economy, on animal health, and on business and trade, and reporting these diseases is therefore mandatory.

The objective of the present study is to report the presence of MCF in different ruminant species in the Mexican Highlands and provide a timeline of how the disease disseminated, including observed macroscopic and

microscopic lesions, severity of lesions, and mortality in each ruminant species.

## MATERIALS AND METHODS

This study was undertaken on a 186-hectare farm in the Mexican Highlands, at 10°36'13.88" North latitude and 99°55'02.91" West longitude, at an altitude of 1913 asl. By August 2018, the farm had 169 Holstein, New Zealand, Jersey, and crosses (dairy cows), 109 Limousine (feedlot), 271 dairy goats, 246 Suffolk sheep and crosses, and 103 red deer. The distance between each herd ranged from 1.14 to 2.8 km. Biosecurity measures on the farm are: vehicle wash, disinfection mats with 0.5% sodium hypochlorite, work clothing specific to different work areas, and footbaths for use both before and after farm activities.

**Chronological study:** From August to December 2018, a log of all animals with signs and lesions suggestive of MCF was prepared, and a report was emitted to the Mexico-United States Commission for the Prevention of Foot and Mouth Disease and Other Exotic Animal Diseases (CPA), the organization in charge of disease diagnosis and ruling out differentials. Simultaneously, a chronological study of affected species was completed.

**Postmortem examination:** Throughout the outbreak, a total of 23 dead animals of different species were submitted for postmortem examination to the Diagnostic Verification Services Unit (USEDICO) of the CEIEPAA, FMVZ-UNAM. Tissues were fixed in 4% neutral buffered formalin, embedded in paraffin, cut into 3 µm sections, and stained with hematoxylin and eosin.

**Complementary tests:** The immunological and molecular diagnosis was carried out in the CPA level 3 biosafety laboratory. From September to December 2018, CPA staff took samples to rule out other vesicular diseases: serum from cows and goats, analyzed by ELISA for Foot-and-Mouth Disease (*Aphthovirus*) and Vesicular Stomatitis (*Rhabdovirus*), bovine serum was tested by Neutralizing Peroxidase-Linked Antibody Assay for Bovine Viral Diarrhea (*Pestivirus*), samples of deer organs (tongue, brain, submandibular lymph nodes, kidney and spleen), analyzed by RT-PCR for Bluetongue (*Orbivirus*). These protocols were used in accordance with the WOA manuals.

**Viral DNA extraction:** In the case of MCF, the samples were grouped in a pool of organs per animal (oral lesions, tongue, brain, submandibular lymph nodes, kidney, and spleen) and kept at refrigeration temperature (4°C), subsequently the nucleic acids were extracted through of the trizol method. A polytron plus 500 µl of trizol (Qiagen) was used for the disintegration of the organs and the homogenate of these, later 750 µl of the disaggregated samples were transferred to sterile 1.5 ml microcentrifuge tubes plus 200 µl of phenolchloroform, they were homogenized with the aid of the vortex and centrifuged at 9275 relative centrifugal force (rcf) for 15 min at 4°C. The aqueous phase was transferred into a 1.5 ml sterile microcentrifuge tube plus chloroform at a ratio of 200 µl for each ml of the aqueous phase, homogenized with a

vortex and centrifuged at 9275 rcf for 15 min at 4°C. Subsequently, the upper aqueous phase was obtained and transferred to a sterile 1.5 ml microcentrifuge tube plus the same volume of isopropanol, it was homogenized with the vortex and allowed to precipitate for 4 h at 4°C, after this time it was centrifuged at 9275 rcf for 15 min at 4°C, followed by discarding the supernatant. The resulting pellet was washed with 75% ethanol diluted with Diethyl pyrocarbonate (DEPC) treated water at 4°C, then centrifuged at 9275 rcf for 1 min at 4°C. The supernatant was decanted and centrifuged again at 9275 rcf for 1 min and the excess ethanol was removed. The ethanol could evaporate for 5 min and 15 to 30 µl of DEPC-treated water was added to it. For the quantification and evaluation of the purification, a spectrophotometric analysis was carried out at an absorbance of 260 and 280 nm. The samples were found with a value of 1.9.

**PCR amplification and sequencing:** The detection of the gene for the integument protein of MCF virus (*Ovine gammaherpesvirus-2*) was based on a semi-nested PCR reaction with 2 reverse oligonucleotides called a and b, this protocol was based on the WOA manuals (WOAH, 2018). The Platinum Taq DNA polymerase kit (Invitrogen, 10966018) was used. After extraction of the nucleic acids, the reactions were carried out according to the manufacturer's instructions with a 10 X buffer mix, 50 mM MgCl<sub>2</sub>, dNTP mix 10 mM, 0.2 µl of Platinum taq DNA polymerase, 10 µM forward oligonucleotide, 10 µM reverse oligonucleotide "a", 5 µl of the warm and nuclease-free water for a volume of 50 µl. The cycling conditions were with a cycle at 95°C for 15 min; followed by 25 cycles of 94°C for 60 sec, 54°C for 60 seconds, and 72°C for 60 sec, with a final extension at 72°C for 10 min. For the second amplification, the same mix and protocol was used with the reverse oligonucleotide "b" and 5 µl of the first amplified as a template. The oligonucleotides used were for the detection of a fragment of the gene for the integument protein with a size of 422 bp of the first amplification and 236 bp of the second amplification with the following sequences: Forward: 5'-GGC YCA YAA YCT ATG CTA CTC CAC -3', Reverse a: 5'- AAA AAC TCA GGG CCA TTC TG -3', Reverse b: 5'- ATT RTC CAC AAA CTG TTT TGT -3'.

## RESULTS

**Chronology of events:** The first suspicious case of MCF was seen on August 29<sup>th</sup>, 2018, during an autopsy of a 6-month-old goat from a newly introduced herd with ulcerative lesions on the tongue and larynx. On September 3<sup>rd</sup>, oral lesions were observed in 6 goats from the same herd and 15 Holstein cows who were 1.78 km away. CPA personnel completed 2 serologic studies on 6 Holstein cows to rule out vesicular diseases; the cows were negative for both foot and mouth disease and vesicular stomatitis. The first confirmed diagnosis of MCF associated with *Ovine gammaherpesvirus-2* was obtained on October 4<sup>th</sup> via semi-nested PCR of whole blood samples from all 6 Holsteins. Later, on November 6<sup>th</sup>, oral lesions were seen in 21 deer of varying ages, including fawns and adults and on November 7<sup>th</sup> a diagnosis of MCF was confirmed via semi-nested PCR on whole blood samples of 5 of these deer. An

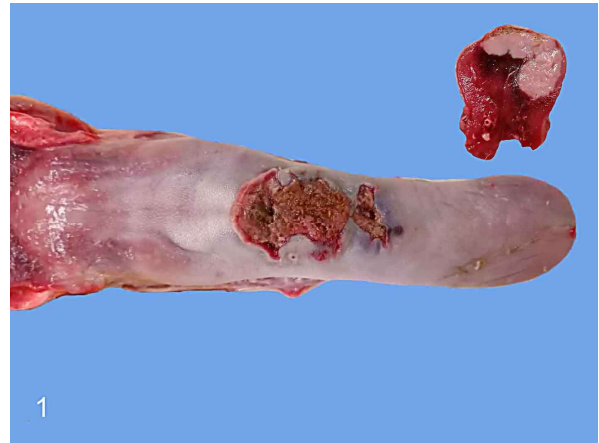
MCF diagnosis was also achieved later through samples of tongue, encephalon, lymph nodes, spleen, and kidneys of three deer (November 19<sup>th</sup>). On November 13<sup>th</sup>, the first case of ulcerative lesions in Limousine cattle was seen, and 8 cows tested positive on November 21<sup>st</sup>. In sheep, 10 cases of lesions suggestive of MCF were seen after November 15<sup>th</sup> and confirmed on the 21<sup>st</sup> of the same month in oral lesions. A case in goats was diagnosed via semi-nested PCR of a lung sample on November 29<sup>th</sup>.

The number of clinical cases of MCF with oral lesions increased as time passed, reaching a total of 41 affected animals in the month of November (9 Limousine cattle, 21 deer, 10 sheep, and 1 goat), and 35 affected sheep in December. Throughout the outbreak, morbidity due to MCF in various species was dairy cows (15/169, 8.8%), feedlot (8/109, 7.3%), sheep (37/246, 15%), milk goats (8/271, 2.9%) and red deer (21/103, 20%). Mortality in fawns (14/103, 14.43%) and goats (1/271, 0.36%). In the other species, no deaths directly due to MCF occurred.

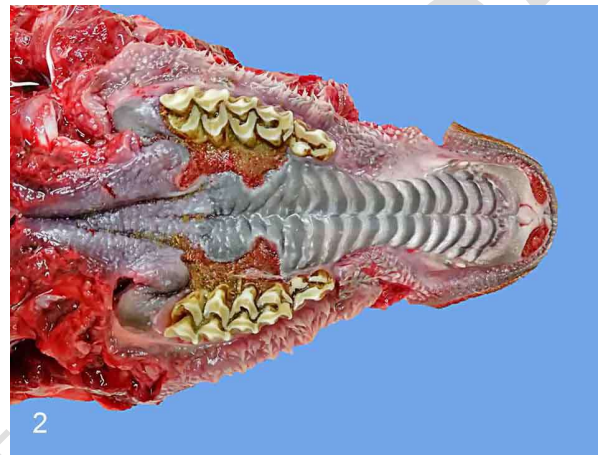
**Postmortem examination:** A total of 23 autopsies were performed throughout the outbreak, of which 14 fawns (5-month-old), 5 goats (three adults and two 6-month-olds), 2 sheep (one 7-month-old and one 1.6-year-old), one dairy cow, and one feedlot cow presented findings suggestive of MCF, namely ulcerative lesions in the oral cavity. All deer had injuries consistent with MCF and death was directly related to the disease, but only 9 were processed for histologic evaluation, as 5 had advanced postmortem changes at the time of autopsy. In the other species, while the animals submitted to postmortem examination presented macroscopic and microscopic lesions suggestive of MCF, mortality was associated with other problems, such as: bacterial pneumonia, coccidiosis, septicemia secondary to cecal perforation, clostridiosis, pancreatitis, and hepatitis in goats; abomasal impaction and peritonitis due to dystocia in cows; and bacterial pneumonia and paratuberculosis in sheep.

**Macroscopic lesions:** The most representative lesions suggestive of MCF were ulcerative stomatitis, pseudomembranous and ulcerative rumenitis, corneal opacity, lymphadenomegaly, and splenomegaly (Table 1). Deer were the most affected species, oral lesions were moderate to severe and involved a large part of the oral cavity, especially around the molars, premolars, and tongue; deep necrosis was noted upon incision, especially on the tongue (Fig. 1 and 2). Four deer and one kid presented multifocal ulcerative rumenitis covered by fibrin (pseudomembrane), which was located mainly in the rumen pillars; one deer had similar lesions in reticulum and omasum (Fig. 3). Corneal opacity (Fig. 4) and submandibular, retropharyngeal, tracheal, and ruminal lymphadenomegaly were seen in all deer, accompanied by necrosis and hemorrhages.

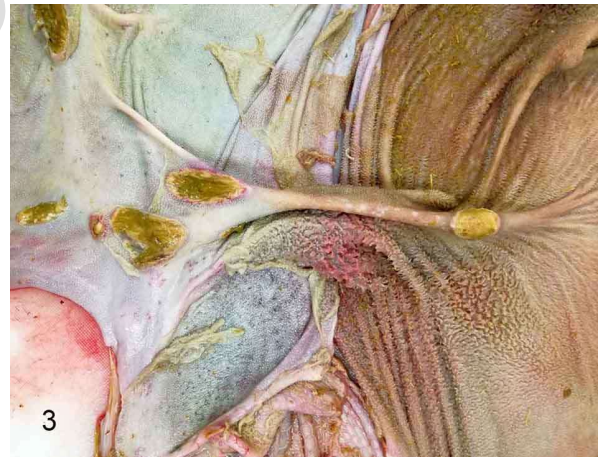
**Microscopic lesions:** The most noteworthy lesion was vasculitis and perivasculitis, with fibrinous necrosis of blood vessels, surrounded by lymphocytes and some lymphoblasts, this lesion was observed in submucosa of the oral cavity (tongue, palate, dental pad, vestibule and pharynx) (Table 1; Fig. 5). Hyperplasia was the most



**Fig. 1.** Ulcerative lesion on a deer's tongue; on a cross-section, extensive areas of necrosis are noted.



**Fig. 2.** Ulcerative lesion on the dental pad and palate.



**Fig. 3.** Ulcerative and necrotic rumenitis on the rumen pillars.

common lesion in lymphoid organs (lymph nodes and spleen), except in a feedlot cow, where lymphoid depletion was seen. Likewise, in deer, necrosis and hyperplasia were more evident (Fig. 6). Multifocal hepatic necrosis was moderate to severe in all species. Corneal edema was observed in 7 deer (Fig. 7). No lesions in the central nervous system, kidney or urinary bladder were observed.



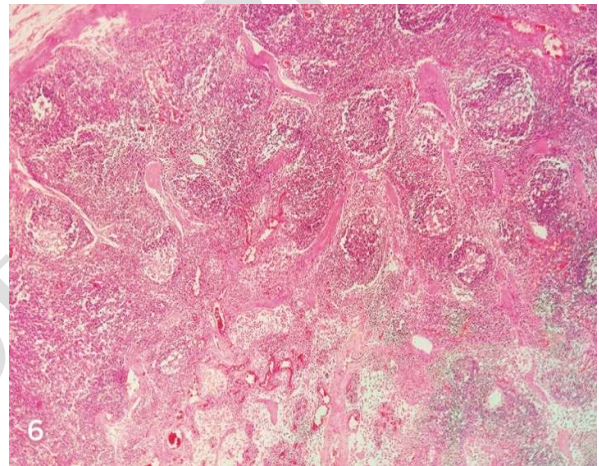
**Table 1:** Macroscopic and microscopic lesions produced by MCF (ovine herpesvirus 2) in domestic ruminants

Species		Feedlot	Dairy cattle	Sheep	Goats*	Goats	Deer	
Age		Adult	Adult	7 M-1.6 Y	6 M	Adults	5 M	
(# of autopsies)		(1)	(1)	(2)	(2)	(3)	(14)	
Macroscopic lesions	Ulcerative stomatitis	+	+	+ / ++	+	+ / ++	+ / +++	
	Alimentary tract	o Tongue	+	+	+	+	+	+++
		o Palate	-	-	-	-	-	+++
		o Dental pad	+	+	-	-	-	++
		o Vestibule	-	-	++	+	++	-
		o Pharynx	-	-	+	+	+	-
	Ulcerative rumenitis	-	-	-	- / +	-	+ / ++	
	Intedigital fold	-	-	-	- / +	- / +	- / +	
	Eye	-	-	-	-	-	++ / +++	
	Lymph nodes	-	-	-	- / +	-	++ / +++	
Spleen	-	-	-	- / +	- / +	++ / +++		
Microscopic lesions	Oral cavity	Perivasculitis and vasculitis	NE	NE	++	++	++	++ / +++
		Hyperplasia	-	++	++	- / +	++ / +++	++ / +++
	Lymph nodes	Necrosis	++	-	- / +	+	-	++ / +++
		Depletion	+++	-	-	- / +	-	- / +
		Hyperplasia	-	++	- / +	- / +	-	+ / ++
	Spleen	Necrosis	++	-	+	+	-	+ / ++
		Depletion	+++	-	- / +	- / +	++	- / +
		Periportal hepatitis	-	++	+ / ++	-	- / +	-
	Liver	Necrosis	+++	+++	+ / ++	++	+ / ++	++ / +++
		Hyaline inclusion bodies	-	+++	- / +	++	+ / ++	- / +
	Lung	-	-	-	- / +	-	-	
	Kidney	-	+	-	-	-	-	
	Eye	-	-	-	-	-	-	++ / +++

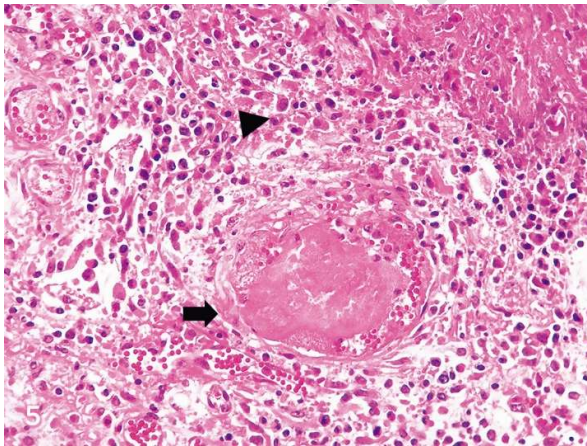
M = months; NE = not evaluated; Y = years; - = absent; + = mild; ++ = moderate; +++ = severe; \* Introduced herd.



**Fig. 4.** Corneal opacity associated with edema was observed in most of the deer, likewise, over the conjunctiva presented moderate fibrinous exudate.



**Fig. 6.** Lymph node showing follicular hyperplasia of the cortex. H&E (magnification: x4).



**Fig. 5.** Cross section of tongue showing necrotic vasculitis with thrombosis (arrow), surrounded by inflammatory infiltrate composed of lymphocytes with a lymphoblastic appearance and plasma cells (arrowhead). H&E (magnification: x40).



**Fig. 7.** Epithelial erosion of the cornea (arrow). H&E (magnification: x40).

## DISCUSSION

When an exotic animal disease is suspected in Mexico, it must be reported to pertinent government agencies, such as the CPA. Mandatory notification is especially imperative if a vesicular disease such as FMD is suspected. FMD caused momentous economic repercussions between 1946 and 1955, resulting in the loss of 2 million slayed animals and 250 million dollars (Cervantes *et al.*, 2011). According to one study (O'Toole and Li, 2014), MCF caused by OvHV-2 is a moderately economically relevant disease. In 2003 in the United States of America, bison breeders reported 800 MCF-associated bison deaths, a loss of one million dollars (Pinheiro de Oliveira *et al.*, 2019). Taking this information into account, it is essential to emphasize that recognizing exotic diseases depends not only on the intervention of authorities and surveillance entities, but also on the veterinarian's knowledge of laws, agreements, and national and international procedures to immediately report any suspicious exotic disease (Roth *et al.*, 2010; Cervantes *et al.*, 2011).

The distance between different herd of the farm ranged from 1.14 to 2.8 km. Previous studies (Spickler, 2019) indicate that sheep-associated MCF transmission has occurred at a distance of 70 m, with an outbreak occurring in bison separated by 5 km from a corral of affected lambs. To date, a minimum distance of separation between species to avoid spread is unknown; however, this is considered a method of MCF prevention. In this study, the introduction of new goats to the farm was considered a possible pathway of MCF dissemination; this remains uncertain, as the new herd was quarantined 1.78 km away from the dairy cows. It must be noted that the farm is part of a university teaching center and receives more than 1,000 students annually, in addition to personnel who move between areas of the farm throughout their daily activities. Therefore, movement of people and vehicles throughout the farm is constant. Other semiintensive productions and backyard systems of unknown sanitary status are also located around the farm. Proximity to the highway and other minor roadways where outside animals and food products are constantly transported may also be considered a possible source of infection (Cervantes *et al.*, 2011; Russell *et al.*, 2009; Spickler, 2019).

The incubation period of MCF varies from 2-12 weeks depending on the virus, the host species, and other factors (Sood *et al.*, 2013). This is consistent with what was observed in the present study, in which the maximum period of disease spread between species was 4 weeks during of period September 3<sup>rd</sup> to November 7<sup>th</sup> (Al-Lethie *et al.*, 2018; Jacobsen *et al.*, 2007). The biosecurity measures established on the teaching farm were insufficient to limit disease dissemination on the premises.

Sheep are not particularly susceptible to OvHV-2-associated MCF, and they tend to have few lesions. Sheep have even been considered reservoirs with no clinical signs, which contrasts with what was observed in the outbreak detailed in this study, as sheep also had mild to moderate oral lesions (Amoroso *et al.*, 2017; Spickler, 2019; WOA, 2020). It has been described that sheep can develop infection like other species when they are experimentally infected with high doses of OvHV-2 (Pesavento *et al.*, 2019). A possible theory for this, in addition to a high dose,

is that the primary exposure of a strain with high virulence affected goats and sheep since at present the disease behaves subclinically. For this reason, more studies should be undertaken to determine and sequence the virus in question. Deer are considered one of the most susceptible species to MCF infection, with most cases presenting in a hyperacute manner, causing death often before clinical signs are noted (within a few days). This coincides with our study, as mortality in deer was causally related to MCF, with lesions preventing food ingestion and subsequent emaciation (Foyle *et al.*, 2013; Schultheiss *et al.*, 2007; Spickler, 2019). Reported mortality rate of MCF in susceptible species can reach up to 100%; in this study the highest mortality rate, 14.43%, was seen in fawns younger than 5 months old (O'Toole and Li, 2014).

Other ulcerative and vesicular diseases, such as foot and mouth disease, vesicular stomatitis, bovine viral diarrhea and bluetongue were ruled out through immunological and molecular tests. Generally, MCF is diagnosed by history and clinical signs, epidemiological data, and microscopic and macroscopic lesions; histopathology is essential, as it is recognized by the World Organisation for Animal Health (WOAH) as the definitive diagnostic tool for the disease; in the case of areas without this disease it is important to carry out complementary tests (Martins *et al.*, 2017; Sharma *et al.*, 2019; WOA, 2018; Arlington *et al.*, 2021), and was confirmed via molecular tests such as semi-nested PCR in the cases in this study.

Oral lesions were involved in the majority of MCF cases and presented as: erosive, ulcerative, and necrotic lesions associated with vascular damage (vasculitis). Such lesions may also be observed in the esophagus and gastric compartments, as was seen in some deer. Other characteristic findings that were seen in these cases are: lymphadenomegaly, splenomegaly, and corneal opacity; these lesions, however, are not considered pathognomonic (Coradduzza *et al.*, 2022). Most studied animals had proliferative lesions in lymph nodes and spleen. Such hyperplasia is common, as MCF is a lymphoproliferative disease, with dysregulation of T-lymphocytes (CD8) due to NK cell dysfunction and uncontrolled proliferation of lymphoblastic cells (Jacobsen *et al.*, 2007). A recent study (Saura-Martínez *et al.*, 2021) indicates that locally proliferating OvHV-2-infected T cells, monocytes, and macrophages contribute to vasculitis in MCF. Other representative lesions that were not observed in this study include: meningoencephalitis, interstitial nephritis, and cystitis (Uzal *et al.*, 2016). The interstitial nephritis that was seen was associated with leptospirosis, diagnosed via microscopic agglutination. Only one goat presented interstitial pneumonia, but no etiologic agent was identified.

Mononuclear perivasculitis with necrotic and fibrinous vasculitis is characteristic of MCF (Costa *et al.*, 2009; Headley *et al.*, 2020). Hepatic necrosis was a frequent finding in all species and has previously been mentioned by other study (O'Toole and Li, 2014).

There are currently no effective vaccines to prevent MCF; however, field vaccines are being developed in some parts of the world to reduce incidence (Lankester *et al.*, 2016; Li *et al.*, 2006). While there is also no effective treatment for MCF, the stability of the virus between pH 5.5-8.5 allows for use of alternating alkaline and acidic

solutions to lower virus load, such as acetic acid, bicarbonate, mineral salts, and anti-inflammatories (WOAH, 2020). In a 2018 report in Egypt (Al-Lethie *et al.*, 2018), phenytoin was utilized topically to treat aphthous fever lesions in cows. Phenytoin, which is normally employed as an anticonvulsant, has also been used to accelerate scar formation. The study reported a reduction in inflammation, edema, transudation, and pain in affected animals, as compared to other treatments.

**Conclusion:** MCF is widely distributed globally, and this study represents the first molecular and pathological diagnosis of the disease in the Mexican highlands. We report the lesions in different ruminant species such as sheep, goats, cattle and deer; and the chronology, main factors and transmission routes to consider. An immediate report to the animal health authorities is recommended, increase biosecurity and displace the transit of people and movement of animals from production units, in case of having suspicious animals.

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