



Diagnostic Exercise

From the CL Davis/SW Thompson Foundation

Case # **219**; Month: **August**; Year: **2023**
Answer Sheet

Title: Malignant catarrhal fever in a cow

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Clinical history: A 6-year-old Angus cross cow euthanized due to being down and seizing for 12 hours. Opaque corneas had been seen in both eyes and treated with local antibiotics.

Gross findings: the carcass was in poor nutritional condition, with no fat reserves, mild but generalized muscle atrophy and serous atrophy of fat. The four chambers of the heart were moderately dilated. The lungs were edematous and congested. Both corneas were opaque and had whitish/blueish discoloration (Fig. 1). A formalin-fixed cut section of the eye is shown in Fig. 2.



Figure 1: severe corneal edema showing typical whitish/blueish discoloration.

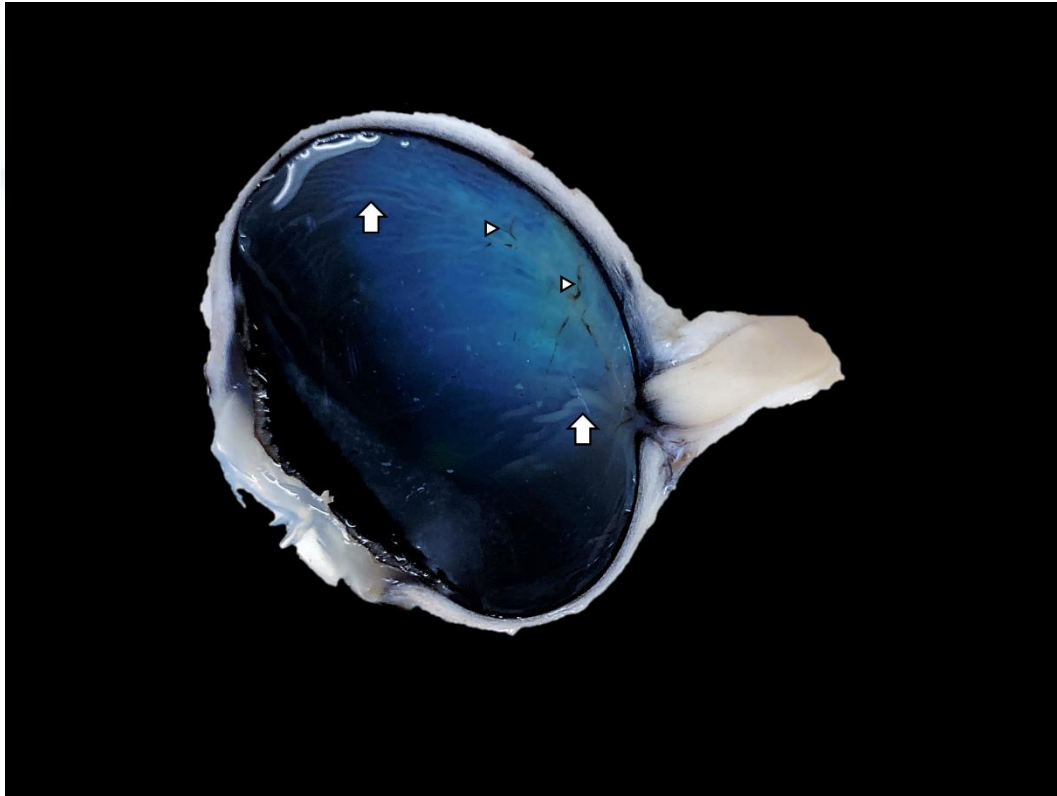


Figure 2: cross section of the eye showing thickened retinal vessels (white arrows) and congested/hyperemic vessels (arrowheads)

Microscopic images:

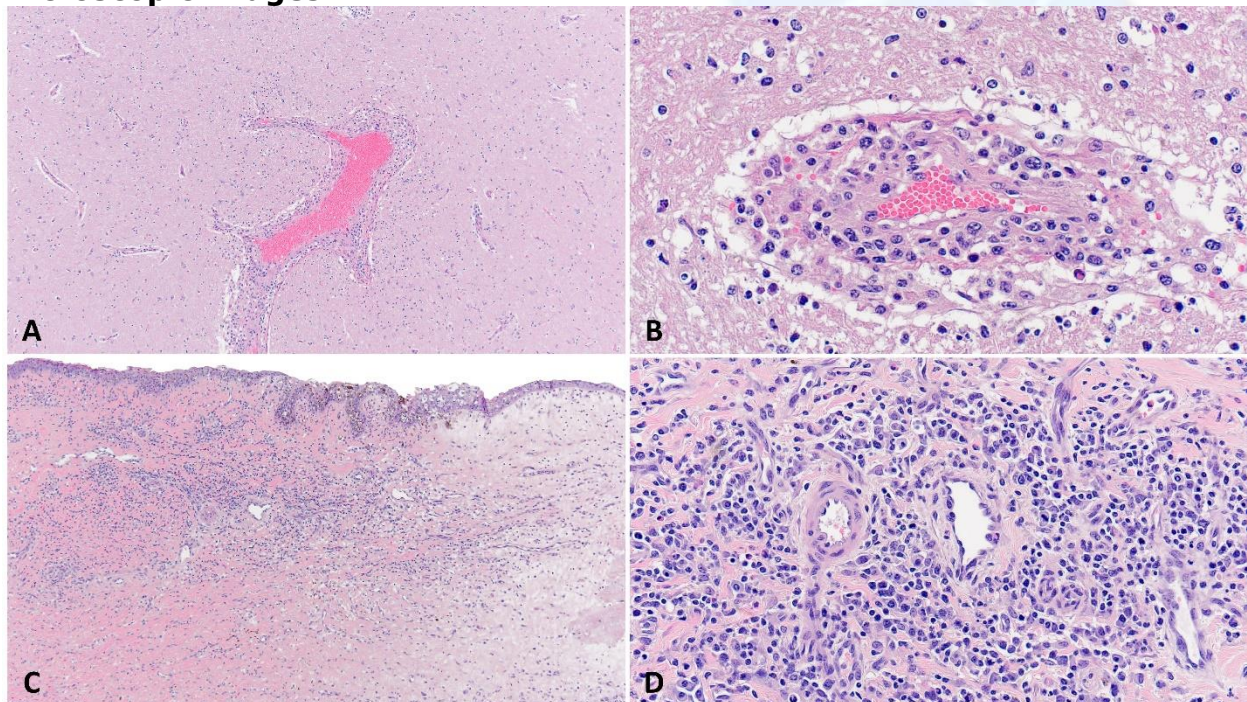


Figure 3: multifocal lymphocytic vasculitis in the brain (A, B) and cornea (C, D). Hematoxylin-eosin, 100× (A, C), 400× (D), and 600× (B).

Follow-up questions:

- (1) Histologic description
- (2) Morphologic diagnoses
- (3) Name the disease
- (4) Etiology

1-Histologic description:

Brain. Multifocally, affecting mostly the brain arteries and arterioles, and to a lesser degree veins, there is a transmural and perivascular infiltration of lymphocytes and fewer macrophages and plasma cells. The inflammatory infiltrate within the vascular walls, expands and separates the vascular layers (Fig. 3A and 3B). There is an increased number of microglial cells and mild vacuolation in the perivascular neuroparenchyma.

Eye, cornea. Multifocally affecting arterioles located predominantly in the corneal-sclera junction, there is a transmural infiltration of lymphocytes and fewer macrophages and plasma cells (Fig. 3C) that extends to the perivascular areas in the corneal interstitium (Fig. 3D). The corneal epithelium contains an increased number of melanin-laden macrophages, and there is epithelial infiltration of lymphocytes (exocytosis). Collagen fibers forming the corneal stroma are diffusely separated by unstained spaces (Fig. 3C, right side). The uvea, including the iris and ciliary bodies, and the retina are moderately to minimally affected (not shown).

Similar vascular lesions were observed in the trachea, lung (Fig. 4A), heart, liver, and kidney (Fig. 4B). In some of these lesions, fibrinoid necrosis and arterial thrombosis can be observed (Fig. 4B).

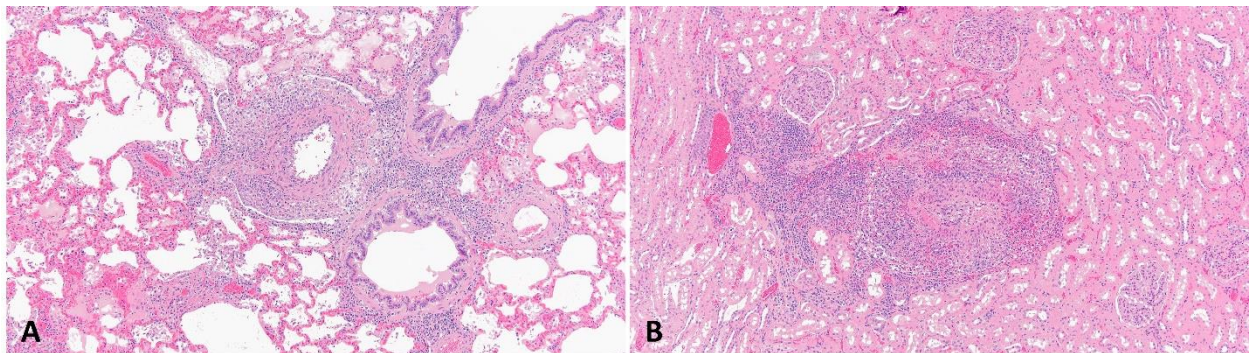


Figure 4: multifocal lymphocytic vasculitis in the lung (A) and kidney (B), and fibrinoid necrosis and thrombosis (B). Hematoxylin-eosin, 100×.

2-Morphologic diagnosis:

- i) Brain: vasculitis, lymphocytic, multifocal, subacute, severe with occasional fibrinoid necrosis.
- ii) Cornea: keratitis-corneal vasculitis, lymphocytic, multifocal, subacute, moderate with corneal edema.

3-Name the disease: Malignant catarrhal fever.

4-Etiology: Ovine herpesvirus type 2

Ancillary test results: Ovine herpesvirus type 2 was detected in spleen by PCR. Various tests for bovine viral diarrhoea virus (PCR, IHC), border disease virus (PCR), and bovine herpesvirus type 1 (IHC) were negative. Bacterial culture of liver and lung yielded no growth results after 48 hours.

Comments: The malignant catarrhal fever (MCF) virus group (genus *Macavirus*, subfamily *Gammaherpesvirinae*) comprises ten members up to now, most of which cause disease in domestic and wildlife ungulates (Table 1). Other members of the *Macavirus* genus, such as bovine gammaherpesvirus 6, amongst others, are not considered to cause MCF. Novel isolates from captive ungulates suffering from MCF-like disease suggest that MCF may be caused by other gammaherpesviruses genera aside of *Macavirus* (7).

Table 1. Members of the MCF virus group. Based on O'Toole & Li, 2014 (6), and updated (1, 4, 7, 8)

	Reservoir host	Susceptible domestic hosts	Susceptible wildlife hosts
Ovine gammaherpesvirus 2 (OvHV-2) "Ovine-associated MCF"	Domestic sheep (<i>Ovis aries</i>) Bighorn sheep (<i>Ovis canadensis</i>) Mouflon (<i>Ovis aries orientalis</i>)	Domestic cattle (<i>Bos taurus</i>) Domestic goat (<i>Capra hircus</i>) Domestic sheep (<i>Ovis aries</i>) Domestic pig (<i>Sus scrofa</i>) Banteng (<i>Bos javanicus</i>) Water buffalo (<i>Bubalus bubalis</i>)	African buffalo (<i>Syncerus caffer</i>) American bison (<i>Bison bison</i>) Bighorn sheep (<i>Ovis canadensis</i>) European bison (<i>Bison bonasus</i>) Moose (<i>Alces alces</i>) Père David's deer (<i>Elaphurus davidianus</i>) Rusa deer (<i>Cervus timorensis</i>) Sika deer (<i>Cervus nippon</i>) White-tailed deer (<i>Odocoileus virginianus</i>)
Caprine gammaherpesvirus 2 (CpHV-2)	Domestic goat (<i>Capra hircus</i>)	Domestic pig (<i>Sus scrofa</i>) Water buffalo (<i>Bubalus bubalis</i>)	Moose (<i>Alces alces</i>) Pronghorn (<i>Antilocapra americana</i>) Pudu (<i>Pudu puda</i>) Roe deer (<i>Capreolus capreolus</i>) Sika deer (<i>Cervus nippon</i>) White-tailed deer (<i>Odocoileus virginianus</i>)
White tailed deer-MCF virus	Domestic goat (<i>Capra hircus</i>)	-	Red brocket deer (<i>Mazama americana</i>) White-tailed deer (<i>Odocoileus virginianus</i>)
Alcelaphine gammaherpesvirus 1 (AIHV-1) "Wilbebeest-associated MCF"	Wilbebeest (<i>Connochaetes</i> spp.)	Domestic cattle (<i>Bos taurus</i>) Watusi (<i>Bos taurus africanus</i>)	-
Alcelaphine gammaherpesvirus 2 (AIHV-2)	Hartebeest (<i>Alcelaphus buselaphus</i>) Topi (<i>Damaliscus lunatus</i>)	-	Barbary red deer (<i>Cervus elaphus barbarous</i>)
Hippotragine gammaherpesvirus 1 (HipHV-1)	Roan antelope (<i>Hippotragus equinus</i>) Scimitar-horned oryx (<i>Oryx dammah</i>)	-	-
Ibex-MCF virus	Ibex (<i>Capra ibex</i>)	-	Bongo (<i>Tragelaphus eurycerus</i>)

	Nubian ibex (<i>Capra nubiana</i>)		Duikers (<i>Cephalophus</i> spp.)
Gemsbok-MCF virus	Gemsbok (<i>Oryx gazella</i>)	-	-
Muskox-MCF virus	Muskox (<i>Ovibos moschatus</i>)	-	-
Aoudad-MCF virus	Aoudad (<i>Ammotragus lervia</i>)	-	-

Ovine herpesvirus type 2 (OvHV-2) is the major member of this group, and it is distributed worldwide. Sheep are natural reservoirs of OvHV-2 and usually do not exhibit clinical disease. However, recent investigations have associated OvHV-2 to sporadic necrotizing vasculitis and chronic interstitial pneumonia in adult sheep and lambs (8). Most bovine cases of MCF occur after contact with sheep or in environments where sheep have been housed before (sheep-associated malignant catarrhal fever -SA-MCF-). Outbreaks of SA-MCF in cattle are sporadic, and for unknown reasons usually affect only a few animals in the herd (most commonly from 8 to 24 months of age) (5,9).

Five patterns of clinical signs are recognized (peracute, head and eye, alimentary, neurological, and cutaneous) most of which overlap, being the head and eye form the most common. Clinical signs for any of these clinical forms are fever ($>41^{\circ}\text{C}$), inappetence, and ocular and nasal discharge (5,9). Other specific clinical signs may follow specific disease patterns, such as neurological signs or slobbering.

The main gross findings of MCF in cattle include corneal edema, keratoconjunctivitis, lymphadenomegaly, alimentary tract ulcers, and rhinitis. These lesions, especially those in the upper alimentary tract, need to be distinguished from those produced by bovine viral diarrhea, infectious bovine rhinotracheitis, bluetongue, epizootic hemorrhagic disease, vesicular stomatitis, foot and mouth disease viruses, and photosensitization (5).

The microscopic characteristic lesions of MCF are systemic vasculitis and inflammation of multiple organs, and ulcers in the alimentary tract, superior respiratory tract, and urinary bladder (5,9). The vasculitis is mostly lymphocytic and affects mainly arteries in most organs (5,9,10). The lymphocytes are mostly cytotoxic T-cells, with a low number of B-cells. T-cells reach the arteries thorough the vasa vasorum, although it has recently been suggested that recruitment of leukocytes from the arterial lumen also occurs. This dual origin of the inflammatory infiltrate leads to a superimposed infiltration of the intima and media (5,10). While macrophages, plasma cells and neutrophils are seen in small numbers; macrophages have been recently regarded as key cells in the pathogenesis of MCF as their release of pro-inflammatory cytokines exacerbates vascular lesions (2). Regardless of the organ, in chronic cases, a proliferative arteriopathy is observed, characterized by obliterating arteriosclerosis (3,6). Severe vascular proliferation may be misdiagnosed as neoplasia.

Necrosis of the tunica media of arteries and arterioles is notably observed in acute cases. However, if the central nervous system is affected, which occurs in up to 90% of MCF cases of cattle, the histological lesions are those of a lymphocytic to lymphohistiocytic vasculitis, lacking necrosis in most cases (2). In this diagnostic exercise, lymphocytic vasculitis was prominent in the central nervous system and eye, but fibrinoid necrosis was mostly observed in parenchymatous organs such as

kidneys and lungs. The severe central nervous system lesions are compatible with the clinical history of seizures in this cow.

Ocular lesions, manifested grossly as the characteristic “blue eye”, are due to corneal edema that occurs following vasculitis in any ocular layer (5). Ocular sequelae in surviving cattle are synechiae, corneal fibrosis, corneal ulcers, or panophthalmitis (5, 6). All the lesions observed in this cow were consistent with the acute phase of the disease.

References and Recommended Literature:

1. Carvallo FR, Uzal FA, Moore JD, Jackson K, Nyaoke AC, Naples L, Davis-Powell J, Stadler CK, Boren BA, Cunha C, Li H, Pesavento PA. Ibex-associated malignant catarrhal fever in duikers (*Cephalophus* Spp). *Vet Pathol.* 2020 Jul;57(4):577-581. doi: 10.1177/0300985820918313.
2. Hierweger MM, Boujon CL, Kauer RV, Meylan M, Seuberlich T, Oevermann A. Cerebral ovine herpesvirus 2 infection of cattle is associated with a variable neuropathological phenotype. *Vet Pathol.* 2021 Mar;58(2):384-395. doi: 10.1177/0300985820970493.
3. Milliron SM, Stranahan LW, Rivera-Velez AG, Nagy DW, Pesavento PA, Rech RR. Systemic proliferative arteriopathy and hypophysitis in a cow with chronic ovine herpesvirus 2-induced malignant catarrhal fever. *J Vet Diagn Invest.* 2022 Sep;34(5):905-908. doi: 10.1177/10406387221112450.
4. Modesto P, Grattarola C, Biolatti C, Varello K, Casalone C, Mandola ML, Caruso C, Dondo A, Gorla M, Rocca F, Decaro N, Leonardi C, Iulini B, Acutis PL. First report of malignant catarrhal fever in a captive pudu (*Pudu puda*). *Res Vet Sci.* 2015 Apr; 99:212-4. doi: 10.1016/j.rvsc.2015.02.010.
5. O'Toole D, Li H. The pathology of malignant catarrhal fever, with an emphasis on ovine herpesvirus 2. *Vet Pathol.* 2014 Mar;51(2):437-52. doi: 10.1177/0300985813520435.
6. O'Toole D, Li H, Miller D, Williams WR, Crawford TB. Chronic and recovered cases of sheep-associated malignant catarrhal fever in cattle. *Vet Rec.* 1997 May 17;140(20):519-24. doi: 10.1136/vr.140.20.519.
7. Partin TG, Schrenzel MD, Braun J, Witte CL, Kubiski SV, Lee J, Rideout BA. Herpesvirus surveillance and discovery in zoo-housed ruminants. *PLoS One.* 2021 Jan 28;16(1):e0246162. doi: 10.1371/journal.pone.0246162.
8. Pesavento PA, Dange RB, Ferreras MC, Dasjerdi A, Pérez V, LaRoca A, Silván JB, Diab S, Jackson K, Phillips IL, Li H, Cunha CW, Wessels M. Systemic necrotizing vasculitis in sheep is associated with ovine herpesvirus 2. *Vet Pathol.* 2019 Jan;56(1):87-92. doi: 10.1177/0300985818795166.
9. Russell GC, Stewart JP, Haig DM. Malignant catarrhal fever: a review. *Vet J.* 2009 Mar;179(3):324-35. doi: 10.1016/j.tvjl.2007.11.007.
10. Saura-Martinez H, Al-Saadi M, Stewart JP, Kipar A. Sheep-associated malignant catarrhal fever: role of latent virus and macrophages in vasculitis. *Vet Pathol.* 2021 Mar;58(2):332-345. doi: 10.1177/0300985820978310.

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