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Sheep Associated-Malignant Catarrhal Fever: Past, present, and future

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ABSTRACT

Members of *Artiodactyla* can contract the infectious disease Malignant Catarrhal Fever (MCF), which has a wide range of symptoms. Ten known viruses contribute to the disease, the two most significant ones being *Ovine gamma herpes virus 2* (OvHV-2) and *Alcelaphine gamma herpes virus 1* (AIHV-1). In the African subcontinent, AIHV-1 is seen in most MCF cases. In the Indian scenario, *Ovine gamma herpes virus-2* is the main culprit. MCF is reported in certain pockets of India. Its threat to wildlife is not yet completely understood. In AIHV-1, wildebeests serve as the primary MCF reservoir, whereas with OvHV-2, the primary MCF reservoir is sheep. In India, OvHV-2 causes MCF in deer species, bison, and water buffaloe. The life cycle and properties of this virus are not yet wholly deciphered. To understand the impact of the disease and the threat it may pose in the future, we need to have diagnostic techniques in place. Currently, PCR is the most commonly used diagnostic technique. Work should be done on field-oriented tests like ELISA and LFA, which are helpful in areas without sophisticated lab facilities. Treatment protocols must be in place, as culling bovines is not an accepted policy in India. Probable plans for overcoming all these problems are discussed in this article.

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1 Introduction

Malignant Catarrhal Fever (MCF) is an intriguing lethal condition that affects *Artiodactyla* members like cattle, bison, deer, water buffalo, and pigs (Russel et al. 2009; Cordduzza et al. 2022). Lymphoid hyperplasia in lymphoid organs, lymphoid cell accumulation in non-lymphoid organs, and various organ failures brought on by immunological dysregulation are the disease's hallmarks (Nelson et al. 2010). Currently, 10 viruses of the genus *Macavirus* (Subfamily: *Gammaherpesvirinae*, Family: *Herpesviridae*) causes MCF disease (O'Toole and Li 2014). Wildebeests commonly harbor *Alcelaphine gamma herpes virus-1*(AIHV-1), and sheep harbor *Ovine gamma herpes virus 2* (OvHV-2) without showing any clinical signs and act as a source of infection to susceptible animals. The AIHV-1 is mainly found in Africa and some zoological enclosures in different parts of the world. OvHV-2 cases are reported worldwide and affect deer species, bison, and water buffaloe. OvHV-2 infections are also reported in some zoological collections.

OvHV-2 has never been isolated in cell culture, although lymphoblastoid cell lines from clinically sick animals contain viral DNA despite AIHV-1's lengthy history of cell culture isolation (OIE 2018). MCF illness can manifest as an acute form in which mortality may occur within hours or as a chronic type consisting of symptoms like high temperature, excessive nasal and ocular discharge, bilateral corneal opacity, and muzzle necrosis (Headley et al. 2020a; Iván et al. 2022). Diagnosis of the disease is possible by histopathology, DNA detection by PCR, and serological assays (OIE 2018).

2 History

In Africa, Malignant Catarrhal Fever linked with wildebeest (WA-MCF) was discovered in the early 1900s. In 1929 transmission of sheep-associated MCF (SA-MCF) from blood was observed. Plowright et al.(1960) isolated the *Alcelaphine gamma herpes* virus from wildebeest for the first time and successfully propagated it in cattle, rabbits, and monolayer tissue cultures. Based on a histological investigation, sheep-associated MCF (SA-MCF) was first described in India in 1975 (Parihar et al. 1975). OvHV-2 identification in sheep provides proof of the presence of SA-MCF illness (Wani et al. 2006; Banumathi et al. 2008; Sood et al. 2014; Kumar et al. 2021). The secrets this pandora's box holds are not yet wholly unveiled.

3 Virion properties

Order *Herpesvirales* is divided into 3 families (*Herpesviridae, Alloherpesviridae,* and *Malacoherpesviridae).* Our interest here is in *Herpesviridae*, which affects mammals and birds. The *Alphaherpesvirinae, Betaherpesvirinae,* and *Gammaherpesvirinae* subfamilies make up the *Herpesviridae* family. Double-stranded DNA viruses from the *Macacvirus* genus of the *Gammaherpesvirinae* subfamily are the agents of MCF illness (Davison et al. 2009). *Macavirus* consists of the 10 MCF-causing viruses, including *Alcelaphine gamma herpes virus 1, Alcelaphine gamma herpes virus 2, Hippotragine herpes virus, Oryx MCF, Ovine gamma herpes virus 2, Caprine herpes virus 2, Caprine herpes virus 3, Ibex MCF virus, Muskox MCFV, and Aoudad MCFV*. Common reservoirs and susceptible hosts of some MCF-causing viruses are given in Table 1.

Among these, *Alcelaphine gamma herpes virus 1* and *ovine gamma herpes virus 2* are the most important ones. In Indian conditions, *Ovine gamma herpes virus 2* is the primary pathogen causing the disease in water buffaloe, cows, deer species, and gaur. Sheep act as reservoirs for OvHv-2 and result in disease transmission to susceptible hosts.

Table 1 Common reservoirs and susceptible hosts of some MCF-causing viruses

Virus	Reservoir	Clinically susceptible
Alcelaphine gamma herpes virus 1	Wildebeest	Cattle, Deer
Alcelaphine gamma herpes virus 2	Hartebeest	Cattle, Deer
Hippotraginegamma herpes virus 1	Roan antelope	No reported cases of MCF
Oryx MCF *virus*	Oryx	No reported cases of MCF
Ovine gamma herpes virus 2	Sheep	Cattle, Gaur, Deer, Pig, Giraffe
Caprine gamma herpes virus 2	Goat	White-tailed deer
Caprine gamma herpes virus 3	Goat	Reindeer
Ibex-MCFV	Ibex	Bongo, Anoa, Pronghorn
Muskox-MCFV	Muskox	No reported cases of MCF
Aoudad-MCFV	Aoudad	No reported cases of MCF

Source: Li et al. 2014

Alcelaphinegamma herpes virus 1 has an estimated genomic size of approximately 110 kbps (Seal et al. 1989). The essential structural components of the *Herpesvirus* are nucleocapsid, tegument, and envelope. DNA is covered by a capsid that protects, transports, and delivers nucleic acid inside the host cell. Tegument has multiple functions, such as capsid transport, regulation of transcription, translation, apoptosis, replication, and viral assembly (Kelly et al. 2009). Amines, lipids, and glycoproteins are present in the envelope interacting with the host immunity.

Hart et al. (2007) used a clinically MCF-affected bovine lymphoblastoid cell line for complete sequencing of the OvHV-2 genome and reported the genome size was 130 kbps. Sequencing disclosed the presence of 73 ORFs (Open Reading Frame), of which 62 showed homology with other *Gamma herpes viral* genes. This research also revealed a few unique genes that could be utilized in planning control strategies, such as Ov7 and Ov8 genes that code for viral glycoprotein. It's a fact that the virus's surface glycoproteins are crucial in viral attachment to the host cell, which is the first step of viral replication. Products of these genes can be effectively used in designing a vaccine (Russel et al. 2009). The details of the same will be discussed in control strategies.

4 Geographical distribution

AIHV-1-associated MCF is predominantly seen in the African subcontinent, where a significant wildebeest population intermixes with cattle during grazing periods. AIHV-1 is a severe concern in Africa. In susceptible domestic species and ruminants in international wildlife parks, OvHV-2 is the primary cause of MCF.

5 Disease transmission

5.1 *Alcelaphine gamma herpes virus*-1 (AIHV-1)

The virus is transmitted through direct contact, contaminated pastures, and aerosols from reservoir animals. Newborn wildebeests are exposed to the AIHV-1 virus within three months of their age, and it's calves secrete the virus from their nasal and ocular secretions. Interestingly, wildebeests never formally manifest the disease, but they shed viruses that are the primary source of infection in vulnerable animals (Mushi et al. 1981).

5.2 *Ovine gamma herpes virus 2* (OvHV-2)

Transmission is predominantly through aerosols and direct contact (Kim et al. 2003). Lambs are exposed to viruses and become reservoirs as early as 3 months of age. Sheep transmit the disease to susceptible animals. The disease is reported when reservoirs and cattle are separated by 70 meters and in bison up to 5 km (WOAH 2022).

6 Replication of virus

Not much research has been done to understand the complete replication of different MCF-causing viruses. However, as they are herpes viruses, let's consider that MCF-causing viruses share similar replication steps (Figure 1). The entry of the virus occurs after membrane fusion or endocytosis of an associated virion, both of which are facilitated by glycoprotein complexes that contain glycoprotein B, gH, and gL (Myster et al. 2020). Immediate early genes carry out the regulation of succeeding gene expressions. The DNA replication complex, as well as many enzymes and other proteins involved in altering host cell metabolism, are encoded by early (E) genes, while late (L) genes largely encode virion proteins (Gatherer et al. 2021). After primary infection, on activation of immediate early genes, lytic replication will be seen in the case of herpes viral infection. If immediate early genes are not activated, there will be an establishment of latency in neurons, lymphocytes, etc. (Riaz et al. 2017). This unique phenomenon of herpes viruses has led to the introduction of a postulation called 'Herpes harmony'. It explains that in herpes viral infection if the host responds with a robust immune response, it leads to the establishment of latency. If the host's immune response is weak, it leads to lytic replication and active infection. However, suppose there is an

Table 2 Geographical distribution of the MCF

S. N.	MCF causing virus	Geographical distribution
1	*Alcelaphine gamma herpes virus 1*	Africa
2	*Alcelaphine gamma herpes virus 2*	Africa
3	*Ovine gamma herpes virus 2*	Africa, Asia, Europe, North America, South America
4	*Caprine gamma herpes virus 2*	Europe, North America, Asia
5	*Caprine gamma herpes virus 3*	North America
6	*Hippotragine gamma herpes virus 1*	North America
7	*Ibex*-MCFV	North America

Source: Headley et al. 2020b

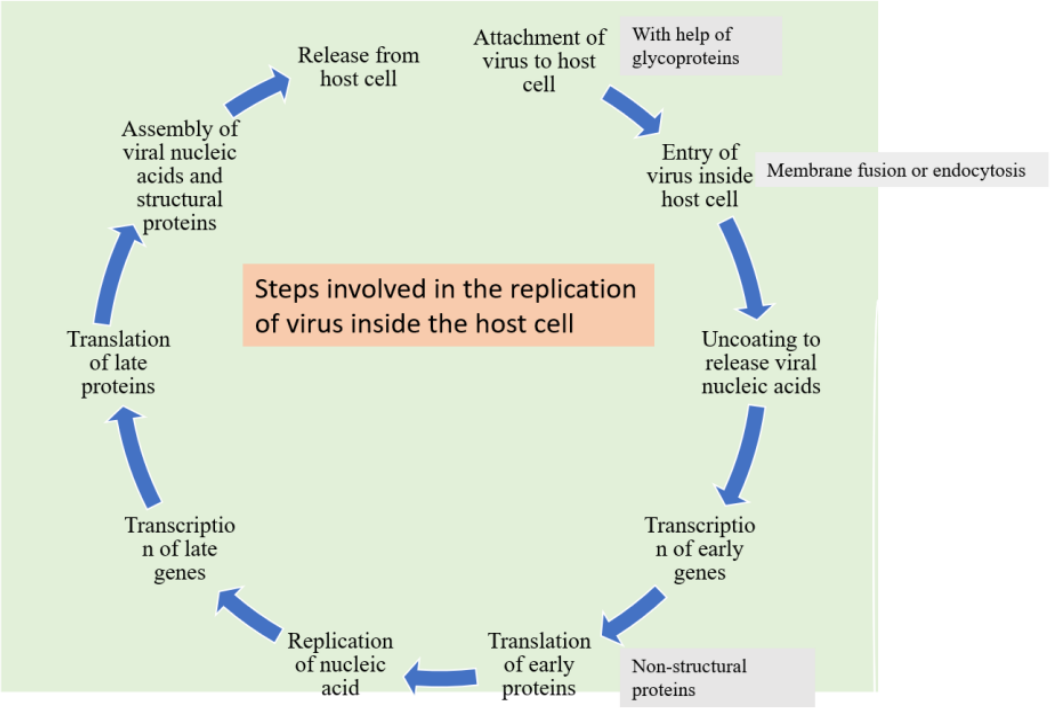

Figure 1 Replication of virus inside the host cell

immune-compromised condition in latency-established animals due to host-associated (very young or very old, immunodeficiency due to chemotherapy, other concurrent infections, organ failures)/ pathogen-associated (altered tissue tropism, condition of the non-native host)/latency may be converted to lytic replication, and active disease may be seen (Sehrawat et al. 2018).

6.1 Intranuclear events in herpes viral infection

Herpes viral naked DNA that enters the host cell's nucleus resembles double-stranded breaks (DSB). Naked viral DNA help in the triggering of DNA damage response proteins (DDRPs). DDRPs are ubiquitously present in the host cell, and they result in the initiation of a cascade of events which in turn activates p53, a tumor suppressor protein, and the result is the cell cycle arrest. This mechanism is in place to avoid replicating cells with damaged DNA. Since viral DNA resembles damaged DNA inside the nucleus, its presence inhibits the cell cycle (Full and Ensser 2019).

6.2 Importance of *ORF 73* in *MCF* infection

AIHV-1 genome is maintained as latent episomes and is a classic example of herpes viral latency. A unique genome maintenance protein coded by ORF 73 is responsible for latency induction and maintenance. It was once believed that ORF 73 was solely necessary for installing latency. However, it is now known that ORF 73 is also crucial for the induction of infection. So ORF 73 deleted recombinant virus can be effectively tried as a vaccinal candidate (Palmeira et al. 2013).

6.3 Immune evasion strategies by herpes viral infection

The Herpes virus utilizes multiple strategies (Figure 2) to evade the host immune system (Griffin et al. 2010). The methods included in viral evasion are (a) Downregulation of peptide transport to MHC (Major Histocompatibility Complex) class I molecules, (b) MHC class I molecule expression is downregulated, (c) MICA (MHC class I polypeptide-related sequence A) and MICB shedding inhibits NKG2D (Natural killer group 2D) receptors of NK cells, (d) The HLA-G is expressed and secreted (Human leucocyte antigen-G) that binds to KIR2DL4, ILT2 (Immunoglobulin-like transcript 2), ILT4 (Immunoglobulin-like transcript 4) and inhibit NK (Natural killer) and cytotoxic cells, (e) Increased expression of PDL1 (Programmed death Ligand-1) which results in avoiding attack by immune cells, and (f) Viral micro RNAs inhibit the production of pro-inflammatory cytokines.

6.4 Interference of virus in host *micro-RNA* generation

Host micro-RNAs are essential in cell development, immunity, maintenance, and death. Mature mi-RNAs generated by host cells are inhibited by *Alcelaphine gamma herpes virus*1 and *Ovine gamma herpes virus* 2, which results in the availability of ribosomes for viral transcription and translation (Bruscella et al. 2017).

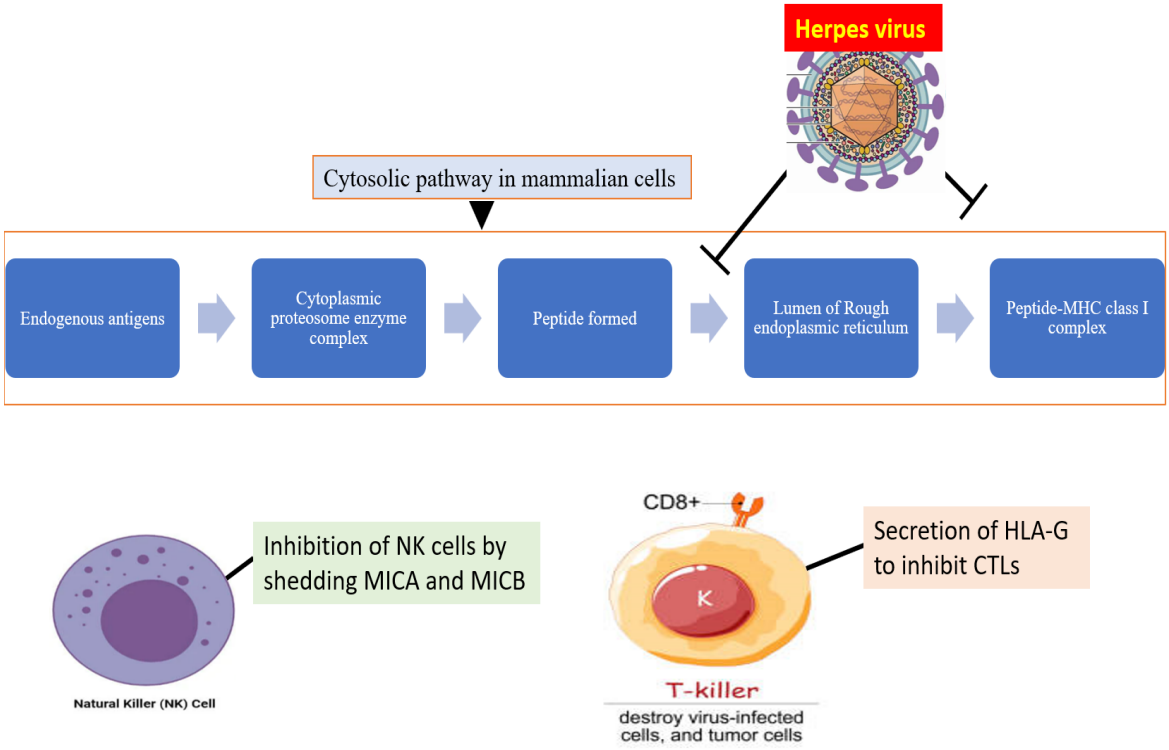

Figure 2 Herpes virus strategies to evade the host immune system (Source: Jasinski et al. 2020)

7 Clinical signs

Affected animals developed fever, corneal opacity, ocular discharges, nasal discharges, and rarely abortion. Suffering animals will have dried muzzles, lack of appetite, and dehydration. Less frequently, interdigital ulcerations, glossitis, and ulcerative gingivitis are also seen (Bildfell et al. 2017; Headley et al. 2020a).

8 Diagnostic techniques

8.1 Histopathology

Histological changes such as epithelial deterioration, vasculitis, hyperplasia, and necrosis of lymphoid organs, as well as significant interstitial accumulations of lymphoid cells in non-lymphoid organs, have been used to demonstrate the presence of MCF (OIE 2018). In the infected animals, Cytotoxic T lymphocyte has been seen in higher number than Helper T cells (Dewals and Vanderplasschen 2011). Epithelial degeneration and necrosis are seen in multiple organs (Sharma et al. 2019).

Recently conventional histopathology has been replaced by Immunohistochemistry, Immunofluorescence, and in-situ PCR (Headley et al. 2020b). Among them, in-situ PCR is helping to understand the complicated life cycle of multiple viruses causing MCF (Simon et al. 2003).

8.2 PCR

To specifically detect Ovine gamma herpes virus 2 DNA in naturally occurring and experimentally induced cases of sheep-associated Malignant Catarrhal Fever, Baxter et al. (1993) developed a hemi-nested PCR. This method helped identify the tegument protein coded by the ORF75 region of the *Ovine gamma herpes virus 2*. This standardized PCR is utilized to identify MCF in suspect cases. The sheep population in Karnataka was subjected to a cross-sectional study (Premkrishnan et al. 2015). A Hemi-nested PCR test was used to identify the OvHV-2 genome in blood samples, revealing that 24.4% of sheep were carriers.

One more unique gene in the case of SA-MCF is glycoprotein B, coded by the Ov-8 gene. PCR is standardized to identify the Ov-8 gene present in different variants. Dunowska et al. (2001) noticed the similarity in glycoprotein (gB) sequences from bovine and healthy ovines indicating transmission between them.

8.3 Viral isolation

As discussed earlier, Dr. Plowright isolated the *Alcelaphine gamma herpes virus 1* for the first time in 1960. In 1970 he isolated the C500 strain in bovine thyroid cells from an ox suffering from the clinical disease. To this day C500 strain is considered a wild-type strain (maintained with as minimum passages as possible) and used in challenge studies.

AIHV-1 can be isolated in bovine embryonic bovine tracheal cells, VERO cells, and Madin-darby bovine kidney cell line (Hristov and Peshev 2016). It has been challenging to gather enough virus DNA to decode the genome of OvHV-2 because the virus has not yet been propagated in vitro. However, a lymphoblastoid cell line BJ1035 is maintained, which consists of a virus and is used for sequencing (Hart et al. 2007).

8.4 Enzyme-Linked Immunosorbent Assay (ELISA)

Li et al. (1994) developed a competitive inhibition ELISA using mAb-15A for an antigen conserved in all types of MCF viruses to understand the antibody response in different animals for different MCF viruses. Powers et al. (2005) also observed that cattle could become infected with OvHV-2 without developing clinical signs of MCF and that PCR assay and CI-ELISA can be readily used to detect OvHV-2 and MCFVs infected cattle, respectively. Russel et al. (2022) developed an indirect ELISA using recombinant ORF65 (capsid protein) expression to identify antibodies against OvHv-2 in sheep and cattle. An effective commercial kit is not yet available based on the above-described method.

8.5 Electron microscopy

To comprehend the structure of the WC 11 strain of the Alcelaphine gamma herpes virus, Castro and Daley (1982) used electron microscopy.

9 Prevention and control

The best way of prevention is to keep infected and carrier animals apart from susceptible species. Strict quarantine and testing of new animals entering the herd in the zoo and domestic enclosures is necessary. Infection can also be prevented by providing separate grazing and water-drinking areas for sheep and bovines. Extension activities regarding disease symptoms in endemic regions are essential to facilitate better reporting and control of the disease. In zoological enclosures, only seronegative animals should be introduced.

9.1 Vaccination

Plowright et al.(1975) injected formalized preparations of *Alcelaphine gamma herpes virus 1* developed in cells, mixed with Freund's incomplete adjuvant, and reported the presence of neutralizing antibodies. Despite this, there was no discernible defense against parenteral challenges involving pathogenic viruses. The reason may be due to MCF viruses' multiple immune evasion strategies.

The significance of ORF 73 in the induction of infection and latency was established by Palmeira et al. (2013), and the disruption of ORF 73 may be a potential candidate for a vaccine. Further, Myster et al. (2020) identified that the spreading of AIHV-1 between cells was held with the help of the A7 gene and propagated through the A8 gene. Strains with altered or deleted A7 and A8 genes can be effectively tried as a vaccine candidate. Similarly, Shringi et al. (2021) used recombinant BoH-4 to deliver OvHV-2 glycoprotein. It conferred partial immunity against MCF in the Rabbit model.

9.2 Antiviral drugs

Anti-herpes viral drugs could be used, but their efficacy in treating animals is poorly documented. Thymidine analogs such as iododeoxyuridine and guanosine analog antiviral drugs such as acyclovir could also be tried.

9.3 New strategies

ATF3, which is known as a stress-induced transcription factor, functions in a way relatable to ORF A2 and ORF Ov2. ATF3 results in the induction of latency-associated transcript (LAT). It might be possible to inhibit the induction of LAT and the development of latent infection if the mechanism of ATF3 induction were to be identified. Increased LAT leads to increased neuronal survival, host micro-RNA silencing, and decreased apoptosis of infected cells. Thus, ATF3 inhibition may help in putting a well-waited pin in the coffin of herpes viruses (Knipe et al. 2015).

Conclusion

To this date, PCR-based identification is most commonly used. As of right now, sheep-specific commercial ELISA kits are not accessible. Field-oriented antigen detection tests are not researched until now, which could be a good tool for early disease identification. The culling policy is not a well-accepted option for disease-affected bovines in India. So, some treatment protocols could be standardized to care for infected animals. Much research regarding epidemiology, life cycle, and novel diagnostic techniques has to be carried out.

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