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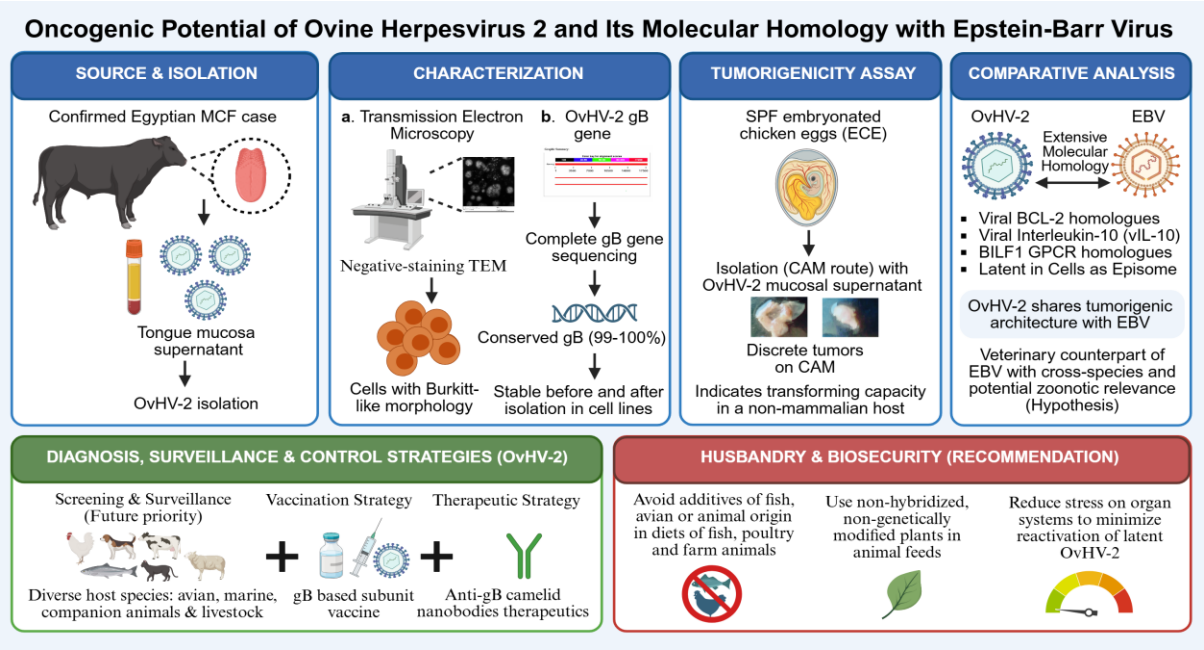
Oncogenic Potential of Ovine Herpesvirus 2 and Its Molecular Homology with Epstein–Barr Virus

Iman M. Bastawecy[1], Morcos I. Yanni[1], Fatima-Alzahraa Gamal[2] and Mohamed Abdelmonem[3,*]

1. Department of Virology, Animal Health Research Institute, Dokki, Giza, Egypt
2. October Pharma S.A.E., 1st Industrial Zone, 6th of October City, Giza, Egypt
3. Department of Pharmaceutics and Industrial Pharmacy, Faculty of Pharmacy, October University for Modern Sciences and Arts (MSA), Giza 12451, Egypt



Abstract: Ovine herpesvirus 2 (OvHV-2) causes malignant catarrhal fever (MCF), a lymphoproliferative disease that is often fatal and economically important in cattle and many other susceptible artiodactyls. However, its ability to cause cancer, and its relationship to Epstein-Barr virus (EBV), the classic human tumour gammaherpesvirus, is still unclear. In this study, we combined a critical review of the molecular biology of both viruses with new findings from an Egyptian OvHV-2 isolate to test whether OvHV-2 shares the tumour-forming architecture of EBV. Tongue-mucosa supernatant from a confirmed Egyptian MCF case, previously characterised by complete glycoprotein B (gB) gene sequencing, was examined by negative-staining transmission electron microscopy (TEM) and grown in specific pathogen-free embryonated chicken eggs through the chorioallantoic membrane (CAM) route. TEM showed morphology typical of Burkitt's lymphoma, and CAM growth produced distinct tumours, indicating that OvHV-2 can transform cells even in a non-mammalian host. The comparison showed broad homology between the two viruses, including conserved viral BCL-2, interleukin-10 and BILF1 G-protein-coupled-receptor homologues. The OvHV-2 gB sequence was 99-100% identical to reference genomes and remained stable after passage in cell lines. These results suggest that OvHV-2 is the veterinary equivalent of EBV, with cross-species and possibly zoonotic importance, and raise the possibility that the two are the same virus. We recommend electron microscopy supported by gB sequencing as a rapid first-line diagnostic, and urge screening of cell cultures and a wide range of hosts. For control,

we propose OvHV-2 gB subunit vaccination and anti-gB camelid nanobody treatments, and the removal of animal-origin additives from animal feed.

Keywords: Ovine herpesvirus 2, malignant catarrhal fever, Epstein-Barr virus, Burkitt's lymphoma, glycoprotein B, electron microscopy, gammaherpesvirus, oncogenesis.

INTRODUCTION

OvHV-2 is economically important and is the most commonly recognised cause of MCF worldwide. It can infect many organs and hosts, including more than 33 species and almost every domestic sheep. This makes it a serious concern and makes reliable cross-species detection an important goal, including detection within the cell-culture systems used for different species (O'Toole&Li, 2014; Cunha et al., 2019; Bastawecy et al., 2025).

Ovine herpesvirus 2 (OvHV-2) is a gammaherpesvirus found in sheep flocks worldwide, and it causes the lymphoproliferative disease malignant catarrhal fever (MCF) (Hart et al., 2007). MCF affects several body systems. Its main features are lymphoid hyperplasia together with widespread vascular, epithelial and mesothelial lesions that are, in morphological terms, linked to lymphoid cells. At the histological and ultrastructural level, many MCF lesions resemble those of lymphoreactive disorders, and signs often grouped with the rheumatic diseases, such as synovitis or arthritis, are common (Liggitt&DeMartini, 1980a). Chronic illness and recovery make up a large part of the clinical picture. Even so, a recovered animal stays latently infected, and stress can trigger recurrence (Russell et al., 2009). OvHV-2 outbreaks are favoured by heat stress, severe weather, the co-grazing of cattle with sheep, and poor-quality feed. This is because temperature extremes reduce pasture; and since green grass is richer in Omega 3 than conserved forage, grazing animals are then left with too little feed and water and become prone to dehydration and acidosis (Andriyanov et al., 2025). Epidemiological evidence also suggests that omega-3 fatty acids protect against cardiovascular disease and hyperlipidaemia (Siscovick et al., 2017).

Once disease is clinical, almost any organ can be involved. In cattle, skin lesions have sometimes appeared with no other signs and may resolve without treatment (Bastawecy et al., 2015; O'Toole&Li, 2014). The typical lesions are necrotising vasculitis, thrombosis, and infiltration of tissue by dividing lymphocytes and macrophages (Liggitt&DeMartini, 1980a), because in cattle and other ruminants the virus drives T-lymphocyte proliferation and transformation (Baxter et al., 1993). Reported prevalence is very high, reaching 99% in adult sheep tested by nested PCR and up to 100% in cattle (Li et al., 2011; Thonur et al., 2006; Rosato et al., 2021). The disease occurs worldwide and has been recorded in more than 33 species, including cattle, bison, buffalo, deer, sheep, goats, swine, camelids, equines, giraffes, guinea pigs, rabbits and hamsters (Russell et al., 2009; Loken et al., 1998; O'Toole&Li, 2014; Madrigal-Valencia et al., 2023; Bianchessi et al., 2024). Sheep and goats were once thought to be symptomless carriers, but they show the same signs as other susceptible hosts. Every sheep breed is thought to acquire OvHV-2, and newborn lambs, like calves, are as susceptible to aerosol infection as adult animals (Taus et al., 2006). Incidence may also depend on climatic conditions that affect how long the virus survives in the environment, on vectors or fomites, on differences in stocking density, and on the level of stress (Li et al., 2011). Reducing stress can therefore help prevent MCF in animals that are

subclinically or only mildly affected (Russell et al., 2009). The virus has also been found in ruminants kept in zoos and wildlife parks. Spread occurs mainly through direct contact with nasal and ocular secretions, and aerosol exposure to the secretions of infected sheep is the main route (Taus et al., 2006; O'Toole&Li, 2014). Transmission has also been described by the airborne route, by vectors, through contaminated feed or water, and via the alimentary and urogenital tracts, and the virus has been detected in the faeces, colostrum, milk and semen of asymptomatic animals (Bastawecy, 2022). In susceptible hosts, latent infection may progress to clinical disease even without any contact with sheep (O'Toole&Li, 2014). The length of the incubation period depends on the size of the initial viral dose (Taus et al., 2006), while morbidity ranges from single cases involving one or a few animals to large outbreaks (Russell et al., 2009). The disease occurs throughout the year but rises during lambing, when pregnancy-related immunosuppression in ewes allows latent OvHV-2 to reactivate or permits new epithelial infection (Russell et al., 2009). A second peak occurs when most of the lamb crop reaches 6-9 months of age; this reflects adolescence (Bastawecy, 2022) and the hormonal stress that comes with it. Because the recognised forms (peracute, head-and-eye, intestinal and mild) overlap greatly, and a single animal may show mixed signs, some workers regard this division of the clinical picture of MCF as of limited value. In the peracute form, some animals die before the typical signs appear, whereas others follow a slower course and show some clinical signs.

Across susceptible species, MCF is marked by the build-up of lymphocytes and by necrotic foci in many tissues. Its pathology therefore resembles that of certain autoimmune disorders, in which disordered IL-15 expression, and in turn tumour necrosis factor-alpha, keeps cytotoxic cells active. This suggests that large amounts of IL-15 are produced during MCF and that, as long as IL-15 is present, cytotoxic cells stay active and add to the tissue injury seen in the disease (Anderson et al., 2008). IL-15 promotes both the proliferation of T lymphocytes and the persistence of their cytotoxic activity.

The pathogenesis of MCF results mainly either from direct virus-cell interactions or from immune-mediated attack on infected cells (Simon et al., 2003), and almost no organ is spared (O'Toole&Li, 2014). The presentation is wide-ranging, from mild cases with barely noticeable signs to severe illness ending in multiple organ failure (Russell et al., 2009). An affected animal may show any combination of the following: sudden, severe depression, anorexia, agalactia and a high fever of 40-42 °C (a persistent fever, sometimes lasting several weeks, that also fluctuates is characteristic of MCF), plus tachycardia of 100-120 beats per minute; nasal and ocular discharges that progress from serous through mucopurulent to purulent; severe dyspnoea with stertor; a fragile mucosa that splits easily; a slippery mouth and tongue; copious, ropey, bubbly salivation that hangs from the lips and produces a smacking sound; erosive mucosa, whether local or diffuse; haemorrhagic cheek papillae liable to erode; lymphoid hyperplasia; vasculitis; inflammation of the digestive tract, especially the oral cavity; interdigital erosions; lameness; renal disease; focal crustaceous dermatitis; skin necrosis; ulcerative vulvitis and balanitis; a swollen, reddened vulva with fresh or ruptured vesicles; multifocal penile ulceration; profuse sweating; alopecia; thickening; hyperkeratosis; focal skin ulceration; weight loss; apathy; adipsia; skin rashes; synovitis, especially of the tibio-tarsal joint; a horn or hoof that may slough; and skin of the teats, vulva and scrotum that in acute cases can slough when touched or become covered with dry, tenacious scabs; trismus; lymph nodes that may be visible or enlarged; faeces ranging from constipation to profuse, sometimes bloody, diarrhoea; haematuria;

swollen limb joints; diphtheresis of the oral membranes; cystitis; recumbency; opisthotonus; paddling; jaundice; and raised total bilirubin and AST. In the digestive tract the lesions appear as ulcers, vesicles, plaques, pustules, erosions or tears. Other findings include cutaneous hyperaemia and swelling, a subcutaneous mass, lump or nodule, coughing, abortion, stillbirth, undersized offspring, fetal anomalies, reproductive failure, an enlarged spleen and liver, gall-bladder enlargement, dehydration and emaciation. Ocular changes include exophthalmos, photophobia, lacrimation, nystagmus, conjunctivitis, blepharospasm, eyelid oedema, episcleral injection, keratitis, anterior uveitis, mucopurulent ocular discharge, impaired vision, corneal opacity that can cause blindness, corneal ulceration that may progress to perforation with iris prolapse, corneal melanosis, hypopyon, a blue and/or opaque eye, blindness, and persistent bilateral leucomata. Neurological signs include ataxia, tonic-clonic spasm, disorientation with head tremor, muscular trembling, convulsions, weakness in a single leg, an uncoordinated gait, a demented appearance, head-pushing, paralysis, a stiff-legged gait, circling, seizures, unusual aggression towards people, rigidity of the neck and limbs, difficulty standing, hind-limb paralysis, dehydration, acidosis, acute lymphoid panarteritis, arteriosclerosis, and swollen limb joints (Russell et al., 2009; O'Toole&Li, 2014; Bastawecy, 2022; Headley et al., 2023). The disease results from tissue self-destruction driven by cytotoxic lymphocytes that MCF virus infection triggers, and cells cultured from OvHV-2-infected cattle usually have the phenotype of T cells or natural killer cells (Anderson et al., 2008). Recovery was accompanied by clearing of the acute lymphoid panarteritis typical of the acute phase and by the appearance of widespread chronic obliterative arteriosclerosis, lesions found most easily in the rete mirabile (O'Toole&Li, 2014). In some recovering animals, ulcerated and exudative skin lesions appeared, which could develop hardened scabs linked to epidermal necrosis and were often confined to the perineum, udder and teats (O'Toole&Li, 2014). Under the microscope, the oral mucosa and oesophagus contain (sub)epithelial mononuclear infiltrates in which lymphocytes and lymphoblasts outnumber a small number of macrophages, the latter increasing as lesions worsen; also seen are phagocytosis of degenerate epithelial cells, acantholysis, epithelial-cell necrosis, erythema multiforme-like ulcerated skin lesions, transepidermal apoptosis with satellitosis, interface dermatitis, folliculitis and dermal arteritis (O'Toole&Li, 2014). The bilateral leucomata arise partly from focal loss of corneal endothelium following acute endothelialitis. The main feature in cattle is a severe lymphocytic arteritis (and, to a lesser degree, phlebitis) in which the endothelium is swollen and vacuolated and the tunica media undergoes necrosis (O'Toole&Li, 2014). Cutaneous lesions show hydropic degeneration and microvesicle formation within the epidermis, which give way to erosion with exudate over the epidermal surface, while oedema and lymphoid inflammation mark the dermis beneath (Liggitt&DeMartini, 1980b). Within the kidney, thrombi and degenerate arterioles produce infarcts (O'Toole&Li, 2014).

The post-mortem (PM) findings reflect how severe the clinical signs were. The PM lesions include arteritis, perirenal haemorrhage with multiple renal infarcts, serous-to-fibrinous effusion in some body cavities, vasculitis, thrombosis, lymphocytic infiltration of tissues, enlarged and sometimes haemorrhagic lymph nodes, hepatomegaly and splenomegaly, pulmonary and cerebral congestion, haemorrhagic cystitis, a dilated, filled intestine, myocarditis, and haemorrhage in the parenchyma of both testicles (O'Toole&Li, 2014). The submandibular and mesenteric lymph nodes, the appendix and the spleen enlarge first; lymphocytes then invade non-lymphoid tissue, and necrosis develops in lymphoid and non-lymphoid tissue alike (O'Toole&Li, 2014). Histopathology reveals a pansystemic

vasculitis with lymphocytic infiltration of both lymphoid and non-lymphoid organs (Zaki et al., 2016; Liggitt&DeMartini, 1980a). Other PM lesions include a prominent, tortuous arteritis with thickened walls, multifocal tiny white spots scattered through the liver and kidney, ulcerative oesophagitis, pericarditis, severe lymphocytic myocarditis with cardiac muscle necrosis, encephalitis, encephalomyelitis, clouding of the meninges, nephritis, hepatitis with a liver that is sometimes friable, pneumonia or else pulmonary emphysema or focal atelectasis, interstitial lymphocytic nephritis, and renal tubules that balloon amid vascular degeneration (O'Toole et al., 2002; O'Toole&Li, 2014). It also shows a lymphohistiocytic vasculitis with fibrinoid necrosis of the vessel walls across several organs (lymph nodes, liver, kidney, brain, retina and rete mirabile), along with lymphohistiocytic meningitis, pericholangitis and multifocal ulcerative oesophagitis (Liggitt&DeMartini, 1980a). The most consistent and severe changes are inflammation and ulceration of the digestive tract, especially the oral cavity, oesophagus, forestomachs, abomasum, caecum and colon, while in haemorrhagic cystitis the urothelium lining the renal pelvis, ureter and urethra is degenerate and/or sloughed (O'Toole et al., 2002). A typical, sometimes very widespread, finding is the interstitial gathering of lymphoid cells in non-lymphoid organs, especially the renal cortex and the outer regions of the liver, producing many raised white foci, each 1-5 mm across; the deposition of immunoglobulin and complement within the glomeruli points to an immune-mediated element (O'Toole&Li, 2014). In rabbits with experimentally induced MCF, the OvHV-2 structural proteins ORF25 (capsid) and ORF73 (tegument) were traced to the epithelial cells and M-cells of the appendix. This implies that M-cells and the large-intestinal epithelium are important for viral replication and/or pathogenesis (Meier-Trummer et al., 2009).

Glycoprotein B (gB), encoded by ORF8, is one of the most highly conserved herpesvirus glycoproteins, and it takes part in viral entry and in cell-to-cell spread (Bastawecy and Abd El-Samee, 2012; AlHajri et al., 2017). Its sequence has also been used to measure phylogenetic relationships among herpesviruses, because it reliably predicts these relationships when several conserved genes are examined (McGeoch et al., 1995).

Sequencing OvHV-2 is an essential first step towards understanding both the pathogenesis and the treatment of MCF. The virus carries an ORF, Ov2.5, that encodes an IL-10 homologue of the cellular IL-10 protein (Hart et al., 2007). This viral IL-10 behaves much like the host protein: it drives mast-cell proliferation while suppressing the production of inflammatory chemokines by macrophages (Jayawardane et al., 2008).

The virus also carries BCL-2 homologues, and protecting cells from apoptosis has been linked to sustaining persistent B lymphocytosis (Russell et al., 2009). Its Ov4.5 ORF encodes a protein resembling EBV BALF1 and cellular BCL-2 that limits apoptosis and so controls cell death (Hart et al., 2007). In contrast, OvHV-2 also encodes pro-apoptotic proteins, including the mitochondrion-targeting pOv8.25 (Shrestha et al., 2020).

Gammaherpesviruses encode receptors that cross the membrane seven times and are similar in structure and function to those of the host (Lyngaa et al., 2010). These G protein-coupled receptors are called seven-transmembrane receptors because they pass across the cell membrane seven times (Trzaskowski et al., 2012). As integral membrane proteins, GPCRs let cells convert signals from outside into responses within, and several herpesviruses carry their own GPCRs to rewire host signalling for immune evasion and spread (de Munnik et al., 2015). Ov5 is related to EBV BILF1, a GPCR that signals constitutively, independent

of ligand, and reshapes intracellular signalling (Beisser et al., 2005; Paulsen et al., 2005); so the Ov5 protein may perform a similar function in cells infected with OvHV-2 (Hart et al., 2007).

MicroRNAs are short non-coding RNA molecules of 18-30 nt that act after transcription to control gene expression (Lee et al., 1993; Bartel, 2004). Working with an immortalised lymphoblastoid cell line linked to MCF, researchers found that OvHV-2 encodes at least eight microRNAs directed at viral genes that govern latency (Riaz et al., 2014).

Two inocula were prepared: one was held at 37 °C for one hour with anti-OvHV-2 sheep serum, and the other with negative sheep serum as a control. Every sheep became infected; however, judged by OvHV-2 DNA detection and seroconversion against the control, the positive serum lowered the infectivity of the virus 1000-fold. Immune serum protected the rabbits that received it, whereas the controls later developed MCF. This shows how important antibody is for blocking entry of OvHV-2. In keeping with this, a vaccine based on glycoprotein B protects against sheep-associated MCF (Cunha et al., 2022).

OvHV-2 resembles Epstein-Barr virus (EBV) in several ways. The lesions of MCF are dominated by CD8+ T lymphocytes carrying OvHV-2 and closely resemble the histopathological and ultrastructural features of lymphoreactive conditions (Simon et al., 2003). At the molecular level, the two viruses share substantial genetic homology. Each encodes viral B-cell lymphoma-2 (vBCL-2) proteins that mimic the host cellular BCL-2 proteins, and each carries genes for interleukin (IL)-10, for G-protein-coupled receptors and for other proteins. In practice, PCR detection of OvHV-2 uses 238-bp nested primers homologous to the EBV BNRF1 gene (Baxter et al., 1993). OvHV-2 open reading frame (ORF) 59 provides a main antigen comparable to the EBV antigen used in ELISA diagnosis of nasopharyngeal carcinoma (Coulter&Reid, 2002). One sign of OvHV-2 infection is a rise in IL-15 that triggers tumour necrosis factor-alpha production, which is central to the activation of cytotoxic cells (Anderson et al., 2008). The OvHV-2 genome is about 131-135 kbp (Coulter&Reid, 2002), whereas the full EBV sequence is close to 172 kbp; however, once the repeat regions are allowed for, the unique coding stretches of the two are of similar length, because the EBV genome has terminal repeats at both ends as well as extra internal repeats (Baer et al., 1984). In humans, EBV turns B lymphocytes into proliferating lymphoblastoid cell lines that keep the viral DNA as a nuclear episome (Münz, 2019). This similarity raises the question of whether OvHV-2 might infect people and be mistaken for EBV, or even whether both are a single virus known as OvHV-2 in veterinary medicine and as EBV in human medicine.

EBV was the first herpesvirus shown to be linked to human cancers, and it infects most of the world's population (El-Sharkawy et al., 2018; Damania et al., 2022). Its BHRF1 gene encodes a viral BCL-2 homologue that strongly blocks apoptosis and appears to escape some of the controls that regulate the cellular equivalents (Bellows et al., 2002; Kvansakul et al., 2010). Because the death of infected cells can limit viral output and spread, BHRF1, a co-opted prosurvival gene, prevents apoptosis and is linked with cancer (Kvansakul et al., 2010). As a major human pathogen, EBV is causally linked to a number of lymphomas and carcinomas and spreads mainly through saliva and other body fluids (Damania et al., 2022; Bastawecy, 2021). It was first detected in 1964 in a lymphoblastoid cell line derived from a B-cell lymphoma (Epstein et al., 1964). The virus produces both a cytokine and a cytokine receptor that can adjust the immune system so that infection persists. EBV BCRF1 encodes

IL-10, a homologue of the host cytokine that supports the virus by suppressing gamma-interferon synthesis (Cohen, 2000) and by promoting mast-cell proliferation (Jayawardane et al., 2008). Its BARF1 gene encodes a novel soluble colony-stimulating factor-1 receptor that acts as a decoy, neutralising CSF-1 and disrupting the differentiation and activation of macrophages (Strockbine et al., 1998). In malignant tumours, host colony-stimulating factor 1 and its receptor are expressed and may promote tumour growth, migration and invasion (Cannarile et al., 2017). The BCRF1 and BARF1 proteins therefore help EBV escape the immune response, whether during acute infection or upon reactivation in latently infected cells (Cohen, 2000). EBV also carries a G-protein-coupled receptor called BILF1 that is essential to the immunosuppression and oncogenesis it drives (Tsutsumi et al., 2021).

This retrospective study of malignant catarrhal fever (MCF) caused by ovine herpesvirus 2 (OvHV-2) examines whether the virus can induce Burkitt's lymphoma and other tumours in susceptible species, and the close similarity between OvHV-2 and EBV. It also considers the susceptibility of avian species. OvHV-2 was recovered in SPF-ECE through both the yolk-sac and the chorioallantoic membrane routes, which produced a range of effects on the embryos, including fetal anomalies, laceration and stunted growth.

MATERIAL AND METHODS

The tongue-mucosa supernatant used earlier by Bastawecy and Abd El-Samee (2012) to extract viral DNA and to sequence glycoprotein B, together with the isolate obtained from it, was processed by Macrogen (South Korea). Glycoprotein B (gB) is one of the most strongly conserved herpesvirus glycoproteins. This paper reports the full gB gene sequence of the OvHV-2 isolated and confirmed in Egypt (2012), so that it can serve as a reference and guide for molecular genetic research, for comparing herpesviruses, and for designing accurate primers for polymerase chain reactions (PCRs). For this study, the tongue-mucosa supernatant underwent:

1. Transmission electron microscopy (TEM), performed as described by Bastawecy and Abd El-Samee (2012).
2. Isolation in 10 days old SPF-ECE by the CAM route, carried out as described by Bastawecy (2022), over an isolation period of more than 7 days.

RESULTS

When the sequences were submitted to GenBank, the output was: a nucleotide sequence of 17,800 letters; molecule type, nucleic acid; and query length, 17,800. Alignment was done using the greedy algorithm of Zhang, Schwartz, Wagner and Miller (2000).

- *Figures 1-5: graphic summaries of the sequence alignments for the submitted sequences.*
- TEM results: examination of the tongue-mucosa supernatant showed Burkitt's lymphoma (Figure 6).
- Isolation results: after the tongue-mucosa supernatant was grown in SPF-ECE by the CAM route, tumours were seen in the CAM (Figure 7a and b) on day 9 of isolation.

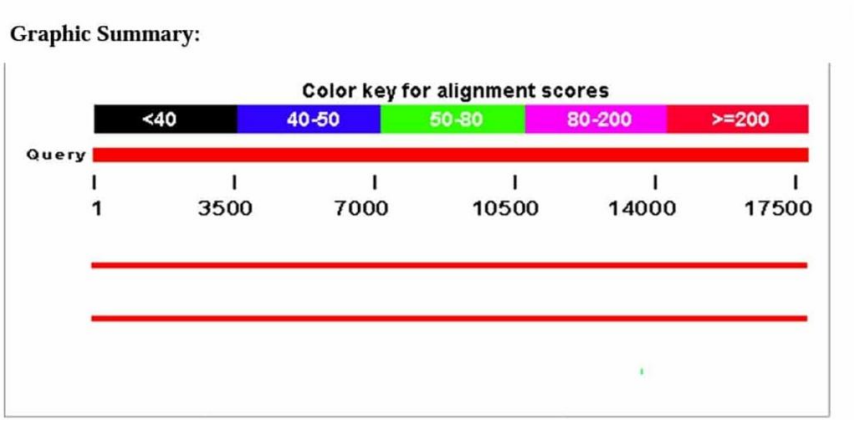


Figure (1): BLAST graphic summary of the OvHV-2 gB gene query (17,800 bp) against the GenBank nucleotide database; two red bars (score ≥ 200) mark full-length matches to reference OvHV-2 genomes.

Figure (2): Pairwise alignment of the OvHV-2 gB query with the OvHV-2 complete genome (DQ198083.1): 100% identity (17,800/17,800 bp; 0 gaps; E = 0.0).

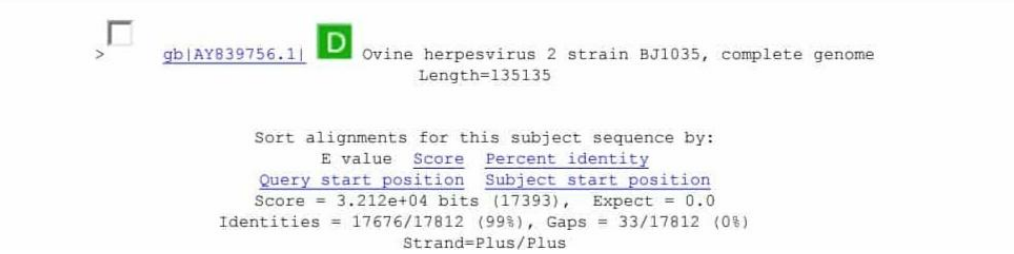


Figure (3): Pairwise alignment with OvHV-2 strain BJ1035 (AY839756.1): 99% identity (17,676/17,812 bp; 33 gaps; E = 0.0).

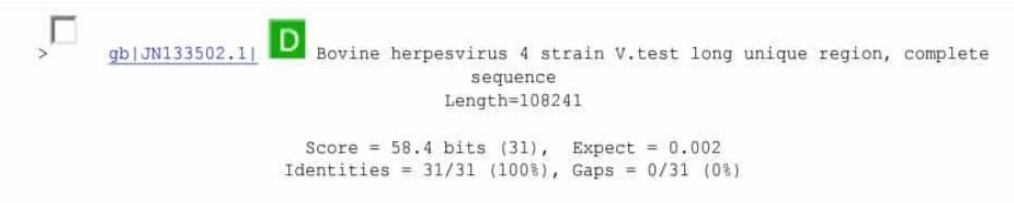


Figure (4): Pairwise alignment with bovine herpesvirus 4 strain V.test (JN133502.1): only a 31-bp match (E = 0.002), i.e. negligible homology.

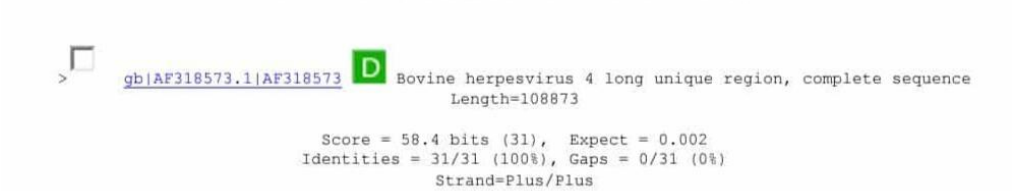


Figure (5): Pairwise alignment with bovine herpesvirus 4 (AF318573.1): only a 31-bp match (E = 0.002), confirming extremely low similarity to BoHV-4.

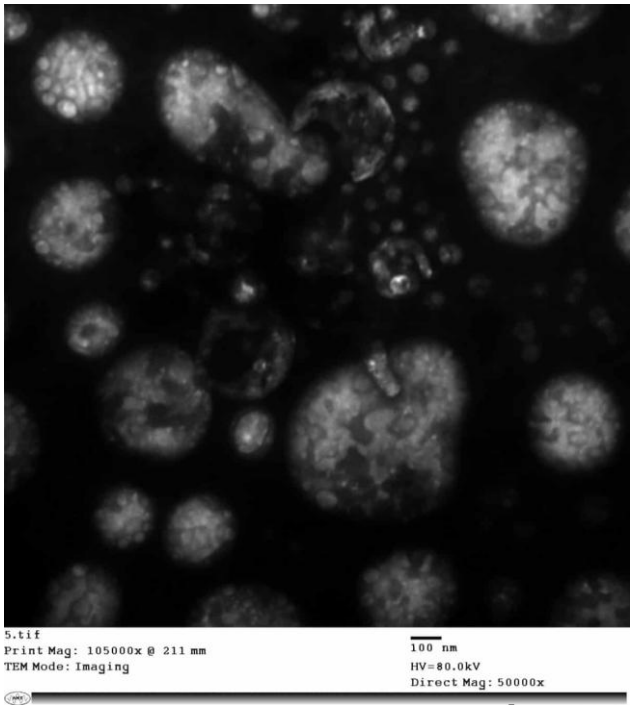


Figure (6): TEM reveals Burkitt's lymphoma in supernatant of the tongue mucosa.

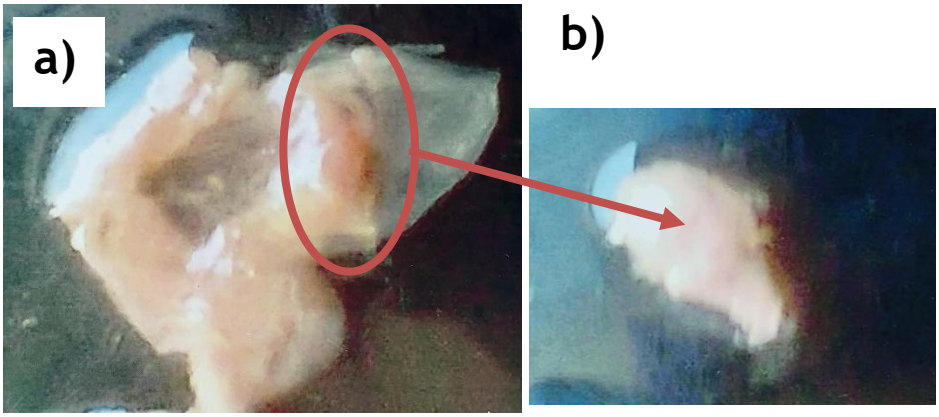


Figure (7 a and b): CAM reveals tumors on day 9 of isolation as detected in a and b.

DISCUSSION

EBV is a major human oncogenic virus. It was the first oncogenic virus recognised in humans and adds greatly to the worldwide burden of infection-related cancers (de Martel et al., 2020; Damania et al., 2022). Once infection is established, it is never eliminated (Babcock et al., 1998), and EBV was the first human virus linked to lymphoid and epithelial oncogenesis, including Burkitt's lymphoma, Hodgkin's disease, gastric adenocarcinoma and nasopharyngeal carcinoma, as well as leiomyosarcoma and breast cancer (El-Sharkawy et al., 2018). The virus is found in most Burkitt's lymphoma cases worldwide (Al-Khreisat et al., 2023) and is also implicated in most malignancies that follow transplantation (Damania et al., 2022). It was first seen by electron microscopy in a malignant Burkitt's lymphoma (Epstein et al., 1964). It remains the model human tumour virus, directly implicated in the oncogenesis of lymphoid and epithelial tumours (Münz, 2025). Several factors explain the persistence and oncogenic capacity of EBV: (1) its ability to keep its genome within cells

without threatening host survival; (2) the ways it evades the host immune system; and (3) its power to switch on pathways that control cell growth (Münz, 2019). In Burkitt's lymphoma cells carrying EBV, many proteins central to killing by cytotoxic T cells are suppressed: the transporters linked to antigen processing, cellular adhesion molecules, and the MHC class I molecules by which cytotoxic T cells identify virus-infected cells (Brady et al., 2007). Stress reactivates latent EBV (Glaser et al., 1991; Coskun et al., 2010).

Through its pathogenesis, EBV can over-activate T cells and macrophages, so that too many cytokines are produced. At its most severe, this causes fatal coagulopathy, with or without central pontine myelinolysis, and secondary or acquired haemophagocytic lymphohistiocytosis may follow from intense immunological activation of normal T lymphocytes and macrophages (Damania et al., 2022). Earlier reports held that the virus first multiplies in oropharyngeal epithelial cells and only later infects B cells, but other findings suggest that oropharyngeal B cells may be the first site, with the amount of infection rising sharply once epithelial cells come into contact with infected B cells (Münz, 2019).

Virally encoded microRNAs were first identified in EBV, within the nucleus of several Hodgkin's and Burkitt's lymphoma cell lines (Pfeffer et al., 2004), and these microRNAs help drive both immune evasion and tumorigenesis (De Re et al., 2020). The Gly-Ala residues of EBV nuclear antigen 1 (EBNA1) block processing of the antigen by the proteasome, which keeps the protein from being presented on MHC class I molecules and so hides it from immune recognition (Levitskaya et al., 1995). EBV BILF1 encodes a seven-transmembrane G-protein-coupled receptor produced in the lytic cycle that relays signals from outside the cell into internal responses; the GPCRs of EBV sequester host chemokines, promote cell-to-cell adhesion and reshape the intracellular signalling network to enable viral replication (Lyngaa et al., 2010; de Munnik et al., 2015). BILF1 is mainly responsible for immune evasion and acts as a tumour-promoting factor both in vitro and in vivo (Lyngaa et al., 2010); in other words, it causes immunosuppression and oncogenesis (Tsutsumi et al., 2021). The EBV oncoproteins LMP1, LMP2A and EBNA1 are recognised as agents that initiate and/or amplify epithelial-mesenchymal transition (EMT), which is regarded as a hallmark of cancer progression and metastasis (Cyprian et al., 2018; Wang&Ning, 2021). Cytokines including IL-6 and IL-1 may also act as autocrine growth factors for B cells infected with EBV (Damania et al., 2022).

For diagnosis, PCR and sequencing are best done after the open view that electron microscopy (EM) provides, because EM helps with morphological identification. It therefore serves as a means of differential diagnosis and belongs at the start of the diagnostic process. Negative-staining EM allows the causative agent to be recognised as a herpesvirus (Goldsmith&Miller, 2009;Bastawecy and Abd El-Samee,2012). Its advantages are simple sample preparation and quick analysis, giving a same-day result, while its undirected open view allows rapid morphological identification and differential diagnosis among the various agents in the specimen (Hazelton&Gelderblom, 2003). For this reason, EM should be a frontline diagnostic method (Goldsmith&Miller, 2009). Even so, a definitive diagnosis still requires molecular confirmation of OvHV-2 by PCR and sequencing (Li et al., 2011; Riaz et al., 2021).

Running the PCR on whole blood rather than on peripheral blood leukocytes alone can improve the assay, perhaps because free virus is present in the plasma of the infected

animal (Zaki et al., 2016); quantitative and digital PCR formats now allow sensitive detection and quantification of OvHV-2 in these samples (Pinheiro de Oliveira et al., 2019; Headley et al., 2024). For identifying viral particles by morphology in tumours such as Burkitt's lymphoma, study under the electron microscope is more decisive than light microscopy (Goldsmith&Miller, 2009). TEM, together with isolation in SPF-ECE by the CAM route and harvest 9 days later, produced a notable finding. To our knowledge, this is the first study to demonstrate oncogenic properties in OvHV-2, even though the virus was already known to have every factor required for oncogenesis.

Using negative-staining electron microscopy (EM), the virus responsible for MCF can be recognised as a herpesvirus. Because negative-staining EM offers simple sample preparation, rapid same-day detection, and an undirected open view that supports quick identification as well as differential diagnosis of the several agents in a sample (Hazelton&Gelderblom, 2003), it is regarded as a frontline diagnostic technique (Goldsmith&Miller, 2009). The method can also help rule out other viruses previously suspected in Egypt of causing mouth lesions, lameness or skin lesions. Phylogeny among herpesviruses is measured from the gB gene sequence, which is the most accurate of the conserved genes for this purpose (McGeoch et al., 1995). In the sequencing described by Bastawecy and Abd El-Samee (2012), the complete gB gene ran to 17,800 residues, and its layout gave 100% query coverage with 100% maximum identity to the matching region of the OvHV-2 complete genome (accession number DQ198083.1), and 100% query coverage with 99% maximum identity to the matching region of the OvHV-2 (strain BJ1035) complete genome (accession number AY839756.1). By contrast, query coverage fell to 0% against the bovine herpesvirus 4 long unique region, complete sequence, and the bovine herpesvirus 4 strain V.test long unique region complete sequence (accession numbers AF318573.1 and JN133502.1, respectively).

Screening every species, including avian, marine and companion animals, for susceptibility to EBV or OvHV-2 is needed, a need highlighted by the recent detection of OvHV-2 in atypical hosts such as the horse and further artiodactyls (Madrigal-Valencia et al., 2023; Bianchessi et al., 2024) and by its link to acute respiratory disease in cattle (Headley et al., 2023). At the same time, securing accurate herpesvirus diagnosis by sequencing the entire glycoprotein B gene will strengthen both our understanding and our management of this widespread virus. Tumours in any species should also be tested for OvHV-2 and EBV, because latent EBV or OvHV-2, which persists as circular double-stranded DNA called an episome, can be mistaken for papillomavirus. The glycoprotein B subunit of OvHV-2 could serve as a vaccine, as it has already been shown to protect against sheep-associated MCF, while anti-OvHV-2 glycoprotein B camelid nanobodies could be produced for treatment and for emergency use in valuable animals (Cunha et al., 2022). Routinely checking the cell cultures used in human, animal and insect systems for contamination with OvHV-2 and EBV is also recommended, in order to protect the quality and safety of biological products (Bastawecy et al., 2025).

In summary, the sequencing shows that the OvHV-2 circulating in Egypt (2012) carried unchanged sequences, identical before and after isolation. Once EM has detected it, the complete glycoprotein B gene sequence is advised for any herpesvirus thought to infect any species .Also , testing all species including humans, avian and marine species forOvHV-2 and EBV, because both EBV and OvHV-2 encode long non-coding (lnc) RNAs that may be misread and sequenced as RNA viruses.

RECOMMENDATION

One key recommendation is that farm animals, poultry and fish should be given feeds free of any additive derived from animals, birds or marine sources, and that the plants used in their rations should be free of hybridization or genetic modification, since feeds of that kind are regarded as stressors that can reactivate latent OvHV-2.

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