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**Original Article**

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# Overview on transmission, epidimeology, pathogenesis, pathological aspects and alternate veterinary medicines of bovine papillomatosis

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## INTRODUCTION

Livestock plays a vital and deciding role in the rural economy as family income source and for generation of employment in the rural sector, particularly in landless labourers, small and marginal farmers and women (Kumbhar, 2011). Bovines are the key constituent species of livestock; they are raised as livestock in india mainly for dairy production (milk), meat purpose and as draught animals (pulling carts, ploughing etc.). One of the biggest concerns responsible for decreased growth and production in bovines in field conditions are neoplasms. The bovine neoplasms may cause economic losses due to hard hitting negative impact on productivity, animal health leading to reduced gains to farmers and dairy industry (Sharma *et al*., 2020). Neoplasms are broadly classified into benign and malignant neoplasm also known as carcinoma. Benign neoplasms are mainly localized, single, showing slow and limited growth and do not show recurrence whereas malignant neoplasms are single/ multiple showing rapid and unlimited growth and recurrence after removal. Malignant tumours metastasize which can spread from primary site to distant secondary site within the host body. Malignant tumours grow by expansion, they also invade or infiltrate adjacent tissues by growing between cells along the tissue spaces (Udharwar *et al*., 2008). Bovine papillomaviruses (BPVs) are oncogenic small non-enveloped DNA viruses with icosahedral symmetry are capable to produce benign cutaneous or mucosal epithelial lesions. The malignant tendencies of squamous cell carcinomas (malignant neoplasm of epithelial origin) in cattle and their aetiology has been linked to BPV especially (Rutten *et al.,* 1992). They replicate inside the squamous epithelial cells and produce wart-like outgrowths on skin and mucosal epithelium (Antonnson and Hansonn, 2002; de villiers *et al*., 2004). They infect epithelial cells and fibroblasts in the dermis layer of skin, causes carcinoma of urinary tract of bovines (Shafti-Keramat *et al*., 2019). Bovine papillomatosis is the viral infection commonly affecting heifers and milch animals. Warts are usually found on the head, neck, shoulders and sensitive parts of body *i.e.* the vaginal

mucosa. Cutaneous papillomatosis is also known as warts, which is an epithelial cell over growth, infectious in nature and appears approximately eight weeks after exposure to the infectious virus. It is highly contagious disease that can be easily spread from one animal to other by close contact. Generally, the benign tumours affecting the skin or mucosa regress spontaneously due to lack of angiogenesis, but under special conditions, may lead to carcinoma, mainly due to mutagens and immunosppressents from bracken fern. Till now thirteen different bovine papillomavirus genotypes are related with skin and mucosal tumours in bovines, from which only four types (BPV-1, -2, -5 and -13) are evident of cross infection in other species. Recent studies *in vivo* have divulged new insights into the pathogenesis and distribution of this viral infection. Attempts should be made to study the viral epidemiology of bovine papillomaviruses, analysis on BPV genome structure and viral antigens associated with the cellular events and new pathological aspects of both cutaneous and mucosal tumours in bovines. Investigations regarding active immunization should also be addressed. Bovine papillomavirus produces warts or papilloma in alimentary tract, urinary tract, teat and udder, skin of cattle and other mammals that can be transformed to malignant form of carcinoma. The Classification of this virus is into two or three subgroups including epitheliotropic and delta group of papilloma virus. Epitheliotroic group consists of BPV-3, BPV-4, BPV-6 whereas BPV-1and BPV-2 belongs to Delta group of viruses. Predisposing factors are required to induce malignancy and one of the most common one is the bracken fern ingestion which leads to immunosuppression when ingested, E5 is the major oncoprotein in the virus that transforms the benign lesion into malignant form. Bovine papillomavirus type 1 and 2 can cause equine sarcoid, bovine papillomatosis is the contagious illness that transmitted by direct contact or indirect contact, recent studies discovered new treatment like ivermectin and also by autogenous vaccine.

**Epidemiology**

The oncogenesis of benign carcinomas is often related with predisposing factors for eg. feeding on bracken fern is associated with Enzootic bovine hematuria and bovine urinary bladder carcinoma, chromosomal aberrations are observed in peripheral blood lymphocytes caused due to bovine papillomavirus (BPV) infection from cows, which were chronically affected with haematuria due to feeding on bracken fern pastures (Dos Santos *et al.*, 1998). Consumption of bracken fern (*Pteridium aquilinum)* has also been related with hematuria. Bracken fern is present in most tropical and subtropical and some temperate climate countries (Dos Santos *et al.*, 1998). Bovine papillomavirus infects large ruminants worldwide, abundance of cases are recorded in regions having great density of *Pteridium aquilinum* (Italy, United Kingdom, Germany, Japan, India, United States of America and Brazil) as per these sources(Campo & Jarrett, 1986; Campo, 1995; Ogawa *et al.*, 2004; Singh *et al.* 2009; Schmitt *et al.*, 2010; Carvalho *et al.*, 2012). In Italy, Furthermore, BPV-1/-2 DNA was discovered by Roperto in the placenta of pregnant cows suffering from chronic enzootic hematuria (Roperto *et al.*, 2012). BPV-1 infection in the water buffalo was demonstrated by is While Silvestre which was associated with cutaneous, perivulvar and vulvar fibropapilloma (Silvestre *et al.*, 2009). In Scotland, BPV was reported to be associated in the occurrence of cancers of the gastro-intenstinal tract and urinary bladder in cattle (Campo *et al.*, 1985). In India, as per reports of recent researches conducted on cutaneous warts in bovines indicate that the DNA of BPV-1 and BPV-2 is present in both cutaneous warts as well as in normal skin, while in buffaloes, the tested samples were diagnosed with single or mixed infections,

corroborate the high prevalence of the infection in bovines (cattle and buffaloes) (Pangty *et al.*, 2010). Recently, detection of BPV-2 DNA in urine and urinary bladder lesions in cows in the CEH endemic regions of India (Pathania *et al.*, 2012). The occurence of BPV-5 infection along with BPV-1 and BPV-2 has been reported in wart-like lesions in rumen of buffaloes, indicating the increase of the prevalence of these virus types and their ability to jump the species (Kumar *et al.*, 2015).

**Transmission**

There is dearth of literature on the transmission of papillomatosis between animals. But confined populations are found more vulnerable because of the dissemination of virus by indirect (via contaminated objects) or direct contact (from animal to animal) (Hama *et al*., 1988; Nasir & Campo, 2008). Besides the skin–skin transmission, transmission through arthropod vector and vertical transmission has been evident (Freitas *et al.*, 2003; Finlay *et al.*, 2009). Although these alternative pathways of transmission might be less efficient (Bravo *et al*., 2010). Vertical transmission of papillomavirus has been deliniated (Dos Santos *et al.*, 1998; Freitas *et al.*, 2003; Yaguiu *et al.*, 2008). Occurence of equine sarcoid by BPV-1 which is one of the locally aggressive and invasive skin tumors in equines is example of cross-species transmission of a papillomavirus (Trewby *et al.*, 2014). Vector transmission of BPV virus by flies can occur between bovines and equines (Nasir & Campo, 2008; Finlay *et al.*, 2009). Transmission of BPV-2 may occur through stable management practices or penetration through open wounds from contaminated pasture, there is need for more investigation from researchers on these transmission pathways (Chambers *et al.*, 2003).

**Pathogenesis of papillomavirus**

Oncogenesis due to papillomavirus (PV) infection was first discovered in rabbits and cattle. In early 1900's, in vitro studies of animal PV proteins have imparted greatly to the understanding of the mechanisms of cell transformation. As animal PVs cause dreadful diseases in both farm as well as in companion animals, for eg. teat papillomatosis in cattle, equine sarcoids and oral papillomatosis in canines therefore the determination of pathogenesis of these infections is essential (Campo, 2002). The major oncoprotein of several BPVs is E5 protein which is hydrophobic, short transmembrane protein with many oncogenic properties, E5 causes cell transformation through activation of the cellular β receptor for the platelet derived growth factor (PDGFβ-r) and decrease the cell surface expression of major histocompatibility complex class I (MHC I) helping virus to evade the immune system, another protein E7 is weak transforming gene but in collaboration with E5, results in cell transformation during development of carcinoma (Corteggio *et al.*, 2013). In bovines it is related to delayed immunological response associated to the presence of BPV (Knowles *et al.*, 1996; Zur Hausen, 2002). Among the several constituents of the fern, the flavonoid quercetin posess immunosupressive and mutagenic properties and probably related to carcinogenic synergic action in association with BPV-4 which leads to the malignancy(Pennie & Campo, 1992).

**Pathological aspects**

Multiple white round to irregular mass, small pendunculated, papillomatous (wart like) growths with verrucous surface (Fig.1) on the skin of face, neck, back and shoulder region are commonly

observed in bovines. Ptaquiloside (toxin of backen fern) suppresses bone marrow, causes acute hemorrhagic syndrome and has carcinogenic activities in bovines. The animal is more susceptible to infection due reduced number of leucocytes. Bracken fern (Pteridium aquilinum) may eleviate the progressive papillomas caused by bovine papilloma virus.

Fig. 1 Cutaneous warts in bovine papillomatosis; Holstein Friesian Heifer (Kumar *et al*., 2022)

**Alternate Veterinary Medicines:**

Alternative veterinary medicine defined as the use of alternative medicine in the treatment of animals. Types alternative therapies used for veterinary treatments may include, but are not limited to, acupuncture, herbal medicine, homeopathy, ethno medicine and chiropractic, In case of bovine papillomatosis homeopathic way of alternate medicine is used. Herbal medicine can also be used as an alternative medicine in case of bovine papillomatosis.

Homeopathic treatment: **Thuja** is a plant derivative obtained from ***Thuja occidentalis*** which is used for homeopathic preparation available in market with a brand name of **Thuja-30**. Treatment with oral administration of 10 drops of thuja extract twice a day and topical application of thuja ointment at the site of wart for four weeks. Treatment with Thuja occidentalis (thuja-30, a homeopathic medicine) at the rate of 10 drops twice a day along with application of Thuja ointment on the affected area for a span of four weeks was found to be very effective in complete sloughing of wart and development of normal tissue and results in recovery of wart after continuous oral administration of Thuja for three weeks in dairy cattle.

Injectables: Injection **Anthiomaline®** (Fig) containing lithium antimony thiomalate (60mg/ml) @ 20ml deep intramuscular in cattle at weekly intervals, 50ml vial of anthiomaline injection are commercially available for the treatment of bovine papillomatosis.

Herbal treatment: Bai-Mast® herbal capsules arre available for treatment of mastitis and skin infection in cattle. In recent days herbs had been proven effective against many bacterial and viral diseases without any side effect. Based on this principle, Bai-Mast® herbal capsule was used for the treatment of bovine papillomatosis in cattle. The papilloma starts regressing after 5th day of treatment and complete recovered after 18-22th day of treatment. There was no recurrence of papilloma after complete recovery.

A formalinized suspension of bovine papilloma with inactivated virus provides a vaccine for effective treatment and prevention of papillomatosis in cattle (Barthold *et al.*, 1976; Hunt, 1984; Lesnik *et al.*, 1999; Suveges & Schmidt, 2003). Ivermectin can also be effective in treatment for bovine cutaneous papillomatosis as either single or double dose applications, for treatment of cutaneous papillomatosis (Börkü *et al.*, 2007).

**Prevention**

Commercial vaccines available may help prevent warts in cattle not previously infected, autogenous vaccines prepared from chemically treated warts taken from bovines in a herd. These autogenous vaccine may have the strain or type of papillomavirus causing the contagious warts in a herd than some of the commercial vaccines, instruments and tack used on infected animals should be sanitized before use on other animals. The infected bovines may not have visible papilloma, but still contamination of equipment is possible. Tattoo or tagging pliers can be disinfected when they are used between the calves, with a 2 to 4% solution of formaldehyde and wash off blood or tissue before immersing in the formaldehyde (Morter & Horstman, 1987). Usually cattle have poor immune response for papillomavirus. This may be due to the life cycle of the virus is limited to the epithelia, which could also be the underlying cause of the persistent infection (Campo, 1997). BPV-2 L1 vaccines induce production of virus neutralizing antibodies which prevent reinfection (Jarrett *et al.*, 1991).

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