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Invited Review Article

Cutaneous Bovine papillomatosis: Etio-pathology and disease status in India

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Abstract

Bovine papillomatosis is a chronic viral disease of cattle and buffaloes caused by bovine papillomavirus (BPV) under *Papillomaviridae* family. It is characterized by the presence of warts at various anatomical locations. In India, the prevalence of this condition has significant implications for the dairy and agricultural sectors, affecting animal health, productivity, and economic viability. Cutaneous bovine papillomatosis is manifested as cutaneous wart (CW) and teat wart (TW). Twenty-eight BPV biotypes have been reported globally till date, and several new biotypes have also been reported with various clinical consequences from India in the last 2 decades. Pathologically, CWs are characterized as fibropapilloma, true papilloma and occult papilloma which deserve more attention by researchers. Diagnosis of disease includes clinical history, histopathology, polymerase chain reaction (PCR), *in-situ* hybridization and demonstration of viral antigen in tissue by immunohistochemistry. This review is focused on the etiology, viral structure, transmission, pathogenesis, macroscopic pathology, immunology, treatment regimen and control of the disease in affected livestock.

Keywords: Bovine papillomavirus, Cutaneous bovine papillomatosis, Pathology

Highlights

- The review article focused on the etiology, transmission, pathogenesis, and gross and microscopic pathology of Bovine Papillomavirus (BPV).
- Twenty-eight BPV types have been reported globally, and 6 types from India.
- Hyperkeratosis, the presence of koilocytes, and rete pegs were characteristic features.
- Diagnosis, good health care, awareness and new generation vaccines are required to combat the issue.

INTRODUCTION

Bovine papillomatosis is a chronic viral disease of large ruminants and is associated with heteromorphic hyper-proliferative lesions in the cutaneous and mucosal epithelium. The cutaneous form is most noticeable benign skin tumors in large ruminants, particularly in cattle and buffaloes. It is characterized by the presence of warts of various sizes at diverse anatomical locations. Lesions are most frequently detected on the head, neck, back, abdomen, udder, teat and perineum of cattle (Borzacchiello and Roperto, 2008; Singh *et al*., 2019). The disease is caused by bovine papillomaviruses (BPVs) belonging to the family *Papillomaviridae* (Araldi *et al.*, 2015). The disease leads to considerable economic losses in bovine population in many states of India due to its clinical consequences and depreciation of the aesthetic as well as economic values of animals. It also causes feeding, breathing and reproductive disturbances when affecting mouth, nose and reproductive organs, respectively (Elzein *et al*.,1991). Lesion on teat also predisposes to opportunist bacterial infections in the mammary glands and udder which can cause mastitis, pain, haemorrhage and a reduction in milk yield. Further, it is linked with difficulty in machine milking. The occurrence of BPV infections was also reported in other animals including buffalo, captive tapir, giraffe, antelope, zebras, horses and yaks (Tomita *et al*., 2007; Kidney and Berrocal, 2008; Silvestre *et al*., 2009; Singh and Somvanshi, 2010; Bam *et al*., 2013; Roperto *et al*., 2013). The disease can also be induced experimentally in hamsters (Singh and Somvanshi, 2010). Mucosal form occurs less frequently as exophytic papilloma and causes alimentary and bladder cancers. Histopathologically, the most characteristic features of cutaneous papillomas are hyperkeratosis and acanthosis of various degrees, presence of koilocytes and proliferative rete pegs of epidermis layer penetrating deep into the dermis. Histopathology and molecular tests are often used for the diagnosis of cutaneous warts (CWs), as conventional virology and serological tests are difficult to perform. However, PCR amplification followed by DNA sequencing of the L1 gene represents

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the most common method to identify and typify BPVs (Araldi *et al*., 2014; Melo *et al*., 2014).

Bovine papilloma is an old disease of veterinary significance, having several issues and challenges for control. Numerous in-depth studies have been carried out in the niche area of prevalence, pathology, virus biology, genomics, diagnostics and therapeutics across the globe including India. This review article summarizes the etiology, virus biology, pathology, and relevant occurrences of farm animals in India, as well as recent research advancements.

Etiology and its biology

The BPVs are non-enveloped spherical particles having circular double-stranded DNA genomes of44 7.2 to 8.0 kbp in size. The whole genome has three regions viz., early (E), late (L) and long control region (LCR) (Bocaneti *et al*., 2016; Araldi *et al*., 2017a). The early genes encode proteins responsible for virus replication and transcription (E1, E2), cell transformation (E5, E6, and E7) and virion production (E4). Two late genes (L1 and L2) encode for capsid protein (Table 1) (Daudt *et al.*, 2018). LCR is a small region between the 5' end of the E and the 3' end of the L region, which codes for wart-specific late RNA. In the mature virion, the viral DNA is associated with host cell histone proteins H2a, H2b, H3 and H4 in a chromatin-like complex. Additionally, it is organized within the virion like cellular DNA in a minichromosomal (episomal) form (King *et al*., 2012). L1 protein is targeted in the classification and detection of BPV types. Currently, 28 BPV types (BPV-1 to -28) have been described from 5 different genera namely, *Deltapapillomavirus* (BPV-1, -2, -13 and -14), *Epsilonpapillomavirus* (BPV-5 and -8), *Xipapillomavirus* (BPV-3, -4, -6, -9, -10, -11, -12, -15, -17, -20, -23 and -24), *Dyoxipapillomavirus* (BPV-7) and *Dyokappapipillomavirus* (BPV-16, -18, -22). Two types, BPV-19 and BPV-21, have yet to be classified (Araldi *et al*., 2017a; Daudt *et al.*, 2018a). BPVs have a specific tropism for squamous epithelial cells. Viral replication, including the synthesis of DNA, capsid proteins and assembly of virion, occurs only in the more terminally differentiated squamous epithelial cells (Borzacchiello and Roperto, 2008). The absolute requirement of

Table 1. Different genes of BPV and their role in pathogenesis

Gene	Major role	Reference
E1	Encodes a protein that binds to the viral origin of replication in the LCR viral genome and exerts helicase activity that separates DNA strands for replication.	Bogaert *et al.*, 2007
E2	It serves as a master transcriptional regulator for viral promoters located in the LCR. It facilitates the binding of E1 to the viral origin of replication. E2 utilizes Bromodomain-4 (Brd4), a cellular protein to tether the viral genome to cellular chromosomes.	McBride *et al.*, 2004
E4	The E4 protein facilitates virions release into the environment by disrupting intermediate filaments of keratinocytes cytoskeleton.	McBride *et al.*, 2004
E5	E5 protein plays a role as an oncogene primarily by activating the cell growth-promoting signaling of platelet-derived growth factor receptors. It has also been observed to down-regulate the surface expression of MHC-I proteins, which may protect the infected cell from destruction by cytotoxic T cells/killer T cells.	Bogaert *et al.*, 2007
E6	E6 protein inactivates the tumor suppressor protein p53.	McBride *et al.*, 2004
E7	E7 protein inactivates members of the retinoblastoma protein/pRb family of tumor suppressor proteins. Together with E6, E7 functions to promote cell-cycle progression, thus priming the cell for replication of the viral DNA. E7 also participates in the immortalization of infected cells.	McBride *et al.*, 2004
L1	It encodes capsid protein, which is crucial for infection and immunogenicity. L1 ORF is most conserved. This gene is used for bio-typing of BPVs.	Bogaert *et al.*, 2007; Haga *et al*., 2013
L2	It is a minor capsid protein and helps in virus encapsidation. It also induces virion assembly by binding to viral DNA.	Borzacchiello and Roperto, 2008
L3	L3 has been described as present exclusively in BPV-4. However, its function remains unclear.	Catroxo *et al.*, 2013

terminal differentiation of squamous epithelial cells for the expression of the virus-specific genes for virus replication is probably the reason for the difficulty in propagating these viruses in tissue culture. The *in vitro* models, especially in cell culture systems, have been extensively employed for virus replication. BPV-1 and -2 are the only PVs shown to have a reproducible effect in tissue culture. These changes included altered morphology, piling up and an increase in acidity of the medium. Subsequently, cell-free extracts of cutaneous papillomas were shown to induce morphological transformation of primary embryonic bovine skin cells, mouse embryo cell cultures and hamster embryo cells. In 2017, researchers explained BPV productive infection in cell lines derived from cutaneous papilloma, fibropapilloma and esophageal carcinoma (EC) (Araldi *et al*., 2017b), but further studies need to be carried out for virus kinetics and putative vaccine candidate screening. BPVs are species-specific and site-specific; however, there are reports regarding cross-species infection with BPV-1, -2, -5 and -13. The few examples are sarcoid in horses (Nasir and Campo, 2008); cutaneous fibropapillomas in giraffe and a sable antelope (Van Dyk *et al*., 2011); cutaneous papilloma in yaks (Bam *et al*., 2013) and cutaneous papilloma and urinary bladder carcinoma in buffalo (Pangty *et al*., 2010). The recent studies on cutaneous warts in cattle revealed co-infections of BPVs (Table 2).

Pathology

The pathology of cutaneous bovine papillomatosis is elucidated under pathogenesis, gross pathology and microscopic lesions.

Pathogenesis: Skin abrasions are necessary for BPV entry (Nasir and Brandt, 2013) since the viruses can not actively penetrate the host's skin. Therefore, the virus exposure to one or more epithelial lesions results in infection, transformation, and proliferation of basal cells, which eventually progresses to benign warts. In cattle, BPV-2 was detected in blood as a source of infection (Singh *et al.*, 2009), and there is evidence that infection can be vertically transmitted to calves (Stocco dos Santos *et al.*, 1998). The viral replication in basal epithelial cells stimulates hyper-proliferation and hyperplasia with the formation of warts and benign papillomas. The life cycle of the virus goes parallel to the differentiation

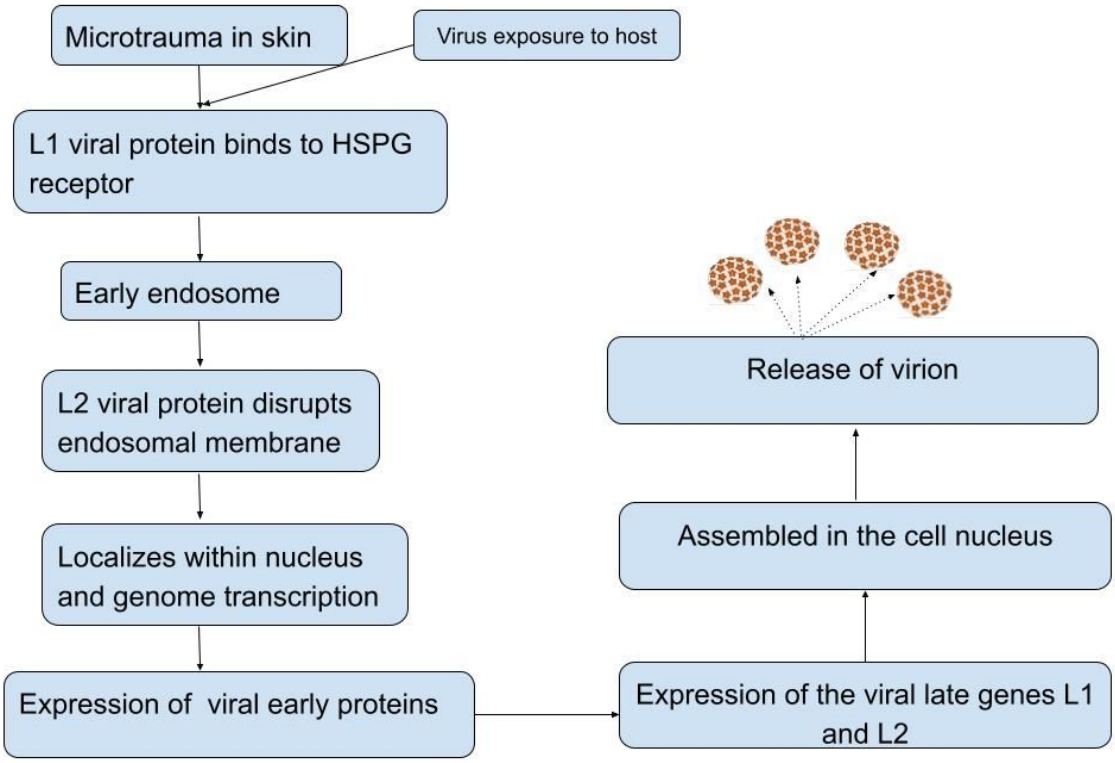

Diagram 1. Schematic representation of pathogenesis of BVP in cattle

process of the epithelial cell. The virus infects the keratinocytes of stratum basale, expresses early genes in the basal and suprabasal layers, replicates its genome in differentiating spinous and granular layers, expresses its structural genes and packages its DNA in the squamous layers, and a new infectious virus is finally released with the keratinized squamous layer (Campo *et al.*, 1994). A schematic representation of the pathogenesis of BVP in cattle is presented in Diagram 1.

Gross pathology: In cattle, the cutaneous warts are dry, rough and crusty in appearance and are mostly present as single, circumscribed with broad base at different anatomical locations (Fig. 1). In some cases, they are cauliflower-like in appearance and multiple in number (Jangir and Somvanshi, 2021). They are hard in consistency and appear as homogenous, glossy connective tissue covered with hyperplastic epidermis on the transverse section. In teat, the papillomatous growths appeared as elongated, filamentous exophytic projections with narrow base, affecting single or multiple teats. But in few cases, they appear as white, fleshy and dome shaped growth, mostly multiple in number. Some authors found the growth as small papillomas with rice grain-like appearance (Singh *et al*., 2019). Cutaneous papillomatous lesions in buffalo are mostly noticed as multiple grey–white papillary growths of tough consistency. Some of the tumours were ulcerated with areas of necrosis, and the surface showed sessile vegetative outgrowths (Silvestre *et al*., 2009). Generally, growths are solitary or multiple and manifested on different anatomical locations of skin including the head, neck, teat, legs, genital and paragenital areas. Warts were cauliflower-like with horny papillae or dome-shaped of 0.5-2.0 cm in diameter varying in number from 1 to 6 (Somvanshi, 2011).

Histopathology: Tissues from the papillomatous growth of the cattle and buffaloes show thickening of epidermis mainly due to hyperplasia of keratinocytes in the stratum spinosum layer. Histologically (Fig. 2), intranuclear eosinophilic inclusion bodies in the keratinocytes are usually seen (Singh *et al*., 2009; Kumar *et al*., 2013). Proliferative changes in basal cells were also noticed, which ultimately leads the penetration of rete pegs deep into the dermis with marked proliferation of fibrous connective tissue (Singh and Somvanshi, 2010; Kumar *et al.*, 2013). Another prominent histological feature is the presence of koilocytes, which are characterized by perinuclear cavitation, nuclear enlargement and hyperchromasia (Araibi *et al.*, 2004; Maeda *et al*., 2007). Some authors have also classified BPV associated cutaneous warts as true papilloma, exophytic fibropapilloma, endophytic papilloma and fibroblastic/ occult papilloma (Singh *et al*., 2009).

Global status

The majority of BPV type-specific prevalence was reported in Japan and Brazil. Out of 24 types, 22 types and putative new types have been reported from Brazil only (Batista *et al*., 2013; Lunardi *et al.*, 2016; Daudt *et al.*, 2018b). Novel putative type BPV11 and their co-infections were detected in cattle in Brazil (Carvalho *et al*., 2012). Different biotypes like BPV-1, BPV-3, BPV-5 and BPV-6 were detected from teat papillomas in Japan (Ogawa *et al*., 2004). The presence of BPV 6, 7, 8, 10 and 12 were first time reported from Italy (Savini *et al*., 2016). Similarly, the first molecular characterization of BPV-1 and BPV-2 in cattle CWs was done in Mexico (Anaya *et al.*, 2016). In Australia, BPV-1 from CWs in cattle has been detected (Spadrow and Ford, 1983). In South Africa, BPV-1 and BPV-2 were detected in giraffe and sable antelope by real-time PCR (Van Dyk *et al.*, 2011).

Status in India

Various workers have reported incidences of cutaneous papillomatosis in India from time to time. Nair and Sastry (1954) reported 6.7% (126 cases) incidence of bovine papillomas in Madras State during 1940-51. Gupta *et al.* (1989) observed an outbreak of papilloma in dairy cattle in Haryana. Many cases of oral papilloma cutaneous fibroma in bovines were reported from Orissa. Five cases of warts were investigated in crossbred cattle maintained at the ICAR-IVRI dairy farm in Mukteswar (Somvanshi *et al.*, 1986). Infected animals had multiple, hard, typical pedunculated or non-pedunculated, keratinized or non-keratinized horny warts of diverse sizes and shapes on the teats and the udder, belly, head, face, neck, back and legs. All cases were fibropapilloma. Degloorkar *et al*. (1992) reported 0.5% prevalence of papilloma in Parbhani, Maharashtra. Wangikar *et al.* (2001) recorded 2/29 cases of papilloma from Maharashtra. Mitra (2005) reported 27 cases of cutaneous papillomatosis of crossbreed cattle from West Bengal. In Andra Pradesh, a study diagnosed 21.05% of warts out of 57 tumour samples screened in cattle and buffaloes (Shruthi *et al*., 2018). Leishangthem *et al.* (2008) first identified BPV-1 and BPV-2 DNA from CWs in cattle and buffalo calves in India by analyzing partial sequences of the L1 gene. Singh *et al.* (2009) diagnosed 53 cases of cattle CWs histopathologically as fibropapilloma and fibroblastic/occult papilloma with the presence of koilocytes, keratohyaline granules and intracytoplasmic inclusion bodies. Several types of BPVs were also reported in ruminants in different states of the country (Table 2).

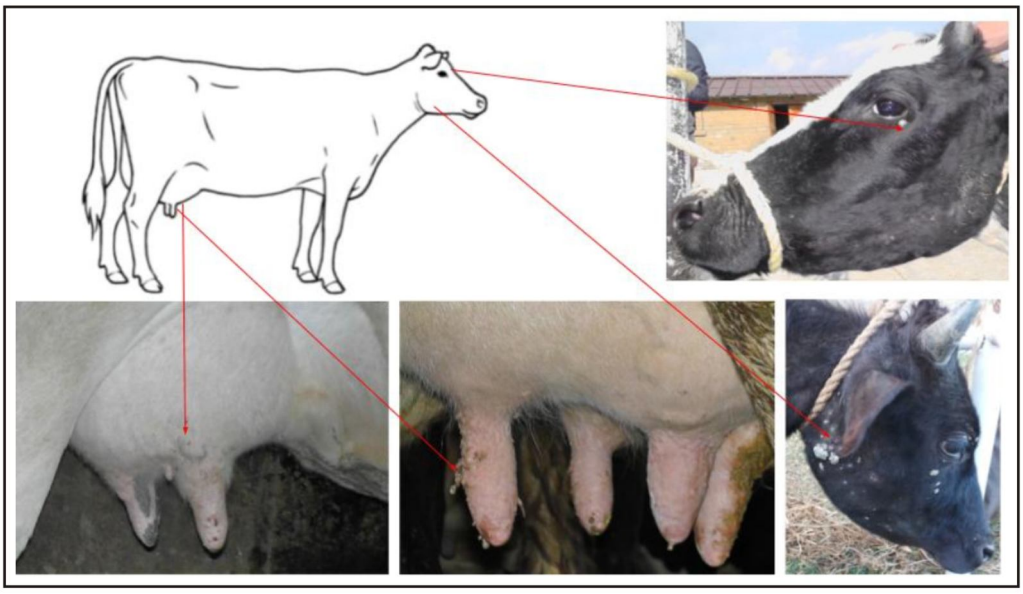

Fig. 1. Cutaneous papillomas at different anatomical sites of cattle

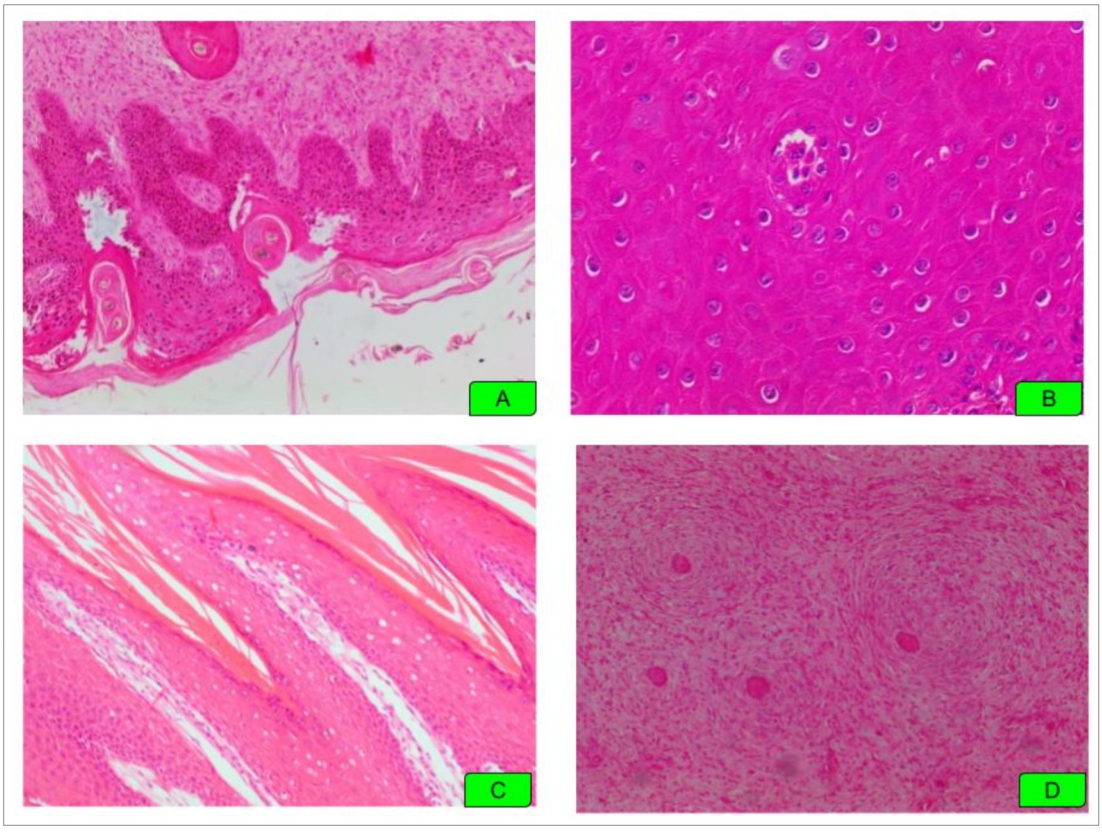

Fig. 2. Microscopic lesions of wart a) Rete pegs formation, b) Koilocytes, c) Digit like growth, d) Fibropapilloma (Source: Singh *et al*., 2019)

Table 2. Types of bovine papillomavirus reported from different states of India in ruminants

Sl. No.	Species affected	BPV types detected	Pathological lesion	Geographical location	Reference
1	Cattle and Buffalo	BPV-1 & -2	CW	Uttar Pradesh	Leishangthem *et al.* 2008; Pangty *et al*., 2010
2	Cattle	BPV-2	CW (tissue and blood)	Uttarakhand, Uttar Pradesh	Singh *et al*., 2009
3	Buffalo	BPV-2	CW	Uttar Pradesh	Singh and Somvanshi, 2010
4	Yak	BPV-1 & -2	CW	Arunachal Pradesh	Bam *et al*., 2013
5	Cattle	BPV-2	EBH (urine and urinary bladder)	Uttarakhand	Pathania *et al*., 2012
6	Cattle	BPV-10	Teat wart	Uttarakhand	Kumar *et al.*, 2013 a
7	Cattle	BPV-1 & -2	CW	Uttar Pradesh	Kumar *et al*., 2013 b
8	Cattle	BPV-1 & -10	Teat wart	Uttar Pradesh	Kumar *et al*., 2013 b
9	Cattle	BPV-1 & -2	Mucosal papilloma	Uttar Pradesh	Kumar *et al*., 2015
10	Buffalo	BPV-1, -2 & -5	CW	Uttar Pradesh	Jangir *et al*., 2017
		BPV-1 &-2	CW	West Bengal	
11	Cattle	BPV-1	CW	Uttarakhand	Singh *et al*., 2019
12	Cattle	BPV-1, -2 & -5	CW	Andhra Pradesh	Prameela and Veena, 2020
13	Cattle	BPV-1, -2 & -5	CW	Uttarakhand, Uttar Pradesh	Jangir *et al*., 2021
		BPV-1 &-2	CW & TW	West Bengal	
		BPV-1, -2 & -5	TW	Uttarakhand	

Diagnosis of BPV

BPV can be detected by conventional methods like gross lesions, histology and molecular methods like PCR. The molecular method like PCR detects the DNA of different types of BPV involved in BP from warts and tissue fluids and is further confirmed by nucleotide sequencing of PCR amplicons or by Southern blotting (Kumar *et al*., 2013b). Carvalho *et al*. (2003) used PCR for the detection of BPV-2 in reproductive tract tissues, ovarian and uterine tissue fluids, oocytes and cumulus cells of slaughtered normal bovine females, and further confirmation was done by southern blotting. BPV-1 DNA in peripheral blood, warts and plasma samples of bovines affected by cutaneous papillomatosis were detected by molecular assay (Freitas *et al*., 2003). BPV-1 has also been detected in warts, blood, placenta and amniotic fluid obtained from a bovine and her calf thus showing the evidence of vertical transmission of BPV-1. DNA can also be detected by *in situ* hybridization methods (Jelinek and Tachezy, 2005).

Leishangthem (2008) used histopathology, PCR, cloning and sequencing techniques for the diagnosis of BPV-1 and -2 in cattle and buffalo in India. CISH is also an additional method used to demonstrate the physical state of these viruses (Melo *et al*., 2014). Another additional technique to identify PVs is L1 immunodetection (Araldi *et al*., 2014), which not only allows the identification of the viral presence but also provides important evidence of productive infection (Melo *et al*., 2014).

Immunity

Host immune responses to PV infection are not well understood. In general, the infection is acquired by the young ones, and warts persist for variable periods, after which the tumors regress. The host is left immune to reinfection with the same virus. Information is available only for BPV-1 and -2 infections.

Liu-Xiao *et al*. (2002) stated that the route of administration of BPV-1 determines the character of the induced immune responses. Immune responses following mucosal administration were generally weaker than following systemic administration. Inoculation by

scarification induces dermal fibromatosis at 3 weeks and epidermal papillomatosis after 2 to 3 months. However, only fibroma is induced on intradermal inoculation. Calves vary in susceptibility to primary BPV infection, and all calves do not develop mature fibropapillomas. Tumors may regress spontaneously during any stage of development.

Multiple bovine warts usually regress on an individual animal simultaneously, but this occurs later than the development of resistance to reinfection with BPV. Regressing fibromas are infiltrated with mononuclear leukocytes (lymphocytes) in perivascular areas. The intensity of infiltration is proportional to the rate of fibroma regression. The presence of precipitating antibodies does not protect against reinfection unless the warts have undergone resolution. However, a small percentage of animals whose fibromas have regressed are still susceptible to reinfection, but the resultant lesions undergo early regression.

Treatment against cutaneous bovine papillomatosis

Bovine papillomatosis is generally regarded as a self-limiting disease, although the duration of warts varies considerably. Number of drugs and different therapeutic trials have been made to treat papilloma with variable results. Some authors used antimony preparations for treating bovine cutaneous warts with varying degrees of success. Surgical excision of papillomas is often practiced in field (Muro *et al.*, 2008). Although frequently employed, this method is inefficient in cattle with a high incidence of BPV, because it is impracticable to perform the excision of papillomas in all cattle. Another strategy frequently employed is self-hemotherapy (Leto *et al.*, 2011). This method consists of the removal and intramuscular reinjection of a volume of 10 mL of venous blood, inducing a nonspecific immune stimulus that can promote the "shedding of the warts" (Leto *et al.*, 2011). Autohemotherapy was reported to cause a complete cure of papillomatosis in cattle. However, this technique does not avoid BP reoccurrence, thus being a palliative method. Another possibility to reduce the incidence of BP is to control ectoparasite populations since it was demonstrated that the biological control of ticks reduces the incidence of BPV.

The idea to develop a vaccine against BPV began in the 1930s decade. Scientists demonstrated that the papillomavirus, though non-detectable by the usual infection test, can induce an immunity response. Since then, different vaccine models have been proposed in the literature. Vaccines have been developed against BPV-2 and BPV-4. Immunity was type-specific and protected calves from infection with the BPV type of the vaccine but not from other types. BPV-2 L2 vaccines induced regression of warts in which large infiltration of lymphocytes and macrophages was seen. Antibodies produced against the antigen were not neutralizing (Campo *et al.*, 1994). Prophylactic vaccination was achieved with BPV-1 virion and virus neutralizing antibodies were elicited by vaccination with BPV-1 L1 protein (Campo, 1997). Sreeparvathy *et al.* (2011) claimed autogenous wart vaccination as an effective treatment method for bovine papillomatosis. Experimentally, the WCS peptide vaccine was reported to have therapeutic effects in the early stage of an induced tumor in hamster (Pangty *et al.*, 2011). However, none of them became a commercial product (Araldi *et al.*, 2017a).

In addition to the above treatment methods, herbal therapy has also been described to have therapeutic effects in bovine cutaneous papillomatosis. Hemmatzadeh *et al.* (2003) reported that both salicylic acid and fig tree latex had similar therapeutic effects in treating teat warts in cows. Marins *et al.* (2006) studied the efficiency of homoeopathy and herbal therapy in the treatment of bovine cutaneous papillomatosis. Apaydin *et al.* (2010) studied the effect of *Paronychia kurdica* on teat and udder papillomatosis in cows. Kavithaa *et al.* (2014) reported that topical thuja ointment was 57% effective against cutaneous papillomatosis. Zahid *et al.* (2015) reported that *Tarantula cubensis* extract applied in normal therapeutic doses was more effective against teat papillomas than levamisole. Kumar and Pant (2017) reported that Bai-Mast® capsules containing plant extracts have compounds that inhibit papillomavirus and secondary bacterial infection, which may help in the regression of warts.

Conclusion

This review critically focused on etiopathology with immunity, and it was revealed that new types had been detected in bovine papillomatosis with various clinical consequences. Therefore, it may perhaps attract clinicians to record clinical cases spontaneously and researchers to undertake further investigations, particularly on etiopathology and immunoprophylaxis.

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Authors' contribution: CJ: Drafting the article; RT: Drafting and tabulating data; PK- Editing the article.

Data availability statement: No specific research data was used for the review article and information is compiled from the available literature.

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