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Review of Comparative Pathology and Virology of *Bovine Papillomavirus*

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1. INTRODUCTION

Papillomaviruses (PVs) is one of the agents among many etiological agents that produce tumour or tumour like conditions in bovines. PVs first identified in the early 20th century. In 1935 Francis Peyton Rous, who had previously demonstrated the existence of a cancer-causing sarcoma virus in chickens, showed that a papillomavirus could cause skin cancer in infected rabbits. This was the first demonstration that a virus could cause cancer in mammals (Finlay, 2011). Several hundred types of papillomaviruses have been identified, including more than 100 PV types found in humans. PVs are normally strictly species-specific and have been found to infect all birds and mammals also a small number of reptiles, in particular turtles and tortoises (De Villiers *et al.,* 2004). BPV cause both benign and malignant epithelial and mesenchymal tumors in cows and equids (Borzacchiello and Roperto, 2008). The only known case of cross-species infection is the infection of horses and other equids by BPV type 1 or BPV 2 type. Papillomas caused by some types, however, such as human papillomaviruses (HPV) 16 and 18, carry a risk of the development of malignant disease, in particular cancer of the cervix and uterus (Munoz *et al.,* 2006).

2. MORPHOLOGY & GENERAL CHARACTERISTICS

Bovine papillomavirus belong to family Papillomaviridae genus papillomavirus, 14 BPV types have been identified and characterized (Araldi *et al.,* 2017). Non-enveloped with icosahedral capsids, 55 to 60 nm diameter. Contain a single molecule of circular double-stranded DNA, 7.2-8.0 kb (Quinn *et al.,* 2002). Members of the genus are resistant to lipid solvents, acid, and heating at 60°C for 30 minutes. Conventional cell cultures not suitable, produce cell transformation instead of CPE. No reports available for growth on CAM. In unweaned hamsters and certain strains of mice s/c inoculation, tumor at site of inoculation within 100 days.

3. CLASSIFICATION

Earlier Papillomaviruses was grouped in Papovaviridae. The name Papovaviridae is derived from the first letters of the names of important members of the family: papillomaviruses, polyomaviruses and vacuolating agent. Then due to different genomic organization and different genome size it is classified as new family Papillomaviridae. The family contains a Two subfamily, First Papillomavirinae and Second Papillomavirinae and different genus like Alpha-, Beta-, Gamma-, Delta-, Epsilon-, Zeta-, Eta-, Theta-, lata-, Kappa-, Lambda-, Mupa-, Nupa-, Xipa-, Omikron and Pipa papillomavirus etc.

Among those Bovine papillomavirus infectin caused by three genera within the family Papillomaviridae: Deltapapillomavirus δ (BPV-1, BPV-2 and BPV-13), Xipapillomavirus ξ (BPV-3, BPV-4, BPV-6, and BPV-9 to -12) and Epsilonpapillomavirus ε (BPV-5 and BPV-8), which show important inter-generic differences (e.g. xipapillomaviruses lack the E6 gene) Classification of BPV-7 remains to be determined (Gil da Costa and Medeiros, 2014).

Delta and Epsilonpapillomavirus are associated with both papillomas and fibropapillomas, while Xipapillomavirus, only to squamous papillomas (Araldi *et al.,* 2017).

In cattle, infection with different BPV types is associated with the development of cutaneous, udder and teat papillomas and fibropapillomas and cancer of various organ systems. In particular, BPV-4 causes upper digestive tract papillomas, while BPV-2 and, less commonly, BPV-1 are associated with urinary bladder tumours (Gil da Costa and Medeiros, 2014).

Table 1. Classification of different Bovine papilloma types

Abbreviation	Classification	Isolated from	Reference
BPV1	Deltapapillomavirus 4	Cutaneous fibropapillomas	Chen et al. (1982)
BPV2	Deltapapillomavirus 4	Cutaneous fibropapillomas	Groff and Lancaster (unpublished)

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BPV3	Xipapillomavirus 1	Cutaneous papilloma	Terai et al. (2002)
BPV4	Xipapillomavirus 1	Oral/esophageal papilloma	Patel et al. (1987)
BPV5	Epsilonpapillomavirus 1	Udder fibropapilloma	Terai et al. (2002)
BPV6	Xipapillomavirus 1	Udder papilloma	Jarrett et al. (1984)
BPV7	Dyoxipapillomavirus 1*	Teat papilloma and healthy skin	Ogawa et al. (2007)
BPV8	Epsilonpapillomavirus 1	Cutaneous papilloma	Tomita et al. (2007)
BPV9	Xipapillomavirus 1	Teat papilloma	Hatama et al. (2008)
BPV10	Xipapillomavirus 1	Teat papilloma	Hatama et al. (2008)
BPV11	Xipapillomavirus 1	Cutaneous papilloma	Hatama et al. (2011)
BPV12	Xipapillomavirus 2*	Tongue epithelial papilloma	Zhu et al. (2012)
BPV13	Deltapapillomavirus 4*	Ear cutaneous papilloma	Lunardi et al. (2013)
BPV14	Deltapapillomavirus 4*	Feline sarcoid	Munday et al. (2015)

(Araldi *et al.*, 2017)

4. DIFFERENT TYPES OF BPVS

In cattle 14 types have been identified: BPV-1, 2 and BPV-5 which cause fibropapillomas and BPV-3,4,6,9 and 10 which cause true epithelial papillomas. BPV-1 and BPV-2 can also induce sarcomas and fibrosarcomas in other mammals, including equids (equine sarcoid) and, experimentally rabbits, hamsters and mice. These two causes cross infections.

BPV- 1 causes frond fibropapillomas of teat skin and penile fibropapilloma. BPV- 1 and BPV-2 - fibropapilloma of the skin of the anteroventral part of the body including the forehead, neck and back, the common cutaneous wart. BPV-2 - cauliflower-like fibropapillomas of the anogenital and ventral abdominal skin. BPV-2 - associated with bladder cancer in cattle in association with the ingestion of bracken fern (Pteridium *spp.*). BPV-3 - cutaneous papilloma. BPV-4 - papilloma of the esophagus, esophageal groove, fore stomachs and small intestine; this is capable of becoming malignant, particularly in animals fed bracken fern. BPV-4 has site specificity to the upper alimentary tract. BPV-5 - rice grain

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fibropapilloma on the udder and teat. BPV-5 has also been demonstrated in cutaneous skin warts. BPV-6 - frond epithelial papillomas of the bovine udder and teats. Coinfection with multiple BPV types in the same lesion is a frequent event, which may influence lesion development (Carvajal-Reina *et al.,* 2025; Sauthier *et al.,* 2021).

5. GENETIC ORGANIZATION

BPVS non-enveloped with icosahedral capsids which contain a single molecule of circular double-stranded DNA genome of approximately 8 kb in size, which can be divided into three regions; early, late and LCR (long control region).

The E region contains E1, E2, E4, E5, E6 and E7 (ORFs). The L region of the genome and contains two additional ORFs, L1 and L2, that code for structural proteins of the virus capsid. Between the 5' end of the early region and 3' end of the late region, there is a region of the viral genome which has been referred to as the non-coding region (NCR) but more recently term the long control region (LCR) is used because a small coding exon for wart-specific late RNA has been mapped to this region (Nasir and Campo, 2008).Two regulatory proteins; E1 and E2, modulate (transcription and replication), and two structural proteins; L1 and L2, compose the viral capsid, necessary for virion formation, transmission and spread, regulate early viral gene products, Induce cytoskeleton rearrangements (E4), and cause cell-cycle deregulation (E6 and E7).Three oncogenes, E5, E6, and E7, modulate the transformation process, E5 is the major BPV transforming oncoprotein (Mauldin and Peters-Kennedy, 2016). The E1, E2, L1, and L2 ORFs are particularly well conserved among all members of the family. Most cis-responsive elements are in the long control region (LCR) between L1 and E6, a segment with little sequence conservation.(De Villiers *et al.,* 2004).

6. VIRULENT GENES

6.1 E5

The papillomavirus E5 proteins are short hydrophobic polypeptides (from 83 amino-acid residues in human papillomavirus type 16 (HPV-16) to 42 residues in BPV-4), many of which have transforming activity.

BPV-1 E5 oncogene encodes for a 44-amino acid protein that is the major BPV transforming oncoprotein. It is a type II transmembrane protein which is expressed in the deep layers of the infected epithelia and is largely localized to the membranes of the endoplasmic reticulum (ER) and Golgi apparatus (GA) of the host cells. BPV E5 is expressed in the cytoplasm of both basal and suprabasal transformed epithelial cells with a typical juxtanuclear pattern due to its localization in the GA. It may be also expressed in neoplastic cells of mesenchymal origin such those of endothelial origin. BPV E5 has no intrinsic enzymatic

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activity and its transformation activity is related to the activation of several kinases, from growth factor receptor to cdk cyclins. E5 interacts with the 16-K subunit c protein a component of the vacuolar H+ -ATPase pump. This proton pump acidifies the lumen of intracellular compartments, (endosomes, lysosomes, and GA) that process growth factors so that E5 binding may result in alteration of this processing. Another consequence of E5 mediated impaired acidification is the down-regulation (both in vivo and in vitro) of the Major Histocompatibility Complex class I (MHC-I) expression, representing one of the mechanisms by which the BPV evade the immunoresponse by the host (Borzacchiello and Roperto, 2008). E5 is the major BPV transforming oncoprotein. It is believed to be critical in driving cell transformation, especially by activating platelet-derived growth factor receptor β (PDGFRβ). The binding of BPV-1 E5 to PDGFRβ results in activation of the phosphatidylinositol-3-kinase (PI3K)-AKTcyclin D pathway, leading to cell cycle deregulation (Mauldin and Peters-Kennedy, 2016).

6.2 E6

The BPV-1 E6 gene of Xi BPV encodes an oncoprotein of 137 amino acids. It binds to paxillin blocking its interaction with vinculin and the focal adhesion kinase. It also binds to several others cellular proteins being able to transform cells alone by itself (Borzacchiello and Roperto, 2008).

6.3 E7

The BPV E7 gene encodes a 127 amino-acids zinc binding protein which cooperates with E5 and E6 in inducing cell transformation. Once E7 is co-expressed with E5 and E6, its transformation capacity increases many folds, and such co-expression may also occur in tumors of mesenchymal origin. BPV-1 E7 transformation function correlates with its binding to a cellular target p-600 (Borzacchiello and Roperto, 2008).

7. TRANSMISSION

The method of spread is by direct contact with infected animals, infection gaining entry through cutaneous abrasions or by fomites Virus can also persist on inanimate objects in livestock buildings and infect animals rubbing against them The calf can contract infection through direct contact during suckling (Radostits *et al.,* 2000). Crops of warts sometimes occur around ear tags, at branding sites or along scratches made by barbed wire, and can be spread by tattooing implements, dehorning shears and by procedures such as tuberculin testing. An extensive outbreak of perianal warts is recorded in beef heifers, the infection reported to be spread by rectal examination for pregnancy. Congenital infection is recorded in the foal and calf, but is rare (Stocco *et al.,* 2018). Vertical transmission from cow to fetus and

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detection of BPV DNA in reproductive tissues has been reported, indicating non-cutaneous routes of spread (Pontes *et al.,* 2024). Papillomaviruses also cause transmissible fibropapillomas of the genitalia of young cattle, with venereal spread analogous to that of human genital warts.

8. PATHOGENESIS

Papillomaviruses are reproduced in keratinocyte nuclei. They gain access through defects in the epithelium and infect cells of the stratum basale. for viral replication to occur, infected cells must become terminally differentiated, and therefore PVs attempt to increase both proliferation of basal cells and terminal keratinocyte differentiation (Mauldin and Peters-Kennedy, 2016).

The expression of BPV-1 and -2 early and late genes is highly regulated in the natural host, at both transcription and post-transcriptional levels and strictly tied to the differentiation of keratinocytes. For example, in papilloma formation, the virus initially infects the basal keratinocytes. Papillomaviruses gain access to keratinocyte stem cells through small wounds in the skin or mucosal surface. Interactions between L1 and sulphated sugars on the cell surface promote initial attachment of the virus. The virus is then able to enter from the cell surface via interaction with a specific receptor, likely to be the alpha-6 beta-4 integrin, and is transported to endosomes. The capsid protein L2 disrupts the membrane of the endosome, allowing the viral genome to escape and transit, along with L2, to the cell nucleus (Kamper *et al.,* 2006). The early region genes are then expressed in the undifferentiated basal and suprabasal layers. Viral DNA is replicated in the differentiating spinous and granular layers and, in the upper, terminally differentiated layers of the host epithelium, the late genes L1 and L2 are transcribed/translated and serve as structural proteins which encapsidate the amplified viral genomes. The new viral particles are released into the environment as the cells die. Expression of the early virus genes, the consequences of which are an uncontrolled proliferations and loss of differentiation of the infected cells. Persistent viral infection is required for neoplastic progression and failure of virus clearance is attributed to a poor immunological response (Campo, 1997).

9. BPVS ASSOCIATION WITH CANCER

Persistent PV-induced lesions are at risk of progression to cancer. Cancer, including PV-associated cancer, is a multi-factorial disease and several steps are required before full neoplastic transformation is achieved. Bracken fern has been identified as a major environmental co-factor in BPV-induced carcinogenesis in cattle. Bracken fern contains immunosuppressants and a number of mutagens. Bracken-induced immunosuppression is

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associated with two marked haematological changes. The first of these is a dramatic fall in polymorph nuclear leucocytes. If unchecked, this leads to severe acute immunosuppression with invasion of the bloodstream by alimentary bacteria and death from septicaemia. This is the well described veterinary syndrome of Acute Bracken Poisoning (ABP). The second effect of bracken feeding is a chronic drop in circulating lymphocytes. Even during periods of bracken withdrawal, the lymphocyte count remains very low. In addition, bracken-eating cattle develop chronic enzootic haematuria, urinary bladder cancers and chromosomal abnormalities (Campo, 2006).

10. BPV-4 AND GASTROINTESTINAL TUMORS

In cattle, BPV-4 infects the mucosa of the upper gastrointestinal (GI) tract leading to the formation of papillomas and/or fibropapillomas. BPV-4 infection and associated tumors of the upper GI tract have been found in Brazil, Nasampolai Valley of Kenya, and the Western Highlands of Scotland and in the South of Italy. Healthy cattle normally recover from papillomatosis in approximately one year time through a cell mediated immune response, but some animals may even die due to widespread papillomatosis if they are not able to reject the infection. Chronic exposure to immunosuppressants leads to the persistence and spreading of the papillomas. Commonly, immunosuppression in cattle results from exposure to bracken fern, but may even due to some other factors such as infection with bovine viral diarrhoea virus. The fern induces immunosuppression and the fibropapillomas spread; the animals with extensive papillomatosis are at high risk to develop cancer such as squamous cell carcinoma. The latent BPV is activated and full malignant transformation depends on others mutagens such as quercetin and ptaquiloside that act synergistically with the virus in the carcinogenic process, triggering BPV gene expression and leading to the development of cancer (Borzacchiello and Roperto, 2008). The BPV-4 E7 oncoprotein cooperates with quercetin for neoplastic transformation, in so doing the ras oncogene is activated, the p53 is mutated and the number of the cellular receptors for epidermal growth factors is increased (Campo, 2002) . These transforming events are probably due to bracken fern mutagens, but still remain to be established in vivo. It is worth noting that some human GI cancer may have the same etiology: papillomavirus and bracken suggesting that similar molecular mechanisms underlying bovine cancer may even occur in humans (Borzacchiello and Roperto, 2008).

11. BPV-1/2 AND URINARY BLADDER TUMORS

In cattle, tumours of the urinary bladder are commonly associated with a syndrome known as Chronic Enzootic Haematuria due to prolonged ingestion of bracken fern with a prevalence as high as 90% in adult animals. Field cases of urinary bladder cancer in cattle

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occur wherever the bracken-fern is spread. Human exposure to bracken fern directly or indirectly through milk from bracken eating cattle has been linked to human GI cancer. The cancer is of both epithelial and mesenchymal origin (mostly haemangioma and its malignant counterpart) with different epithelial histological variants identified. The epithelial tumors express the urothelium tumor marker Uroplakin III .and do not metastatise frequently probably due to the content of sialic acid and gangliosides. The BPV-2 is involved in both epithelial and mesenchymal tumors, testifying that the virus is not a pure epitheliotropic agent in its natural host. The virus infects the urinary bladder mucosa inducing an abortive and latent infection with no production of virions. The exposure to immunosuppressants, mutagenic and carcinogenic principles from bracken triggers viral gene expression leading to cell transformation. In both epithelial and mesenchymal cancers, the BPV-2 E5 oncoprotein is expressed and is in complex with the activated form of the PDGFβ receptor. Additionally, in urothelial cancers the telomerase activity is upregulated, the expression of ras oncogene and cyclooxygenase-2 (COX-2) is increased and, as already observed in HPV associated cervical cancer, the fragile sites are disrupted and the expression of the tumor suppressor fragile histidine tetrads (FHIT) is down-regulated. Lymphocytes from bracken feeding cows harbour BPV DNA , which has been found also into the blood stream and chromosomal abnormalities have been demonstrated (Borzacchiello and Roperto, 2008).

12. SARCOIDS

Sarcoid, known to be associated with BPV-1, BPV-2, and most recently BPV-13. Sarcoids are locally aggressive, nonmetastatic fibroblastic skin tumors of horses, mules, donkeys, and zebras. They are the most common skin tumor of horses, accounting for up to 90% of tumors. A combination of factors appears to be involved in development of the tumors, including exposure to a viral agent, cutaneous trauma, and a genetic predilection. Sarcoids frequently develop in areas subjected to trauma or at sites of wounds 6-8 months after wound healing. Sarcoids develop anywhere but are most common on the head, legs, and ventral trunk. They may be single or multiple. Young horses 1-7 years of age are at increased risk, with rare reports in older horses (Mauldin and Peters-Kennedy, 2016).

13. CLINICAL ASPECT OF SARCOID

The tumors are classified according to their gross appearance as occult, verrucous, nodular, fibroblastic, mixed, and malignant (malevolent). Many horses have multiple tumors, and all types of sarcoids can be present in the same horse. 1) Occult sarcoids are focal areas with alopecia, scaling, hyperkeratosis, and hyperpigmentation. Common locations are neck, face, sheath, medial thigh, and shoulder. 2) The verrucous sarcoid is a small wart-like growth,

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usually measuring <6 cm in diameter, with a dry, rough surface and variable alopecia. This type is usually found in the head, neck, axilla, and groin. 3) Nodular sarcoids are spherical dermal to subcutaneous masses. The overlying skin may be normal but can become alopecic and ulcerated. This type is common on the eyelid, groin, and prepuce.

4) The fibroblastic sarcoid is more variable in appearance and may range from a well-circumscribed firm nodule with intact surface to large masses, >25 cm in diameter, with an ulcerated surface prone to hemorrhage and resembling exuberant granulation tissue. Common locations are axilla, groin, legs, and periocular. 5) Malignant/malevolent sarcoids are aggressive and locally invasive. These tumors extend widely into the adjacent skin and subcutis and infiltrate lymphatic vessels(Nasir and Campo, 2008). The occult and verrucous and, to a lesser extent, the nodular sarcoid can remain static for years if not traumatized. Any type of sarcoid lesion can develop into an aggressive fibroblastic or malignant/ malevolent tumor if traumatized. Spontaneous remission is rare. The tumors are characterized by a high rate of recurrence, up to 50%, following surgical excision (Mauldin and Peters-Kennedy, 2016).

The BPV exists as episomally and its major oncoprotein E5 is expressed, thus suggesting the viral genes are expressed. Equine sarcoids is a biologically attractive tumor since it is the only known case of natural crossspecies PV infection. Moreover, while BPV infection in cattle produce benign lesions that may regress, the sarcoids are non-permissive for virus production, locally aggressive and non-regressing.

Cell cycle regulatory proteins are involved in the pathogenesis of equine sarcoids: p53 is stabilised in sarcoid cells being expressed in the nuclei as well as in perinuclear region, however its transactivation function is abrogated (Martens *et al.,* 2001, Nixon *et al.,* 2005). Low levels of cell proliferation are characteristic of sarcoids with no overexpression neither of cyclin A, p27kip1 nor of CDK-2 (Nixon *et al.,* 2005) . The loss of p53 function and the low levels of cell proliferation indicate that sarcoid cellular and molecular pathology may not be associated with abnormal cell cycle control mechanisms (Borzacchiello and Roperto, 2008). Histopathology is necessary for definitive diagnosis of a sarcoid. Sarcoids are typically biphasic tumors composed of both epidermal and dermal components. The epidermal component.

14. CLINICAL FINDINGS AND GROSS PATHOLOGY

The incubation period for cutaneous warts produced by BPV is about 30 days, and the duration of naturally and experimentally produced fibropapillomas ranges from 1-12 months before regression. The solid outgrowths of epidermis may be sessile or pedunculated. Most

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common type in cattle occurs on head and neck and has cauliflower like appearance, but lesion site and appearance vary with papilloma type. In the horse, Warts are occurred anywhere on the body but are most commonly seen on the head and neck area, teats and scrotum. Warts vary greatly in shape from almost flat pea-sized lumps to large orange sized balls on stalks. Warts on the teats manifest with different forms depending on the papillomavirus type and may show an increasing frequency with age. The frond form has filiform projections other forms are a flat, round type which is usually multiple, always sessile and up to 2 cm in diameter. The third form has an elongated structure appearing like a rice grain. Teat warts may regress during the dry period and recur with the next lactation. Genital warts on the vulva and penis make mating impracticable because the lesions are of large size, are friable, and bleed easily. They commonly become infected and flyblown Alimentary tract warts are rarely observed clinically in farm animals in most countries, Papillomas occur on the lateral and dorsal aspects of the tongue, the soft palate, oropharynx, esophagus, esophageal groove and rumen. Paillomas occurring in the esophageal groove and in the reticulum are a cause of chronic ruminal tympany. Less common manifestations of papillomatosis in cattle include lesions in the urinary bladder, which cause no clinical signs but may predispose to enzootic hematuria. BPV-4 papillomas in the upper alimentary tract of cattle being fed bracken fern are the focus for transformation to squamous cell carcinomas. Cattle fed bracken fern are immunosuppressed which promotes the persistence and spread of the papilloma virus, and mutagens in bracken fern cause neoplastic transformation of papilloma cells (Radostits *et al.,* 2000).

15. MICROSCOPIC PATHOLOGY

Different types of lesions are often difficult to distinguish as they exhibit similar histologicalchanges including dermal proliferation of spindle-shaped fibroblasts forming whorls, epidermal hyperplasia and hyperkeratosis and rete peg formation (Nasir and Campo, 2008). Papillomas are characterized by epithelium hyperplasia, showing an enlargement of interpapillary ridge that extend above dermis. The typical papilloma is a 1-2 cm wart-like, filiform, exophytic, and hyperkeratotic mass composed of hyperplastic epidermis supported by thin, inconspicuous dermal stalks with dilated capillaries. Lesions can be anatomically extensive and multiple. The stratum corneum exhibits variable degrees of orthokeratotic to parakeratotic hyperkeratosis. Most of the hyperplasia is due to marked expansion of stratum spinosum cells, which have pale basophilic cytoplasm. Cells of the spinous and/or granular layer have swollen eosinophilic to lightly basophilic cytoplasm (ballooning degeneration) and enlarged, condensed, or multiple nuclei (koilocytes). Degenerating keratinocytes may have

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condensed eosinophilic cytoplasmic inclusions that represent aggregates of keratin, a result of the viral cytopathic effect. These inclusions should not be confused with the cytoplasmic inclusions associated with poxvirus infections. The stratum granulosum has large, variably sized and shaped basophilic keratohyaline granules.

Cells of the stratum spinosum and granulosum may have vesicular nuclei with intranuclear pale basophilic viral inclusions that contain virus particles visible with electron microscopy and viral antigen detectable by immunohistochemistry, but these may not be numerous.

Fibropapillomas appear as nodules or plaques covered by a variably hyperplastic and hyperkeratotic epidermis. In bovine fibropapilloma and equine sarcoid, microscopic lesions typical of fibropapillomas include the features of acanthosis, hyperkeratosis, and downgrowth of rete ridges, but dermal proliferation predominates. The proliferating cell is a large, plump fibroblast. The cells are arranged in haphazard whorls and fascicles rather than in perpendicular sheets, as in granulation tissue. In some, the epidermal proliferation is minimal and is seen only as slight acanthosis and accentuation of rete pegs, whereas, in others, the hyperplasia resembles full-fledged papillomas (Mauldin and Peters-Kennedy, 2016).

16. DIAGNOSIS

In most cases the diagnosis is obvious by History and clinical sign, Histopathology, DNA identification by PCR, Biopsy or tissue scraping, Immunohistochemical staining, Southern blotting, Chromogenic in-situ hybridization (CISH), Electron microscopy (Araldi *et al.,* 2017).

17. VACCINATION

Vaccines against BPV types 1, 2 and 4 have been developed, because as we seen both are implicated in cancer.

17.1 Prophylactic vaccination in cattle (i.e., vaccination of wart-free animals to prevent infection) with whole virus (e.g. formalin-killed wart tissue suspension), virus-like particles (L1 or L1+L2), L1 protein or (for BPV-4) L2 protein confers long-lasting protection against challenge with the same BPV type, but is generally ineffective against existing warts. Protection appears to be mediated via type-specific neutralising antibodies Vaccination of calves as early as 4–6 weeks might be necessary to prevent infection.

17.2 Therapeutic vaccination in cattle (i.e., vaccination of animals with existing warts) with BPV-4 E7 or BPV-2 L2 induces early regression of warts. Wart rejection involves a cell-mediated immune response, with infiltration of the site by large numbers of lymphocytes and macrophages (Nasir and Campo, 2008).

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17.3 Therapeutic vaccination in equids the presence of viral antigens in equine sarcoids presents the opportunity to evaluate anti-BPV vaccination strategies. To this end we vaccinated sarcoid-bearing donkeys in a placebo-controlled trial using chimeric VLPSs (cVLPs) comprising BPV-1 L1 and E7 proteins. The choice of vaccine was determined by the fact that L1 provides antibody protection and E7 stimulates tumour regression, cVLPs are a promising therapeutic vaccine (Nasir and Campo, 2008).

18. TREATMENT

There is no completely effective treatment, particularly for severe cases. Simple surgical removal or if the warts have a significant stalk using a rubber ring. Cryosurgery with liquid nitrogen has recently come into use and should be very effective when the cutaneous papillomas are not too large. Autogenous vaccine reported to be successful.

19. CONCLUSIONS

Bovine papilloma viruses (BPV) are dsDNA (family Papillomaviridae), replicate in keratinocyte nuclei, and are classified into 14 types under 3 genera (Delta, Xi, Epsilon). BPVs are host specific except BPV-1 and BPV-13. E5, E6 and E7 oncogenes modulates the transformation process in infected cells. BPVs induced cell cycle deregulation by interaction with PDGFRβ. Bracken fern promotes BPVs induced papilloma by promoting genomic instability, resistance to apoptosis and cell cycle deregulation by inactivating p53 and activating ras. BPVs are associated with several types of cutaneous lesions, including squamous papilloma, inverted papilloma, equine sarcoids, fibropapillomas and squamous cell carcinoma. BPVs can be used as role model for studying HPV and interaction between virus and co-factors.

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