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PAPILLOMATOSIS IN CATTLE: ETHIOPATHOGENIC, MORPHOCLINICAL AND THERAPEUTIC STUDY (PART ONE)

PAPILOMATOZA BOVINĂ: STUDIU ETIOPATOGENIC, MORFOCLINIC ŞI TERAPEUTIC (PARTEA I-A)

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ABSTRACT | REZUMAT

This study summarizes the research results in cattle papillomatosis and also the research of our pathology and clinical surgery department due to the fact that there is a rich casuistry.

The first part includes ethiopathogenic and morphoclinical data, since early 1822 Lubke's research and 1902 Rayere's experimental reproduction. Since then, it's viral origin was suspected, but only after 25 years was it demonstrated through reproducing the disease by inoculation of the filtered cell, and also acquired immunity of the animal passes through illness or after administration of the papilloma vaccine preparation. The disease affects predominantly undernourished and animals in poor condition.

The study presents data related to encountered clinical forms, papilloma size and spread on the body surface, skin papillomas being found in all body regions like head, neck, thorax, abdomen, mammary gland, and generally having an affinity for delicate skin. Mucosal papillomatosis is usually localized into the oral cavity and on the galactophore sinus or nipple's papillary channel.

Keywords: bovine papillomatosis, ethiopathogenic, morphoclinical

Se sintetizează rezultatele cercetărilor din papilomatoza la bovine dar şi din activitatea de cercetare a disciplinei de patologie şi Clinică Chirurgicală, având în vedere că a existat o cazuistică bogată.

În prima parte sunt cuprinse datele etiopatogenice şi morfoclinice a papilomatozei începând cu primele cercetări ale lui Lubke din 1822 şi reproducerea experimentală a lui Rayere din 1902. Încă de atunci se presupunea originea ei virală, dar abia după 25 de ani s-a reuşit şi s-a demonstrat prin reproducerea bolii prin inoculare de filtrat celular, dar şi imunitatea dobândită de animalul care trece prin boală sau după administrarea de vaccin preparat din papilomi. Afectează mai mult animalele subnutrite şi rău îngrijite.

Sunt prezentate date legate de formele clinice întâlnite, mărimea papilomilor şi răspândirea lor pe suprafaţa corpului, putând fi întâlniţi papilomi cutanaţi pe toate regiunile corporale începând cu capul, gâtul, toracele, abdomenul, glanda mamară, în general având afinitate pentru pielea fină. Papilomatoza localizată pe mucoase: bucală şi pe sinusul galoctofor, mamelonar sau chiar pe canalul papilar al mamelonului.

Cuvinte cheie: papilomatoza bovină, etiomorfopatoclinic

Among many disorders that have cutaneous location, papillomas are formations that emerge in skin thickness and spread especially to the sides of the neck region, face, eyelids, mammary gland and also other parts of the body. They belong to benign tumors, although etiological factors are not definitively established yet. However, today it is believed that papilomas are caused by viruses from Papovaviridae family. This family also includes polyoma virus and the vacuolating virus in addition to papillomatosis virus.

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1. Etiological factors

Knowledge of etiologic factors that causes papillomatosis has concerned many researchers.

If at first it was a lack of medical knowledge, the expressed assumptions were even more exaggerated, some blaming the occurrence of papillomas on the practices of black magic.

Later, with the development of medical knowledge and laboratory techniques, these assumptions have been replaced with the scientific evidences.

In this respect, in 1822, Lubke showed based on clinical observations that papillomatosis is transmitted to cattle, and in 1902 Rayere manages to reproduce it experimentally. Among many researchers, Amedeo (1903)

made some assumptions and claimed that malignant tumors have a viral origin. However, to prove that viral agents are involved in the development papillomatosis more than 25 years had to pass, until 1929, when Magalhaes et al. demonstrated the reproduction of the disease by inoculating a cell filtrate in rabbits. Also Levy et al. [7, 13], have succeed to identify the causative virus by electron microscopy.

Shortly after that, many researchers communicate the success of reproducing the disease in other species: skin papilloma in rabbit, oral papilloma in wild rabbit (genus Silvagus), canine oral papilloma, horse cutaneous papilloma, bovine papilloma, etc. Papovaviridae family includes double-stranded DNA viruses with cubic symmetry, molecular weight between 3-5x106 Daltons and sizes of 50-55 nm (small viruses). They contain in their structure 6-9 polypeptides, between 3-82 kd and a high percentage of lipids.

From an antigenic point of view, the viruses are not identical, and the immunity conferred by one of them will not protect against the others. In cattle, Nostac et al., (1968) and Paul (1996) [10], identifies six types of viruses known as "Bovine papillomavirus 1-6" (BPV 1-6). This were classified into two subgroups A and B, according to the nature of the injuries that are caused and also the DNA molecular weight. Subgroup A includes 1,2,5 BVP subtypes, each with 7-9 kbp genomic weight and are considered responsible for developing fibropapillomas. Subgroup B include 3,4 and 6 BVP subtypes, each with a molecular genomic weight of 2-7 kbp, and are responsible for the appearance of epithelial papillomas. The 6 types of papilloma viruses tend to be located in different anatomic sites, but with specificity for each type.

Type 1 localises on teats and male genital organs; Type 2 causes fibropapilomas in the pectoral, head and neck regions; Type 3 is incriminated in the production of squamous cell carcinoma; Type 4 produces papillomas on the digestive tract and skin. It is believed that it is responsible for transforming papillomas in squamous cell carcinomas. At first the tumors have the characteristics of benign papillomas; then become bloody, showing buds implanted at the base, with new points of epithelial proliferation and invasion. It seems that papillomas induced by BPV 4 become malignant in areas where the cattle are moved to the pasture, on various kinds of fern pastures containing radioactive agents and immunosuppressants [2]. Type 5, or "rice grain wart" is responsible for warts that affect cattle of any age, especially lactating. Papillomas do not regress spontaneously, so that the healing is performed by medical or surgical treatments. This virus is transmitted to humans, in particular in milkers and butchers. Type 6 is formed more frequently on the dorsal or posterior interdigital space, regardless of breed.

Depending on the preferred location of the virus, Paul I. [10] shows that may be encountered the following types of warts:

- cutaneous papillomatosis mainly caused by BPV 3;
- mucosal papillomatosis produced by BPV 2, BPV 4 and BPV 6;
- Bovine genital fibropapilloma caused by BPV 1.

2. Local factors

Adaptation and comfort conditions creates favorable conditions for papilloma development. Irritation are key factors in the occurrence of the disease and include exogenous irritations of mechanical, physical, chemical origin and irritations animated by viruses, bacteria and parasites. In viral tumors, the virus and virus-specific nucleic acids plays the role of infectious factor. These nucleic acids alter the animal metabolism and predisposes to disease. Benign papillomatosis in young cattle is favored by mucosal lesions caused by Fusobacterium nodosum.

Papillomatosis is more common in young cattle with poor body hygiene, with unhygienic shelters, with poor drainage leading to increased level of ammonia. The growth system positively influences papillomatosis lesions in animals due to overcrowding conditions that may cause skin lesions through direct contact between animals. Concrete floors without bedding, improvised cages, rough walls are factors that can favor an increase in the incidence of papillomatosis by creating gateways for the virus. As for the weather, it is believed that summer increase the number of cases under the influence of heat (skin circulation is activated) and winter decreases its frequency. In cattle, it is believed that even improper hoof trimming promotes pathogens engraftment and triggers papillomatosis. Endogenous factors (hormonal imbalances) are also responsible for an increased incidence.

3. General factors

Heredity, according to most researchers, appears to have no influence of papillomatosis in domestic animals [5]. Papillomatosis affects a large number of species, but the first affected are cattle and horses.

Under natural conditions, the disease most commonly affects cattle and deer. In respect of the latter, it is considered that the small number of submitted cases to date are due to poor research concerns of and

rather small number of studies on these animals rather than natural resistance to the virus.

Race and gender do not seem to have an influence in the disease development, but it was found to be more common in females and in more selective breeds. In terms of age, all researchers agree that papillomatosis generally affects young cattle up to three years. It is more frequent in young calves up to 2 years and affect adult animals a rate of only 10%, especially those aged over six years (more often 8-9 years). However, studies made by Williams et al. [1] in Italy, have diagnosed papillomatosis,in particular cutaneous form, more frequently in cows (55.8%), but also in heifers (27.9%), and calves (11.63%).

Apparently, a higher incidence of papillomavirus in young animals compared to adults are due to acquired immunity resulting from apparent or hidden infections that occur at a young age [6]. Others consider papillomatosis a congenital disease, an idea supported by numerous diagnosed cases immediately after birth.

4. Contamination

In many cases, contamination is realized via direct contact with the sick animal. This is not a general rule, because in some cases, in young cattle populations where papillomatosis occurred, not all animals get sick. Also, contamination can be achieved by means of secondary sources (abrasions, micro trauma, scratching or rubbing against hard objects). Important role in the transmission of infection have hematophagous insects, especially Stomoxys calcitrans. Papillomatosis located on the quarters or teats can be transmitted through calf sucking, and affects nose skin, lips and oral mucosa. Additionally, the milkers can be contaminated by the lactating cows with udder papillomatosis. Some observations show that from 110 calves, in a one and a half year period 74.5% animals have contacted the disease. There are still debating some relations between bovine papilloma viruses and squamous cell carcinomas localized on the eye. Although particles of BPV were detected in 33% of cattle with eye carcinomas, they are considered only precursors or carcinogen co-factors, the occurrence of ocular carcinomas being linked to solar irradiation factors, skin pigmentation, some herpesviruses and unidentified genetic factors (Runtten et al., 1992).

Experimental papillomatosis can be easily replicated in animals belonging to the same species, both using papilloma extracts or suspensions, or by intradermal injection or application on scarified skin.

Interestingly, in cattle over 4 years, the reproduction of the disease through skin scarification technique was unsuccessful.

5. Etiopathogenesis and its mechanisms

There are questions about the mechanisms of its particular appearance and sometimes miraculous disappearance but also other sequences of its evolution. The virus replicates in the body through the local epithelial cells and induce a tumor type proliferation, resulting the occurence of fibropapillomas. Some authors, including Campo et al. [4] argue that BPV virus type 1 and 2 are resting into circulating lymphocytes where they can be activated by immunosuppression or physical trauma. In some cases, a rapid development is seen, then stagnates for a variable time, and finally the regression occurs without scarring traces. Among others, Sioni [9] assigned the role of cell-mediated immune mechanisms in regression of the lesions. The division of the basal cells of the epithelium appears to be the core activity of the virus.

Virus information is inserted in the genome. The genetic information is transferred to the genome in three regions:

- the first contains structures used for initial transcription, numbered with the letter E and the numbers 1-8, in decreasing order of their size;

- a second region containing the transcriptional endings;

- the third (final region), contains the necessary structures for capsid protein transcription, denoted by L1 and L2, responsible for the transformation in "vitro" and virus replication in the cells.

Changes induced by the virus does not appear immediately, but later, because it is stored in a latent form. Hyperplasia caused by the virus results from multiple basal cell division and delayed maturation of the spinous layer. The cells are merging on various strains. The viral replication start from the spinous layer and appears to be dependent on the specific cell environment of the less differentiated cells. Viral particles are spread mainly in the nucleus, organized in systemic structures, visible by electron microscopy.

Fibropapillomas show a marked proliferation of fibroblasts within the dense collagen matrix, which occurs in the first week after infection. In the first week after infection occurs fibroplasia, while epithelial hypoplasia in most cases is not visible before 4-6 weeks.

The cross sections of the papillomas were examined under the microscope and was observed a massive growth of dermal papillomas and hypergranulosis. The experimental reproduction of the disease has

a long incubation period of 20-65 days, in contrast to natural infection, which can reach up to 120 days.

Vlăduţiu (1966) [11], showed that disease evolution can distinguish two phases:

- the proliferative phase, with a duration period ranging from 2-8 months;

- a degenerative stage, followed by resolution and total disappearance through papillomas regression and necrosis and spontaneously detaching, leaving a small scar that heals fast, without any treatment.

Papillomas occurring at the site of inoculation - primary nodules - develops very slowly by multiplying proper cell without the participation of other tissues, and take different shapes and sizes, which can be isolated or confluent, forming tumor masses with a broad implantation based.

6. Symptomatology

Papillomatosis symptoms are broadly shared with symptoms of benign tumors. The disease occurs spontaneously in most cases, without a specific cause identified and without manifesting signs of onset, so the disease is not noticed by the owner or caretaker.

The same pattern is followed by spontaneous healing, which apparently is determined by tissue-mediated immunity.

Papilloma formations have poor aesthetics, and if are accidentally traumatized, secondary bacterial infections and septic complications may occur. They have different size and shapes, from a pinhead size to an egg, can be pediculated or sessile, with small or wide base of implantation, itching in many cases, forcing the animal to scratch the surrounding objects.

The shape of papillomas can be spherical, oval, nodular, arborescent, lobular or branched, in many cases warty, cauliflower or aciform. The color is similar to the tissue of origin, but during the degenerative phase it changes to gray-brown. At first, during the proliferative phase, the papilloma retains the skin characteristics, but subsequently, during the regression phase, the surface might become horny, rough and with crevasses; the corneous layer may be detached, resulting a superficial bleeding.

Papilloma development is somewhat seasonally linked, during winter remaining stationary, and in spring and summer they rapidly develop.

Regardless of their volume, they do not directly affect the overall condition, but their presence may affect by compression, occlusion or dislocation some organs, or can trigger septic complications when bacterial flora overlap.

There are horn papillomas or warts, which grow on the skin dermal papillae and form a series of painless vegetations, with different sizes and shapes, more or less large or with a villous appearance.

Mucosal papillomas are formed on the mouth, pharynx, but can also be observed in the bladder mucosa, genital, into the papillary canal or teat sinus. They result from a process of papillary neoformation. They are considered contagious, and with partial excision, oral papillomatosis usually disappears by autoimmunity.

Cutaneous papillomatosis is caused by BPV 3, with a long incubation period of 45-120 days, after which a variable number of gray-whitish nodules appear in the form of conglomerates. The nodules may be spherical, oval, lobular, sessile or pedicle, with a more or less implantation base, painless, with dry surface, rough or sometimes horny.

Preferably they localize to the skin of the udder, teats ("teat warts") on the scalp, neck sides (Fig.1.), withers, back, limbs, trunk, genitals, navel or perianal region, perivulvar. Often they are found located in the external ear, sometimes after the tattoo individualization, when entrance gates for viruses is made, hence the name "tattoo papillomatosis" (Cheli, 1984; Student, 1988) [8, 9]. Over time, due to scratching, papillomas may bleed, become contaminated with pyogenic flora and cause septic processes, malodorous. After a long period of time, they may regress and disappear, and the animals become resistant.

Mucosal papillomatosis is caused by BPV 2, 4 and 6, and is characterized by papillomas and fibropapilomas localized on the mucosa of the oral cavity, esophagus, larynx, ruminal, intestinal and also bladder. Campo et al., (1992) have shown that they isolated BPV 2 from 46% of the cows with bladder cancer associated with bovine enzootic hematuria. This BPV virus may persist latent into the bladder cells and is activated in time by the co-existing carcinogens from fern or by immunosuppression.

In young cattle, Jensen et al., 1981 [3], indicate an increased incidence of papillomatosis on the pharyngeal region, favored by the presence of lesions caused by Fusebacterium nodosus.

Genital papillomatosis is caused by BPV 1 and occurs in males by the presence of pediculated gray-reddish formations, located at the base or tip of the genital. In females the presence of cauliflower growths located on the vaginal and vulvar mucosa.

Udder papillomatosis is common and comprises mostly the skin of the udder and tits, with the tendence of abdominal expansion. Papillomas can invade

the galactophori sinus mucosa, teat sinus, being able to obstruct and hinder milking.

Fig. 1. Massive papilloma invasion on the head, neck and dewlap

It can be said that papillomatosis usually locates on the delicate skin regions, the mouth region, around the nostrils, eyelids, sides of the neck, medial front of the head (Fig. 2), genital organs, front part of the shank, the udder, but also in other regions. Initially are masked by hair, then developed taking an oval, medullar and cauliflower shape.

Fig. 2. Warty papillomas located on the lips, nostrils, and eyelid region in calf

Through licking and scratching, papillomas can break and bleed, and the body can immunize, often resulting in spontaneous healing. Most researchers believe that the degenerative process and disappearance of the papillomas are an immunization consequence, that are consolidated during the last period of the proliferation phase. Acquired immunity is lifelong and the serum of the sick animals used for vaccination produce healing within 30-45 days.

7. Pathology picture

All viruses within the family Papovaviridae have as common effect tumoral hyperplasia of the epidermal cells, in conjunction in some cases with dermal papilla cell hyperplasia, hence the name "papillomas" and "fibropapillomas". Some researchers, including Campo et al. (1995) draw attention to a latent infection with BPV 1 and BPV2, induced in circulating lymphocytes, where they are activated by immunosuppression or physical trauma [4].

Studies have shown that the first reaction takes place at the level of the dermis, the dermal papilla cell hyperplasia, although the virus can be detected in the epidermal cells producing microscopic inclusions and hyperplasia into the cells of Malpighi layer. Identically, specific epidermal hyperplasia occurs and installs gradually, as the dermal reaction regress and is accompanied by lymphoplasmacytic inflammation in the stroma. The incubation period is very different, but once the growing process is triggered, it is very fast and after a stationary period, papilloma regression occurs without leaving a scar. Their mechanism of regression and involution is still debated. Lymphoplasmacytic infiltrates of the mature tumors lead us to cell-mediated immune mechanisms (Sioni, 1988) [8].

The most common evolution is benign, being able to occur spontaneous healing especially in young animals. Likewise, papillomas can persist for months, as a result of an immune deficiency [11].

8. Diagnosis

The diagnosis does not pose difficulties; the presence of papilloma, it's appearance, the manner of spread in certain regions, age, care and maintenance conditions helps in an accurate diagnosis. Histopathology helps us to specify the nature of the tumor.

9. Prognosis

Typically, the prognosis of bovine papillomatosis is favorable, with frequent spontaneous healings. Generally, the disease evolution depends on the general state of the animal and possibly the local changes that they can produce.

It can be appreciated that in large papillomas, with wide base of implantation and multiple locations, the prognosis can become reserved or even guarded, due to septic complications that can occur. Also, the same reserved or guarded prognosis is encountered when there is evidence of papilloma malignisation. The presence of the papilloma and chaotic spreading significantly decreases the value of the animal.

Mammary papillomatosis comprising all quarters, with broad-base or generalized have a poor economic prognosis, especially during lactation, with great difficulties in terms of surgical intervention and drug therapy. The presence of mammary papilloma with internal location in the papillary channel or teat sinus triggers complicate the milking. Animals with teat papillomatosis become agitated and sometimes aggressive faced to the intention of applying the milking machine. Reserved prognosis is considered also if papillomas are widespread.

The disease has a high infectivity and can be easily transmitted through hands caregivers or milking machines.

From observations it has been found that the disease is more common in cattle with poor general status. However, animals raised in the same maintenance conditions, do not get sick alike, which demonstrate that the immunity plays an important role in the occurrence of the disease.

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