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BOVINE PAPILLOMATOSIS: AN ETIOPATHOGENETIC, MORPHO-CLINIC AND THERAPEUTIC STUDY

PAPILOMATOZA BOVINĂ: STUDIU ETIOPATOGENETIC, MORFOCLINIC ȘI TERAPEUTIC

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ABSTRACT | REZUMAT

Bovine papillomatosis is a common viral infection that lately has decreased in frequency. It is still present in large flocks, so, it requires measures to combat, with improved care and nutrition and by knowing the different treatment techniques.

Thus, in this study, there are synthesized the various methods applied on the casuistry of our surgery clinic. There are several therapeutic approaches that we have grouped into: medical, surgical, biological and nonspecific techniques.

Researches have shown good results in bovine papillomatosis by using the autovaccine, magnesium sulfate 25% solution and Thuja (*Thujastandishii*) extract. Various surgery techniques have been applied obtaining significant results, such as: the ablation of a papilloma and the cauterization; the ablation of a large papilloma and the suture or extirpation with the electric scalpel; the partial ablation of the papilloma combined with the autovaccine.

Keywords: papillomatosis, treatment, different methods

Papilomatoza bovină este o infecție virală comun descrisă la aceste animale, dar a cărei frecvență s-a redus în ultima perioadă. Totuși, aceasta este încă prezentă în efectivele mari de animale, fiind necesare măsuri de combatere, printr-o nutriție corespunzătoare și o îngrijire atentă a acestora, dar mai ales prin cunoașterea diferitelor tehnici de tratament. Prin urmare, în acest studiu sunt sintetizate diversele metode aplicate pe cazuistica clinicii noastre de chirurgie. Există mai multe abordări terapeutice pe care le-am grupat în: tehnici medicale, chirurgicale, biologice și nespecifice.

In urma cercetărilor efectuate, s-au obținut rezultate bune în tratamentul papilomatozei bovine, prin utilizarea autovaccinului, sulfat de magneziu 25% soluție și extract de tuia (Thuja standishii). Au fost aplicate diferite tehnici chirurgicale, obținându-se rezultate semnificative, precum: ablația papilomului și cauterizare, ablația unui papilom mare și sutura sau extirparea acestuia cu bisturiul electric, ablația parțială a papilomului combinată cu autovaccinul.

Cuvinte cheie: papilomatoză, tratament, metode diferite

Bovine papillomaviruses are one of the most studied viruses (8), whose epidemiology, classification and genome features continues to be of high interest in virological research (5, 11, 19).

Before and after the etiopathogenetic cause of papillomatosis was discovered and experimental tests revealed the viral nature of the etiologic agent, researches had increased to understand the oncogenic mechanisms of BPV (1, 5, 15) and to find effective treatment (4, 14, 16, 17). Also, several molecular studies revealed the diversity of bovinepapillomatosis genotypes (2, 7, 11, 19). The necessity to establish a treatment, have derived from the medical, economic and even aesthetic implications of this cutaneous disease.

It is true that in most cases the evolution is benign, without any impact on the general condition of animal or influencing the productive capacity of the animals. The existence of pseudotumoral formations on the skin decreases the value of animals; also, the localization on the teats negatively influences milking.

The medical implications reside from transmission of some types of papillomaviruses from cattle to humans, with the appearance of palmar papilloma, and with equine sarcoid (3, 6, 10, 12, 20).

Over time, different methods of treatment have been conceived, with different outcomes and some treatments have been dropped out. Currently, there are several treatment options, some with good results, others are still under investigation. Various therapies were tested in veterinary and human medicine and there are still unknown aspects in this direction.

Generally, according to the therapy and medica-

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tion used, the treatment of bovine papillomatosis can be divided into four categories: drug, surgical, biological and nonspecific treatment.

1. DRUG TREATMENT

A wide range of drugs have been used in the treatment of papillomatosis. The results, however, vary greatly from one drug to another, that is why some of these drugs have been abandoned, and others are still used until today. Medication is presented in solid or liquid form; can be administered parenteral, orally or by direct application on the papilloma. Many of these drugs are for human use and are applied according to the manufacturer instructions and the dose is adapted to the live weight of the animal. The purpose of drug treatment is the degeneration of papilloma, by local or general medication.

Ointment with colchicine 0.05%, in lanolin - is a natural product extracted from plants of the genus *Colchicum* (*Colchichum autumnale*). The ointment is applied 3-4 times a day within 2-3 days. It stops proliferation by influencing mitosis of papilloma cells.

Verucurine 698 - is an ointment used in veterinary medicine, regresses papillomas and increases healing. A 10 ml dose is administered, once a week, for 3 to 4 weeks; it is administered easily, does not cause any dysfunction in milk production and the milk is free from residues.

Anthiomaline *(the active substances are ammonium thiomalate and lithium).* It was used by Wadha et.al., in 1986(4) at a dose of 15 ml intramuscularly, at a two days period, for 5 to 6 times; has a healing rate of approximately 30%. The papilloma gradually diminishes, and after a while, it disappears.

Vegetable tar - also known as Oleum Cadinum (*Juniperus oxycedrus*), used as local treatment, stops papilloma evolution.

Silver Nitrate *bars or pencils* - are usually applied once localy, with good healing results. After cauterization, an emollient is applied locally to support crust loss. It has the disadvantage that when a large number of papillomas are present, the healing process takes a longer time.

Pecus ointment - is applied locally on the papilloma, similar to silver nitrate and has a chemical cauterization effect.

Olicov solution - acts like a chemical cautery, it is applied locally and cautiously, on a limited number of papillomas, because animals can lick the solution and thus produce irritations on the tongue, or remove the applied ointment, so the treatment has no results.

Magnesium sulfate 25% solution - is injected intramuscularly at the dose of 0.005-0.05 g/kg. Parenteral administration is combined with surgical ablation, which gives better results; some papillomas are excised and autoimmune conditions are created.

Antihiperin - is a drug for human use, prepared by Bucharest Oncology Institute and contains soluble protein genes extracted from the *Vaccinia* virus. It has a role in disturbing viral replication and is mainly used for the prevention and treatment of herpes infections. It is appliedlocally on scarified skin, every two days, for a total of ten times.

Virustator - *Moroxydine hydrochloride* - is a medicine for human use, manufactured by the Institute of Chemical-Pharmaceutical Research, Bucharest. It is given orally, 2 or 3 times every 7 days. It acts by disturbance of viral replication and generates regression of papillomas in about two mounts.

Immunostimulant SRE - is made from *Corynebacterium parvum* culture, at the Cantacuzino Institute and has a role in balancing immune status. It is given alone or in combination with an antivirus, at a dose of 100-130 ml. Administration is by 2-3 injections, 4 times, at a period of 7 days. It may cause adverse reactions at the site of administration; edema may occurre, also induration or pain. The results are good; the medicine causes the involution of papilloma in 80% of cases, but healing process is longer.

Other medicines used in the treatment of bovine papillomatosis are cauterization substances such as acetic acid, trichloroacetic acid and 20% salicylic acid tincture. They are applied on the papilloma several times until the papilloma dries out and diminish.

Magnesium chloride and procaine 2% solution may also be used parenteraly, they stimulate papilloma involution.

2. SURGICAL TREATMENT

Surgical treatment is the safest. There are several techniques, from simple, to complex surgery.

Simple procedures

Ligature and strangulation of the papilloma with organic or synthetic thread may be applied to pedunculated and a reduced number of papillomas. The ligature is made from hair of the mane or tail of horse, or in its absence, with surgical wire. A tight ligature is applied at the base of the papilloma; with the thread so applied, the papilloma is deprived of blood, causing dry gangrene. Eventually, the papilloma wane and healing takes place under the crust. It is

a simple method and may be used when the number of papillomas is small.

Thermocauterization can be used for pedunculated and a reduced number of papillomas. It should be applied at the base of the papilloma, as deep as possible, to prevent cell debris, that may proliferate. The resulting wound will be monitored and treated to prevent septic complications.

Surgical procedures

Surgical treatment is primarily aimed at ablating papillomas by various techniques. All papillomas are ablated - in the case of reduced number, or at least 15% when they're number is large. The partial ablation is very efficient, and determines papilloma regression; regression is achieved in 3-4 weeks.

The main surgery techniques in the treatment of bovine papillomatosis are:

- *The ablation of papillomas by simple excision;*
- *The ablation of papillomas by large incision and dilaceration;*
- *The ablation by excision and suture;*
- *The ablation by excision and thermocouple;*
- *The ablation by using the electric scalpel*.

In order to accomplish the treatment, it is necessary to achieve proper anesthesia, to prepare the site of surgery, the surgical instruments, hemostasis and suture.

Anesthesia of the animal.

Neuroleptanalgesia is usually recommended but neuroplagia with local anesthesia also gives good results. Neuroleptanalgesia is achieved with Xylazine 0.05-0.1 mg/kg and ketamine 2-3 mg/kg, i.v., with very good results(18).

Anxious animals could be treated with the combination of 0.05 mg/kg Xylazine, 0.02 mg/kg Butorphanoland 2 mg/kg ketamine. Neuroplagia is achieved by Xylazine at a dose of 0.1-0.2 mg/kg i.v., with good analgesia and sedation effects. Local anesthesia, by infiltration with Xilina 1%, at the base of the papilloma, reduces pain during surgery.

Preparation of the surgery site.

The hair around the base of the papilloma has to be trimmed; the area must be washed with warm water and soap and disinfected with iodine or alcohol (Fig. 1).

Surgical instruments and materials.

Surgery may be performed by using: scalpel with replaceable blade, hemostatic forceps, scissors, traumatic needles, needle holders, suture wire, electric scalpel and cauterization device, hemostatic solutions, gauze pads, iodine tincture, alcohol, etc.

Preparation of the animal.

The animal can be restrained in lateral recumbency on the operating table, with the fixation of the hind legs, which are bound together; also it can be fixed in standing position, with the nose tong applied in the nasal septum.

Fig. 1. Preparation of the surgical site by trimming and disinfecting the area with iodine solution

Simple ablation of papillomas, by excision.

The procedure can be used for pedunculated papillomas, with a small base of implantation. Surgical antisepsis is achieved by hair removal and disinfection at the base of papilloma, with iodine, betadine and alcohol. Local anesthesia is achieved by infiltration with Xilina 1% solution. Ablation is performed by section of the papilloma with curved scissors. Hemorrhage may occur and if it is significant hemostasis can be achieved by pressure or by applying the Koker or Pean pens.

The resulting wound is treated daily with healing solutions (Oximanisorm, Manis, Naftaloxon, etc.) and sprays, until proper healing. If the number of papilloma is large, excised ones can be used for auto vaccine preparation.

Ablation through large incision and broad dilaceration.

The method gives good results in ablation of papilloma and other tumors(13). The location and shape of the papillomas must be considered for this technique. It is advisable for the incision lines to be as far as possible on the vertical or oblique large axis, so traction on the operator wound is minimal and drainage is advocated.

After local anesthesia with Xilina at the base of the papilloma, surgery can be performed.

The ablation of the papilloma is achieved by elliptical incision, oblique from top to bottom, around the papilloma. Incisions interest the skin and subcutaneously connective tissue, to ease dilaceration. It is followed by the isolation of the papilloma as wide and deep as possible. Isolation begins at the edge of the incision, on the lateral side, progressive and in-depth, until complete separation, until excision of diseased tissues. Hemostasis is achieved by pad pressure, forcipressure or unlimited torsion. When larger vessels are cut they must be ligaturated. The surgical wound is treated daily, with sprays and healing powders (Oximanirom, Manis, etc.), until healing.

Ablation by excision and suture.

It is a method with good results. After the ablation of the papilloma, the traumatic outbreak is closed by suture threads.

The method is recommended for large papillomas with large base of implantation. In order to achieve the surgery, it is necessary to restrain the animal in lateral recumbency. Antisepsis and aseptic measures are the same as previously described, also local anaesthesia at the base of the papilloma.

The surgical technique consists in the incision of the skin and subcutaneously connective tissue with the scalpel, at the base of the papilloma.

Incisions should be wide and elliptically, in oblique or vertical position. The scalpel incision is progressive, starting from the edge of the formation, penetrates until the implantation base and the pseudo tumoral tissue is removed. During dilaceration, hemostasis is achieved by padding or forcipressure.

Fig. 2. Ablation of the papilomas by excision and suture

The wound is impregnated with healing powders (Oximanium, antibiotic powder, etc.) and then, it is closed by simple interrupted suture (Fig. 2), preferably with synthetic resorbable suture material (Dexon, Vikril). The suture is sprayed with scarring medication. Healing powders in the traumatic site prevents septic complications and provides better scarring conditions.

The method also gives good results in pediculated or well-isolated papillomas, with minimal trauma and haemorrhage. Since this process does not require dilaceration, but only a linear section, this also performs haemostasis by suturing the vessel in the wire loop.

Fig. 3. Simmentaler Fleckvieh with pedunculated papillomatosis

A morpho-clinic particularity was encountered in a 2-year-old Simmentaler Fleckvieh who presented pedunculated papillomatosis in the sub-abdominal region on the umbilical cord - a width of 5 cm laterally the mammary gland and a band about 10 cm on both sides of the abdomen (Fig. 3).

Large numbered papilloma formations had the appearance of a bunch, of different shapes and sizes, with uneven, vegetal surfaces, ditches in the form of circumvolution, and of different depths. The tumours had a verrucous aspect and a large base of implantation.

General anaesthesia was achieved with Xylazine and Butorphanol; then the animal was restrained in lateral recumbency, with hind legs bound together. The area was trimmed, disinfected and local anaesthesia was performed at the base of the papillomas.

The surgical technique was achieved by excision and suture. An elliptical incision was performed at the base of the papilloma and hemostasis was achieved by padding. The wound was closed by simple interrupted sutures, with resorbable synthetic wire. After surgery, the wound was treated with Propolis-Vet Spray, which forms a protective film - propolis and iodoform promote healing *per primam intentionem*.

Ablation by excision and thermocouple.

It is a more laborious method, which uses the thermocouple for haemostasis. After the surgical ablation of the tumoral tissue, instead of padding or suture, the thermocouple was used to achieve haemostasis.

Before the surgery, the same rules of antisepsis, local anaesthesia and the animal's immobilization in lateral recumbency are performed. The thermocouple is prepared by heating the cautery on fire or gas flame.

Immediately after ablation, the resulting wound is padded until the thermocauter is applied and haemostasis is achieved. The thermocautery is applied directly on the wound site. Cauterization is a very painful procedure, so local anesthesia is very important (Fig. 4). The cauterizer must be changed several times, until perfect cauterization. Healing solutions may be applied to avoid septic complications(14).

Fig. 4. Ablation by excision and thermocouple of papilomas and postoperatively medical treatment

Ablation of papillomas with electric pencil.

It is a modern method with very good results. The advantage is that tissue incision and haemostasis are achieved simultaneously. The animal is fixed in lateral decubitus and general and local anaesthesia are performed. After fixing the metal plate (negative electrode), under the thorax, parameters of the surgical pencil are adjusted.

The surgery starts by applying the surgical pencil on a side of the papilloma and guiding it as deeply as possible, to its base. If the electric scalpel's parameters are well established, the tumour isolation process takes place very fast. The procedure is not as traumatic as surgery ablation. If bleeding continues the surgical pencil must be applied until definitive haemostasis is achieved. By cauterization, a crust is formed at the surface of the wound. The scar protects the deeper tissues, where proliferation and healing processes, can take place. It is necessary to oversee the evolution of scarring processes in order to avoid potential septic processes (14).

3. BIOLOGICAL TREATMENT

Over time, several biological products have been tested for the treatment of papillomatosis.

Serums and vaccines can be prepared in advance or can be bought as commercial products.

Autovaccine - is prepared from papilloma tissue harvested from cattle. It provides very good results.

For autovaccine preparation, papillomas are harvested by excision, as described before. If the number of papillomas is large, 10-15% of them are excised. Ablated tumoral tissue is weighed, so that finally there is a quantity of 10-15 g. The papillomas are then cut into small pieces and triturated in a jar or glass or in the Biomix apparatus. 1:5 saline solution is added (e.g., 50 ml of saline solution is needed for 12 g of papilloma triturate), then the solution is centrifuged. The Biomix machine is set at a 6000 revolutions per minute speed; the tissue suspension is milled and homogenized with saline solution for 20 minutes. After milling, the solution is transferred into sterile jars and saline solution is added until a final dilution of 1:10 (one part triturated to 9 parts saline solution).

The solution thus obtained is left in the refrigerator between 6 and 24 hours and then filtered under strict sterile conditions. 2000 IU/ml penicillin and 0.02 g Streptomycin/ml are added. The vaccine sterility is controlled by cultivation on proper culture media - broth or agar. The petri plates or tubes are thermostated for 24 hours, after which, the samples are analysed. If there is a slight turbidity of the broth, a modest deposit on the bottom of the tube or colonies developed on the agar, Gram method stains are prepared to identify the bacteria. Then, antibiogram is performed; according to the results, antibiotics are added. Sowing on proper culture media is achieved until the tissue solution is sterile. When the autovaccine is sterile, it is administered to the same animal from which papillomas were harvested.

The dose and administration depends on the bovine age and weight. Calves can receive three or four doses of autovaccine. The first dose is 5-10 ml and is administered on aside of the neck; the second dose is 10-20 ml s.c., and is administered after a week. The third dose is administered as previous and the fourth is optional. Another vaccination scheme is of a 10 ml dose administered s.c. at 2-3 days interval, for three times. The best results are obtained by the combined

method of partial papilloma ablation and autovaccine, especially when the number of papillomas is large.

Heterovaccine - is a vaccine prepared from one animal`s papillomas and administered to another animal. The obtaining procedure is the same as previous. The administration method is also the same. If the vaccine is prepared from another animal's tissue, it is necessary to desensitize the animal by intradermal inoculation of 0.1-0.2 ml heterovaccin, in the neck skin. After inoculation, the animal is kept under observation for 2 hours, to observe any allergic phenomena, at the site of inoculation or in the general state of the animal. If the animal does not show any signs of allergic reactions, and the cardiovascular and respiratory status are normal, the test is negative. The heterovaccine can be administered.

Instead, if allergic signs are present, the heterovaccine cannot be used. During the treatment, the animal is kept under strict observation to evaluate negative phenomena, any changes of colour, volume or intense keratinization at the inoculation site.

The hyperimmune serum - is obtained from animals infected with papilloma virus. The serum is administered intramuscularly in a 25 ml dose, every 5 days, three times. After administration, the animal could show signs of allergy or anaphylaxis. Immediate emergency treatment must be administered: non-steroidal anti-inflammatory drugs, atropine sulfate 0,1 ml/kg, s.c., for cardio-respiratory regression - adrenaline 1‰, 4-8 ml i.m. and the dose can be repeated after 15-20 minutes.

Immunotherapy. The therapy of neoplastic disease of animals has noticed increased progress over the last few years.

A remarkable work appeared in "Veterinary Cancer Medicine" under the editorial team of two researchers in veterinary oncology, Gordon H. Theileu and Bruce R. Madewell quoted by Britt J. et.al. (1996) (4).

Authors assume that tumours develop preferably in immunodepressed animals. As for, adapting immunotherapy to oncology, is a surveillance method of cancer, by reducing tumour cells and by stimulating the defensive systems of the body. Thelen and Madewell quoted by Gaukroger J. et. al. (1996), admit that immunotherapy is the best therapy for small and well-isolated tumours, such as papillomas (9).

In specific immunotherapy, several **types of vaccines** are used:

- live attenuated vaccines (the virus is viable, native or allogeneic);

- inactivated vaccines (the virus is killed by thermal, chemical, irradiation or inactivated with Mitomycin);

- modified virus, to increase the antigenicity (by the addition of carrier protein, addition of haptens, chemical treatment, neuraminidase treatment or addition of plant lecithin)

- vaccines made of subcellular components (virus extracts, isolated virus membranes, isolated virus antigens).

Phenolate vaccines are usually prepared for the treatment of bovine papillomatosis.

It is very important that therapy is started as early as possible, but therapeutic effects are better when anticipated by surgical ablation. Vaccines have yielded excellent results in papillomatosis, including oral papillomatosis. It gives very good results in significant affected patients, with large, diffused papillomas, localized on several regions or on a large body surface.

Inactive vaccines are usually prepared by using 4‰ formaldehyde solution. There is a multitude of papilloma viruses, and the type, location and appearance of the tumour must be considered when material is harvested for vaccine preparation. Also, the stage of development is important because the virus is present in larger amounts in old papillomas (5, 17).

The treatment has an 80-85% rate of success after 3 to 6 weeks from vaccination. The vaccine can be administered as a single dose or can be repeated after one or two weeks.

4. NONSPECIFIC TREATMENT

Nonspecific treatment of papillomatosis varies a lot and good results are obtained.

Total extract of Thuja (***Thujastandishii***) - is prepared by percolation. One part of Tuja leaves are chopped and mixed with 5 parts of 70° alcohol. The mixture is introduced into the percolator, where is kept for 24 hours. Then the percolator tap is opened at a low flow rate and extraction takes place within 3-5 days. The extracted solution is stored for 6 days in a darkroom, and then is filtered. The extract is applied on the wound, after surgical ablation of the papilloma. The method gives good results in papillomatosis localized on nipples. The excision site and the nipples are treated daily with the extract; treatment is followed by 50 mg/kg of 25% magnesium sulphate solution in procaine - as an excipient. Daily application of the treatment is required until proper healing.

Polidin vaccine - contains a mixture of 13 heat-inactivated germs prepared in 3% saline solution and 3% phenol suspension. The total concentration of the solution is 48 million germs/ml. It is a vaccine used in

human medicine. There was a veterinary product with the same properties, called "Omnadin" and it contained protein substances extracted from a pathogenic bacteria, bile lipoids, salts of bile and alkaloids in saline solution. Polidin stimulates the non-specific defense body mechanisms, by increasing opsonophagocytic activity and properdin levels. It is an adjuvant to specific therapy with sulfamides and antibiotics, in the treatment of non-specific and local infections. The vaccine dose of 10-30 ml s.c., is administered daily, until total recovery. It is not recommended in the acute phase of diseases.

Diathermocoagulation - is a method of electrotherapy based on the action of high frequency radiation heat, concentrated on a small-sized electrode, which, in contact with diseased tissues, causes coagulation. Depending on the nature and intensity of the radiation, the action can be delimited to the contact area, determining superficial coagulation, or its action can radiate around the electrode, producing massive or diffuse coagulation. The action of massive coagulation is highly necrotic and can be used on tumours by implanting the electrode into the tumour tissue.

As a technique, diathermocoagulation can be applied in two forms: polar (using the electro-scalpel) and bipolar using the radio-scalpel. By the last method, the tumour is placed between the two electrodes.

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