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Application of *Euphorbia tirucalli* sap in sarcoid treatment in horses – case report

[*Aplicação da seiva de* Euphorbia tirucalli *no tratamento de sarcoide em equinos – relato de caso*]

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ABSTRACT

Sarcoid is the most common cutaneous neoplasm in horses, with no established therapy, due to the variable neoplastic manifestation and the oscillating individual response to therapies. The *Euphorbia tirucalli* plant, known as Aveloz, has terpenes and sterols in its latex with antitumor activity, being widely used in popular medicine. Eight horses were referred to the Veterinary Hospital diagnosed with sarcoid, and they were treated only with an aqueous solution containing *Euphorbia tirucalli*. The most common location of tumors was base of the ear and pectoral; seven of the eight animals had tumors in more than one region. The intratumoral injection containing the sap of Aveloz was applied until the tumor became turgent, visualizing blackening, dryness, and a detachment of the sarcoid in 24 to 72 hours. The use of *Euphorbia tirucalli* sap showed 87.5% efficacy in the treatment of sarcoids and adverse effects were observed in the seven animals in which the technique was effective. The treated horses were evaluated for three months to seven years, and none had tumor recurrences. The intralesional application of *Euphorbia tirucalli* sap has been proved to be effective, safe, and low-cost in the treatment of sarcoid in horses, being a viable alternative for this type of cutaneous neoplasm.

Keywords: antitumor, Aveloz, cutaneous, neoplasia, tumor

RESUMO

O sarcoide é a neoplasia cutânea mais comum nos equinos, não apresentando uma terapêutica estabelecida, devido à variável manifestação neoplásica e à oscilante resposta individual às terapias. A planta Euphorbia tirucalli, *conhecida como Aveloz, possui em sua seiva terpenos e esteróis com atividade antitumoral, sendo amplamente empregada na medicina popular. Foram atendidos, no Hospital Veterinário, oito animais diagnosticados com sarcoide e tratados unicamente com a solução aquosa contendo a seiva de* Euphorbia tirucalli. *As regiões predominantemente acometidas pelos tumores eram base de orelha e peitoral; sete dos oito animais apresentaram tumores em mais de uma região. A injeção intratumoral contendo Aveloz foi aplicada até a turgência do tumor, visualizando-se, em 24 a 72 horas, o enegrecimento, o ressecamento e o desprendimento do sarcoide. O uso da seiva de* Euphorbia tirucalli *apresentou 87,5% de eficácia no tratamento de sarcoide, e foram observados efeitos adversos nos sete animais em que a técnica se mostrou eficaz. Os equinos tratados foram acompanhados no intervalo de três mês a sete anos e nenhum apresentou recidivas do tumor. A aplicação intralesional da seiva da* Euphorbia tirucalli *se apresentou eficaz, segura e de baixo custo no tratamento de sarcoide em equinos, sendo uma alternativa viável para esse tipo de neoplasia cutânea.*

Palavras-chave: antitumoral, Aveloz, cutâneo, neoplasia, tumor

INTRODUCTION

Sarcoids are locally invasive, non-metastatic skin tumors and represent the most common cutaneous neoplasms in horses, having three macroscopic presentations, the verrucous, fibroblastic, and mixed forms (McGavin and Zachary, 2013). Its etiology is associated with infection by bovine papillomaviruses (BPV-1 and BPV-2) and the individual genetic predispositions of each animal (Staiger *et al.*, 2016).

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There are several options for the treatment of sarcoids, however there is no established protocol due to the wide variation in the manifestation of the disease and the high oscillation of the individual response to treatments (Haspenlagh *et al*., 2016). Among the treatment alternatives are immunotherapies, topical use of antivirals, chemotherapy, electrochemotherapy, cryotherapy, radiotherapy, laser removal and surgical resection (Taylor and Haldorson, 2013; Tozon *et al*., 2016).

The *Euphorbia tirucalli* plant of the Euphorbiaceae family, known as Aveloz, has a wide geographic distribution, simple propagation, and cultivation, in addition to being widely used in folk medicine, mainly for the treatment of neoplasms (Dutra, *et al*. 2016). Its sap has a high concentration of terpenes and sterols, which have antitumor activity, having as a mechanism of action the apoptosis of tumor cells (Archanjo *et al*., 2013). Considering the wide use in medicine and the antitumor effects of *E. tirucalli*, this report will describe the effects of intralesional application of an aqueous solution of Aveloz sap in eight horses diagnosed with sarcoid.

CASUISTRY

Between 2012 and 2019, eight horses were treated at the Veterinary Hospital of the Federal University of Paraná (HV-UFPR) with skin tumors diagnosed by histopathological examination as sarcoid, these animals were treated solely with intratumoral application of aqueous solution of Aveloz.

In this group of animals there was a predominance of males (75%), crossbred (75%) and age ranged between one and 25 years old. Regarding the location of tumors, it was more frequently observed in the base of the ear and pectoral regions; followed by the groin, periocular, limbs; thoracic, abdominal, preputial, and scapular region, since seven out of the eight patients had tumors in more than one region. The most common classification of the tumor present in treated patients was fibroblastic.

In the initial clinical examination, the mapping and identification of the region of tumors in the animal was performed, then samples were collected for histopathological examination. After confirming the diagnosis of sarcoid, the applicability of the technique in question was evaluated, considering the size and location of the tumor, regardless of its macroscopic classification.

The aqueous solution of *E. tirucalli* was prepared at the time of the procedure, being collected manually, using disposable gloves, directly from the plant (Fig 1). Eight drops of sap (approximately 0.4ml) were extracted in a sterile container containing 10ml of distilled water, and after collection, the solution was homogenized, obtaining a whitish liquid preparation.

Figure 1. Collection of *Euphorbia tirucalli* sap (white liquid shown by the arrow). Identification by the UPCB Herbarium, registration number 99640, available for consultation at http://upcb.jbrj.gov.br.

In the tumoral and peritumoral regions, standard trichotomy and antisepsis were performed. If necessary, the animal was sedated, where five of the eight animals needed to be sedated. The intratumoral injection was performed with a 1ml syringe and a 0.45x13mm needle, so that the sarcoid would become turgent until the liquid leaked through it. Therefore, the volume was not pre-established, as there was variation according to the size of the tumor, ceasing the injection only when the injected content overflowed. It was observed that larger gauge needles promote laceration of the neoplasm and extravasation of the solution, which does not allow obtaining the desired effect due to the low intratumoral concentration of the solution containing Aveloz.

When effective on first application, during the first 24 hours after treatment, blackening of the sarcoids was observed, suggestive of necrosis (Fig. 2B) and between 48 and 72 hours, there

was dryness, reduction, and tumor detachment (Fig. 2C). As a result of the fall in the neoplasm, skin discontinuities remained at the site of the tumor, which were treated daily, topically, with an oily solution of the sap of Aveloz; composed of 15ml of Cod Liver Oil (Farmos, Brazil), 15mL of Dimethylsulfoxide (Dimesol™, MarcoLab, Brazil) and 60 drops of *E. tirucalli* (approximately 3ml), until complete healing. The application of the oily solution aimed to prevent recurrences if viable tumor cells remained.

Figure 2- Sarcoid in left forelimb before intralesional application of Aveloz aqueous solution (A), 24 hours (B) and 48 hours (C) after the procedure.

In three animals, more than one procedure of intratumoral application of Aveloz's solution was necessary, in one of these, one repetition was enough to resolve it, and in the other two, three applications were necessary for the complete drop of the sarcoids to occur. In animals in which the first infiltration was not effective, 96 hours passed before the next procedure was performed. However, in one animal the treatment was not effective, even after eight applications of the solution. Thus, efficacy was obtained in seven of the eight animals treated with the aqueous solution of *Euphorbia tirucalli*, comprising 87.5% of the animals (Table 1). The requirement to repeat the procedure may be related to the quality of the injection, tumor size and the animal's indocile behavior. Therefore, it is believed that the non-homogeneous application of the solution in the sarcoid may compromise its effectiveness.

Table 1. Location and size of the sarcoid in treated horses, and the effectiveness of aqueous solution Aveloz infiltration

Horses	Location of sarcoids	Sarcoid size	Effectiveness
Male, 25 years old	Pectoral	12cmx10cm	Effective with 1 application
Male, 12 years old	Base of the ear, groin, and limbs	3cmx2cm, 5cmx4cm, 2cmx2cm	Effective with 2 applications
Female, 6 years old	Pectoral and scapular region	8cmx6cm, 6cmx4cm	Effective with 1 application
Female, 7 years old	Base of the ear, periocular and neck	3cmx2cm, 2cmx2cm, 3cmx2cm	Effective with 3 applications
Male, 1 year old	Groin and preputial region	5cmx4cm, 3cmx2cm	Not effective, even with 8 applications
Male, 3 years old	Periocular, limbs, thorax, and abdomen	3cmx2cm, 4cmx3cm, 5cmx4cm, 5cmx6cm	Effective with 3 applications
Male, 10 years old	Pectoral, limbs, and scapular region	7cmxcm, 3cmx4cm, 6cmx5cm	Effective with 1 application
Male, 5 years old	Pectoral, base of the ear and thorax	6cmx6cm, 2cmx2cm, 5cmx6cm	Effective with 1 application

Adverse effects were observed in seven of the eight animals (87.5%) evaluated, that is, in all animals that the technique was shown to be effective. Pain, tissue inflammation, edema and production of purulent secretion were observed at the site. Adverse effects were clinically controlled, not requiring the administration of anti-inflammatory drugs, since the local inflammatory reaction is part of the action of the substance. The oily solution presented as adverse reaction redness and cutaneous irritation in healthy tissue, however, discontinuation of use was enough for the signs to cease.

The monitoring of patients ranged from three months to seven years, and none had sarcoid recurrence after treatment with *Euphorbia tirucalli* solution (Fig. 3).

Figure 3 – Sarcoid in lower eyelid before application of *Euphorbia tirucalli* (A) and the same animal seven years after treatment (B).

DISCUSSION

The treatment of sarcoids in horses represents a challenge due to the variable response to therapy and the high occurrence of relapses. Several studies have been published comparing different treatment protocols and their effectiveness, however, no method is appointed as the gold standard. In a study conducted by McConaghy *et al*. (1994), immunotherapy was identified as the most effective method in relation to surgical incision and cryotherapy. In another study, with a larger number of animals, surgical excision with an electric scalpel had a higher success rate (86.6%) when compared to intralesional injection of a drug containing platinum, cryosurgery, and topical application of acyclovir. More favorable results were also observed with the association of the treatments associated with immunostimulants (intratumoral application of BCG vaccine, cryosurgery and topical imiquimod) (Haspeslagh *et al*., 2016). Electrochemotherapy has a 92.3% success rate as a single treatment or associated with surgical excision (Tozon *et al*., 2016), thus, being one of the techniques with the best results. The effectiveness observed with the intratumoral use of Aveloz sap demonstrates how promising its application might be, and the necessity for more studies with a larger number of animals.

The mechanism of action of the terpenes found in *E. tirucalli* latex is not yet fully understood, however, *in vitro* studies found that latex has an immunomodulatory effect on CD4+ and CD8+ T lymphocytes, stimulating the production of TNF-α and IFN-γ (Avelar, 2010). CD4+ T lymphocytes have antitumor and antiviral action and the good results of the application of Aveloz in sarcoids corroborates the idea that the immune response is strongly involved in the success of sarcoid treatment.

Rosendo *et al*. (2017), reported the intralesional and topical application of *E. tirucalli* sap for the treatment of sarcoid in a horse and observed the same adverse effects. The adverse reactions reported may occur due to the cytotoxic property of the solution, together with its non-sterility, since the latex collection is done manually and its contact with the tree branch is inevitable. Therefore, it is advisable to avoid the extravasation of the solution to the subcutaneous tissue during application, to avoid adverse effects on the peritumoral tissue. In the report by

Rosendo *et al*. (2017) the treatment was also effective and four intratumoral applications were necessary for complete sarcoid regression. Despite 87.5% of the animals evaluated presented adverse reactions, the reversal of signs was fast and the regression and disappearance of sarcoids was effective.

Finally, the easiness to cultivate the *Euphorbia tirucalli* plant in Brazilian territory stands out, making the reported treatment accessible and of low cost.

CONCLUSION

The application of Aveloz sap (*Euphorbia tirucalli*) in the treatment of sarcoids in horses can be an alternative with a high success rate, safe for the patient, accessible and of low cost.

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