

<https://doi.org/10.31533/pubvet.v16n07a1163.1-5>

Canine cutaneous hemangioma treated with Parvulan® (*Cutibacterium acnes*): Case report

Alex Lucas Spadetti¹, Francisca das Chagas Sobral Silva^{2*}, Andrey Junio Moreira Fernandes³, Rodrigo de Lima Pimentel⁴

¹Médico Veterinário, Laboratório e Extratos Alergênicos MQ, Rio de Janeiro, Brasil.

²Pós-doutorado em Processos Químicos e Bioquímicos, Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brasil.

³Graduando em Medicina Veterinária, Universidade Federal Fluminense, Niterói, Rio de Janeiro, Brasil.

⁴Biomédico, Laboratório e Extratos Alergênicos MQ, Rio de Janeiro, Brasil.

*Autor para correspondência: franciskasobral@gmail.com

Abstract: Immunomodulators are substances that act on the immune system by modulating various functions of the innate or acquired immune response. One of these immunomodulators is *Cutibacterium acnes* (*C. acnes*), an active agent of Parvulan®. The aim of this case report is to expound on the application of *C. acnes* as an immunomodulator in the treatment of a dog affected by benign hemangioma in the perineal region. The thirteen-year-old male animal, of no defined breed (NDB), presented a dark nodule, measuring 2.0 cm in diameter. A biopsy of the nodule was performed for diagnosis and confirmation of hemangioma. Treatment started with 0.3 ml doses of Parvulan® with intramuscular (IM) applications. In the first month, there was a 35% (0.7 cm) regression of the tumor. In the second phase of the treatment, applications were made once a week for 2 months. During this period there was a regression of 45% (0.9 cm) of the tumor, and after three months 65% (1.3 cm). In the third phase, Parvulan® was applied every 15 days for two months. In the course of this period, a 100% regression concerning the initial value was obtained. Throughout the entire treatment (approximately 5 months) the tumor completely regressed, with the nodule disappearing. The results showed the efficiency of *C. acnes* lysate in the treatment of canine cutaneous hemangioma, being an alternative to non-surgical intervention with no tumor recurrence. However, it is necessary to carry out more studies with other dogs that present a diagnosis of hemangioma in order to obtain a more accurate and precise protocol.

Keyword: Canine cutaneous hemangioma, cutaneous nodule, *Cutibacterium acnes*, immunomodulator

Hemangioma cutâneo canino tratado com Parvulan® (Cutibacterium acnes): Relato de caso

Resumo. Os imunomoduladores são substâncias que atuam no sistema imunológico, modulando várias funções da resposta imune inata e adaptativa. Um destes imunomoduladores é o *Cutibacterium acnes* (*C. acnes*), agente ativo de Parvulan®. O objetivo deste relato de caso é a utilização do *C. acnes* como imunomodulador no tratamento de um cão acometido por hemangioma benigno na região perineal. O animal macho, com idade de treze anos, sem raça definida (SRD), apresentou o nódulo medindo 2,0 cm de diâmetro, de coloração escura. Foi realizada biópsia do nódulo para diagnóstico e confirmação de hemangioma. O tratamento teve início com doses de 0,3 ml de Parvulan®, com aplicação intramuscular (IM). No primeiro mês houve uma regressão de 35% (0,7 cm). Na segunda fase do tratamento as aplicações ocorreram uma vez por semana por 2 meses, neste período obteve-se regressão de 45% (0,9 cm) do tumor, e após três meses 65% (1,3 cm). Na terceira fase, o Parvulan® foi aplicado a cada 15 dias durante dois meses. Nesse

período obteve-se uma regressão de 100% em relação ao valor inicial. Ao longo de todo o tratamento (cerca de 5 meses) o tumor regrediu totalmente, com o desaparecimento do nódulo. Os resultados mostraram a eficiência do lisado de *C. acnes* no tratamento de hemangioma cutâneo canino, sendo uma alternativa para não intervenção cirúrgica, não havendo recidiva do tumor. Contudo, é necessário realizar mais estudos com outros cães que apresentem diagnóstico de hemangioma para se ter um protocolo mais apurado e definido.

Palavras-chave: *Cutibacterium acnes*, imunomodulador, hemangioma cutâneo canino, nódulo cutâneo

Introduction

C. acnes is an immunostimulant, a base of pleomorphic gram-positive cells that has the function of stimulating the synthesis of cytokines, activating macrophages which increases the activity of cytotoxic T cells and natural killer (NK) cells, favoring the resolution of neoplastic processes ([Atherton et al., 2016](#); [Batschinski et al., 2018](#)). Hemangioma and hemangiosarcoma are mesenchymal neoplasms that originate from the vascular endothelium ([Cummins & Johnson, 1972](#); [Dréno et al., 2018](#)). The incidence of cutaneous neoplasm in dogs has been reported quite frequently in different parts of the world ([Freitas & Forlani, 2019](#); [García-Iglesias et al., 2020](#)). In Brazil, epidemiological data are presented in all regions of the country in the form of hemangioma and hemangiosarcoma (malignant) neoplasms ([Kim et al., 2020](#)). With regards to hemangiomas, they manifest as benign vascular lesions, arising from cell mutations but their causes are still unknown. Research shows that older dogs are statistically more affected by hemangiomas ([Lucas et al., 2021](#); [Yamamoto et al., 2013](#)), which can affect the skin and subcutaneous tissues, tongue, conjunctive, among other areas of the animal's body, requiring surgical removal ([Nasser, 2012](#)).

The treatment of choice for cutaneous hemangioma is usually surgical with palliative purposes, and its resectioning must be aggressive, respecting safety margins that vary from 2-3cm in all planes around the tumor, aiming at the complete excision of affected tissues ([Palmieri & Vadalà, 2021](#)). In this case report, a canine cutaneous hemangioma was treated solely with applications of the bacterial lysate of *Cutibacterium acnes*, an immunomodulatory active agent presents in Parvulan®, with the aim of verifying its effectiveness without the need of surgical intervention. The potential of *Cutibacterium acnes* in the process of activating inmates' immunity has been described in a large number of scientific publications ([Pigatto et al., 2011](#)). The bacterial lysate of *C. acnes*, when injected intramuscularly, acts on the defense cells with nonspecific immunomodulatory activity, presenting reports of regression and cure of tumors in humans and animals ([Rutten et al., 1990](#); [Santos et al., 2020](#); [Schultheiss, 2004](#)).

Case report

A 13-year-old medium/large short and light haired male neutered dog, No Defined Breed (NDB), weighing approximately 24 kg, affected by a benign tumor with dimensions of 2.0 cm in diameter in the perianal region. On physical examination, a mass adhered to the skin, blackened, malleable, soft with compact brown cut surface was observed. No other clinical modifications were observed. On palpation, the animal showed no signs of pain; presenting a non-palpable inguinal lymph node, while ensuring that all parameters are within the normal range of the patient.

Trichotomy was performed in the region, and the dimension/size of the nodule was monitored throughout the treatment with the aid of a caliper. The histopathology of the nodule biopsy ([Figure 1](#)) delineates the superficial dermis presenting a marked inflammatory infiltrate, rich in foamy macrophages, lymphocytes and plasma cells and few neutrophils. The deep dermis presented vascular proliferation coated by robust or elongated endothelium, supported by a dense stroma with rare apocrine glands and compromised surgical margin, confirming mixed dermatitis and hemangioma.

The nodule was not completely excised at the time of the biopsy, only a fragment was removed considering the dog's advanced age, its weakness and the animal's owner's interest. The use of the *C. acnes* lysate was chosen as an alternative to the procedure, considering its efficiency in the tumor regression response, a fact that is supported by the action of *C. acnes* as a non-specific immunomodulator by stimulating the activity of NK cells, from the release of interferon and tumor necrosis factor. NK cells, together with cytotoxic cells stimulated by the action of *C. acnes*, would present an increase in tumoricidal activity, favoring the resolution of neoplastic processes ([Soares et al., 2017](#)).

Therapy was initiated from five applications of 0.30 mL of Parvulan®, intramuscularly around the perimeters of the nodule in a single dose. In this first phase of treatment, the procedure was repeated twice a week, with intervals of 3 to 4 days for a period of 1 month with a total of 9 applications. During this period there was a reduction in the size of the nodule, from 2.0 cm to 1.3 cm (35%) and a change in the color of the nodule.

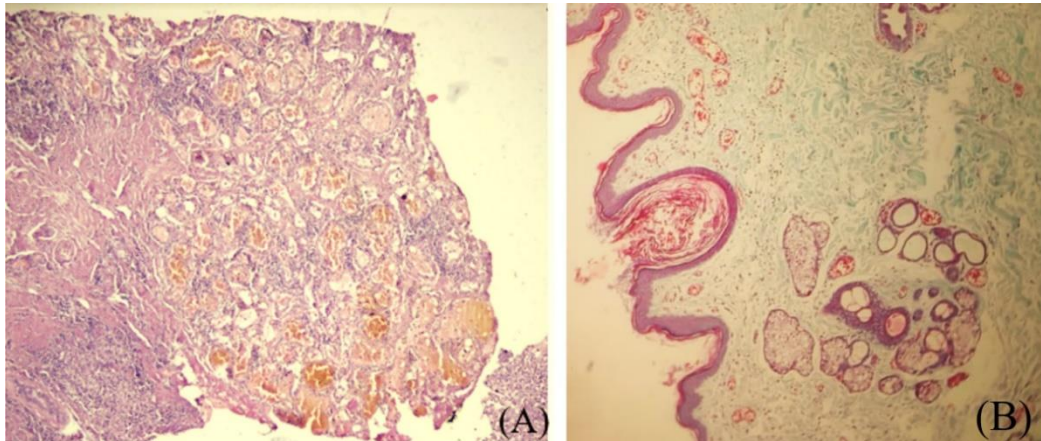


Figure 1. (A): Histopathology for superficial dermis with inflammatory infiltrates and vascular neoformations compatible with canine cutaneous hemangioma. Image with 40x magnification. (Photomicrograph: Personal file of the author); (B): Histopathology of the superficial (100x magnification) dermis after treatment with Parvulan®.

In the second phase, the previous protocol was repeated with five applications of 0.30 mL of Parvulan® around the nodule with weekly application for a period of two months, with a total of applications. In the course of this period, the nodule regressed from 1.3 cm to 1.1 cm (45%) in the second month and later from 1.1 cm to 0.7 cm (65%) in the third month. Finally in the third phase, applications were performed every 15 days for 2 months, making a total of 4 applications, with three applications of 0.30 mL of Parvulan® around the nodule. A total disappearance of the tumor, healing of the animal and resumption of physical vigor was observed ([Figure 2](#)).

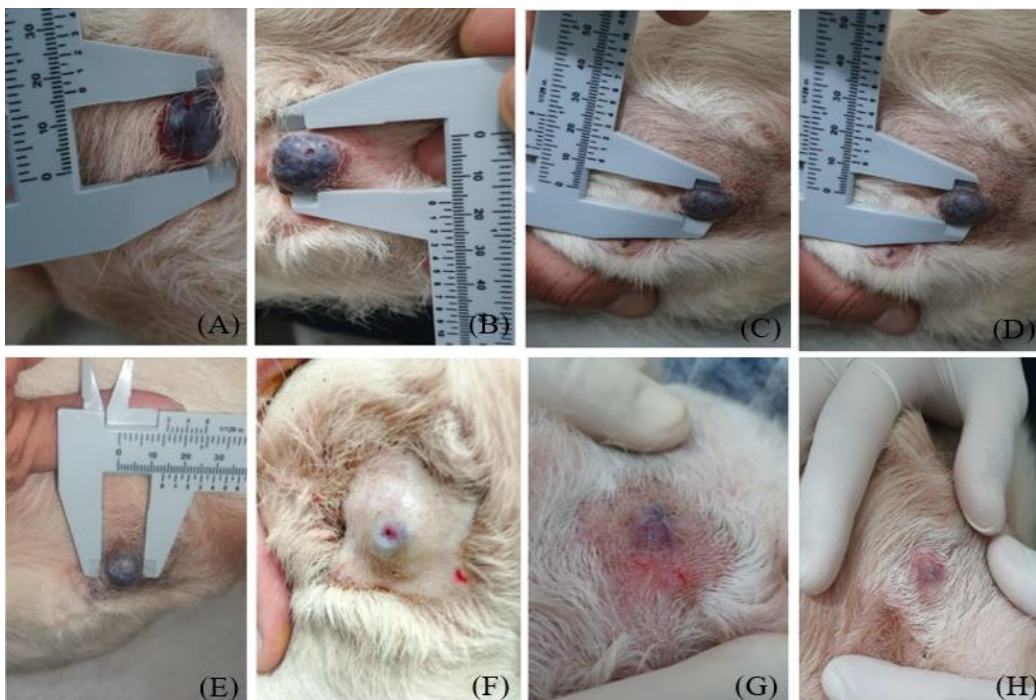


Figure 2. Regression of the nodule (hemangioma) after repeated applications of the bacterial lysate of *C. acnes*, Parvulan®. (A-B) after the first month of application, where the beginning of lesion regression is observed. (C-E) second month. (F-G) third to fifth and (H) After 5 months of treatment, giving complete resolution of the disease.

Discussion

The potential of *C. acnes* lysates has already been confirmed in different studies, where the mechanism of action functions by stimulating the production of macrophages, NK cells and cytotoxic T cells, inferring in the regression and cure of tumors, as initially reported, (Soares et al., 2017) which confirms the effectiveness in the present case report. Surgical removal of the hemangioma is reported as a treatment (Lucas et al., 2021; Ward et al., 1994), however the desire of the animals guardian is not to put it under the surgical process, in view of the weakness of the dog and its advanced age, which was brought as an alternative to immunotherapy from bacterial lysis of the *C. acnes*, which proportioned the total regression of the tumor, without the occurrence of a relapse.

In extreme cases of animal debilitation, such as the one presented in this case report, the use of *C. acnes* Lysate (Parvulan®) is proposed because it is less invasive, reducing the chances of metastases, in addition to the fact that surgical anesthetics often work as immunosuppressant, which is not favorable for recovery; monthly, quarterly or semiannual doses with prophylactic function can also be implemented (Karayannopoulou et al., 2022). Success with *C. acnes* lysate was also achieved by Abreu et al., (2015) for the canine oral papillomatosis. The authors report that after three weeks of treatment, involution of the papillomas was observed, followed by the complete cure of the disease in three months.

Conclusion

The use of Parvulan® containing *C. acnes* treatment had an excellent efficacy in the treatment of the hemangioma nodule without the need for the animal to undergo a surgical procedure and/ or chemotherapy, being a total clinical treatment, much less invasive, less expensive and effective. The animal showed improvement in daily walks, appetite, water consumption, playing, going up and down stairs, being more active and alert, showing a considerable improvement in the general clinical state of the animal.

References

- Abreu, C. B., Luiz E. Duarte O., Paula B., Juliana A. C., Tatiana S., and Rodrigo B.N. 2015. Associação de Sulfato de Vincristina e Propionibacterium Acnes No Tratamento de Papilomatose Oral Canina. *Veterinária Notícias – Relato de Caso*, 21, 11-17.
- Atherton, M. J., Morris, J. S., McDermott, M. R., & Lichty, B. D. (2016). Cancer immunology and canine malignant melanoma: A comparative review. *Veterinary Immunology and Immunopathology*, 169, 15–26. <https://doi.org/10.1016/j.vetimm.2015.11.003>.
- Batschinski, K., Nobre, A., Vargas-Mendez, E., Tedardi, M. V., Cirillo, J., Cestari, G., Ubukata, R., & Dagli, M. L. Z. (2018). Canine visceral hemangiosarcoma treated with surgery alone or surgery and doxorubicin: 37 cases (2005-2014). *Canadian Veterinary Journal*, 59(9), 967–972.
- Cooney, D. R., Allan D. L., Wayne W., Abdur, R. K., and Melvyn P. K. 1984. The Effect of the Immunomodulator Corynebacterium Parvum on Hemisplenectomized Mice. *Journal of Pediatric Surgery* 19, 810-817.
- Cruvinel, W. D. M., Danilo M. J., Júlio A., P. A., Tânia T., and Takao C., 2010. Immune System – Part I Fundamentals of Innate Immunity With. *Bras J. Rheumatol.* 55, 434–61. <https://doi.org/10.1590/S0482-50042010000400008>.
- Cummins, C. S. & Johnson, J. L. 1972. Corynebacterium parvum: a Synonym for Propionibacterium acnes? *Journal Gen. Microbiol.* 8, 433–442. Doi: <https://doi.org/10.1099/00221287-80-2-433>.
- Dréno, B., Pécastaings S., Corvec S., Veraldi S., Khammari A., and Roques C. 2018. Cutibacterium Acnes (Propionibacterium Acnes) and Acne Vulgaris: A Brief Look at the Latest Updates. *Journal of the European Academy of Dermatology and Venereology* 32:5–14. <https://doi.org/10.1111/jdv.15043>.
- Freitas, J., Lin C. Y. and Gustavo S. F. 2019. Canine Hemangiosarcoma: Review. *Pubvet* 13(8):1–9: <https://doi.org/10.31533/pubvet.v13n8a389.1-9>.
- García-Iglesias, M. J., Jose Luis, C.H., Ana B. S., Maria G. D. G., Laura P., Paula P., Jorge G. F., Beatriz F.M., and Claudia P. M. 2020. Immunohistochemical Detection of P53 and Pp53 Ser392 in Canine

- Hemangiomas and Hemangiosarcomas Located in the Skin. *BMC Veterinary Research* 16(1):239. <https://doi.org/10.1186/s12917-020-02457-6>.
- Karayannopoulou, M., Tilemachos A., Apostolia M., Kritsepi-Konstantinou M., Dimitra P., Angelos L. T., Ioannis S. 2022. Effect of Major versus Minor Mastectomy on Host Immunity in Canine Mammary Cancer. *Veterinary Immunology and Immunopathology* 246(4):110–403. <https://doi.org/10.1016/j.vetimm.2022.110403>.
- Kim, S. H., Choi, W. S., Seung, B. J., Cho, S. H., Lim, H. Y., Bae, M. K. and Sur, J. H. 2020. Statistics of Canine Skin Tumors in Korea during 2005–2018. *Pakistan Veterinary Journal* 40(2):169–74. <https://doi.org/10.29261/pakvetj/2019.014>.
- Lucas, J., Costa D., Francisca M., Sousa B., Rubia A., Guedes S., Rafael L. O., Ricardo B. D. L., Saulo P. P., Marcelle B. B., Jean L. D. A. 2021. Cutaneous Hemangiosarcoma in a Buff-Throated Saltator (Saltator Maximus) with Lung Metastasis. *Brazilian Journal of Veterinary Pathology*. 14 (2), 107–110. <https://doi.org/10.24070/bjvp.1983-0246.v14i2p107-110>.
- Nasser, N. 2012. Treatment of Common Warts with the Immune Stimulant Propionium Bacterium Parvum. *Brazilian Annals of Dermatology* 87(4):585–89. <https://doi.org/10.1590/s0365-05962012000400011>.
- Palmieri, B. & Maria V. 2021. Corynebacterium Parvum (Propionibacterium Acnes): Cytokines Cells, Innate Immunity, and Putative Antiviral Adoption. *Journal of Interferon and Cytokine Research* 41(3):132–36. <https://doi.org/10.1089/jir.2020.0216>.
- Pigatto, J. A. T., Luciane, A., Paula S. H., Ana, C. V. R.A., Fernanda N., and Juliano S. L. 2011. Squamous Cell Carcinoma in the Third Eyelid of a Horse. *Acta Scientiae Veterinariae* 39(1):1–4. <https://doi.org/10.22456/1679-9216.111729>.
- Rutten, V. P. M. G., Misdorp, W., Gauthier, A., Estrada, M., Mialot, J. P., Parodi, A. L., Rutteman, G. R. and Weyer, K. 1990. Immunological Aspects of Mammary Tumors in Dogs and Cats: A Survey Including Own Studies and Pertinent Literature. *Veterinary Immunology and Immunopathology* 26(3):211–25. [https://doi.org/10.1016/0165-2427\(90\)90092-7](https://doi.org/10.1016/0165-2427(90)90092-7).
- Santos, I. R., Ana C. M. P. L., Hugo H. F., Brunna R. R., Anderson R. S., and Adriana S. S. 2020. Canine Cutaneous Neoplasms in the Metropolitan Region of Goiânia, Goiás State, Brazil. *Brazilian Veterinary Research* 40(8):614–20. <https://doi.org/10.1590/1678-5150-PVB-6531>.
- Schultheiss, P. C. 2004. A Retrospective Study of Visceral and Nonvisceral Hemangiosarcoma and Hemangiomas in Domestic Animals. *Journal of Veterinary Diagnostic Investigation* 16(6):522–26. <https://doi.org/10.1177/104063870401600606>.
- Soares, N. P., Alessandra A. M., Matias P. J. S., Ednaldo C. G., Lígia G. F., and Thaísa R. S. 2017. Hemangiomas and Hemangiosarcomas in Dogs: Retrospective Study of 192 Cases (2002–2014). *Brazilian Animal Science* 18(0):1–10. <https://doi.org/10.1590/1089-6891v18e-30889>.
- Talib, W.H. & Suhair S. 2015. Propionibacterium Acnes Augments Antitumor, Anti-Angiogenesis and Immunomodulatory Effects of Melatonin on Breast Cancer Implanted in Mice. *PLoS ONE* 10(4):1–13. <https://doi.org/10.1371/journal.pone.0124384>.
- Tchaptchet, S., Jörg K., Nikolaus, F., Wolfgang W. A. S., Chris G., and Marina A. F. 2010. Innate, Antigen-Independent Role for T Cells in the Activation of the Immune System by Propionibacterium Acnes. *European Journal of Immunology* 40(9):2506–16. <https://doi.org/10.1002/eji.200939860>.
- Ward, H., Leslie E. F., Maron B. C., Alan S. H., and Guillermo C. C. 1994. Cutaneous Hemangiosarcoma in 25 Dogs: A Retrospective Study. *Journal of Veterinary Internal Medicine* 8(5):345–48. <https://doi.org/10.1111/j.1939-1676.1994.tb03248.x>.
- Yamamoto, S., Katsuichiro, H., Atsushi, H., Syuuichi C., Masayuki K., and Noboru M. 2013. Epidemiological, Clinical and Pathological Features of Primary Cardiac Hemangiosarcoma in Dogs: A Review of 51 Cases. *Journal of Veterinary Medical Science* 75(11):1433–41. <https://doi.org/10.1292/jvms.13-0064>.

Article History:

Received: May 17, 2022.

Accepted: June 6, 2022

Available online: June 27, 2022

License information: This is an open-access article distributed under the terms of the Creative Commons Attribution License 4.0, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.