

# Tongue plasmacytoma in a dog treated with adjuvant metronomic melphalan

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## ABSTRACT

A 9-year-old female crossbred dog was referred due to a tongue neof ormation. A marginal resection was performed to proceed with the histopathological examination, which indicated malignant round cell neoplasia, and immunohistochemical staining diagnosed the mass as plasmacytoma. The owner refused another surgical intervention to extend margins and approach another growth verified on the ventral surface of the base of the tongue. Thus, the patient underwent three months of metronomic chemotherapy with melphalan. The disease progression was not detected after two years of follow-up. This report shows that daily low-dose melphalan may be used as an adjuvant treatment option for oral plasmacytoma in dogs when clean margins cannot be achieved.

Extramedullary plasmacytomas are neoplasms composed of atypical solitary collections of monoclonal plasmacytes that arise within soft tissues (10, 19). The median age of occurrence in dogs is 9 to 10 years (19). Other tumors of the plasma cell lineage include solitary bone plasmacytomas and multiple myelomas (8, 21). Previous studies described the most likely sites of occurrence for extramedullary plasmacytomas as being 86% cutaneous, 9% oral and mucous membranes (including tongue), and 4% in the rectum and colon; other sites represent less than 1% of observations (stomach, intestines, spleen, genitalia, and eyes) (4, 8). Despite canine cutaneous plasmacytoma and multiple myeloma being neoplastic entities of plasma cell origin, only 1% of the cases may occur as part of systemic multiple myeloma (19). A study reported ten dogs diagnosed with multiple plasmacytomas without signs of systemic disease (14).

Of all tongue tumors in dogs, plasmacytomas represent 2% (19). A 10-year retrospective study with 302 dogs showed that extramedullary plasmacytomas were 5.2% of all oral tumors, of which four were located in the tongue (21). Oral extramedullary plasmacytomas generally present locally destructive infiltrating growth (13); nevertheless, they rarely metastasize (19). Thus, surgical excision with clean margins or local therapy with electrochemotherapy has carried a good to excellent prognosis, with long-term survival and low metastasis rates (4, 19). Some studies have used radiation or chemotherapy with melphalan with or without prednisone association as adjuvant treatment in cases of residual extramedullary plasmacytoma (5, 7, 21). This report aims to elucidate a case involving a canine tongue plasmacytoma, managed through marginal resection and metronomic melphalan, showcasing a lack

of disease progression throughout a two-year follow-up period.

A 9-year-old, 10-kg female crossbred dog was referred to the Veterinary Hospital due to a tongue neof ormation identified during a periodontal cleaning. The owner had not recognized the lesion since the dog did not exhibit any clinical signs. On presentation, the dog was bright, alert, and in good body condition. The examination of the oral cavity showed an ulcerated nodule, adhered, multilobulated, with fibroelastic consistency, located on the left edge in the middle third of the tongue and measuring 2.7 x 2 x 1.1 cm (Figure 1). A complete blood count (CBC) demonstrated mild anemia (hematocrit 35%; Reference Range (RR): 37–55%). Serum biochemical analyses revealed mild alterations in total protein (7.3 g/dL; RR: 5.4–7.1 g/Dl), borderline-decreased albumin (2.5 g/dL; RR: 2.6–3.3 g/dL), and elevated globulin (5.5 g/dL; RR: 2.7–4.4 g/dL). Gamma-glutamyl transferase (4.8 IU/L; RR: 1.2–6.4 IU/L), alkaline phosphatase (125 IU/L; RR: 20–156 IU/L), creatinine (0.8 mg/dL; RR: 0.5–1.5 mg/dL), and urea (36.0 mg/dL; RR: 21.4–59.92 mg/dL) were within the reference interval. No abnormality was found on the abdominal ultrasound examination.

Under routine general anesthesia, marginal excision (the surgical approach aiming at removing only the gross disease) (3) was performed to proceed with the

histopathological examination. In addition, a mass of approximately 0.5 x 0.5 cm, round in shape and non-ulcerated, located on the ventral surface of the base of the tongue was also found (Figure 2). Because the mass had adherence to tissues and was located near the deep lingual vein, it was decided to wait for the histopathology results of the large tumor. After surgery, analgesics and antibiotics were prescribed. Recovery was uneventful, and the dog can eat and drink water without difficulty.

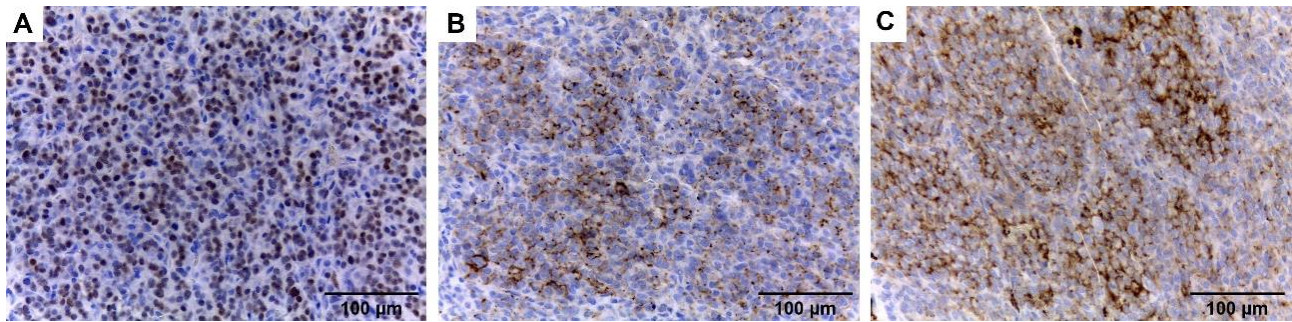
Histopathological analysis of the mass with hematoxylin and eosin staining revealed poorly delimited proliferation in the submucosa, infiltrative aspect, interspersed with fibro-collagenous stroma, demonstrating intense pleomorphism, anisocytosis, and anisokaryosis. Fifty-four mitotic figures were observed in ten fields of higher magnification (400x), in addition to cytomegaly, karyomegaly, macronucleoli, bi, and multinucleation. The histopathological findings indicated malignant round-cell neoplasia. Because the histopathological analysis was inconclusive, immunohistochemical staining was performed. The markers used for the sample were Multiple Myeloma Oncogene 1/Interferon Regulator Factor 4 (MUM1/IRF4), Naive Cell Lymphoid Lineage Antigen (CD45RA), and Lambda Immunoglobulin Light Chain. Plasmacytoma was diagnosed since all markers were positive on neoplastic cells (Figure 3).



**Figure 1.** Dorsal surface of the tongue. Note the multilobulated nodule located on the left edge of the tongue.



**Figure 2.** Ventral surface of the tongue. Note the round in shape and non-ulcerated mass (arrow).



**Figure 3.** Photomicrographs of immunohistochemistry slides with positive staining of neoplastic cells. A. MUM1/IRF4; B. CD45RA; and C. Lambda immunoglobulin light chain.

Based on the diagnosis, a partial glossectomy was indicated to extend the margins and approach the mass located on the ventral surface of the base of the tongue. Due to the owner's refusal to undergo surgery, metronomic chemotherapy was suggested. After the acceptance, melphalan (Alkeran®) was given orally once daily at a dose of 1.5 mg/m<sup>2</sup> for three months. Blood tests were performed after two months of treatment. CBC demonstrated leucocytes in the lower borderline, with lymphopenia as the main alteration and other parameters within the expected range. In serum biochemical analyses, total serum protein was normalized, and mild hypoalbuminemia and slightly elevated globulin remained (Table 1).

**Table 1.** Relevant parameters of CBC and serum biochemical analysis after two months of treatment with melphalan.

Parameter	Value	Reference range
Leucocytes	6.1 x 10 <sup>3</sup> /µL	6.0 - 17.0 x 10 <sup>3</sup> /µL
Lymphocytes	2%	12 - 30%
Serum albumin	2.5 g/dL	2.6 - 3.3 g/dL
Serum globulin	4.5 g/dL	2.7 - 4.4 g/dL

The animal responded well to metronomic chemotherapy, and the tumor was controlled within three months post-surgery and reported to have improved two years after the procedure.

The gross appearance of the tumor in the present case resembles the previously described extramedullary plasmacytoma, such as a raised nodule, pink in color, most 1 to 2 cm in size, some ulcerated, and polypoid (2). Clinical signs of the oral extramedullary plasmacytoma are generally not specific (19), which increases the difficulty of early diagnosis, as verified in this case.

Histopathological diagnosis of canine cutaneous round cell tumors can be challenging due to their similar morphology (12). Especially in poorly differentiated plasmacytomas, immunohistochemical analysis is helpful in differentiation from other round-cell tumors (19). In the present case, immunohistochemical analysis was

performed to differentiate plasmacytoma from melanoma, two hypotheses put forward in the histopathological study. Positivity for CD45RA confirmed the B-cell origin of the tumor (16). The MUM1/IRF4 marker is involved in lymphoid cell differentiation, particularly in the production of plasma cells, and is very specific for plasmacytomas; a study with canine formalin-fixed paraffin-embedded tissues verified that 94% of plasmacytomas were positive for MUM1/IRF4 (15). The staining for Lambda Immunoglobulin Light Chain also helped the diagnosis, considering that the extramedullary plasmacytoma is an immunoglobulin-producing tumor of plasma cellular origin (9, 10, 19).

Plasmacytomas generally demonstrate histopathological malignancy criteria, including infiltrative growth, and are locally destructive (13), as found in this case. However, they tend to grow slowly and rarely invade adjacent tissue or metastasize (11, 19). Usually, the prognosis is good after surgical excision (19). The main reason for local recurrence is the failure to remove sufficient tissue during surgery (2). To prevent it, chemotherapy was chosen since the owners were reluctant to take a new surgical approach.

Melphalan was chosen for this case because it is the most commonly used drug for extramedullary plasmacytoma in dogs (7, 18, 19, 20). The authors reported its use in metastasis cases and residual disease after a surgical procedure or radiation therapy (7, 18, 19). Drug administration can treat multiple myeloma, cutaneous plasmacytosis, and solitary osseous plasmacytoma, as well as cancers of other plasma cell lineages (1, 19). In addition, metronomic chemotherapy has shown some advantages for selected patients and specific tumors, including lower cost, a better toxicity profile, and easier handling compared to the maximum tolerated dose used in conventional chemotherapy regimens (17). Side effects related to melphalan in dogs were mostly hematopoietic, especially thrombocytopenia (6), which was not observed in this case.

Except for lymphopenia, the metronomic chemotherapy using melphalan in a low daily dose was

particularly effective in preventing relapses in the present case without adverse events and may represent a therapeutic alternative for the residual disease of tongue plasmacytoma in dogs.

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### Conflict of Interest

The authors declared that there is no conflict of interest.

### Author Contributions

SSR and CB conducted the case. NR performed histopathological analysis. SSR took the lead in writing the manuscript. CB, SCR and MS reviewed and edited the manuscript. All authors provided critical feedback and helped shape the manuscript.

### Data Availability Statement

The data supporting this study's findings are available from the corresponding author upon reasonable request.

### Ethical Statement

This study does not present any ethical concerns.

### Animal Welfare

The authors confirm that they have adhered to ARRIVE Guidelines to protect animals used for scientific purposes.

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