A Case Report - Canine Histiocytic Sarcoma Treated with Zoledronic Acid and Dendritic Cells

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Background & Objective

Histiocytic sarcoma (HS) is a very aggressive tumor that arises from myeloid dendritic cells or macrophages[1-3] and is known for its variable clinical course (localized, disseminated, hemophagocytic, dendritic leucemia) with a fatal outcome[4-6]. Standard treatment involves surgical removal of the tumor, followed by chemo- or radiotherapy. We report on the clinical case of a nine-year-old French Bulldog with HS whose owner preferred cellular immunotherapy in combination with zoledronic acid (ZA) to chemotherapy after tumor removal. The aim of the experimental treatment was to prolong the patient's survival time with good health quality, thereby promoting the animal's well-being and the dog owner's enjoyment.

[1]Affolter VK und Moore PF (2002). Vet Pathol 39(1):74–83. doi: 10.1354/VP39-1-74. [4]Moore PF, Affolter VK, Vernau W (2006). Vet Pathol 43(5):632–45. doi: 10.1354/VP43-5-632. [2]Schmidt JM, Meichner K (2022). In: Kessler M (Hrsg.): Kleintieronkologie. 4. Aufl. Georg Thieme Verlag, Stuttgart, 809–815. [4]Skorupski KA, Clifford CA, Paoloni MC, Lara-Garcia A, Barber L, Kent MS, Leblanc AK, Sabhlok A, Mauldin EA, Shofer FS, Couto G, Sorenmo KU (2007). J Vet Intern Med 21(1):121–26. doi: 10.1111/j.1939-1676.2007.tb02937.x. [5]Hafeman SD, Varland D, Dow SW (2012). Vet Comp Oncol 10(1):44–56. doi: 10.1111/J.1476-5829.2011.00274.X. [6]Takahashi M, Tomiyasu H, Hotta E, Asada H, Fukushima K, Kanemoto H, Fujino Y, Ohno K, Uchida K, Nakayama H, Tsujimoto H (2014). J Vet Med Sci 76(5):661–66. doi: 10.1292/jvms.13-0414.

Anamnesis & Diagnosis & Prognosis

Patient

- French Bulldog;
- Nine-year-old, male, neutered.

Clinical Examination

- Lively and alert, strong and regular heartbeat, rectal body temperature 38.3 °C, typical symptoms of brachycephalic syndrome;
- Defined lumps in the dorsal neck (almond-shaped), left-sided of the neck (pinhead-sized), on the sternum (grape-sized), all firm and mobile.

Blood Count and Blood Chemistry*

- Unremarkable;
- HCT in the lower reference range of 38.5% [37.3–61.7%];
- CRP value elevated at 2.5 mg/dL [0.0–1.0 mg/dL];
- no thrombocytopenia, 539 K/µL [148–484 K/µL]).

*Testkits ProCyte and Catalyst (Idexx Laboratories, Inc., Westbrook, Maine, USA

	Result	Unit	Reference
RBC	6,32	M/uL	5,65–8,87
HCT	38,5	%	37,3–61,7
HGB	14,4	g/dL	13,1–20,5
RETIC	17,7	K/uL	10,0–110,0
WBC	9,97	K/uL	5,05–16,76
PLT	539	K/uL	148–484
CREA	1,7	mg/gL	0,5–1,8
BUN	30	mg/dL	7–27
ALT	40	U/L	10–125
CRP	2,5	Mg/dL	0,0–1,0

Native and Contrast-Enhanced Computed Tomography (CT)

- Homogeneous and soft tissue-dense structure in the sternum, size 22 x 15 x 22 mm (Figure 3) and in the dorsal neck region at Th 5 - 6, size 6 x 17 x 24 mm (Figure 4). The pinhead-sized structure in the left-sided neck region had disappeared at the time of the CT scan and surgery.
- Thoracic region with enlarged cranial mediastinal lymph nodes (Figure 5); thorax, lungs and abdomen free of metastases;
- Liver-like tissue with hypo- to anechoic components on ultrasound caudo-dorsally to the heart (Figure 6).

Cytology prior to treatment

- Sternum nodular tissue: multiple pleomorphic, partially multinucleated round cells, vacuolated cytoplasm, accompanying eosinophilia; immunohistochemistry: large cells IBA1 +ve, cells CD20 –ve, smaller cells CD3 +ve. Suspected mast cell tumor was not confirmed by the tumor-associated c-kit surface protein;
- Dorsal neck node: cellular infiltrates of reactive fibrinous, partly granulomatous panniculitis; no signs of tumor growth;
- Thoracic biopsy: neutrophil granulocytes, round cells, no lymphocytes, possibly inflammatory origin, but neoplastic origin not excluded.

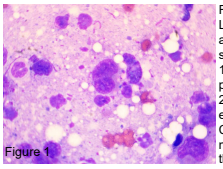

Figure 1

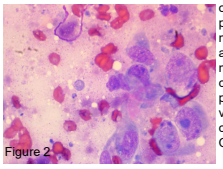

Figure 2

Figure 1 + 2: Lump-associated subcutis (Figure 1) and Lnn. poplitei (Figure 2) on the day of euthanasia. Cytologically, HS manifests itself through large, often highly pleomorphic, mononuclear and sometimes multinucleated cells with partially vacuolated cytoplasm[3]. Diff-Quick staining.

Diagnosis

- Localised HS (Figure 3) with suspected dissemination.

Prognosis

- Infaust, based on estimated MST 33.3 ± 44.4 days upon diagnosis[7].

[7]Coenen C (2009). Doctoral Thesis, Justus-Liebig-University, Veterinary Faculty, 177 pages. http://dx.doi.org/10.22029/jlupub-12398111

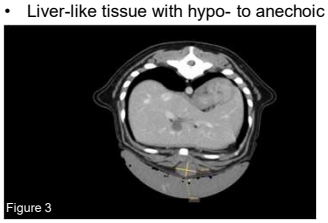

Figure 3

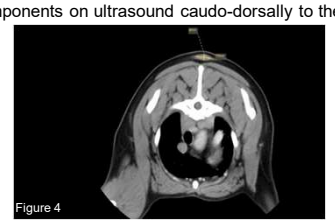

Figure 4

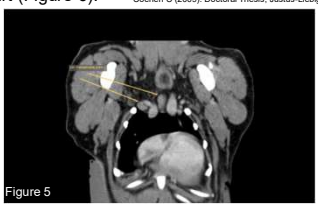

Figure 5

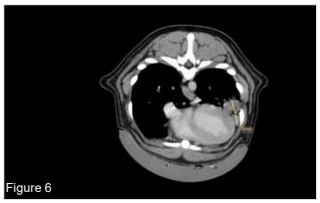

Figure 6

Treatment & Progression of Disease

Surgery

- Complete removal of the lumps in the dorsal neck and sternum, healthy surgical margins;
- Postoperative amoxicillin/clavulanic acid 20 mg/kg three times daily for seven days (Synulox®, Zoetis, Germany), metamizole 40 mg/kg three times daily for four days (Novaminsulfon Lichtenstein 500 mg tablets, Zentiva Pharma GmbH, Germany);
- Regular wound checks, stitches removed 10 days after removal.

Zoledronic Acid (ZA)[8];

- Seven days prior to DCs application, ZA (Zoledronic Acid Hexal®, 4 mg in 100 ml NaCl) administered i.v. at a dose of 0.1 mg/kg body weight over 15 minutes;
- Schedule: week -1, 2, 3, 8,13.

[8]Mullin C (2022): in World Oncology Connection, Veterinary Cancer Society, Columbia.

Autologous Monocyte-derived Dendritic Cells (DCs)[9]

- RPMI 1640, rcGM-CSF and rcIL-4, GMP, seven days;
- 2.0 x 10^6, 2,5 x 10^6, 3,7 x 10^6, 29,9 x 10^6, 4,9 x 10^6 DCs in isotonic sodium chloride solution (0.9 %);
- Quality acceptance: ≥ 10 % of CD-1b positive cells, viability ≥ 90 %;
- Intradermal injection within 24 hours;
- Schedule: week 0, 3, 4, 9, 14.

[9]Spiller V, Vetter M, Dettmer-Richardt C, Grammel T (2024). Vet J 306:106–96. doi: 10.1016/J.TVJL.2024.106196.

Course of Disease

- The treatment was well tolerated;
- No clinical signs of discomfort;
- Lively, alert, normal appetite.

→ Period 12/2022 to 07/2023 no visible lumps identified; no additional CT scans.

→ 331 days after 1st treatment the dog was covered with numerous cherry-sized lumps at poor health .

→ Suspected HS confirmed by cytology (Figures 1 + 2).

→ Euthanasia justified by multiple HS lumps and very poor health.

Discussion & Conclusion

- In the French Bulldog, localised HS was diagnosed at the sternum position based on characteristic cytology[3].
- Generally, localised HS presumes median survival time (MST) of 17–39 days (palliative treatment) and MST of 200–568 days (chemotherapy), respectively[10-12].
- Use of immunotherapy based on autologous DCs complementary to ZA extended ST to 331 days (upon therapy) and 387 days (upon diagnosis).
- The immunomodulating activities of DCs would appear to be supported by the anti-tumor effect of ZA (inhibition of osteoclasts, anti-angiogenesis, cell-to-cell interactions of tumor cells, T-cell activation, apoptosis)[13-18]. ZA is preferably used in pain management for osteosarcoma, idiopathic and tumor-induced hypercalcemia, bone metastases[19-21], well tolerable, no clinical signs of kidney disease[22], and reported to develop azotemia in 4.5%[21] and 6.3%[23] of treated dogs.
- A disseminated course of localised HS could not be ruled out with certainty due to the inconclusive CT findings: 1.) enlarged thoracic lymph nodes, of which the cytology could not be clarified, and 2.) the conspicuous dense mass in the thorax with cytology findings that indicated an inflammatory rather than a neoplastic process. However, ST under therapy, which was extended (331 days) rather than drastically shortened (78–185 days)[10, 24] contradicted the assumption that spread could have occurred.

➢ To conclude: For the French Bulldog, combined treatment with DCs and ZA resulted in similar ST observed in dogs upon chemotherapy. The experimental treatment was very well tolerated and improved quality of life and survival. Evidence-based studies are needed to further evaluate this innovative cancer treatment option.

[10]Dervisis NG, Kiupel M, Qin Q, Cesario L (2016). Vet Comp Oncol 15(4):1–10. doi: 10.1111/vco.12252. [11]Skorupski KA, Rodriguez CO, Krick EL, Clifford CA, Ward R, Kent MS (2009). Vet Comp Oncol 7(2):139–44. doi: 10.1111/j.1476-5829.2009.00186.x. [12]Fidel J, Schiller I, Hauser B, Jausi Y, Rohrer-Bley C, Roos M, Kaser-Hotz B (2006). Vet Comp Oncol 4(2):63–74. doi: 10.1111/J.1476-5810.2006.00090.X. [13]Clézardin P (2005). Cancer Treat Rev 31:1–8. [14]Ory B, Heymann MF, Kamijo A, Gouin FO, Heymann D, Redini FO (2005). Cancer 104(11):2522–29. doi: 10.1002/cncr.21530. [15]Caraglia M, Santini D, Marra M, Vincenzi B, Tonini B, Budillon A (2006). Endocr Relat Cancer 13:7–26. [16]Clézardin P, Ebetino FH, Fournier PGJ (2005). Am Assoc Cancer Res 65:4971–75. [17]Denoyelle C, Hong L, Vannier JP, Soria J, Soria C (2003). Br J Cancer 88:1631–40. [18]Gnant M and Clézardin P (2012). Cancer Treat Rev 38:407–15. [19]Spugnini EP, Vincenzi B, Carusoy G, Baldiy A,Citro G, Santini D, Tonini G (2009). J Small Anim Pract 50(1):44–46. doi: 10.1111/j.1748-5827.2008.00635.x. [20]Schenk A, [21] C, Lane J, Martin O (2018). J Am Anim Hosp Assoc 54(6). doi: 10.5326/JAAHA-MS-6681. 21Vidal SA, Skorupski KA, Wilcox JL, Palm CA, Burton JH (2021). Front vet sci 8:647846. doi: 10.3389/FVETS.2021.647846. 22Lopes MG, Tosi G, McNaught KA, Morris JS (2023). Aust Vet J 101(1–2):58–64. doi: 10.1111/avj.13218. 23Brewer DJ, Macfarlane M, O'Connell E, Bacon NJ (2021). J Vet Intern Med 36(1):253–58. doi: 10.1111/jvim.16335. [24]Cannon C., Borgatti A, Henson M, Husbands B (2015). J Small Anim Pract 56(7):425–29. doi: 10.1111/JSAP.12354.