TRATAMENTO DE LINFOMA MULTICÊNTRICO DE CÉLULAS GRANDES B EM ESTADIO V COM PREDNISOLONA, CICLOFOSFAMIDA E LOMUSTINA NUM PORQUINHO-DA-ÍNDIA (*CAVIA PORCELLUS*): RELATO DE CASO E REVISÃO DE ESCOPO DA LITERATURA

PREDNISOLONE, CYCLOPHOSPHAMIDE AND LOMUSTINE TREATMENT OF STAGE V MULTICENTRIC DIFFUSE LARGE B-CELL LYMPHOMA IN A GUINEA PIG (*CAVIA PORCELLUS*): CASE REPORT AND SCOPING-REVIEW OF THE LITERATURE

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Resumo: *O linfoma é uma neoplasia hematopoiética comum em porquinhos-da-índia (Cavia porcellus), contudo o seu comportamento biológico, classificação e tratamento permanecem pouco caracterizados. O presente relato descreve a apresentação clínica, caracterização diagnóstica e resposta ao tratamento de um porquinho-da-índia macho, com 5 anos de idade, com linfoma difuso de células grandes B em estádio clínico V, tratado com um protocolo de quimioterapia combinada de prednisolona (1 mg/kg, PO, SID), ciclofosfamida (2,5 mL/kg, SC, a cada 2 semanas) e lomustina (4 mg/kg, PO, a cada 2 semanas). Foi observada remissão clínica temporária, evidenciada pela redução progressiva do tamanho dos linfonodos, e normalização no hemograma das contagens de linfócitos circulantes, correspondendo a uma sobrevida livre de progressão de 62 dias e a uma sobrevida global de 77 dias desde o momento da apresentação clínica. Este relato documenta o controlo temporário de linfoma difuso de células grandes B em estádio V com quimioterapia combinada num porquinho-da-índia e destaca a necessidade de estabelecer critérios padronizados de resposta ao tratamento para o linfoma nesta espécie.*

Palavras-chave*: Porquinho-da-Índia, linfoma difuso de células grandes B, prednisolona, ciclofosfamida, lomustina*

Abstract: *Lymphoma is a common hematopoietic neoplasm in guinea pigs (Cavia porcellus), yet its biological behavior, classification, and treatment remain poorly characterized. The present report describes the clinical presentation, diagnostic characterization, and treatment response of a 5-year-old male guinea pig with clinical stage V, diffuse large B-cell lymphoma treated with a combination chemotherapy protocol of prednisolone (1 mg/kg, PO, daily), cyclophosphamide (2.5 mL/kg, SC, every 2 weeks) and lomustine (4 mg/kg, PO, every 2 weeks). Temporary clinical remission was observed by progressive reduction of lymph node size and normalization of hematologic abnormalities,*

corresponding to a progression-free survival of 62 days, and overall survival of 77 days from the time of clinical presentation. This report documents temporary disease control with combination chemotherapy in a guinea pig with stage V B-cell lymphoma and highlights the need to establish standardized response criteria for lymphoma in this species.

***Keywords**: Guinea pig, diffuse large B-cell lymphoma, prednisolone, cyclophosphamide, lomustine*

CASE REPORT

A 5-year-old 1.06 kg male guinea pig (Cavia porcellus) was presented to the Teaching Hospital— Faculty of Veterinary Medicine of Lusófona University, for evaluation of three firm, non-adherent nodules detected in the left cervical region (Day 1). The guinea pig had no relevant history of disease and physical examination was unremarkable.

Total body radiographs, complete blood count, serum biochemistry, total thyroxine (TT4) and fine needle aspirates (FNAs) from the lesions were taken with the animal under anesthesia induced with Midazolam, Butorphanol and Isoflurane (Table 1, day 6).

The complete blood count (CBC) (Procyte DX, IDEXX Laboratories, West-brook, ME, USA) revealed leukocytosis (WBC, 70.76 × 10^3/µL; reference interval [RI] 5.00 – 18.00 × 10^3/µL) with severe lymphocytosis (lymphocytes, 53.06 × 10^3/µL; RI 1.10 – 12.90 × 10^3/µL), moderate monocytosis (monocytes, 2.83 × 10^3/µL; RI 0.10 – 1.80 × 10^3/µL) and mild heterophilia (heterophils, 9.90 × 10^3/µL; RI 1.10 – 8.60 × 10^3/µL) and eosinophilia (eosinophils, 0.49 × 103/µL; RI 0.10 – 1.30 × 10^3/µL)(Table 1). The blood smear, stained with a rapid aqueous based Romanowsky stain (Hemacolor®, Merck KGaA, Darmstadt, Germany) revealed large numbers of intermediate/large lymphoid cells with variable cytoplasmic basophilia, pleomorphic nuclei, sometimes indented, with less condensed chromatin and small lymphocytes with moderate amount of cytoplasm, occasionally with granules and Kurloff bodies; and 4% of blast cells (blast cells, 2.83 × 10^3/µL), with a single prominent nucleolus (Figure 1, A). Serum chemistry abnormalities included mild decrease in creatinine (0.4 mg/dL; RI 0.6 – 2.2 mg/dL), alkaline phosphatase (ALP, 54 U/L; RI 68 – 71 U/L), alanine aminotransferase (ALT, <10 U/L; RI 31 – 51 U/L), hypoproteinemia (3.7 g/dL; RI 4.4 – 6.6 g/dL) with hypoalbuminemia (1.5 g/dL; 2.1 – 3.9 g/dL) and mild decrease in total thyroxine (T4, 1 µg/dL; RI 1.54 – 6.22 µg/dL) (Table 2; day 6). Total body radiographs showed no abnormalities.

Samples of fine needle aspirate (FNA) cytology from the cervical nodules revealed a mixed population of lymphoid cells with predominance of intermediate and large lymphoid cells (>50%) and low numbers of small lymphocytes, rare non-degenerated heterophils and rare macrophages, suggesting a cytological diagnosis of lymphoma (Figure 1, B). Hence there were high numbers of morphologically identical circulating lymphoid cells, the findings were consistent with clinical stage V lymphoma, according to the World Health Organization's clinical staging system for lymphoma in domestic animals.

A mandibular lymph node was surgically excised and submitted for histopathologic and immunohistochemical evaluation. On histopathology, there was a densely cellular proliferation of large lymphocytes organized in sheets, diffusely distributed in the lymph node and disrupting normal corticomedullary architecture, with sinuses compression and perinodal tissue invasion. Fourteen mitotic figures were observed in 2.37 mm2 (Figure 2). For immunohistochemical characterization, a panel of CD3 (rabbit polyclonal, Cell Marque, 1:300 dilution), CD20 (rabbit polyclonal, Invitrogen, Thermo Fisher, 1:300 dilution) and PAX5 (mouse monoclonal, Cell Marque, 1:400 dilution) was applied. Neoplastic cells demonstrated strong nuclear staining for PAX5, strong membranous staining for CD20, and there were only rare CD3-positive cells, interpreted as resident T-cells (Figure 3). The findings were consistent with a B-cell phenotype.

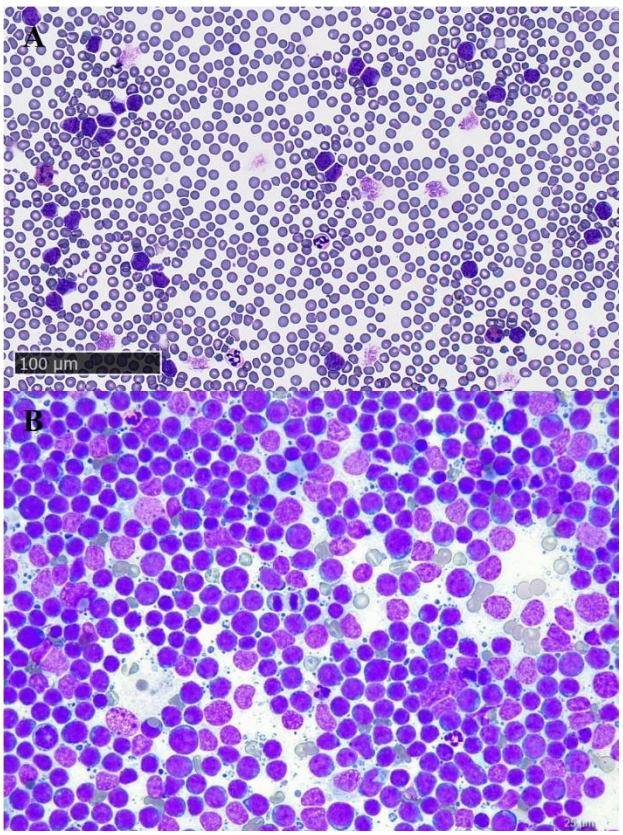

Figure 1 - (A) Peripheral blood smear, guinea pig. Rapid Aqueous Romanowsky stain. Numerous intermediate to large lymphoid cells with small to moderate amounts of basophilic cytoplasm, pleomorphic nuclei with occasional indentation and dispersed fine granular chromatin. Few heterophils are also present x400 magnification. (B) Lymph node, guinea pig. Rapid Aqueous Romanowsky stain. A monomorphic cell population of intermediate to large lymphoid cells, morphologically identical to circulating lymphoid cells is seen. Occasionally, multiple small inconspicuous nucleoli are identified. Heterophils are also present, and a telophase mitotic figure is seen in the center. x400 magnification.

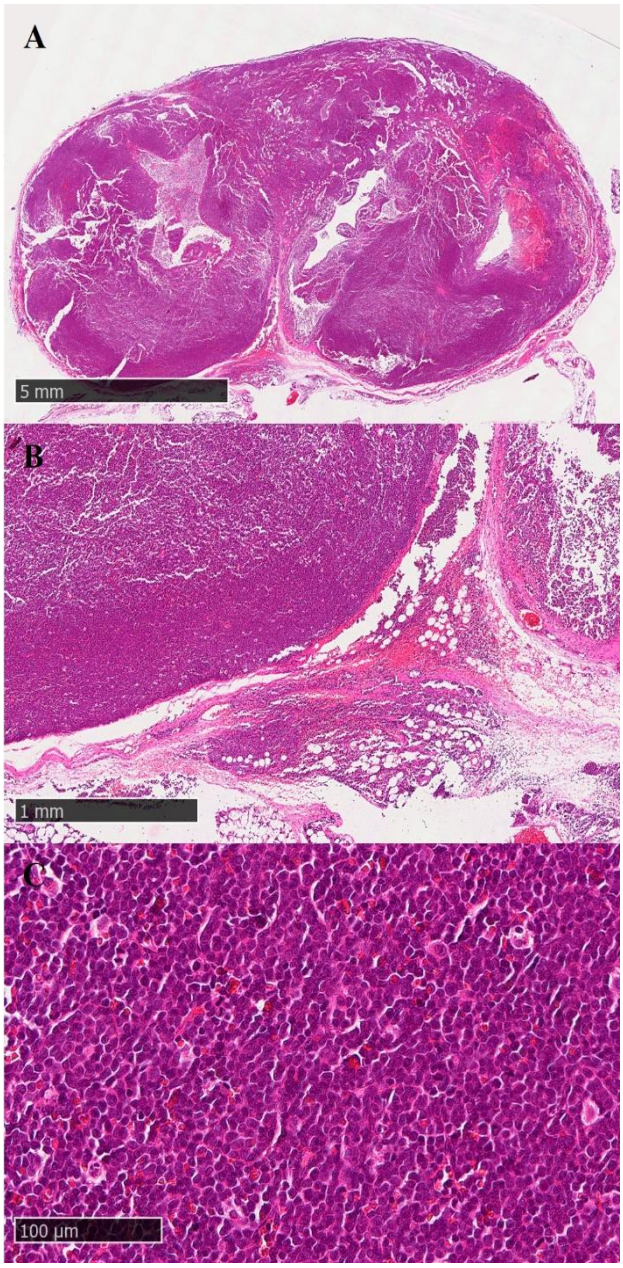

Figure 2 - Lymph node histopathology, Hematoxylin and eosin HE. (A) Diffuse effacement of cortex and medulla by sheets and cords of lymphoid cells on a fine fibrovascular stroma, with subcapsular and medullary sinuses compression, and locally extensive foci of hemorrhage. 1x objective. (B) Neoplastic cells expanding the lymph node capsule and invading the perinodal adipose tissue at the hilar region. 5x objective (C) Neoplastic intermediate to large lymphoid cells have distinct cell borders, small amounts of eosinophilic cytoplasm and round to idented 10-15 µm in diameter nucleus with 1-3 small variably visible nucleoli. 40x objective.

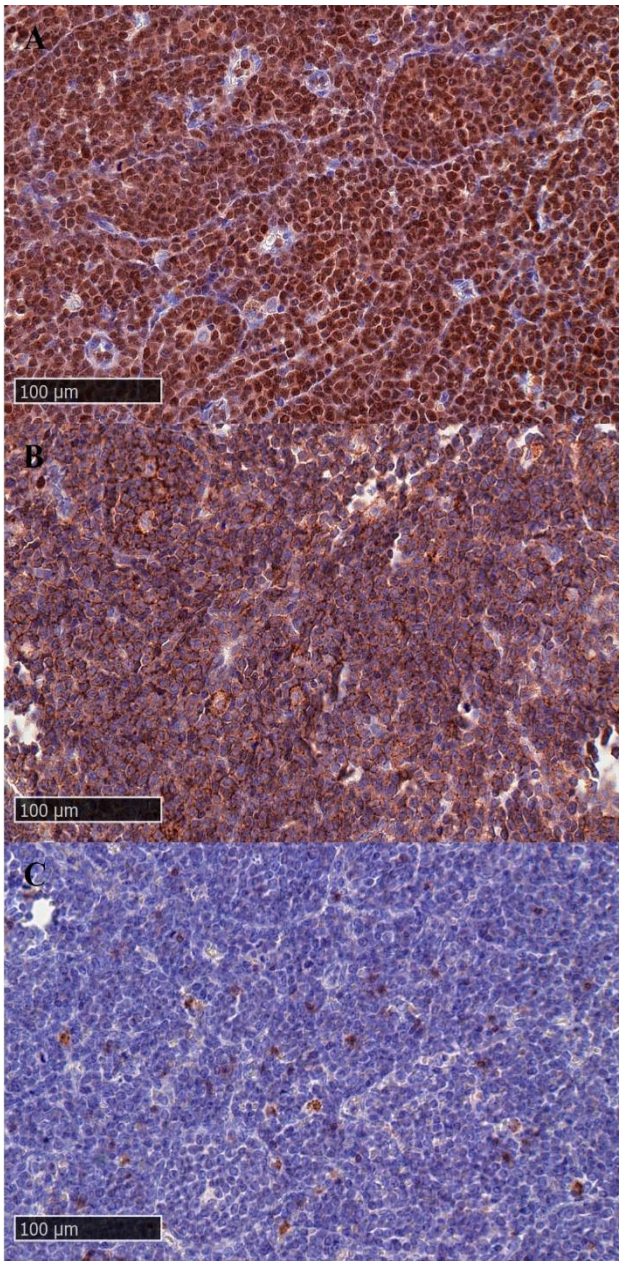

Figure 3 - Lymph node immunohistochemical staining of a diffuse large cell lymphoma. 40x objective. (A) Immunohistochemical staining for PAX5 shows diffuse strong nuclear positivity in the neoplastic cells. (B) CD20 immunostaining demonstrates diffuse membranous staining in the neoplastic cells. (C) CD3 reveals rare membranous and cytoplasmic positivity in the lymph node parenchymal cell population.

Treatment with prednisolone (1 mg/kg, PO, SID; Table 4, Day 15) was initiated. Two weeks later, most of the lymph nodes increased in size and the animal lost weight but maintained appetite (Table 3, Day 28). On CBC the lymphocytosis worsened (Table 1, Day 28) and the blood smear showed large numbers of intermediate/large lymphoid cells morphologically identical to the ones seen in the previous microscopic examination. Prednisolone was maintained and cyclophosphamide (2.5 mL/kg/2 weeks, SC) was added. After two weeks, on day 42, the lymph nodes started to reduce in size (Table 3) and on day 49 the CBC results showed significant improvement with decreased leukocytosis and lymphocytosis (Table 1, Day 49), polychromasia (3-8 polychromatophils/hpf) and mild thrombocytopenia. Mild platelet clumping was also detected on the blood smear. Lomustine treatment (4 mg/kg/2 weeks, PO) was initiated. Timeline of treatment events is presented in Table 4.

One week later, there was a slight weight loss, and the lymph nodes had significantly reduced in size (Table 3, Day 56). The CBC showed no abnormalities and on blood smear examination, intermediate sized lymphoid cells were only occasionally present.

Although in the following weeks mild weight loss ensued, on follow-up examination all the lymph nodes were no longer detectable (Table 3, Day 70), the CBC remained unremarkable, and blood smear results were consistent with the previous findings (Table 1; days 56 and 70). Serum chemistry revealed elevated values of urea (74 mg/dL; RI 9 – 62 mg/dL), creatinine (2.8 mg/dL; RI 0.6 – 2.2 mg/dL), and amylase (2557 U/L; RI 1339 – 1572 U/L), and decreased values of ALP (42 U/L; RI 68 – 71 U/L), ALT (17 U/L; RI 31 – 51 U/L), total bilirubin (0.2 mg/dL; RI 0.3 – 0.9 mg/dL) and inorganic phosphorus (1.7 mg/dL; RI 3.2 – 21.6 mg/dL) (Table 2; day 77).

Despite lymphocyte counts and lymph node size improvements, deterioration of the patient clinical condition due to anorexia and weight loss was observed and the owners elected human euthanasia. Necropsy and histopathology evaluations were rejected.

DISCUSSION

Lymphoma is a poorly characterized neoplastic disease in guinea pigs, with limited published studies of epidemiology, etiology, pathology and clinical features. It has been suggested that there is a lower incidence compared to other animal species due to the serum presence of an enzyme with L-asparaginase activity leading to neoplastic cell starvation (Schalk et al., 2014), however, in a recent study of prevalence of different tumor types by organ system as encountered by autopsy examination in a cohort of 2,474 animals, lymphoma was found to be the most common neoplasm in this species, with a mean age of affected animals of 50.8 months, and no apparent sex predilection (Bertram et al., 2025). In this study, systemic dissemination to multiple organs was found in 83.9% of the cases, suggesting biologically aggressive disease course. In fact, in the few case reports encountered in the literature, manifestation in the blood and/or other organ systems is a consistent finding across case descriptions, and this was also the case in the present report (Allgoewer et al., 1999; Cooper et al., 2025; Koebrich et al., 2011; Martorell et al., 2011; Nagata et al., 2019; Steinberg, 2000; Wing et al., 2025; Table 6). A type-C retroviral infection has been associated with leukemia in laboratory guinea pigs, however, infection status and its role in tumorigenesis has not been investigated in pet animals (Kashuba et al., 2005).

Previous reports of lymphoma in guinea pigs report clinical biochemistry panels within reference intervals (Nagata et al., 2019) or included alterations such as hypoglycemia (Cooper et al., 2025), hyperalbuminemia, elevated alkaline phosphatase (ALP), or hypernatremia (Wing et al., 2025). In the remaining consulted case reports clinical biochemistry results were not available due to either absence of reporting or rejection of investigation by the owners (Allgoewer et al., 1999; Bassan et al., 2022; Koebrich et al., 2011; Martorell et al., 2011; Steinberg, 2000). In the present case, the initial biochemical evaluation revealed decreased creatinine, ALP, and ALT activity, together with hypoproteinemia characterized by hypoalbuminemia, and a mild decrease in T4 concentration. Although decreased liver enzyme activities, total protein, and albumin could suggest reduced functional hepatic mass, globulin concentrations remained within the reference interval (2.2 g/dL; RI 1.7–2.6), and both albumin and total protein values normalized in subsequent evaluations, making clinically significant hepatic insufficiency unlikely. Hyperthyroidism has been reported more frequently than hypothyroidism in guinea

pigs; therefore, although a complete thyroid diagnostic investigation was not performed, the absence of compatible clinical signs or additional biochemical abnormalities suggests that the mild reduction in total T4 most likely reflected non-thyroidal illness syndrome. In the later course of the disease, azotemia was detected, with increased urea and creatinine, which could be explained by renal infiltration by lymphoma with subsequent loss of functional parenchyma and reduced glomerular filtration rate. Concurrently, increased serum amylase activity was observed. Although the pathophysiology underlying alterations in plasma amylase concentrations in guinea pigs remains poorly understood, a recent study reported that guinea pigs with markedly increased amylase concentrations were approximately seven times more likely to die within 30 days than animals with values within the reference interval (Souza et al., 2025). Overall, the biochemical abnormalities observed in this case were considered most likely attributable to analytical variables or systemic effects of neoplastic disease rather than to a concurrent primary metabolic disorder.

Of eight case reports encountered in the literature, lymphoma subtype characterization according to the REAL system was found in five cases and complete clinical staging according to the WHO system in five cases as well (Table 6). Cases where lymphoma subtype characterization and clinical staging were incomplete were due to unreported cell size or undetermined immunophenotype, and lack of blood smear evaluation, respectively.

Five reports described neoplastic lymphoid cells as being of intermediate size, determined by comparison with red blood cells (RBCs), a commonly used method for estimating lymphoid cell size in other species. In those reports, intermediate cells were described as approximately 1.5–2 times the diameter of a RBC. However, in guinea pigs, intermediate lymphocytes are approximately 1.5 times and large lymphocytes approximately 2 times the size of a RBC (Evans & Zimmerman, 2022), making this distinction potentially subtle for human observers. When available, digital pathology tools may facilitate more objective morphometric assessment.

Despite clinical staging descriptions were not always complete with CBC, blood smear, lymph node and bone marrow investigations, in the consulted case reports animals typically present with multiple lymph node involvement and severe lymphocytosis (Table 6). These were considered to be stage V lymphomas

(lymphomas with secondary leukemia) rather than leukemias infiltrating peripheral lymph nodes and extranodal tissue based on the clinical presentation and clinical course. Nonetheless, this distinction is categorical, and both are aggressive tumors with poor prognosis in other animal species (Valli et al., 2017). In our case at initial presentation there were no clinical signs besides regional lymphadenomegaly, however, on day 6 when the first CBC was performed, the animal already had severe lymphocytosis suggesting dissemination/stage V lymphoma. Weather the disease was already at this stage in the first appointment remains unknown, but the rapid progression suggests that clinicians attending guinea pigs with peripheral lymphadenomegaly should aim to initiate diagnostic investigations early.

Evans et al., (2018) have validated a method for immunophenotyping of lymphoma in guinea pigs by means of immunocytochemistry, using anti-CD3 and anti-PAX5 antibodies and this technique can be used in future diagnostic practice allowing immunophenotypic characterization in cases where owners reject surgery or necropsy and only cytological material is available, which ultimately might result in more available data for further epidemiologic, diagnostic, and prognostic studies of lymphoma in guinea pigs. In the consulted reports, phenotyped cases included two epitheliotropic T-cell lymphomas, three diffuse intermediate B-cell lymphomas, and one diffuse large T-cell lymphoma. In our case, the histologic growth pattern was diffuse, the immunophenotype consistent with B-cell origin, and the authors considered neoplastic cells to be of large cell size. In other species, differential diagnosis for lymphomas with these morphomolecular features include Burkitt's type lymphoma, Diffuse Large B-cell Lymphoma (DLBCL), B-cell Acute Lymphoblastic Leukemia (B-ALL), and B-cell Lymphoblastic Lymphoma (B-LBL). The distinction of these disease entities is not straighforward and are based on cytomorphology and clinical features, and is beyond the scope of the present review but can be found elsewhere (Valli et al., 2017). Nonetheless, there are no studies assessing applicability of the REAL system in this species and one should be careful in comparing morphomolecular equivalent disease entities until this classification proves itself useful in guinea pigs.

Treatment descriptions and outcome documentation are limited. A case report of total body irradiation in a 5-year-old male guinea pig with stage V multicentric nodal diffuse intermediate cell lymphoma of undetermined immunophenotype (Nagata

et al., 2019). In this case, after radiation treatment with 1 Gy, lymph node size subjectively diminished and lymphocyte counts decreased to values within reference interval for 49 days (progression free survival), after which lymph node burden increased. A second course of 1.2 Gy total body irradiation was performed but 1 month later (78 days post clinical presentation, overall survival) the patient presented with signs of disease dissemination and was humanely euthanized. Compared to our case, progression free survival was slightly lower, and overall survival nearly identical.

Previous chemotherapy treatment of lymphoma in guinea pigs case reports have not been published, but personal communications indicating 2-3 months survival time with combination therapy of lomustine (12-15 mg/kg PO every 21 days) and prednisolone (1-2 mg/kg PO every 24 hours) can be found (Pignon & Mayer, 2021), which is approximately equivalent to the outcomes reported in our case. Also, Bassan et al., (2022) described in a conference proceedings the use of cyclophosphamide (25 mg/kg/5 weeks), lomustine (5 mg/kg/2 weeks) and methylprednisolone (2 mg/kg/48 hours) combination chemotherapy protocol in a 5-year-old intact male guinea pig presented with stage V intermediate to large cell lymphoma (non-immunophenotyped), reporting 4 months (approximately 122 days) progression free survival and 5 months (approximately 152 days) overall survival, which are considerable longer intervals than in the present case and to what is found in available case reports in the literature.

Palliative treatment was undertaken with prednisolone 2mg/kg, PO, daily in a 4-year-old male guinea pig with stage V multicentric diffuse intermediate B-cell lymphoma but unfortunately the patient died 7 days later (Cooper et al., 2025). In our case, the patient was in prednisolone 1 mg/kg, PO, daily before introducing cyclophosphamide, and during this period the lymph nodes enlarged, and lymphocyte counts increased (Tables 1, 3). A summary of response to treatment in the above mentioned cases can be found in Table 5.

General disease response assessment (e.g. complete response, partial response, stable disease) is not possible because definitions of target and non-target lesions, and mean sum of longest diameter of target lesions have not been established for this species as for others (Vail et al., 2010). However, with the used protocol it was possible to decrease size of lymph nodes into non-palpable lesion size.

Cyclophosphamide is commonly used in multiagent protocols for canine and feline

lymphomas, and lomustine in single or multiagent protocols for canine lymphoma (Gustafson & Bailey, 2020). Toxicities associated with these chemotherapeutic agents include neutropenia, gastrointestinal toxicity and sterile hemorrhagic cystitis for cyclophosphamide (Cox, 1979; Fetting et al., 1982) and myelosuppression with neutropenia and thrombocytopenia, and hepatic dysfunction for lomustine (Heading et al., 2011; Hosoya et al., 2009; Musser et al., 2012). In our case, heterophils remained within reference interval throughout clinical course. Transient thrombocytopenia was observed in days 42, 49 and 56, but these started in the day of the first lomustine administration and normalized and therefore were considered of pre-analytical causes, as platelet aggregation was also detected in the blood smear. Signs of gastrointestinal toxicity were not observed as the patient maintained appetite until the later course of disease and there were no reported vomiting episodes by the owners. As signs of toxicity were inapparent and clinical pathology analytical values were normal, the authors hypothesized that deterioration of the clinical condition was due to disease dissemination and organ failure. Unfortunately, confirmation was not possible due to rejection of autopsy examination by the tutors.

Conclusions in our case are limited by lack of bone marrow assessment which would help differentiating true leukemia from stage V lymphoid neoplasia, and by absence of necropsy procedures to assess disease extension by the time of death. Case reports describing lymphoid neoplasia in this species indicate biological behavior of these diseases is rapid and therefore patients presented with lymphadenomegaly and/or dermatologic disease should initiate diagnostic investigation, clinical staging and treatment as early as possible to prevent disease progression. Chemotherapy with prednisolone, cyclophosphamide and lomustine or total body irradiation might be effective for temporary remission. Veterinary oncologists and small mammal medicine practitioners should define criteria for disease response to treatment in this species. Future case reports and studies of guinea pig (and other small mammals) lymphoid neoplasia should use the REAL classification system for lymphoma subtyping and the WHO clinical staging system in order to assess whether these classification systems are applicable to guinea pigs, and ultimately striving for disease characterization and assessment of the value of guinea pig lymphoid tumors as animal models for the disease counterparts in other species.

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REFERENCES

Allgoewer, I., Ewringmann, A., & Pfleghaar, S. (1999). Lymphosarcoma with conjunctival manifestation in a guinea pig. Veterinary Ophtamology, (2), 117–119.

Bassan, T., Jornet, O., Solanes, F., & Martorell, J. (2022). Cyclophosphamide, Lomustine And Corticosteroids as a Treatment of Lymphoma in a Guinea Pig (Cavia Porcellus). The International Congress on Avian, Herpetological and Exotic Mammal Medicine.

Bertram, C. A., Donovan, T. A., Bertram, B., Sabara, J., & Klopfleisch, R. (2025). Neoplasia in pet guinea pigs: a retrospective analysis of 2,474 autopsy examinations. Journal of Veterinary Diagnostic Investigation, 37(1), 94–103. https://doi.org/10.1177/10406387241288642

Cooper, A. J., Clarke, L., & Mans, C. (2025). Multicentric B-cell lymphoma with otic involvement in 2 guinea pigs. Journal of Exotic Pet Medicine, 52, 53–57. https://doi.org/10.1053/j.jepm.2025.01.002

Cox, P. J. (1979). Cyclophosphamide cystitis—Identification of acrolein as the causative agent. Biochemical Pharmacology, 28(13), 2045–2049. https://doi.org/10.1016/0006-2952(79)90222-3

Evans, S. J. M., Harr, K. E., Thielen, L., & MacNeill, A. L. (2018). Validation of an immunocytochemical assay for immunophenotyping of lymphoma in guinea pigs (Cavia porcellus). Veterinary Clinical Pathology, 47(4), 682–687. https://doi.org/10.1111/vcp.12668

Evans, S. J. M., & Zimmerman, K. L. (2022). Hematology of Cavies. In M. B. Brooks, K. E. Harr, D. M. Seelig, K. J. Wardrop, & D. J. Weiss (Eds.), Schalm's Veterinary Hematology (Seventh, pp. 1043–1049). John Wiley & Sons, Inc.

Fetting, J. H., McCarthy, L. E., Borison, H. L., & Colvin, M. (1982). Vomiting induced by cyclophosphamide and phosphoramide mustard in cats. Cancer Treatment Reports, 66(8), 1625–1629.

Fredholm, D. V., Cagle, L. A., & Johnston, M. S. (2012). Evaluation of Precision and Establishment of Reference Ranges for Plasma Thyroxine using a Point-of-Care Analyzer in Healthy Guinea Pigs (Cavia porcellus). Journal of Exotic Pet Medicine, 21(1), 87–93. https://doi.org/10.1053/j.jepm.2011.11.004

Frohlich, J., & Mayer, J. (2023). Rodents. In J. W. Carpenter & C. A. Harms (Eds.), Carpenter's Exotic Animal Formulary (Sixth, pp. 805–806). Elsevier.

Gustafson, D. L., & Bailey, D. (2020). Cancer Chemotherapy. In D. M. Vail, D. H. Thamm, & J. M. Liptak (Eds.), Withrow & MacEwen's Small Animal Clinical Oncology (Sixth, pp. 182–208). Elsevier, Inc.

Heading, K., Brockley, L., & Bennett, P. (2011). CCNU (lomustine) toxicity in dogs: a retrospective study (2002-07). Australian Veterinary Journal, 89(4), 109–116. https://doi.org/10.1111/j.1751-0813.2011.00690.x

Hosoya, K., Lord, L. K., Lara-Garcia, A., Kisseberth, W. C., London, C. A., & Couto, C. G. (2009). Prevalence of elevated alanine transaminase activity in dogs treated with CCNU (Lomustine)*. Veterinary and Comparative Oncology, 7(4), 244–255. https://doi.org/10.1111/j.1476-5829.2009.00197.x

Kashuba, C., Hsu, C., Krogstad, A., & Franklin, C. (2005). Small mammal virology. Veterinary Clinics of North America: Exotic Animal Practice, 8(1), 107–122. https://doi.org/10.1016/j.cvex.2004.09.004

Koebrich, S., Grest, P., Favrot, C., & Wilhelm, S. (2011). Epitheliotropic T-cell lymphoma in a guinea pig. Veterinary Dermatology, 22(2), 215–219. https://doi.org/10.1111/j.1365-3164.2010.00920.x

Martorell, J., Such, R., Fondevila, D., & Bardagi, M. (2011). Cutaneous Epitheliotropic T-cell Lymphoma with Systemic Spread in a Guinea Pig (Cavia porcellus). Journal of Exotic Pet Medicine, 20(4), 313–317. https://doi.org/10.1053/j.jepm.2011.07.007

Musser, M. L., Quinn, H. T., & Chretin, J. D. (2012). Low apparent risk of CCNU (lomustine)-associated clinical hepatotoxicity in cats. Journal of Feline Medicine and Surgery, 14(12), 871–875. https://doi.org/10.1177/1098612X12453836

Nagata, K., McHale, B., Sladakovic, I., Gutti, J. R., & Mayer, J. (2019). TOTAL BODY IRRADIATION FOR THE TREATMENT OF LYMPHOMA IN A GUINEA PIG (CAVIA PORCELLUS). Journal of Exotic Pet Medicine, 28, 132–136. https://doi.org/10.1053/j.jepm.2018.02.043

Pignon, C., & Mayer, J. (2021). Diseases of Guinea Pigs: Other Common Diseases. In K. E. Quesenberry, C. J. Orcutt, C. Mans, & J. W. Carpenter (Eds.), Ferrets, Rabbits, and Rodents: Clinical Medicine and Surgery (Fourth, pp. 294–295). Elsevier.

Schalk, A. M., Nguyen, H.-A., Rigouin, C., & Lavie, A. (2014). Identification and

Structural Analysis of an L-Asparaginase Enzyme from Guinea Pig with Putative Tumor Cell Killing Properties. Journal of Biological Chemistry, 289(48), 33175–33186. https://doi.org/10.1074/jbc.M114.609552

Souza, A. R., Ozawa, S. M., Sadar, M. J., Gleeson, M. D., James, R., Chen, S., & Di Girolamo, N. (2025). Clinical value of amylase and its prognostic accuracy in guinea pigs (Cavia porcellus). Journal of Small Animal Practice, 66(6), 382–388. https://doi.org/10.1111/jsap.13843

Steinberg, H. (2000). Disseminated T-cell lymphoma in a guinea pig with bilateral ocular involvement. Journal of Veterinary Diagnostic Investigation, (12), 459–462.

Vail, D. M., Michels, G. M., Khanna, C., Selting, K. A., & London, C. A. (2010). Response evaluation criteria for peripheral nodal lymphoma in dogs (v1.0)-a veterinary cooperative oncology group (VCOG) consensus document. Veterinary and Comparative Oncology, 8(1), 28–37. https://doi.org/10.1111/j.1476-5829.2009.00200.x

Valli, V. E., Bienzle, D., & Meuten, D. J. (2017). Tumors of the Hemolymphatic System. In D. J. Meuten (Ed.), Tumors in Domestic Animals (Fifth, pp. 203–321). John Wiley & Sons, Inc.

Wing, A., Wells, T., Witschen, P., Botts, M., Sharpley, J., & Sadar, M. J. (2025). Disseminated B-cell lymphoma of the urogenital tract in a guinea pig (Cavia porcellus). Topics in Companion Animal Medicine, 69, 101020. https://doi.org/10.1016/j.tcam.2025.101020

Tables

Table 1 – Serial hematological assessments of a 5-years old male guinea pig with stage V multicentric B-cell lymphoma

	Day								
	6	28	42	49	56	70	77		
	Prednisolone and Cyclophosphamide			Lomustine					
Test[a]								**RI**	**Units**
Leukocytes	**70,76**	**158,59**	**145,2**	**31,76**	8,33	12,85	6,29	5.00 - 18.00	10^9/L
Heterophils	**9,9**	2,38	**16,4**	4,13	2,38	3,97	1,6	1.10 - 8.60	10^9/L
Lymphocytes	**53,06**	**146,7**	**119,9**	**24,77**	4,55	6,99	3,06	1.10 - 12.90	10^9/L
Monocytes	**2,83**	**7,93**	**2,4**	0,64	1,08	0,76	1,41	0.10 - 1.80	10^9/L
Eosinophils	**2,12**	**1,58**	**3,6**	**1,59**	0,32	1,12	0,22	0.10 - 1.30	10^9/L
Basophils	0	0	0	0	0	0,01	0	0.00 - 0.50	10^9/L
Blast Cells	2,83	NA	2,9	NA	NA	NA	NA	NA	10^9/L
HCT	37,1	38,3	42.2	42,8	46,2	45	40	34.0 - 50.0	%
RBC	4,56	4,46	NA	5,03	5,54	5,48	5,04	3.20 - 8.00	10^{12}/L
HGB	11,7	11,6	NA	12,9	14,4	14	12,7	10.0 - 17.0	g/dL
MCV	81,4	85,9	NA	85,1	83,4	82,1	79,4	71.0 - 96.0	fL
MCH	**25,7**	26	NA	**25,6**	26	**25,5**	**25,2**	26.0 - 29.0	pg
MCHC	31,5	30,3	NA	30,1	31,2	31,1	31,8	28.0 - 38.0	g/dL
RDW	13,5	14,6	NA	14,3	13,4	12,8	13		%
Reticulocytes	**175,1**	**196,2**	NA	**249**	46	47,1	36,3	15.0 - 150.0	10^9/L
Reticulocytes %	3.84	4.34	NA	4.95	0.83	0.86	0.72		%
Platelets	287	202	**114**	**180**	**117**	563	226	200 - 750	10^9/L
PCT	0,26	0,19	NA	0,17	0,11	0,5	0,2		%
MPV	9,2	9,3	NA	9,6	9,7	8,8	8,7	6.0 - 12.0	fL

Note: Bolded results are outside the reference interval.
Abbreviations: HCT - hematocrit; HGB - hemoglobin; MCH – mean corpuscular hemoglobin; MCHC – mean corpuscular hemoglobin concentration; MCV – mean cell volume; MPV – mean platelet volume; NA – not applicable; PCT - plateletcrit; RBC – red blood cell; RDW - red cell distribution width
[a] Procyte DX, IDEXX Laboratories, West-brook, ME, USA

Table 2 - Serial serum biochemical assessments of a 5-years old male guinea pig with stage V multicentric B-cell lymphoma

	Day				
Test[a]	**6**	**70**	**77**	**RI[1]**	**Units**
Urea	10	NA	**74**	9 – 62	mg/dL
Creatinine	**0.4**	0.7	**2.8**	0.6 – 2.2	mg/dL
ALP	**54**	NA	**42**	68-71	U/L
ALT	**<10**	**21**	**17**	31 – 51	U/L
AST	NA	**23**	NA	32 – 51	U/L
Albumin	**1.5**	NA	3.1	2.1 – 3.9	g/dL
Total bilirubin	NA	NA	**0.2**	0.3 – 0.9	mg/dL
Globulines	2.2	NA	NA	1.7 – 2.6	g/dL
Total Protein	**3.7**	NA	NA	4.4 – 6.6	g/dL
Glucose	178	NA	175	89 – 287	mg/dL
Amylase	NA	NA	**2557**	1339 – 1573[2]	U/L
Total Calcium	NA	NA	10.8	9.0 – 11.3	mg/dL
Inorganic Phosphorus	NA	NA	**1.7**	3.2 – 21.6	mg/dL
Total T4[b]	**1**	NA	NA	1.54 – 6.22[3]	µg/dL

Note: Bolded results are outside the reference interval. Treatment with prednisolone and cyclophosphamide was initiated on Day 28 after initial presentation. Lomustine was initiated on Day 49 after initial presentation.

Abbreviations: ALP – Alkaline Phosphatase; ALT – Alanine transaminase; AST – Aspartate aminotransferase; NA – Not applicable

[a]SpotchemTM EZ SP- 4430, Arkray Factory, Shiga, Japan

[b]Catalyst One Chemistry Analyzer, IDEXX Laboratories, Westbrook, USA

[1] Reference intervals from Frohlich & Mayer, (2023) unless otherwise referenced

[2] Souza et al., (2025)

[3] Fredholm et al., (2012)

Table 3 – Serial lymph node measurements

	Day 15	Day 28	Day 42	Day 49	Day 56	Day 70
	Prednisolone					
		Cyclophosphamide				
Lymph node				Lomustine		
Left mandibular	10 mm	16x14 mm	12x10 mm	12x10 mm	11 mm	Non-palpable
Right mandibular	15 mm	11 mm	10 mm	10 mm	Non-palpable	Non-palpable
Left axilar	15x5 mm	25x10 mm	8 mm	8 mm	Non-palpable	Non-palpable
Right axilar	15x5 mm	25x10 mm	8 mm	8 mm	Non-palpable	Non-palpable
Left popliteal	Non-palpable	Non-palpable	Non-palpable	Non-palpable	Non-palpable	Non-palpable
Right popliteal	10 mm	11 mm	9 mm	9 mm	Non-palpable	Non-palpable
Both inguinal	Non-palpable	Palpable	Palpable	Palpable	Non-palpable	Non-palpable

Table 4 – Timeline of treatment events and recommendations

Day	Treatment
15	Prednisolone, 1 mg/kg, PO, daily
28	Cyclophosphamide, 2.5 mL/kg, SC, every 2 weeks Prednisolone, 1 mg/kg, PO, daily
42	Cyclophosphamide, 2.5 mL/kg, SC, every 2 weeks Prednisolone, 1 mg/kg, PO, daily
49	Lomustine, 4 mg/kg, PO, every 2 weeks Prednisolone, 1 mg/kg, PO, daily
56	Cyclophosphamide, 2.5 mL/kg, SC, every 3 weeks Prednisolone, 1 mg/kg, PO, daily
70	Lomustine, 4 mg/kg, PO, every 3 weeks Prednisolone, 1 mg/kg, PO, daily

Table 5 – outcome measurements in treated Guinea Pigs with diagnosis of lymphoma

Patient	Diagnosis	Clinical Stage	Treatment	Progression-free Survival (days)[a]	Overall Survival (days)[b]	Reference
Male, 5 years-old	Multicentric, Diffuse, Large B-cell	Stage V	Prednisolone, Cyclophosphamide, Lomustine	62	77	Present case
Male, 5 years-old	Multicentric, Diffuse, Intermediate cells	Stage V	Methylprednisolone, Cyclophosphamide, Lomustine	122	152	(Bassan et al., 2022)
Male, 5 years old	Multicentric, Diffuse, Intermediate cells	Stage V	Total body irradiation	49	78	(Nagata et al., 2019)

[a]measured from the day of treatment initiation until disease progression or death from any cause
[b]measured from the day of clinical presentation until death from any cause

Table 6 – Guinea Pig lymphoid tumors pathological and clinical features as described in available case reports in the literature

Patient	Anatomic location at diagnosis	Cell Size	Growth Pattern	Immunophenotype	Clinical Stage at diagnosis	Treatment	Overall Survival (days)[a]	Autopsy Findings	Reference
Male, 5 years-old	Nodal, multicentric	Large	Diffuse	$CD3^-$, $CD20^+$, $PAX5^+$	Stage V	Prednisolone, Cyclophosphamide, Lomustine	77	Not performed	Present case
Male, 5-years-old	Nodal, multicentric[†]	Intermediate	Diffuse	Undetermined	Stage V	Total body irradiation	78	Disseminated	Nagata et al., 2019
Male, 2.3-years-old	Nodal, multicentric; Ocular, bilateral involvement	Unspecific[‡]	Not mentioned	Undetermined	Stage V	NA	Not mentioned	Multicentric	Allgoewer et al., 1999
Female, 2-years-old	Nodal, multicentric; Ocular, right-side involvement	Large	Diffuse	$CD3^+$, $CD45RO^-$, $CD20cy^-$	Stage IV or V[§]	NA	Not mentioned	Disseminated	Steinberg, 2000
Female, 5-years-old	Skin	Not mentioned	Diffuse	$CD3^+$	Presumed Stage V[¶]	NA	2	Disseminated	Martorell et al., 2011
Female, 4-years-old	Skin	Intermediate	Diffuse	$CD3^+$, $CD79a^-$	Undetermined[¥]	NA	77	Not performed	Koebrich et al., 2011
Male, 4-years-old	Nodal, multicentric; Otic bilateral involvement	Intermediate	Diffuse	$CD3^-$, $CD79a^+$	Stage V	Prednisolone	7[b]	Disseminated	Cooper et al., 2025
Female, 3.5-years-old	Nodal, multicentric; Otic bilateral involvement	Intermediate	Diffuse	$CD3^-$, $CD79a^+$	Stage V	NA	0	Disseminated	
Female, 4-years-old	Nodal, multicentric; Urogenital involvement	Intermediate	Diffuse	$CD3^-$, $PAX5^+$	Stage V	NA	43	Disseminated	Wing et al., 2025)

Note: cases where only abstracts were available were not considered due to incomplete assessment of information
[a]measured from day of clinical presentation until death from any cause, unless otherwise specified
[b]survival post-treatment initiation, information regarding survival from day of clinical presentation was not available
[†]Bilateral chemosis is mentioned but histopathological evaluation was not performed and ocular involvement was therefore not confirmed
[‡]Throughout the text, "small sized round to oval lymphoid cells" as well as "lymphoblastic cells" are mentioned, terms that are used to describe small and intermediate lymphoid cells, respectively
[§]Complete blood count and blood smear were not performed to assess manifestation in the blood
[¶]Complete blood count was performed revealing severe lymphocytosis but blood smear to assess whether these were circulating neoplastic cells is not mentioned

[¥]Lymphoid neoplasia was diagnosed by histopathology of skin biopsies without previous CBC, blood smear of lymph node cytology investigations, however, the authors mention inguinal and popliteal lymphadenomegaly previously to biopsing the skin, suggesting at least stage II
Abbreviations: NA – Not applicable