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PROCARBAZINE, PREDNISOLONE, AND CYCLOPHOSPHAMIDE (PPC) ORAL RESCUE PROTOCOL FOR RELAPSED MULTICENTRIC LYMPHOMA IN A GERMAN SHEPHERD

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ABSTRACT
Relapsed lymphoma in dogs following initial chemotherapy presents a significant therapeutic challenge. This case report highlights the successful management of relapsed multicentric lymphoma in a 6-year-old intact female German Shepherd with Procarbazine, Prednisolone, and Cyclophosphamide (PPC) oral rescue protocol. The dog had previously completed the Wisconsin-Madison CHOP-19 protocol and achieved remission for three months before presenting with progressive generalized lymphadenopathy. Diagnosis was confirmed through fine needle aspiration cytology, ultrasonography, and radiography. Treatment with the PPC protocol resulted in a 75% remission by the fourth week, with significant improvement in clinical signs and biochemical parameters. This case demonstrates continuous oral combination chemotherapy that can provide effective rescue therapy for relapsed canine lymphoma with minimal side effects, supporting findings from recent studies evaluating this protocol

KEYWORDS: Cyclophosphamide, Procarbazine, Prednisolone, Wisconsin-Madison CHOP-19, Relapsed lymphoma, Rescue protocol, PPC

INTRODUCTION
Canine lymphoma is one of the most common malignancies diagnosed in dogs, representing a heterogeneous group of diseases characterized by the proliferation of malignant lymphoid cells, most frequently of B-cell or T-cell origin, in peripheral and visceral lymph nodes. According to Rocha *et al.* (2025), lymphoma accounts for 24% of all documented canine neoplasms and 85% of hematological malignancies, with multicentric lymphoma corresponding to 84% of all canine lymphomas. Multicentric lymphoma is the most prevalent form, accounting for approximately 80-85% of canine lymphoma cases, with affected dogs typically presenting with generalized, painless lymphadenopathy.

The standard of care for treatment-naïve canine lymphoma is a multi-agent chemotherapy protocol, most commonly the Wisconsin-Madison CHOP-19 protocol, which includes cyclophosphamide, doxorubicin, vincristine, and prednisolone Flory *et al.* (2011). While this protocol induces complete remission in more than 80% of dogs with remission durations of 6-11 months and mean survival times of approximately one year, the majority will eventually experience relapse or become resistant to therapy. A study by Bharath *et al.*(2024) from Madras Veterinary College Teaching Hospital documented that six dogs treated with the CHOP-19 protocol showed remission in clinical signs within a week of therapy, with no evidence of peripheral lymph node enlargement after three weeks. The same study noted that although many chemotherapy protocols have been suggested, doxorubicin-based combination protocols are widely associated with long disease-free intervals and improved duration of survival.

For cases of relapse, rescue chemotherapy protocols are employed with the goal of re-inducing remission and extending survival time. Orally administered daily chemotherapy has emerged as a practical and well-tolerated approach for managing relapsed lymphoma. The Procarbazine, Prednisolone, and Cyclophosphamide (PPC) protocol is one such regimen that has been evaluated in the rescue setting (Vail *et al.* 2020).

A landmark study by O'Connell *et al.* (2022) evaluated the PPC protocol in 50 dogs with multicentric lymphoma, reporting an overall response rate of 70%, including 46% with a complete response and 24% with a partial response. The protocol was noted for its favorable safety profile; only one dog discontinued treatment due to grade 4 thrombocytopenia, and the most common adverse events were mild gastrointestinal toxicities (seven grade I and one grade II). Response to the PPC protocol (complete or partial) and age were identified as the only prognostic factors for survival time from initiation of PPC chemotherapy until death. Recent research by Blaxill and Bennett

(2024) and Parker *et al.* (2024) has further evaluated rescue protocols, with the latter demonstrating that early progression during or after CHOP chemotherapy indicates poor outcome with rescue protocols in dogs with multicentric lymphoma.

Case Presentation

A 6-year-old intact female German Shepherd dog, weighing 26.6 kg, was presented to the Madras Veterinary College Teaching Hospital with a one-week history of progressive enlargement of peripheral lymph nodes. The dog had been diagnosed with multicentric lymphoma six months prior and had undergone a complete course of the Wisconsin-Madison CHOP-19 chemotherapy protocol, achieving clinical remission. At presentation, the owner reported that the dog was dull and depressed with decreased appetite manifested as dysphagia, though urination and defecation were reportedly normal. On physical examination, the dog appeared dull but maintained good bodily condition, with pink and moist conjunctival mucous membranes and a skin tenting test of less than 2 seconds indicating adequate hydration. Vital parameters were within normal limits, with a rectal temperature of 102.0°F (reference range: 100.5-102.5°F), respiratory rate of 20 breaths per minute (reference range: 18-22/min), and heart rate of 80 beats per minute (reference range: 70-120 bpm). Palpation revealed generalized, firm, and painless enlargement of multiple superficial lymph nodes including the submandibular, prescapular, axillary, inguinal, and popliteal lymph nodes, a pattern characteristic of multicentric lymphoma, which accounts for approximately 80-85% of canine lymphoma.

Haematological evaluation revealed thrombocytopenia (platelet count: 1,02,000/µL; reference range: 2-5 L/cmm) and neutrophilia (73%; reference range: 60-70%), while hemoglobin (12.6 g/dL), PCV (37.3%), RBC count (6.08 million/µL), total WBC count (15,200/µL), lymphocytes (22%), and monocytes (5%) remained within normal limits. Serum biochemistry demonstrated significant abnormalities including marked hyperbilirubinemia with total bilirubin of 2.60 mg/dL (reference range: 0.15-0.5 mg/dL) and direct bilirubin of 1.80 mg/dL (reference range: 0.06-0.12 mg/dL), along with hyperphosphatemia (8.20 mmol/L; reference range: 2.6-6.2 mmol/L) and mild hypoalbuminemia (2.0 g/dL; reference range: 2.3-3.8 g/dL). Abdominal ultrasonography revealed a "reticulated" or "Swiss cheese" appearance of the spleen strongly suggestive of splenic lymphoma, while radiography confirmed splenomegaly with normal thoracic findings. Fine needle aspiration cytology of the enlarged lymph nodes revealed a population of monomorphic lymphocytes consistent with lymphoma. Based on the history of prior CHOP-19 therapy, recent onset of progressive lymphadenopathy, and cytological confirmation, a diagnosis of relapsed multicentric lymphoma was established.

Treatment and Management

Given the history of prior CHOP-19 therapy and the confirmed diagnosis of relapsed multicentric lymphoma, a rescue chemotherapy protocol was initiated. The chosen protocol was the PPC (Procarbazine, Prednisolone, Cyclophosphamide) Rescue Protocol, as described by O'Connell et al. (2022), which was selected for its demonstrated efficacy, well-tolerated oral administration, and suitability as a rescue therapy in the clinical setting. On Day 1, an intramuscular loading dose of prednisolone was administered @ 20 mg/m^2, followed by oral prednisolone @ 30 mg/m^2 once daily as maintenance therapy. From Day 2 onwards, a continuous 4-week oral regimen was instituted comprising procarbazine capsules @ 50 mg/m² every 24 hours, cyclophosphamide tablets @ 15 mg/m² every 24 hours, and a tapering prednisolone schedule: 30 mg/m² every 24 hours during the first week, reduced to 20 mg/m² every 24 hours during the second week, and subsequently maintained at 10 mg/m² every 24 hours until treatment withdrawal. Supportive therapy included pantoprazole @ 40 mg once daily for gastric protection, frusemide at 40 mg twice daily to manage potential fluid retention from corticosteroid use, and enrofloxacin at 150 mg once daily as a broad-spectrum antibiotic.

Outcome and Follow-up

By the second week of treatment, a marked clinical improvement was observed. The patient's mentation had significantly improved, and a notable reduction in the size of the previously enlarged lymph nodes was evident, indicating an initial positive response to the rescue protocol. By the end of the fourth week, the dog had achieved a 75% remission of its lymphoma, which was corroborated by follow-up haematological and biochemical evaluations performed at week 5. The follow-up haematology revealed a mild, non-clinically significant decrease in hemoglobin (10.6 g/dL from 12.6 g/dL) and packed cell volume (31.1% from 37.3%), while the red blood cell count decreased marginally to 5.07 million/µL. The white blood cell count showed a slight reduction to 14,900/µL, with neutrophils at 71%, lymphocytes at 17%, and monocytes at 8%, all remaining within permissible ranges. The platelet count decreased mildly to 96,000/µL but remained stable without clinical significance. Serum biochemistry demonstrated substantial normalization of the previously elevated bilirubin levels, with total bilirubin declining from 2.60 mg/dL to 0.48 mg/dL and direct bilirubin from 1.80 mg/dL to 0.32 mg/dL, both approaching reference ranges. Cholesterol decreased to 111 mg/dL (reference range: 135-270 mg/dL), while total proteins (5.50 g/dL) and albumin (2.0 g/dL) remained stable. Renal parameters including blood urea nitrogen (14.28 mg/dL) and creatinine (0.60 mg/dL) improved, though alkaline phosphatase increased to 156 U/L (reference range: 20-156 U/L). Calcium (8.98 mg/dL) and phosphorus (8.20 mmol/L) remained unchanged. This marked improvement in biochemical parameters, particularly the resolution of hyperbilirubinemia, coupled with

the clinical response, demonstrates the effectiveness of the PPC rescue protocol in achieving remission in this case of relapsed multicentric lymphoma.

DISCUSSION

The management of relapsed lymphoma remains a significant challenge in veterinary oncology. While most dogs with lymphoma will respond to initial CHOP-based protocols, relapse and the development of drug resistance are common, and a comprehensive review by Bennett *et al.* (2023) identified that overall outcomes have shown minimal change over the last 40 years, supporting the need for novel therapeutic approaches. The study by Bharath *et al.* (2024) documented that six dogs treated at Madras Veterinary College Teaching Hospital with the CHOP-19 protocol showed remission within a week of therapy, with no evidence of peripheral lymph node enlargement after three weeks. However, as demonstrated in this case, relapse remains a concern even after successful initial therapy.

The PPC protocol offers a well-tolerated, orally administered option that has demonstrated promising results in the rescue setting. The study by O'Connell *et al.* (2022) evaluated the PPC protocol in 50 dogs with multicentric lymphoma, reporting an overall response rate of 70%, with 46% achieving a complete response and 24% a partial response. The protocol was noted for its favorable safety profile; only one dog discontinued treatment due to grade 4 thrombocytopenia, and the most common adverse events were mild gastrointestinal toxicities. Response to the PPC protocol (complete or partial) and age were identified as the only prognostic factors for survival time from initiation of PPC chemotherapy until death.

The choice of the PPC protocol was driven by several factors, including its oral administration, which allowed for outpatient management and reduced stress on the patient and limited monitored visits for the owner. This is particularly relevant in the Indian veterinary context, where referral to specialized practices may be limited. As noted in the Indian literature by Baranidharan et al. 2024, multicentric lymphoma is a disease that the general practitioner can manage without referral to a specialized practice.

The findings of this case report are consistent with the study by O'Connell *et al.* (2022), which demonstrated the utility of the PPC protocol in dogs that have failed prior CHOP-based therapy. The dog's response was significant (75% remission), and the absence of severe adverse effects underscores the tolerability of this regimen in the rescue setting. Recent research by the BMC Veterinary Research group (2025) has further developed prognostic nomograms for canine multicentric lymphoma, incorporating factors such as age, red blood cell count, and albumin-to-globulin ratio to predict overall survival, which may help guide treatment decisions in similar cases.

The use of supportive therapy including pantoprazole, furosemide, and enrofloxacin was appropriate in this case, as prednisolone can cause gastric ulceration and fluid retention, and the immunosuppressive effects of chemotherapy may predispose to infection. The normalization of bilirubin levels by week 5 suggests improvement in hepatic function, likely reflecting the reduction in lymphoma burden

CONCLUSION

This case report demonstrates that the Procarbazine, Prednisolone, and Cyclophosphamide (PPC) oral combination chemotherapy protocol is a viable and effective rescue treatment for relapsed multicentric lymphoma in dogs, particularly following initial CHOP-based therapy, with the patient achieving a significant 75% clinical remission and minimal documented adverse side effects. The PPC protocol offers a well-tolerated, practical option for managing relapsed disease, with oral administration making it suitable for outpatient management, which is particularly valuable in resource-limited settings where referral to specialized oncology practices may not be feasible.

Further prospective studies and standardized reporting of rescue protocols are warranted to better define their optimal use and comparative efficacy, as a recent systematic review by Cannon and Bennett (2026) highlighted the lack of consensus on the most effective rescue protocol and the difficulty in making direct comparisons due to heterogeneous study populations. Nonetheless, the PPC protocol represents a promising option for the management of relapsed canine lymphoma.

This report describes the clinical presentation, diagnosis, and successful management of a case of relapsed lymphoma in a German Shepherd using the PPC rescue protocol. Pet parents should be well informed that lymphoma can rarely be cured and often effectively managed. Remission mostly follows relapse. The patient's quality of life improves with this protocol. Future studies on relapsed lymphoma are expected to make strides in treatment and rescue.

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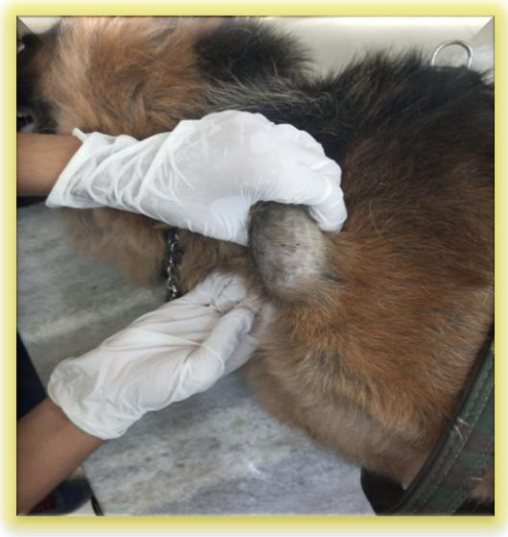
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ENLARGED SUPERFICIAL LYMPH NODES – BEFORE TREATMENT



A. Submandibular Lymph nodes



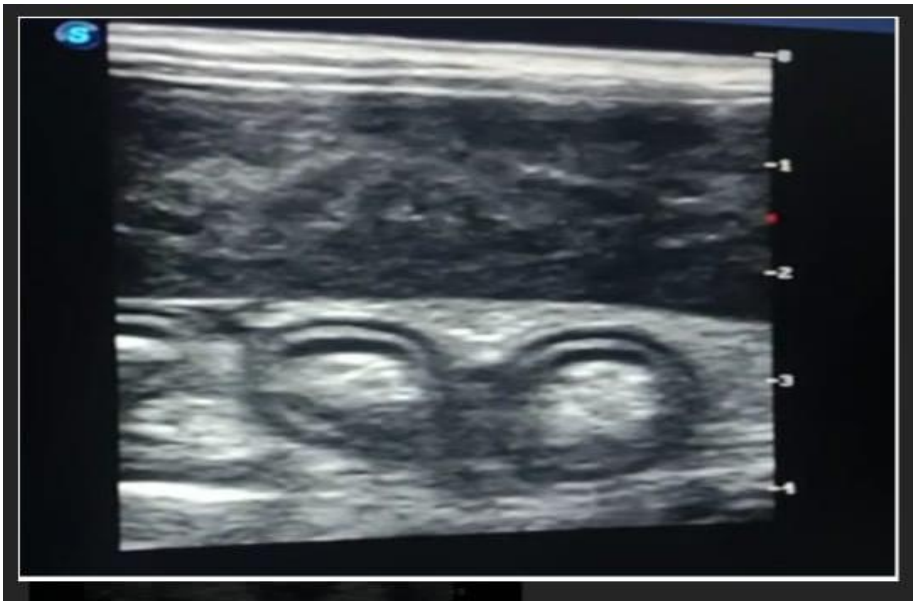
B. Pre-sapular lymph nodes



C. Popliteal Lymph nodes



D. Inguinal Lymph nodes



Ultrasonography of abdomen: Reticulated / Swiss cheese appearance of spleen



FNAC with monomorphic lymphocytes



Day 1 Before Treatment **2ND - Week Rescue Ppc Protocol**



4th - Week
75% Remission
Rescue Ppc Protocol