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SHORT COMMUNICATION Clinical Case Report

Preliminary experience of initial and re-administration of nimustine as a new primary treatment for feline nasal lymphoma: a case report

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Abstract

A 5-year-old spayed female domestic short haired cat presented with chronic nasal obstruction. The cat was diagnosed with B-cell nasal lymphoma based on histological examination of biopsy specimens and intracranial invasion was suspected. We initiated treatment with nimustine (ACNU), known to pass the blood–brain barrier, as the primary protocol with prednisolone, with the owner's consent. The ACNU dose was 20–25 mg/m² (4–5-week intervals, four or six administrations, two courses). The cat remained oligosymptomatic until day 962 after the first dose and no serious adverse events were reported. The cat lived until day 1089. To our knowledge, this is the first report of long-term survival achieved using ACNU as the primary treatment in a cat with nasal lymphoma.

Key Words: cat, nasal lymphoma, nimustine

Lymphoma is a common cancer (neoplasm) in cats, accounting for 50–90% of all feline hematopoietic tumors[21)]. Lymphomas in cats are classified into the following categories based on several anatomical sites: alimentary, mediastinal, nodal, and extranodal (nasal, renal, central nervous system (CNS), cutaneous, and hepatic)[22)]. Among these, nasal lymphoma (NL) accounts for 6.3%[7)]. NL is the most common intranasal tumor in cats[5,12)]. B-cell lymphoma accounts for 61–85% of all NL cases in cats[6,12,15)]. Radiotherapy is effective for NL, with median survival time (MST) reported to be 365–922 days[4,8,13)]. In addition, a combination of chemotherapy and radiotherapy reportedly results in an MST of 174–955 days[4,16)]. However, radiotherapy is available only in a limited number of hospitals, and chemotherapy alone is widely used. Long-term survival with chemotherapy, such as cyclophosphamide, hydroxydaunorubicin (doxorubicin), vincristine, and prednisolone (CHOP), is possible, with an MST of 116–358 days[4,20,21)]. In previous reports, no significant difference was observed in the outcomes of NL among the three treatment methods[4)]. However,

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its efficacy in the presence of intracranial invasion remains unknown, and the MST for CNS lymphoma has been reported to be 21–70 days[20,22]. In addition, nimustine (ACNU), which is highly migratory to nervous tissue, has been reported to be useful for treating CNS lymphoma in dogs[10]. Therefore, for feline cases of intracranial invasion or CNS lymphoma ACNU may be useful as anticancer agents that are highly migratory to the nervous tissue.

ACNU is a nitrosourea alkylating agent that acts as an anticancer agent in the same family as lomustine (CCNU). Pharmacokinetic studies in human brain tumor patients have reported that 7–30% of administered ACNU crosses the blood–brain barrier[9,11]. It is an injectable drug, which makes it easier to adjust the dosage and use it in small animal practice than CCNU, which is an oral drug. In dogs, phase I studies have determined a maximum tolerated dose (MTD) of 25 mg/m^2[17], and there are reports of its use in lymphoma and histiocytic sarcoma, among others[10,17,18]. However, to the best of our knowledge, the MTD in cats has not yet been determined. There are only a few reports of ACNU administration for feline cancer, including chemotherapy after radiation therapy in cats with anaplastic oligodendroglioma[18], as a postoperative and rescue protocol for cats with alimentary lymphoma[2,14], as a rescue protocol for cats with NL[18], and as a primary protocol for cats with alimentary and mediastinal lymphoma[14]. However, no reports of ACNU administration as a primary therapy for feline NL have emerged. To the best of our knowledge, this is the first report on long-term survival achieved using ACNU as the primary protocol in a cat with NL and suspected intracranial invasion.

Because the diagnostic studies and treatments were clinical activities, this study did not require approval from any institution or ethics committee. The cat was treated ethically and humanely throughout all testing and diagnostic procedures, in accordance with the ethical standards of the "Act on Welfare and Management of Animals" (1973, Japan). The Veterinary Cooperative Oncology Group-Common Terminology Criteria for adverse events ver2[24] was used to assess adverse events. The case was client-owned, and the client provided her consent for the publication of information about the patient in the case report.

A 5-year-old spayed female domestic short haired cat weighing 3.85 kg presented to a veterinarian with the chief complaints of nasal obstruction and obstructive ventilatory disturbance in the left nasal cavity (day 1). Antimicrobial and anti-inflammatory drugs was not effective in medical treatment of the cat; therefore, the cat was referred to Miyazaki University Veterinary Teaching Hospital on day 42. At the time of the initial visit to our hospital, the cat was found to have epistaxis in the left nasal cavity but no swelling was observed in the superficial lymph nodes. The body temperature of the cat was 38.8 °C, heart rate was 144 beats/min, and respiratory rate was 24 breaths/min, all of which were within normal ranges. No abnormal values were observed in complete blood counts. The blood chemistry tests showed mild hyperammonemia (133 μ/dL), hypernatremia (158 mEq/L), mild elevation in alkaline phosphatase (ALP) (303 U/L) and glucose (209 U/L), and mild decrease in blood urea nitrogen (13.6 mg/dL). Imaging examinations included plain radiography and computed tomography (CT) scan. CT (Aquilion Lightning; Canon Medical Systems Co., Otawara, Japan) was performed using isoflurane (Pfizer Inc., Tokyo, Japan) inhalation anesthesia, followed by tracheal intubation after the pre-administration of butorphanol (Vetorphale; Meiji Seika Pharma Co., Ltd., Tokyo, Japan) and was induced using propofol (Mylan Seiyaku Co., Tokyo, Japan). Plain radiography revealed an increased radiopaque area in the left nasal cavity. CT revealed an occupying lesion with contrast enhancement by iodine contrast medium (2 mL/kg IV, IOPAQUE 300 Injection, Fuji Pharma, Japan) in the left nasal cavity and infiltration of the right nasal cavity, frontal sinus, and sphenoidal sinus. Additionally, osteolysis of the left orbit, mandible, and cribriform plates was observed. A mild rightward midline shift was also observed in the olfactory bulb (Fig. 1A, 1C). There was no enlargement of regional lymph nodes or pulmonary nodules. Rhinoscopic biopsy samples

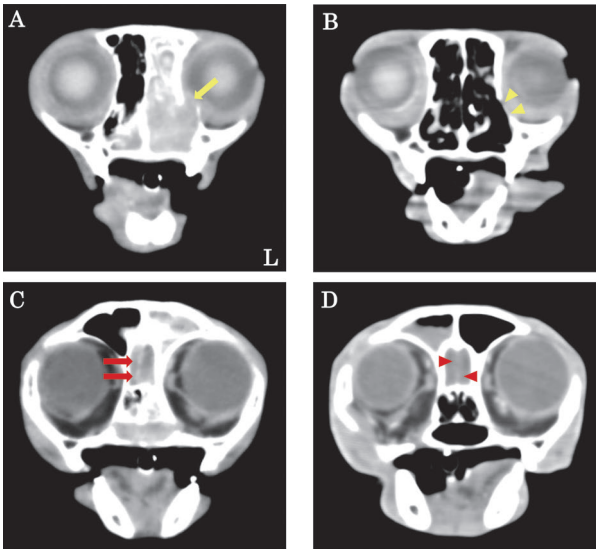

Fig. 1. Computed Tomography images of the head. **A.** On day 42, there are an occupying soft tissue-like lesion with contrast enhancement in the left nasal cavity, infiltration of the right nasal cavity and osteolysis of the left orbit (Yellow arrow). Displacement of the nasal septum is also observed. **B.** The soft tissue-like lesions have completely disappeared and there is ossification at the osteolysis site (Yellow arrowheads) on day 405. **C.** Mild rightward midline shift was observed in the olfactory bulb region (Red arrow) and there is infiltration of the left frontal sinus on day 42. **D.** The midline shift in the olfactory bulb area has disappeared (Red arrowhead) and fluid retention is observed in the right frontal sinus on day 405.
A–D: post-contrast

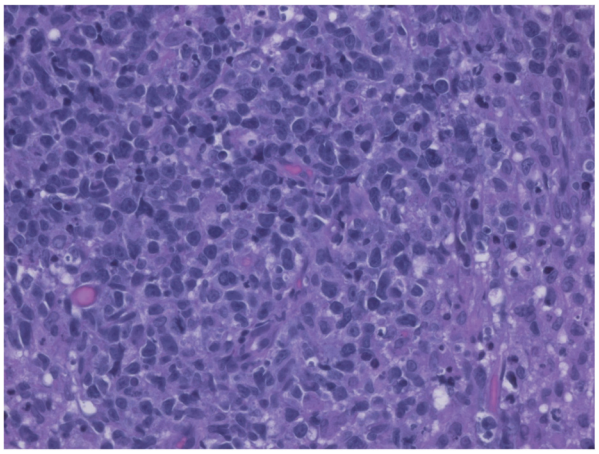

Fig. 2. Image of the histopathologic examination of the nasal lesion (400×). It was composed of diffuse sheets of large round cells admixed with small lymphocytes and macrophages. The large round cells had irregular round nuclei and scant cytoplasm with a single prominent nucleolus.

Table 1. Chemotherapy with nasal lymphoma on the first set in a cat.

Day	Treatment
63	ACNU 20 mg/m² IV once Prednisolone 1.3 mg/kg PO, SID
70	Prednisolone 0.65 mg/kg PO, SID
78	Prednisolone 0.26 mg/kg PO, SID
91	ACNU 22 mg/m² IV once Prednisolone 0.26 mg/kg PO, SID
119	ACNU 22 mg/m² IV once Prednisolone 0.13 mg/kg PO, SID
154	ACNU 22 mg/m² IV once Prednisolone 0.13 mg/kg PO, EOD

IV, intravenous; PO, per os ; SID, semel in die ; EOD, every other day

were obtained after the CT scan. Histopathological evaluation of the samples revealed neoplasia with diffuse sheets of large, round cells (Fig. 2). Immunohistochemistry showed that these cells were negative for the CD3 antibody (Fig. 3A) but diffusely positive for CD20 (Fig. 3B). The cat was diagnosed with diffuse large B-cell lymphoma (DLBCL).

The cat was treated with piroxicam (BAXO Capsules; FUJIFILM Toyama Chemical Co., LTD., Tokyo, Japan) (0.2 mg/kg, PO, on alternate days, for 24 days) for anti-inflammatory purposes until a pathological diagnosis was established. The CT scans suggested intracranial invasion or metastasis, although no neurological symptoms were present. Therefore, we prescribed chemotherapy with ACNU (Nidran; Daiichi-Sankyo Co., Ltd., Tokyo, Japan), which has a high migration to nerve tissue, instead of the common protocol for chemotherapy. Futhermore, ACNU protocol was considered appropriate for this patient as the character of the cat favoured the minimal number of drug administration. Once lymphoma was diagnosed, we initiated combination chemotherapy with ACNU (20–22 mg/m², IV, 4–5week intervals, four administrations) and prednisolone (Prednisolone; Asahikasei-pharma. Co., Tokyo, Japan) on day 63 (Table 1), after taking consent from the owner. Prednisolone was withdrawn on day 196. To monitor ACNU-induced adverse events, blood tests were performed at the time of ACNU administration and then after 1 week.

On first ACNU administration (day 63),

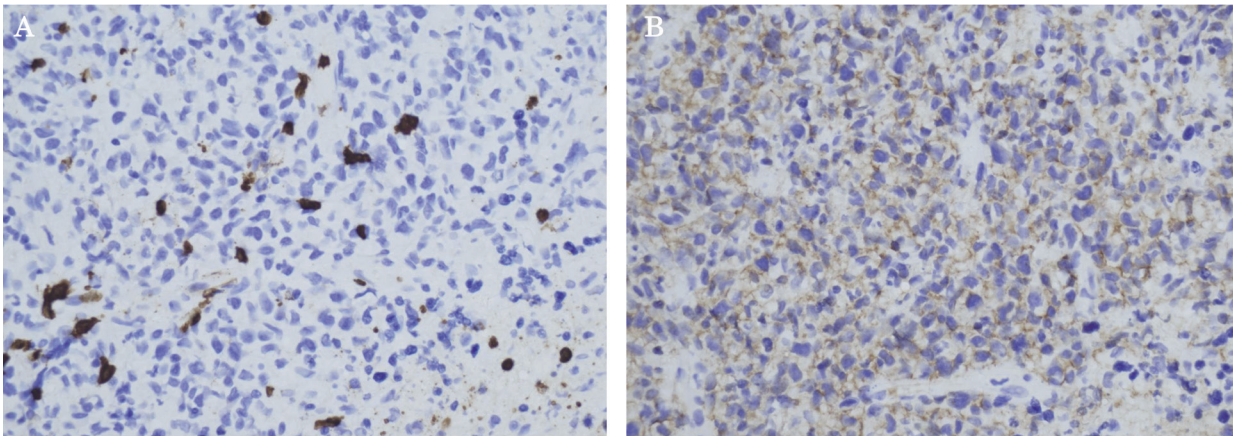

Fig. 3. Images of the immunohistochemistry for CD3 and CD20 (400×). A. The immunohistochemical staining was negative for CD3 antibody. Scattered non-neoplastic T cells were observed. B. The immunohistochemical staining showed a positive cytoplasmic reaction for the CD20 antibody.

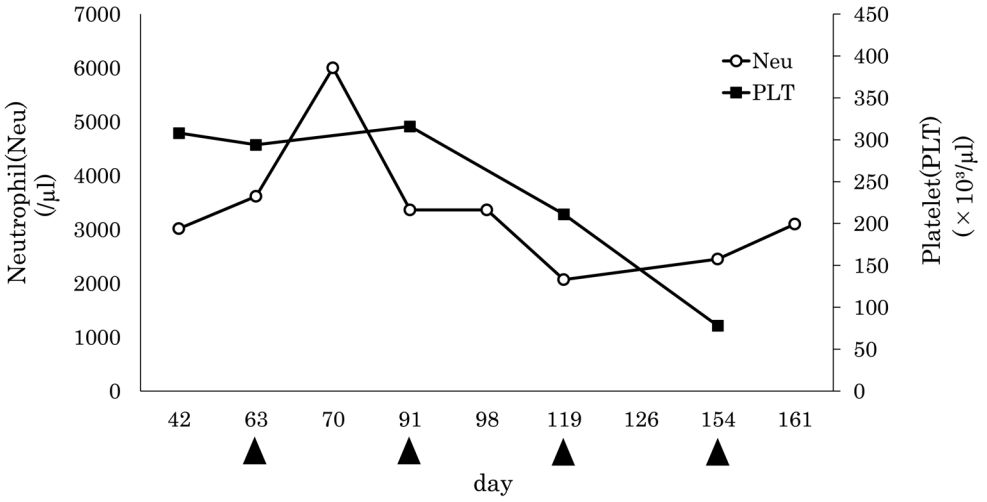

Fig. 4. During the ACNU administration, the lymphocyte and platelet counts. Blood tests were performed before and 7 days after ACNU administration. There are some missing results after 7 days of administration. ▲ : ACNU administration

the nasal obstruction sound had worsened further, and epistaxis was also observed in the right nasal cavity; however, a while after the first administration, the nasal obstruction sound disappeared. On day 154, there were no clinical symptoms such as nasal obstruction or epistaxis, and a follow-up (second) CT scan was performed. The CT scan showed disappearance of the occupying nasal lesion and a midline shift in the olfactory bulb region, and therefore, the fourth dose of ACNU was administered and the first round of the ACNU protocol was finished at this point. On day 405, there was no recurrence of clinical symptoms, such as nasal obstruction or epistaxis. The patient's general condition was good, and a follow-up (third) CT scan was performed. The CT scan showed ossification at the previous osteolysis site and disappearance of soft tissue-like lesions (Fig. 1B, 1D). Based on the clinical findings and CT results, the nasal lymphoma was determined to have a complete response by day 405. During the ACNU administration, the neutrophil and platelet counts temporarily decreased to 2068 /μL and 78×10^3/μL, respectively (Fig.4). ALP levels reached their maximum value of 406 U/L.

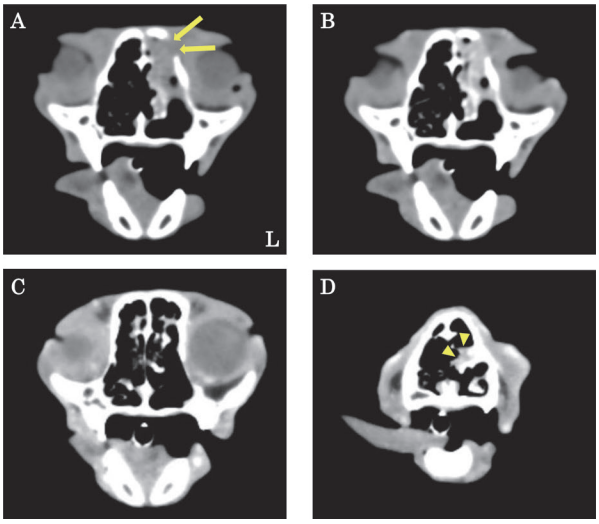

Fig. 5. Computed Tomography images of the head at the fourth molar level during the ACNU re-administration. **A, B.** There was a soft tissue-like lesion with contrast enhancement in the left nasal cavity. In addition, osteolysis of the nasal bone due to the lesion was observed (Yellow arrows) on day 625. **C, D.** On day 882, the contrast enhanced soft tissue-like lesion in the left nasal cavity (Yellow arrowheads).
A: pre-contrast, B–D: post-contrast

Table 2. Chemotherapy with nasal lymphoma on the second set in a cat.

Day	Treatment
657	ACNU 22 mg/m² IV once Prednisolone 1.3 mg/kg PO, SID
663	Prednisolone 0.65 mg/kg PO, SID
671	Prednisolone 0.26 mg/kg PO, SID
686	ACNU 24 mg/m² IV once Prednisolone 0.26 mg/kg PO, SID
714	ACNU 24 mg/m² IV once Prednisolone 0.13 mg/kg PO, SID
749	ACNU 25 mg/m² IV once Prednisolone 0.13 mg/kg PO, EOD
777	ACNU 25 mg/m² IV once Prednisolone 0.13 mg/kg PO, EOD
826	ACNU 25 mg/m² IV once Prednisolone 0.13 mg/kg PO, EOD

IV, intravenous; PO, per os ; SID, semel in die ; EOD, every other day

On day 625, the follow-up (fourth) CT revealed a soft tissue-like lesion in the left nasal cavity with osteolysis of the nasal bone (Fig. 5A, B). Cytological samples obtained from the lesion revealed a mixed population of inflammatory cells with increased numbers of large lymphocytes accounting for approximately 20% of the cell population; lymphoma recurrence was suspected. This cytology sample was submitted for clonality analysis using polymerase chain reaction for antigen receptor rearrangements (PARR) (Kahotechno Co., Ltd.; Fukuoka, Japan). B-cell monoclonal proliferation was detected, and a relapse of the nasal B-cell lymphoma was considered. Although the cat had no clinical symptoms and was in good general condition, the owner requested re-administration of ACNU. Reintroduction of ACNU was attempted (22–25 mg/m², IV, 4–5week intervals, six administrations) along with prednisolone (Table 2). On the same day of the follow-up CT, a cutaneous mass was incidentally found in the left abdomen. The mass was excised on day 657. The patient was diagnosed with a cutaneous mast cell tumor. The mast cell tumors were not treated medically. On day 777, CT revealed no evidence of metastasis; however, a few nasal lesions remained. Therefore, we administered ACNU for the fifth time after CT scan. On day 826, no clinical symptoms were observed, the cat was in good general condition, and a plain CT scan was performed without anesthesia for follow-up at the owner's request. A few nasal lesions were suspected on CT imaging; therefore, we decided to administer ACNU for the sixth time. On day 882, the cat's general condition was good; however, the owner occasionally reported sneezing and bleeding of the nose. A follow-up plain CT scan under sedation revealed soft-tissue-like lesions in the left nasal cavity (Fig. 5C, D), and straw biopsy was performed. Pathological examination of the biopsy specimen suggested lymphoma recurrence. However, the treatment was terminated because the owner did not request further treatment. During the re-administration of ACNU, the neutrophil and platelet counts temporarily decreased to 1300 /μL and 99×10³ /μL, respectively (Fig. 6). The highest ALT and ALP levels observed were 88 and 111 U/L, respectively. On day 962, the cat presented to a referring veterinarian with forward protrusion

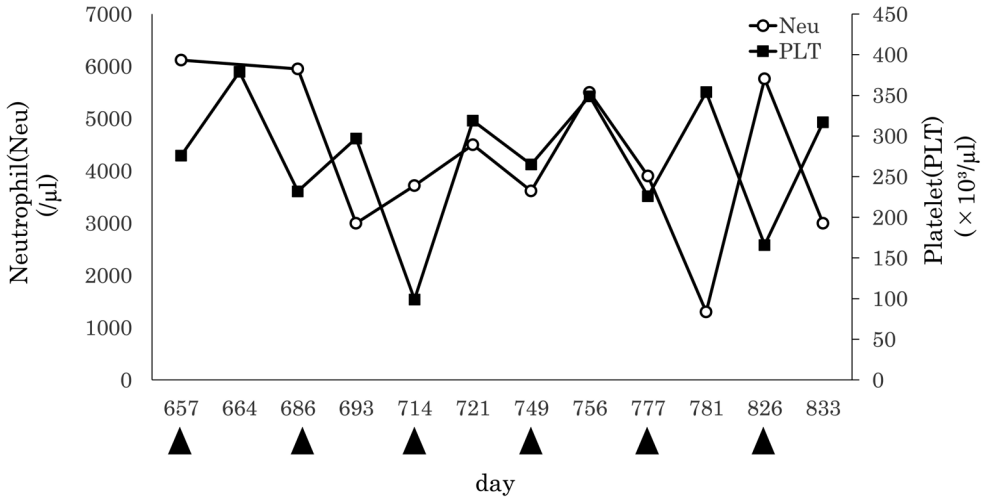

Fig. 6. During the ACNU re-administration, the lymphocyte and platelet counts. Blood tests were performed before and 7 days after ACNU administration. There are some missing results after 7 days of administration. ▲ : ACNU administration

of the left eyeball. Suspecting deterioration of lymphoma, the cat underwent the Wisconsin–Madison Chemotherapy Protocol administered by the referring veterinarian, but treatment was discontinued due to severe adverse events on day 1089, and she was not followed after that.

In this case, we selected ACNU because of its high migration to the neural tissue[9,11] and because intracranial invasion was suspected on the CT scan. The MTD of ACNU has been reported in dogs[17] but not in cats. Therefore, the first dosage was set at 20 mg/m² in accordance with a previous report in dogs[17] and our experience with two dogs[10]; the dosage was increased to 22 mg/m² at the second and subsequent injections based on the clinical examination findings after each injection. As no major clinical abnormalities were observed in the first four courses, the maximum dose was established at 25 mg/m² after re-administration.

In canine lymphoma, ACNU administration improves symptoms for a short period[1]. In this case, the nasal obstruction sound disappeared immediately after the first ACNU administration, and the CT scan showed no nasal lesions on day 405; therefore, the cat was considered to be in remission. Thus, an immediate effect of ACNU on feline lymphomas may be expected. On follow-up CT on day 625, a soft tissue-like lesion was observed in the left nasal cavity; therefore, ACNU was re-administered. After 10 ACNU administrations, the patient was in good general condition, but the pathology on day 882 confirmed a relapse of lymphoma. In a previous report, a cat with mediastinal lymphoma treated with ACNU as the primary protocol survived for 275 days, whereas cats with NL treated with ACNU as a rescue protocol had a progression-free survival of 12–102 days and a survival duration of 43–107 days[15]. In addition, the median survival with conventional chemotherapy protocols for NL in cats has been reported to be 119–358 days[4,19,20]. Moreover, the median survival of cats receiving prednisolone monotherapy for lymphoma is 10–60 days[3,5,20]. In this study, the cat survived for approximately 3 years and the clinical symptoms continued to disappear for 962 days, which is equivalent to or better than that in cats treated with conventional chemotherapy. In the treatment of intranasal lymphoma with radiotherapy alone or combined with chemotherapy, the destruction of cribriform plates is reportedly associated with significantly poorer outcomes[13,16]. Good treatment results were observed in the present case, with suspected destruction of the cribriform plate and intracranial invasion, although the reason for this is unclear. This is expected to be analyzed with the accumulation of more cases in the future.

In this case, a temporary decrease in

neutrophil and platelet counts, and a mild increase in ALP levels were observed during ACNU administration. ACNU causes myelosuppression, gastrointestinal disorders, and hepatotoxicity in cats and dogs[14,15,17]. In this case, neutropenia and thrombocytopenia corresponded to grade 1–2, and myelosuppression was mild-to-moderate. On day 405, after the completion of ACNU administration, the neutrophil and platelet counts generally improved, suggesting that myelosuppression was only temporary. The ALP level was up to 2.5 times higher than the normal level, which was grade 4. However, because alanine aminotransferase and aspartate aminotransferase levels were within the normal range during the treatment period, the increase in ALP levels could not be attributed to hepatopathy caused by ACNU administration, partly because of the effects of the long-term concomitant use of prednisolone. Furthermore, the cat's general condition during ACNU administration was good, and it can be concluded that ACNU administration did not cause any serious adverse events. This was similar to previous reports on cats treated with ACNU at doses of 20–30 mg/m^2[2,14,17]. In addition, allergic reactions have been reported to occur after ACNU administration in cats[14,18]. However, no allergic reaction was reported in this case, which may be because of the concurrent administration of prednisolone with ACNU.

The immunological phenotypes of NL in cats have been reported as follows: B-cell phenotype, 61–85%; T-cell phenotype, 8–29%; mixed B-cell and T-cell phenotype, 12.2%; and non-B, non-T-cell phenotype, 8%[6,12,15]. This case was that of B-cell lymphoma; therefore, treatment with ACNU may be effective in many NL cases in cats. In addition, this case was treated with the Wisconsin–Madison Chemotherapy Protocol from day 962 as a rescue protocol; however, the treatment was discontinued because of many adverse events (inappetence, weight loss, and leukocytopenia). Treatment with ACNU may be an option because no major adverse events occurred during ACNU administration, and the method of administration is simpler than those of the CHOP and Wisconsin-Madison chemotherapy regimens.

In conclusion, ACNU administration as the primary protocol in cats with NL and suspected intracranial invasion resulted in long-term survival and resolution of clinical symptoms without serious adverse events. This suggests that ACNU chemotherapy is an effective treatment option for NL in cats. However, the major limitation of this study is that only one case was reported. The appropriate dosage, protocol, and detailed adverse event risk of ACNU in cats remain unknown and need to be studied in more cases.

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