

CNS Relapsed T-cell Lymphoma in a Young Cat

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Abstract: An 8-month-old domestic shorthair cat presented with decreased activity and anorexia. Diagnostic imaging revealed cranial mediastinal mass and enlarged mesenteric lymph nodes. Fine needle aspirates showed a marked increase in malignant lymphocytes. Multicentric lymphoma (stage V-b) was diagnosed. The cat treated with COP protocol chemotherapy, and complete remission was induced. CNS relapse developed 314 days after the initiation of chemotherapy. Treatment with rescue protocol greatly reduced the clinical signs for a short period. The cat was in partial remission for 33 days and overall survival time was 383 days. Multicentric T-cell lymphoma with brain involvement was confirmed after necropsy by histopathology and immunohistochemistry.

Key words: cat, central nervous system, cytarabine (cytosine arabinoside), relapsed lymphoma.

Introduction

Intracranial tumors account for approximately 0.0035% of tumors in the cat, and 16% of these tumors are secondary lymphoma (LSA) (13). LSA is the second most common spontaneous tumor of the central nervous system (CNS) in cats. In LSA of both dogs and cats, involvement of the CNS usually occurs as part of a multicentric process. Although the phenotype of the cells and clinical aspects of feline secondary intracranial LSA have been described, little information regarding treatment protocols, response to treatment, or survival time is available.

Multicyclic chemotherapy protocols have been successful in the treatment of multicentric LSA in cats. Remission rates of up to 92% and median remission intervals of up to 281 days have been reported, depending on the anatomic location and FeLV status (8). However, remission rates and median survival times of CNS LSA are very low in cats (13). In humans, cytarabine (cytosine arabinoside, ara-C) and methotrexate are used for CNS LSA. Cytarabine is mainly used against canine LSA and granulomatous meningoencephalitis (GME). In cats, cytarabine is not widely used, and little information has been published in the scientific literature regarding this treatment. Cytarabine is a pyrimidine analog that is cell cycle phase-specific; this drug is inexpensive and well tolerated compared to other drugs. Because cytarabine primarily kills cells undergoing DNA synthesis (S-phase) and under

certain conditions blocks the progression of cells from G1phase to S-phase, a continuous-rate infusion is ideal for maximal exposure to cycling cells.

This report describes a cat with CNS relapsed multicentric T-cell LSA treated with cytarabine, dexamethasone, and L-asparaginase for 5 weeks.

Case

An 8-month-old intact female domestic shorthair cat was referred to the Seoul National University Veterinary Hospital with a 4-day history of partial anorexia, weakness, and refusal to jump. The cat was underweight (body condition score, 2/5). All other aspects of the physical examination were unremarkable. The results of blood and serum biochemical analysis revealed increased small to large sized lymphocytes on the differential count (9676/µl, reference 1,000-5,000/µl), increased AST (62 U/L, reference 0-48 U/L) and increased GGT (5 U/L, reference 0-1 U/L). Serologic tests for feline leukemia virus (FeLV) and feline immunodeficiency virus were negative.

An evaluation of the radiography and ultrasonography (thorax and abdomen) revealed cranial mediastinal mass, enlarged intra-abdominal lymph nodes and a fracture line in the cranial endplate of T11. The results of computed tomography (CT) scanning of the thorax also revealed a cranial mediastinal mass and a fracture line of T11 (Fig 1). Cytologic examination of the cranial mediastinal and mesenteric lymph nodes, liver, and spleen revealed increased numbers of small- to medium-sized lymphocytes and occasional large lymphocytes. The majority of the lymphocytes showed fine to reticular chromatin, multiple prominent nucleoli, and

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Fig 1. Diagnostic imaging on the first medical examination (CT scan). A large cranial mediastinum mass with mild and heterogeneous contrast enhancement (sternal/mediastinal lymphadenopathy) was observed on CT scan. Trachea is displaced dorsally and to the right, and cranial vena cava is displaced to the right. There are no remarkable findings associated with an invasion to adjacent vessels (cranial vena cava, aorta, and brachiocephalic trunk).

Table 1. Summary of the chemotherapy protocols for the cat with lymphoma

	Induction/Re-induction	Rescue	
Protocol	Cyclophosphamide 300 mg/m ²	Cytarabine 600 mg/m ² divided 3 times	
	Vincristine 0.7 mg/m ²	Dexamethasone 0.22 mg/kg bid 0.11 mg/kg sid tapere	
	Prednisolone 10 mg/day	L-asparginase 400 IU/kg	
Side effects	Leukopenia	Leukopenia	
	thrombocytopenia		
	discoloration of hair		

The cat had been given two chemotherapy protocols including a conventional (COP) and a rescue protocols. A conventional protocol was applied to induce CR when induction and re-induction, respectively. However, COP protocol couldn't prevent CNS relapse. Therefore rescue protocol including cytarabine was used for a palliative.

deeply basophilic cytoplasm with frequent mitotic figures. Multicentric LSA stage V (substage b) was diagnosed according to the clinical staging system for feline LSA.

The patient was treated with the COP protocol (Table 1) as described for feline multicentric LSA (15) and was evaluated at each treatment. Clinical remission was assessed by physical examination and sometimes by radiography or ultrasonography, depending on the site and extent of the tumor. Complete remission (CR) was defined as the disappearance of all detectable tumors and associated clinical signs. CR was induced with vincristine given weekly at weeks 1, 2, 3 and 4 at a dosage of 0.75 mg/m² IV, cyclophosphamide weekly at weeks 1 and 4 at a dosage of 300 mg/m² PO, and prednisolone daily at a dosage of 10 mg/day PO. CR was maintained from 30 to 172 days, and the COP protocol was continued daily for 155 days. The chemotherapy was delayed for 48 days to perform an ovariohysterectomy at the request of the owner. The chemotherapy protocol was well tolerated by the cat. However, the cat experienced mild side effects. Although mild leukopenia (2,000-2,400/µl, reference 5,000-18,000/µl) and thrombocytopenia (30,000-50,000/µl, reference 120,000-500,000/µl) were observed at 16 and 21 weeks, respectively, the values recovered within 1 week. When adverse side effects were encountered, the doses of cyclophosphamide given subsequently were usually reduced and/or the agents were given over longer than normal intervals. A fracture line in the end plate of T11 was diagnosed as a small sclerite by trauma and it was gradually recovering

On 203 days after the first presentation the cat had a recurrence of LSA in the cranial mediastinal lymph nodes, and CR was reinduced using the same protocol as the one previously adopted. The second CR lasted for 95 days.

After the second CR, the cat began to gradually deteriorate. The patient had neurological and non-specific abnormalities (Table 2). Therefore, several diagnostic examinations were performed. A physical examination revealed enlarged bilateral mandibular and prescapular lymph nodes. The serum chemistry analysis revealed elevated ALP activity (445 U/L, reference 38-165 U/L). The radiographs were not remarkable. The result of FNA (fine-needle aspiration) biopsy for

Table 2. A change of clinical signs from the first presentation to relapse

тепарье			
Clinical Signs	First presentation	Recurrence	CNS relapse
Non-specific signs	Partial anorexia	Partial anorexia	Anorexia
	Weakness	Weakness	Lethargy
	Poor haircoat	Poor haircoat	Weight loss
	Refusal to jump		Poor haircoat
			Dyspnea
Neurologic			Depression
signs			Ataxia
			Disorientation
			Loss of balance
			Blindness
			Nystagmus
			Anosmia
Etc.			Enlargend peripheral lymph nodes (mandibular, prescapular)
Chemotherapy	Induction	Re-induction	Rescue

When CNS relapse occurred, the cat had more severe clinical signs including than other previous signs. Neurological signs also were developed, blindness and nystagmus were remarkable above all things. And enlargement of peripheral lymph nodes that had previously not been observed were appeared.

the mandibular and prescapular lymph nodes showed the same findings as the result of FNA from the initial presentation. A neurologic examination showed progressive neurologic deficits and vestibular ataxia with staggering to the left side, but proprioceptive deficits were not detected. Papillary light reflexes and olfaction were depressed (Fig 2A), and the menace response was absent.

A cranial nerve examination confirmed horizontal nystagmus. Based on the neurologic finding, a lesion within the frontal lobe affecting the cranial nerves was considered likely. A full ophthalmic examination was performed and did not reveal abnormalities. The results of the magnetic resonance imaging (MRI) scan of the skull showed contrast enhancement of the cerebral meninges (Fig 3). An analysis of the CSF obtained via a cerebellomedullary cistern tap revealed a TNCC count of 20,300 cells/µl (reference range, 0 to 8 cells/µl) and a protein concentration of 30 mg/L (reference limit, < 250 mg/L). A cytologic examination of the CSF revealed increased numbers of medium- to large-sized lymphocytes (Fig 4). The results of the diagnostic procedures indicated CNS relapsed LSA and metastases to peripheral lymph nodes.

The COP protocol was considered to be ineffective, and chemotherapy with cytarabine as the primary drug was started (Table 1). The rescue protocol consisted of cytara-



Fig 2. Relapsed CNS lymphoma in a cat. The patient had severe pupil dilation at the time of CNS relapse (A) and improved after chemotherapy (B).

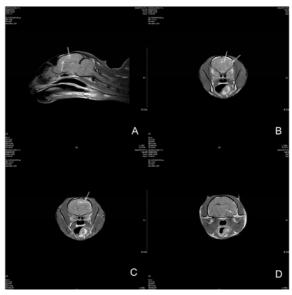


Fig 3. MRI findings in a cat with lymphoma in the cerebral meninges. Signal intensity is hyperintense and shows marked contrast enhancement on the on the sagittal T1-wighted image (A) and transverse postcontrast T1-wighted image (T1WI) (B, C, D).

bine, L-asparaginase, and a corticosteroid. For CNS relapse, the results of a physical examination before each treatment were combined, as appropriate, with blood tests to evaluate

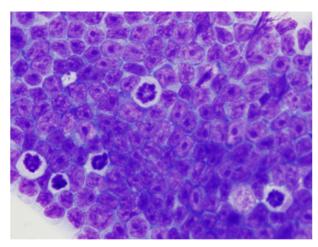


Fig 4. Lymphoma in the cerebral meninges of a cat. Cerebrospinal fluid analysis shows predominant cells are medium to large sized lymphocytes and these cells has fine to reticular chromatin, multiple prominent nucleoli, and deeply basophilic cytoplasm with frequent mitotic figures. Diff Qick stain. × 1000.

the side-effect. The alleviation of clinical signs provided an additional indication of the response. The cat was hospitalized during the continuous infusion of intravenous cytarabine (total dose of 600 mg/m² for three consecutive days). Following day 1 of the chemotherapy, the cat regained the ability to stand up, and the clinical signs improved; on day 3, all of the clinical signs were improved (Fig 2B). However, the clinical condition fluctuated between improvements and a worsening of symptoms during the 12-day interval.

Thirty-three days after starting rescue therapy, the cat died from a tumor-related reason when enlarged lymph nodes blocked the upper airway. The cat had increased large-sized lymphocytosis (7.75 K/μL; reference range, 1.05-5.10 K/μL) and anemia (PCV 12%, reference range 24-45%). Because the neutrophil and erythrocyte counts decreased the week after the chemotherapy, prophylactic antibiotics were administered. Increased circulating nRBCs were consistently observed during the rescue therapy and shortly before death. Peripheral lymphoblasts were noted, with a range of rare to 1600/ ul. Anemia was considered as either tumor related or as a side effect of the chemotherapeutic agents. The survival time was calculated as the interval from the start of treatment to death, and the disease-free period (DFP) was calculated as the interval from the start of remission to relapse. The duration of the first remission was defined as the time from the first confirmation of CR to the relapse of clinical disease. The survival time was the time from the onset of treatment until death.

Gross severe lymphadenopathy (mesenteric, mandibular, and prescapular) and a mild to moderate enlargement of the spleen and liver were noted. Mild shallowing of the gyri was noted in the cerebrum and cerebellum, especially around the frontal lobe. Histologically, an infiltration of monomorphic lymphoid cells was noted in the abdominal lymph nodes,

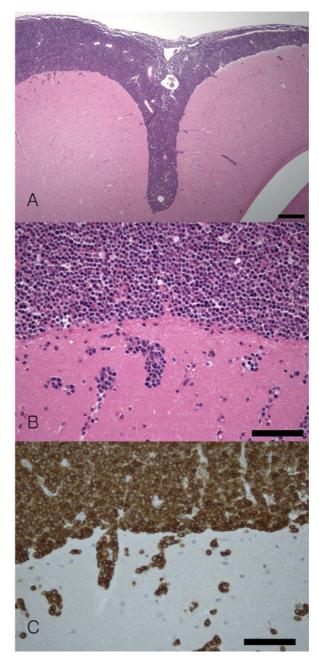


Fig 5. Histopathology and immunohistochemistry of brain. Note marked thickening of the meninges due to infiltration of neoplastic lymphoid cells. Neutrophil infiltration was also noted. HE. \times 40 (A), \times 400 (B). Neoplastic cells were strongly positive to CD3 (C), \times 400.

thoracic lymph nodes, brain, lung, liver, spleen, and mesenteric adipose tissues (Fig 5A and 5B). The neoplastic cells were monomorphic and round, had a low amount of cytoplasm, contained large hyperchromatic nuclei with finely stippled to clumped chromatin and occasionally contained 1 to 3 nucleoli. Consecutive sections of the formalin-fixed brain tissues were immunostained for immunophenotyping of the neoplastic cells. Immunohistochemically, the neoplastic cells

were diffusely and strongly positive for CD3 (Fig 5C) and were uniformly negative for both CD19 and CD20.

Discussion

CNS tumors are a fairly common cause of neurologic dysfunction in animals. Feline secondary CNS LSA is a malignancy for which there is limited published information, particularly in regard to treatments and outcomes. This study discussed a case of feline CNS relapsed LSA and, as such, offers useful information regarding the clinical presentation and outcome in a cat diagnosed with this variant of LSA. The incidence of intracranial tumors is reported as high as 2.6% in dogs and 2.2% in cats (16). The most common secondary brain tumors were shown to be LSA (14.4%) and pituitary tumors (8.8%) in cats (13).

The patient in the current study had pathologic lesions in the meninges of the cerebrum. Previous reports have indicated that intracranial metastases in companion animals most commonly affect the cerebrum (10). In these studies, the most common locations in the brain for secondary intracranial tumors were the cerebral cortex and the cerebellum. CNS metastasis generally occurs by the hematogenous route, and tumors tend to therefore be located in the "watershed" distributions of the intracranial vasculature (12). In cats and dogs, the CNS involvement in LSA usually occurs as part of a multicentric process.

The clinical signs induced by CNS tumors are generally nonspecific and depend on the location of the lesion. Thus, because of the multifactorial nature of the neurologic signs, the course of the disease is usually unpredictable. Signs associated with CNS tumors include seizures, cranial nerve deficits, paresis, changes in behavior, circling, and endocrine dysfunction. The predominant presenting neurological signs of dogs with LSA generally agree with previous reports in which seizures, vestibular dysfunction, and blindness were common clinical signs (10). However, a recent report indicated that the most common clinical signs in cats with brain tumors were altered consciousness (26.2%), circling (22.5%), seizures (22.5%), lethargy (20%), and inappetence (18.1%) (13). Neurological signs of the patient in this study included ataxia, blindness, and nystagmus (Table 2). In humans, a change in personality is the most common presenting symptom. It is noteworthy that these symptoms and signs caused by meningeal infiltration of high intracranial pressure are possibly misdiagnosed as neurosis or depression.

In this study, after a diagnosis of secondary CNS LSA had been established, the treatment protocol included corticosteroids, cytarabine, and L-asparaginase. Steroids are easy to use and rapidly effective, but the response is transient. The median survival time with corticosteroid treatment was shown to be 21 days for CNS LSA cats (n = 9) (range 9-270 days) (13). Similar poor survival times have been reported even in analyses of human patients with secondary CNS LSA (11). The cat in this study had leptomeningeal infiltration. Malignant

infiltration of the leptomeninges is a much-feared complication of human LSA. In leptomeningeal metastasis, the prognosis is generally poor; without treatment, the median survival time is 4 to 6 weeks (4). Even with current standards of care (radiotherapy and/or intrathecal or systemic chemotherapy), the median survival time is only 4 to 6 months (3).

In humans, the introduction of cytarabine has been proposed for CNS LSA. However, because such a protocol is so invasive that severe bone marrow suppression occurs frequently, marrow transplantation is essential for human patients. In this study, because the cat was clinically well, the protocol could not be altered except for the addition of cytarabine. The authors believe that the treatment was sufficiently successful for a palliative therapy, because hospitalization was only for 3 days from the first day the case was presented to us, and only a relatively small amount of time was necessary for the administration of cytarabine. Based on our data, cytarabine-based chemotherapy in a cat with secondary CNS LSA may result in improved clinical signs. However, the benefit is debatable because there was no significant difference in survival between cytarabine-based chemotherapy patients and corticosteroid therapy patients, with a median survival of 33 and 21 days, respectively.

Cytarabine is the treatment modality of choice in human medicine for most CNS LSA patients and provides superior remission rates for lesions compared to conventional chemotherapy protocols. The primary advantages of cytarabine over other conventional chemotherapeutic agents used in veterinary medicine include the inexpensive cost, the ability of the drug to penetrate the blood-brain barrier, and the reported tolerance of the drug. Cytarabine is more sensitive than corticosteroids for the treatment of primary and metastatic brain tumors and GME. The relative disadvantages of cytarabine include a longer infusion time and a high rate of side effects compared to conventional chemotherapeutic agents.

The majority of CNS recurrences in human patients with LSA occur during or shortly after the completion of induction chemotherapy (2). The timing of these recurrences suggests that occult microscopic disease may already be present at the time of diagnosis. Before the addition of a CNS penetrating agent to chemotherapy regimens, these recurrences preferentially involved the leptomeninges in approximately 70% of reported cases (5,14). Similarly, there has been a report describing CNS relapse that occurred during chemotherapy in 3 dogs with B-cell LSA (9). And the cat in this study also had CNS relapse during conventional chemotherapy.

The tumor immunophenotype was shown to have a significant effect on survival; cats with T-cell tumors were more likely to be long-term survivors, whereas cats with B-cell tumors were more likely to be short-term survivors (6). However, a paucity of information exists on the immunophenotype of CNS LSA in cats. In humans, most primary CNS LSA cases have a B-cell origin, and T-cell LSA cases are extremely rare (7). The findings are similar in dogs and cats. Until more reports with immunohistochemical verification are published,

however, the true proportion of CNS LSA that is derived from T cells will remain speculative. Immunohistochemical evaluation of LSA allows cases to be classified as derived from T cells or B cells. In humans, primary CNS T-cell LSA has a propensity for sole involvement of the leptomeninges. A similar pattern of neoplastic infiltration was observed in the cat described here.

The prognosis of cats with CNS-relapsed LSA is reported to be poor. In humans, when CNS involvement developed at the time of systemic relapse or progression, the median survival time was 2 months (1). This situation is often observed in the terminal stage of the clinical course. In some cases, small numbers of LSA cells exist in the CNS at presentation as an occult CNS invasion and then gradually proliferate to assume the form of isolated CNS relapse after systemic complete remission. It is possible that some systemic LSA cells become resistant to antineoplastic agents and enter the CNS, where the blood-brain barrier impedes the entry of most systemically administered agents. In this study, because neurologic signs developed, the cat was maintained in partial remission and survived for 33 days while being treated with cytarabine, dexamethasone, and L-asparaginase. Further studies are required to develop an effective treatment for CNS Tcell LSA in cats.

Conclusion

In conclusion, this is the first study reporting the efficacy of cytarabine in combination with a conventional chemotherapeutic protocol for the treatment of feline secondary CNS T-cell LSA with systemic nodal enlargement. The clinical results reported here show some effect of cytarabine on short-term remission and overall survival. Furthermore, the side effects were acceptable, suggesting that cytarabine can be incorporated with other chemotherapeutic agents. However, the need for hospitalization during the infusion and its transient effect make this agent more difficult to administer, and owner compliance may be the most important factor limiting its use.

Recently, the clinical impact of secondary CNS LSA has become important as a consequence of the prolongation of survival times due to improvements in systemic chemotherapy that does not target the CNS. The results from this study suggest that feline secondary CNS T-cell LSA is an aggressive disease with a poor prognosis that is only minimally responsive to the standard LSA chemotherapy protocol. Future directions in the study of this disease may include in vitro studies to evaluate sensitivity to various chemotherapeutic agents in order to identify more effective chemotherapeutic drugs for this form of LSA. In addition, prospective studies evaluating the efficacy of different chemotherapy protocols in LSA are needed.

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어린 고양이에서 발생한 중추신경계로 재발한 T세포 림프종

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요 약: 8개월령의 단모종 집고양이가 감소된 식욕과 활력 저하로 내원하였다. 진단을 위한 영상 검사에서 종격동의 종괴와 종격동 림프절의 비대 소견을 확인할 수 있었다. 이어서 진행한 세침흡인술 검사로, 악성 림프구를 다수 확인할 수 있었으며, 이 고양이는 다발성 림프종 (병기 V-b)로 진단되었다. 치료는 COP 프로토콜을 사용하였으며, 완전 완화를 확인할 수 있었지만, 항암 치료를 시작한 후 314일 째 재발과 함께 중추신경계로 전이된 소견을 확인할 수 있었다. 구조화학 요법을 실시하여, 단기적으로는 임상증상의 큰 개선을 확인할 수 있었지만, 부분완화만이 관찰되었으며, 처음 내원 부터 약 383일 정도 생존하였다. 부검과 조직병리학적 검사를 통해, 다발성의 T 세포 림프종으로 확인하였으며, 뇌에서도 병변을 확인할 수 있었다.

주요어 : 고양이, 중추신경계, 시타라빈, 재발성 림프종