

Secondary lymphoma development after chemotherapy in three dogs

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Abstract

Lymphoma is widely recognized in veterinary medicine. However, studies focused on secondary lymphoma after chemotherapy do not exist in veterinary medicine. An 11-year-old, spayed female Shih-Tzu dog was diagnosed with mammary gland carcinoma. Twenty-five months after carboplatin treatment, the dog developed generalized lymphadenopathy (GL), diagnosed as high-grade T-cell lymphoma by immunohistochemistry. Another spayed female Shih-Tzu dog who was 15-year-old had biopsy-induced gastrointestinal stromal tumour. Three months after being treated with Toceranib, the dog developed GL that was diagnosed by PCR for antigen receptor rearrangement as T-cell lymphoma. An eight-year-old, castrated male Mongrel dog was diagnosed with mast cell tumour. The dog was treated with vinblastine, but 14 months later, GL was revealed. Fine-needle aspiration indicated lymphoma. The owner declined to investigate the cell lineage. All three dogs developed GL after chemotherapy. We suggest that secondary lymphoma can develop in dogs after chemotherapy for a primary cancer, and thus long-term follow-up is necessary.

KEYWORDS

canine, chemotherapy, lymphoma, lymphosarcoma

1 | INTRODUCTION

Lymphoma is widely recognized in veterinary medicine as the most commonly diagnosed neoplasia in dogs. Most lymphomas in dogs can be managed well with chemotherapy, leading to an extended survival time (Zandvliet, 2016).

For a long time, the prevalence of canine lymphoma has been increasing, with a similar tendency detected in humans (Cartwright et al., 1999). Canine lymphoma and human non-Hodgkin lymphoma (NHL) have many other similarities, including molecular biology, clinical presentation, treatment options and responses of treatment (Teske, 1994). Some publications highlight the similarities in molecular changes in dogs and humans, promoting the possibility of using the dog as a potent model for human hematopoietic malignancies,

including lymphoma (Cruz Cardona et al., 2011; Suter et al., 2011; Thomas et al., 2011; Wolfesberger et al., 2012).

Research of secondary malignancies is actively conducted in humans. It has been known for long time that patients treated properly with chemotherapy for various cancers might develop secondary malignancies. Some chemotherapeutic drugs are known to affect the pathogenesis of therapy-related acute myeloid leukaemia (Pedersen-Bjergaard et al., 1995). Alkylating agents and topoisomerase II inhibitors are well known for their carcinogenic effects (Ferguson, 1998; Saffhill et al., 1985; Sanderson et al., 1996).

A study in humans suggested the possibility of an NHL occurrence secondary to cancer chemotherapy. According to a summary of cancer therapy-associated studies covering 17 years, the weighted average percentage of secondary NHL following cancer therapy was

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calculated to be 5%. Compared with other primary cancers, secondary NHL prevalence is notably higher in patients treated for Hodgkin lymphoma (HL) (Krishnan & Morgan, 2007).

Chemotherapy as the cause of secondary myelodysplasia has been scarcely studied in dogs. Drugs related to myelodysplasia include cephalosporins (Deldar et al., 1988), chloramphenicol (Harvey et al., 1985) and vincristine (Alleman & Harvey, 1993). One study reported secondary myelodysplastic syndromes in 21 dogs. It suggested that secondary myelodysplastic features may have been caused by drugs (melphalan, cyclophosphamide, chlorambucil and vincristine) reported to promote myelodysplasia in humans (Weiss & Aird, 2001). Another study reported that large-cell lymphoma has developed in 9.9% (12/121) of cats treated for small-cell lymphoma. This report proposed that exposure to chemotherapeutic drugs can increase the risk of secondary hematopoietic malignancies (Wright et al., 2019).

Hematopoietic malignancies following chemotherapy administration have been reported in human and veterinary medicine (Weiss & Aird, 2001). However, studies focused on secondary lymphoma exist in human but not veterinary medicine. The purpose of this study was to report three cases of secondary lymphoma in dogs treated with chemotherapeutic drugs for other tumours.

1.1 | Case presentation

1.1.1 | Case 1

An 11-year-old, 4.4 kg, spayed female Shih-Tzu dog was referred to the hospital for chemotherapy after mastectomy at another hospital. The biopsy confirmed low-grade mammary gland carcinoma with neoplastic cells present in the deep surgical margin (Figure 1). Six carboplatin (200 mg/m², intravenous; Korea United Pharm.) treatments were conducted over 4 months. Twenty-five months after the

last treatment, the dog revisited the hospital, showing GL. Lymph node fine-needle aspiration (FNA) indicated over 80% lymphoblasts, along with mitotic figures (Figure 2). The result of immunohistochemistry was consistent with high-grade T-cell lymphoma. Five days after lymphoma diagnosis, the dog died at home due to seizures and other neurological symptoms. Because of the owner's refusal, an autopsy could not be performed (Table 1).

1.1.2 | Case 2

A 15-year-old, 4.3 kg, spayed female Shih-Tzu dog visited the hospital with abdominal distention. Computed tomographic examination identified an abdominal mass suspected of being a gastrointestinal stromal tumour (GIST) (Figure 3). The mass was surgically removed and results of histopathology confirmed GIST (Figure 1).

Toceranib (2.75 mg/kg, orally, three times a week; Zoetis), a tyrosine kinase inhibitor, was administered for approximately 2.5 months after surgery, 30 times in total. Three months after the end of treatment, GL developed and lymph node FNAs showed that small lymphocytes with uropods comprised over 75% of the cells, with a lymphoblast rate of approximately 20% (Figure 2). It was assumed to be B-cell and T-cell lymphoma based on PCR for antigen receptor rearrangement (PARR). The lymph nodes remained almost the same size, without clinical symptoms, for approximately 220 after the lymphoma diagnosis, at which time the dog died of an unrelated cause. An autopsy was offered to the owner and declined (Table 1).

1.1.3 | Case 3

An 8-year-old, 6.2 kg, castrated male Mongrel dog visited the hospital with an axillary mass. The mass was diagnosed as a mast cell tumour based on FNA (Figure 4). The mass size did not decrease

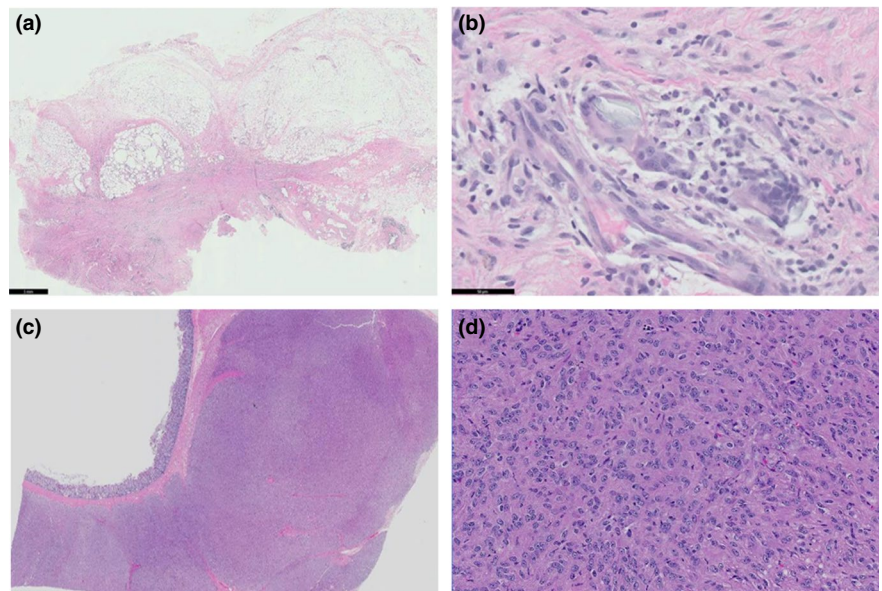


FIGURE 1 (a), (b) Cytology of mammary gland carcinoma (IDEXX Inc., Westbrook, US). Neoplastic cells were present in the deep surgical margin (Case 1). (c), (d) Cytology of abdominal mass (IDEXX Inc., Westbrook, US). The mass was surgically removed and resulted in GIST (Case 2)

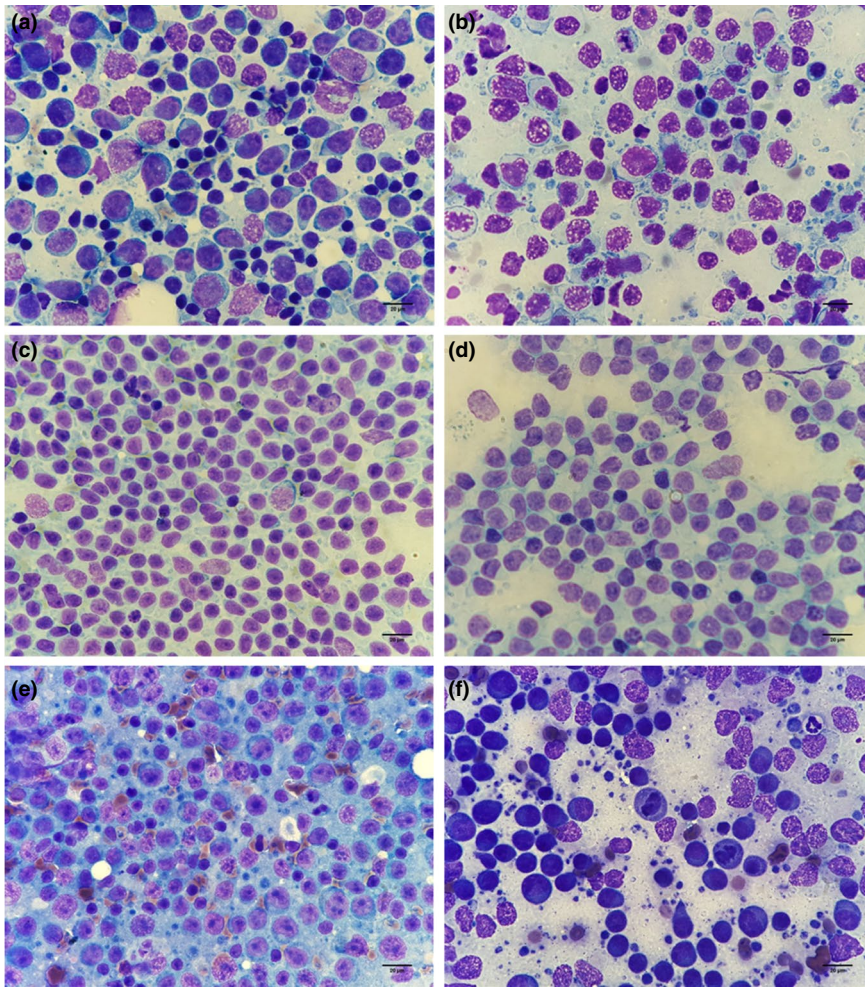


FIGURE 2 FNA was implemented in the enlarged lymph nodes. (a) Left axillary lymph node of Case 1. The rate of lymphoblast is 50%–65%, with plasma cell and mitotic figure. (b) Left prescapular lymph node of Case 1. The rate of lymphoblast is 75%–80%, with plasma cell and mitotic figure. (c) Left submandibular lymph node. (d) Left popliteal lymph node of Case 2. Small lymphocytes with uropod were found to comprise over 75% of the sample, with a lymphoblast rate of about 20%. (e) Left prescapular lymph node of Case 3. The lymphoblast rate is about 75% with mitotic figure. (f) Right submandibular lymph node Case 3. The lymphoblast rate is over 90%, with mitotic figure

Characteristic	Case 1	Case 2	Case 3
Breed	Shih-tzu	Shih-tzu	Mongrel
Age	11-year-old	15-year-old	8-year-old
Sex	Spayed female	Spayed female	Castrated male
Primary neoplasia	Mammary gland tumour	Gastrointestinal stromal tumour	Mast cell tumour
Chemotherapeutic agents	Carboplatin	Toceranib	Vinblastine
Period from 1st chemotherapy	29 months	6 months	15 months
Period from the end of chemotherapy	25 months	3 months	14 months
Survival after second cancer development	5 days	239 days	762 days

TABLE 1 Characteristics of the three dogs with secondary lymphoma

substantially after two vinblastine injections (1.8 mg/m², intravenous; Teva, Petah Tikva, Israel), as neoadjuvant chemotherapy. Fourteen months after the second injection, the dog visited the hospital due to GL. The lymph nodes were aspirated and cytology was consistent with lymphoma with a lymphoblast rate over 90% (Figure 2). Further molecular biology examination could not be performed because of the owner's refusal. On the day of the lymphoma diagnosis, the dog was treated with an L-CHOP protocol (L-asparaginase, vincristine, cyclophosphamide and doxorubicin).

Complete remission (CR) was confirmed 240 days later at the termination of the protocol. However, the dog relapsed 462 days after the lymphoma diagnosis, and L-CHOP treatment was initiated again. The owner requested to discontinue the chemotherapy after the dog was administered the first L-CHOP cycle, and the patient received prednisolone that was adjusted according to the dog's condition from 0.5 mg/kg once a day to 2 mg/kg twice a day. About 10 months later, it died of respiratory distress. Because the owner declined, an autopsy could not be performed (Table 1).

FIGURE 3 Post-contrast sagittal (a) and axial (b) computed tomography imaging of abdominal region. A mass (arrow) of 13.4×8.7×6.3 cm occupied most of the abdominal cavity, from the great curvature of stomach to the level of bladder in the lower abdomen. It was diagnosed as a gastrointestinal stromal tumour (GIST) derived from the gastrointestinal tract

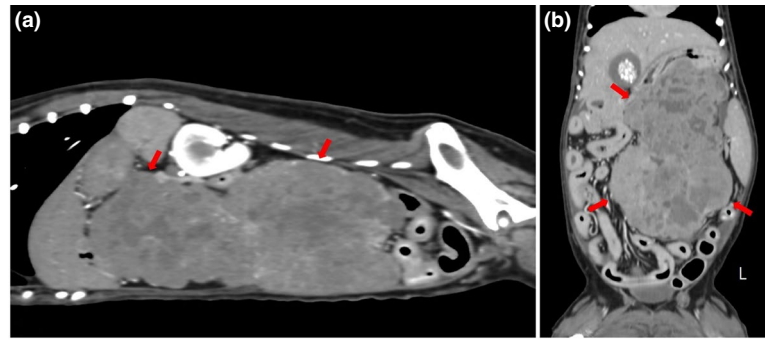
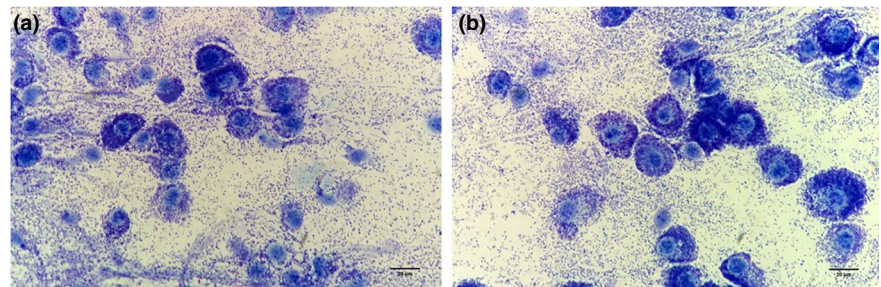


FIGURE 4 (a), (b) FNA was implemented in the axillary mass of Case 3. A lot of mast cell was observed with well-differentiated granule by toluidine blue staining. The dog was diagnosed with mast cell tumour



2 | DISCUSSION

Only a few cases of secondary myelodysplastic syndrome following chemotherapy have been reported in dogs (Weiss & Aird, 2001), and there are no reports on secondary lymphoma. However, in human medicine there have been many studies on secondary NHL occurrence after proper treatment of various tumours with chemotherapy (Krishnan & Morgan, 2007). There have also been many attempts to find similarities between human NHL and canine lymphoma, aiming to use dogs as research models for the human disease. The possibilities of doing so are already well known (Cruz Cardona et al., 2011; Suter et al., 2011; Teske, 1994; Thomas et al., 2011; Wolfesberger et al., 2012), as secondary NHL in humans and lymphoma in dogs might occur in a similar way.

In a human study on NHL after cancer therapy, three possible mechanisms were presented, including radiation, cytotoxic drugs and immunosuppression (Krishnan & Morgan, 2007). We suggest that the use of previous cytotoxic drugs for chemotherapy is the mechanism for secondary lymphoma in the cases described in this report. However, cytotoxic chemotherapy is likely to cause immunosuppression. Therefore, secondary lymphoma development was likely associated with either or both cytotoxic chemotherapies and immunosuppression.

Many carcinogenic drugs have been reported to cause secondary cancer including NHL (Ferguson, 1998; Saffhill et al., 1985; Sanderson et al., 1996). There is a study suggesting that cisplatin is carcinogenic. Carboplatin, used in one of the above cases, is an analogue of cisplatin. Cisplatin causes mainly intra-strand DNA-DNA cross-links, and was shown to be greatly mutagenic and carcinogenic in experimental models. Although its action may be fundamentally similar to cisplatin, there is limited data on the mutagenic and carcinogenic effects of carboplatin, which is considerably less toxic (Sanderson et al., 1996).

The possible relationship between HL therapy and the development of myeloid neoplasia and epithelial solid tumours is well-known, as is the incidence of NHL in patients treated for HL (Armitage et al., 1983; Favier et al., 2009; Jacquillat et al., 1984; Krikorian et al., 1979; Miettinen et al., 1983; Swerdlow et al., 2011; Xavier et al., 2013). A study on the long-term risk of developing secondary malignancy after chemotherapy for HL reported a higher risk after chemotherapy alone and an even higher risk after combined treatment with chemotherapy and radiotherapy (Swerdlow et al., 2011). Various types of chemotherapy protocols are used by different clinicians to treat HL patients, however, most include vinca alkaloids. Although an independent study on the carcinogenesis of vinca alkaloids does not exist yet, they can affect the occurrence of secondary NHL after chemotherapy administration for HL. Recent years have seen a broad application of tyrosine kinase inhibitors in chemotherapy for dogs. Research and case reports on the carcinogenic effects of Toleranib are still lacking. However, Toleranib might contribute to secondary malignancies.

Besides the effects of chemotherapeutic drugs, there might be other potential mechanisms involved in secondary lymphoma development in dogs. Such cases might be genetically predisposed to lymphoma, but it is difficult to find out in this report.

There is a possibility that primary tumours cause secondary lymphoma. However, there are no such reports in veterinary medicine. In a long-term human study on the mortality of breast cancer patients, 12/493 (2.4%) patients with secondary malignancies after cancer therapy were reported to have NHL (Hoening et al., 2006). Moreover, there is a report of leukaemia (14/2,067) occurring in patients treated with chemotherapy for gastrointestinal cancer (Boice et al., 1983). However, both studies tended to attribute the occurrence of secondary malignancies to the use of anticancer drugs rather than to the primary tumour effect. Therefore, rather than

being attributed to primary tumours, it is postulated that secondary lymphoma developed from multiple factors.

All of the above cases showed a time delay of at least several months between treatment with chemotherapy and the development of lymph node enlargement (25, 3 and 14 months). Carboplatin, used in case 1, is an analogue of cisplatin, known to be carcinogenic. Vinblastine, used in Case 3, is a member of the vinca alkaloids family. There is a report that myelodysplasia can occur in canine bone marrow after treatment with vincristine, a vinca alkaloid analogue (Alleman & Harvey, 1993). Furthermore, vinca alkaloids are almost always administered to human HL patients, although their carcinogenic effect has not been proven yet. Given the considerable number of reports on the occurrence of secondary NHL after the chemotherapy administration for HL, the possibility that the vinca alkaloids included in the treatment protocol might be the cause cannot be ruled out. Case 2 was administered Toseranib, a member of the tyrosine kinase inhibitors family. Although there are no studies on tyrosine kinase inhibitors with regard to carcinogenesis, it is possible that secondary lymphoma can be caused by this drug. However, the secondary lymphoma in Case 2 could also have occurred due to other factors because the time between the end of treatment and the appearance of the secondary lymphoma was shorter than in the other cases (3 months). For the report of NHL humans treated with HL chemotherapy, development of secondary cancer showed a peak 5 to 9 years after first treatment (Swerdlow et al., 2011). Given that shorter life span, a shorter time frame between initial treatment and development of secondary cancer would likely be expected in dogs.

Lack of molecular biologic examination results in Case 3 and absence of autopsy data in all cases are limitations of this study due to the owners' decline. If further examination results had been obtained from these patients, it may have been possible to acquire additional evidence to support the diagnosis of secondary lymphoma.

3 | CONCLUSION

This report might be the first to suggest the occurrence of secondary lymphoma following chemotherapy in dogs. Long-term follow-up is recommended for dogs diagnosed and treated for primary cancer as secondary lymphoma might develop months to years after completing the chemotherapy course.

ACKNOWLEDGEMENT

This study was assisted by "Cooperative Research Program of Center for Companion Animal Research" (Project No. PJ014045022021) for the publication: Rural Development Administration, Republic of Korea.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

PEER REVIEW

The peer review history for this article is available at <https://publons.com/publon/10.1002/vms3.474>.

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How to cite this article: Kim JM, Yi HJ, Song KH, Seo KW. Secondary lymphoma development after chemotherapy in three dogs. *Vet Med Sci*. 2021;7:1144–1149. <https://doi.org/10.1002/vms3.474>