

Lymphoma in 3 related Rottweilers from a single household

R G Lobetti^a

ABSTRACT

Over a period of approximately 1 year, 2 sibling Rottweilers and their dam in the same household developed stage IV and stage III lymphoma, respectively. All 3 initially responded to doxorubicin chemotherapy but relapsed after approximately 3 months and were subsequently euthanased. As no obvious environmental trigger could be identified in these dogs, it is speculated that an underlying genetic predisposition could have played a role in the development of lymphoma in these related dogs.

Keywords: canine, dog, environment, familial cancer, lymphoma.

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INTRODUCTION

Lymphoma arises from the malignant clonal expansion of lympho-reticular cells.

Both the primary lymphoid organs (bone marrow, thymus) as well as secondary lymphoid structures (lymph nodes, spleen, and respiratory and gut-associated lymphoid tissue) are potential sites of neoplastic transformation. However, because of continuous lymphocyte trafficking, the malignant transformation of lymphocytes can occur virtually anywhere²⁰. Lymphoma is reportedly the most common haematopoietic neoplasm affecting the dog, with an incidence approaching 0.1 %²; 80 % of lymphomas are seen in 5–11-year-old dogs⁷.

The precise aetiology of lymphoma in the dog has not been identified although several hypotheses have been investigated but none definitely proven. Suggested aetiologies for canine lymphoma include retroviral infection, environmental contamination with phenoxycetic acid herbicides, magnetic field exposure, chromosomal abnormalities, and immune dysfunction^{1,3,5,6,17,21}. A weak to moderate association with the use of herbicides, exposure to strong magnetic fields, or residence in industrial areas has been observed in preliminary epidemiological studies^{3,5,6,14,24}. Both somatic and germ line mutations in the tumour suppressor gene p53 have been reported in some cases²¹ and occasional clustering in related dogs has suggested a heritable component in limited instances¹⁷.

In a prospective study in the Bull mastiff

it appeared that the incidence rate was higher and that the distribution pattern of the cases displayed a familial pattern¹². Clustering has been reported in the Rottweiler and Otterhound¹⁷. In the Rottweiler referred to by Teske¹⁷, both parents and 1 offspring were confirmed to have lymphoma and it was suspected but not demonstrated in 2 of the siblings, whereas lymphoma of the myocardium was found in 3 closely related Otterhounds.

In humans, familial Hodgkin's lymphoma is estimated to represent approximately 1–1.5 % of all cases of Hodgkin's disease with a 3-fold increased risk of Hodgkin's lymphoma in 1st-degree relatives¹⁹. It also has been reported that there is a 4-fold increased risk for siblings of young adult cases and no increased risk for siblings of older adult cases⁴. Proposed causes for familial Hodgkin's lymphoma are shared environmental factors, viral disease and genetic determinants¹⁹.

Treatment of lymphoma in the dog is often rewarding, with the majority of dogs initially responding favourably to chemotherapy. Dogs treated with combination cyclophosphamide, doxorubicin, vincristine and prednisolone protocols generally achieve a complete response rate of 80–90 %, with expected median survival times of 1 year^{8,9}.

This article describes lymphoma in 2 Rottweiler siblings and their dam, all 3 bitches having lived in the same household and having been exposed to the same environment.

CASE HISTORIES

Case 1

A 5-year-old female Rottweiler was referred for evaluation of acute onset

generalised peripheral lymphadenomegaly. On clinical examination the dog was bright and alert, rectal temperature was normal, with generalised peripheral lymphadenomegaly and splenomegaly on abdominal palpation. Fine-needle aspirate cytology from the peripheral lymph nodes showed a homogeneous population of large lymphoblastic lymphocytes with large nuclei and moderate amount of cytoplasm. Diffuse hyper-echoic splenomegaly and mesenteric lymphadenomegaly were evident on abdominal ultrasonography. Fine-needle aspirate cytology from the spleen and mesenteric lymph nodes showed a homogeneous population of large lymphoblastic lymphocytes similar to those evident on the cytology of the peripheral lymph nodes. Full haematology and serum biochemistry were within normal limits. Serum thymidine kinase (TK) activity was 5.7 U/l (normal <7). A diagnosis of stage IV lymphoma was made.

Doxorubicin chemotherapy was started and repeated at 3-weekly intervals for a total of 5 treatments. For each treatment the dose used was 30 mg/m² given intravenously. The dog showed minimal reaction to the chemotherapy and at the completion of the regimen the splenomegaly and lymphadenomegaly had resolved. Serum TK activity 4 weeks after the last chemotherapy was 1.6 U/l. Three months later the dog developed generalised peripheral lymphadenomegaly, which was diagnosed as a centroblastic lymphoma on histopathology of a lymph node biopsy. Abdominal ultrasonography, full haematology, and serum biochemistry were all within normal limits. The dog was started on a cyclophosphamide, vincristine and prednisolone (COP) protocol, to which there was an initial response but 3 months later, despite still being on the COP chemotherapy, the peripheral lymph nodes enlarged, and were cytologically diagnosed as lymphoma. Owing to the poor prognosis the dog was euthanased.

Case 2

Two months after initial diagnosis of case 1, the full sister was referred for evaluation of acute onset generalised peripheral lymphadenomegaly. The only

^aBryanston Veterinary Hospital, PO Box 67092, Bryanston, 2021 South Africa. E-mail: rlobetti@mweb.co.za
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pertinent finding on clinical examination was generalised peripheral lymphadenomegaly. Mild splenomegaly with multiple anechoic areas was the only abnormality evident on abdominal ultrasonography. Fine-needle aspirate cytology from the peripheral lymph nodes and spleen showed the presence of a homogeneous population of lymphoblastic lymphocytes with large nuclei and moderate amount of cytoplasm. Full haematology and serum biochemistry were within normal limits. Serum TK activity was 33.7 U/l. A diagnosis of stage IV lymphoma was made.

As with case 1, doxorubicin chemotherapy was similarly initiated, with the dog showing minimal side effects to the chemotherapy and at the completion of the regimen the splenomegaly and lymphadenomegaly had resolved. Serum TK activity 3 weeks after the last chemotherapy was 2.9 U/l. One month later the dog developed generalised peripheral lymphadenomegaly, which was diagnosed as a centroblastic lymphoma on histopathology of the lymph nodes. Abdominal ultrasonography, full haematology, and serum biochemistry were all within normal limits. She was started on a COP chemotherapy protocol but despite being on chemotherapy showed a relapse within 2 months and was euthanased.

Case 3

Thirteen and 11 months after the initial diagnoses of cases 1 and 2, respectively their 7-year-old dam was referred for evaluation of acute onset generalised peripheral lymphadenomegaly. A diagnosis of stage III lymphoma was made. Serum TK activity was not measured.

As with the 2 previous cases, 5 treatments of doxorubicin chemotherapy were given. Three months later she developed generalised peripheral lymphadenomegaly, which was again diagnosed as a centroblastic lymphoma on lymph node histopathology. She was then treated with a combination of doxorubicin and L-asparaginase, to which there was minimal response, and was euthanased 4 months later.

DISCUSSION

Lymphoma is an important and relatively common canine tumour, with an increased breed prevalence reported in one study in the Boxer, Scottish terrier, basset, Airedale terrier, Chow, German shepherd, Poodle, Beagle, Golden retriever, Bulldog and St Bernard²², but not in the Rottweiler. In another study, breed predilection for lympho-proliferative diseases was identified and also that certain breeds (Golden retrievers, Labrador retrievers, Cocker spaniels, Rottweilers, Boxers,

German shepherd, and Doberman pinschers) were more likely to develop lymphomas¹¹, whereas there was no association with sex and neutering status. It remains, however, unusual that 2 Rottweiler siblings would develop stage IV lymphoma within 3 months of each other, both having a similar response to chemotherapy, and both showing subsequent relapse. In addition, the dam of the 2 siblings developed stage III lymphoma approximately 1 year after the siblings. Possible aetiologies for lymphoma in these Rottweilers would be genetic and/or environmental factors and/or infectious agents as the dogs were kept in the same household and fed the same food. Approximately 6 months after the lymphoma diagnoses in the 2 siblings the sire, also resident in the same household and exposed to the same food and environment, developed osteosarcoma of the distal radius. Osteosarcoma has no apparent environmental factor or infectious agent trigger but may have a genetic trigger^{13,15}. As diet can play a role in the development of tumours in humans, it is possible that the trigger for the lymphoma in these 3 dogs could have been a dietary carcinogen or a lack of essential fatty acids in the diet, possibly due to heat treatment, that might offer protection against environmental carcinogens. However, no one brand of food was exclusively fed to these dogs and there have been, to date, no reports of an increase in the incidence of lymphoma and other tumours associated with commercial dog food.

Although impaired humoral and cellular immunity have been described in dogs with lymphoma¹⁸, they have not been directly linked to a possible aetiological role. The immune system was not specifically assessed in these 3 Rottweilers but prior to chemotherapy all 3 dogs had normal white cell counts and distribution and normal serum globulins. There was also no report of chronic diseases that could have been associated with an impaired immune system such as pyoderma, respiratory and intestinal tract infections and chronic ehrlichiosis.

Exposure to herbicides has been speculated but not proven to be associated with lymphoma in the dog¹⁸. No herbicides were reported to have been used on the property where these Rottweilers were kept. After the initial diagnosis, the owners searched the property for any possible toxin, without finding any. In addition, no other dogs in the immediate area appeared to be affected and to date there has not been any evidence of other dogs or people from the area being diagnosed with lymphoma, or any other tumours. Further evidence against environmental

factors^{3,5,6} playing a role was that the dogs did not reside in an industrial area and there were no magnetic fields in the immediate surroundings.

Dogs with lymphoma have been shown to have a 2–180 times higher serum thymidine kinase (TK) activity than normal dogs and dogs with a TK activity >30 U/l had significantly shorter survival times²³. Of the dogs in this report 1 had a normal TK activity, whereas both had an activity of 33.7 U/l. In its sibling bitches TK activity was within normal range at the completion of the chemotherapy. Serum TK activity was not determined at the time of relapse. Thymidine kinase is a cellular enzyme which is involved in a salvage pathway of DNA synthesis and is activated in the growth phase of the cell cycle. Its activity has been shown to correlate with the proliferative activity of tumour cells. Clinical studies have reported high serum TK concentrations in a variety of neoplasias, the majority being haematological malignancies. Thymidine kinase appears to be a useful, non-invasive marker in lymphoma, where it correlates with clinical staging and provides marked prognostic information on survival¹⁰. It has also been shown that TK can be used as a powerful objective tumour marker for prognosis and for predicting relapse before recurrence of clinically detectable disease in dogs with lymphoma undergoing chemotherapy²³.

Single agent lymphoma chemotherapy protocols, except for doxorubicin, have a lower response rate that is not as durable as combination chemotherapy²⁰, which was apparent in the responses seen with these 3 dogs. The doxorubicin protocol was used because of the owner's travelling constraints.

In humans sporadic lymphomas account for the majority of lymphomas; however, familial predisposition alone or in combination with environmental or occupational exposures account for approximately 5 % of cases¹⁶. The genetic factors that influence the relative risk for lymphoma have been borne out by sib-pair, population genetic, and pedigree-based studies¹⁶. Increased risk of lymphoma in family members suggests an underlying genetic predisposition or defect; it may also result from shared exposure to environmental carcinogens, such as pesticides and herbicides¹⁶. Genetic studies in people with lymphoma have identified genes at both the HLA class region I and II loci¹⁶.

In humans familial Hodgkin's lymphoma is estimated to represent approximately 1–1.5 % of all cases of Hodgkin's lymphoma, with environmental factors, viral agents, and genetic determinants having

been proposed to explain familial aggregation of risk of Hodgkin's lymphoma¹⁹. Environmental factors and impaired immunity appear to be unlikely in this cohort of related Rottweilers and thus, as in people, it would appear that a genetic origin would be the most likely cause for the lymphoma in these 3 Rottweilers. Further substantiation for a familial link would be that all 3 dogs had a similar remission time and an overall poor prognosis, despite receiving chemotherapy.

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