Lymphoma in 3 related Rottweilers from a single household

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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.


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 anywhere. Lymphoma is reported most commonly as a haematopoietic neoplasm affecting the dog, with an incidence approaching 0.1%; 80% of lymphomas are seen in 5–11-year-old dogs.

The precise aetiology of lymphoma in the dog has not been identified although several hypotheses have been investigated but none definitively proven. Suggested aetiologies for canine lymphoma include retroviral infection, environmental contamination with phenoxyacetic acid herbicides, magnetic field exposure, chromosomal abnormalities, and immune dysfunction. 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.

Both somatic and germ line mutations in the tumour suppressor gene p53 have been reported in some cases and occasional clustering in related dogs has suggested a heritable component in limited instances.

In a prospective study in the Bull mastiff

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 spleen 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 centrolastic lymphoma on histopathology of the lymph nodes. Abdomi nal 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 centrolastic 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 Bernard,27 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 lymphomas28, 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.29,30 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 dog.23 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 factors254 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 times.22 Of the dogs in this report I 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 survival.18 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 chemotherapy.27 Single agent lymphoma chemotherapy protocols, except for doxorubicin, have a lower response rate that is not as durable as combination chemotherapy29 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 cases.36 The genetic factors that influence the relative risk for lymphoma have been borne out by sibpair, population genetic, and pedigree-based studies.36 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 herbicides.29 Genetic studies in people with lymphoma have identified genes at both the HLA class region I and II loci.11

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 lymphoma'. 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.

REFERENCES

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