

Overview of the Health Seminar at Cambridge held 5th October, 2013

Notes by

Liz Branscombe RVN, Dip AVN (Surgical); Member of the Health Sub-Committee Flatcoated Retriever Society

The morning session consisted of an overview of cancer and advances in diagnostics and treatment followed by an update on the department's work with Flatcoats including tumour survey, health study and death register.

Advances in diagnosis and treatment of cancers

- Advanced imaging-CT and MRI
- Immunohistochemistry- to aid diagnosis and grading of tumours via different staining techniques.
- Targeted treatments, directed at tumour growth factor receptors e.g. tyrosine kinase inhibitors, and cell surface antigens e.g. canine melanoma vaccine.

Tumour survey

Since its inception in 1990 over 3,000 samples have been processed (approx. 150 samples/year).

Most common tumour type of those submitted (>600) was benign histiocytomas.
>500 Soft Tissue sarcomas (histiocytic sarcoma), commonly forelimb, elbow region. Mean age 8-11yrs.

One third of the histiocytic sarcomas were located in internal organs commonly the spleen and often associated with anaemia.

Cause of death register

110 entries on register to Sept 2013, 80 dogs died from tumour related cause of which most were sarcomas.

Jane Dobson was keen to stress that they would like people to register all deaths and not just those that were tumour related*

Dr Fernando Constantino Casas, a pathologist gave an interesting lecture on the processes that are used to prepare and examine the tumour samples.

Dr David Sargan spoke next about the genetic aspects and difficulties associated with mapping genes within the genomes and highlighting markers. The summary given at the end of this lecture was:

- A DNA based test for histiocytic sarcoma still some way off
- Some mutations may be widespread throughout the breed however the full resolution of these mutations may offer prospects for more effective therapy.
- A new sarcoma classification tool is under development.

The next lecture was given by Dr Ola Marchniowska on Regulatory T cells and tumour immunity, Ola described the different forms of immunity, innate and adaptive and how these systems interact with tumours. Some tumours seem able to down regulate the immune system by stimulating regulatory T cells and for the first time the Cambridge group have documented the presence of regulatory T cells in histiocytic sarcomas. In order to investigate the role of immunity in histiocytic sarcomas fresh tumour samples are required.*

**Notes by Bärbel Kilian - General Committee of the Swiss Retriever Club;
(Breeding Committee of the Swiss Retriever Club 2004-2012; President of
the Breeding Committee 2006-2012)**

First of all I would like to thank Deborah Miller for the perfect organization of the seminar and the speakers for the very interesting lectures!

Dr Jane Dobson started the morning explaining what tumour suppressor genes are for. Tumour suppressor genes control cell division. If a cell has a defect the tumour suppressor genes either repair it or kill it to block uncontrolled growth of the defect cell. If tumour suppressor genes are mutated or even deleted the risk to develop cancer increases.

Overview

Approximately 20% of all dog cancers are soft tissue sarcomas (e.g. histiocytic sarcoma, osteosarcoma, hemangiosarcoma). Only 1% of human cancers are sarcomas. On the other hand dogs have no problems with lung cancer even if they live in a smoker household possibly due to their short life span. Also cancer of the colon and rectum is not seen very often in dogs due to different feeding (less saturate fats and red meat).

Unfortunately there is no dog cancer register available in the UK.

Certain dog breeds develop certain types of cancer which suggests that they have a genetic predisposition. This may be due to selection (unintentionally) on certain genes in pedigree dogs. The breeds with the highest incidence of cancer are: Bernese Mountain Dog, Flatcoated Retriever, Irish Wolfhound, Boxer, St. Bernard.

Treatment

Standard treatment options are:

- Surgery
- Radiation Therapy
- Chemotherapy

If a soft tissue sarcoma has been treated with surgery and radiation therapy 75% of dogs live longer than two years. With radiation therapy only 25% of dogs live longer than two years. Radiation therapy should be only used if necessary as the radiation itself can kick off cancer.

The survival time for dogs' diagnosed with lymphoma is poor as the dogs get resistant against the chemotherapy.

Early diagnosis

Is very complicated as there are no tumour markers available for dogs. Most of the tumour growth occurs before it can be seen on x-rays or any other modern imaging system.

Immunohistochemistry

Immunohistochemistry is used for better tumour diagnosis, grading as well as for targeted treatment of the tumour.

In earlier times it was not easy to determine if a cancer had a histiocytic background. Today immunohistochemistry is used to prove in samples/tissues antigens (e.g. proteins, bacteria etc.) using marked antibodies. Antigens connected to histiocytic sarcoma are vimentin, CD18 and MHC II.

Jane Dobson as well as Fernando Constantino Casas showed many pictures of tissues prepared with antibodies.

New treatment options

- Tyrosine kinase inhibitors e.g. Masivet used for treatment of mast cell tumours grade II and III
- monoclonal antibody, Herceptin – human breast cancer.
- Oncept (Merial) vaccination against canine oral melanoma. According to the producer the survival rate is 389 days against 60 – 150 days without vaccination. Jane Dobson stressed that the vaccination is expensive and the effect is not yet confirmed.

Jane Dobson has sent out letters to many owners of FCRs who provided blood/samples. She is interested to see if there is a connection between histiocytomas and cancer in either way (e.g. if histiocytomas at a young age lead to a better immunity). There are no results available at present.

Tumour survey

The survey started in 1990. Meanwhile 3000 samples of FCR were collected. 40% were malignant and 44% benign. (Related Study: Histopathological survey of neoplasms in flat-coated retrievers, 1990 to 1998)

174 Flatcoats took part in a lifetime study of which 42% died of tumours and 35% for other reasons. (Related Study: Mortality in a cohort of flat-coated retrievers in the UK)

Lately a cause of death register was set up. Jane Dobson emphasized that this is not a cancer register. Up to now most of the deaths reported were cancer related.

Tumor survey – what happens to your samples (Dr. Fernando Constantino Casas)

Dr. Casas explained how samples are processed, which different techniques were used to diagnose the type of cancer and how samples are stored. All participants were invited to have a look at samples Dr. Casas brought with him.

Regulatory T-cells (Tregs) & Tumour Immunity (Dr Ola Marchniowska)

The human immune system comprises of:-

- ❖ Innate immunity (fast and effective)
Macrophages, part of the innate immunity, are killer cells. They also stimulate lymphocytes to respond to pathogens.
- ❖ Adaptive (acquired) immunity (much more effective but takes longer to activate)
The cells of the acquired immune system are B- and T-lymphocytes. They are produced in the bone marrow. A subset of T-lymphocytes are Tregs (regulatory T cells).

Regulatory T cells may suppress the immune system's response to cancer cells, allowing them to grow and spread. The Cambridge group have identified the presence of T regs in histiocytic sarcomas using FOXP3 as a marker for these cells. This has important implications in understanding the role of the immune system in these cancers and potentially may provide a target for future therapies.

Jane Dobson and Ola Marchniowska have asked for “fresh samples” for their future studies into lymphocytes in histiocytic sarcomas. As soon as samples are stored in formaldehyde many new available tests cannot be performed.*

Genetic aspects of Cancer Dr David Sargan

David Sargan explained why after more than 20 years of research we are still waiting for the breakthrough: “National differences in genetic make-up caused difficulties!” The lead in mapping has the Ostrander Lab at the NIH in the States, working together with Cambridge, Reims/F (André) and Utrecht/NL (Rutteman). The latest news: Elaine Ostrander presented only a few days ago in Boston a large locus which is associated with visceral HS in FCRs. This locus still contains 8 million base pairs.

The DLA class II (dog leukocyte antigen) is not connected to a predisposition to develop cancer in FCRs. As in many other breeds, in FCRs two haplotypes are dominating. But they are shared between cases and controls.

Studies showed that in FCRs tumour suppressor genes are mutated. These mutations are heritable.

Some of the mutations may be widespread in the FCR population and might be a “founder effect”.

For the Bernese Mountain Dog a haplotype three genes were found on chromosome 11 which is connected to HS/osteosarcoma/fibrosarcoma. (Study: The MTAP-CDKN2A Locus Confers Susceptibility to a Naturally Occurring Canine Cancer, <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3392365/>)

David Sargan mentioned that a new sarcoma classification tool is under development.

Gastric dilatation & volvulus syndrome (GDV) (James Warland)

It is still not quite clear what causes GDVs. There are many studies but with totally different results. E.g. one study confirms a higher risk for females another one a higher risk for males.

What seems to be proven that first comes the gas and then the twist. A failure of gastric emptying/eructation (burping) occurs. Deep chested dogs and certain breeds (e.g. Great Dane) have a higher risk to develop GDV.

Why a GDV is an emergency:

- ❖ blockage of blood vessels
- ❖ damage to spleen and pancreas
- ❖ stops blood getting back to the heart
- ❖ insufficient oxygen to the heart

Risk factors:

- ❖ increasing age
- ❖ once daily feeding
- ❖ close relatives with GDV
- ❖ Stress/hospitalisation/kennelling
- ❖ feeding from a height

As a precautionary measure in breeds with disposition for GDV James Warland recommended that the stomach should be permanently fixed to the abdominal wall (gastropexy) e.g. when the dog is spayed. This should also be done after spleen removal.

Skin & Ear Disease (Dr Mark Reading)

Mark Reading started saying that Flatcoat owners can be happy because their dogs do not have many problems with skin & ear disease. That's why he was presenting no specific skin diseases in FCRS. Many skin diseases are a zoonosis. That's why he always asks the owner if he is facing skin problems as well.

- ❖ Demodex mites

It is now definitely confirmed that every dog has a couple of Demodex mites in his skin. The localized form doesn't need any treatment. It disappears itself. The generalized form is a severe condition. Affected dogs should not be used for breeding.

- ❖ Sarcoptes mites
- ❖ Ring worm (fungal infection)
- ❖ Herpes

Never use steroids in treating skin disease before you have a diagnosis as steroids can make it worse (e.g. Herpes, ring worm infections).

Idiopathic Epilepsy (Dr Nick Bexfield)

Epilepsy is not a disease itself but a clinical description for recurrent seizure activity. About 1.5 – 5.7% of the dog population are affected compared to 1 – 7% of humans. The difference is that a certain percentage of humans affected grow out of this condition. Idiopathic stands for: no known cause.

The death rate for a status epilepticus is 25 – 38% in dogs and about 22% in humans. Treatment depends on several factors. It always has to be taken into account that medication has many side effects.

According to several studies the Flatcoated Retriever is not a breed that has a higher incidence of epilepsy than the average dog population.

Nick Bexfield mentioned the study "Prevalence of inherited disorders among mixed-breed and purebred dogs":

<http://animalbiology.ucdavis.edu/Accomplishments/Inherited%20disorders%20with%20dogs.pdf>

Dilated Cardiomyopathy (DCM) Dr Barbara Skelly

DCM is a disease with a very poor prognosis and is an acquired disorder. Therefore it cannot be diagnosed at an early age.

There are at least four different forms of DCM in dogs:

- ❖ Boxer
- ❖ Doberman
- ❖ Other large dogs (Weimeraner, Dalmatian, Golden Retriever, Flatcoated Retriever)
- ❖ Giant dogs (Irish Wolfhound, St. Bernard, Great Dane)

For the Boxer and Doberman breed a DNA test is available which does not cover all cases of

DCM in these breeds.

For the development of DCM several genes some with a major and some with a minor impact as well as environment, feeding and exercise play a role.

Average survival time after diagnosis is 3 – 6 months for Dobermans and 6 – 12 months for Golden and Flatcoated Retrievers.

Barbara Skelly checked the Cambridge records for DCM cases in Flatcoated Retrievers and couldn't find many records. Also studies confirm that the Flatcoated Retriever is not prone to DCM.

(*These issues are being addressed)