Oncology: Case Report – Lymphoma

Abstract

This case study style lecture draws upon the previous oncology lectures to provide an in depth case study report of oncology veterinary nursing in practice. It follows the case of a canine patient with lymphoma through from presentation to diagnosis and to treatment and discusses the case in detail, so is an ideal lecture for any VN who has an interest in oncology.

Learning Outcomes

- Application of previous oncology knowledge in case study
- In-depth understanding of Lymphoma presentation, diagnosis and treatment.

Notes

Case: Buffy, a two year old female neutered Bernese Mountain Dog, with Multicentric Lymphoma

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Presentation:

The patient presented to her referring veterinary surgeon with a three week history of generalised lymphadenopathy, congested sclera, pyrexia, decreased exercise tolerance and upper respiratory tract noise during exercise. Thoracic radiographs (performed by the referring veterinary surgeon) revealed an area of consolidation at the caudal left lung lobe (considered to be lymphoid tissue) and a biopsy of the right pre-scapular lymph node revealed histopathological changes suggestive of lymphoma. Complete blood count revealed a marked lymphocytosis (10.29 x10^9/l – normal range 0.5-4.9). The dog was referred to our hospital for further oncological investigation and treatment. The dog had been vaccinated yearly and had not travelled outside the U.K.

Figure 1: The patient, Buffy, with massively enlarged submandibular lymph nodes.
On clinical examination at our clinic, the patient was bright, alert and responsive with a body weight of 45.6kg and a body condition score of 3/5. Rectal temperature was normal; pulse was strong and regular; respiratory rate was within normal limits, with inspiratory noise, but no increased effort. Much of the clinical examination was consistent with that of the referring veterinary surgeon, as detailed above. A generalised peripheral lymphadenopathy was evident (figure 1), and on abdominal palpation hepato-splenomegaly was marked. Polydipsia or polyuria was not reported. There was a healing incision over the biopsy site on the pre-scapular lymph node.

The patient's problem list was as follows: non-painful peripheral lymphadenopathy, bilaterally, reddened sclera, increased respiratory noise (whilst at exercise), lymphocytosis, decreased exercise tolerance, hepato-splenomegaly.

**Differential Diagnoses:**

- Lymphadenopathy may lead to a diagnosis involving infectious, neoplastic, immune-mediated or inflammatory causes.
  
  Lymphoma is a common neoplastic cause of multicentric lymphadenopathy in the dog.

  Other causes could include:

  - Reactive hyperplasia – a benign lymphadenopathy, reflecting activity of the node as part of the normal immune response.
  - Lymphadenitis (inflammation of the node) – primary or secondary. Due to an inflammatory/infectious process in the tissue drained by the node.
  - Mineral-associated lymphadenopathy – granulomatous lymphadenitis in which crystalline, mineral material accumulates within the node.
  - Metastatic neoplasia – may affect any lymph node which drains malignant neoplastic tissue.
  - Lymph node haemorrhage, infarction or oedema – due to changes in surrounding tissues.

- Lymphocytosis may indicate antigenic stimulation or lead to a diagnosis of leukaemia, depending on severity and lymphocyte morphology, e.g. acute lymphoblastic or chronic lymphocytic leukaemia.

**Diagnostics and Results:**

- Blood samples for a complete blood count (CBC), serum biochemistry and ionised calcium were taken. On CBC the total white blood cell count was 26.4 x10^9/l (6-15). The lymphocyte count was 13.4 x10^9/l (0.7-4.8). Atypical lymphocytes were noted on blood smear. Serum biochemistries, including ionised calcium were within normal limits.
- Urinalysis, including sediment examination was unremarkable.
Three-view inflated thoracic radiographs revealed marked cranial mediastinal and tracheobronchial lymphadenopathy (figure 2).

Abdominal ultrasound showed gross enlargement of the sublumbar and mesenteric lymph nodes. The liver and spleen contained multiple variably sized hypoechoic nodules throughout the parenchyma.

Transabdominal fine needle aspirate (FNA) biopsies from hepatic and splenic nodules and a mesenteric lymph node were sent for cytological examination. All sites were found to have a high number of abnormal lymphoid cells.

Bone marrow aspirates were taken from the left humeral tubercle. These had similar characteristics and cell numbers to the FNA samples (increased number of lymphoid cells – medium sized lymphocytes with multiple nucleoli and occasional mitosis) (figure 3).

Immunohistochemistry for T and B lymphocyte markers (CD3 and CD79a, respectively) showed the patient had B-cell LSA.

Tissue samples were not taken from the conjunctiva, but ocular involvement was suspected. (Signs resolved on commencement of chemotherapy.)

Figure 2: Cranial mediastinal lymphadenopathy ('photo: Andrew Denning, Imaging Referrals)

Figure 3: Equipment/set-up required for bone marrow aspiration – a Jamshidi needle was used. Slides are set up at a 45° angle in preparation for sample. Aseptic preparation of the patient is required.
Diagnosis and Prognosis:

Lymphoma (LSA) – stage V a (table 1)

Patients with stage V lymphoma are reported to have a worse prognosis and have a poorer expected response to chemotherapy with shorter remission times.

The patient was predicted to survive for one year – the median survival time for patients treated with a CHOP chemotherapy protocol.

Treatment:

Chemotherapy: Madison-Wisconsin (“CHOP”) protocol. CHOP stands for cyclophosphamide, hydroxydaunorubicin (doxorubicin), Oncovin® (vincristine), and prednisolone. When used in dogs, these drugs are rotated over a 19 week protocol (table 2).

Case Discussion:

Lymphosarcoma, or lymphoma (LSA), is the most common haematopoietic tumour in dogs. It is a systemic disease, which is quickly progressive and fatal without treatment. LSA is a round cell tumour which arises from lymphoid tissues, commonly bone marrow, thymus, lymph nodes and spleen, but may occur in any lymphoid cells. Patients are usually middle-aged, with Golden Retrievers, Boxers and Bull breeds being over-represented.

Clinical signs are often non-specific, e.g. anorexia, pyrexia, lethargy and/or unexplained weight loss, and depend on the anatomic region and extent of disease. Canine LSA occurs in various forms, with multicentric LSA (MC LSA) most commonly diagnosed. Signs may have a rapid onset, with peripheral lymphadenopathy, which may be localised or generalised – nodes may be non-painful, with patients remaining well, as in this case. Hepato-splenomegaly may be found on physical examination, indicating organ infiltration of malignant lymphocytes. Associated paraneoplastic syndromes may include hypercalcaemia, anaemia, thrombocytopenia, neutropenia, eosinophilia, myasthenia gravis and cancer cachexia.

Left untreated MC LSA can progress rapidly from presentation to the terminal stages in four-eight weeks. In end-stage disease, patients with a large tumour burden show signs of systemic illness, e.g. lethargy, weakness, anorexia and/or depression, usually being euthanased due to poor quality of life (QOL).

Diagnosis is made on FNA cytology or biopsy sample from affected lymph nodes. This patient was referred with a suspected diagnosis on cytology, but a wedge biopsy was taken from a superficial node to confirm. On histology, neoplastic cells were seen to replace lymph node parenchyma and bone marrow. As the patient had a lymphocytosis, bone marrow sampling was indicated, allowing confirmation of LSA and excluding leukaemia. Histopathology also allows grading of the tumour and may provide morphologic information, giving more accurate prognosis. The patient's tumour was not histologically graded as, whilst some oncologists consider that grade may affect prognosis. However, low grade lymphoma may have a more indolent course and different treatment than moderate-high grade lymphoma.
When a diagnosis of LSA has been reached, determining the extent of organ involvement with LSA is standard before treating – this is known as staging. Staging in this case included is detailed above. Staging aids prognostication and may help identify unrelated or concurrent problems (which are not uncommon in middle-aged or elderly patients) and may have an influence on prognosis or treatment planning.

Prognostic indicators include stage and sub-stage of disease, histological type, presence of paraneoplastic signs (e.g. hypercalcaemia), response to therapy, phenotype, pre-treatment steroid therapy (which can induce drug resistance). There was no evidence of hypercalcaemia in this case, the phenotype was B-cell (which is currently thought to reach longer survival, compared with T-cell), the patient remained well, responded rapidly to therapy and had not been pre-treated with steroids therefore, despite being a stage V, offered a more optimistic prognosis.

Systemic haemopoietic cancers, e.g. multicentric LSA are sensitive to chemotherapy. Successful treatment of MC LSA uses combination chemotherapy. This can induce a rapid response and improve and maintain patient quality of life. Current thinking suggests that relatively short, but intensive chemotherapy protocols (e.g. 19/25 week CHOP protocols containing doxorubicin), as opposed to maintenance protocols (such as COP protocols), provide higher remission rate and prolonged survival times, therefore CHOP is first-line protocol used at our hospital. On CHOP it is expected that >80% of patients will go into remission and median survival times are quoted as one year, with 50% patients exceeding this.

Combining cytotoxic drugs is an important, effective strategy, designed to target different parts of the cell cycle to increase the proportion of total tumour cells that are killed. When drugs are used in combination, they often enhance each other’s activities. Combining drugs also minimises dose-limiting toxicities and helps reduce the development of tumour resistance – cells resistant to one drug may be sensitive to another within that regimen.

Single-agent chemotherapy is considered less effective, but can be used for palliation only. Corticosteroids are an option for owners who are not keen to pursue chemotherapy, with a 50% response and clinical remission maintained from few weeks up to 2-3 months. However sick patients, with advanced stage disease are unlikely to benefit from steroid therapy and, if a clinical improvement is not noticed, euthanasia should be considered to prevent further deterioration and suffering due to the tumour.

Cytotoxic treatment of tumours relies on triggering programmed cell death (or apoptosis). Normal cells have the ability to detect toxic insult and undergo appropriate apoptosis. Treatment of LSA is aimed at exploiting this response to kill a susceptible cell population. However, cancer cells are genetically unstable and undergo mutations at each replication, allowing for drug resistance. Cells which were originally susceptible to chemotherapy drugs develop resistance by multi-drug resistance (MDR). MDR is thought to be the reason for treatment failure in many canine lymphoma patients – when this occurs the patient will relapse.

LSA treatment in humans offers significantly higher cure rates than veterinary medicine and therapy includes bone marrow transplantation, combined with high-dose chemotherapy. However these strategies have high toxicity rates, which would be unacceptable for veterinary patients' quality of life. Doses used in veterinary oncology are approximately 1/3 those used in human cancer therapy, with the caveat that cure is unlikely; nevertheless long-term survivals are achieved.
Whatever the treatment options pursued, owners should be made aware from the outset that the goal in the majority of cases is to maintain optimum QOL for their pet, as opposed to longevity. When the diagnosis of LSA was made, the owners were carefully counselled on what to expect during the pet’s chemotherapy, the anticipated chances and duration of remission, potential side-effects, health and safety issues, as well as estimated cost of treatment. (See this author’s previously published article on the Use of Chemotherapy for Veterinary Nurses in Practice). The CHOP protocol is expensive and weekly treatments involve a substantial commitment of time and emotion from owners. The owners elected to commence therapy in this patient.

Following confirmation of diagnosis, the patient was prepared for chemotherapy and the 1st dose of vincristine (0.7mg/m²) was given intravenously.

The patient was hospitalised overnight to monitor for possible tumour lysis syndrome, given presence of a high tumour burden. This syndrome may occur when cancer cells are rapidly killed and results in metabolic complications, including hyperkalaemia, hyperphosphataemia, hyperuricaemia, hypocalcaemia and acute renal failure. It may be seen in LSA patients, as multiple organs / nodes may carry a heavy tumour burden

A monitoring and emergency action plan was drawn up for the patient; however she remained well, with no problems encountered overnight and was discharged the following day. A 4 week course of prednisolone was dispensed (initially 2mg/kg orally every 24 hours, with food), decreasing weekly (table 2).

Steroids are commonly used in the treatment of LSA. However, it is contra-indicated to use corticosteroids before a definitive diagnosis is made. As well as inducing drug resistance, their rapid lymphocytolytic effects may obscure a diagnosis unless lymph nodes aspirates or biopsy samples have been obtained in advance. Steroids may be started after obtaining samples in patients whose clinical signs are unmanageable or are hypercalcaemic, but ideally they are introduced at the beginning of a chemotherapy protocol.

The patient was seen one week later for re-examination and cyclophosphamide administration. She was bright, alert and responsive and the owners reported no adverse effects following treatment; temperature, pulse and respiration were within normal limits and there had been a dramatic response to therapy – whilst the peripheral lymph nodes were still palpable, they were smaller and softer and on abdominal palpation the liver and spleen were markedly decreased in size.

When administering cyclophosphamide, users should be aware of a serious potential side-effect of the drug, which is sterile haemorrhagic cystitis – this is caused by excretion of irritant drug metabolites. Regular urine sampling prior to each cyclophosphamide treatment was performed in this patient to avoid problems and adequate hydration was maintained during administration. Our hospital protocol pre-medicates canine patients with 1mg/kg furosemide to encourage diuresis; this has shown to decrease risk of development of bladder toxicity. No blood was detected in the urine and CBC was within normal limits, so the drug was administered without incident. The owners were advised to allow frequent toilet opportunities on each evening following administration of cyclophosphamide.

The patient was seen on a weekly basis and managed as an outpatient. Each week a physical examination and collection of blood for CBC +/- urine samples was performed. The CHOP chemotherapy protocol was checked, completed and updated weekly, with salient points noted as appropriate. The owners were regularly liaised with to assess progress / address any questions or concerns and to provide regular home-care advice. The patient remained
persistently bright and well, with a stable body weight and condition score and the owners were pleased with progress. She maintained a solid partial remission until the first doxorubicin administration at week four of the protocol. Following this treatment the patient went into complete remission and was clinically normal, with no palpable lymph nodes or organomegaly. The patient had no adverse events or treatment gaps until week 18 of the protocol. At this point treatment had to be delayed as the neutrophil count was low – 1.62 x10^12/l (3.6-12). Neutropenia occurs due the myelosuppressive effects of cytotoxic drugs. The nadir generally occurs at seven-ten days post-treatment, therefore performing a CBC before subsequent therapy is essential. The patient’s blood counts were within normal limits the following week and the protocol was resumed. We do not routinely re-stage patients at the end of chemotherapy, unless there are any clinical concerns, but monitor their clinical status on a monthly basis. This patient is currently at her one-year re-visit and is still in remission. She remains fit and well and lives a normal life, unaffected by her cancer or its treatment.

Bibliography/Further Reading:

- Study of dog and cat owners’ perceptions of medical treatment for cancer.
- Brønden LB, Rutteman GR, Flagstad A, Teske E.

Table 1 – Modified WHO lymphoma staging:

<table>
<thead>
<tr>
<th>Stage I:</th>
<th>Involvement limited to a single node or lymphoid tissue in a single organ (excluding bone marrow)</th>
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</thead>
<tbody>
<tr>
<td>Stage II:</td>
<td>Involvement of multiple lymph nodes in a regional area</td>
</tr>
<tr>
<td>Stage III:</td>
<td>Multiple sites on either side of the diaphragm</td>
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<tr>
<td>Stage IV:</td>
<td>+ Hepato-splenomegaly</td>
</tr>
<tr>
<td>Stage V:</td>
<td>+ Bone marrow +/- Pulmonary involvement</td>
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</tbody>
</table>

Sub-stages:

- a) without systemic signs, i.e. patient is clinically normal
- b) with systemic signs, i.e. patient is unwell, has paraneoplastic signs, etc.
Table 2 – 19 Week Canine ("CHOP") Lymphoma Protocol

<table>
<thead>
<tr>
<th>Week</th>
<th>Drug</th>
<th>Dosage</th>
<th>Route</th>
<th>Kg/m²</th>
<th>Dose</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Vincristine</td>
<td>0.5-0.7mg/m²</td>
<td>IV</td>
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<tr>
<td></td>
<td>Prednisolone</td>
<td>2mg/kg SID</td>
<td>PO</td>
<td></td>
<td></td>
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<tr>
<td>2</td>
<td>Cyclophosphamide</td>
<td>250mg/m²</td>
<td>IV/PO</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Furosemide</td>
<td>1mg/kg</td>
<td>IV/SC</td>
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</tr>
<tr>
<td></td>
<td>Prednisolone</td>
<td>1.5mg/kg SID</td>
<td>PO</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>3</td>
<td>Vincristine</td>
<td>0.5-0.7mg/m²</td>
<td>IV</td>
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<td></td>
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</tr>
<tr>
<td></td>
<td>Prednisolone</td>
<td>1.0mg/kg SID</td>
<td>PO</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Doxorubicin</td>
<td>30mg/m²</td>
<td>IV</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Prednisolone</td>
<td>0.5mg/kg SID</td>
<td>PO</td>
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<td>5</td>
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<td></td>
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<tr>
<td>6</td>
<td>Vincristine</td>
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<tr>
<td>7</td>
<td>Cyclophosphamide</td>
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<td></td>
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<tr>
<td>8</td>
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<td>IV</td>
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<tr>
<td>9</td>
<td>Doxorubicin</td>
<td>30mg/m²</td>
<td>IV</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

If patient is in complete remission at week 9, continue onto page 2 and repeat cycle as above to 19 weeks.

**N.B. perform a routine haematology prior to and 7 days after each treatment.**