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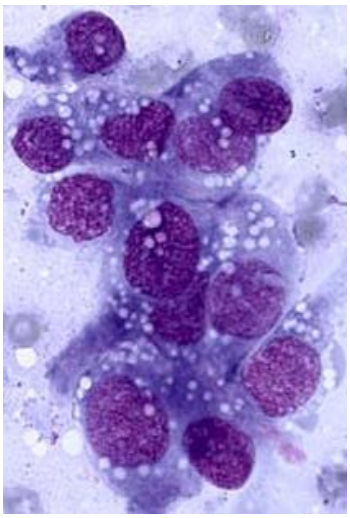
Treating aggressive sarcomas & carcinomas in Small Animal Practice Mini Series

Session Two: All about bone tumours & splenic tumours



Treating Aggressive Sarcomas and Carcinomas
Study Notes: Session 2

2a: Splenic Tumours & Haemangiosarcoma

I've got a dog with a splenic mass lesion. What are the chances of it being a haemangiosarcoma?

Approximately 2/3 of canine splenic tumours are malignant, and out of those a further 2/3 are haemangiosarcomas. So, in other words about 44% are haemangiosarcomas. In the context of a haemoabdomen however, haemangiosarcoma accounts for approximately 2/3 of the cases. Some of the other malignant differentials can have good survival times with splenectomy alone, for example marginal zone lymphoma (not to be confused with a "normal" multicentric lymphoma) or some sarcomas. Histiocytic sarcoma or haemangiosarcoma of the spleen represent two of the most important aggressive tumours of the spleen for which chemotherapy is indicated.

How can I tell whether a splenic tumour is benign or malignant without biopsy or splenectomy?

There's no reliable way other than visualizing metastases. The absence of mets doesn't rule out a malignancy though! A large primary mass in the absence of metastasis is *suggestive* of a benign lesion or low-grade malignancy however we can't rely on this alone! The occurrence of haemoabdomen makes a malignant tumour more likely although any kind of splenic lesion can rupture.

The dog has obvious metastases. There's no hope. Right ?

The survival time for metastatic haemangiosarcoma cases is actually not different from non-metastatic cases, providing they are treated appropriately with chemotherapy post surgery. The reported median survival time for surgery + chemo is in the region of 6 months, versus 6-8 weeks for surgery alone. In the case of splenic histiocytic sarcoma however (a much rarer diagnosis), the existence of metastasis at diagnosis will negatively affect the prognosis.

The most important consideration in dealing with a haemangiosarcoma (of any location other than dermal, or perhaps lingual) is that it should be considered a systemic, medically-treated disease. It develops from malignant transformation of circulating blood vessel precursor cells (produced in the bone marrow); although the cancer cells are often found in a discrete mass lesion, the fact that malignant transformation has occurred elsewhere underlines that the cells are mobile and disease is systemic. In metastatic cases there is often debate about whether one tumour is "primary" and the others represent metastasis, or whether the disease is simply multicentric in nature. Owing to a large proportion of cells actively dividing, haemangiosarcoma is equivalently chemosensitive and should expect a similar overall survival time to many cases of multicentric T cell high-grade lymphoma. Surgery does not directly treat the disease, it is simply a "first-aid" measure to address catastrophic haemorrhage or to address "ticking time-bombs" (lesions about to rupture). Splenic or right-auricular lesions are frequently considered good surgical candidates (in the latter case this is because the lesions are *usually* well-pendunculated).

Can haemangiosarcoma occur elsewhere ?

Yes – it can occur anywhere with blood vessels ! However visceral locations are the most common. The localisation of the disease will affect the metastatic propensity and survival times. Most visceral locations will expect a metastatic rate of at least 90% (kidney slightly less), whereas the subcutaneous or intramuscular masses have a varied rate of metastasis between 30-80%. Dermal lesions have a metastatic rate of 0-30% and are often cured with surgical excision. Lingual lesions (rare in the UK) behave similarly. A small number of primary lymph node haemangiosarcomas (among other locations) have been described and their course of disease has been aggressive.

What chemotherapy treatments are recommended for haemangiosarcoma?

The standard-of-care is one injection of doxorubicin every 3 weeks for up to 6 doses. Other chemotherapy drugs can be given in between doxorubicin doses to intensify the treatment if desired but few studies have shown survival times beyond 6-9 months for the majority of dogs. Metronomic chemotherapy has been shown to produce survival times of approximately 6 months post surgery in non-metastatic cases (exactly how they fare when disease is widely-metastatic is unknown). Tyrosine kinase inhibitors are sometimes used as well, although evidence to hand does not support their use.

After 6 cycles of doxorubicin-based chemotherapy, tradition has involved stopping all treatment. In the face of an unwaveringly aggressive disease this is a peculiar practice. Although we are right to be concerned about making dogs unwell with an extended course of chemotherapy, consideration should be given to trying to maintain the disease control using, for example metronomic chemotherapy rather than "submitting" to the disease. This approach hasn't been well-evaluated at the moment, but it is the choice of the author to transition dogs onto a metronomic chemotherapy protocol after six cycles of doxorubicin-based treatment and to maintain this, with regular imaging until disease recurs. When disease recurs, rescue agents like dacarbazine have been used with varying success.

Use of doxorubicin is a subject that courses much concern to many vets, but often for the wrong reasons. It is certainly a highly-vesicant drug, but providing a perfectly-placed first-stick IV catheter is used, and the infusion given with diligent monitoring, the risk of extravasation can be successfully controlled. Doxorubicin is certainly cardiotoxic too and pre-treatment echocardiography is advisable, however the risk of cardiotoxicity is often over-shadowed by rapid and aggressive dissemination of cancer which will occur if doxorubicin is not given, making the balance of risk and benefit clear. Providing doxorubicin is given over 20-30 minutes, continuous monitoring with ECG is not necessary.

The most common and often the dose-limiting toxicity of doxorubicin is gastrointestinal; typically diarrhoea and vomiting occurring 2-4 days post dosing. In some cases this can be serious and necessitate hospitalisation of the dog for intravenous fluids and supportive care. When the author uses doxorubicin, an initial dose of 27mg/m2 (a 10% reduction from the normal starting dose of 30mg/m2) is used for cases with pre-existing GI disease (or a history of poor dietary tolerance of many foods). Maropitant is given before the procedure (either IV or oral) and then for 3-4 days afterwards at home. Omeprazole and metronidazole are used to treat mild to moderate gastrointestinal upsets as an outpatient. Most cases of doxorubicin treatment are without severe adverse event however, and the benefit of the drug clearly outweighs the attendant risk.

What about haemangiosarcoma in cats ?

In cats, haemangiosarcoma lesions are equally-distributed between skin/subcutis and visceral sites. The cutaneous / subcutaneous tumours are extremely invasive (a 60-80% rate of local recurrence has been reported) but the rate of metastasis is considered to be low (owing to the rarity of these tumours a metastatic rate has not been established). Complete excision could therefore cure cats with local disease only, however high rates of recurrence are reported. Feline visceral haemangiosarcomas have a metastatic rate similar to their canine counterparts.

2b: Bone Tumours & Osteosarcoma

Do I need to take a bone biopsy?

Why not do an FNA? Fine needle aspiration of bone lesions can be an effective way of demonstrating cancer cells and this is often all the information you need to decide the first step in treatment (surgery in most cases). The precise tumour type (e.g. chondrosarcoma versus osteosarcoma) is usually less important at this stage, but knowing whether the lesion is inflammatory or neoplastic is key.

To get a good cell harvest with an FNA of a bone you need a very different aspirate technique to that for a lymph node however. Try the following and see what you think :

- Use a long 21g needle with 10ml syringe attached
- Insert into the middle of the lesion and apply 5-10mls negative pressure.
- Move the needle back and fore / re-angle it several times, keeping negative pressure applied.
- Release negative pressure immediately before withdrawal of the needle.
- You will get a lot of blood with this method, but also a decent yield of neoplastic cells, so make at least 10 slides, and stain 1-2 in-house and check to make sure you have caught cells other than blood / inflammation before sending them off.
- This technique is cheaper, and quicker than a bone biopsy, and avoids the risk of pathologic fracture!

If the radiologic findings convincingly demonstrate a bone tumour, isn't it a waste of the client's money to pursue a diagnosis before amputation?

The successful treatment of most osteolytic cancers will hinge around local control of the tumour, and in many cases this will involve limb amputation. Nevertheless histiocytic sarcoma is a notable exception where hypofractionated radiation therapy produces great results, returning most cases rapidly to full weight-bearing. The dog's breed and the anatomic location of the lesion may affect the suspicion of this particular malignancy versus osteosarcoma. Cytology should be adequate for diagnosis of a histiocytic sarcoma (or even rarer bone tumours for example lymphoma or plasma cell tumours which can sometimes be treated medically).

Do I really need to x-ray the chest ?

Although metastasis at the time of osteosarcoma diagnosis is uncommon (less than 20%), the presence of gross pulmonary metastasis will significantly diminish the prognosis for canine osteosarcoma from approximately 1 year to approximately 3 months. The client may find this staging information useful in deciding whether to proceed with surgery and chemotherapy.

Additionally, a number of bone tumours are in fact metastatic lesions (for example urogenital carcinomas), or part of a systemic disease process (for example multiple myeloma, haemangiosarcoma or lymphoma).

Should the dog have an orthopaedic assessment first?

In most cases, dogs will have been effectively 3-legged for the last few weeks due to non-weight-bearing lameness, so the ability to cope on 3 legs will have already been demonstrated. However, it is always prudent to consider the orthopaedic function of the remaining limbs before an irreversible amputation surgery, and in these increasingly-litigious times we should document that we have done this. Particularly where chronic orthopaedic disease exists or is suspected assessment from by an orthopaedic surgeon may be very helpful.

Is limb-sparing surgery any good ?

Limb-sparing surgery has its' place, but it's not appropriate for every case. Currently, the procedure is only suitable for distal radial tumours, with a small tumour size and minimal involvement of soft tissues. Sadly many bone tumours are diagnosed at other locations or at a more advanced stage. The majority of dogs receiving limb-sparing operations (regardless of technique) have a high rate of complications for example infection and implant failure. Dogs with scapula tumours or ulna tumours can do very well simply with scapulectomy or ulnectomy however.

If I know it's a cancer do I need to send the amputated leg for histo?

For the tumours which are treated with amputation, post-operative chemotherapy is indicated in some diagnoses, but not others. And for those where chemo is indicated, the drugs used and protocol will differ depending on the diagnosis. So, for prognostic and therapeutic purposes then, obtaining the diagnosis is vital!

"I'd go for surgery, but I wouldn't put him through chemo…"

This attitude is understandably held by a number of clients, but their perception is ill-founded! Chemotherapy in dogs (in particular the treatments used for osteosarcoma) will be associated with a normal quality of life throughout treatment; side effects will either be absent, or mild and self-limiting. Therefore we need to educate our clients that side effects of chemo will be no more likely or no more severe than treatment for many other chronic medical conditions, and is often "putting him through" much less than surgery!

What does the post-op chemo consist of?

The standard-of-care adjuvant chemotherapy treatments would either be carboplatin or doxorubicin, single-agent, given intravenously. Neither drug has been found to be superior, and an alternating protocol has shown no benefit. Since carboplatin is cheaper, and has fewer potential side effects, this drug is used as single-agent most commonly.

Carboplatin can cause acute nausea and so premedication with maropitant (oral or IV) is necessary. Providing anti-nausea medication is given, gastrointestinal adverse effects are very rare. The point of maximal myelosuppression can be very variable with this drug however, and delayed neutropaenias (and thrombocytopaenias) are infrequently recognised. Rather than checking for neutropaenia 7 days after the drug is given, 2 blood tests at 10 days and 14 days is more commonly practiced. Once the nadir has been established as "safe" the author does not perform further nadir checks after subsequent injections. Carboplatin can cause nephrotoxicity (although it is much less nephrotoxic than cisplatin!) and so it is advisable to check kidney function before each dose, and consideration should be given to administration of the drug in running saline.

Client refuses surgery. Is there any benefit of just medical treatment ?

This situation is always a concern. Osteolytic lesions are extremely painful, and care has to be taken to preserve the dog's welfare. The stoic nature of many dogs may lead clients to erroneously believe that their pets are not as painful as they actually are. If the client opts for palliative treatment, palliative-intent radiation therapy (1 dose, once weekly for 3-4 weeks at most centres) is the most analgesic treatment we can consider and all RT centres will be happy to provide this. Osteoclast inhibitors (for example pamidronate or zoledronate, given by intravenous infusion every few weeks), are also very analgesic and can be used with or without radiation therapy. Systemic analgesics should be used in all cases but even a combination of a non-steroidal drug, tramadol and gabapentin are unlikely to be adequate on their own. With multi-modality palliative care, the average survival time is in the order of 5-6 months.

What about bone tumours in cats ?

Primary bone tumours in cats are rare, but 67-90% are malignancies. Approximately 70-80% of the malignant lesions are osteosarcomas, with fibrosarcoma, chondrosarcoma and haemangiosarcoma making up the bulk of the remainder. Osteosarcomas in cats are much less aggressive than those in dogs, with fewer than 10% being reported to metastasize. Radiographic findings can look deceptively non-aggressive! Osteosarcomas of the appendicular skeleton are often cured with limb amputation however those of the axial skeleton have a reported median survival time in the order of 7 months; in many cases this is due to the difficulty of adequate local control rather than any inherent difference in the biology of the disease. Adjunctive chemotherapy in cats is not indicated after adequate local control.

Reference Books for this Course:

- Withrow, Vail, Page; "Withrow & Macewen's Small Animal Clinical Oncology;" 5th Edition; Elsevier.
- Raskin, Meyer; "Canine and Feline Cytology: A Color Atlas and Interpretation Guide;" 3rd Edition; Elsevier

Further Reading for Session 2:

- VAC Protocol for Treatment of Dogs with Stage III Hemangiosarcoma; Alvarez, Hosoya, Lara-Garcia et.al; J Am Anim Hosp Assoc 2013; 49:
- Evaluation of outcome associated with subcutaneous and intramuscular hemangiosarcoma treated with adjuvant doxorubicin in dogs: 21 cases (2001–2006); Bulakowski, Philibert, Siegel et.al; J Am Vet Med Assoc 2008;233:122–128
- Survival time of dogs with splenic hemangiosarcoma treated by splenectomy with or without adjuvant chemotherapy: 208 cases (2001–2012); Wendelburg, Price, Burgess et.al ; J Am Vet Med Assoc 2015;247:393–403
- Continuous Low-Dose Oral Chemotherapy for Adjuvant Therapy of Splenic Hemangiosarcoma in Dogs; J Vet Intern Med 2007;21:764–769
- Comparison of Carboplatin and Doxorubicin-Based Chemotherapy Protocols in 470 Dogs after Amputation for Treatment of Appendicular Osteosarcoma; L.E. Selmic, J.H. Burton, D.H. Thamm, S.J. Withrow, and S.E. Lana; J Vet Intern Med 2014;28:554–563
- Osteosarcoma following tibial plateau leveling osteotomy in dogs: 29 cases (1997–2011); Selmic et.al.; J Am Vet Med Assoc 2014;244:1053–1059
- The Immunotherapy of Canine Osteosarcoma: A Historical and Systematic Review; K.L. Wycislo and T.M. Fan; J Vet Intern Med 2015
- Carboplatin versus alternating carboplatin and doxorubicin for the adjuvant treatment of canine appendicular osteosarcoma: a randomized, phase III trial; Skorupski et.al; et Comp Oncol. 2016 Mar; 14(1): 81–87.
- Limb-sparing surgery versus amputation for dogs with bone tumors; Straw, Withrow; Vet Clin North Am Small Anim Pract. 1996 Jan;26(1):135-43
- Percent tumor necrosis as a predictor of treatment response in canine osteosarcoma; Powers et.al; Cancer. 1991 Jan 1;67(1):126-34