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Case Report
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Malignant pilomatricoma in a dog with local and distant metastases treated with chemotherapy and bisphosphonates

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Abstract
A ten-year-old male neutered cross breed dog presented for evaluation of a mass associated with the left scapular bone, identified as a carcinoma. The dog had a malignant pilomatricoma removed from the left lateral thigh 6 months earlier. Histopathology review of the cutaneous and scapular mass identified the same tumour type, confirming metastatic disease; additional metastases to the inguinal lymph node, liver and lungs were identified. Chemotherapy resulted in partial responses/stable disease of very short duration. Bisphosphonates were administered due to lack of a measurable response and worsening of the associated lameness. The patient ultimately developed a symptomatic vertebral metastasis and was euthanased. The dog survived 255 days since medical treatment was started and 455 days since surgical removal of the primary tumour. This case report suggests that medical treatment with the addition of analgesia may be able to palliate clinical signs and possibly extend survival in dogs with metastatic epithelial cancer.
Keywords: Bisphosphonates, Chemotherapy, Dog, Malignant pilomatricoma, Metastases.

Introduction

Cutaneous carcinomas are infrequently reported in dogs. Their biological behaviour has not been extensively characterised, although carcinomas originating from any anatomic location are reported to metastasize to regional lymph nodes, lungs, brain and internal organs (Trost *et al*., 2014; Simmons *et al*., 2015). Pilomatricoma is an adnexal neoplasm with follicular differentiation similar to matrical cells of the hair bulb, which occurs in middle-aged to older dogs; although it is more commonly reported to have an indolent behaviour, the presence of its malignant counterpart has been described, though the incidence appears to be extremely low (Goldschmidt *et al*., 1981; Goldschmidt, 2002).

The current literature about malignant pilomatricoma is mainly limited to histopathological and immunohistochemical studies (Carroll *et al*., 2010; Bongiovanni *et al*., 2011; da Silva *et al*., 2012); nuclear expression of β-catenin has been described in a single case report (Martano *et al*., 2013), where the authors concluded that its upregulation could be involved in the pathogenesis of malignant pilomatricoma. In the same study, surgical excision of the primary tumour was performed but the dog subsequently developed bone metastases treated with amputation of the affected limb; following this, the patient was eventually euthanased with no further treatment.

When looking at the veterinary literature, malignant pilomatricoma appears to metastasise to different organs. Previous reports of metastases to lymph nodes (Sells and Conroy, 1976; Rodriguez *et al*., 1995; Carroll *et al*., 2010), bone (Sells and Conroy, 1976; Rodriguez *et al*., 1995; Carroll *et al*., 2010; Martano *et al*., 2013), lungs (Sells and Conroy, 1976; Johnson *et al*., 1983; Rodriguez *et al*., 1995; Carroll *et al*., 2010) and skin (Johnson *et al*., 1983; Martano *et al*., 2013) exist. These tumours appear to metastasise less commonly to the liver and spleen (da Silva *et al*., 2012) and the mammary gland (Carroll *et al*., 2010).

Neoplasms that arise primarily from the bone can involve the skeleton or secondarily invade or metastasise to it. Several additional tumour types have a predilection to involve bone, including metastatic carcinoma (Fan, 2014). Bone cancer is capable of compromising bone mineral density and therefore causing severe pain, and can increase the risk of a pathologic fracture (Fan, 2014). Palliative treatment for bone cancer involves various treatment strategies, including radiotherapy (Coomer *et al*., 2009) and bisphosphonates (Fan *et al*., 2005, 2007), which can be considered when owners decline amputation or in case of metastatic tumours. Zoledronate (Fan *et al*., 2008) and pamidronate (Fan *et al*., 2005, 2007) have been shown to effectively control cancer pain. Intravenous pamidronate appears to attenuate malignant bone resorption, improves weight-bearing capacity of diseased limbs and alleviates bone cancer pain associated with focal malignant osteolysis (Fan *et al*., 2005, 2009).

The use of adjuvant chemotherapy in those pilomatricomas that have locally metastasized at the time of diagnosis has never been described and it is therefore unclear whether this type of treatment may be

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able to delay the onset of distant metastases. Similarly, it is unclear whether chemotherapy and/or palliative treatments may have the potential to extend survival by delaying time to progression and attenuate clinical signs in those cases that are metastatic at the time of diagnosis.

The aim of this case report was to describe a case of malignant pilomatricoma that had metastasised to multiple organs including bone, and had been treated with chemotherapy and bisphosphonates. To the authors' knowledge, there are no cases of a metastatic malignant pilomatricoma treated with chemotherapy or other palliative treatment.

Case details

A ten-year-old, male neutered cross breed dog, was referred to our institution with a history of acute onset of a 10/10 left fore limb lameness and a left scapular mass involving the bone, cytologically and histopathologically diagnosed as a carcinoma. A matrical cell carcinoma (pilomatricoma) was removed from the left flank 6 months earlier by the referring veterinarian. When staging was performed at that time, thoracic radiographs and abdominal ultrasound did not show any evidence of distant metastases. Surgical margins could not be assessed due to only a portion of the mass being submitted for histopathology.

On physical examination, the dog was bright, alert and responsive. Body weight at the time of initial presentation was 15 kg (BCS 5/9). Mucous membranes were pink and moist with a capillary refill time of 1 second. Examination of the oral cavity was unremarkable as well as thoracic auscultation. Abdominal palpation was not painful and showed no abnormalities. However, the left inguinal lymph node was found to be enlarged and firm, measuring 2.5 x 3 cm. A 14 x 12.7 cm, hard and fixed bony mass was identified at the level of the left scapula and was not overtly painful on palpation. Rectal examination was unremarkable. Upon admission, a complete blood cell count (CBC), biochemistry profile and urinalysis were performed. There was evidence of a mild thrombocytosis (PLTs 554 x 10^9/L, RI 150-400), suspected to be either paraneoplastic or possibly consistent with gastro-intestinal bleeding and an elevated alkaline phosphatase (ALP, 216 U/L, RI <130 U/L), consistent with either the presence of a bone tumour contributing to elevation of the bone ALP (BALP) due to osteolysis and/or concurrent cholestasis/hepatopathy. Urinalysis was unremarkable.

The dog was sedated for a contrast-enhanced computed tomography (CT) of the thorax and abdomen. CT showed the presence of a destructive bony mass at the level of the left scapular bone (Fig. 1), with associated contrast-enhancing liver nodules. Occasional, small nodules were also present in the left cranial lung lobe.

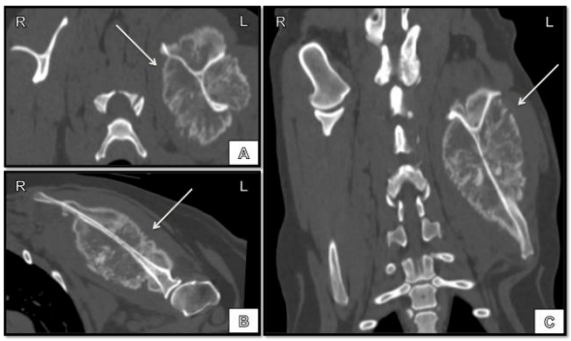

Fig. 1. Sagittal **(A)** and transverse **(B, C)** view of the scapular mass (arrow), histopathologically confirmed to be a metastatic carcinoma.

Following the CT scan, ultrasound-guided fine needle aspirates (FNAs) of the liver and FNAs of the left inguinal lymph node was performed; FNAs of the left scapular mass were repeated to assess for the presence of the same neoplastic population within all the sampled organs. The cytology samples were examined by a board-certified clinical pathologist, showing the same population of atypical epithelial cells, consistent with a metastatic carcinoma (Fig. 2A-C). The biopsy sample collected from the left scapular mass by the referring veterinarian and the one originally submitted from the cutaneous mass 6 months earlier were sent for a second opinion and examined by a different board-certified pathologist.

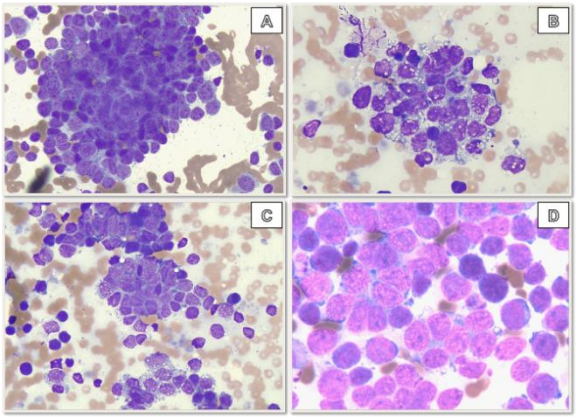

Fig. 2. Cytology of carcinoma metastases identified during the course of the disease: **(A):** left scapular mass (Wright Giemsa, 50x magnification); **(B):** liver (Wright Giemsa, 50x magnification); **(C):** left inguinal lymph node (Wright Giemsa, 50x magnification); **(D):** right orbital mass (Diff-Quick, 100x magnification). There are high numbers of atypical cells. They are seen in variably sized, apparently cohesive clusters. Occasional acinoid formations are found. The N:C ratio is high and anisokaryosis and anisocytosis are mild. Nuclei are medium sized, round and central to paracentral. Occasional hyperchromatic nuclei are seen. The chromatin is coarsely stippled and occasionally multiple small, round and variably prominent nucleoli are present. The cytoplasm is scant and lightly to moderately basophilic.

The sample removed from the left flank was composed of skin and subcutis. Within the subcutis there was an irregular neoplastic nodule with a few areas of infiltration into the surrounding adipose tissue. The nodule was composed of cuboidal to polygonal epithelial cells arranged in solid lobules and cystic structures with central accumulation of keratin. The keratinization was abrupt with formation of ghost cells (cells with faded nuclei) indicating matrical differentiation (Fig. 3).

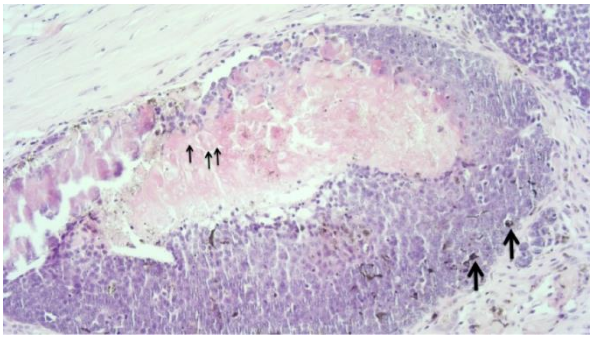

Fig. 3. Malignant pilomatricoma (left flank mass). Neoplastic lobule composed of epithelial cells with high nuclear/cytoplasmic ratio and occasional intracytoplasmic melanin (thick arrows). Neoplastic cells surround a central area of keratin accumulation with numerous ghost cells with faded nuclei (thin arrows). Haematoxylin and eosin, 10x magnification.

Multifocal foci of dystrophic calcification and osseous metaplasia were also noticed within the accumulated keratin. Neoplastic cells had a high nuclear/cytoplasmic ratio, scant eosinophilic cytoplasm and hyperchromatic round nuclei with indistinct nucleoli. Melanin was noticed in the cytoplasm of a few neoplastic cells. Anisocytosis and anisokaryosis were moderate and mitoses ranged from 2 to 5 per high power field (40x). Scattered throughout the neoplasm there were a few apoptotic cells, small foci of necrosis and a few areas of fibrosis and inflammation (macrophages, lymphocytes and multinucleated giant cells). At the periphery of the neoplasm, a neoplastic embolus was noticed in a lymphatic vessel.

These histological features and in particular the extensive matrical differentiation and lymphatic vascular invasion allowed to classify this tumour as a malignant pilomatricoma.

The biopsy collected from the left scapular mass mainly consisted of trabeculae of immature bone (remodeled bone), multifocally infiltrated by neoplastic epithelial cells (Fig. 4). These neoplastic cells were similar to those observed in the left flank mass and therefore consistent with a bone metastasis of the previously diagnosed malignant pilomatricoma. The bone was surrounded by areas of fibrosis and a few atrophic striated muscle fibers.

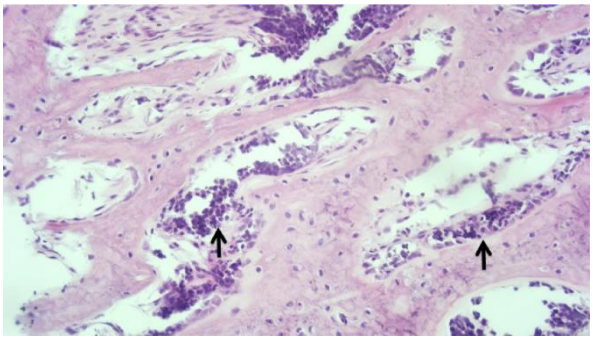

Fig. 4. Bone metastasis of malignant pilomatricoma (biopsy from left scapula). Epithelial cells (arrows) with high nuclear/cytoplasmic ratio and hyperchromatic nuclei infiltrate the space between trabeculae of remodeled woven bone. Haematoxylin and eosin, 10x magnification.

The dog was started on an intended initial dose of 3.25 mg/kg of toceranib phosphate PO 3 times/week (on Monday, Wednesday, Friday), which was rounded to the closest 3 mg/kg dose and firocoxib 5 mg/kg PO q 24 hours (on the days toceranib phosphate was not administered). Additional oral analgesia was prescribed as gabapentin at 10 mg/kg q 8 hours and codeine phosphate plus paracetamol at 10 mg/kg PO q 12 hours. The patient experienced no adverse events other than transient anorexia (VCOG grade I toxicity) for 48 hours and a full haematology and biochemistry profile repeated 3 weeks later was unremarkable. The owner also reported the dog appeared comfortable, although still reluctant to walk at times. A repeat CT scan 43 days later showed evidence of stable disease (SD), with no gross variation in appearance and measurements of the scapular mass, left inguinal lymph node, liver and pulmonary nodules.

The dog was seen 15 days later and showed evidence of progressive disease (PD) on measurements of the scapular mass. Following a full haematology and biochemistry that did not show any remarkable findings, intravenous carboplatin was therefore administered at a dose of 300 mg/m^2 as a slow IV bolus over 10 minutes diluted with 0.9% NaCl, following premedication with IV maropitant at 1 mg/kg, once every 21 days. Additional oral maropitant at 2 mg/kg was prescribed after discharge to be used for up to 4 days if necessary. No toxicity was identified after the first carboplatin treatment and the patient received the second treatment uneventfully. However, at the time of the third carboplatin treatment (43 days since the first one was administered), PD was evident based on measurements of the scapular mass and inguinal lymph node and and the lameness also progressed further. At that time, palliative radiotherapy for analgesia and/or other alternative chemotherapy were offered but declined by the owner. They opted to start palliative treatment with bisphosphonates. Following a biochemistry profile, which revealed normal renal

parameters, pamidronate was started at 2 mg/kg as an IV infusion over 2 hours every 21 days. At this time the lameness score was 8/10 and the dog experienced a significant improvement in the pain score following the first 2 treatments (42 days later), following which his lameness was graded as a 6/10. The owner also felt the dog's quality of life was vastly improved and his demeanour was back to normal.

Seventy-seven days later, the dog's clinical examination revealed the presence of a hard, bony lesion at the level of the right periorbital area, which was confirmed to be a metastatic carcinoma on cytology (Fig. 2D). Treatment with pamidronate was continued, but given the clinical evidence of PD, metronomic cyclophosphamide was started at 15 mg/m^2 q 24 hours, along with carprofen at 2 mg/kg q 24 hours. Oral analgesia was also continued with gabapentin and paracetamol/codeine as before.

A dry cough developed 31 days later and thoracic radiographs were performed. They did not show any evidence of progression of the previously identified pulmonary metastases and the cough resolved after a course of antibiotics (in case of infectious aetiology) and codeine (as a cough suppressant) initiated by the referring veterinary surgeon. However, PD was incidentally found at the time the dog represented to us and restaged with three-view thoracic radiographs: an additional metastasis to the right scapular bone was identified and confirmed on cytology. The patient received another pamidronate infusion (at the previously used dose) on the same day and this was repeated 21 days later.

After 231 days since metastatic disease was diagnosed and treatment started, the dog developed progressive weakness on the rear limbs and associated discomfort. The dog presented at day 235 and a neurological examination identified mild proprioceptive deficits on both hind limbs. A contrast CT of head, thorax and abdomen was performed. CT of the head confirmed an osteolytic lesion at the level of the right maxillary bone (Fig. 5A) and the previously reported metastatic lesion at the level of the right scapular bone (Fig. 5B). There were multiple pulmonary nodules as previously described on the initial CT study and an additional lytic lesion at the level of L4, with spinal cord compression, which was compatible with a vertebral metastasis. A fourth pamidronate infusion was administered and oral analgesia continued (gabapentin and carprofen with the addition of tramadol). The dog's condition improved and appeared comfortable again. At day 255 the patient developed hyporexia and worsening neurological signs; at that stage, the dog was humanely euthanased. The overall survival was 255 days after the dog first presented to us and 455 days since the dog underwent surgical removal of the primary tumour.

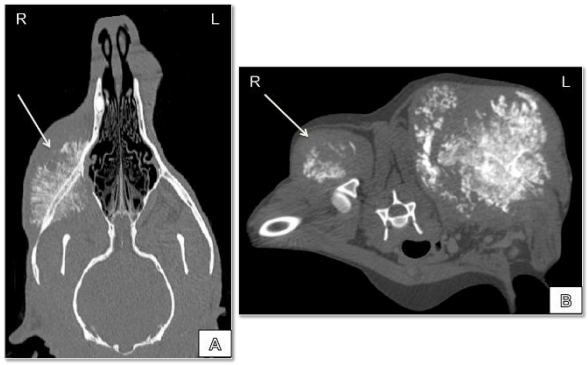

Fig. 5. (A): transverse view of the right orbital bone metastasis (arrow); **(B):** sagittal view of bilateral scapular metastases at the time of the patient's last restaging. Note the arrow indicating the bone metastasis involving the right scapular bone (previously identified on radiographs) and progression of the left scapular mass when compared to the initial CT study (Fig. 1).

Discussion

This case report describes a case of a malignant pilomatricoma that had metastasised 6 months after surgical removal, highlighting the need for tumour staging at the time of diagnosis. Although most tumours of this kind may have a perceived low risk for metastases, there is evidence that some of them may exhibit aggressive behaviour; therefore serial monitoring may be indicated, particularly in the first 6-12 months, which was the presumed time frame for onset of distant metastases in our case. Clinical signs usually manifest when osseous metastases develop, with subsequent osteolysis and the need for medical intervention. In this case, metastases to multiple bones developed during the course of the disease, despite chemotherapy, and neurological signs became evident at the time the vertebral metastasis was identified. It is unclear whether metastases to the inguinal lymph node developed prior to distant bone metastasis, as they were found simultaneously, and it is possible that the left inguinal lymph node enlargement went undetected because of its external location. Tumour margins could not be determined but the dog did not develop tumour recurrence over the months, which may imply complete excision was achieved; however, this was largely irrelevant given the widespread metastases found at the time of referral.

Chemotherapy with TKIs or other conventional, cytotoxic chemotherapy was started 6 months after surgery was performed, at the time local and distant metastases were identified; thus was able to provide SD for a short period of time (58 and 43 days, respectively), but we cannot exclude that no adjuvant treatment could have equally resulted in SD. It is possible therefore that early, adjuvant chemotherapy may be able to delay the onset of distant metastases in such cases if used

immediately following surgery rather than treating in the setting of macroscopic metastatic disease.

The use of toceranib phosphate has been reported to achieve partial responses or SD in dogs with different solid tumours (London *et al*., 2012), including various types of carcinomas. In this dog, toceranib was used as first line due to ease of administration and tolerability, which was important to the owner. Conventional chemotherapy with platinum agents was chosen based on reported efficacy in various types of carcinomas (Boria *et al*., 2005; Dominguez *et al*., 2009) as well as metronomic chemotherapy, which has been previously administered to dogs with different solid tumours (Burton *et al*., 2011; Spugnini *et al*., 2014), although we were able to achieve only short-lived responses.

The dose of bisphosphonates was chosen based on a recent study where dogs treated at 2 mg/kg were found to have lower levels of N-telopeptide in the urine, suggesting a reduction in focal osteolysis, earlier than dogs receiving a dose of 1 mg/kg, although the difference was not statistically significant (Fan *et al*., 2007). The dose appeared to be well tolerated despite the administration schedule was shorter than the one previously described (Fan *et al*., 2005, 2007). Concurrent use of NSAIDs and other analgesic drugs was only able to marginally control the pain prior to bisphosphonates use, and as such pain alleviation can most likely be attributed to treatment with pamidronate. Additionally, response to bisphosphonates should not be exclusively assessed based on the lameness score, as this may simply reflect a functional problem rather than ongoing pain, and quality of life (QoL) scores should also be considered. In fact, generalised pain, discomfort and deterioration of QoL were the main reasons that led the owners to elect for euthanasia in this case.

This case report suggests that patients with metastatic carcinomas treated palliatively with chemotherapy, bisphosphonates and other analgesic drugs may enjoy a prolonged survival despite the presence of widespread metastases at the time of diagnosis.

The use of chemotherapy and bisphosphonates in dogs with osseous metastases warrants further investigation and the use of adjuvant chemotherapy alone may be able to delay the onset of distant metastatic disease in those pilomatricomas that have already metastasised to the draining lymph node. In addition, medical treatment may be able to prolong survival by providing analgesia and possibly delaying disease progression.

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Conflict of interest

The authors declare that there is no conflict of interests.

References

Bongiovanni, L., Malatesta, D., Brachelente, C., D'Egidio, S. and Della Salda, L. 2011. beta-catenin in canine skin: immunohistochemical pattern of expression in normal skin and cutaneous epithelial tumours. J. Comp. Pathol. 145, 138-147.

Boria, P.A., Glickman, N.W., Schmidt, B.R., Widmer, W.R., Mutsaers, A.J., Adams, L.G., Snyder, P.W., DiBernardi, L., de Gortari, A.E., Bonney, P.L. and Knapp, D.W. 2005. Carboplatin and piroxicam therapy in 31 dogs with transitional cell carcinoma of the urinary bladder. Vet. Comp. Oncol. 3, 73-80.

Burton, J.H., Mitchell, L., Thamm, D.H., Dow, S.W. and Biller, B.J. 2011. Low-dose cyclophosphamide selectively decreases regulatory T cells and inhibits angiogenesis in dogs with soft tissue sarcoma. J. Vet. Intern. Med. 25, 920-926.

Carroll, E.E., Fossey, S.L., Mangus, L.M., Carsillo, M.E., Rush, L.J., McLeod, C.G. and Johnson, T.O. 2010. Malignant pilomatricoma in 3 dogs. Vet. Pathol. 47, 937-943.

Coomer, A., Farese, J., Milner, R., Liptak, J., Bacon, N. and Lurie, D. 2009. Radiation therapy for canine appendicular osteosarcoma. Vet. Comp. Oncol. 7, 15-27.

da Silva, E.O., Green, K.T., Wasques, D.G., Chaves, R.O., dos Reis, A.C. and Bracarense, A.P. 2012. Malignant pilomatricoma in a dog. J. Comp. Pathol. 147, 214-217.

Dominguez, P.A., Dervisis, N.G., Cadile, C.D., Sarbu, L. and Kitchell, B.E. 2009. Combined gemcitabine and carboplatin therapy for carcinomas in dogs. J. Vet. Intern. Med. 23, 130-137.

Fan, T.M. 2014. Pain management in veterinary patients with cancer. Vet. Clin. North Am. Small Anim. Pract. 44, 989-1001.

Fan, T.M., Charney, S.C., de Lorimier, L.P., Garrett, L.D., Griffon, D.J., Gordon-Evans, W.J. and Wypij, J.M. 2009. Double-blind placebo-controlled trial of adjuvant pamidronate with palliative radiotherapy and intravenous doxorubicin for canine appendicular osteosarcoma bone pain. J. Vet. Intern. Med. 23, 152-160.

Fan, T.M., de Lorimier, L.P., Charney, S.C. and Hintermeister, J.G. 2005. Evaluation of intravenous pamidronate administration in 33 cancer-bearing dogs with primary or secondary bone involvement. J. Vet. Intern. Med. 19, 74-80.

Fan, T.M., de Lorimier, L.P., Garrett, L.D. and Lacoste, H.I. 2008. The bone biologic effects of zoledronate

in healthy dogs and dogs with malignant osteolysis. J. Vet. Intern. Med. 22, 380-387.

Fan, T.M., de Lorimier, L.P., O'Dell-Anderson, K., Lacoste, H.I. and Charney, S.C. 2007. Single-agent pamidronate for palliative therapy of canine appendicular osteosarcoma bone pain. J. Vet. Intern. Med. 21, 431-439.

Goldschmidt, M.H. 2002. Tumours of the skin and soft tissues, Vol. 4th Edition. Meuten DJ, Ames.

Goldschmidt, M.H., Thrall, D.E., Jeglum, K.A., Everett, J.I. and Wood, M.G. 1981. Malignant pilomatricoma in a dog. J. Cutan. Pathol. 8, 375-381.

Johnson, R.P., Johnson, J.A., Groom, S.C. and Burgess, L. 1983. Malignant pilomatrixoma in an old english sheepdog. Can. Vet. J. 24, 392-394.

London, C., Mathie, T., Stingle, N., Clifford, C., Haney, S., Klein, M.K., Beaver, L., Vickery, K., Vail, D.M., Hershey, B., Ettinger, S., Vaughan, A., Alvarez, F., Hillman, L., Kiselow, M., Thamm, D., Higginbotham, M.L., Gauthier, M., Krick, E., Phillips, B., Ladue, T., Jones, P., Bryan, J., Gill, V., Novasad, A., Fulton, L., Carreras, J., McNeill, C., Henry, C. and Gillings, S. 2012. Preliminary evidence for biologic activity of toceranib phosphate (Palladia®) in solid tumours. Vet. Comp. Oncol. 10, 194-205.

Martano, M., Navas, L., Meomartino, L., Abramo, F., Restucci, B., Maiolino, P. and Muzio, L.L. 2013. Malignant pilomatricoma with multiple bone metastases in a dog: Histological and immunohistochemical study. Exp. Ther. Med. 5, 1005-1008.

Rodriguez, F., Herraez, P., Rodriguez, E., Gomez-Villamandos, J.C. and Espinosa de los Monteros, A. 1995. Metastatic pilomatrixoma associated with neurological signs in a dog. Vet. Rec. 137, 247-248.

Sells, D.M. and Conroy, J.D. 1976. Malignant epithelial neoplasia with hair follicle differentiation in dogs. Malignant pilomatrixoma. J. Comp. Pathol. 86, 121-129.

Simmons, J.K., Hildreth, B.E., 3rd, Supsavhad, W., Elshafae, S.M., Hassan, B.B., Dirksen, W.P., Toribio, R.E. and Rosol, T.J. 2015. Animal Models of Bone Metastasis. Vet. Pathol. 52, 827-841.

Spugnini, E.P., Buglioni, S., Carocci, F., Francesco, M., Vincenzi, B., Fanciulli, M. and Fais, S. 2014. High dose lansoprazole combined with metronomic chemotherapy: a phase I/II study in companion animals with spontaneously occurring tumors. J. Transl. Med. 12, 225.

Trost, M.E., Inkelmann, M.A., Galiza, G.J., Silva, T.M. and Kommers, G.D. 2014. Occurrence of tumours metastatic to bones and multicentric tumours with skeletal involvement in dogs. J. Comp. Pathol. 150, 8-17.