Pulmonary metastatectomy in the management of four dogs with hypertrophic osteopathy

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Abstract
The efficacy and outcome of pulmonary metastatectomy in the management of hypertrophic osteopathy (HO) secondary to metastatic osteosarcoma was retrospectively evaluated in four dogs. Metastatectomy was performed by subpleural enucleation, partial lung lobectomy or complete lung lobectomy through either a median sternotomy or thoracoscopically. Perioperative morbidity was minimal. Clinical signs associated with HO resolved within 24 h of pulmonary metastatectomy in all dogs. Durable remission of symptomatic HO was achieved in all dogs (range, 50–294 days), although recurrence of HO was noted in one dog, 246 days postmetastatectomy due to metastasis to the lungs and chest wall. Pulmonary metastatectomy resulted in a rapid and prolonged resolution of HO, and the clinical benefits of metastatectomy potentially exceed the morbidity associated with the surgical procedure.

Keywords
hypertrophic osteopathy, metastasis, metastatectomy, osteosarcoma, thoracoscopy

Introduction
Hypertrophic osteopathy (HO) is a poorly understood condition commonly associated with primary and metastatic pulmonary neoplasia (Brodey, 1971; Hansen-Flaschen & Nordberg, 1987). Other reported causes of HO in dogs include non-neoplastic intrathoracic diseases and extrathoracic, non-metastatic genitourinary malignancies (Brodey, 1971; Halliwell & Ackerman, 1974; Caywood et al., 1980; Rendano & Slauson, 1982; Randolph et al., 1984; Caywood et al., 1985; Hesselink & van den Tweel, 1990; Wylie et al., 1993; Masegi et al., 1994; Hara et al., 1995; Peeters et al., 2001). The pathophysiology of HO is unknown. An autonomic neurovascular reflex mediated by afferent branches of the vagus or intercostal nerves and resulting in a rapid increase in peripheral blood flow is the most commonly proposed cause of HO (Brodey, 1971). Peripheral vasodilation results in the characteristic smooth to palisading periostium proliferation in long bones of the extremities (Pineda et al., 1987; Allan, 1998). In contrast to humans, articular involvement has not been reported in animals and the term HO is preferred to hypertrophic osteoarthropathy (Brodey, 1971).

Vasodilation-induced periostitis causes the characteristic clinical signs of HO, such as non-oedematous and painful swelling of the distal limbs, lameness and a reluctance to rise or ambulate (Brodey, 1971; Hansen-Flaschen & Nordberg, 1987). These signs often precede and have a more profound negative impact on quality of life than the clinical signs associated with the primary disease (Brodey, 1971). Treatment options for
HO include surgical removal or irradiation of the inciting cause, sectioning of the vagal or intercostal nerves to interrupt afferent stimulation, chemotherapy and palliative analgesia using agents such as non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, opioids, octreotide and pamidronate (Watson & Porges, 1973; Uchiyama et al., 1985; Hansen-Flaschen & Nordberg, 1987; Campeau et al., 1989; Hahn & Richardson, 1989; Roos, 1996; Yeo et al., 1996; Johnson et al., 1997; Speden et al., 1997; Suzuma et al., 2001; Garske & Bell, 2002). Surgical resection is the preferred technique but is not always feasible, particularly with diffuse metastatic disease. Pulmonary metastatectomy has been recommended in dogs with metastatic osteosarcoma (OSA) when local disease is controlled for more than 300 days and there are less than three metastatic lesions (O’Brien et al., 1993). However, the role of metastatectomy in the management of HO in dogs with metastatic OSA is poorly defined, particularly if the guidelines for pulmonary metastatectomy are not satisfied. The aim of the present study was to report the outcome and feasibility of metastatectomy in dogs with HO secondary to metastatic OSA.

Materials and methods

The medical records at Colorado State University Veterinary Teaching Hospital were reviewed for dogs in which pulmonary metastatectomy was performed to manage HO secondary to metastatic OSA between June 1987 and December 2002. Inclusion criteria included dogs with metastatic OSA to the lungs, performance of metastatectomy with the intention of managing clinical signs associated with HO and the availability of complete medical records with adequate follow-up information.

The records of each dog were reviewed and information recorded on signalment, site and treatment of the original OSA lesion, presenting signs, physical examination and surgical findings, adjunctive treatment and postoperative outcome. Outcome was evaluated from the medical records and telephone interview with the owner and referring veterinarian. The onset of response was defined as the period from metastatectomy to resolution of clinical signs associated with HO. The duration of response was defined as the period between resolution of clinical signs and either recurrence of these symptoms or death. Metastasis-free interval (MFI) and survival time were defined as the period from surgical ablation of the primary OSA to diagnosis of metastasis and death, respectively.

Results

Case 1

A 4-year-old, male Great Dane was diagnosed with an OSA of the mid-diaphysis of the right ulna. Regional, thoracic and bone survey radiographs confirmed localized, stage IIB OSA with no evidence of metastasis. Initial treatment included two doses of neoadjuvant intra-arterial cisplatin at 70 mg m$^{-2}$, 10 fractions of 2.8 Gy of preoperative radiation to the right ulna using a Monday-Wednesday-Friday protocol for a total dose of 28 Gy, and a limb-sparing procedure with segmental resection of the tumour and reconstruction of the diaphyseal defect with an intercalary cortical allograft stabilized with an intramedullary pin proximally and two crossed Kirschner wires distally. Histological examination of the bone specimen revealed incomplete resection with neoplastic cells at the distal and proximal osteotomy sites. Postoperative chemotherapy was not administered. The dog recovered uneventfully with good to excellent postoperative limb function.

The dog was examined 183 days after limb-sparing surgery because of a 5-day history of lethargy, shifting four-legged lameness and swelling of the distal aspects of all four limbs. The dog was obtunded with difficulty rising from a recumbent position, tachycardic (heart rate 160 beats per minute), pyrexic (rectal temperature 39.9 °C) and the distal aspect of all four limbs were swollen, warm and painful on palpation.

A mild elevation in serum alkaline phosphatase (ALP) activity (106 IU L$^{-1}$) [reference range (RR) 18–86 IU L$^{-1}$] was the only abnormality detected on routine screening with haematology, serum biochemistry and urinalysis. Three-view thoracic radiographs confirmed a right osteosarcoma with mediastinal adenopathy. A second postoperative episode of HO was managed with a combination of opioids and intravenous saline and meloxicam. The dog was observed without further episodes of HO until 18 months after limb-sparing surgery when a computed tomography scan confirmed a right thoracotomy approach to resection of OSA with concurrent right thoracotomy to resect the mediastinal lymph node. The dog underwent right thoracotomy approach to OSA resection and was discharged without complication.
radiographs revealed four soft-tissue densities, ranging from 1 to 5 cm in diameter, in the right and left lung fields. Abnormalities on regional radiographs of the right antebrachium included a focal area of cortical bone lysis in the mid-radius adjacent to the allograft, progressive lysis of the distal allograft and a periosteal reaction along the diaphysis of all four metacarpal bones. These radiographic findings were consistent with multifocal pulmonary metastasis, local recurrence of the bone tumour and HO.

A median sternotomy was performed with the intent to explore the thoracic cavity and resect grossly evident pulmonary nodules. Six metastatic lesions were detected in the right cranial (1), right middle (1), cranial and caudal lobes of the left cranial (2) and left caudal lung lobes (2). These masses were resected by complete lobectomy of the right cranial lung lobe using a surgical stapler [thoracoabdominal (TA)-55 mm stapler (Auto Suture TA Premium 55; United States Surgical Corporation, Norwalk, CT, USA)], partial lobectomy of the right middle and left cranial lung lobes with a TA-55 stapler, and subpleural enucleation of two lesions in the left caudal lung lobe. Oxymorphone was administered subcutaneously every 4 h for postoperative analgesia. Metastatic OSA was confirmed following histological assessment of the pulmonary masses.

Clinical signs attributed to HO, such as lethargy, lameness and pyrexia, resolved within 24 h of surgery. The radiographic signs of HO were resolving 4 weeks postoperatively despite evidence of a new metastatic lesion in the left cranial lung lobe. Symptomatic relief of HO continued without ancillary treatment until the dog was euthanased 50 days postmetastatectomy for metastatic disease. A necropsy revealed multifocal metastasis to the left cranial lung lobe, right ventricle, liver, kidneys, adrenal glands, left eye, and multiple appendicular and axial skeletal sites. The overall MFI was 183 days and survival time was 239 days.

Case 2

A 6-year-old, female spayed Golden Retriever was diagnosed with OSA in the left distal humerus. Treatment included forequarter amputation and chemotherapy starting 18 days postoperatively with cisplatin at 70 mg m$^{-2}$ (2) and carboplatin at 300 mg m$^{-2}$ (2) administered sequentially every 3 weeks for four doses in total.

The dog was examined 243 days postoperatively because of a 3-week history of lethargy, lameness and swelling of the distal aspects of all three legs. Doxycycline was administered prior to evaluation and did not improve the signs. On physical examination, the dog was lethargic, reluctant to ambulate, pyrexic (rectal temperature 40.0°C) and had painful swelling of the distal aspect of the three remaining limbs. No abnormalities were detected on haematology, serum biochemistry or urinalysis. A single soft-tissue density was noted in the caudodorsal thorax on thoracic radiographs.

A median sternotomy was performed to explore the thoracic cavity. A TA-30 stapler was used to resect a single lesion in the accessory lung lobe. Intrapleural lidocaine and bupivacaine was administered every 4 h for postoperative analgesia. Metastatic OSA was confirmed following histological assessment of the pulmonary mass.

Lethargy and lameness resolved within 24 h of surgery. The dog was treated with piroxicam following metastatectomy. Radiographic evidence of HO was present 4 weeks postoperatively despite resolution of clinical signs. Clinical signs of HO did not recur and the dog was euthanased 51 days postmetastatectomy as a result of metastatic splenic haemangiosarcoma. The overall MFI was 243 days and survival time was 295 days.

Case 3

A 7-year-old, male castrated Labrador Retriever was diagnosed with OSA of the left proximal tibia. Treatment included pelvic limb amputation and adjuvant chemotherapy with an alternating course of doxorubicin at 30 mg m$^{-2}$ and carboplatin at 300 mg m$^{-2}$ administered every 3 weeks for six doses in total. The dog recovered uneventfully from surgery and completed the chemotherapy course without complication.
Pulmonary metastasis was suspected 623 days postoperatively when a single, ill-defined, 1 cm diameter mass was noted superimposed over the cardiac silhouette in the right middle or caudal lung lobe. However, metastatic disease could not be confirmed due to the ill-defined radiographic appearance, and the growth rate of the mass was observed with thoracic radiographs repeated on a monthly basis. In 5 months, the mass had increased in size by approximately 50% to 1.5 cm in diameter and no new masses were evident. Biopsy of a diaphyseal lesion in the left third metatarsal bone confirmed metastatic OSA.

Digit amputation and metatarsalecтомy were performed 680 days postamputation.

The dog was examined 929 days postoperatively because of a 2-week history of shifting lameness. On physical examination, the dog had a non-painful swelling of the distal aspect of the three remaining limbs. Mild anaemia was noted on haematology [packed cell volume (PCV) 39%, RR 43–58%]. Serum biochemical abnormalities included mild hypoalbuminaemia (2.9 g dL\(^{-1}\), RR 3.0–4.5 g dL\(^{-1}\)) and increased ALP activity (209 IU L\(^{-1}\)). Thoracic radiographs revealed two soft-tissue densities in the right caudal lung lobe. Radiographs of the left thoracic and right pelvic limbs showed a diffuse periosteal reaction, ranging from smooth to palisading, along the metacarpi, radius, ulna, metatarsi, calcaneus, tibia and fibula.

A technetium\(^{99m}\) hydroxymethylene diphosphonate (Tc\(^{99m}\) HDP) (Mallinckrodt Inc., St. Louis, MO, USA) scan was performed with delayed-phase images showing focal areas of intense uptake in the distal right ulna, proximal right humerus, distal left antebrachium, proximal left humerus, second and fifth metacarpal bones and right metatarsal bones. Metastatectomy was recommended for palliation of the clinical signs of HO as the lameness did not resolve following administration of two doses of pamidronate 4 weeks apart.

The dog was placed in left lateral recumbency, and thoracoscopic examination of the right hemithorax was performed following bronchoscopic placement of a bronchial blocker in the right mainstem bronchus and initiation of one-lung ventilation. Three intercostal portals were inserted for a 30\(^{\circ}\) forward oblique 5.0 mm rigid thorascopic retractor and scissors with cautery connection. A large mass was identified in the right caudal lung lobe; however, no further lesions were noted. Complete lobectomy of the right caudal lung lobe was performed by sequential stapling with a 60 mm, 45 mm and then 30 mm endoscopic linear stapler (Endo GIA; United States Surgical Corporation). The resected lung lobe was grasped with an endoscopic clamp and lateralized to the thoracic wall. The portal incision was then extended into a mini-intercostal thoracotomy for removal of the lung lobe. Postoperative analgesia included a continuous rate infusion of fentanyl for 36 h, intrapleural lidocaine and bupivicaine every 4 h for 36 h, oral morphine for 5 days and oral piroxicam for 21 days. Metastatic OSA was confirmed following histological assessment of the pulmonary mass.

Lameness resolved within 24 h of thoracoscopic lung lobectomy. The dog was treated with piroxicam and pamidronate following metastatectomy. There was no change in the severity of the periosteal reaction for 8 months postoperatively based on serial radiographic examinations. Shifting lameness and swelling of the distal limbs recurred 246 days postmetastatectomy. Thoracic radiographs revealed multiple pulmonary metastases. The dog was euthanased 15 days after recurrence of symptomatic HO due to metastasis to the lungs, multiple subcutaneous sites, and right thoracic wall and humerus. The overall MFI was 623 days and survival time was 1191 days.

**Case 4**

An 8-year-old, female spayed Rottweiler was diagnosed with OSA of the left distal radius. Regional and thoracic radiographs and whole body Tc\(^{99m}\) HDP scan confirmed localized, stage IIB OSA with no evidence of metastatic disease. The limb was salvaged with resection of the distal radial tumour and reconstruction of the radial defect with an investigational endoprosthesis. An alternating course of doxorubicin at 30 mg m\(^{-2}\) and carboplatin at 300 mg m\(^{-2}\) was administered every 3 weeks for six doses in total.

The dog was examined 221 days postoperatively because of a 2-week history of lethargy, shifting four-legged lameness and swelling of the distal...
aspects of all four legs (Fig. 1). Clinical signs were not improved by oral carprofen administration. On physical examination, the dog was lethargic and reluctant to rise from a recumbent position with painful swelling of the distal aspect of the limbs. Abnormalities detected on routine screening tests included anaemia (PCV 35%) and increased serum ALP activity (233 IU L⁻¹). Thoracic radiographs revealed two soft-tissue densities, 3 cm in diameter, in the right cranial and middle lung lobes (Fig. 2). Radiographs of the left and right thoracic and pelvic limbs showed a diffuse periosteal reaction, ranging from smooth to palisading, along bilateral metacarpal and carpal bones, radii, ulna, metatarsal and tarsal bones, tibia, fibula and femurs (Fig. 3). A Tc⁹⁹m HDP scan was performed with delayed-phase images showing areas of intense uptake in all four limbs distal to the mid-humeri and mid-femurs (Fig. 4).

The dog was placed in left lateral recumbency, and thoracoscopic examination of the right hemithorax was performed as previously described. Large pulmonary masses were detected in the dorsal aspect of the right cranial and caudal lung lobes. Complete lobectomy of both lobes was performed with a 60 mm endoscopic linear stapler (Fig. 5). Postoperative analgesia included a continuous rate infusion of fentanyl for 18 h, intrapleural lidocaine and bupivacaine.

Figure 1. Distal thoracic limb (A) and pelvic limb (B) of an 8-year-old Rottweiler with diffuse, non-oedematous swelling of all four limbs as a result of hypertrophic osteopathy secondary to metastatic osteosarcoma.
every 4 h for 18 h and oral piroxicam for 21 days. Metastatic OSA was confirmed following histological assessment of the pulmonary mass.

Lameness resolved within 24 h of thoracoscopic lung lobectomy. The dog was initially treated with two doses of cisplatin at 70 mg m\(^{-2}\) starting 10 days after metastatectomy. Cisplatin was stopped when a single metastatic lesion was detected on thoracic radiographs 4 weeks postmetastatectomy. Antiangiogenic treatment was started and included metronomic chemotherapy and alternative therapies. Metronomic chemotherapy consisted of doxycycline, piroxicam and low-dose cyclophosphamide [personal communication, Knapp D.W. (2003) from Mutsaers A.J., Mohammed S.I., DeNicola D.B., Bennett P.F. & Knapp D.W. (2001). Metronomic chemotherapy in veterinary oncology: a pilot study. Proceedings of the Twenty-First Veterinary Cancer Society Conference, 41.]. Alternative therapy included artemisinin and vascustatin. The suspected metastatic lesion was no longer evident after 2 weeks of antiangiogenic therapy. Subcutaneous metastases over the larynx, left tarsus and left hip were diagnosed 203 days postmetastatectomy. The dog died of unknown causes 294 days postmetastatectomy and 517 days postlimb sparing surgery with no evidence of recurrent HO.

**Discussion**

HO is a well-documented condition in dogs and humans and often associated with intrathoracic neoplasia, particularly primary lung tumours and metastatic OSA (Brodey, 1971). Surgical resection of the inciting cause is recommended for the treatment of HO in humans but is rarely performed in dogs due to the poor prognosis associated with metastasis-induced HO (Hansen-Flaschen & Nordberg, 1987). Pulmonary metastatectomy has been investigated in dogs with metastatic OSA but is poorly described for the management of HO (Brodey, 1971; O’Brien et al., 1993). A survival benefit is reported for dogs with metastatic OSA when the following criteria for metastatectomy are
satisfied: control of local disease with a MFI of >300 days and less than three radiographically evident metastatic lesions (O’Brien et al., 1993). In the present series, however, these criteria were only satisfied in one dog as metastatectomy was performed with the intention of managing HO rather than metastatic disease (Table 1). Metastatectomy was performed through median sternotomy and thorascopically in two dogs each. The number of metastatic lesions removed ranged from one to six, and these lesions were resected using subpleural enucleation and partial and complete lung lobectomy. The removal of all metastatic masses is important in dogs with HO, as there are no clinical, cytological or biochemical features to differentiate causative from non-causative lesions (Brodey, 1971). Palpation of lung tissue is the most sensitive technique for detection of metastatic lesions. Lateral thoracotomy is the preferred approach for metastatectomy.

**Figure 4.** Technetium$^{99m}$ hydroxymethylene diphosphonate scans of the Rottweiler in Figs 1–3. A diffuse and bilateral increase in uptake of the radiolabelled technetium is noted extending from the distal metacarpi to the mid-humerii.

**Figure 5.** Pulmonary metastatectomy was performed via thoracoscopic surgery in the Rottweiler in Figs 1–4 by complete lobectomy of the right cranial and caudal lung lobes using a 60 mm endoscopic stapler. The metastatic lesions are indicated by arrows and the length of the ruler is 100 mm.
in humans as all lung lobes within the surgical field can be palpated for evidence of metastatic disease and conservative resection of metastatic lesions can be performed if required (Antunes et al., 1999; Thompson et al., 2002). In contrast, palpation of the dorsal lung fields is limited when exploratory thoracotomy is performed through a median sternotomy and palpation is very restricted with minimally invasive thoracoscopic surgery (Snyder et al., 1990). The importance of palpation is highlighted in the present series by the palpation of two new lesions in addition to the four radiographically visible metastases in case 1 and the inability to detect a suspected second metastatic lesion during thoracoscopic exploration in case 3. However, future cases of thoracoscopic metastatectomy can be aided by the use of advanced imaging techniques which are more sensitive than thoracic radiographs for the detection of metastatic lesions (Waters et al., 1998). Furthermore, there are no differences in either disease-free interval or survival rates between thoracoscopic and open metastatectomy in humans (Mutsaerts et al., 2002).

Thoracoscopic surgery is also limited by the difficulty in performing conservative metastatectomy. Preservation of sufficient pulmonary function is an important consideration with metastatectomy, particularly when more than one lung lobe is involved (Snyder et al., 1990; Antunes et al., 1999; Thompson et al., 2002). The majority of pulmonary lesions in humans with metastatic OSA are either peripheral or subpleural in location (Crow et al., 1981). Subpleural enucleation should be performed in preference to partial or complete lung lobectomy for such lesions (O’Brien et al., 1993). Thoracoscopic surgery was performed in the present series in an attempt to reduce the morbidity commonly associated with open thoracotomy techniques (Walsh et al., 1999; Mutsaerts et al., 2002). Experimental comparisons of thoracoscopic and open pericardectomy show significantly worse postoperative pain in dogs undergoing intercostal thoracotomies (Walsh et al., 1999). However, morbidity is absent to minimal in veterinary and human retrospective analyses of pulmonary metastatectomy using open thoracotomy techniques (Snyder et al., 1990; O’Brien et al., 1993; Antunes et al., 1999; Thompson et al., 2002), and in the present study, there were no differences in operative morbidity or duration of thoracostomy tube placement between dogs treated with open or minimally invasive techniques.

The use of aggressive surgical procedures is controversial in the management of metastatic disease as long-term survival is rare (O’Brien et al., 1993; Antunes et al., 1999). However, the clinical benefit of pulmonary metastatectomy in dogs with HO seems to outweigh the morbidity associated with the surgical procedure. Lameness and reluctance to ambulate resolved within 24 h in all dogs in the present series, and moreover, these dogs appeared more alert and active, despite undergoing major surgical intervention. Similar findings have been reported in dogs and humans with HO (Brodey, 1971; Madewell et al., 1978; Suzuma et al., 2001). In cases 3 and 4, limb radiographs 4 weeks postoperatively showed minimal resolution of periosteal proliferation. These radiographic signs are slow to subside in dogs and

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**Table 1. Summary of dogs with hypertrophic osteopathy secondary to metastatic osteosarcoma treated with pulmonary metastatectomy**

<table>
<thead>
<tr>
<th>Case number</th>
<th>OSA site</th>
<th>OSA surgery</th>
<th>Metastasis-free interval (days)</th>
<th>HO surgery</th>
<th>Other HO treatment</th>
<th>Response time (days)</th>
<th>Response duration (days)</th>
<th>Survival time (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ulna</td>
<td>Limb-spare</td>
<td>183</td>
<td>Sternotomy</td>
<td>–</td>
<td>&lt;1</td>
<td>50</td>
<td>239</td>
</tr>
<tr>
<td>2</td>
<td>Humerus</td>
<td>Amputation</td>
<td>243</td>
<td>Sternotomy</td>
<td>Piroxicam</td>
<td>&lt;1</td>
<td>51</td>
<td>295</td>
</tr>
<tr>
<td>3</td>
<td>Tibia</td>
<td>Amputation</td>
<td>623</td>
<td>Thoracospy</td>
<td>Piroxicam</td>
<td>&lt;1</td>
<td>246</td>
<td>1191</td>
</tr>
<tr>
<td>4</td>
<td>Radius</td>
<td>Limb-spare</td>
<td>221</td>
<td>Thoracospy</td>
<td>Cisplatin Metronomics Artemisinin</td>
<td>&lt;1</td>
<td>265</td>
<td>488</td>
</tr>
</tbody>
</table>

OSA, osteosarcoma; HO, hypertrophic osteopathy.
humans with HO following surgical treatment (Madewell et al., 1978; Orts et al., 2000). Nuclear scintigraphy, which was not performed postoperatively in the present series, provides a more accurate determination of response to therapy, as radiolabelled technetium uptake decreases rapidly with the reduction in osteoblastic activity associated with periostitis (Hansen-Flaschen & Nordberg, 1987).

Pulmonary metastatectomy not only resulted in a rapid resolution of clinical signs but also a durable response in all dogs. Postoperative treatment with systemic narcotic agents and intrapleural local anaesthetics may have contributed to this response but are unlikely to have provided the sustained improvement observed in these dogs. Symptomatic HO recurred in one dog (case 3) 246 days postmetastatectomy as a result of further metastasis to the lungs and chest wall. HO did not recur in the remaining three dogs. In case 1, the cause of death was widespread metastatic OSA 50 days postmetastatectomy. Six metastatic lesions were resected in this dog. The number of metastatic lesions is often cited as a prognostic factor in canine and human studies of metastatectomy (O’Brien et al., 1993; Thompson et al., 2002). The outcome in case 1 correlates with the median survival time of 53 days for dogs with three or more metastatic lesions and the poorer survival time for dogs with HO and multiple metastases (Brodey, 1971; O’Brien et al., 1993). On the basis of these findings, alternative treatment options, such as vagotomy or radiation therapy, should be considered in dogs with more than two metastatic lesions and more sensitive imaging techniques than radiography, specifically computed tomography, should be used to screen dogs for multifocal disease prior to metastatectomy (Lang et al., 1986; Campeau et al., 1989; Waters et al., 1998). In the remaining two dogs, case 1 was euthanased 51 days postmetastatectomy due to metastatic haemangiosarcoma, and case 4 died of unknown causes 294 days postmetastatectomy with subcutaneous metastatic OSA, both with no evidence of recurrent HO.

A number of ancillary treatments were used following pulmonary metastatectomy, including NSAIDs, pamidronate, cisplatin and alternative therapies, and these may have contributed to the sustained control of HO in the present study. In humans, a response to NSAID is occasionally used as a criteria for the diagnosis of HO, and NSAIDs are frequently used to manage pain associated with HO-induced periostitis (Hansen-Flaschen & Nordberg, 1987; Peeters et al., 2001). Piroxicam, a NSAID, was used in three dogs in this study, and its contribution to the durability of the postmetastatectomy response is unknown and cannot be excluded. Pamidronate, a class of bisphosphonate with potent antiosteoclastic activity, has been shown to be efficacious in humans with HO refractory to other analgesic therapies (Speden et al., 1997; Suzuma et al., 2001; Garske & Bell, 2002). Pamidronate is unlikely to have contributed to the observed response in case 3, as metastatectomy was performed in this dog as a result of the poor response to preoperative pamidronate therapy. Cisplatin and other chemotherapeutic agents have been effective in alleviating clinical signs associated with HO in both dogs and humans (Uchiyama et al., 1985; Hahn & Richardson, 1989). However, these cases had not previously been treated with chemotherapy. Cisplatin was probably not involved in the postmetastatectomy response observed in case 4 due to the suspected development of platinum drug resistance, as pulmonary metastasis and HO developed after adjuvant chemotherapy using a related platinum compound, carboplatin, and further metastasis was documented during the postmetastatectomy cisplatin chemotherapy course. Interestingly, this pulmonary metastatic lesion completely regressed following treatment with metronomic and alternative therapies (Gately & Kerbel, 2001). Metronomic chemotherapy involves cytotoxic drugs delivered at low and constant doses to target tumour angiogenesis [personal communication, Knapp D.W. (2003) from Mutsaers A.J., Mohammed S.I., DeNicola D.B., Bennett P.F. & Knapp D.W. (2001). Metronomic chemotherapy in veterinary oncology: a pilot study. Proceedings of the Twenty-First Veterinary Cancer Society Conference, 41.] However, this approach is considered palliative and such a marked response to metronomic chemotherapy is very unlikely. Artemisinin is cytotoxic in the presence of...
ferrous iron and has in vitro antineoplastic activity in cells with increased intracellular iron concentrations (Singh & Lai, 2001). The intracellular concentration of iron is unknown in dogs with OSA, although serum concentrations of iron are significantly decreased while serum ferritin concentrations are increased (Kazmierski et al., 2001). The relationship between intracellular and serum concentrations of iron and ferritin are uncertain but do not exclude the possibility that artemisinin may have been involved in regression of the metastatic lesion and sustained control of HO in this dog. Despite the unknown role of adjunctive therapeutics in controlling HO in the present series, pulmonary metastatectomy has been shown to result in sustained control of HO even when new metastatic lesions develop in the lungs (Brodey, 1971).

Conclusions

Pulmonary metastatectomy was performed with the intention of palliating symptomatic HO in four dogs with metastatic OSA. Clinical signs of HO resolved within 24 h, and durable remission was achieved in all dogs (range, 50–294 days). Three dogs remained HO-free, while recurrent HO was diagnosed in one dog 246 days post-metastatectomy as a result of metastasis to the lungs and chest wall. Adjunctive therapies, such as piroxicam, pamidronate, cisplatin and artemisinin, were also used and may have contributed to the prolonged postoperative control of HO. Pulmonary metastatectomy resulted in a rapid resolution and prolonged remission of HO and should be considered for the palliation of dogs with HO secondary to metastatic pulmonary neoplasia, particularly if there are less than three metastatic lesions.

References

Metastatectomy for hypertrophic osteopathy


