Portal site metastasis after thoracoscopic resection of a cranial mediastinal mass in a dog

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Case Description—An 11-year-old castrated male Vizsla was evaluated for excision of a cranial mediastinal mass.

Clinical Findings—The dog had a 1-month history of a cough that had recently increased in frequency. On physical examination, the dog had a grade 2/6 left systolic heart murmur and multiple subcutaneous masses. A soft tissue mass was observed in the cranioventral aspect of the thorax on radiographs. Results of a CT scan revealed a well-defined, 2.8 × 3.2 × 3.9-cm soft tissue mass in the cranial mediastinum.

Treatment and Outcome—The dog underwent video-assisted thoracoscopic removal of the mediastinal mass and recovered routinely. Histologic examination of excised tissues revealed malignant thymoma. Approximately 6.5 months after surgery, the dog was evaluated because of polyuria, polydipsia, decreased appetite, and vomiting. On physical examination, masses were found in both axillary regions. Results of serum biochemical analysis indicated hypercalcemia. Thoracic ultrasonography revealed pulmonary metastases and a large mass in the right caudoventral region of the thorax. The dog received supportive care and medical treatment for hypercalcemia, but clinical signs recurred. Euthanasia was elected; necropsy and histologic examination revealed thymic carcinoma.

Conclusions and Clinical Relevance—Descriptions of the development of portal site metastasis in canine patients are rare. In this patient, portal site metastasis developed rapidly after thoracoscopic resection of a malignant thymic mass and was associated with hypercalcemia. As use of thoracoscopic procedures increases in veterinary medicine, it will be important to monitor the development of major complications such as those in the patient of this report. (J Am Vet Med Assoc 2015;247:793–800)
The dog was reevaluated 1.5 months later because of a 1-month history of a dry, hacking, nonproductive sporadic cough that was most notable when the dog tried to swallow; the cough had recently been increasing in frequency. No vomiting or regurgitation had been observed at home, and the results of physical examination were unremarkable except for the previously detected heart murmur and multiple subcutaneous masses (lipomas). Results of hematologic and serum biochemical analysis were within respective reference ranges. The possibility of a CT examination and surgical treatment options, including possible thoracoscopic removal of the thoracic mass, were discussed with the owner. The owner elected to proceed with CT and surgery 2 weeks later (approx 10 months after initial detection of the mediastinal mass).

The CT images revealed a well-defined soft tissue mass in the cranial mediastinum that measured 3.9 cm ventrodorsally, 3.2 cm lateromedially, and 2.8 cm craniocaudally. A mediastinal lymph node was visualized and appeared mildly enlarged. There was increased density and volume loss at the periphery of the caudal aspect of the left cranial lung lobe, which was compatible with atelectasis. After administration of a nonionic iodinated contrast medium, there was mild heterogeneous enhancement of the cranial mediastinal mass (Figure 2). The mass was located caudal to the internal thoracic arteries and ventral to the cranial vena cava; however, these structures did not appear to be invaded by the mass. No evidence of pulmonary metastasis was detected.

Following the CT, the dog was prepared for VATS removal of the mass. Morphine sulfate (1.0 mg/kg [0.45 mg/lb], SC) and atropine sulfate (0.02 mg/kg [0.009 mg/lb], SC) were administered as premedications, and general anesthesia was induced with ketamine hydrochloride (5.2 mg/kg [2.4 mg/lb]) and diazepam (0.47 mg/kg [0.21 mg/lb]). A Robert Shaw double-lumen endotracheal tube was placed with endoscopic guidance to allow for 1-lung ventilation. Anesthesia was maintained with isoflurane in oxygen. The double-lumen endotracheal tube became occluded with mucus and was replaced with a standard endotracheal tube approximately halfway through the procedure; from that point forward, the procedure was performed without 1-lung ventilation.

The patient was placed in dorsal recumbency. The fur was clipped ventrally from the midabdominal area to the midcervical region and laterally to the level of the dorsal aspect of the thorax. The skin was prepared with an aseptic technique. A 1-cm incision was made in a right paraxiphoid position, and a 6-mm trocarless threaded cannula was introduced into the thorax. A 29-cm, 30° telescoped was then introduced through the cannula into the thorax. A 1-cm incision was made at the level of the right fourth intercostal space in the ventral third of the thorax, and a second 6-mm trocarless threaded cannula was introduced. A third 1-cm incision was made at the level of the left third intercostal space adjacent to the mediastinal mass, and an 11.5-mm thoracic trocar cannula assembly was introduced at this site. Insufflation was not required for visual access.

The mass was located in the cranial mediastinum and was displacing, but tightly adhered to, the internal thoracic arteries laterally. The mass was closely adhered to the cranial vena cava on the right lateral surface and to the pericardium caudally. Dorsally, the mass was adhered to the surrounding fatty tissues. Dissection of the mass proceeded in a caudal-to-cranial direction until the mass could be grasped and mobilized from side to side. Dissection was performed with a vessel-sealing device and thoracoscopic right-angle forceps. The mass was manipulated by grasping the ventral portion of the adherent fatty tissue with a Kelly hemostat. As the mass was partially freed from the surrounding
tissue, a digit was introduced through the incision to perform more blunt dissection and better position the mass for complete dissection. Nearing the completion of dissection, the mass was found to be very tightly adhered to tissues in the cranial mediastinum, and capsular rupture occurred during dissection. When the mass was completely dissected from surrounding tissues, surgical gloves were changed and mass removal was performed by placing the mass in a specimen retrieval bag and removing the bag through the left third intercostal space. A thoracostomy tube was percutaneously introduced into the thorax through the ninth intercostal space. Thoracic lavage was not performed. The endoscopic cannulae were removed, and the incisions were closed routinely.

The patient was moved to an intensive care unit for recovery and received supplemental oxygen. Hydromorphone hydrochloride was administered (0.05 mg/kg [0.023 mg/lb], IV, q 4 to 6 h as needed) for analgesia. The patient was discharged from the hospital the following day. Results of histologic examination were consistent with malignant thymoma with prominence of epithelial and lymphoid components (Figure 3). Malignancy was determined on the basis of invasion of the surrounding capsule and adipose tissue by neoplastic epithelial cells.

Six months after surgery, the dog was evaluated because of a 3-day history of polyuria, polydipsia, decreased appetite, and vomiting. On physical examination, the dog had a high rectal temperature (39.9°C [103.9°F]; reference range, 37.9° to 39.9°C [100.2° to 103.8°F]). Further examination revealed 2 new subcutaneous masses that included firm, 1-cm masses attached to the body wall in both axillary regions. A CBC, serum biochemical analysis, and urinalysis were performed. Results of the CBC were within the reference ranges, the serum biochemical analysis revealed hypercalcemia (total calcium concentration, 14.7 mg/dL; reference range, 9.6 to 11.2 mg/dL), and specific gravity of the urine sample was 1.016. Serum parathyroid hormone and ionized calcium concentrations were measured for further evaluation of the hypercalcemia. Results indicated a low circulating parathyroid hormone concentration (0.30 pmol/L; reference range, 0.50 to 5.80 pmol/L) and confirmed hypercalcemia (ionized calcium concentration, 1.92 mmol/L; reference range, 1.25 to 1.45 mmol/L). These findings were likely attributable to a paraneoplastic effect, considering that the dog’s preoperative circulating total calcium concentration had been within the reference range.

Three-view thoracic radiography and abdominal and thoracic ultrasonography were performed. Abdominal ultrasonographic evaluation identified a large, heterogeneous, caudal thoracic mass that was visualized through the diaphragm (Figure 4). The previously identified splenic nodule appeared unchanged. Thoracic ultrasonography confirmed a large caudal thoracic mass that was centered in the right caudoventral region of the thorax but extended both cranially and to the left side. The left axillary lymph nodes were also markedly enlarged and extended toward the cranial mediastinum. Thoracic radiography revealed multiple, variably sized masses in the thorax and abdomen.

Figure 3—Photomicrograph of a section of the cranial mediastinal mass excised by means of VATS from the same dog as in Figure 1. A mixed population of cohesive epithelial cells organized in clusters and trabeculae admixed with sheets and interspersed colonies of lymphocytes is present. Findings were consistent with a diagnosis of thymoma. H&E stain; bar = 50 µm.

Figure 4—Images obtained during abdominal (A) and thoracic (B) ultrasonography of the dog in Figure 1 during evaluation because of clinical signs of polyuria, polydipsia, decreased appetite, and vomiting 6 months after resection of the cranial mediastinal mass. A—A mass (arrow) is evident in the thorax adjacent to the diaphragm (arrowhead). The liver is indicated (asterisk). B—Thoracic ultrasonography, the mass (arrow) is centered in the right caudoventral region of the thorax. CD = Caudal. R and RT = Right. TH = Thorax. The scale on the right side of the image indicates measurement in centimeters.
sized, soft tissue pulmonary nodules consistent with pulmonary metastasis. On the left lateral projection, the largest of the masses appeared to displace the ventral margin of the lung dorsally. Given the pattern of the metastatic lesions, these findings suggested tumor cell seeding at thoracoscopic portal sites in both axillary regions and at the paraxiphoid location. With limited capacity for evaluation, however, it was not possible to distinguish a definitive metastatic process at that time.

Fine-needle aspirates of the axillary lymph nodes were obtained; cytologic results were consistent with epithelial cells highly suggestive of metastatic carcinoma. No nodal cells were identified, suggesting that the lymph node was effaced. The owner was advised to discontinue a previously prescribed carprofen treatment that the dog had been receiving for suspected osteoarthritis and to administer prednisone (1.0 mg/kg, PO, q 24 h) 2 to 3 days after discontinuing the NSAID. Further medical management recommendations included administration of lactated Ringer solution (46 mL/kg [21 mL/lb], SC, q 24 h) and administration of tramadol hydrochloride (2.5 mg/kg [1.1 mg/lb], PO, q 8 to 12 h as needed) for analgesia.

Four days later, the dog was admitted to the hospital for pamidronate treatment after this was offered as an option to treat the hypercalcemia. Results of serum biochemical analysis indicated mildly progressive hypercalcemia (total calcium concentration, 15.6 mg/dL) with no azotemia. The dog received an IV infusion of pamidronate (2.2 mg/kg [1.0 mg/lb] in 1 L of saline [0.9% NaCl] solution over 2 hours). The dog was discharged from the hospital that afternoon, and the owner was instructed to continue prednisone and subcutaneous fluid administration.

One week after pamidronate treatment, the dog was returned for reexamination. The owner reported the dog’s appetite and energy level had improved substantially, and no vomiting had been observed. Results of serum biochemical analysis indicated that the patient was normocalcemic (total calcium concentration, 10.9 mg/dL). Continued prednisone treatment and subcutaneous fluid administration and reevaluation of the dog’s circulating calcium concentration in 1 week were recommended.

At the follow-up visit 1 week later, the owner reported that the dog had a normal appetite with no

Figure 5—Photographs obtained at necropsy of the dog in Figure 1. A and B—Variable sized, multifocal, poorly circumscribed to well-defined nodular masses are present throughout the thoracic cavity. C—Coalescing, white, firm nodular masses are present in the dissected mediastinum. D—The pleura overlying the thoracic wall and lung lobes contains white, firm, lobulated to botryoid masses, ranging in size from 0.4 to 3 cm in diameter. Major increments on the scalpel handle (panels A and D) and rule (panels B and C) indicate measurement in centimeters.
vomiting and a mildly decreased energy level. Serum biochemical analysis revealed mild hypercalcemia (total calcium concentration, 11.5 mg/dL). The owner was advised to continue prednisone administration and subcutaneous fluid administration and to return the dog for measurement of circulating calcium concentration in 1 week.

At the next weekly visit, the owner reported that the patient's appetite and energy level were decreased, compared with the previous week's observations. Blood was collected for hematologic and serum biochemical analysis. Results of the CBC were within reference ranges, and the biochemical tests revealed moderate hypercalcemia (total calcium concentration, 13.8 mg/dL). The owner elected euthanasia at that time. On necropsy, firm, white, multilobulated masses (4 to 5 cm in diameter) were identified in the subcutaneous tissue of the left axilla and the right parasternal region. Both masses were firmly adhered to the body wall, and on cut surfaces, the centers were dark red. Directly opposing these areas within the thoracic cavity were similar appearing firm masses surrounded by botryoid clusters of 0.1- to 0.3-cm-diameter nodules. Similar masses (0.1 to 6 cm in diameter) were multifocally present on the thoracic aspect of the diaphragm (Figure 3), the parietal and visceral pleura, and the mediastinum. Histopathologic examination revealed that the masses exclusively comprised clusters and sheets of disorganized epithelial cells supported by a prominent fibrous matrix (Figure 6). Given the overall lack of lymphoid components characteristic of a thymoma, a diagnosis of thymic carcinoma with carcinomatosis was made. Tumor cells were immunoreactive for cytokeratin by immunohistochemical analysis, consistent with thymic carcinoma.

Discussion

Since its advent, VATS has replaced conventional techniques in the investigation and treatment of many thoracic conditions in humans, including malignant disease.\(^1,4\) Common indications for VATS include mass lesions of the mediastinum, pleura, lungs, and lymph nodes; pleural effusion of unknown origin; chylothorax; pericardial effusion with or without mass lesions; spontaneous pneumothorax; and persistent right aortic arch.\(^5\) In veterinary medicine, more commonly performed thoracoscopic procedures include lung lobectomy; pericardial window procedure, subtotal pericardiectomy; ligation of patent ductus arteriosus, thoracic duct ligation, and treatment of pyothorax.\(^6\)

In human and canine patients, reported advantages of VATS over open thoracotomy include a lesser degree of postoperative pain, faster recovery of pulmonary function, lower postoperative circulating concentrations of interleukin-6, and shorter general and intensive care hospital stays.\(^1,6,10\) However, long-term complications such as portal site metastases can occur following minimally invasive surgical procedures. In humans, portal site metastases have been reported after thoracoscopic\(^2,3\) and laparoscopic\(^11,12\) resection of various malignant tumors. The true incidence of portal site metastasis in humans is unknown. Stemming primarily from research conducted in the late 1990s, reports generally indicate portal site metastasis rates of < 4%.\(^3,13,15,16\) Whether the incidence of metastasis is more common in minimally invasive versus open procedures is also unclear.\(^18\) Results of 1 study\(^19\) revealed that tumor manipulation was the most accurate indicator of the likelihood of tumor spread in rats that underwent laparoscopic or open procedures. It is possible that minimally invasive procedures involving extensive tumor resection may require greater tumor manipulation, compared with that needed for excision by open procedures.

To our knowledge, portal site metastasis in a dog has only been reported once in the veterinary literature\(^20\). In that dog, portal site metastasis was identified 3 weeks after diagnostic thoracoscopy and evaluation of biopsy specimens of the pleura, mediastinum, and pericardium revealed invasive mesothelioma and pericardial fibrosis. In humans, tumor seeding at portal sites has been identified as early as a few days after surgery, with a typical time frame of 14 to 15 months after surgery for detection of such metastases.\(^13,21,22\) Similar to the report by Brisson et al,\(^20\) diagnosis of portal site tumor seeding in the dog of the present report was made earlier (6.5 months after surgery). The etiology of portal site tumor seeding is not well understood, but it is likely multifactorial. It is postulated that the pathophysiology involves the implantation of malignant cells in the surgical wound through direct wound implantation, contamination of instruments, aerosolization of tumor cells, a so-called chimney effect (where tumor cells congregate at incision sites after being aerosolized during the procedure), local and systemic effects of the pneumoperitoneum created with carbon dioxide (in procedures that require insufflation), excessive manipulation of the tumor, hematogenous spread, or some combination of these.\(^3,12\)

In the dog of this report, a vessel-sealing device and digital manipulation were used to dissect the cranial mediastinal mass away from surrounding tissues. The VATS method provides limited 2-D visual access with limited tactile manipulation at the surgical site. Considering that surgical technique has been correlated with
contamination rates, it is possible that a VATS approach might contribute to imprecise definition of tumor margins or unnecessary tumor handling and therefore an increase in the risk of tumor disruption and dissemination. Yamashita et al showed that the proportion of patients with stage I non–small cell lung cancer that developed detectable carcinoembryonic antigen mRNA (a measure of micrometastatic cells) in the circulation during tumor resection by VATS (16/18) was significantly greater than that of similar patients who underwent lobectomy via open thoracotomy (18/35). Those investigators postulated that these cells (expressing carcinoembryonic antigen mRNA) might increase the risk of subsequent thoracic and hematogenous tumor spread, and that tumor cell shedding may be exacerbated by manipulation of the tumor for placement in an extraction bag, accidental grasping of the tumor directly, or forceful manipulation of internal structures for better visibility. Interestingly, biopsy specimens in the case described by Brisson et al were removed through cannulas without the use of specimen bags, indicating that minimal tumor manipulation may be sufficient to cause portal site metastasis. In the dog of the present report, a collection bag was used to remove the mass as a means of preventing contact with the tissues of the body wall. However, owing to the presence of multiple adhesions between the mass and surrounding tissue, clean resection of the mass was challenging. As a result of the adhesions, the tip of a vessel-sealing device was passed through the assist incision positioned at the left third intercostal space, and the surgeon used the same site for digital access to the mass. Extensive manipulation of the mass during removal resulted in disruption of the tumor capsule, possibly facilitating the spread of tumor cells.

The recurrent and metastatic nodules in the dog of this report were morphologically different from the originally resected tumor. It is unknown whether a neoplastic transformation occurred or if the original tumor may have also contained components of thymic carcinoma. The initial mass was found to contain a mix of epithelial and lymphoid cell populations, whereas the recurrent and metastatic foci were exclusively epithelial with a prominent schirrous response and areas of necrosis, similar to carcinomas of many other organs. Prognosis on the basis of tumor cell population (lymphocyte rich, mixed, or epithelial cell predominant) has not been extensively investigated in veterinary medicine; however, there is some evidence that patients with lymphocyte-rich tumors have a more favorable prognosis. Despite the cellular components identified, the histologic evidence of capsular and adipose tissue invasion in the originally resected mass conferred a guarded prognosis. Thymic carcinoma is a rare malignancy in humans and dogs and is generally identified at a locally advanced stage with an aggressive histologic appearance. In human medicine, increasing concern regarding the efficacy of minimally invasive approaches to thymic tumor resection has been raised. Recent research indicates that the single most important prognostic factor in treating thymomas and thymic carcinomas in human patients is complete resection. Although VATS provides distinct benefits, it also may limit surgical exposure, perhaps resulting in incomplete tumor resection.

In the dog of this report, although insufflation was not used and the mass was primarily manipulated through the incision at the left third intercostal space, metastasis developed at all portal site incisions as well as throughout the thorax after surgery. These results suggest that metastasis cannot be solely explained as a result of gas effects or direct contamination. It is possible that, because of the degree of manipulation required, tumor implantation may have occurred through secondary contamination from tumor cell–bearing instruments coming into contact with portal site incisions during the attempt to retract the mass from the surrounding tissues.

Local changes in immune system functionality associated with minimally invasive surgery techniques may also promote tumor metastasis. Although most reports discuss immune function in the context of laparoscopic portal site seeding, effects of thorascopic procedures are likely similar. Research evaluating the effects of intraperitoneal endotoxin administration on abdominal implantation of adenocarcinoma cells and portal site metastasis in rats indicated a lower propensity of tumor seeding in the presence of endotoxins. These effects were presumed attributable to endotoxin stimulation of cytokines such as tumor necrosis factors, which are essential mediators in the activation of lymphocytes that may have a role in killing tumor cells.

Although exact mechanisms for portal site metastasis are unknown, it is likely that employment of several principles can help decrease their incidence. Following strict oncological techniques as for open surgery, including careful handling of the specimen, adequate surgeon training and experience, and proper patient selection, may contribute to prevention of portal site metastasis. In a large, prospective study involving 533 human patients who underwent laparoscopic procedures because of various intra-abdominal malignancies, the incidence of portal site metastasis in patients with advanced disease at the time of laparoscopy (3/71 [4%] patients) was significantly greater than that for patients without advanced disease at that time (1/462 [0.2%]). Surgical modifications such as excision of portal sites following procedures involving malignancies have been recommended. A disadvantage of adopting this strategy includes negation of the principles of minimally invasive surgery. Given the likely multifactorial etiology of portal site seeding, the possible advantages of portal site excision may not be sufficient to warrant exploration.

Hypercalcemia, as found in the dog of this report, is a common finding in humans and dogs with malignant neoplasia. Although to the authors’ knowledge, hypercalcemia associated with thymic carcinoma in dogs has not been described in the literature, a recent study reported hypercalcemia in 40 of 116 (34%) dogs with thymoma. Often, paraneoplastic syndromes parallel the underlying malignancy, and it is common place to find that successful treatment of the tumor will lead to elimination of the paraneoplastic condition. Similarly, recurrence of paraneoplastic syndromes can
often indicate recurrence of the tumor, preceding de-
tection of the tumor itself.41 The most common cause of hypercalcaemia in dogs is neoplasia,41,19 and it is most typically associated with lymphoma.55–65 Given that hypercalcaemia can be a potential medical emergency in severe instances, determining the underlying cause and instituting the appropriate treatment is paramount. In the case described here, mild to moderate hypercalcaemia warranted supportive care with the administration of corticosteroids, fluid therapy, and pamidronate. The owner ultimately elected for euthanasia because of the patient’s compromised quality of life.

Findings in this patient, as well as the previous description of portal site metastasis in a dog,56 indicate that this possible result should be conveyed to the owner as a potential, albeit rare, risk associated with interventional oncological thoracoscopy. It is important to note that in cases of advanced oncological disease, the effect of portal site metastasis subsequent to tumor biopsy is unknown and may not drastically affect the ultimate rapid progression of the disease. The ability to quickly and accurately diagnose the nature of the disease for implementation of treatments such as chemotherapy may therefore warrant the procedure, despite the possible risk of portal site metastasis (which is anticipated to be low).

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