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Anesthesia Case of the Month

History

A 13-year-old 20.8-kg (45.8-lb) spayed female Husky was evaluated at Veterinary Dental Services for multiple episodes of oral bleeding noticed by the owner. The episodes seemed spontaneous and unrelated to any specific activity. Results of recent blood work indicated that the dog's CBC and total thyroxine concentration were within reference limits but that the dog had mild azotemia (SUN concentration, 48 mg/dL [reference range, 6 to 31 mg/dL]; serum creatinine concentration, 2.3 mg/dL [reference range, 0.5 to 1.6 mg/dL]). In addition, the dog had a history of anxiety and aggression and was receiving atenolol (1.8 mg/kg [0.8 mg/lb], PO, q 12 h) for treatment of hypertrophic cardiomyopathy (HCM) and subaortic stenosis diagnosed previously. The dog was scheduled for a complete dental examination and prophylaxis, with extraction and biopsy if needed.

Food but not water was withheld 8 hours before the anesthetic event. Atenolol was administered as prescribed, and to help mitigate the dog's anxiety and aggression, gabapentin (14 mg/kg [6.4 mg/lb], PO) was also administered the night before and the morning of the planned procedure.

On physical examination the morning of the procedure, the dog was bright, alert, and responsive but panted continuously and showed signs of anxiety and aggression; therefore, the physical examination was brief. The dog had a heart rate of 80 beats/min (reference range, 70 to 120 beats/min) with a grade 2/6 heart murmur, pink mucous membranes with no obvious oral bleeding, and a body condition score of 5 (on a scale from 1 to 9).

The dog was premedicated with butorphanol (0.4 mg/kg [0.18 mg/lb]), acepromazine (0.01 mg/kg [0.005 mg/lb]), midazolam (0.2 mg/kg [0.09 mg/lb]), and alfaxalone (0.5 mg/kg [0.23 mg/lb]), with all preanesthetic agents combined in 1 syringe for IM administration. Although the administered dose of alfaxalone, albeit conservative, necessitated a higher volume of formulated drug product than would have been required of other agents for IM delivery (eg, ketamine or dexmedetomidine), alfaxalone was chosen because it supports relative cardiovascular stability better than would other agents, and our included use of butorphanol, acepromazine, and midazolam reduced the dose and volume of alfaxalone needed and allowed for a multimodal anesthesia protocol.

Within 10 minutes after being premedicated, the dog became sternal and tractable and was lifted onto an examination table, where oxygen (1.5 L/min) was delivered by mask. An 18-gauge over-the-needle catheter was secured in the dog's right cephalic vein. Because of the level of sedation achieved with premedication, the dog did not require an induction agent and, following preoxygenation, was intubated with an 11-mm-internal-diameter cuffed endotracheal tube that was then connected to an anesthetic machine with a rebreathing circuit. General anesthesia was maintained with sevoflurane (vaporizer setting, 1.5%) in oxygen (2 L/min). The dog was instrumented for monitoring of its oxygen saturation of hemoglobin, end-tidal carbon dioxide concentration, rectal temperature, heart and respiratory rates, and ECG with a multiparameter monitor.[a] Indirect arterial blood pressure was measured with a Doppler ultrasonic flow detector[b] over the dorsal pedal artery with a No. 3 cuff applied around the mid to distal region of the tibia. Results for initial measurements of vital signs were within reference limits. Administration of a multiple-electrolyte solution[c] (5 mL/kg/h [2.3 mL/lb/h], IV) was initiated and continued throughout the procedure.

Cone-beam CT,[d] full-mouth dental radiography,[e] oral examination, and dental cleaning were performed. The dog had advanced periodontal disease requiring multiple extractions but had no evidence of other abnormalities (eg, oral ulcerations or neoplasia) to otherwise explain the chief complaint of spontaneous oral bleeding. Substantial gingival inflammation was present around multiple teeth, and gingival bleeding was noticed on probing and may have been the source of occasional spontaneous bleeding noticed by the owner.

In preparation for the extractions, a right infraorbital nerve block was performed (bupivacaine hydrochloride; 1 mg/kg [0.45 mg/lb]) with aspiration before injection to confirm no vascular uptake. In addition, fentanyl (3 µg/kg [1.36 µg/lb], IV bolus, followed by 5 µg/kg/h [2.27 µg/lb/h]) was administered for additional analgesia.

During anesthesia, there was minimal variation in the dog's heart rate (median, 110 beats/min; range, 94 to 120 beats/min) or respiratory rate (median, 8 breaths/min; range, 3 to 12 breaths/min; reference range, 10 to 20 breaths/min), and the dog's oxygen saturation of hemoglobin, end-tidal carbon dioxide concentration, and rectal temperature also remained within reference limits. However, the dog had 3 episodes of hypertension with indirect systolic blood pressure > 200

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mm Hg (reference range, 80 to 120 mm Hg) that lasted 2 to 3 minutes, and each episode was immediately followed by hypotension with a systolic blood pressure of < 50 mm Hg that lasted 3 to 4 minutes. During the first 2 episodes of hypertension (at approx 20 and 65 minutes after onset of sevoflurane administration), the dog's heart rate remained within reference limits; however, the dog became tachycardic (140 beats/min) during the third episode (at approx 100 minutes after onset of sevoflurane administration). The episodes were unrelated to surgical stimulation or patient positioning, and there was no evidence of other underlying causes (eg, bladder enlargement, regurgitation, endotracheal tube movement, vertebral or pelvic malpositioning, or colonic pressure) that may have resulted in hypertension. During each of these hypertensive episodes, the dog's anesthetic depth was evaluated with cranial nerve assessments in conjunction with results for cardiorespiratory measurements and was considered adequate. Hypertension during each episode was verified by oscillometric blood pressure measurements obtained with the multiparameter monitor. No attempt was made to obtain direct arterial blood pressure because of the lack of such pressure monitoring modules in the multiparameter machine.

Question

What could have caused the episodic blood pressure fluctuations in this dog, and what, if any, intervention may have been indicated?

Answer

Possible causes for the 3 interoperative episodes of sudden-onset hypertension in this Husky included inadequate anesthesia, technical errors (eg, inappropriate cuff placement or sizing), Cushing disease, malignant hyperthermia, increased intracranial pressure, and catecholamine-secreting neuroendocrine tumors (eg, thyroid gland adenocarcinoma, pheochromocytoma, or paraganglioma[1–4]). Potential causes considered unlikely were hypertension secondary to fluid overload because the isotonic crystalloids solution administered would have quickly shifted from intravascular to interstitial space; pharmacologically induced because no vasopressors were delivered during this time period and the dog received its atenolol the morning of surgery as prescribed; tachyarrhythmias because interoperative ECG revealed no abnormalities, except tachycardia (heart rate, 140 beats/min) during the third hypertensive episode; severe systemic thyroid or renal disease because results of recent blood work indicated that the dog had a total thyroxine concentration within reference limits and only mild azotemia; or vasculitis because the dog had no history or current evidence of vascular disease.

Intervention for the episodes of severe hypertension could have included administration of nitroglycerin or sodium nitroprusside, both of which are potent vasodilators with rapid onset and short duration of action.[5] However, nitroprusside was not very effective in controlling severe hypertension in a dog with a catecholamine-producing thyroid carcinoma and a functional carotid body tumor.[2] Other interoperative treatment options included increasing the concentration of delivered sevoflurane (induces hypotension by vasodilation) or administering phentolamine (a nonselective α-adrenoreceptor antagonist with short action), nicardipine (a calcium-channel blocker), magnesium sulfate (decreases the blood pressure by various mechanisms including vasodilatation and inhibition of catecholamine release), a short-acting β-adrenoceptor blocker such as esmolol hydrochloride[5] (for hypertension accompanied by tachycardia with heart rates higher than observed in our patient), or another low dose of acepromazine. Preoperatively, midazolam may have been used alone as the single sedative agent; however, we feared its solo use could have also worsened the dog's existing unpredictable aggressive behavior, and we chose to include a very low dose of acepromazine for its sedative properties and because it would help avoid increasing cardiac work, a key concern given the patient's existing HCM. Further, in patients with pheochromocytoma previously diagnosed, α-adrenoreceptor antagonists (eg, phenoxybenzamine) may be administered preoperatively to avoid potential intraoperative hypertensive crises.

During anesthesia, this dog's cardiovascular status was closely monitored by the veterinary dentist, cardiologist, and anesthesiologist. Because the episodes of hypertension were limited in frequency and duration, no intraoperative intervention was elected. Instead, the dental procedures were completed, with a total duration of 2 hours. The total duration of general anesthesia was 122 minutes, and the dog's blood pressure was monitored during recovery and remained within reference limits. The dog recovered from anesthesia without complication and was discharged later the same day with a prescription for gabapentin (9.7 mg/kg [4.4 mg/lb], PO, q 12 h for 7 days).

During a follow-up communication with the owner the next day, the owner described the dog as having had no abnormal signs. A diagnostic plan to identify the underlying cause of the dog's paroxysmal blood pressure changes during anesthesia was discussed, and the owner elected to have abdominal ultrasonography performed. The dog received gabapentin (15 mg/kg [6.8 mg/lb], PO) the night before and the morning of the procedure and after admittance was sedated with a combination of butorphanol (0.35 mg/kg [0.16 mg/lb]), alfaxalone (1 mg/kg), and acepromazine (0.01 mg/kg), with all agents combined in 1 syringe for IM administration. The dog did not require further sedation or induction of general anesthesia. Abdominal ultrasonography revealed a right caudal retroperitoneal mass (approx 5.12 × 3.52 × 3.23 cm) with intracaval extension **(Figure 1)**,

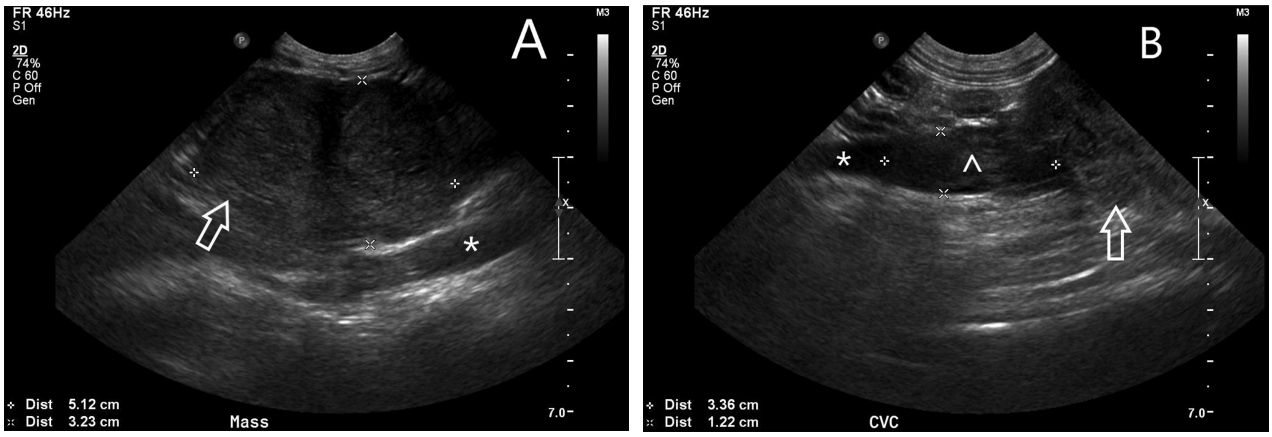

Figure 1—Abdominal ultrasonographic images of a right caudal retroperitoneal mass (approx 5.12 X 3.52 X 3.23 cm; arrows) in a 13-year-old 20.8-kg (45.8-lb) spayed female Husky that had hypertrophic cardiomyopathy, mild azotemia, and advanced periodontal disease and had 3 short episodes of paroxysmal hypertension with rebound hypotension during general anesthesia for dental procedures. A—Sagittal ultrasonographic image at the level just caudal to the right kidney showing the mass (arrow) arising between the caudal pole of the right kidney and the bifurcation of the caudal vena cava (asterisk). B—Sagittal ultrasonographic image at the level of the right kidney showing the caudal vena cava (asterisk) distended by an intraluminal portion (caret) of the mass (arrow) that occupies approximately 90% of the caval lumen and extends cranially within the lumen to approximately 1.0 cm caudal to the right adrenal gland. In each image, the calipers indicate the size of the mass in the particular view, and the scale on the right is in centimeters (dashes), with each half centimeter (dots) also indicated.

which was confirmed with power flow Doppler ultrasonography (not shown). The adrenal glands and other abdominal structures appeared ultrasonographically normal. Thoracic radiography (not shown) revealed microcardia, suggestive of hypovolemia; aortic arch prominence, suspected to have represented poststenotic dilation secondary to subaortic stenosis; and diffuse dilation of the descending aorta, suspected to have resulted from systemic hypertension. However, there was no evidence of intrathoracic metastases or underlying lung disease that could explain the intraoperative episodes of hypertension.

Fine-needle aspiration of the retroperitoneal mass was performed with ultrasound guidance, and results of cytologic examination of the sample indicated neuroendocrine carcinoma with long-term, active hemorrhage. In addition, the dog's urine normetanephrine-to-creatinine ratio was 9,894 µg/g (reference range, 28 to 380 µg/g), 26 times the upper reference limit and far beyond an established cutoff of 4 times the upper reference limit used in diagnosing pheochromocytoma.[3,6,7] Thus, the intraoperative hypertension was attributed to malignant neuroendocrine neoplasia, and on the basis of its location, the mass was most likely a metastatic lesion from a malignant neuroendocrine neoplasm elsewhere, such as a tumor of the adrenal gland (eg, pheochromocytoma or adrenocortical carcinoma), carcinoid, thyroid carcinoma, or malignant chemoreceptor tumor. The dog was prescribed phenoxybenzamine (0.48 mg/kg [0.22 mg/lb], PO, q 12 h) to accompany the existing prescription of atenolol, and surgical treatment of the retroperitoneal mass was declined by the owner. During a recent follow-up communication with the owner 3 months after diagnosis of malignant neuroendocrine neoplasia, the dog was alive, receiving phenoxybenzamine and atenolol as prescribed, and intermittently taken to its regular veterinarian for blood pressure measurements, which remained within reference limits.

Discussion

Pheochromocytomas and paraganglioma are catecholamine-secreting neuroendocrine tumors. Pheochromocytomas arise from the adrenal medulla, whereas paragangliomas, also called chemodectomas, are extra-adrenal tumors that arise from sympathetic and parasympathetic paraganglia.[8] In dogs, the most common location of these catecholamine-secreting neuroendocrine tumors is the base of the heart; however, mediastinal and extra-adrenal retroperitoneal paraganglioma have also been reported.[2,8] Both pheochromocytomas and paragangliomas are characterized by overproduction of catecholamines.[9] Paragangliomas are reported to be especially prevalent in brachycephalic breeds; however, the endocrine activity of paragangliomas in dogs has not been clearly demonstrated.[10–13]

Catecholamine-secreting neuroendocrine tumors present substantial challenges to veterinary anesthetists, especially when the tumors are undiagnosed, as was the case in the dog of the present report, because the tumors can produce life-threatening intraoperative cardiovascular complications.[14] Catecholamine-induced cardiomyopathy has been described as a form of myocardial stunning from the toxic effects of catecholamine on the myocardium.[15] Human patients with previously diagnosed catecholamine-secreting neuroendocrine tumors and that do not have appropriate preoperative medical treatment (eg, to control for volume expansion, hypertension, and tachycardia) have high mortality rates because of deadly hypertensive crises, severe arrhythmias, and

failure of multiple organs.[14,15] Similar findings are true in affected dogs.[16]

Additionally, the dog of the present report had a history of aggression and anxiety issues, both of which may have been linked to its neuroendocrine tumor. In veterinary patients with catecholamine-secreting tumors, reducing stress and anxiety prior to entering the hospital and receiving premedication is paramount.[5,14,15] Trazadone alleviates stress in hospitalized dogs[17]; however, trazadone should be used with caution in patients with severe cardiac, hepatic, or renal disease because it may cause cardiac conduction disturbances and reduction in heart rate or blood pressure.[18] Alternatively, gabapentin, which has been used in dogs and cats to control anxiety, impulsivity, phobias, panic disorders, and compulsive disorders,[19,20] was administered to the dog of the present report the night before and the morning of the anesthetic procedure.

For any patient with hypertension during anesthesia, preanesthetic and anesthetic medications affecting blood pressure should also be considered as underlying causes. Aggressive patients, such as the dog in the present report, may be difficult to anesthetize for various reasons, and common preanesthetic regimens for aggressive patients often include a combination of agents such as butorphanol, dexmedetomidine, ketamine, and alfaxalone. We avoided the use of dexmedetomidine and ketamine because of their vasoconstrictive and sympathomimetic effects, respectively, given that this dog had HCM, and followed a multimodal analgesic and anxiolytic plan, including phenothiazines, benzodiazepines, opioids, and local anesthetic. None of these agents could account for the severe and episodic hypertensive episodes observed.

Patients with catecholamine-secreting tumors may have tachycardias and tachyarrhythmias during anesthesia; however, they may also have normocardia attributed to higher parasympathetic tone in patients with an unusual spectral form of vagal activity that may be responsible for low cardiac sympathetic tone, compared with that in patients with primary hypertension.[21] In addition, the dog of the present report received its prescribed atenolol the morning of the anesthetic procedure, which could have contributed to normocardia observed during the first 2 hypertensive episodes.

Although the dog of the present report was initially evaluated because of episodes of oral bleeding, later attributed to advanced periodontal disease, and our multimodal anesthetic protocol was tailored for cardiovascular support of the dog's preexisting HCM, cardiovascular complications occurred intraoperatively and led to subsequent postoperative diagnostic procedures by which malignant neuroendocrine neoplasia was diagnosed. It is important for veterinarians to be aware of the possibility of a functional neuroendocrine tumor as a cause of intraoperative hypertension, especially when wide fluctuations in blood pressure occur independent of painful stimuli.

Footnotes

a. Cardell Touch Monitor, Midmark Corp, Dayton, Ohio.
b. Ultrasonic Doppler Flow Detector, Parks Medical Electronics Inc, Aloha, Ore.
c. Normosol-R, Hospira Inc, Lake Forest, Ill.
d. Planmed Verity, Planmeca USA Inc, Hoffman Estates, Ill.
e. Progeny, VetPro DC digital imaging dental radiography system, Midmark Corp, Dayton, Ohio.

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